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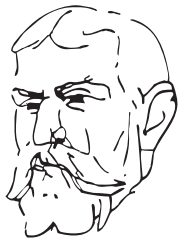

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ORIGINAL ARTICLE

PHYSIOTHERAPY OF PREMATURELY BORN CHILDREN TAKING INTO ACCOUNT THE DEGREE OF BIOLOGICAL IMMATURITY

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ABSTRACT

The aim: 1. Clinical characteristics of premature babies taking into account the complications of the perinatal period. Determining the importance of physiotherapy and defining its place in the therapeutic process carried out in children born prematurely with varying degrees of biological immaturity. 2. Evaluation of the most commonly used physiotherapeutic methods in premature babies.

Material and methods: The study, using a self-authored survey, included parents of 42 premature babies who were between the ages of 1 and 14 months.

Results: As many as 53% of premature babies were born in late preterm (34-36 weeks of pregnancy). 48% of children had low birth weight (1501-2500 grams). The most common complications of the perinatal period among premature babies were respiratory disorders (47%). Physiotherapy of premature babies took place in 50% of the subjects (21 children) due to psychomotor retardation resulting from their biological immaturity. The most commonly used physiotherapeutic method among premature babies was the NDT-Bobath neurodevelopmental method. It was used in as many as 74% of premature babies.

Conclusions: Most premature babies are born in late preterm with low birth weight. Extremely early births are rare. The most common complications of the perinatal period among babies born prematurely are breathing disorders. Most premature babies require physiotherapy, and the main indication for it is psychomotor retardation, resulting from biological immaturity. The most commonly used physiotherapeutic method among premature babies is the NDT-Bobath neurodevelopmental method.

KEY WORDS: premature babies, premature birth, physiotherapy

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INTRODUCTION

Premature babies are babies born prematurely between 22 and 37 weeks of gestation, weighing between 501 and 2500 grams. They belong to the high-risk group of diseases, complications and deaths. Their condition is dependent on many factors occurring in the prenatal, perinatal and postnatal periods [1-3]. Prematurity, depending on the week of pregnancy in which the birth occurred, can be divided into [4-6]: extremely premature at 22-27 weeks of gestation, very premature between 28-31, moderately premature 32-33, and late premature around 34-36. There is also a division into an important factor, which is the birth weight [4-6]: extremely small 501-750 grams, excessively small – 751-1000 grams, very small 1001-1500 grams and small – 1501-2500 grams.

Premature birth can be caused by a variety of biomedical and social factors. There are more types of the former and these include [6, 7]: maternal diseases (gestational diabetes, hypertension), infections causing intrauterine infections (toxoplasma, shingles, cytomegalovirus, rubella), multiple pregnancies, fetal defects, abnormal fetal and umbilical cord position, defects within the uterus (placenta frontal, oligohydramnios, polyhydramnios), pressure-cervical insufficiency, pregnancy at risk, bleeding, serological conflict, premature contractions, previous aborted pregnancies. Social causes include [6, 7]: social position, level of health education, significant stress, excessive effort, physical strain, work in harmful conditions.

The perinatal period is the time when a newborn changes its living environment from intrauterine and adapts to extrauterine and experiences new sensory stimuli. If they have developmental immaturity, care should be implemented that best imitates the conditions prevailing intrauterinely. Premature babies belong to such a group, which requires appropriate adaptation of environmental conditions to their premature birth, hence the work of a physiotherapist begins in the neonatal ward [6].

The aim of physiotherapy of premature babies is to prevent complications, eliminate pathological reflexes and (with disability) achieve the best possible functional state of the child. The cooperation between parent and physiotherapist is a very important issue is(education of parents and their involvement), because the progress of therapy depends on it [4, 8, 9]. Physiotherapy achieves the best results in the 1st year of the child's life, when their motor skills are formed, conditioning the correct movement patterns [1, 4, 10].

THE AIM

1. Clinical characterization of premature babies taking into account the complications of the perinatal period. Also determining the importance of physiotherapy and defining its place in the therapeutic process of children born prematurely with varying degrees of biological immaturity.
2. Evaluation of the most commonly used physiotherapeutic methods in premature babies.

MATERIAL AND METHODS

The study included parents of 42 children born prematurely at 1-14 months of age, including 18 girls (43%) and 24 boys (57%). The study was conducted in 3 facilities in Łódź: Rehabilitation Clinic of the Institute of the Polish Mother's Health Center, Rehabilitation Center "Kraszewski", Intermedicus Rehabilitation Center "Sojczyński".

The form of the study was non-invasive and did not require the consent of the Bioethics Committee of the Medical University of Łódź. Participation in the study was anonymous and voluntary, and an informed consent agreement was signed by the parent.

The study used a self-authored survey with 47 questions, including: 22 closed type, 2 descriptive, 23 semi-open questions. The document was completed by a parent, it consisted of 3 parts: I – aimed to provide basic data about the child and parents, II – contained information on the course of pregnancy and childbirth, III – concerned detailed information about the child. The answers given by the parents were also based on medical records and information obtained from the child's physiotherapist.

Each parent received detailed information about the study, on the basis of which they could get acquainted with the aims and purpose of the study.

Statistical analysis of research results was developed using Microsoft Excel 2021.

RESULTS

As many as 12 premature babies (29%) were born at 33-34 weeks of gestation, including 5 girls (12%) and 7 boys (17%). The group of 24% (10 people) were children born between 35-37 weeks of pregnancy. This group was also dominated by boys (Fig. 1).

Birth weight in the case of most respondents was in the range of 1501-2500 grams – 20 people (48%). As many as 7 children (17%) were born with a body weight exceeding 2500 grams. Less than 750 grams had only 1 girl (2%), the whole is illustrated by Fig. 2.

Complications related to childbirth and prematurity were not found in 60% of children (25 people). In the remaining 40% (17 people), on average there were 2 complications per 1 child. The most common were: apnea (11 people – 27%), bronchopulmonary dysplasia (8 people – 20%), less often (12% each, i.e. 5 people each): intracranial bleeding, persistent Botalla ductus arteriosus and retinopathy. The least numerous complications of the study group were: cerebral palsy, hearing loss, clavicle fracture – each occurring in 1 person (2%). Among 4 premature babies (10%), other complications were found, such as: atrial septal defect, tachycardia, myocarditis, as well as clubfoot (Fig. 3).

According to medical records and information provided to parents by a physiotherapist, the reason for referral to therapy in 21 children (50%) were psychomotor retardations. Increased muscle tone was also indicated as a common reason – declared by 13 parents (31%). The problem of decreased muscle tone in their children was indicated by 8 parents (19%), and asymmetry of body position 6 (14%). The rarest cause of physiotherapy in premature babies was cerebral palsy and foot defect, which occurred in 2 children (5%), as shown in Fig. 4.

Physiotherapeutic improvement was carried out using one or several methods. Of these, the NDT-Bobath concept was the most widely used – together with other methods, it was used in 31 premature babies (74%). Among them, a group of 12 children (29%) was treated with NDT-Bobath 40% (17 people) of children attended Vojta physiotherapy, Shantala massage was performed on 17 children (40%). Both sensory integration and pool kinesitherapy were used on 3 premature babies (7%) (Fig. 5).

The children attended physiotherapy mostly 2 times a week (20 premature babies – 48%). Bearing in mind the opinion of the parents, 12 of them (29%) believed that therapy 2 times a week was sufficient. Only 2 (5%) thought the opposite, and 6 of them (14%) could not assess it. 16 children (38%) underwent physiotherapy once a week. According to 8 parents (19%), this amount was sufficient, and 6 (14%) had the opposite opinion. Physiotherapy was carried out 3 times a week in 6 children (14%) – for 5 parents (12%) it was a satisfactory amount, only 1 person did not share this opinion (Fig. 6).

DISCUSSION

Premature births prevent the development of a human body fully prepared for extramural life. Both biological immaturity and complications associated with childbirth itself pose a risk of many complications, which requires multi-specialist and comprehensive medical care. In order for premature babies to match healthy babies, they require physiotherapy. The effects of which are most quickly achieved in 1 year of life. Improvements in psychomotor development are observed primarily by parents [1, 11].

In this study, the largest group of babies (29%) were born in late preterm, i.e. at 33-34 weeks of gestation, and 24% between 35-37 weeks and with a low birth weight – 1501-2500 grams (48%).

In the research of Baumert et al. [12] Among the group of premature babies, children born medially prematurely (24%) and with low birth weight – on average 1995 grams also dominated the group.

Bręborowicz [13] in his work reported that as many as 75% of premature babies were born between 34-37 weeks of pregnancy.

Bucholc et al. [14] showed the presence of 60% of premature babies with low birth weight (1501-2500 grams).

This relationship may be justified by the fact that premature births most often occur within 2 months before the planned birth, and extreme births are rare.

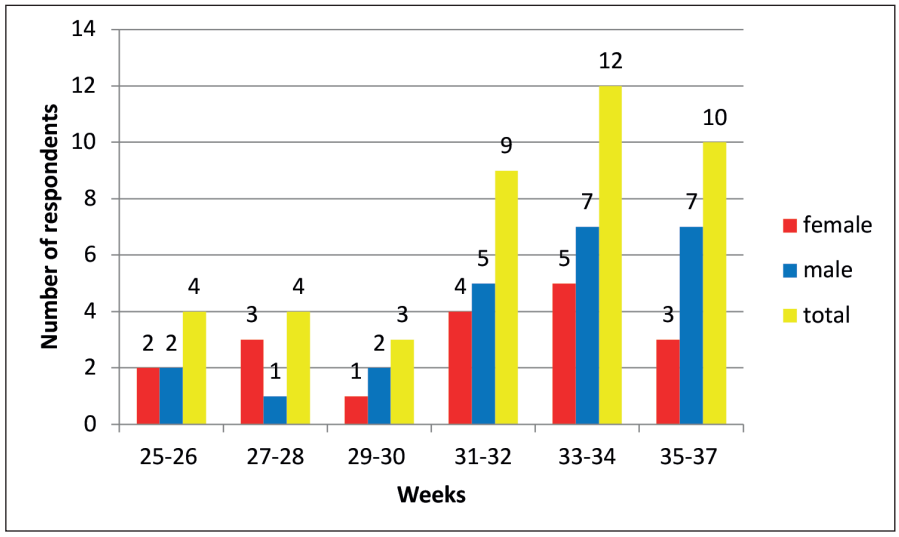

Fig. 1. Duration of pregnancy in the control group.

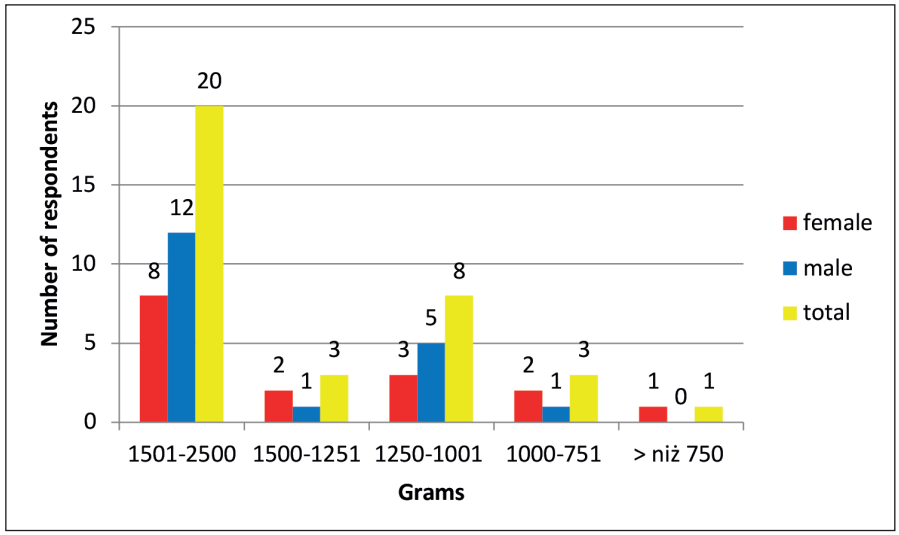

Fig. 2. Bodymass of preterm children divided by sex.

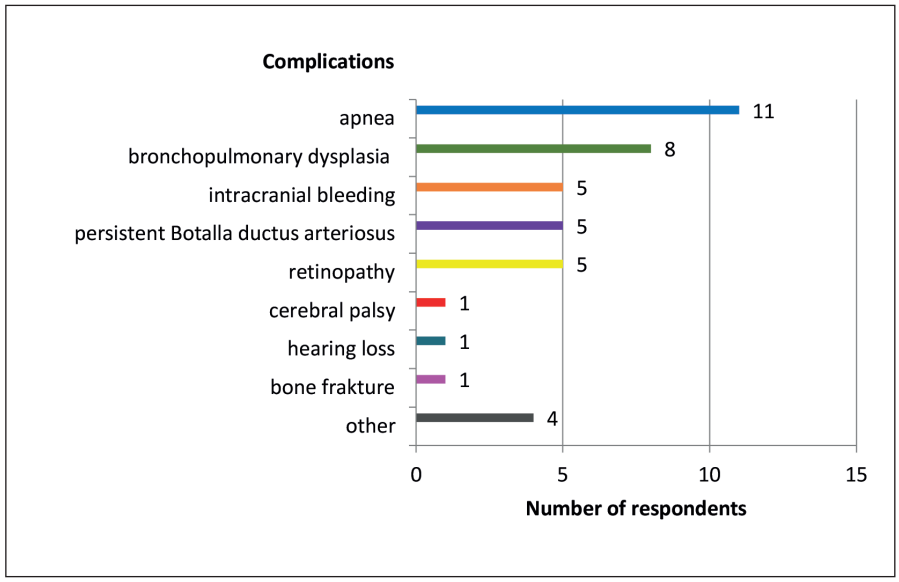

Fig. 3. Preterm complications in the control group.

It is estimated that about 8% of premature babies are born in Poland every year [4-6,15]. This group is numerous, because we will call a premature baby born extremely prematurely, which is very immature and requires intensive medical care, as well as that born in late preterm without the features of prematurity [4-6]. The premature baby, as not fully adapted to life outside the mother's body, requires intensified specialist care to maintain normal vital

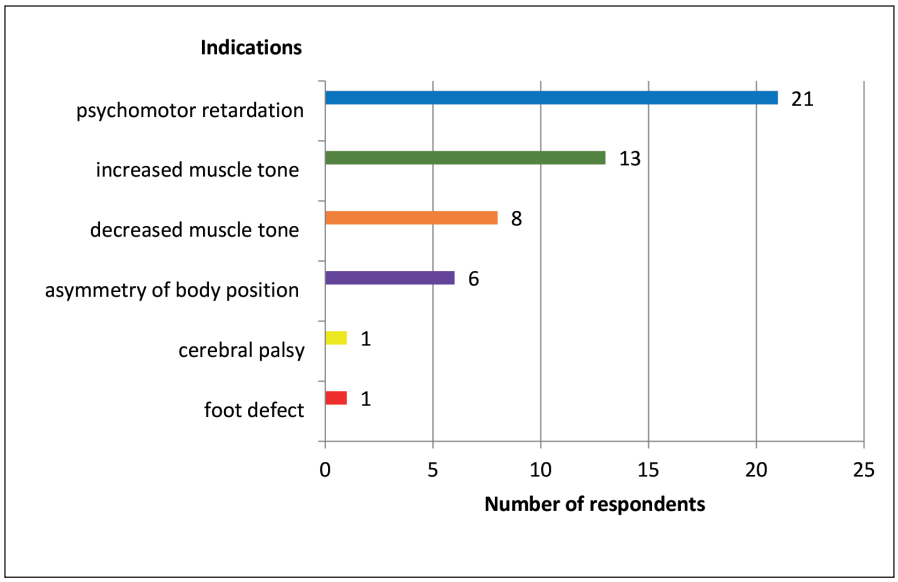

Fig. 4. Most common indications for physiotherapy in the control group.

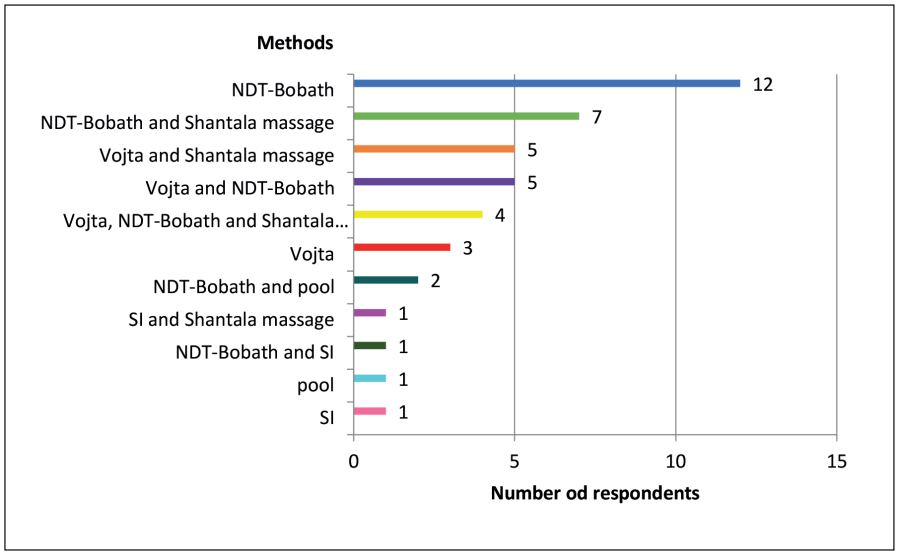

Fig. 5. Physiotherapeutical methods used in the control group.

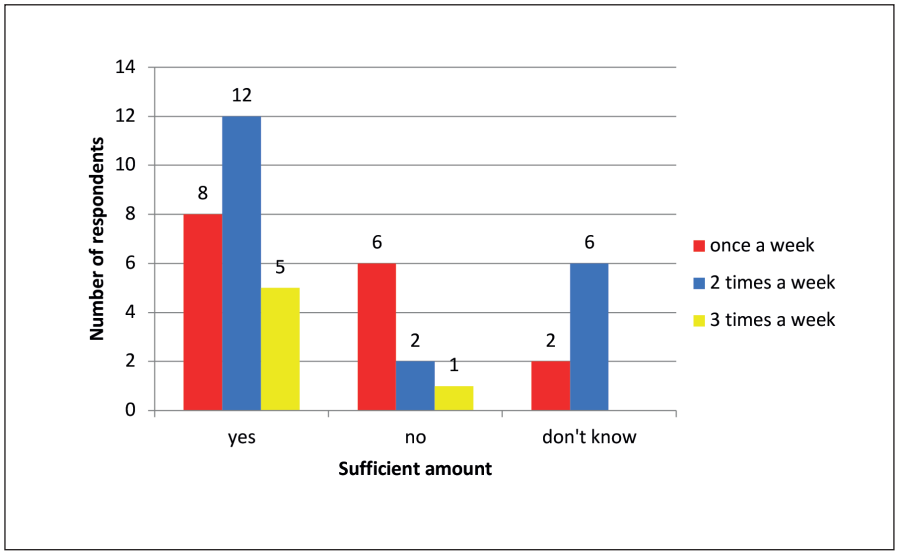

Fig. 6. Sufficient amount of physiotherapy in a week according to children's parents.

functions and provide adequate conditions after birth [7, 16]. Thanks to the development of medicine, and thus the emergence of new physiotherapeutic and therapeutic methods, the survival rate of premature babies is increasing. Today, even children born extremely prematurely with extremely low body weight can be kept alive [4, 5, 7,

15, 16]. However, premature birth is still associated with many clinical complications. The reason for this is the fact that premature babies have difficulties with physiological dysfunction and developmental retardation, often resulting in disability. Therefore, in morphological and psychomotor terms, they are significantly different from fully developed peers [4, 5, 7, 15, 16].

Perinatal complications accompanying premature babies are related to: the course of pregnancy, the birth itself, conditioned biological immaturity [7, 15].

Among the 42 children born prematurely, only 40% had complications, but in other publications [14, 17] 100% of the premature babies studied had them. The most common complications were breathing disorders, which was also shown by Dymczyk-Ociepka et al. [18].

In this study, intraventricular hemorrhages, persistent ductus arteriosus and retinopathy occurred in the same amount – 12% each (5 people each). The research of Baumer et al. [12], in which the following appeared: thermoregulation disorders, intraventricular hemorrhages, breathing disorders, infections.

Complications of premature babies in Dymczyk-Ociepka et al. [18] were presented in descending order: infections, persistent ductus arteriosus, intraventricular hemorrhages, retinopathy. Armanian et al. [17], as the most common complications of prematurity, they indicated: respiratory distress syndrome, sepsis, persistent ductus arteriosus, intraventricular hemorrhage.

To sum up, premature births can have many complications, appearing in different order, but most often the same ones occur. This may confirm that most of the children were in good clinical condition.

Due to the incompletely formed lungs, the child is respiratory inefficient, which requires support by intubation and mechanical ventilation. As a consequence, the premature baby is exposed to: bronchopulmonary dysplasia, apnea, pneumonia [5]. Another common complication of prematurity (related to the circulatory system) is the Botalla ductus arteriosus, which can lead to: necrotizing enterocolitis, pulmonary edema, circulatory failure, cerebral ischemia [6]. Damage to the nervous system is irreversible, and with premature birth, intraventricular bleeding, periventricular leucomalacia, hypoxic-ischemic encephalopathy may occur [5]. The result of these disorders in premature babies are: cerebral palsy, hydrocephalus, epilepsy, delayed development, psychomotor hyperactivity disorder [7]. Disorders can also affect the organ of vision, most often causing retinopathy, which in consequence may even result in blindness [6, 7]. Damage to the central nervous system also leads to dysfunction of the hearing apparatus. Other complications are [5-7]: bone fractures, scoliosis, growth disorders, insufficient body weight, increased or decreased muscle tone, body asymmetry.

The analysis of own research shows that the most common cause of physiotherapy of premature babies (50%) was psychomotor delay, less often increased (31%), or decreased muscle tone (19%) and asymmetry of body position (14%). Only 1 child (2%) developed cerebral palsy or foot defects.

Dytrych [19] also came to similar conclusions, in which only premature babies were the study group. Psychomotor delay was observed in 30.7% of children – 1 of them presented decreased muscle tone. Cerebral palsy occurred in one premature baby.

Taczała et al. [20] report that in the study group of premature babies, 20.7% attended physiotherapy due to a delay in psychomotor development, while 13.8% of children underwent therapy due to cerebral palsy.

In the light of the above, it may seem that cerebral palsy is not closely related to prematurity, and is only its possible complication.

Biological immaturity is an integral result of prematurity. Any child born prematurely is biologically immature, and the degree of immaturity depends mainly on the time of delivery and thus the fetal development that has been interrupted [10, 20]. With age, the criteria for assessing maturity change, as the child's achievement of developmental norms and the occurrence or disappearance of primary reflexes are taken into account.

The first scale that assesses the general condition, including the maturity of the newborn, is the Apgar scale. The number of points obtained in the 1st and 5th minute after delivery determines the scope of therapeutic activities undertaken in the first days after birth – a child in a more severe condition requires more intensive medical care [16].

Natal immaturity does not have to result in a delay in development at a later age and the Dubowitz and/or Ballard scales are used to assess it [4]. In later months, the maturity of the child is assessed on the basis of the achievement of subsequent developmental norms, skills obtained at a certain age, but also the presence and severity of primary reflexes, on which the following are based, among others: the infant motor skills test (TIMP), the infant motor development scale (AIMS), the functional scale of large motor skills (GMFM) [10]. Immaturity in premature babies can occur to varying degrees and is also dependent on comorbidities, as a child with cerebral palsy will show psychomotor deffects than a healthy child. With the passage of time – in most cases thanks to physiotherapy, the infant matures and equals his peers [10, 21].

Not every child born prematurely requires physiotherapy. Before referring a premature baby for treatments, the most important thing is to make the correct diagnosis, which allows to choose the right therapy. The range of developmental disorders is extensive, since physiotherapy can take place due to abnormal muscle tone, but also as a result of cerebral palsy. It is most beneficial to start therapy as soon as possible, and its duration depends on the clinical condition of the patient [22].

In order to start physiotherapy of premature babies, it is important to know the development of the child already in fetal life, as well as the formation of the body in 1 year of life. Therapy should be adjusted individually, having information about the week in which the premature baby was born and what he did not develop intrauterinely, and at what motor stage he should be, as well as whether he is equal to his reported peers [6, 22].

There are many methods used in improving children, and each is adapted to the appropriate disorder [22]. The most commonly used methods of improving premature babies, according to Dytrych [6], are the NDT-Bobath method and the Vojta method.

In this study, 74% of children were treated with the NDT-Bobath method, although the choice of method is selected individually to the needs of the premature baby by the attending physician. In both patients diagnosed with a developmental disorder and premature babies exposed to many complications, NDT-Bobath remains the guiding method of physiotherapy, but always supplemented by other therapeutic strategies [23].

There are many physiotherapeutic methods designed for premature babies. An appropriate therapeutic target should be chosen to support the chosen therapeutic target [4,5,10,22]. Physiotherapy is undertaken after the psychomotor assessment of the child using diagnostic methods based on milestones of child development. The following scales are used: Munich functional developmental diagnostics, assessment of global motor patterns using the Prechtl's method, Brazelton's scale for assessing newborn behavior, neurodevelopmental assessment according to the Vojt's method, neurodevelopmental assessment according to the NDT-Bobath concept [8, 9]. After the diagnostic evaluation, appropriate improvement should be carried out by the chosen method [1, 4, 10].

Children of the surveyed parents before therapy were assessed according to the methods that were then treated with.

In premature babies, kinesitherapy and massage are primarily used. The most commonly used in prematurity are: NDT-Bobath method, Vojt's method, sensory integration, PNF for children, Veronica Sherborne's method, Shantal's massage [22].

A good complement to physiotherapy, supporting the functioning of premature babies, is spa treatment, introduced after 3 years of age. Depending on the general psychophysical condition, the child may benefit, among others, from: hydrotherapy, aerosol therapy, peloidotherapy [24-26].

The analysis of own research shows that in premature babies physiotherapy was sufficient and most often carried out 2 times a week, which is confirmed by the results of Dytrych [19]. However, for proper development, in addition to systematically conducted therapy, the premature baby needs stimulation performed by parents.

In this study, all parents implemented exercises given by a physiotherapist in the circadian rhythm of premature babies. Dytrych also demonstrated this in her work [19].

Sędek et al. [23], by studying a group of children with cerebral palsy determined that the optimal number of times of physiotherapy per week, according to parents, was on average 3 times a week, using social security measures and 3 times a week using other sources of financing. It can be noted that the greater number of the disorders in children, the more physiotherapeutic treatments they may need to achieve the intended effects of therapy.

Own research showed that the main indication for physiotherapy of premature babies was a delay in psychomotor development. Early actions taken create conditions to eliminate deficits, and also give a chance to match healthy and born on time peers. It is also related to the fact that a quick return to full ability eliminates the future need to continue physiotherapy, and thus – additional, often high costs for both patients and the state budget.

CONCLUSIONS

Most premature babies are born in late preterm with low birth weight. Extremely early births are rare.

The most common complications of the perinatal period among babies born prematurely are breathing disorders.

Most premature babies require physiotherapy, and the main indication for it is psychomotor retardation, resulting from biological immaturity.

The most commonly used physiotherapeutic method among premature babies is the NDT-Bobath neurodevelopmental method.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

THE RELATIONSHIP OF CLINICAL AND MORPHOLOGICAL DATA IN COMMINUTED FRACTURES OF THE LOWER JAW

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ABSTRACT

The aim is to establish the relationship between some clinical, physiological and morphological parameters in patients with the consequences of an acute injury considering the features of pathological and reparative changes in the bone fragments of the lower jaw formed during a fracture using clinical and morphological methods.

Materials and methods: The material of the study was bone fragments of the lower jaw, removed during osteosynthesis operations in 20 patients with traumatic comminuted fractures. Also, the material of the study was the data obtained during the examination of the above patients. Morphological parameters characterizing the state of the fragments tissues removed during surgical treatment of fractures of the lower jaw and clinical parameters characterizing the patient's condition in cases of traumatic fractures of the lower jaw treatment were identified for frequency and correlation analysis. Different of frequency of individual indicators' gradations cases was determined by the χ-square test, correlations between parameters (correlations of pairs of parameters "clinic – morphology", "clinical and laboratory data – morphology") – by calculating the Pearson association coefficient.

Results: The main pathological and reparative changes are determined in the bone fragments of the lower jaw after a traumatic fracture: osteomedullary ischemic necrosis (traumatic bone infarction), nonspecific productive inflammation, endosteal and periosteal bone regenerates. The severity and frequency of pathological and reparative changes in the bone fragments of the lower jaw vary, leading to various correlations between clinical and morphological indicators of the fragment tissues conditions. Reliable correlations were established between individual clinical and morphological indicators of the state of bone fragments corresponding to the values of the association coefficient in the range of 0.3-0.7, in particular: in the pair "age of the patient" – "endosteal regenerates" – the dependence is negative, of medium strength, significant ($p<0.05$); in the pair "age of the patient" – "periosteal regenerates" – the dependence is negative, of medium strength, significant ($p<0.05$); in the pair "fragment surface area" – "osteonecrosis" – the relationship is negative, weak, significant with the probability of error in assessing the value $|r_a|$ $p<0.1$; in the pair "locus of a fracture in the lower jaw" – "type of inflammation in the bone marrow" – the dependence is positive, of medium strength, highly reliable ($p<0.01$).

Conclusions: A comprehensive clinical and morphological examination made it possible to calculate quantitative data that characterize the frequency parameters of the occurrence of certain pathological changes in the bone fragments of the lower jaw after a fracture and the features of individual clinical and morphological parameters conjugation in patients with the consequences of a mechanical jaw injury. The obtained data on the correlation dependences of the type "clinic – morphology" can be used to predict the severity of morphological parameters according to the known values of clinical parameters in patients with the consequences of mandibular fractures.

KEY WORDS: mandibular fracture, bone splinters, clinical indicators, morphological indicators, frequency analysis, correlation analysis

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INTRODUCTION

A characteristic feature of mandibular fractures is a high likelihood of complications [1, 2], primarily of an inflammatory nature. According to the literature, their incidence reaches 37.2% [3]. In 16.8% of cases, patients develop chronic traumatic osteomyelitis with sequestration of bone fragments and the formation of false joints, extensive post-traumatic defects and jaw deformities [4]. Comminuted fractures, often accompanied by ruptures of the mucous membrane, damage of the teeth, alveolar process, are most susceptible to complications in the form of inflammatory processes [5]. According to numerous studies, such injuries are accompanied by the highest frequency of postoperative complications and represent the greatest difficulty for surgical treatment [6].

It is logical to assume that bone tissue, bone marrow, mandibular periosteum, paraosseous soft tissues undergo characteristic changes after a fracture, including traumatic-ischemic, dystrophic, inflammatory and reparative ones. The authors studied dynamics of such changes in fragments of long bones during osteotomies in the experiment [7, 8]. However, there is no mention of the research on the relationship between clinical indicators characterizing the condition of patients with mandibular fractures and morphological indicators reflecting the state of fragment tissues in the literature.

THE AIM

The aim is to establish the relationship between some clinical, physiological and morphological parameters in

Table I. Clinical parametric and nonparametric parameters characterizing the patient's condition in cases of traumatic fractures of the lower jaw treatment

Parametric parameters			
Clinical parameters	**Number of recorded cases**	**Median**	**Mean value and standard error**
Age of the patient at the time of injury, years	20	39.00	40.05±3,03
Duration of injury, days	20	12.00	11.40±1.55
Injury index, points	20	11.50	11.45±0.65
Fragment surface area, mm×mm	19	15.00	21.76±3.77
Rheographic index	20	0.65	0.695±0.046

Nonparametric parameters			
Clinical parameters	**Description of parameter gradations**	**Number of recorded cases**	**Frequency of occurrence in the material**
Nature of injury	Low degree: low energy	4	20.0 %
	High degree: high energy	16	80.0 %
Locus of fracture in the lower jaw	Low degree: fracture of the articular process or in the area of the jaw angle	11	55.0 %
	High grade: fracture in the jaw body	9	45.0 %
Treatment result	Low grade: complete union or delayed consolidation	13	65.0 %
	High grade: pseudarthrosis or bone defect	7	35.0 %

patients with the consequences of an acute injury considering the features of pathological and reparative changes in the bone fragments of the lower jaw formed during a fracture using clinical and morphological methods.

MATERIALS AND METHODS

The material of the study was bone fragments of the lower jaw, removed during osteosynthesis operations in 20 patients with traumatic comminuted fractures. Fragments were repositioned during the operation, small fragments were removed (used for histological examination) and other fragments were fixed with mini-plates on the surface of the damaged bone.

All examined patients were traumatized by high-energy trauma (gunshot wounds, traffic accidents, industrial injuries). Comminuted fractures in the area of the angle and condylar process of the jaw were open in 11 (55%) cases and closed in 9 (45%) cases.

Before the operation, the patients underwent clinical, laboratory and X-ray studies, as well as tissue rheography of the damaged area. According to the rheography data, a decrease of the rheographic index was determined by more than 50% (rheographic index = 0.28-0.31 ohm) [9].

During patient examination, we took into account 10 main clinical and biological indicators of the state of tissues in the area of damage: the general status of the patient, the duration of the injury, the number of fragments of the lower jaw in the area of the fracture, the number of sources of extraosseous circulation of the larger fragment, the size of the large fragment, the degree of rupture of the oral mucosa and exposure bones, displacement of fragments, etiology of injury, volume of diastasis between the contact surfaces of fragments, impaired blood circulation of the bone according to rheography. We evaluated these main indicators according to the degree of their clinical severity in points (0-1-2) and then summarized the scores. The resulting scores were called the "injury index" [10]. The maximum surface area of the fragments was calculated by multiplying the two parameters of the length of the fragments obtained by measurements on the radiograph.

The removed fragments were usually used without grinding for histological examination. The tissues were fixed with 10% formalin, the pieces were decalcified with 5% nitric acid, and embedded in celloidin. The resulting sections with a thickness of 10 μm were stained with hematoxylin and eosin, hematoxylin-picrofuchsin according to van Gieson. The slides were examined using an Olympus BX-41 microscope (Japan).

To carry out frequency and correlation analysis, the authors identified a number of morphological parameters characterizing the state of the fragments tissues removed

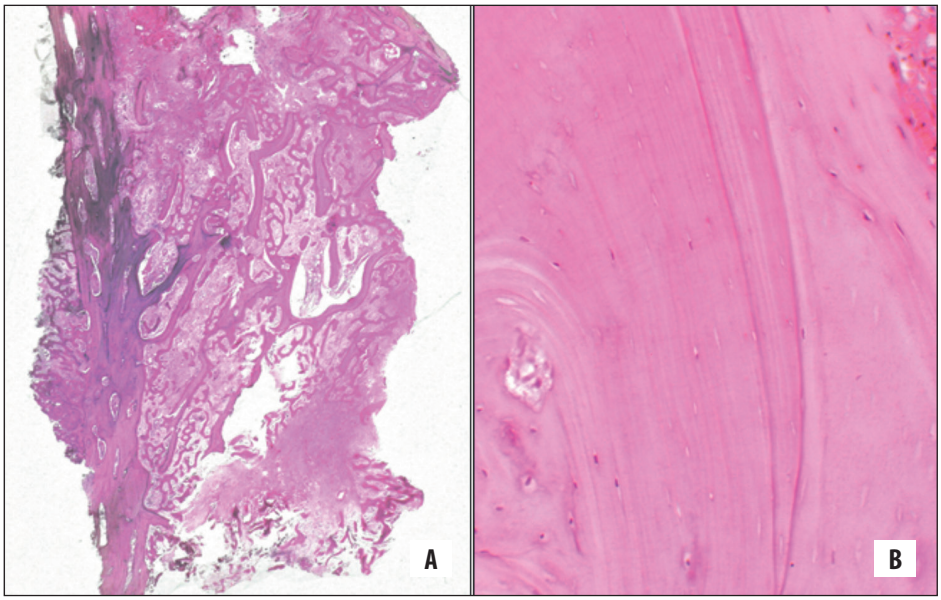

Fig. 1A. General view of a fragment of the articular process of the lower jaw: periosteal regenerate on the surface of the cortex; hemorrhages, fibrosis and endosteal regenerates in spongiosis. Stained with hematoxylin and eosin, × 20.
Fig. 1B. Large interstitial osteonecrosis in the cortex. Stained with hematoxylin and eosin, × 150.

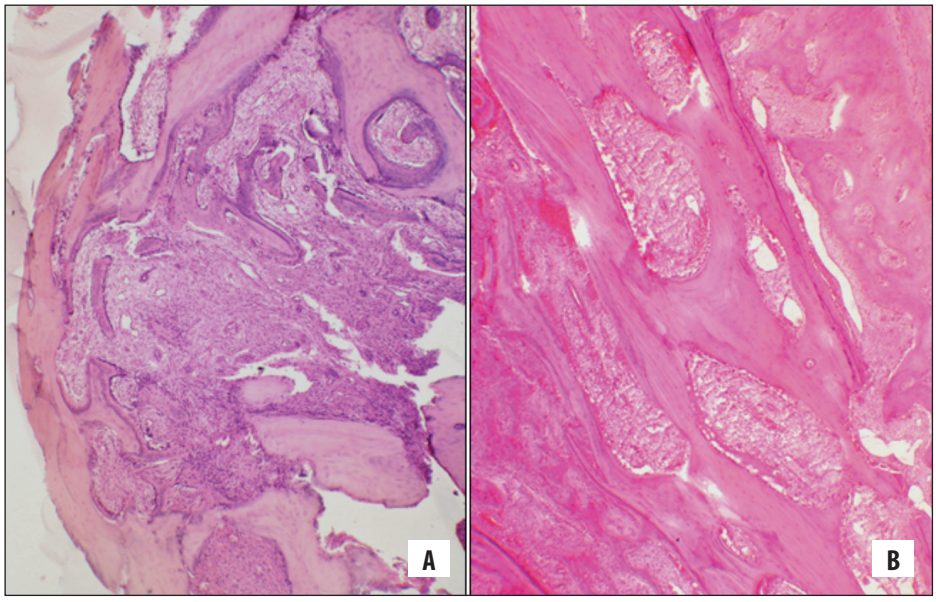

Fig. 2A. Large focal osteomedullary necrosis and endosteal regenerates. Stained with hematoxylin and eosin, × 30.
Fig. 2B. Cortex osteonecrosis restructuring: extensive resorption cavities, endosteal regenerate, periosteal regenerate. Stained with hematoxylin and eosin, × 30.

during surgical treatment of fractures of the lower jaw and clinical parameters characterizing the patient's condition in cases of traumatic fractures of the lower jaw treatment. Different of frequency of individual indicators' gradations cases was determined by the χ-square test, correlations between parameters (correlations of pairs of parameters "clinic – morphology", "clinical and laboratory data – morphology") – by calculating the Pearson association coefficient.

RESULTS

Analyzing the clinical data of the group of patients shown in table I, the authors found out that most of the reported cases corresponded to high-energy trauma, were localized in the posterior parts of the jaw. They led to complete fusion or delayed consolidation of fragments after installation of fixators.

Histological examination of the removed fragments of the lower jaw revealed a number of characteristic pathological changes in the bone marrow and bone tissue, the extent and severity of which varied from case to case and reflected a topographically complex combination of dyscirculatory, reactive-inflammatory and reparative changes in the tissues of the jaw after an acute injury (Fig. 1A). So, we found osteonecrosis of various sizes in all studied fragments, localized in the cortex and spongiosa crossbeams, regardless of the fracture location. However, in some cases, there were signs of ongoing pathological restructuring, in the cortex tissue subjected to ischemic damage with the formation of extensive resorption lacunae. Distribution of osteonecrosis area was uneven: sometimes there were necroses in the form of small groups of empty osteocytic lacunae – up to 20 objects. Such changes were characterized as small interstitial osteonecrosis. Groups of empty osteocytic cells with several tens of lacunae localized in the cortex and spongiosis were designated as large interstitial osteonecrosis (Fig. 1B). Finally, areas of bone marrow and bone tissue with dimensions of 2 mm or more were

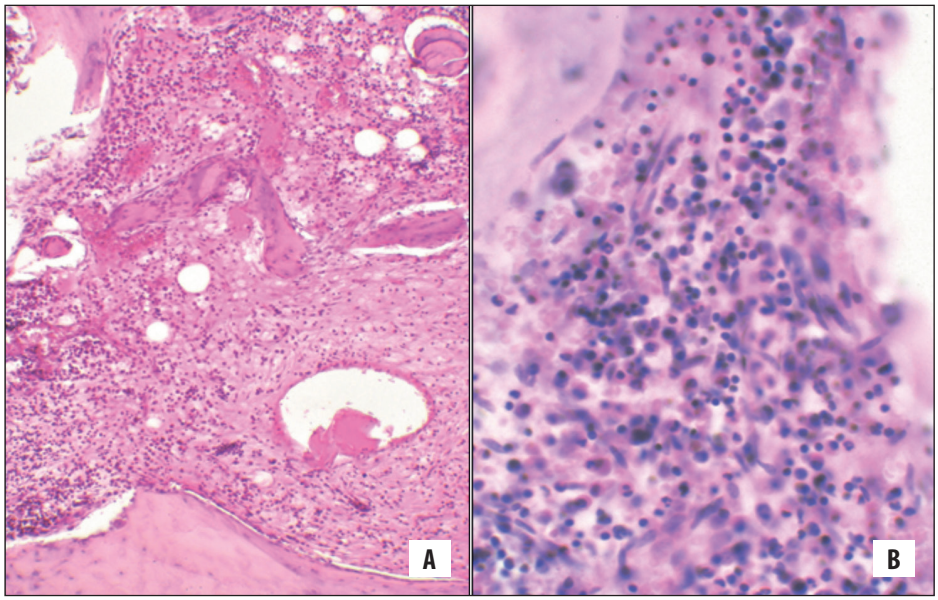

Fig. 3A. Loose leukocyte infiltration in the bone marrow. Stained with hematoxylin and eosin, × 30.
Fig. 3B. Intensive leukocyte infiltration with a predominance of mononuclears in the bone marrow. Stained with hematoxylin and eosin, × 300.

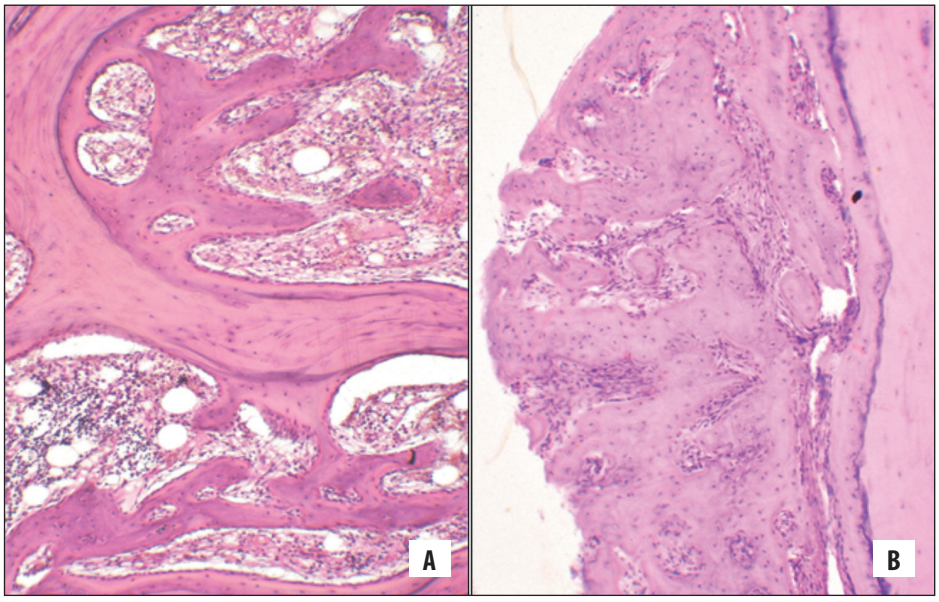

Fig. 4A. Endosteal regenerates, spongiosis bars in a state of osteonecrosis. Stained with hematoxylin and eosin, × 75.
Fig. 4B. Periosteal regenerate with signs of moderate compaction on the surface of the cortex containing osteonecrosis. Stained with hematoxylin and eosin, × 75.

regarded as focal osteonecrosis. Necrotized bone marrow in them was often replaced by immature fibrous tissue, while the areas with empty osteocytic lacunae persisted (Fig. 2A). Enlarged resorption cavities with an increased number of multinuclear osteoclasts on the walls were often determined in the cortex where osteonecrosis occurred. (Fig. 2B).

Among the immature fibrous tissue occupying the bone marrow spaces of the studied bone fragments of the lower jaw, there were accumulations of leukocytes, macrophages and plasma cells, and these inflammatory infiltrates had a different density and, more often, a small-focal distribution. Low-density, small-focal infiltrates corresponded to productive-infiltrative inflammation of low activity (Fig. 3A), denser, confluent accumulations of infiltrate cells corresponded to productive inflammation of high activity (Fig. 3B).

An important manifestation of bone tissue repair processes are endosteal and periosteal bone regenerates, which were most pronounced in fragment tissue areas adjacent to the fracture surface. Endosteal regenerates were usually more voluminous and resembled small-beam reticulated stratifications on the endosteal surface of a partially necrotic cortex and necrotic bone bars (Fig. 4A). Periosteal bone regenerates were usually inferior in size to endosteal ones, often had an insignificant thickness and were more or less compacted. Sometimes, the surfaces of their crossbars were covered with a palisade of active osteoblasts, and sometimes – with flattened, less active cells (Fig. 4B).

The data in table II indicate that osteonecrosis was somewhat more common in the form of small and large interstitial objects than macrofocal osteonecrosis. Cases with productive high-grade inflammation in the bone marrow of splinters were less common than cases with no or low-grade inflammation. Cases with endosteal and periosteal bone regenerates of a high degree of severity were found in the biopsy material of the fragments more often than cases with a low degree of these signs.

Table II. Morphological parameters characterizing the state of the fragments tissues removed during surgical treatment of fractures of the lower jaw

Morphological parameters	Description of parameters gradations	Number of recorded cases	Frequency of occurrence in the material
Osteonecrosis	Low grade: interstitial small and large osteonecrosis	11	55.0 %
	High grade: large focal osteonecrosis	9	45.0 %
Inflammation in the bone marrow	Low grade: no inflammation or inflammation of low activity	9	60.0 %
	High grade: high activity inflammation	6	40.0 %
Endosteal regenerates	Low degree: absent or minimal	7	43.7 %
	High degree: well expressed	9	56.3 %
Periosteal regenerates	Low degree: absent or minimal	5	35.7 %
	High degree: well expressed	9	64.3 %

Table III. Correlations between the clinical parameters of patients and the morphological parameters of affected tissues of the fragments removed during the surgical treatment of mandibular fractures (gradations of parameters – see tables 1, 2)

Clinical parameters	Morphological parameters	n, number of recorded cases with values of both parameters	Pearson's tetrachoric coefficient of association (association coefficient) r_a	Estimation of the significance r in k=n-1 by Student's criterion, the error significance
Patient's age *	Osteonecrosis n	20	+0.219	>0.05
	Type of inflammation in the bone marrow n	15	+0.218	>0.05
	Endosteal regenerates n	16	-0.524	<0.05
	Periosteal regenerates n	14	-0.559	<0.05
Age of injury **	Osteonecrosis	20	-0.287	>0.05
Injury index ***	Periosteal regenerates	14	+0.244	>0.05
Fragment surface area ****	Osteonecrosis	19	-0.382	<0.1
	Periosteal regenerates	13	-0.386	>0.05
Rheographic index *****	Osteonecrosis	20	+0.285	>0.05
Nature of injury °	Osteonecrosis	20	-0.302	>0.05
Locus of fracture in the lower jaw	Type of inflammation in the bone marrow	15	+0.667	<0.01
	Periosteal regenerates	13	-0.300	>0.05
Treatment result °	Periosteal regenerates	14	+0.344	>0.05

Notes: * – gradations: "low" – less than 40 years old, "high" – equal to or more than 40 years old; ** – gradations: "low" – less than 10 days, "high" – more than 10 days; *** – gradations: "low" – less than or equal to 11 points, "high" – more than 11 points; **** – gradations: "low" – less than 15 mm2, "high" – more than 15 mm2; ***** – gradations: "low" – less than or equal to 0.65, "high" – more than 0.65; ° – gradations of clinical nonparametric parameters see table 1; n – gradations of morphological nonparametric parameters see table II.

The results of the correlation analysis of relationships (table III) indicate that most of the correlation pairs "clinic – morphology" have absolute values in the range of weak $0.3<|r_a|<0.5$, or very weak $|r_a|<=0.5$, or the values of the association coefficient were not reliable. A couple of indicators with the highest values of the association coefficient deserve discussion:

- in the pair "age of the patient" – "endosteal regenerates" – the dependence is negative, of medium strength, significant ($p<0.05$);
- in the pair "age of the patient" – "periosteal regenerates" – the dependence is negative, of medium strength, significant ($p<0.05$). In both cases, this means that older patients are more likely to have low grade regenerates;
- in the pair "fragment surface area" – "osteonecrosis" – the relationship is negative, weak, significant with the probability of error in assessing the value $|r_a|$ $p<0.1$. This means that large-focal osteonecrosis is more common in smaller fragments compared to larger fragments;

- in the pair "locus of a fracture in the lower jaw – "type of inflammation in the bone marrow" – the dependence is positive, of medium strength, highly significant ($p<0.01$). This means that we observe productive inflammation of high activity or exudative inflammation more often when a fracture is localized in the area of the body lower jaw in the bone marrow.

DISCUSSION

The histological study showed that the severity of pathological changes in the bone fragments of the lower jaw is different, can be presented and taken into account in the form of separate gradations, and the frequency of cases of each gradation in the array of the studied clinical and morphological material varies [11]. The most permanent histological changes in the bone fragments of the lower jaw are traumatic-ischemic osteonecrosis, nonspecific productive inflammation in the fibrous bone marrow, endosteal and periosteal bone regenerates. Morphological gradation indicators, reflecting the severity of these pathological and reparative changes in the tissues of the fragments, can correlate differently and significantly only with some clinical indicators, determining their different diagnostic value.

A traumatic bone fracture always leads to impaired blood supply at the ends of the fragments. This is due to mechanical damage to the vascular networks of the cortex and bone marrow. In the case of a high-energy fracture, if there is a significant displacement of the fragments and the intraorgan branches of the main feeding artery can be torn, quite extensive zones of ischemic necrosis appear at the ends of the long bone fragments, which we designated as traumatic bone infarcts [12-16]. The presence of extensive osteonecrosis reflects the decompensated nature of impaired blood supply to bone tissue and bone marrow fragments. Pathological changes in the tissues of the lower jaw after its traumatic fracture have not been studied before, although their results are important for understanding the viability of bone tissue. Variations in the size of osteomedullary necrosis are probably associated with the degree of damage to the sources of blood supply to the bone tissue: the main supply artery, metaphyseal and periosteal vessels. Restoration of the blood supply to the fragment occurs both through the preserved blood vessels due to recirculation from the preserved sources, and through the vessels growing into the focus of osteomedullary necrosis, i.e. in the process of revascularization necrosis. The development of both endosteal and periosteal bone regenerates is impossible without at least partial restoration of the blood supply to the fragments.

The revealed correlation dependences in pairs of indicators "clinic – morphology" suggest a certain author's comment. The negative dependence of the average strength between the age of the patient and the severity (in fact, the volume) of endosteal and periosteal bone regenerates: the higher the age, the smaller the volume of bone regenerates, indicates the quantitative age-related features of the reparative reaction in certain age periods, and seems natural. It is likely that the decrease in the size of bone regenerates in mandibular fragments is associated with age-related reduction of the microvasculature of the mandible tissues, although angiomorphological study was not the subject of this work. The negative relationship between the size of the fragments and the size of osteonecrosis (in the series: small, large interstitial, large-focal) indicates a greater damage, in terms of ischemic impact on them, of small bone fragments compared to larger fragments. The positive dependence of the average strength between the fracture locus (from low to high in the series: articular process – jaw angle – jaw body) and the type (in fact – morphological signs) of inflammation in the bone marrow of the bone fragment can be explained by more intense blood supply to the bone tissue of the jaw body.

From the results of the correlation analysis carried out in this paper, such facts as, for example, a very weak relationship between the "prescription of injury", on the one hand, and "endosteal regenerates" and "periosteal regenerates", on the other hand, seem to be informative and previously unobvious. This can be explained by unequal formation rate of regenerates of various sizes at different time after injury in individual patients. Very weak dependencies with unreliable values of the association coefficient exist between the "injury duration", "injury index", "rheographic index", "injury character" (+/- high-energy injury) – on the one hand, and a number of morphological indicators of the state of bone fragments – on the other hand.

In our clinical and morphological study, we calculated quantitative data that characterize the frequency parameters of the occurrence of certain pathological changes in the bone fragments of the lower jaw after a fracture and the features of individual clinical and morphological parameters conjugation in patients with the consequences of a mechanical jaw injury. The obtained data on the correlation dependences of the type "clinic – morphology" can be used to predict the severity of morphological parameters according to the known values of clinical parameters in patients with the consequences of mandibular fractures.

CONCLUSIONS

1. The main pathological and reparative changes are determined in the bone fragments of the lower jaw after a traumatic fracture: osteomedullary ischemic necrosis (traumatic bone infarction), nonspecific productive inflammation, endosteal and periosteal bone regenerates.
2. The severity and frequency of pathological and reparative changes in the bone fragments of the lower jaw vary, leading to various correlations between clinical and morphological indicators of the fragment tissues conditions.
3. Reliable correlations were established between individual clinical and morphological indicators of the state of bone fragments corresponding to the values of the association coefficient in the range of 0.3-0.7, in particular: in the pair "age of the patient" – "endosteal regenerates" – the dependence is negative, of medium strength, significant

($p<0.05$); in the pair "age of the patient" – "periosteal regenerates" – the dependence is negative, of medium strength, significant ($p<0.05$); in the pair "fragment surface area" – "osteonecrosis" – the relationship is negative, weak, significant with the probability of error in assessing the value $|r_a|$ $p<0.1$; in the pair "locus of a fracture in the lower jaw" – "type of inflammation in the bone marrow" – the dependence is positive, of medium strength, highly reliable ($p<0.01$).

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Conflict of interest:

The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

RHEUMATOID ARTHRITIS AS A PREDISPOSING FACTOR FOR INCREASED RISK OF DIABETES MELLITUS INCIDENCE

DOI: 10.36740/WLek202210103

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ABSTRACT

The aim: Recent advances in diabetic mellitus (DM) care are focusing emphasis on comorbidities including rheumatoid arthritis (RA). The goal of this study is to determine the relationship between RA and diabetes as a risk factor.

Materials and methods: Participants whose diagnosis of RA was confirmed by rheumatologists were recruited into a cross-sectional observational cohort using data from government and private clinics. Participants filled out detailed questionnaires. We included patients with DM and combined DM and RA who was diagnosed with both conditions by specialists between (October 2021 to April 2022) in Al Kut city, Iraq.

Results: Our finding shows no difference between the two groups DM and DM+RA in age, BMI, and smoking. However, the health status represented by hospitalization was more frequent in the DM+RA group. The inflammatory pathway in RA also increases the incidence of DM where we show an increase in the ESR in the DM+RA group. Interestingly Glycated hemoglobin (Hb a1c) indicator of DM was significantly increased in DM+RA compared to the DM group.

Conclusions: In conclusion, RA is linked to an increased chance of developing diabetes. This data backs up the theory that inflammatory pathways play a role in diabetes development.

KEY WORDS: rheumatoid arthritis, diabetes mellitus, risk factor, incidence

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune and inflammatory disease characterized by chronic synovial inflammation that causes cartilage and bone deterioration [1]. In industrialized nations, this illness affects 0.5-1.0 % of individuals [2]. Inflammation appears to be a major component in the genesis and progression of diabetes, according to mounting research [3]. Systemic inflammation linked to RA may increase the chance of acquiring diabetes later in life. In persons with RA, markers of active inflammation, such as CRP, are linked to an increased risk of diabetes. Other classic risk factors for type 2 diabetes mellitus (T2DM) are also common in patients with RA, which may contribute to increased diabetes risk [4]. In persons with RA, metabolic syndrome is very common [5]. Physical inactivity is widespread in persons with RA as a result of persistent pain, oedema, and stiffness in the joints, which leads to T2DM by reducing calorie burning [6].

Inflammation has been linked to the development of diabetes. Some of the standard T2DM risk factors are also quite common in patients with RA. As a result, diabetes might be more common in persons with RA. Several observational studies have looked at the link between RA and the occurrence of diabetes, but the results have been mixed [7, 8]. A recent meta-analysis included cohort studies (five eligible studies) published before January 2014 and discovered that patients with RA had a statistically significant higher risk of diabetes [relative risks (RR), 1.24; 95% confidence intervals (CI), 1.14-1.35] [9]. Three more cohort studies have been published since then [10-12]. We want to validate the findings of a study that linked two illnesses. So we aimed in the current study to determine the relationship between RA and diabetes as a risk factor.

MATERIAL AND METHODS

Participants whose diagnosis of RA was confirmed by rheumatologists were recruited into a cross-sectional observational cohort using data from government and private clinics. Participants filled out detailed questionnaires. We included patients with DM and combined DM and RA who was diagnosed with both conditions by specialists between (October 2021 to April 2022) in Al Kut city, Iraq. We have main two groups (1) DM group (reference) and (2) DM+RA group.

Data were collected after obtaining official approval from the ethical committee in Wasit University, from governmental and private clinics.

STATISTICAL ANALYSIS

The baseline characteristics of patients with RA with and without incident DM were described using means and percentages as stated, and t-test or chi-square tests were

Table I. Baseline characteristics. *

Variables	Total	DM		p value
		DM	DM+RA	
Age, years	53.882	54.219	53.546	0.087
BMI	25.843	25.882	25.805	0.081
Years since diabetes diagnosis	8.188	8.344	8.031	0.327
Education				
No education	119	43.72 %	40.21 %	0.9352
Primary school	95	32.79 %	36.08 %	
Secondary school	41	14.75 %	14.43 %	
Bachelor's	21	7.65 %	7.22 %	
Postgraduate	4	1.09 %	2.06 %	
Smoking status				
Never	181	61.75 %	70.10 %	0.1488
Past	76	27.87 %	25.77 %	
Current	23	10.38 %	4.12 %	

* Unless otherwise stated, all values are provided as mean
BMI – body mass index

used to compare them. These two tests were also used to compare illness markers including blood sugar level and Hb level. All *p* values were calculated on a two-sided basis with a significance threshold of 0.05. GraphPad Prism V.5.00 was used for all statistical analyses (1992-2007 GraphPad Software Inc.).

RESULTS

There were 183 diabetic patients in our research, with a mean age of 54.219 years and an average illness duration of 8.344 years. Patients with combined DM and RA, with a baseline, mean age of 53.546 years and disease duration of 8.031 years. Table I shows that there was no significant difference in age and illness duration between the two groups (p = 0.087 and 0.087, respectively). In our study, BMI, educational level, and smoking show no significant relation to developing the combined illnesses, p = 0.081, 0.9352, and 0.1488 for parameters respectively also shown in table I.

The majority of diabetic patients with DM type 2 needed no insulin administration [13]. In the present study low percentage (~ 7%) of patients in both groups were insulin-dependent with no significant difference (p = 0.8957) as shown in table II. Physical health (represented as walking aids and tendency to fall) and required hospitalization were all shown in table two. No significant difference was found between the two groups regarding walking aid (p = 0.1846) and falls tendency (p =0.4143). However, patients with combined illness required hospitalization more than DM on its own (p =0.0301).

Steroids are selectively used to treat RA [14], however, they may lead to insulin resistance and hence develop DM [15]. In our result, we show that the more steroid a patient uses, the greater risk of developing DM. When it came to steroid use, there was a significant difference between the two groups (p =0.0023), with 24.59 % in DM patients and 42.27 % in mixed disease patients.

Combined chronic diseases, absent and present up to four diseases, were show no statistical difference between two groups (p =0.7016), particularly no significant difference for arthritis (p =0.968), cardiovascular diseases (p = 0.6076), chronic kidney disease (p =0.238), and diabetic eye disease (p =0.3029). Peripheral neuropathy is one of the common diseases associated with diabetes and at the same time, it can be associated with rheumatoid arthritis [16]. The combined illness group was shown to be more affected (43.30%) compared to DM on its own (31.69%) with a p value close to significant (p =0.0538).

Inflammatory diseases such as RA are known for their effect on glucose metabolism and may lead to increase sugar levels [17]. A combination of RA and DM significantly increases blood sugar ($p < 0.001$) compared to DM on its own, however fasting blood sugar does not change ($p = 0.089$) as shown in figure 1.

Glycated haemoglobin (Hb a1c) level is an indicator of diabetes where the level of ≥ 6.5% is considered a diabetic level [18]. Combined DM with RA significantly increase the level of Hb a1c ($p = 0.005$) as shown in figure 2.

Erythrocyte sedimentation rate (ESR) increases with inflammation; however, it has also been found to increase with diabetes [19]. Therefore, our result of the ESR test for the two illnesses together was significantly more than ($p < 0.001$) that of diabetes alone (Fig. 3).

DISCUSSION

The majority of studies that met the criteria made no difference between different kinds of diabetes. As a result, we couldn't rule out the potential that the statistics supplied represented the whole number of diabetes kinds. T2DM, on the other hand, accounts for more than 90% of all diabetes globally [20], and the average age of both groups is ~54 years. It is appropriate to refer to our findings as primarily describing the relationship between RA and T2DM incidence.

Table II. Treatments and health conditions.

Variables	Total	DM		P value
		DM%	DM+RA%	
On insulin				
No	259	92.35	92.78	0.8957
Yes	21	7.65	7.22	
Walking aids				
No	223	81.97	75.26	0.1846
Yes	57	18.03	24.74	
Fall				
No	224	81.42	77.32	0.4143
Yes	56	18.58	22.68	
Hospitalization				
No	247	91.26	82.47	0.0301
Yes	33	8.74	17.53	
Steroid use for more than 3 months				
No	194	75.41	57.73	0.0023
Yes	86	24.59	42.27	
Arthritis				
No	214	76.50	76.29	0.968
Yes	66	23.50	23.71	
Chronic disease				
No chronic disease	77	30.05	22.68	0.7016
1	79	27.87	28.87	
2	71	24.59	26.80	
3	36	11.48	15.46	
4	17	6.01	6.19	
Cardiovascular diseases				
No	182	63.93%	67.01%	0.6076
Yes	98	36.07%	32.99%	
Peripheral neuropathy				
No	180	68.31%	56.70%	0.0538
Yes	100	31.69%	43.30%	
Chronic kidney disease				
No	226	78.69%	84.54%	0.238
Yes	54	21.31%	15.46%	
Diabetic eye disease				
No	255	92.35%	88.66%	0.3029
Yes	25	7.65%	11.34%	

Because both RA and DM are chronic illnesses that largely affect the elderly, a substantial positive correlation has been postulated. Probably, these people are genetically predisposed to autoimmune disorders, which typically appear in childhood [21].

Inflammation appears to be a major component in the formation of diabetes, according to mounting data. The β-cell has a high density of interleukin-1β (IL-1β) receptors [22] and is vulnerable to innate mediators' harmful effects [23]. IL-1β, which is highly expressed in RA [24], stimulates the production of cytokines and chemokines such as IL-6, IL-8, IL-33, and TNF-α. These mediators attract macrophages and other immune cells to the islet, causing β cell malfunction and death, relative and absolute insulin insufficiency, and finally diabetes mellitus (DM) [25]. Overproduction and overexpression of TNF-α and IL-6 are important mechanisms in the pathogenesis of RA [25]. In animal studies, TNF-α and IL-6 have a negative impact on

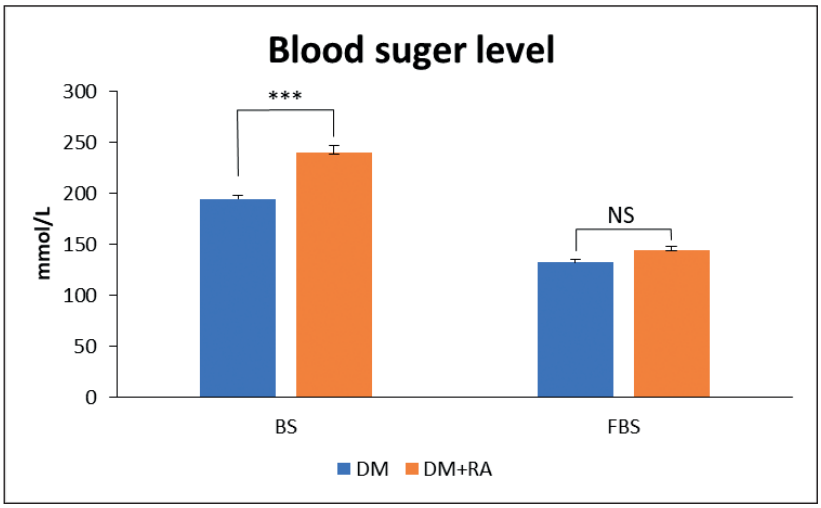

Fig. 1. Blood sugar level in both cohorts (DM and DM+RA).

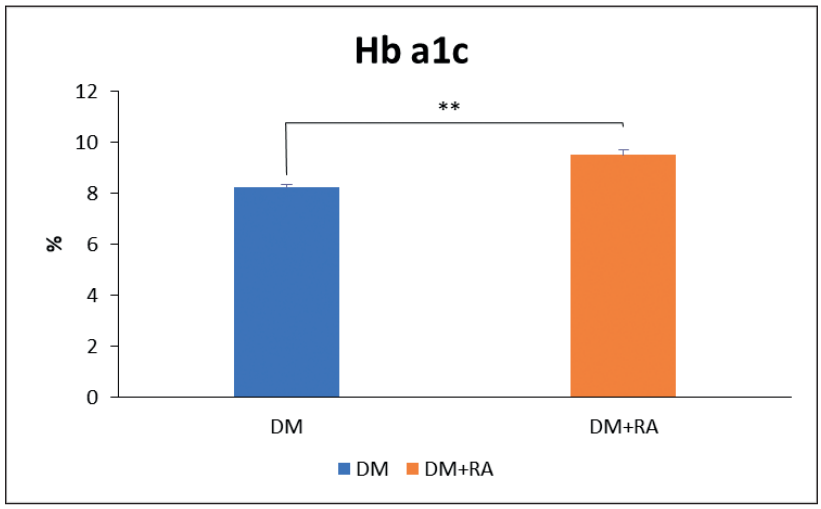

Fig. 2. Hb a1c level in both cohorts (DM and DM+RA).

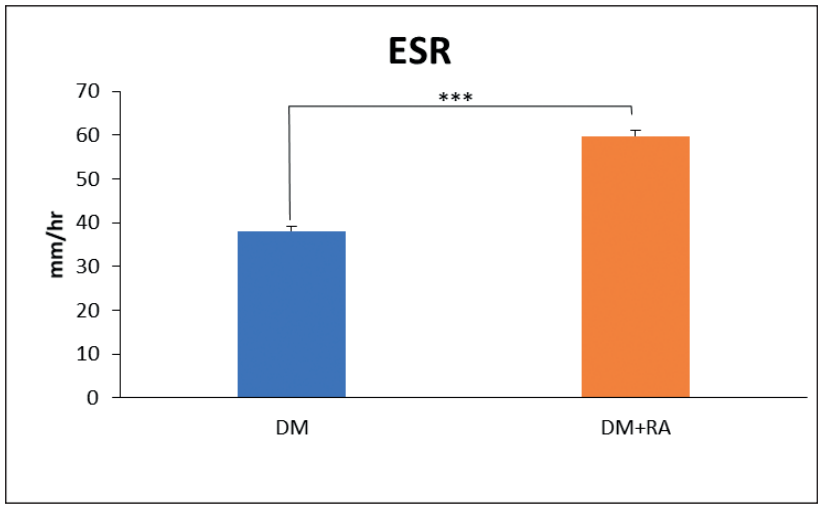

Fig. 3. ESR level in both cohorts (DM and DM+RA)

insulin sensitivity and are implicated in blocking insulin signalling, hence inducing insulin resistance [26], which is linked to DM. In addition, we looked at ESR levels and discovered that they were greater in the DM+RA group, indicating that inflammation is a risk factor for DM.

Hb a1c tests and BMI were used to screen for diabetes risk factors in both groups. Because of an increase in Hb a1c levels but no variation in BMI, people with RA are more likely to acquire diabetes. We believe that screening is necessary for RA patients to prevent and decrease diabetic morbidity.

CONCLUSIONS

Finally, RA is linked to an increased chance of developing diabetes. This data backs up the theory that inflammatory

pathways play a role in diabetes development. In persons with RA, we believe that more comprehensive screening and stricter control of DM risk factors should be addressed.

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ORIGINAL ARTICLE

ASSESSMENT OF COLON MICROBIOCENOSIS DISORDERS IN PATIENTS WITH CHRONIC HEPATITIS C

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ABSTRACT

The aim: To investigate the peculiarities of colon microbiocenosis disorders in patients with chronic hepatitis C.

Materials and methods: 142 patients with CHC were under observation, determination of the degree of liver fibrosis (FibroMax), bacteriological examination of stools and pancreatic elastase was performed.

Results: It was found that 59.2% of patients with CHC had gut dysbiosis (DB), of which 61.9% had increased body weight. Intestinal microbiocenosis disorders were manifested by constipation in 57.1% of patients, diarrhea in 31% of patients, and alternating constipation and diarrhea in 11.9% of patients. Bacteriologically, gut dysbiosis was characterized by suppression of the growth of normal microflora: Escherichia coli in 47.6%, bifidobacteria in 61.9%, lactobacilli in 53.6%, complete absence of bifidobacteria in 20.2% of cases. In patients with CHC combined with DB deep stages of liver fibrosis (F2-3 and F3-4) are registered 3.6 times more often compared to patients without intestinal dysbiosis (53.6% versus 24.1% and 11.9% versus 3.4%). The degree of gut DB increased in proportion to the stage of liver fibrosis ($p<0.05$). 32.1% of patients with CHC with dysbiosis were diagnosed with exocrine insufficiency of the pancreas.

Conclusions: Gut dysbiosis occurs more often in CHC patients with increased body weight and is characterized by constipation in 59.2% of patients. Intestinal microbiocenosis is characterized by suppression of the growth of normal microflora. In 32.1% of CHC patients with intestinal dysbiosis, according to the results of the pancreatic elastase-1 test, pancreatic exocrine insufficiency of various degrees was found.

KEY WORDS: chronic hepatitis C, colon microbiocenosis, liver fibrosis, pancreas

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INTRODUCTION

Identifying clinical signs typical for early intestinal dysbiosis in patients with CHC is a difficult task, because against the background of polymorbidity characteristic to this contingent of patients, various clinical symptoms are layered and masked, which does not allow clearly differentiating the clinical picture of one specific pathology [1,2].

For today the factors of progression of chronic hepatitis C (CHC), which have not been finally clarified, continue to be studied [3]. The activation and dominance of opportunistic microorganisms and their associations (staphylococci, Proteus, Escherichia, Klebsiella, Pseudomonas aeruginosa and fungi) worsen the functional state of the biliary tract and liver [4]. With a long course of intestinal dysbiosis, the risk of developing metabolic liver diseases, such as non-alcoholic fatty liver disease (NAFLD), cholestasis, hepatocellular dysfunction and dyskinetic disorders of the biliary tract increases [5-7]. The presence of NAFLD in patients with CHC contributes to the emergence and further progression of fibrosis from the initial stages to liver cirrhosis within a short time. On the one hand, the hepatitis C virus itself has a direct cytotoxic effect on the liver and, in a genotype-specific way, causes its fatty degeneration. On the other hand, insulin resistance, increased body weight, obesity, intestinal dysbiosis lead to the independent formation of NAFLD, which affects the development of the necrobiotic process in the liver tissue and leads to the progression of fibrosis [8-10].

There are several reasons for the development of microbiocenosis disorders in the large intestine. These are primarily immunodeficiency states that occur with severe infections, AIDS, tumors. The second common cause of dysbiosis is long-term treatment with antibiotics, which destroy not only pathogenic, but also beneficial microorganisms. The third cause of dysbiosis is the lack or absence of some digestive enzymes, especially in patients with impaired exocrine function of the pancreas. Normal human microbiota is a natural biosorbent of the gastrointestinal tract. According to modern ideas, the basis of the normal microbiota of the human colon is autochthonous obligate anaerobic bacteria (genera *Bifidobacterium, Lactobacillus, Propionibacterium*). Bacterial translocation from the intestine into the systemic circulation plays an important role in the progression of liver diseases, in particular CHC, but the literature data are contradictory [11-13].

Therefore, the study of the intestinal microbiome in patients with CHC and assessment of its relationship with the stages of liver fibrosis is relevant.

THE AIM

To investigate the peculiarities of colon microbiocenosis disorders in patients with chronic hepatitis C.

MATERIALS AND METHODS

142 patients with CHC were under observation, of whom 47.8% (65) were men, 54.2% (77) were women. The control group consisted of 20 healthy people. The diagnosis of HCV was made according to the International Classification of Diseases of the 10th revision and confirmed by the detection of total IgG class antibodies to HCV by enzyme immunoassay, as well as by the detection of RNA-HCV in the blood by polymerase chain reaction. General clinical, biochemical, serological, molecular genetic studies were conducted in certified laboratories. The functional state of the liver was assessed by the activity level of alanine and aspartic aminotransferases (ALT, AST), alkaline phosphatase (ALP), bilirubin, and gamma-glutamyl transpeptidase (GGT). The lipid spectrum of blood was determined: total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. All patients underwent USO of the abdominal organs and determination of the degree of steatosis and liver fibrosis using a non-invasive diagnostic method – FibroMax. Patients were evaluated for their trophic status according to generally accepted anthropometric indicators. Anthropometric criteria for obesity were considered to be the Quetelet index, or the body mass index (BMI), with the help of which 89 out of 142 (62.7%) people were found to have an increased body weight.

The state of microbiocinosis of the intestine was determined by microbiological examination of feces. To detect dysbiosis of the large intestine, a quantitative count of microorganisms that grew on agar, Saburo, Endo and 5% blood agar based on 1 g of feces was carried out, taking into account the dose of the inoculated material and the degree of its dilution. Identification of cultures was carried out on the basis of biochemical tests and the "Enterotest" system. At the time of material collection, all patients did not have acute infectious diseases, did not receive antibacterial, pre- or probiotic therapy. According to the unified working classification of dysbacteriosis (I.B. Kuvayeva, K.S. Ladodo, 1991), 4 degrees of intestinal dysbiotic disorders were distinguished:

I degree was characterized by a decrease in bifido- and lactobacteria 10^{5}-10^{6} CFU (with a norm of 10^{7}) and other microflora indicators within the norm.

II degree – reduction of bifidobacteria (10^{4}), lactobacilli (10^{4}), Escherichia coli with normal enzymatic activity (10^{5}) and growth of conditionally pathogenic microflora (proteus 10^{6}) of CFU.

III degree – a decrease in the number of bifido- and lactobacteria several times below the norm (10^{3} and 10^{3}) CFU and their complete absence, the appearance of proteus + hemolytic enterococci, proteus 10^{7}, replacement of full-fledged escherichia with bacteria of the genera Klebsiella, Enterobacter, Citrobacter, opportunistic flora acquires aggressive properties.

IV degree – is characterized by the complete absence of bifido- and lactobacteria, a significant decrease in the number of Escherichia coli and its qualitative changes, the subsequent increase and dominance of opportunistic and pathogenic microorganisms, fungi of the genera Candida.

Simultaneously with the bacteriological examination of feces, all patients underwent fecal coproscopy and determination of pancreatic elastase-1 and fecal calprotectin by ELISA method.

According to the obtained results, all patients were divided into two groups: 1st group (n=84) patients with CHC+DB – and 2nd group (n= 58) patients with CHC without intestinal DB; group 1, in its turn, was divided into 1a (n=56) – patients with CHC + DB and 1b (n = 28) – patients with CHC + DB + chronic pancreatitis (CP).

The analysis and processing of the results of the examination of patients was carried out using the Statistics for Windows v.7.0 computer program (StatSoft Inc, USA) using parametric and non-parametric assessment methods. The difference was considered to be significant at $p<0.05$.

RESULTS

It was established that 59.2% (84/142) of CHC patients had intestinal DB, of which 52 people had increased body weight, which was 61.9%.

Clinical manifestations of intestinal microbiocenosis disorders in 57.1% of patients consisted in the predominance of constipation (48/84), in 31% of people (26/84) ($p<0.001$) – the appearance of a typical diarrheal syndrome and in 11.9% of people (10/84) – alternating constipation and diarrhea. The predominance of constipation was contributed not only by intestinal DB, but also by other related factors, such as lifestyle. Thus, 35.4% of patients were engaged in mental work and led a sedentary lifestyle, 6.1% performed work that was associated with business trips in uncomfortable conditions, irregular nutrition was noted by 38.1% (32/84) of patients, insufficient use of vegetable fiber and liquid was noted by 16.7% (14/84) of patients, and only 4.8% (4/84) indicated self-administration of antibiotics 3 months before inclusion in the study. Intestinal dysfunction was observed in 53.6% (45/84) of patients in the form of a decrease in the number of defecation, changes in the consistency of fecal masses, the need for additional straining and the feeling of incomplete bowel emptying. These complaints were not found in patients with CHC without DB.

Also, 82.1% (69/84) of patients complained of reduced work capacity, headache, mood depression, and sleep disturbances, which confirmed the presence of asthenovegetative syndrome. In patients with CHC without intestinal DB asthenovegetative syndrome was noted in a smaller number of patients (32/58), namely in 55.2%.

The study of clinical manifestations of DB in patients with CHC revealed their connection with the degree of DB. It was established that 15 patients had DB of the I degree, DB of the II degree – 39, 30 patients of the III degree, and DB of the IV degree – was not detected in any patient.

Table I. Severity of liver fibrosis in the examined patients

Stage of fibrosis	Group, (abs./%)					
	1 (n=84) CHC+ DB			2 (n=58) CHC		
	1 genotype (n=75)	not 1 genotype (n=9)	total (n= 84)	1 genotype (n=52)	not 1 genotype (n=6)	total (n= 58)
F0-1	7/9,3	1/11,1	8/9,5	19 / 36,5	3 /50,0	22/37,9
F1-2	16/21,3	5/55,5*	21/25,0	18 /34,6	2 /33,3	20/34,5
F2-3	42/56*	3/33,3*	45/53,6*	13 /25,0	1 /16,7	14/24,1
F3-4	10/13,3*	0	10/11,9*	2 /3,8	0	2/3,4

Note. Significance of the difference:* – in comparison with the indicator of group 2 (the indicator is calculated according to the Mann-Whitney test, $p<0.05$).

Table II. Degree of dysbiosis and stages of liver fibrosis

Stage of fibrosis	Degree of dysbiosis (n=84) abs/%			
	1 (n=15)	2 (n=39)	3 (n=30)	4 ((n=0)
F0-1 (n=8)	5/62,5	3/37,5	0	0
F1-2 (n=21)	7/33,3	13/61,9*	1/4,8	0
F2-3 (n=45)	2/4,4	20/44,4	23/51,1*	0
F3-4 (n=10)	1/10,0	3/30	6/60*	0

Note. Significance of the difference:* – in comparison between degrees of dysbiosis ($p<0.05$)

In 9 patients with CHG with DB of the III degree periodical discomfort with localization in the lower abdomen was significantly more often registered (30.0%), compared to patients with I and II degrees of DB (13.3% and 20.5%), respectively. The presence of this localization of discomfort in patients with CHC is obviously explained by an increase in dysbiotic processes and a violation of intestinal function. This was confirmed by the presence of a reliable connection of discomfort in the lower abdomen with dyspeptic manifestations, such as: nausea ($p=0.007$), flatulence ($p=0.02$), decreased appetite ($p=0.003$).

The next most frequent complaint was flatulence, which was observed in 38.1% (32/84) of patients with DB. The frequency of flatulence increased against the background of the progression of DB and was one of the persistent dyspeptic complaints that are difficult to correct with medication in patients with CHC. Flatulence was constantly present in 100% of patients with the III degree of DB, in persons with the II degree it bothered much less often (69.4%), and was not registered at all in the I degree of DB.

Analysis of the results of microbiological research in patients with CHC showed that the intestinal microbiocenosis disturbance is characterized by inhibition of the growth of normal microflora: Escherichia coli in 47.6% (40/84 patients), bifidobacteria 61.9% (52/84), lactobacilli 53.6 % (45/84); complete absence of growth of bifidobacteria was found in 20.2% (17/84) of cases. In 22.6% (19/84) of patients, an increase in Escherichia coli with reduced enzymatic properties was noted. In general, quantitative and qualitative changes in Escherichia coli were found in 69.0% (58/84) of the examined persons. Along with deviations of the normal intestinal microflora, 54.8% (46/84) of 54.8% (46/84) of patients with CHC had opportunistic microflora, represented mainly by gram-negative bacteria. It was hemolytic Escherichia coli 43.4% (20/46), Klebsiella 30.4% (14/46), Enterobacter 15.2% (7/46). In addition, Staphylococcus aureus was isolated in 14.3% (12/84) of people and Proteus in significant amounts in 33.3% (28/84) of patients.

As the degree of CHC activity increased, there were statistically significant changes in the normal intestinal microflora, which mainly related to the number of Escherichia coli, bifidobacteria, and lactobacilli.

It should be noted that the expressiveness of the degree of liver fibrosis also depended on the presence of intestinal DB, and not only on the HCV genotype. It was established that in patients with CHC combined with intestinal DB, deep stages of liver fibrosis (F2-3 and F3-4) are registered 3.6 times more often compared to patients without DB (53.6% vs. 24.1% and 11. 9% against 3.4% $p<0.05$) (Table I).

The degree of intestinal microbiocenosis disorders increased in proportion to the stage of fibrotic changes in the liver ($p<0.05$) (Table II).

Simultaneously with the bacteriological examination of feces, all patients underwent fecal coproscopy, where the appearance of a small amount of neutral fat, altered muscle fibers, and extracellular starch in the stool of these patients made it possible to suspect a violation of the exocrine function of the pancreas and the formation of chronic pancreatitis (CP). Next, the exocrine function of the PZ was evaluated based on the results of pancreatic elastase-1 in feces, which gave the reason to distinguish a group of patients with CHC combined with CP. The obtained data showed that 32.1% (27/84) of patients with CHC under the

condition of DB have lower than normal levels of the fecal elastase test and correspond to: exocrine insufficiency of mild degree in 25.9% (7 out of 27) of patients, moderate in 55.5% (15) and severe – in 18.5% (5) people.

DISCUSSION

We have established various kinds of violations of the normal flora of the colon cavity in 59.2% of patients with CHC. We found similar studies in the literature, however, without dividing patients with CHC with different body weights [14]. Analyzing the degree of dysbiosis, we found a difference in the violations of the normal flora of the colon in patients with CHC with constipation and patients with CHC with exocrine pancreatic insufficiency. In the majority of CHC patients with constipation, the microbiocenosis of the colon was characterized by the disappearance or decrease in the number of obligate representatives (Bifidobacterium spp. and Lactobacillus spp.), an increase in the population level of conditionally pathogenic microflora (Bacteroides spp, bacteria of the genera Clostridium) and corresponded to the 2nd degree of DB. These patients had increased body weight, which, in our opinion, played a significant role in the formation of colon dysbiosis. Data on the participation of microbiota in the development of obesity have been proven by many studies [15-17]. There are a number of reports that the composition of the gut microbiota differs between overweight and lean or normal weight individuals, suggesting that microbiota imbalances may contribute to weight change. Changes in the intestinal microbiotic landscape lead to increased intestinal permeability, endotoxemia, which is a link in the pathogenesis of chronic systemic inflammation in CHC, contribute to the development of obesity and other metabolic-associated diseases [18].

In CHC patients with insufficiency of the exocrine function of the pancreas, the quantitative changes of the microflora were more pronounced, and they showed a significant, statistically reliable deficiency of bifidobacteria and lactobacilli compared to patients with normal exocrine function (p=0.02), and they more often had the 3rd degree DB. Violations of the intestinal microbiocenosis in patients with CHC of this group, in our opinion, are due to the long persistence of the virus and its direct cytotoxic effect on the pancreatocyte with the formation of exocrine insufficiency of the pancreas. Researches of recent decades prove the extrahepatic replication of the hepatitis C virus, which allows HCV infection to be considered not as a liver disease, but as a systemic (generalized) infection, which explains one of the mechanisms of the development of insufficiency of the exocrine function of the pancreas [19-21]. The data on the damage to the pancreas caused by the hepatitis C virus are consistent with the data of other scientists who report that concomitant CHC worsens the course of CP, as evidenced by reliable negative changes in the indicators of the exocrine activity of the pancreas [22]. Enzymatic insufficiency of the digestive tract leads to disturbances in digestion processes and entry of incompletely digested food ingredients into the intestinal cavity, which is a nutrient medium for microbial flora [23], as a result of which the formation of intestinal dysbiosis in patients with CHC is possible.

CONCLUSIONS

1. Intestinal dysbiosis occurs more often in CHC patients with increased body weight and is characterized by constipation in 59.2% of patients.
2. In CHC patients, the intestinal microbiocenosis is characterized by inhibition of the growth of normal microflora: Escherichia coli in 47.6% of patients, bifidobacteria in 61.9%, lactobacilli in 53.6%, and the complete absence of bifidobacteria growth in 20.2% of people.
3. In 32.1% of CHC patients with intestinal dysbiosis, according to the results of the pancreatic elastase-1 test, pancreatic exocrine insufficiency of various degrees was found.

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ORIGINAL ARTICLE

PECULIARITIES OF THE HUMAN MANDIBLE MORPHOGENESIS

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ABSTRACT

The aim: To find out the sources of formation and the chronological sequence of the morphogenesis of the mandible at the early stages of human ontogenesis.

Materials and methods: 14 series of consecutive histological specimens of human embryos and prefetuses (4,0-66,0 mm of parietal-coccygeal length) aged from 4 to 11 weeks of intrauterine development with the use of a complex of modern morphological methods of investigation (anthropometry, morphometry, microscopy, and 3D computer reconstruction) were studied.

Results: On the basis of a complex of morphological research methods, data were obtained that made it possible to establish the general patterns of development of the human mandible: separation of the pharyngeal apparatus (4th week), convergence and fusion of the jaw processes (5-8th weeks), formation of tooth buds (7-8th weeks), which allows considering the specified periods as critical in the formation of possible anomalies in the facial part of the skull. At the same time, a tendency of heterochrony of morphological transformations in the mandible and maxilla was revealed.

Conclusions: 1. At the beginning of the 4th week of intrauterine development, 3 pairs of pharyngeal arches are formed. Detachment of the mandibular and maxillary processes of the mandibular pharyngeal arch is planned. 2. During the 7th week of intrauterine development, the maximum convergence of the maxillary processes with the lateral and medial nasals occurs, and in embryos of 20.0 mm PCL grow with the frontal process, forming the maxilla and upper lip. During the 8th week of intrauterine development, the bone base of the jaws is modeled as a result of the increase in the size of osteogenic islands and their fusion, alveolar processes are formed. 3. During the 9-10th weeks of intrauterine development, the primary palate is formed as a result of the fusion of the palatine processes. 4. At the 11th week of intrauterine development, the bone base models both jaws. Due to the processes of histogenesis of the soft tissues of the maxillofacial apparatus, the face acquires anthropomorphic definitive human features.

KEY WORDS: morphogenesis, mandible, human ontogenesis

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INTRODUCTION

Research of sources and age periodization of morphogenesis of the facial bones of the skull at the early stages of prenatal human ontogenesis is an actual issue of modern morphology, age-related and variation anatomy, surgical stomatology and reconstructive surgery. Congenital malformations occupy one of the first places in the structure of causes of child mortality and disability [1-3]. Among them – cleft lip and/or palate – the most common craniofacial congenital defect in the human body, occurring once in 500-2500 live births worldwide. From 420 to 450 children with cleft lip are born annually in Ukraine. More than 300 Mendelian syndromes in humans include cleft lip as part of the phenotype [4, 5].

The mandible is formed by the fusion of facial processes with the participation of many genetic and environmental factors [5, 6].

In modern scientific literature there is uncertainty regarding the temporal sequence of morphological processes and mechanisms that lead to the formation of the normal structure of the mandible, topographic relationships of the structures of the middle part of the human face in ontogenesis, and the formation of congenital defects of the face.

A clear understanding of the development of the structure and formation of the topography of the facial part of the head will allow to create a theoretical basis for improving the methods of interpretation of diagnostic medical imaging and surgical correction of congenital defects of the maxillofacial region [6].

THE AIM

The aim of the study is to find out the sources of formation and the chronological sequence of the morphogenesis of the mandible at the early stages of human ontogenesis.

MATERIALS AND METHODS

14 series of consecutive histological specimens of human embryos and prefetuses (4,0-66,0 mm of parietal-coccygeal length (PCL)) aged from 4 to 11 weeks of intrauterine development (IUD) with the use of a complex of modern morphological methods of investigation (anthropometry, morphometry, microscopy, and 3D computer reconstruction) were studied. Dynamics of morphological changes of structural components of the pharyngeal arches were stud-

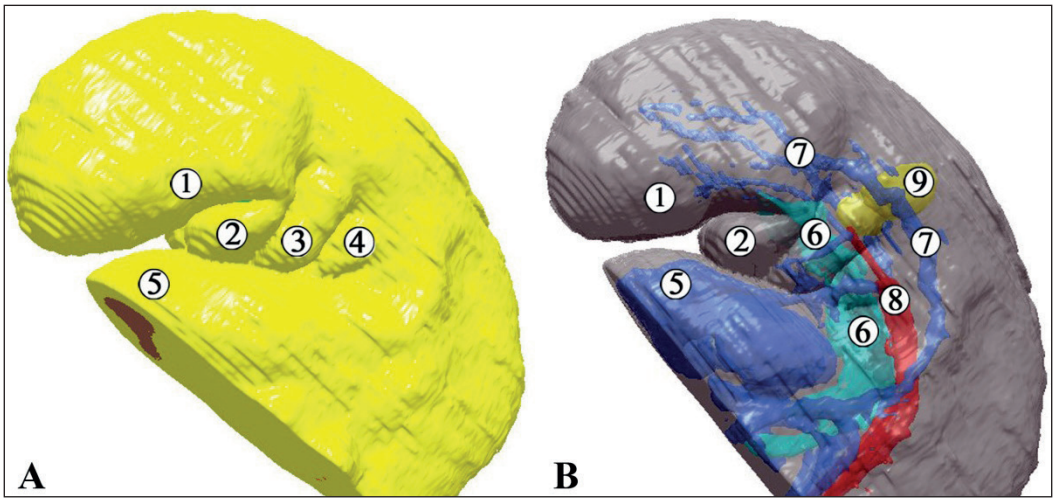

Fig. 1. Three-dimensional computer reconstruction model of the upper half of a human embryo 4.5 mm PCL (4th week of IUD). Left side projection. A – external covers, B – internal structures. x12: 1 – frontal process; 2 – maxillary process of the I (mandibular) branchial arch; 3 – mandibular process of the I branchial arch; 4 – II (hyoid) branchial arch; 5 – cardiac hump; 6 – internal contours of the foregut; 7 – cardinal veins; 8 – left dorsal aorta.

ied on series of archival microspecimens from collection of Department of Histology, Cytology and Embryology of Bukovinian State Medical University.

The study was carried out in compliance with the basic bioethical provisions of the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the Helsinki Declaration of the World Medical Association on ethical Principles of Scientific Medical Research with the participation of Human beings (1964-2008), as well as the order of the Ministry of Health of Ukraine No. 690 of 23.09.2009.

RESULTS

During the study of a series of histological sections of human embryos 3.5-4.5 mm PCL (the end of the 3rd – the beginning of the 4th week of IUD), the presence of 3 pairs of branchial arches was established. Together with the frontal process, the first pair limits on both sides the entrance to the primary oral cavity – the stomodeum, which is lined with ectodermal simple cuboidal epithelium. Caudally, it adjoins the cranial end of the rudiment of the foregut. Between the stomodem and the foregut is the pharyngeal membrane, which is also lined with a single-layer cuboidal epithelium of endodermal origin from the side of the intestinal tube. Characterizing the morphology of the beginnings of the branchial arches, it should be noted that the largest of them are the mandibular, and the rudiment of the III arch are still weakly expressed. The branchial arches are separated by paired branchial grooves, of which the first are the deepest. In the thickness of the mesenchyme of the mandibular and hyoid branchial arches, the rudiments of branchial arteries are visualized in the form of hollow formations of various sizes.

In a 4-month-old human embryo (4.5 mm PCL), separation of the maxillary and mandibular processes was detected in the paired rudiments of the mandibular branchial arch (Fig. 1).

In human embryos of the 5th week of IUD, the rudiments of all 4 branchial arches from the side of the skin surface are covered with a 1-2-layer cuboidal epithelium, under which mesenchyme is located. In some places, signs of the basement membrane are determined. The primary oral cavity is lined with a sinple single-row epithelium. In embryos of this age group, the depth of branchial grooves and pockets reaches a maximum, as a result of which their ectodermal and endodermal epithelial linings come into direct contact with each other, and the mesenchymal layer between them disappears. At the end of the 5th week of IUD (embryos of 7.5 mm PCL), bilaterally located mandibular primordia converge as much as possible. The rudiments of the maxillary processes, which are directed cranially in relation to the mandibular processes, become clearer. On cross-sections of the head, the paired nasal medial and lateral processes that limit the nasal fossae, between which the frontal ridge is located rostrally, are clearly visible.

Analysis of serial histological sections of 5-week-old embryos showed that mandibular and maxillary processes, formed from the first branchial arch, differentiate asynchronously. We noted that the rate of morphogenesis in the maxillary processes is less pronounced than in the mandibular processes. In particular, this is manifested by the fact that at this stage of the IUD in the maxillary processes, we did not find clear areas of mesenchymal compaction, which would indicate its divergent differentiation.

By the end of the 5th week of IUD, both already formed primary hemocapillaries and their predecessors in the form of peculiar slit-like formations are determined in both mandibular and maxillary rudiments (Fig. 2). In the indicated vascular formations, formed elements of blood are still missing. Along with this, blood islands in the form of clusters of megaloblasts are also found, around which cells transforming into endotheliocytes are located.

In human embryos of the 6th week of IUD, the maxillofacial apparatus only vaguely resembles anthropomorphic facial features, since during this period the nasal processes that converge with each other and with the maxillary processes do not yet fully form the maxilla as such. By the end of the 6th week of IUD (embryos 12.0-13.0 mm PCL), the ventral processes of the mandibular arch are as close as possible to each other, forming the mandible.

Therefore, in the 6th week of IUD in the rudiments of the

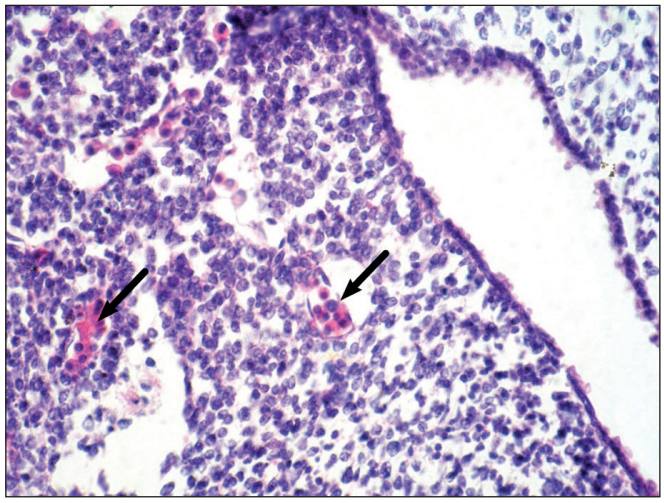

Fig. 2. Section of the maxillary process of I branchial arch of the human embryo 7.0 mm PCL (5th week of IUD). Staining with hematoxylin and eosin. Photomicrograph. x100. Blood islands in the mesenchyme are indicated by arrows.

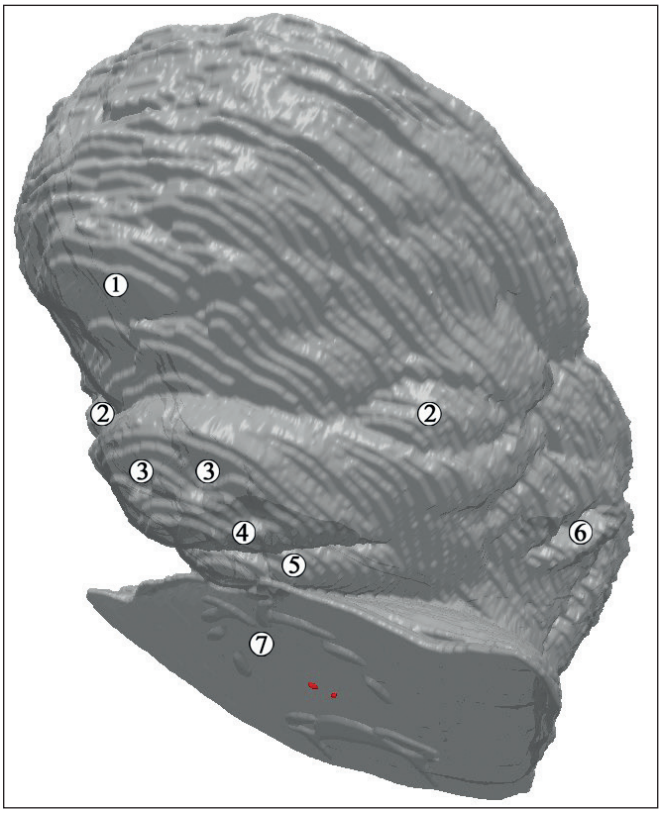

Fig. 3. 3D reconstruction model of the upper part of the human embryo 15.0 mm PCL. Left anterio-lateral projection. x15: 1 – frontal process; 2 – eye placodes; 3 – rudiment of external nose; 4 – rudiment of the maxilla; 5 – rudiment of the mandible; 6 – ear placode; 7 – cardiac hump.

maxillofacial part of the human head, the rates of cyto- and histogenetic rearrangements are more accelerated compared to the previous stages. This is manifested by increased proliferation of mesenchymocytes in peri-epithelial zones and their divergent differentiation towards both fibroblastic and osteogenic differentiation, which, we believe, is directly related to accelerated vasculogenesis in this area. At the same time, signs of asynchrony of morphogenetic transformations in mandibular and maxillary rudiments persist even in the 6th week of IUD.

On 3D reconstructions of serial sections of 7-week-old embryos, external signs of the formation of the visceral part of the head are more clearly defined, as a result of which human facial features are acquired (Fig. 3). Histological specimens of embryos 16.0-17.0 mm PCL in the epithelium lining the maxilla and mandible from the side of the primary oral cavity reveal small thickenings immersed in the underlying mesenchyme, which are the rudiments of the vestibular plates (Fig. 4).

At the end of the 7th week of IUD (embryos 19.0-20.0 mm PCL) qualitative morphological transformations occur in the maxilla – the maxillary, lateral and medial nasal processes come into contact with each other, as a result of which we can speak of signs of the completion of the formation of the maxilla. But, unlike the mandible, osteogenic islands are less pronounced in the maxillary rudiments, and cartilaginous rudiments are absent.

The rudiments of the maxillofacial apparatus are covered with epithelium, the structure of which is different on the outside and on the side of the oral cavity. Thus, the skin surface of the lips and cheeks is covered with a 1-2-layered epithelium, and when moving to the future border of the lips, the number of cell layers increases. The mucous membrane of the oral cavity is also lined with a stratified epithelium. The epithelium is separated from the mesenchyme by a clearly contoured basement membrane.

By the end of the 7th week of embryogenesis in the converging mandible and maxillary processes, the formation of dental plates is noted, which on sections have the appearance of continuous epithelial cords consisting of densely packed cells immersed in the gingiva from their distal ends. A new feature that characterizes progressive transformations in the human maxillofacial apparatus during the 7th week of IUD is the beginning of the formation of masticatory muscles and muscles of face expression, which are represented by myoblasts. Morphological transformations in the constituent parts of the rudiments of the maxillofacial apparatus are accompanied by an increased course of vasculogenesis.

So, in the 7th week of IUD, there is an intense pace of differentiation of the structures of the maxillofacial apparatus. Frontal and lateral nasal processes forming the maxilla converge. Osteogenesis occurs more actively in the mandible. In the maxilla, mesenchyme densification cells begin to turn into osteogenic islands. The formation of the oral vestibule and dental plates are noted, and by the end of the 7th week of IUD, the rudiments of tooth buds are noted. Separation of masticatory muscles and muscles of facial expression are determined. At the same time, the rate of histogenetic transformations in the maxillary primordia continues to lag behind in comparison with the mandibular primordia.

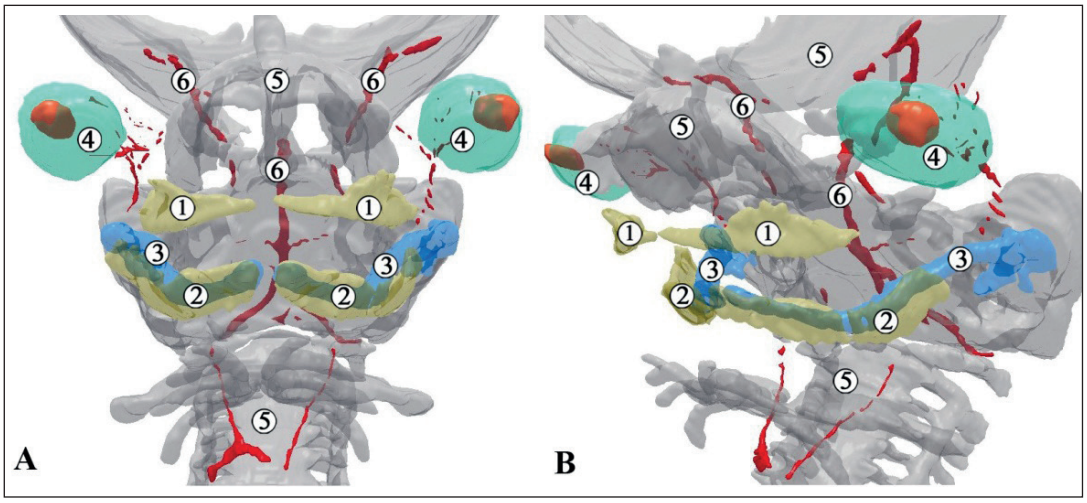

Fig. 4. 3D reconstruction model of the upper part of the human embryo 17.0 mm PCL. A – front projection, B – left anterolateral projection. x12: 1 – maxillary vestibular plates; 2 – mandibular vestibular plates; 3 – Meckel's cartilage; 4 – eyeballs; 5 – cartilaginous rudiments of bones; 6 – blood vessels.

At the end of the embryonic period (the 8th week of VUR), high rates of embryogenesis are observed, accompanied by pronounced step-by-step dynamic qualitative and quantitative transformations in the structures of various organ sources, including those that form the maxillofacial apparatus.

The analysis of the 3D-reconstructional models made from a series of micro-specimens showed that during the 8th week of IUD at the organ level, due to the convergence of the processes forming the maxilla, the formation of the upper lip is completed, and in the mandible, the convergence of the ventral ends of Meckel's cartilage continues. The resulting palatal plates begin to acquire a horizontal position, being located bilaterally from the tongue. They have osteogenic structures. Medially between the converging palatal plates is the nasal septum, in which foci of osteogenesis are also found. At the tissue level, the shaping processes of the oral vestibule become more pronounced. Vestibular plates, formed by stratified epithelium, in the form of parallel strands separate the lips and cheeks from the gingivae. Shallow grooves are found in them, which is evidence of separation of the gingival surface of the lips and, accordingly, the labial surface of the gingivae, which are lined with stratified epithelium.

In both jaws, 3D reconstructions of serial histological sections clearly show dental plates that sink into the gingival mesenchyme in the form of cords, on the outer surface of which there are forming tooth buds (Fig. 5).

In the maxilla, the centers of osteogenesis are visualized in the form of separate osteogenic islands of different sizes, which are stained oxyphilically, along the periphery of which osteoblasts are localized, and in the middle of such islands, single osteocytes, separated from each other by the intercellular matrix, can be seen. Some of the osteogenic islands are at the initial stages of osteogenesis in the form of osteoid masses surrounded by osteogenic cells. There are still no cells in the middle of such formations.

It should be emphasized that oxyphilia in the foci of osteogenesis of the maxillary rudiments is less pronounced than in the osteogenic islands of the mandible. Thus, the morphological features and tinctorial properties of the intercellular matrix of osteogenic rudiments testify to the heterochrony of bone formation in the mandible and maxilla.

The structural components of the rudiments of the lips, cheeks, and gingivae, which are located around the dense rudiments of both jaws, are represented by mesenchymocytes that differentiate in different directions, therefore, in different zones of the mesenchyme, their morphology and distribution density are not the same. Some of the mesenchymocytes are transformed into cellular elements of loose fibrous connective tissue, others continue to participate in vasculogenesis. At the same time, together with exchange channels, primordial hemocapillaries and blood islands, vessels of a more complex structure are already revealed.

At the end of the 8th week of IUD, the rudiments of the buccal muscles, as well as the omohyoid muscle and the muscles of the tongue are more clearly visible, the separation of which occurs earlier than anything else.

Therefore, by the end of the embryonic period of human development, morphogenetic processes in the maxillofacial apparatus are characterized by further transformations, as a result of which a dense base of the jaws is formed, and the soft tissues surrounding them lose the features characteristic of mesenchyme, transforming into structures of loose fibrous connective tissue and muscle tissue. Corresponding progressive changes are also observed in the ectodermal derivatives of the maxillofacial apparatus, which participate in the formation of the oral cavity and in the formation of tooth buds.

During the 9th week of IUD, morphogenetic transformations in the sources of the maxillofacial apparatus of human fetuses continue to be characterized by qualitative and quantitative changes that are manifested both at the organ and tissue levels. Thus, at the organ level, there is a consolidation of the lateral palatine processes that form the hard palate, which in the ventro-dorsal direction merge over a longer distance with each other, as a result of which the oral cavity is separated from the nasal cavity. The nasal septum comes into contact with the lateral palatal plates that depart from the maxillary processes. In the places of

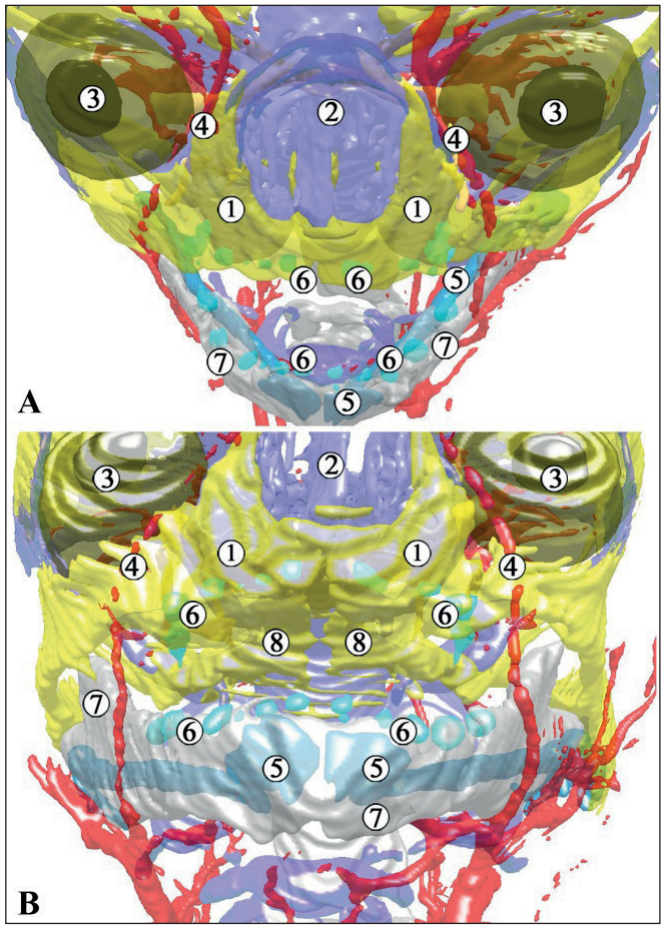

Fig. 5. 3D reconstruction model of the upper part of the human embryo 22.0 mm PCL. A – front projection, B – anterior-inferior projection. x10: 1 – rudiment of the maxilla; 2 – cartilaginous nasal capsule; 3 – eyeballs; 4 – blood vessels (facial artery); 5 – Meckel's cartilage; 6 – tooth buds; 7 – mandible.

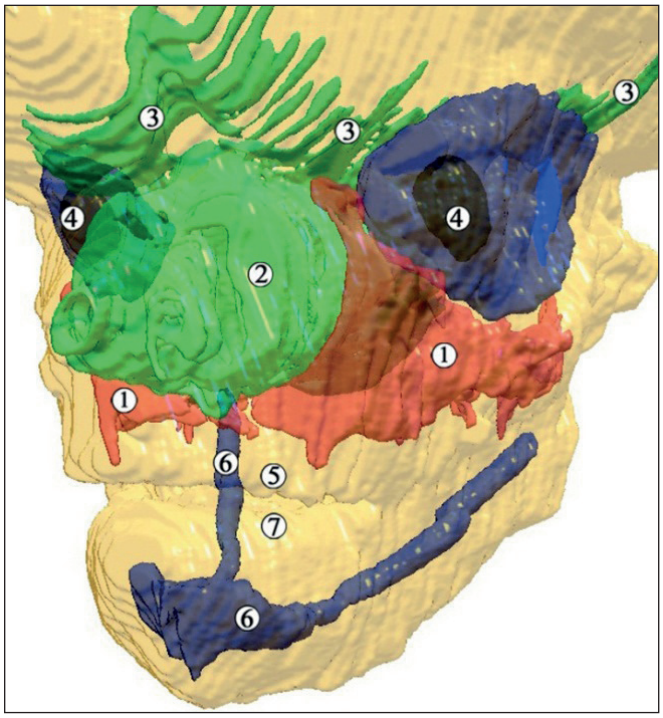

Fig. 6. 3D reconstruction model of the upper part of the human embryo 48.0 mm PCL. Left antero-lateral projection. x10: 1 – maxilla; 2 – cartilaginous tissue of the nasal capsule; 3 – rudiments of the bones of the skull base; 4 – eyeballs; 5 – soft tissues of the upper lip; 6 – soft tissues of the lower lip; 6 – Meckel's cartilage.

contact of the palatal plates with each other and with the nasal septum, clear boundaries are defined. The basis of the septum is hyaline cartilage, which slightly expands downwards. Osteogenic formations surrounded by compacted young connective tissue are located around it in a narrow strip. Osteogenesis is actively taking place in both jaws, as a result of which their bone base is formed. In the maxilla, foci of osteogenesis noticeably increase compared to the previous stage of development and consolidate. In both jaws, alveolar processes are formed in the form of bone plates that connect at the base.

Soft tissue structures that form around the dence base of the jaws are involved in the formation of gingivae, lips and cheeks. The outer lips and cheeks are covered with a stratified epithelium of ectodermal origin, the number of cell layers in which reaches 3-4. The epithelial lining of the lateral palatine processes from the side of the oral cavity is represented by a single layer of cuboidal cells with spherical nuclei, and during its transition to the inner surface of the gums, it becomes two-layered.

Therefore, by the end of the 9th week of the human IUD, the formation of a secondary oral cavity occurs, which is accompanied by further complication of intercellular and intertissue relations in heterogeneous rudiments of the maxillofacial apparatus.

In the 10th week of IUD, the rate of differentiation of hard and soft tissues of the human maxillofacial apparatus continues to increase. As our studies have shown, in fetuses in the middle of the 9th week of IUD (36.0 mm PCL), the separation of the primary oral cavity, which began at the end of the 2nd month of gestational age, into the definitive oral cavity and nasal cavity due to the convergence and fusion of the palatine processes, practically ends, and only the edges of both halves of the soft palate in the very final section are still at some distance from each other.

The nasal septum also grows along the middle line for a longer period with palatal processes, where in places there are islands of compactly located epitheliocytes undergoing apoptotic changes, the signs of which are more intense staining of their cytoplasm, compaction of the matrix and shrinkage of the nuclei. In the distal part, the surface of the nasal septum in contact with the palatine processes is still completely covered by a stratified squamous epithelium.

The maxilla is modeled by islands of bone tissue that merge with each other (Fig. 6), and the hard base of the mandible, together with bone tissue, continues to form Meckel's cartilage. The bone plates of both jaws have a typical structure characteristic of bone tissue. In places along their periphery, signs of periosteum formation are revealed, in which the presence of outer and inner layers can be ascertained. Fuchsinophilic stained collagen fibers

are found in the outer layer, and osteoblasts are localized in the inner layer.

The matrix of bone tissue contrasts heterogeneously. Its peripheral zone exhibits oxyphilic properties, and the central zone is stained with basic dyes. Lacunae with osteocytes with cytoplasmic processes are defined in it. In the mandible, the foci of ossification in the lateral zones are more developed than in the medial direction, where they form the palatine processes and the hard palate.

Therefore, during the 10th week of the human IUD, the formation of connective tissue structures continues in the soft tissues of the maxillofacial apparatus, and facial and masticatory muscles differentiate.

During the 11th-12th weeks of IUD, a complete separation of the oral and nasal cavities occurs due to the completion of the formation of the soft palate, the oral cavity is formed, as a result of which the lips and cheeks are separated from the gingivae by a deep furrow, the bottom of which is lined with several layers of epithelial cells. The maxilla is represented by bone trabeculae that unite with each other.

DISCUSSION

In our study, we used the method of making three-dimensional computer reconstructions of a series of consecutive histological sections, which made it possible to clearly determine the syntopy of the component rudiments of the maxillofacial apparatus, as well as to trace the features of histo- and organogenesis in the dynamics of prenatal human development.

In 4-week-old embryos, the stomodeal depression is clearly visualized, and at the 5th week of IUD, the structural components involved in the formation of the maxillofacial apparatus are well defined [7-9].

Thus, it is stated that on the 33-36th day, when the parieto-coccygeal length of the embryos reaches 7.0-9.0 mm, the rudiments of both jaws are determined [5]. However, according to other data, the presence of mandibular and maxillary processes is visualized earlier, on the 25-26th day, when embryos have from 14 [10] to 20 [11] pairs of somites, and even earlier – in 21-day-old embryos [12].

Our research established that the division of the distal parts of the mandibular arch into paired dorsal (maxillary) and ventral (mandibular) processes is visualized in the embryo of 4.5 mm PCL. At the same time, the formation of the structures of the processes initially occurs asynchronously. This is manifested in the difference in their sizes and, in our opinion, is due to the fact that in the mandibular rudiments the rates of cell proliferative processes and their differentiation are more accelerated than in the maxillary ones, therefore the latter lag behind in their growth and in the further stages of embryogenesis, which is manifested by the delay of their convergence between themselves in comparison with the mandibular processes.

According to our data, during the 5th week of embryogenesis, the mandibular processes of 7.0 mm PCL embryos converge as much as possible, while the maxillary processes are still at a sufficient distance from each other during this period. Their convergence with the nasal processes occurs in embryos of 19.0 mm PCL and only by the end of the 8th week (embryos of 26.0 mm PCL) it is possible to talk about the completion of the formation of the mandible.

As the facial part of the head forms in the sources of the maxillofacial apparatus, progressive morphogenetic transformations take place, when initially seemingly homogeneous, indifferent structures of the mesenchyme under the influence of various inducers and conditions [13] undergo divergent differentiation, as a result of which it is transformed into various types of connective tissue [14]. The transformation of mesenchyme into connective tissue is based on phylo- and ontogenetic determination, i.e. programming of the path of cellular differentiation, the characteristic feature of which is its wide range [15]. At the same time, "the main general feature of cell differentiation of mesenchyme derivatives, unlike cells of other tissue types, is the pronounced ability to form intercellular substance" [16].

In the maxilla, foci of direct (membranous) osteogenesis appear at the end of the 6th week of IUD, that is, a week later than in the mandible, after the fusion of the maxillary processes with the nasal and middle frontal processes. As noted by researchers [17-19], foci of membranous ossification in both jaws are clearly defined in embryos 8-week-old embryos (23.5 mm PCL), totally stained with alizarin and illuminated in xylene. At the same time, there are several centers of ossification in the maxilla, which develop from heterogeneous sources. In particular, its incisal part is formed from the material of the medial nasal processes, and the branches originate from the maxillary ridges of the mandibular pharyngeal arch. In the future, the bone tissue of these branches of the maxilla is the first to undergo calcification, while in its incisor part this process is carried out somewhat later.

According to literature data [18, 19], human embryos of 12.5-13.0 mm PCL already have a primary palate. It is known to be isolated as a result of the fusion of the distal ends of the palatine processes, observed, according to some data [20, 21], somewhat later, on the 7th week, in embryos 15,0-18,0 mm PCL, due to which the central part of the upper lip is also formed [22]. According to other information [23], this process occurs in the 8th week of embryogenesis. In the fetal period, which begins at the 9th week of IUD, the proximal parts of the palatine processes continue to converge, the fusion of which is completed for a longer period at the end of the 9th week of IUD (33.0 mm PCL), as a result of which the secondary palate is formed. These data are confirmed in our research. Other sources also state that this process only begins in the 7-8th week, and ends only in the 10th week [21, 24]. Attention is focused on the fact that precisely in such periods, when certain embryonic rudiments are isolated, there is a danger of development anomalies caused by both hereditary and environmental factors [21, 23].

According to literature data [24], on the 9th week of IUD, the beginnings of the maxillary sinuses separate in the form

of small cavity formations. In the maxilla, the process of formation of the alveolar groove is slightly behind in time compared to the mandible.

On the 10th week of IUD, osteogenic islands continue to consolidate in the maxilla. Merging with each other, they gradually spread into palatal processes, which in the area of the hard palate are already growing along the entire length, and only in the zone of formation of the soft palate there is still a small slit-like lumen between them.

In 6-week-old embryos, the formation of the lower lip is completed, and the formation of the upper lip occurs during the 7-8th week of IUD as a result of the maximum convergence and fusion of the maxillary processes with the medial nasal processes of the frontal ridge. At the same time, if the lower lip is completely derived from the mandibular arch, then the upper lip is formed from heterogeneous rudiments: its lateral parts are formed by maxillary processes, and the middle part is formed by medial nasal processes [25]. Together with these processes, the cheeks and alveolar processes of both jaws are formed, while the own plate of the mucous membrane of the oral cavity is formed from the ectomesenchyme [16].

In the oral region, as a result of complex reciprocal relations between the epithelium and the proper mesenchyme, the formation of maxillary and mandibular vestibular plates occurs, which separate the rudiments of the lips and cheeks from the gingivae, as a result of which the formation of the oral cavity begins. According to our data, the leading role in its formation belongs to the epithelium, which actively proliferates and gradually sinks into the proper mesenchyme. At the same time, the laying of epithelial dental plates takes place, which grow in the form of continuous cords into alveolar processes, on the outer surface of which tooth buds are formed during the 7-8th week of IUD, and by the end of the 8th week of IUD, mesenchyme growth is observed in them in the form small papillae, as a result of which enamel organs are formed. In the 9th week of IUD, they begin to acquire the shape of a "cap", which is also indicated in other works [19, 21, 26-30].

CONCLUSIONS

1. On the basis of a complex of morphological research methods, data were obtained that made it possible to establish the general patterns of development of the human mandible: separation of the pharyngeal apparatus (4th week), convergence and fusion of the jaw processes (5-8th weeks), formation of tooth buds (7-8th weeks), which allows considering the specified periods as critical in the formation of possible anomalies in the facial part of the skull. At the same time, a tendency of heterochrony of morphological transformations in the mandible and maxilla was revealed.
2. At the beginning of the 4th week of intrauterine development, 3 pairs of pharyngeal arches are formed. Detachment of the mandibular and maxillary processes of the mandibular pharyngeal arch is planned. In embryos of the middle of the 5th week of intrauterine development, the nasal medial and lateral processes are structurally formed, between which the rostral overhangs the frontal process. At the 6th week of intrauterine development, the ventral processes of the mandibular arch are connected along the midline, forming the mandible.
3. During the 7th week of intrauterine development, the maximum convergence of the maxillary processes with the lateral and medial nasals occurs, and in embryos of 20.0 mm PCL grow with the frontal process, forming the maxilla and upper lip. Osteogenic islands are defined in the maxillary processes. During the 8th week of intrauterine development, the bone base of the jaws is modeled as a result of the increase in the size of osteogenic islands and their fusion, alveolar processes are formed. The palatal plates, in which osteogenic formations are defined, begin to change their position to a horizontal one.

During the 9-10th weeks of intrauterine development, the primary palate is formed as a result of the fusion of the palatine processes, the separation of the oral and nasal cavities begins, and the nasal septum is formed, which comes into contact with the lateral palatal plates. In both jaws, the mass of bone tissue grows, enamel organs are separated.

At the 11th week of intrauterine development, the bone base models both jaws. Due to the processes of histogenesis of the soft tissues of the maxillofacial apparatus, the face acquires anthropomorphic definitive human features.

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ORIGINAL ARTICLE

THE ANALYSIS OF THE IMPACT OF THE TYPE OF CONTRACEPTION USED BY WOMEN ON THE LEVEL OF THEIR SEXUAL SATISFACTION AND COMFORT OF USE

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ABSTRACT

The aim: To compare satisfaction of women using oral contraception to satisfaction of women using the levonorgestrel-secreting intrauterine system. In the comparison the following factors were taken into account: comfort of use, menstrual cycle, libido level, well-being and the impact on the relationship with a partner.

Materials and methods: The study involved 129 randomly selected women who had to fill in the research survey questionnaire.

Results: It has been proved that patients are more willing to use the intrauterine system secreting levonorgestrel because of a more reliable contraceptive effect and convenience of use. This kind of contraception has a beneficial effect on libido and relationships with a partner. Women using oral contraception did not report such advantageous influence of their method of contraception. An increase in libido was noticed for 24 women in the group of patients using the levonorgestrel-secreting intrauterine system and for 8 women in the group of users of oral contraception, which corresponds to 33.8% and 13.8%. Patients used oral contraception more often in order to regulate their menstrual cycle and to reduce heavy menstrual bleeding.

Conclusions: The study identifies groups of women for whom a specific method of contraception would be appropriate. The greatest benefits of using the levonorgestrel-secreting intrauterine system will have patients who appreciate the convenience of use, as well as those who have sex drive disorders or for whom oral contraception causes undesirable symptoms. Women with hormonal disorders, irregular menstrual cycles and heavy menstrual bleeding will benefit most from the use of oral contraception.

KEY WORDS: sexual satisfaction, libido, levonorgestrel intrauterine system, oral contraceptive pill

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INTRODUCTION

Birth control is an extremely important issue. Due to parents' current need to consciously decide about the family size and the number of children they want to have and also because of the early age of sexual initiation, contraception is a very important aspect of human life. One should also not forget that getting pregnant may carry a risk of deterioration of woman's health due to her abnormal original condition.

Proper education about contraception and its use has a great impact on psychological, sociological and economic aspects of the society. Ideal contraception should be safe, effective, reversible, simple to use, widely available and it also has to be affordable [1]. Since 60s of the twentieth century, the constant development of hormonal contraception has been observed which is due to global trends in the field of birth control. Currently, contraception is expected to be not only effective, but also comfortable.

In oral hormonal contraception (OCP – oral contraceptive pill) there are two methods: single-component – containing gestagen (POP – progesteron-only pill) and two-component – containing gestagen and estrogen derivative (COCP – combined oral contraceptive pill). Both of these methods are characterized by the low Pearl index, and unplanned pregnancy most often results from patients' inappropriate use of contraceptive pills, so the basic principle of application OCP is to conscientiously take the pills at a fixed time of day. If there is a risk of thromboembolism, occasional libido impairment, burdened hepatic metabolism and anticipated reduction in efficacy for drug interactions or gastrointestinal disorders, a method of contraception other than OCP should be considered.

Levonorgestrel intrauterine hormonal contraceptive systems (LNG-IUS) evolved from previously introduced non-hormonal intrauterine devices (IUD- intrauterine device). The LNG-IUS is applied to the uterus. After that it slowly releases the hormone levonorgestrel from the built-in tank. This hormone makes the endometrium insensitive to endogenous estrogens and progesterone and induces decidualization of the stroma. Intrauterine agents with levonorgestrel differ from each other because of the content of the hormone (13.5 mg, 19.5 mg, 52 mg). Those with a lower content of the hormone do not inhibit menstrual bleeding and the progestogenous effect on the surrounding tissues is smaller. In this case fertilization is prevented by thickening cervical mucus and limiting estrogen-dependent endometrial growth. Levonorgestrel releasing intrauterine devices have the lowest Pearl index, which means that they are the most effective method of contraception. Patients using LNG-IUS do not have to be

specially conscientious or engaged using this method of contraception. The return to fertility after removal of the LNG-IUS is possible during the first natural menstrual cycle. Smaller intrauterine devices can be used by nulliparous women [2]. LNG-IUS with a higher content of the hormone can lead to inhibition of menstrual bleeding, which in case of some diseases may be an advantage. The basic indication for using the LNG-IUS is its contraceptive effect. In addition, it is a method used in a treatment of endometrial hyperplasia, treatment of abnormal vaginal bleeding and endometrial suppression during hormone therapy for breast cancer. However, while LNG-IUS is being inserted, there is a risk of damage to the walls of the uterus, as well as possible pains which might occur during inserting the device. Sometimes intrauterine infection and abnormal vaginal bleeding is possible. Occasionally, LNG-IUS slips out, which may reduce its effectiveness.

THE AIM

The aim of the study was to compare satisfaction of women using OCP with satisfaction of women using LNG-IUS. In order to compare levels of satisfaction the following factors were taken into account: comfort of using these two different contraceptive methods, regulation of the menstrual cycle, level of libido, well-being of women and the impact of these methods on the relationship with the partner. This work also answers the question: What is the impact of these two types of contraception on both the quality of sexual life and the daily life of women?

MATERIAL AND METHODS

The survey conducted from 10/05/2021 to 03/11/2021 in the Kujawsko-Pomorskie voivodship included patients who were under the care of a gynecological clinic. The study involved 129 randomly selected women using OCP or LNG-IUS. The study was approved by the Bioethics Committee. A specially developed questionnaire on women's sexual satisfaction was the research tool. The survey questionnaire consisted of single and multiple choice questions. It included questions about the reason for using a given type of contraception and the source of information about a given method of contraception. In addition, the questionnaire gave information about the impact of a given contraception on the relationship with a partner, libido, patient's satisfaction, well-being and possible negative impact on her quality of life and the nuisance of using OCP and LNG-IUS. It also informed about the benefits of OCP and LNG-IUS, as well as the patient's willingness to continue the specific method of contraception. Each patient signed an informed consent form to participate in the study.

129 women participated in the study. There were two groups of women. Group 1 including 71 women (55%) and group 2 including 58 women (45.0%). The 1st research group included women who used an intrauterine system with levonorgestrel: 13,5 mg – 5 women (7%), 19.5 mg – 24 women (33.8%), 52 mg – 42 woman (59.2%) and the 2nd group of women who used oral contraceptive pills: progestogenic – 6 women (10.3%) and two-component – 52 women (89.7%). The mean age of women [in years] in group 1 was 39.7 ± 7.6, and in group 2 it was 31.7 ± 9.5. In the groups, who took part in the study, the highest number of women had secondary and higher education. Respectively, secondary education: 28.2% (20 women) and 41.4% (24 women) and higher: 67.6% (48 women) and 41.4% (24 women).

In order to describe the groups of women who took part in the research, the arithmetic mean and standard deviation (SD) were calculated in the analysis of measurable features, and for non-measurable features the structure index [%]. The statistical analysis of the tested non-measurable features (variables) was performed on the basis of the non-parametric Person's Chi^2 test, Yates's Chi^2 test and the Fisher's exact test. The statistical and graphical analysis was performed by means of the Statistica's 13 program. The lowest level of statistical significance was $p<0.05$.

RESULTS

On the basis of the analysis of the reason for using a given method of contraception in the study group, it was shown that patients more chose LNG-IUS more willingly due to its more reliable contraceptive effect: 57 patients with LNG-IUS and 31 patients using OCP, which corresponds to 80.3% and 53.5%. Patients receiving OCP justified their choice almost twice as often with the need to treat heavy menstruation than patients using LNG-IUS. The need to regulate the cycle was three times more frequent in the OCP group, respectively 27.6% – OCP and 8.5% – LNG-IUS. Recurrent vaginal bleeding was rarely an indication for the use of OCP and LNG-IUS and therefore no significant statistical differences were found (Table I).

There were no statistically significant differences between the frequency of obtaining information about the method of contraception from various sources in the OCP and LNG-IUS groups. In both groups, patients most often learned about the advantage of the method from their gynaecologist. Friends, media or patients' families were less often the source of information (Table II).

It has been found that there is a positive effect of LNG-IUS on the relationship between a patient and her partner. It was better in comparison to the influence of OCP on relationships of patients using it. 54 patients using LNG-IUS reported an improved relationship with their partners, in comparison to 27 women using OCP, which corresponds to 76.1% and 46.6%. The significance level in the Pearson's Chi^2 test was 0.0012 (Table III).

According to the information obtained from patients from these two groups, it was found that the use of LNG-IUS had a much better effect on the increase in libido than the use of OCP. The increase in libido was noted among 24 women in the LNG-IUS group and among 8 women in the OCP group, which corresponds to 33.8% and 13.8%. There was no change in libido in the LNG-IUS group – 53.5% and OCP – 60.3%, respectively. In the OCP group, women

Table I. Analysis of reasons for the use of a given method of contraception by patients. The interest does not add up because it was a multiple-choice question.

Patient's decision about the type of contraception	Method of contraception						Statistical analysis	
	Levonorgestrel intrauterine system		Oral contraceptive pills		Total		Type of test	Significance level
	n (N=71)	[%]	n (N=58)	[%]	n (N=129)	[%]		
Contraceptive effect	57	80,3	31	53,5	88	67,4	Pearson's Chi^2 =9,40	0,00217
Haevy menstruation	17	23,9	25	43,1	42	32,7	Pearson's Chi^2 =5,34	0,02088
Irregular menstruation	6	8,5	16	27,6	22	17,1	Pearson's Chi^2 =8,26	0,00405
Recurrent vaginal bleeding	1	1,4	2	3,5	3	2,3	Fisher's exact test	0,42408
None of the above	5	7,0	8	13,8	13	10,1	Yates's Chi^2 =1,02	0,31258

Table II. Analysis of sources of information about a given method of contraception. The interest does not add up because it was a multiple-choice question.

Source of information about the type of contraception	Method of contraception						Statistical analysis	
	Levonorgestrel intrauterine system		Oral contraceptive pills		Total		Type of test	Significance level
	n (N=71)	[%]	n (N=58)	[%]	n (N=129)	[%]		
Gynaecologist	57	80,3	38	65,5	95	73,6	Pearson's Chi^2 =3,59	0,05830
Family members	3	4,2	6	10,3	9	7,0	Yates's Chi^2 =1,02	0,31258
Friends	9	12,7	13	22,4	22	17,1	Pearson's Chi^2 =2,14	0,14351
Media	11	15,5	10	17,2	21	16,3	Pearson's Chi^2 =0,72	0,78902
None of the above	1	1,4	2	3,5	3	2,3	Fisher's exact test	0,31258

Table III. Analysis of patients' subjective assessment of the relationship with their partners during applying a given method of contraception.

Positive influence on the relationship with the partner	Method of contraception					
	Levonorgestrel intrauterine system		Oral contraceptive pills		Total	
	n	[%]	n	[%]	n	[%]
Yes	54	76,1	27	46,5	81	62,8
No	4	5,6	3	5,2	7	5,4
No change noticed	13	18,3	28	48,3	41	31,8
Total	71	100,0	58	100,00	129	100,00
Statistical analysis	Pearson's Chi^2 =		13,46	Significance level		0,0012

Table IV. Analysis of the impact of a given method of contraception on the level of libido, in patients' opinion.

Influence of contraception on patient's libido level	Method of contraception					
	Levonorgestrel intrauterine system		Oral contraceptive pills		Total	
	n	[%]	n	[%]	n	[%]
Increase of libido	24	33,8	8	13,8	32	24,8
Decrease of libido	9	12,7	15	25,9	24	18,6
No change noticed	38	53,5	35	60,3	73	56,6
Total	71	100,0	58	100,0	129	100,0
Statistical analysis	Pearson's Chi^2 test =		8,40	Significance level		0,0150

reported worsening of libido twice as often. The differences were statistically significant. The significance level in the Pearson's Chi^2 test was 0.015 (Table IV).

In both groups included in the study, a majority of patients recommend the hormonal contraceptive they were using. In the LNG-IUS group, 67 women answered posi-

Table V. Analysis of a general patients' satisfaction with a given method of contraception.

Recommending used by a patient's method to other women	Method of contraception					
	Levonorgestrel intrauterine system		Oral contraceptive pills		Total	
	n	[%]	n	[%]	n	[%]
Yes	67	94,4	48	82,8	115	89,2
No	4	5,6	10	17,2	14	10,8
Total	71	100,0	58	100,0	129	100,00
Statistical analysis	Pearson's Chi^2 test =		4,45	Significance level		0,0349

Table VI. Analysis of reasons for patients' recommendation of a given method of contraception. The interest does not add up because it was a multiple-choice question.

Reasons for recommending used by a patient's method to other women	Method of contraception						Statistical analysis	
	Levonorgestrel intrauterine system		Oral contraceptive pills		Total		Type of test	Significance level
	n (N=67)	[%]	n (N=48)	[%]	n (N=115)	[%]		
Comfort of use	66	98,5	24	50,0	90	78,2	Yates's Chi^2 = 38,68	0,0000
Well-being	34	50,8	15	31,2	49	42,6	Pearson's Chi^2 = 4,35	0,0371
Increase of libido	16	23,9	4	8,3	20	17,4	Yates's Chi^2 = 4,71	0,03007
Possitive effect on cycle regulation	25	37,3	36	75,0	61	53,9	Pearson's Chi^2 = 15,95	0,0001
None of the above	0	0,0	2	4,2	2	1,7	Fisher's exact test	0,1728

Table VII. Analysis of reasons for the continued use of a given method of contraception by patients'. The interest does not add up because it was a multiple-choice question.

The reason for further use of the same type of contraception	Method of contraception						Statistical analysis	
	Levonorgestrel intrauterine system		Oral contraceptive pills		Total		Type of test	Significance level
	n (N=66)	[%]	n (N=44)	[%]	n (N=110)	[%]		
Comfort of use	61	92,4	25	56,8	86	79,1	Pearson's Chi^2 = 19,62	0,00001
Well-being	31	47,0	14	31,8	45	41,8	Pearson's Chi^2 = 2,51	0,11333
Increase of libido or no negative influence on it	22	3,3	5	11,4	27	25,5	Yates's Chi^2 = 5,75	0,01654
Possitive effect on regulation of periods, skin conditio etc.	26	39,4	29	65,9	55	50,0	Pearson's Chi^2 = 7,24	0,00644
None of the above	1	1,5	2	3,5	3	2,7	Fisher's exact test	0,35066

tively to the question whether they would recommend the type of contraception they are using to other women, and in the OCP group 48 women, which corresponds to 94.4% and 82.8%. Three times more often in the OCP group than in the LNG-IUS group, women would not recommend their contraception method to other women, 17.2% and 5.6%, respectively. Most of the patients in the LNG-IUS and OCP groups intend to continue their contraception in the future, 88.7% and 79.3%, respectively (Table V).

The analysis of responses to the multiple-choice question regarding the reason for recommending a given method of contraception to other women showed that in the LNG-IUS group, convenience of use was most often indicated, then well-being, and finally, increased libido. In these aspects, a statistically significant advantage of LNG-IUS over OCP was found. Patients in the OCP group recommended their method of contraception twice as often, due to its positive influence on the regulation of the menstrual cycle than patients in the group using LNG-IUS. Due to the small number of women who do not recommend the method of their own contraception, the statistical analysis was abandoned (Table VI).

Patients from the LNG-IUS group, when asked about the advantages of their contraceptive methods, gave similar answers to the previous ones, emphasizing the convenience of use, no effect on the level of libido or its increase, and well-being. In the OCP group, patients emphasized regulating of the menstrual cycle and reduction of the amount of menstrual bleeding (Table VII).

DISCUSSION

The importance of oral contraception in treating heavy menstrual bleeding has been documented. A meta-analysis in the Cochrane database by Lethaby et al. proved that the use of two-component OCP for 6 months significantly reduces blood loss during menstruation [3]. It is a well-known fact that heavy menstrual bleeding is most often associated with endometrial hyperplasia. Untreated endometrial hyperplasia can lead to atypia and progression to endometrial cancer later in life. Research by Mittermeier et al. proved the superiority of LNG-IUS over single-component OCP and placebo in the treatment of endometrial hyperplasia. Hysterectomy had to be performed less frequently in cases of endometrial hyperplasia, when women used LNG-IUS contraception method, than in the remaining groups during one-year follow-up period. Because of the fact that the adverse systemic effect was lower for women with LNG-IUS, their satisfaction with treatment was higher than in the OCP group. However it should be noted that vaginal spotting was more common with women using LNG-IUS than in the OCP group [4].

The gestagens used in OCP differ in the profile of non-contraceptive action, which is used in the personalization of the procedure, i.e. the selection of the most favorable action profile of the gestagen used for a given woman. Well-known benefits of OCP also include antiandrogenic activity among patients with symptoms of hyperandrogenism. It results from the increase of concentration of sex hormone binding globulin (SHBG) and thus the decrease in the fraction of free testosterone in the blood serum [5].

The systemic effect of OCP, apart from the advantages, resulting from the regulation of the menstrual cycle, has also significant disadvantages limiting its use. With age, the risk of cardiovascular disease increases. OCP contraception method additionally increases it. The greatest risk of thromboembolism is associated with the use of two-component OCP due to the estrogenic component (6-fold increased risk). It was noticed that there was a slight influence of this hormone on the increase of blood pressure and the risk of heart attack (1.5 times). The estrogenic component reduces the concentration of antithrombin, increases the concentration of fibrinogen, increases the ability to aggregate platelets and increases the concentration of vitamin K. The risk is greater for women over 35 years of age and for smokers. It was found that OCP has an influence on the carbohydrate metabolism, so it is allowed to use this method if women do not have serious health problems and other ailments. OCP has also a negative effect on a bile transport. The estrogen component increases the concentration of triglycerides and HDL, and lowers the concentration of LDL. The gestagenic component causes the increase of LDL concentration. It is worth mentioning that no increase in the risk of breast cancer has been noted. However, there has been an increase in the risk of cervical cancer for women with HPV infection but it has been found that OCP prevents the development of ovarian cancer for 30 years after giving up taking birth control pills. What is more, there has been a reduction of the risk of developing endometrial cancer for 15 years after giving up taking the pill. The most common side effects of oral contraception include: nausea and vomiting, vaginal bleeding and spotting, headaches, weight gain (increased appetite) and skin changes (acne, seborrhea and hirsutism). It should be remembered that the effectiveness of oral contraception is influenced by the regularity of its intake, interactions with other medications and disturbance of the bacterial flora. A disadvantage of this method is the fact that there are a lot of contraindications to its use, which occur relatively frequently, such as smoking, hyperlipidemia, diabetes or migraine headaches [1].

The systemic effect of LNG-IUS is negligible so it is advantageous to use this method in the group of middle-aged women. It should be emphasized that each hormonal contraception, to a greater or lesser extent, increases the risk of breast cancer, therefore regular breast control is recommended [6].

Numerous studies of the sexuality of women using OCP have shown that there are various effects of this method on sex drive. A review of the literature by Burrows et al. showed that while most women did not notice a difference in libido levels, there are common problems associated with OCP such as deterioration of vaginal lubrication, pain and tenderness of the vagina, general weakness and water retention in the body, which may worsen the quality of sexual life. It was found in various studies that 20-30% of women reported the reduction of sexual desire while taking OCP. The authors emphasize that patients should be informed about the possible negative impact of OCP on libido [7].

Intrauterine devices are widely appreciated because of their high efficiency and convenience of use. Initially, the use of IUDs was controversial due to reports of inflammation of the appendages and, consequently, infertility associated with the use of this method of contraception. Recent studies, however, show a low rate of salpingitis among IUD users. Data indicate that the duration of the use of an IUD does not affect fertility, however nulliparous women who use this method of contraception for more than 78 months wait longer for getting pregnant after the removal of the IUD [2].

Unlike OCP, it has been proven that LNG-IUS contraception method has no negative impact on the quality of female sexual life. Chinese studies compared a group of women of childbearing age using LNG-IUS and a group of women using non-hormonal intrauterine systems over a two-year follow-up period. There were no significant differences in the quality of sexual life and the level of libido [8]. Another study by Malmborg et al. included 153

patients who had an intrauterine contraceptive system inserted. The study showed less frequent intercourse and less frequent orgasms in the LNG-IUS group compared to the non-hormonal IUD group. Most patients in both groups were satisfied with their method of contraception, but the advantage of IUD was found in this matter and no significant differences in the patients' satisfaction with the quality of sex life were found. Perhaps studies on larger groups with randomized control and meta-analysis will allow for a more accurate answer to the question about the optimal method of contraception at different stages of the patients' lives [9].

CONCLUSIONS

The study, comparing various factors affecting the satisfaction of patients using LNG-IUS and OCP, allowed to identify groups of women for whom specific methods of contraception would be appropriate. The LNG-IUS method will be the most recommended method of contraception for patients who appreciate the convenience of use, as well as for those who have sex drive disorders and undesirable symptoms associated with the use of OCP. Whereas OCP is the most beneficial method of contraception for patients with hormonal disorders, irregular menstrual cycles and heavy menstrual bleeding. Before offering a patient a specific method of contraception, her general health should be taken into account and it should be checked if this specific method is accepted by her. For some patients, it may be a problem that they have to take contraceptive pills regularly and for others the discomfort caused by the fact this form of protection against pregnancy is associated with an application of LNG-IUS into the uterine cavity. In addition, the economic factor related to the availability of the method in terms of price should also be mentioned. When comparing the prices of contraception, it should be noticed that although OCP is a method relatively more expensive than LNG-IUS in terms of the period of its use for 3-5 years, the costs of this method are spread over time. Thus, to sum up, the choice of a method of contraception is a very complex matter, because it is influenced by many factors, such as the patient's preferences, her general health condition, indications or contraindications for the use of a given method, as well as the economic factor that determines the availability of a given method for a specific woman.

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The Author declare no conflict of interest.

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ORIGINAL ARTICLE

C-REACTIVE PROTEIN AS A MARKER OF CLINICAL AND LABORATORY REMISSION IN PATIENTS WITH ACUTE NECROTIZING PANCREATITIS

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ABSTRACT

The aim: To estimate the role of C-reactive protein levels as a marker of clinical and laboratory remission in patients with acute necrotizing pancreatitis.

Materials and methods: A single-center retrospective non-randomized study of 68 patients (37 (54%) men, 31 (46%) women) was carried out in the period from September 2019 to October 2020. The patients were divided into two groups: group 1 included 9 (13.2%) patients rehospitalized within a month of observation after being discharged from hospital with improvement, group 2 consisted of 59 (86.8%) patients not readmitted within the observation period. A standard package of Microsoft Excel, program MedStat v.5.2, W-test Wilcoxon and the Fisher transform was used to record, calculate and compare data.

Results: Patients in groups 1 and 2 did not statistically differ in age ($p = 0.727$), gender ($p = 0.202$), body mass index (BMI) ($p = 0.447$), length of hospital stay ($p = 0.913$), volume of pancreatic lesion according to CTSI ($p = 0.313$) and severity of disease ($p = 0.205$). Incidence of pancreatic necrosis infection was 88.8% ($p = 0.007$) in group 1 versus 35.6% in group 2. In the group of rehospitalized patients, the level of C-reactive protein upon discharge was significantly higher ($Me \pm m$ 80.8± 9.734 (66) -88), CI 95%) compared with the patients from the group without readmission ($Me \pm m$ 21.36± 2.285 (16.1-31.1) CI 95%) $p < 0.001$. As the "critical" CRP level for group 1, indicating readmission for infectious complications of AP, was chosen the value of the left limit of 95% CI (confidence interval), which made up ≥64.5 mg / ml.

Conclusions: According to the results of our study, the risk of readmission in patients with CRP level ≥64.5 mg / L prior to being discharged exceeded 41 times the risk of readmission in those with lower CRP values (RR 41.5 ± 1.008 (95% CI 5.75-299, $p = 0.04$)). For each patient with CRP levels≥64.5 mg / L, the risk of readmission within the first month after being discharged was 71% (95% CI 40.7-88.6, $p = 0.03$).

KEY WORDS: C-reactive protein, acute pancreatitis, readmission

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INTRODUCTION

According to the frequency of emergency hospitalizations, acute pancreatitis (AP) ranks third among all abdominal accidents with mortality in this nosology remaining eventually at similarly high levels [1-6]. Infectious complications are one of the main causes of unsatisfactory results in management of patients with acute necrotizing pancreatitis (ANP) [7, 8]. Modern imaging and minimally invasive interventional technologies allow to provide more effective infection source control among this group of patients. Manifestation of infection after discharge from hospital significantly increases the percentage of readmissions, treatment costs, frequency of "late" septic complications [9-12], especially within the first month of observation [13]. There are several highly informative laboratory tests, the evaluation and dynamics of which are considered markers of infection. It is generally accepted to use them at the stage of pancreatic infection contamination: in the early stages of the disease to confirm infection of ANP, to assess the effectiveness of monitoring infection source [14-16]. However, the urgency of acute necrotizing pancreatitis does not only deal with diagnosing infectious complications in primary microbial contamination or signs of sepsis, but also with dynamic monitoring at the final stage of inpatient treatment – the regression stage of the infectious process. With aseptic ANP, there is a constant risk of infection of pancreatic necrosis at different stages of its course [7, 8]. Regression of infectious process is characterized by a relative clinical and laboratory stabilization of ANP course. Nevertheless, at the same time the risk of manifestation of infection of microorganisms persisting in the focus of destruction remains, followed by reinfection in the form of a systemic inflammatory response or sepsis-induced organ failure.

THE AIM

To estimate the role of CRP level as a marker of clinical and laboratory remission in patients with acute necrotizing pancreatitis.

MATERIALS AND METHODS

A single-center retrospective non-randomized study on the treatment results of patients diagnosed with "acute

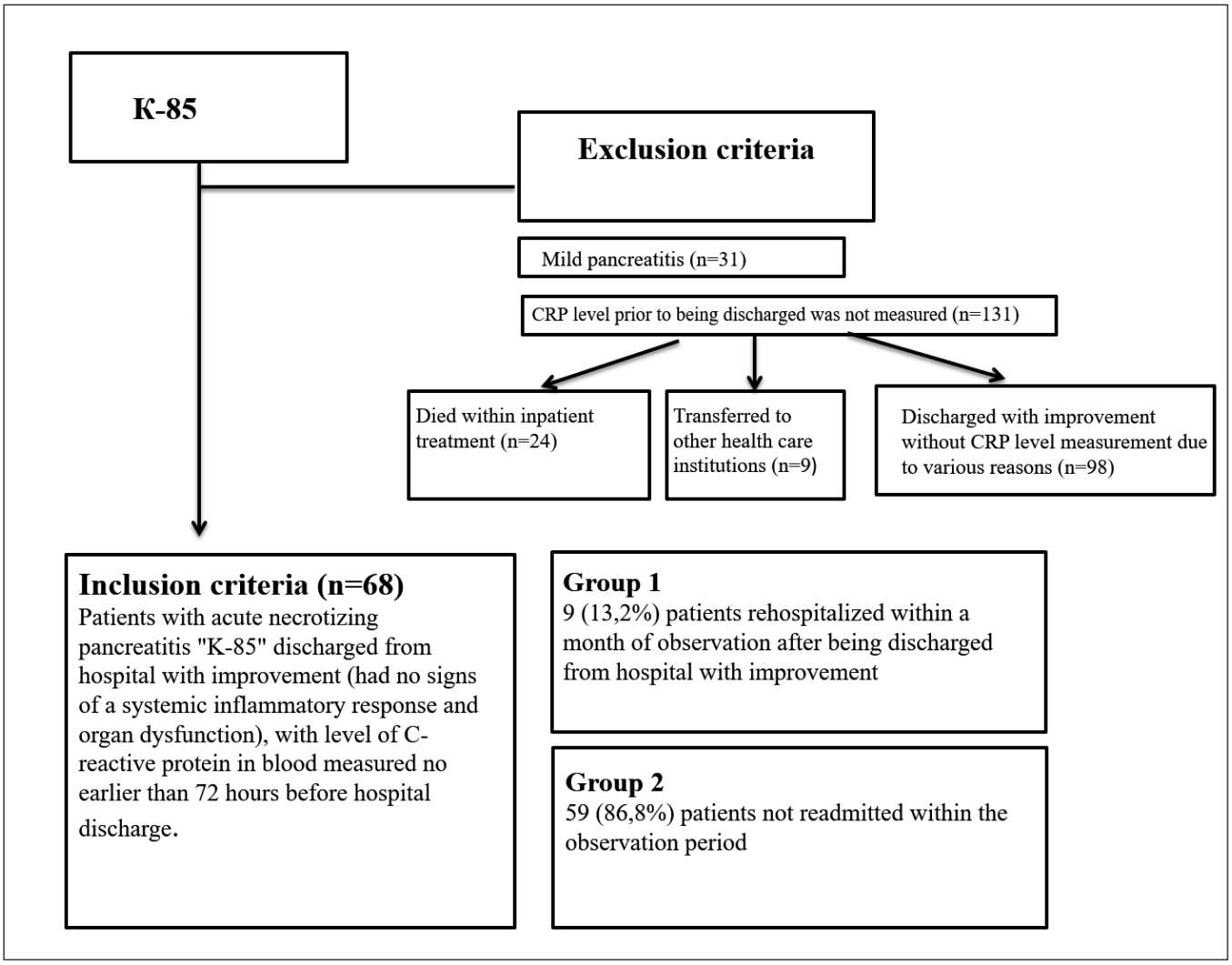

Fig. 1. Study Design

pancreatitis" was carried out. All patients were treated at the clinical base of the Department of General Surgery N1 Bogomolets National Medical University from September 2020 to October 2021. Cases of readmission to surgical hospital over the next month due to the manifestation of the disease were subsequently evaluated.

The patients were divided into two groups: group 1 included 9 (13.2%) patients who were rehospitalized within a month of observation after being discharged from hospital with improvement, group 2 consisted of 59 (86.8%) patients who were not rehospitalized.

Moreover, gender-demographic characteristics and clinical and laboratory criteria for the disease severity were investigated, the level of CRP determined prior to discharge was examined. Clinical and laboratory characteristics of the patients studied were entered into the database. The severity of AP was assessed according to the criteria of the Revision of the Atlanta Classification 2012.

Inclusion criteria: patients with acute necrotizing pancreatitis "K-85" discharged from hospital with improvement (had no signs of a systemic inflammatory response and organ dysfunction), with level of C-reactive protein in blood measured no earlier than 72 hours before hospital discharge.

Exclusion criteria. Patients diagnosed with acute pancreatitis K-85 of mild degree either with or without measurement of CRP levels prior to discharge (n=31).

The study design is presented in schematic fig 1.

The average age of the patients studied was 51.29±1.67 years, out of them 37 (54%) were men and 31 (46%) women. The cause of the disease in 45.5% (n=31) was alimentary, in 29.5% (n=20) biliary, hypertriglyceride in 11.8% (n=8), in 4.4% (n=3) postoperative, 8.8% (n=6) cases of AP were idiopathic. 36.8% (n=25) of patients had severe AP, 63.2% (n=43) had moderate AP. Infected AP was observed in 42.6% of patients (n=29). All patients were treated according to the IAP/APA evidence-based guidelines for the management of acute pancreatitis and the 2019 WSES guidelines for the management of severe acute pancreatitis. The median (QI-QIII) length of a bed-day was 39±3.537 (20-56.5) days. Median (QI-QIII) body mass index (BMI) was 28.6±0.8435 (26.4-30.75) kg/m2. The standard package Microsoft Excel 365 was used to record the patients' data, and the statistical program MedStat v.5.2 was used

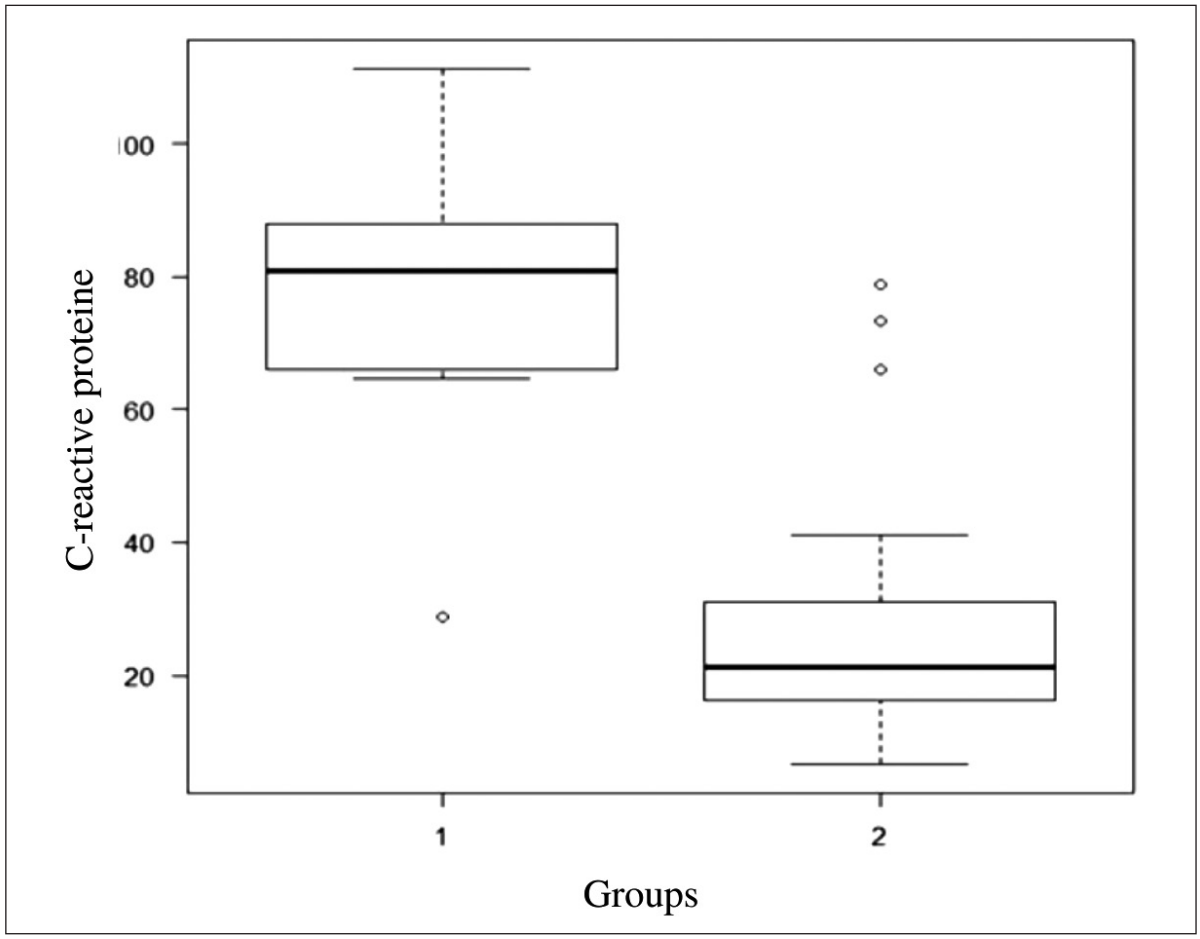

Fig. 2. Point and interval estimates of CRP values among groups, considering the error in the median and 95% CI

for calculation. Analyzing the quantitative data of patients upon obtaining a normal distribution, the mean value and error were used, while with an asymmetric distribution the median and 95% CI of QI-QIII were calculated. Wilcoxon W-test was used to compare the central tendencies of two independent samples, the Fisher angular transformation was used (considering Yates correction) to compare the proportion of two groups. When determining the critical value of CRP, data were taken from the left limit of 95% CI among rehospitalized patients. While comparing groups, Odds ratios with error and 95% CI were calculated, including the chance of finding a risk factor in groups; absolute risk in the control and studied groups with 95% CI limits relative and attributive risk with 95% CI. During the analysis, the p-value of less than 0.05 was considered statistically significant.

RESULTS

Among the 68 examined individuals, 9 (13.2%) patients were readmitted to the clinic due to manifestations of infected necrotizing pancreatitis within a month after discharge and, as mentioned above, these patients formed group 1.

All patients were readmitted with signs of a systemic inflammatory response, the cause of which was the manifestation of infection in pancreatic and parapancreatic necrotic foci. Of these, 1 (11.1%) patient was discharged with aseptic acute necrotizing pancreatitis during primary hospitalization, and 8 (88.9%) with an infected one. Sanitation of infectious foci was carried out by using sonographically controlled puncture-draining interventions. There were no deaths during re-hospitalization. On average, patients were readmitted after 15.13±3.05 days, the average hospital day lasted 12±2.021 days.

Comparative gender-demographic and clinical-morphological characteristics of patients in both groups are presented in Table I.

As shown in the table, patients in groups 1 and 2 were neither statistically different in terms of age (p=0.727), gender (p=0.202), body mass index (BMI) (p=0.447), length of hospital stay (p=0.913) and the volume of pancreatic lesion by CTSI (p=0.313), nor in severity (p=0.205). However, patients in the two groups differed in the incidence of pancreatic necrosis infection (p=0.007) – 88.8% in group 1 versus 35.6% in group 2. When comparing the obtained levels of CRP upon discharge, the groups had statistical differences at a significance level of $p < 0.001$. (Table II, Fig. 2)

The next stage of the study was to determine the strength of the influence of a certain level of CRP on the risk of rehospitalization associated with the manifestation of pancreatic infection in patients with ANP. We chose its

Table I. Comparative table of gender-demographic and clinical-laboratory data among the two groups

Feature		Group 1	Group 2	P
Age, years, X±m		51,53±13,81	49,78±14.66	0,72
Gender, n (%)	Male	29 (49,1)	7 (77,7)	0,2
	Female	30 (50,9)	2 (22,3)	
BMI, kg/m2, Me (QI - QIII)		28,6 (26,5-30,9)	26,5 (25-29,6)	0,44
Severity, n (%)	Moderate	43 (72,8)	4 (44,4)	0,2
	Severe	16 (27,2)	5 (55,6)	
CTSI, points, X ±m		6,932±0,2133	7,444±0,6035	0,31
Infected pancreonecrosis, n (%)		8 (88,8)	21 (35,6)	0,007
Hospital stay, days Me (QI - QIII)		39 (19-55)	25 (23-59)	0,91
C-reactive protein, mg/ml, Me (QI - QIII)		80,8 (66-88)	21,36(16,1-31,1).	<0,001

Table II. Evaluation of the median CRP level between the study groups

Group No	Sample size, n	Median value Me±m	Left (CI 95%)	Right (CI 95%)
Group 1	9	80,8±9,734	64,54	96,6
Group 2	59	21,36±2,285	18,6	26,66

Table III. Observation frequency of factor and resulting features

Factor feature	Readmission		Summary
	Yes	No	
CRP ≥64,5	8	3	11
CRP < 64,5	1	56	57
Summary	9	59	68

Table IV. Absolute risk in the two groups

Group	Absolute risk	CI 95%, p
CRP level ≥64,5	72,7%.	40,1-95,5%, p=0,04
CRP level <64,5	1,8%.	0,0-6,9, p=0,04

value as the "critical" level of CRP based on the above calculations. As shown in Figure 2, the confidence intervals of both groups have ranges within which identical CRP values were observed, despite a statistically significant difference between the medians. It is in this range that the limit of CRP values is located, and above which rehospitalization should be observed in the majority of those studied. We chose the value of the left limit of 95% CI (confidence interval) for group 1 as a "critical" level of CRP, indicating rehospitalization for infectious complications of AP, which was ≥64.5 mg/ml. In the group with rehospitalization we observed only one case below this level with a CRP value of 28.9 mg/ml. Also, 3 cases of acute necrotizing pancreatitis with CRP levels ≥64.5 from group 2 were identified. These patients were not rehospitalized within the month of observation. The distribution according to the selected "critical" level of CRP in the groups is shown in Table III.

The absolute risk of readmission for patients with CRP levels ≥ 64.5 ng/mL made up 72.7% (95% CI 40.1%-95.5%, p=0.04), and for patients with CRP levels upon discharge < 64.5 ng/ml it was 1.8% (95% CI 0.0%-6.9%, p=0.04) (Table 4). The risks of readmission in the groups are statistically significantly different, p<0.001. Relative risk (RR) was 41.5±1.008 (95% CI 5.75-299, p=0.03), whereas a result greater than one indicates a statistically significant increased readmission rate among patients with a CRP level upon discharge ≥64.5. The attributive risk was 71.0% (95% CI 40.7-88.6, p=0.03). This suggests that for each patient discharged with a CRP level ≥64.5 the risk of readmission within a month is likely to be 71%.

DISCUSSION

C-reactive protein is considered a universal and highly informative marker of the inflammatory response induced by bacterial, viral agents, non-infectious components, which may indicate the activity of an autoimmune process, generalization of infection or endotoxemia associated with exposure to tissue destruction products [17-19]. In our work we used CRP as an additional laboratory criterion for a "dangerous" transition from an inpatient disease period to the post-hospital period of observation in order to minimize the risk of readmission for complications of acute necrotizing pancreatitis.

In a retrospective observation, it was found that among the 68 patients studied, 9 (13.2%) patients were readmitted to the hospital for a manifested pancreatic infection within the next month discharged with CRP levels ≥64.5 mg/l (Me±m 80.8±9.734 (95% CI QI-QIII 66-88)). Comparative analysis found that re-hospitalized patients had a significantly higher level of CRP upon discharge from hospital (p<0.001). Furthermore, given the entire range of CRP levels in both groups, a "critical" level of CRP for this sample was determined, crossing the value of which patients were most likely to be readmitted within the month of observation. The value of CRP ≥64.5 mg/l met the given requirements. At the final stage of the study, we determined the strength of the association between readmission and critical CRP levels upon discharge. As the difference in readmission rates among the studied groups is statistically significant, it can be argued that the level of CRP ≥64.5 mg/l is an indicator of probable readmission in our cohort (p<0.001) after discharge. It should be noted that 88.9% out of nine patients in the first group

According to the results of our analysis, the risk of rehospitalization in patients with a CRP level prior to discharge ≥64.5 mg/l was 41 times higher than its risk with lower CRP values (RR 41.5±1.008 (95% CI 5.75-299, p=0.04)). For each patient with a CRP level ≥64.5 mg/l, the risk of readmission within the first month after discharge was 71%. Preliminary studies on the diagnostic role of CRP in patients with AP consider it as a marker of disease severity and a predictor of "early" mortality and complications [20, 21]. Considering FastTrack trends and the fact that the evolution of necrotizing pancreatitis is not limited to inpatient treatment, it is important to identify additional available informative diagnostic criteria for a favorable course of the disease, which will allow the patient to be transferred to the post-hospital stage of treatment and observation. Most authors investigated the role of CRP in terms of the criterion of indications for interventional methods of treatment, the effectiveness of antibiotic therapy, and the like [22, 23]. Our study differs from the previous ones in determining the maximum permissible dangerous level of CRP, which would minimize the risk of readmission in patients with acute necrotizing pancreatitis.

Given the design and scope of the study, we were only able to establish a trend indicating that a CRP level ≥64.5 mg/l is a significant factor in readmission within a month after discharge. However, it would be incorrect to recommend this particular value as a reference one. It undoubtedly requires further multicenter, possibly prospective studies involving the use of multivariate statistical models. Our sample allowed us to achieve clinically and statistically significant results that can be applied in practice. According to the results obtained, patients with CRP levels ≥64.5 mg/l require further inpatient treatment for the purpose of dynamic monitoring, prevention of infection and reinfection.

CONCLUSIONS

1. The frequency of readmission among patients undergoing inpatient treatment for acute necrotizing pancreatitis was 13.2%; the patients were re-hospitalized after 15.13±3.05 days due to the manifestation of pancreatic infection.
2. In the group of rehospitalized patients the level of CRP upon discharge was significantly higher (Me±m 80.8±9.734 (66-88), CI 95%) than in patients of the group without readmission (Me±m 21, 36±2.285 (16.1-31.1) 95% CI, p<0.001.
3. For each patient discharged with a CRP level ≥64.5 ng/ml, the possible risk of rehospitalization within a month was 71% (95% CI 40.7-88.6, p=0.03). The risks of readmission among patients with a lower and higher value of the selected "critical" CRP level were statistically significantly different, p<0.001, the relative risk (RR) was 41.5±1.008 (95% CI 5.75-299, p=0.03).

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ORIGINAL ARTICLE

GENDER AND SOMATOTYPOLOGICAL PECULIARITIES OF INDICATORS OF AEROBIC AND ANAEROBIC PRODUCTIVITY OF ENERGY SUPPLY OF THE BODY IN THE POST-PUBERTAL PERIOD OF ONTOGENESIS IN THE RESIDENTS OF THE ZAKARPATTIA REGION

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ABSTRACT

The aim: To establish gender differences in aerobic and anaerobic productivity in practically healthy residents of the Zakarpattia region in the post-pubertal period of ontogenesis, depending on the somatotypological characteristics of the organism.

Materials and methods: A comparative analysis of physical health status of 456 individuals, was carried out, whit was assessed by indicators of aerobic and anaerobic productivity of the body, depending on the somatotype, which was determined by the Heath-Carter method, and depending on the component body composition which was determined using the impedance method.

Results: The relative value $Vo_{2\,max}$ in females corresponds to "excellent", which guarantees a "safe health level" according to H.L. Apanasenko. At the same time, the level of aerobic productivity in males in terms of the relative value $Vo_{2\,max}$ is "average", which cannot guarantee a "safe health level". The anaerobic productivity of females is lower than in males in terms of the relative value of alactic power, lactic power, and the capacity of lactic energy supply processes by 55.6%, 54.7%, and 38.7%, respectively.

Conclusions: The level of aerobic productivity, regardless of the area of residence, in females is higher than in males according to Ya.P. Pyarnat's criteria. In males the increase in the fat component has a negative effect on the aerobic and anaerobic energy supply of the body. On the contrary, the growth of the muscle component of body mass helps to increase the aerobic and anaerobic capacity of the body.

KEY WORDS: physical health, somatotype, component composition

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INTRODUCTION

Physical health which is determined by the genotype and the phenotype formed on its basis [1-4], should be considered according to the sum of the reserve functional capacity of the organism [5] throughout life [6]. In view of this, health should be assessed not only qualitatively, but also quantitatively so as to provide an objective assessment [7, 8].

The quantitative assessment of health consists in measuring the energy potential of the human body, which is based on macroergic compounds ATP, CrP, GTP, and inorganic pyrophosphate. The greater the power and capacity of the energy potential realized by the body and the efficiency of energy expenditure, the higher the health status of the individual [4, 9]. The aerobic productivity of the body is considered an informative indicator of somatic health as anaerobic energy significantly prevails in the total amount of the energy potential of aerobic energy production [5, 10].

For the quantitative assessment of physical health status, the physiological indicator of such a functional system should be used, which would integrate the functions of most functional systems of the body. According to Yu.M. Furman [4, 5], the maximum oxygen consumption ($Vo_{2\,max}$) is the indicator of the aerobic functional energy supply system that meets these requirements. Its value is determined by the function of the cardiovascular, respiratory, blood systems and the oxygen utilization system in the muscles.

The interest in anthropometric and somatotypological studies has been growing considerably, since they allow to connect the structural features of the human body with the features of metabolism and body functions in normal and pathological conditions [11, 12]. Today, most researchers have come to the conclusion that somatotype should be at the center of the search for such features [13]. Nikitiuk [14] figuratively called the somatotype a "skewer", which can take on any amount of additional information in the form of functional biophysical indicators. Somatotype as a morphological expression of the constitution, is one of the integral characteristics of the human body [8, 13] which reflects the level and harmony of physical development [11, 12]. Today, the dependence of the functional capabilities

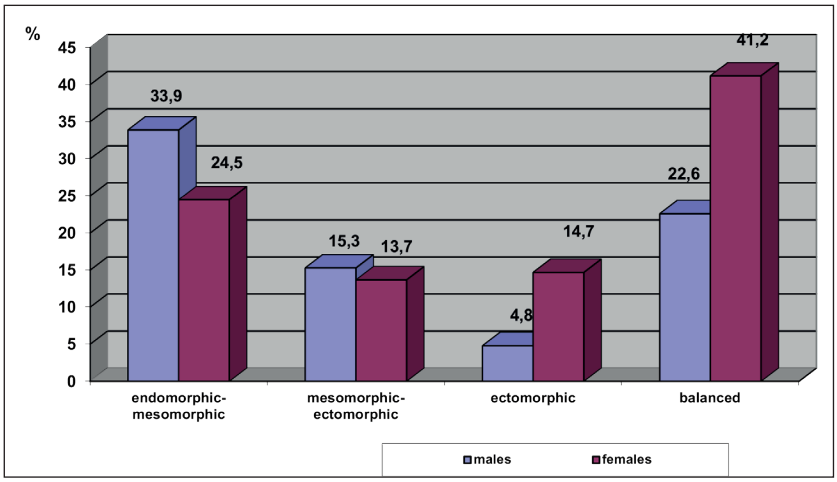

Fig. 1. Distribution of males and females from the mountainous districts of the Zakarpattia region by somatotypes

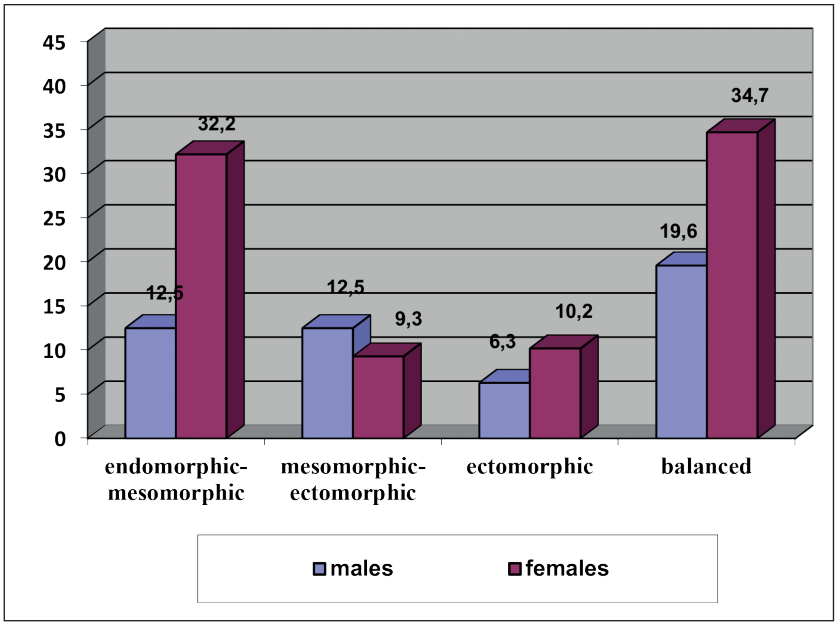

Fig. 2. Distribution of males and females from the lowland districts of the Zakarpattia region by somatotypes

of the body on the components of body composition is of particular interest [15]. Reorientation of anthropology from solely measuring the forms and proportions of the body to studying the dependence of body functions on them, makes the research of heredity and environmental variability at various stages of the organization and functioning of the human organism relevant.

THE AIM

The aim is to establish gender differences in aerobic and anaerobic productivity in practically healthy residents of the Zakarpattia region in the post-pubertal period of ontogenesis, depending on the somatotypological characteristics of the organism.

MATERIALS AND METHODS

Comparative analysis of physical health status of 456 adolescents in the post-puberty period of ontogenesis, aged from 16 to 21 years, was carried out. The number of the examined young males and females was 226 (49.6%) from the mountainous districts and 230 (50.4%) from the lowland districts of Zakarpattia region. Physical health status was assessed by indicators of the aerobic productivity of the body, namely, the maximum oxygen consumption was measured ($VO_{2\ max\ rel.}$) using the bicycle ergometry method. To evaluate the level of aerobic productivity, the Ya.P. Pyarnat's rating scale was used [4]. Indicators of anaerobic productivity of the body were studied by: measuring the power of anaerobic alactic energy supply processes by the Peak Power Output in 10 s (WAnT 10); the power of anaerobic lactic energy supply processes by the Peak Power Output in 30 s (WAnT30), using the Wingate anaerobic test described by Yu.M. Furman et al [4]. The anaerobic lactic productivity of the organism was measured by the Peak Power Output (PPO) in 1 min using A. Shogy and G. Cherebetin's method [4]. The somatotype was determined by the Heath-Carter method [16], which provides a three-component (fat, muscle and bone) anthropometric assessment. This method allows to quantitatively assess the advantage of: endomorphism, or relative obesity; me-

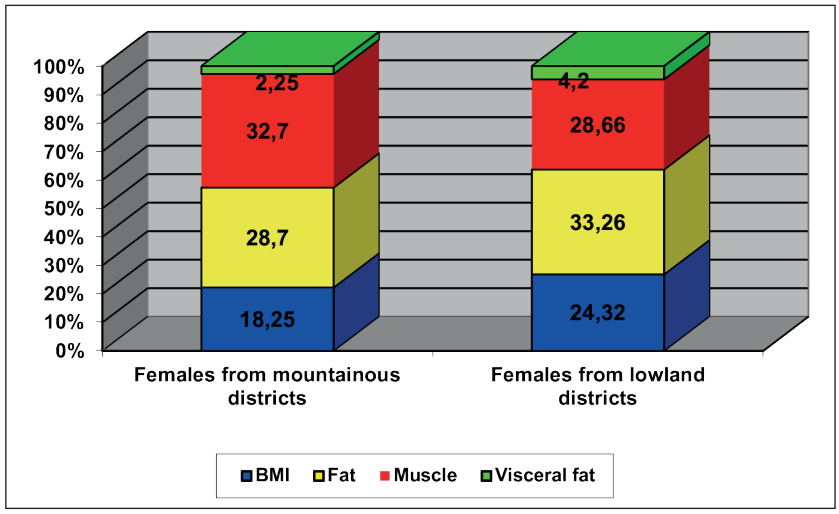

Fig. 3. Component body composition of female residents of the Zakarpattia region who have an excellent level of aerobic productivity according to $VO_{2\ max\ rel.}$ (n=220)

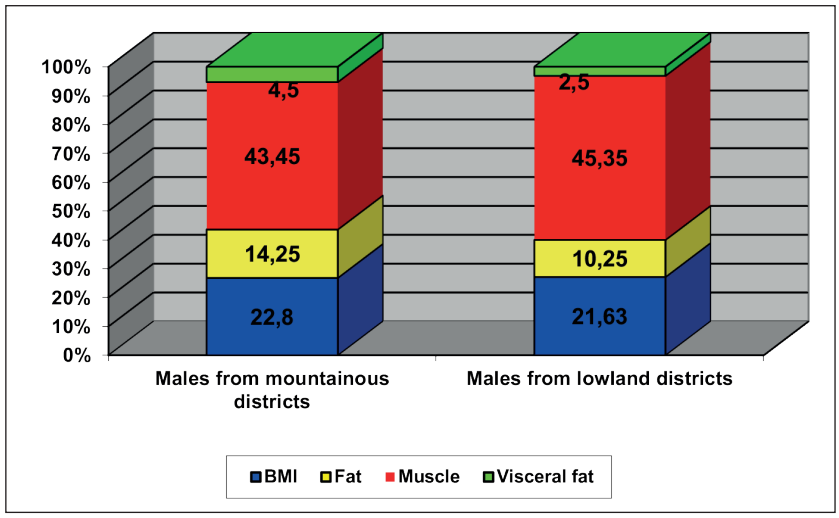

Fig. 4. Component body composition of young residents of the Zakarpattia region who have an average level of aerobic productivity according to $VO_{2\ max\ rel.}$ (n=236)

somorphism, or relative development of the skeletal and muscular system; ectomorphism, or relatively linear and slim body type. The component body mass composition was determined using the impedance method with the application of Omron BF511 Body Composition Monitor to estimate the percentage of fat mass (subcutaneous and visceral fat) and the percentage of skeletal muscle [15]. The statistical processing of the material was carried out in Excel 7.0 and SPSS version 10.0 using Student's t-test to find out the reliability of the difference between the average values.

RESULTS

There are differences in the numerical distribution of individuals in the post-pubertal period of ontogenesis with a prevalence of a certain component body mass composition and somatotype depending on the area of their residence either in lowland or mountainous districts of the Zakarpattia region. The gender factor also affects this distribution. Among females from lowland districts there is a greater number of individuals with a high percentage of fat component (38.1%) and a smaller number (6.8%) with a low fat percentage than among peers from mountainous districts (10.8% and 38.2%, respectively). In males from lowland and mountainous districts, no significant quantitative difference was observed between individuals in terms of the relative value of the fat content. No significant difference was found in the distribution of females from lowland and mountainous districts in terms of the relative value of the muscle content. At the same time, among females from mountainous districts there is a slightly higher number of individuals with high (by 3.6%) and very high (by 3%) percentage of the muscle component, compared to females from lowland districts.

Among males from lowland districts, a larger number of individuals with very high (by 38.7%) and high (by 8%) percentage of the muscle component was registered, compared to those living in mountainous districts. Among males from the mountainous districts, individuals with normal levels of this component prevailed as compared to peers from the lowland districts. The gender difference in the distribution of the youth of lowland and mountainous districts by somatotypes is characterized by the following: mesoectomorphic (9.3%) and endomesomorphic (6.3%) somatotypes represented the smallest number of individuals from lowland districts among females. Regardless of the gender, the largest number of individuals was represented

Table I. Average values of indicators of aerobic and anaerobic productivity of the organism (M±m) in post-puberty adolescents from lowland and mountainous districts of the Zakarpattia region, n= 456

Indicators	Aerobic productivity		Anaerobic productivity					
	Maximum oxygen consumption		power of alactic energy supply processes		power of lactic energy supply processes		capacity of lactic energy supply processes	
	$VO_{2\ max\ rel.}$ ml·min^{-1}·kg^{-1}		$WAnT_{10\ rel.}$, kg-m·min^{-1}·kg^{-1}		$WAnT_{10\ rel.}$, kg-m·min^{-1}·kg^{-1}		$PPO_{rel.}$, kg-m·min^{-1}·kg^{-1}	
Gender	lowland district	mountainous district	lowland district	mountainous district	lowland district	mountainous district	lowland district	mountainous district
Males (n=236)	42,7±0,65	40,3±1,23	57,02±1,32	63,5±1,39	52,1±1,64	61,1±2,01	29,81±1,01	27,96±0,94
Females (n=220)	42,9±0,58	41,7±0,46	41,2±0,32	40,8±0,64	39,4±1,16	39,5±1,08	23,4±0,3	21,5±0,8
P	> 0,05	> 0,05	< 0,01	< 0,01	< 0,01	< 0,01	< 0,05	< 0,05
M	1,03		1,57		1,55		1,39	

Note: P is the probability of a difference in the average values of the indicators of the body of young people within the same type of area (P<0.05); M is the multiplicity of changes in the average values of the indicators of the body of young people of different gender groups

Table II. The average values of indicators of aerobic productivity (M±m) in post-pubertal youth from the lowland and mountainous districts of the Zakarpattia region depending on the somatotype, n= 456

Indicators	Aerobic productivity			
	Maximum oxygen consumption			
	$VO_{2\ max\ rel.}$, ml·min^{-1}·kg^{-1}			
	Females (n=220)		Males (n=236)	
Somatotype	lowland district (n=118)	mountainous district (n=102)	lowland district (n=112)	mountainous district (n=124)
Endomorphs	38,2±1,63	41,4±2,3	-	-
Endomesomorphs	41,8±1,81	45,2±1,93	38,56±0,47*	39,1 ± 0,93*
Mesomorphs	-	-	44,63±1,3	42,2±1,61
Mesoectomorphs	40,8±1,64	38,1±2,11*	46,44±1,45	43,3±1,29
Ectomorphs	39,2±1,7	39,3±1,97*	44,7±1,02	45,8±1,48
Balanced	40,4±1,53	41,8±1,8	40,8±0,62*	41,6±2,13

* - the probability of a difference in indicators between different somatotypes within the same gender (p< 0.05)

by a balanced somatotype. The largest number of individuals with balanced (41.2%) and endomesomorphic (33.9%) somatotypes was registered among females from mountainous districts. At the same time, the largest number of individuals was represented by endomorphs (5.9%) among females, and by ectomorphs among males (Fig. 1 – 2).

Aerobic and anaerobic productivity of adolescents in the post-pubertal period of ontogenesis is determined by the area of residence, as well as the gender factor. The level of aerobic productivity, regardless of the area of residence, in females aged 16-20 is higher than in males aged 17-21, according to Ya.P. Pyarnat's criteria [4]. The relative value $VO_{2\ max}$ (42,9±0,58 ml·min^{-1}·kg^{-1}) in females corresponds to "excellent", which guarantees a "safe health level" according to H.L. Apanasenko [17]. At the same time, in males, the level of aerobic productivity in terms of the relative value $VO_{2\ max}$ (42,7±0,65 ml·min^{-1}·kg^{-1}) is "average", which cannot guarantee a "safe health level" according to H .L. Apanasenko. Anaerobic productivity in females is lower to that of males in terms of the relative value of alactic power, lactic power and capacity of lactic energy supply processes by 55.6%, 54.7%, and 38.7%, respectively, table I.

There are differences in physical health status in terms of the ability to demonstrate the aerobic capacity of the body in young males and females living in lowland and mountainous districts of the Zakarpattia region, depending on the ratio of fat and muscle components of the body (Fig. 3).

In females from lowland districts with normal fat content, normal and high muscle content, and a normal body mass index, the level of aerobic productivity is "excellent", according to Ya.P. Pyarnat's criteria, with the average value of the relative $VO_{2\ max}$ 40,3±1,11 ml·min^{-1}·kg^{-1}, 40,19±1,7 ml·min^{-1}·kg^{-1} and 39,8±1,73 ml·min^{-1}·kg^{-1}, respectively. The level of aerobic productivity in females from lowland districts with a high and low fat content is "good", with relative $VO_{2\ max}$ 35,02±1,58 ml·min^{-1}·kg^{-1} and 35,4±1,65 ml·min^{-1}·kg^{-1}, respectively. The "excellent" and "good" level of aerobic productivity in females from the lowland and

Table III. Average values of indicators of anaerobic productivity of the organism (M±m) in post-pubertal youth from lowland and mountainous districts of the Zakarpattia region depending on somatotype, n= 456

Indicators	Anaerobic productivity			
	power of alactic energy supply processes			
	$WAnT_{10\ rel.}$, kg-m·min^{-1}·kg^{-1}			
	Females (n=220)		Males (n=236)	
Somatotype	lowland district (n=118)	mountainous district (n=102)	lowland district (n=112)	mountainous district (n=124)
Endomorphs	37,1±0,65*	39,4±1,1	-	-
Endomesomorphs	40,25±1,23	42,3±1,36	50,3±1,18*	56,8±1,41*
Mesomorphs	-	-	63,1±1,15	67,5±1,62
Mesoectomorphs	38,5±0,81	37,8±0,84*	62,3±1,37	61,1±1,55*
Ectomorphs	37,4±0,76*	36,9±1,08*	54,8±1,17*	54,5±1,38*
Balanced	40,5±1,28	39,5±1,17	54,9±1,16*	56,6±1,47*

* - the probability of a difference in indicators between different somatotypes within the same gender ($p< 0.05$)

Table IV. Average values of indicators of anaerobic productivity of the organism (M±m) in post-pubertal youth from the lowland and mountainous districts of the Zakarpattia region, depending on the somatotype, n= 456

Indicators	Anaerobic productivity							
	the power of lactic energy supply processes				capacity of lactic energy supply processes			
	$WAnT_{30\ rel.}$, kg-m·min^{-1}·kg^{-1}				$PPO_{rel.}$, kg-m·min^{-1}·kg^{-1}			
	Females (n=220)		Males (n=236)		Females (n=220)		Males (n=236)	
Somatotype	lowland district (n=118)	mountainous district (n=102)	lowland district (n=112)	mountainous district (n=124)	lowland district (n=118)	mountainous district (n=102)	lowland district (n=112)	mountainous district (n=124)
Endomorphs	35,7±0,96*	38,3±0,91	-	-	22,9±0,73	23,4±0,7*	-	-
Endomesomorphs	39,0±1,03	40,83±1,04	50,1±1,48*	56,4±1,64*	20,9±0,59*	26,5±1,3	22,6±0,77*	26,7±0,8*
Mesomorphs	-	-	60,7±1,43	67,0±1,68	-	-	30,6±1,28	28,3±0,9
Mesoectomorphs	37,1±0,5*	35,6±0,78*	62,1±1,51	60,4±1,61*	23,9±0,9	25,2±0,98	33,6±1,43	29,0±1,01
Ectomorphs	35,4±0,72*	35,8±0,73*	53,1±1,36*	53,5±1,53*	24,7±1,08	25,2±0,87	27,3±0,81*	29,7±0,9
Balanced	39,33±0,89	37,7±0,84	55,2±1,47*	54,9±1,69*	22,7±0,68	21,6±0,61*	30,1±1,36	27,3±0,7*

* - the probability of a difference in indicators between different somatotypes within the same gender ($p< 0.05$)

mountainous districts of the Zakarpattia region guarantees a "safe health level". Females from mountainous districts with a high percentage of fat component have an "average" level of aerobic productivity, which does not provide a "safe health level" according to H.L. Apanasenko.

In males, regardless of the area of residence, an increase in the fat component has a negative effect on the body's aerobic energy supply. On the contrary, the growth of the muscle component of the body mass helps to increase the aerobic capacity of the body. Among all examined males, no individuals with "excellent" and "good" level of aerobic productivity of the body were found. Young males from lowland districts with a low fat content and very high muscle content have an "average" level of aerobic productivity, with relative $VO_{2\ max}$ 43,8±1,4 ml·min^{-1}·kg^{-1} and 42,9±1,02 ml·min^{-1}·kg^{-1}, respectively, which provides a "safe health level" according to H.L. Apanasenko. An "average" level of aerobic productivity was also found in males from mountainous districts with low fat content and high or very high muscle content, with relative $VO_{2\ max}$ 44,6±2,1 ml·min^{-1}·kg^{-1}, 42,4±2,0 ml·min^{-1}·kg^{-1} and 43,1±0,97 ml·min^{-1}·kg^{-1}, respectively, which exceeds the "safe health level". Males from lowland and mountainous districts with a high fat content with $VO_{2max\ rel.}$ 31,9±1,76 ml·min^{-1}·kg^{-1} and 33,7±0,93 ml·min^{-1}·kg^{-1}, respectively, have the lowest level of aerobic productivity that does not provide a "safe health level" according to H.L. Apanasenko, whereas males from lowland and mountainous districts with a very high content of muscle component have the highest level (Fig. 4).

Aerobic productivity of the youth of the Zakarpattia region in the post-pubertal period of ontogenesis is determined by somatotype. There are gender differences in this dependence; thus, in females whose somatotype is associated with a significant fat content, the level of aerobic productivity is "excellent". In contrast to females, males whose somatotype is characterized by an increased fat content, have reduced aerobic productivity. Aerobic productivity is higher in males whose somatotype is

associated with a significant percentage of the muscular component. Regardless of the somatotype, females from lowland and mountainous districts have an "excellent" level of aerobic productivity, which guarantees a "safe health level" according to H.L. Apanasenko. In females, regardless of the area of residence, the highest values of the relative $VO_{2\,max}$ were recorded in endomesomorphs – 41,8±1,81 ml·min^{-1}·kg^{-1} in females from lowland districts, and 45,2±1,93 ml·min^{-1}·kg^{-1} in females from mountainous districts, respectively. Endomorph females from the lowland districts ($VO_{2max\ rel.}$ 38,2±1,63 ml·min^{-1}·kg^{-1}) and mesoectomorph females from the mountainous districts ($VO_{2max\ rel.}$ 38,1±2,11 ml·min^{-1}·kg^{-1}) have the lowest aerobic productivity indicators, table II.

Among males, regardless of the area of residence, mesomorphs, mesoectomorphs and ectomorphs showed the best aerobic abilities. The average value of the relative indicator of maximum oxygen consumption in young mesomorphs from lowland and mountainous districts is 44,63±1,3 ml·min^{-1}·kg^{-1} and 42,2±1,61 ml·min^{-1}·kg^{-1}, respectively, in mesoectomorphs 46,44±1,45 ml·min^{-1}·kg^{-1} and 43,3±1,29 ml·min^{-1}·kg^{-1}, respectively, in ectomorphs 44,7±1,02 ml·min^{-1}·kg^{-1} and 45,6±1,48 ml·min^{-1}·kg^{-1}, respectively. The level of aerobic productivity of males with such somatotypes corresponds to "average", and "safe health level" according to H.L. Apanasenko. The lowest aerobic productivity according to the $VO_{2max\ rel.}$ values was found in male endomesomorphs from lowland (38,56±0,47 ml·min^{-1}·kg^{-1}) and mountainous (39,1±0,93 ml·min^{-1}·kg^{-1}) districts, which corresponds to the level "below average" according to Ya.P. Pyarnat and the level of health "below safe" according to H.L. Apanasenko.

Anaerobic productivity of the organism in youth of the Zakarpattia region in the post-pubertal period of ontogenesis is also conditioned by gender and somatotype. There are gender differences in this dependence in females whose level of anaerobic productivity is lower than in males, regardless of the area of residence. Endomesomorph females, regardless of the area of residence, show a higher level of anaerobic productivity among other somatotypes, which is confirmed by the highest values of the relative power of alactic and lactic energy supply processes $WAnT_{10,}$ $WAnT_{30}$ and PPO – 40,25±1,23 kg-m·min^{-1}·kg^{-1}, 39,0±1,03 kg-m·min^{-1}·kg^{-1} in females from lowland, and 42,3±1,36 kg-m·min^{-1}·kg^{-1}, 40,83±1,04 kg-m·min^{-1}·kg^{-1} i 26,5±1,3 kg-m·min^{-1}·kg^{-1} in females from mountainous districts, respectively. Endomorph females from the lowland districts ($WAnT_{10\ rel.}$ 37,1±0,65 kg-m·min^{-1}·kg^{-1}, $WAnT_{30\ rel.}$ 35,7±0,96 kg-m·min^{-1}·kg^{-1}) and ectomorph females from the mountainous districts ($WAnT_{10\ rel.}$ 36,9±1,08 kg-m·min^{-1}·kg^{-1}, $WAnT_{30\ rel.}$ 35,8±0,73 kg-m·min^{-1}·kg^{-1}) have the lowest anaerobic productivity, tables III – IV.

Performing physical exercises in an anaerobic mode requires energy stored in the muscles, therefore there are gender differences in this dependence in young males whose somatotype is associated with a significant percentage of the muscle component. Among males, regardless of the area of residence, the best anaerobic abilities were shown by mesomorphs and mesoectomorphs. The average value of the relative indicator of the power of alactic processes of energy supply $WAnT_{10}$ in young male mesomorphs from lowland and mountainous districts is 63,1±1,15 kg-m·min^{-1}·kg^{-1} and 67,5±1,62 kg-m·min^{-1}·kg^{-1}, respectively, in mesoectomorphs 62,3±1,37 kg-m·min^{-1}·kg^{-1} and 61,1±1,55 kg-m·min^{-1}·kg^{-1}, respectively. The average value of the relative indicator of the power of lactic processes of energy supply $WAnT_{30}$ in young male mesomorphs from lowland and mountainous districts is 60,7±1,43 kg-m·min^{-1}·kg^{-1} and 67,0±1,68 kg-m·min^{-1}·kg^{-1} , respectively, in mesoectomorphs 62,1±1,51 kg-m·min^{-1}·kg^{-1} and 60,4±1,61 kg-m·min^{-1}·kg^{-1}, respectively. The average value of the relative indicator of the capacity of lactic processes of energy supply PPO in young mesomorphs from lowland and mountainous districts is 30,6±1,28 kg-m·min^{-1}·kg^{-1} and 28,3±0,9 kg-m·min^{-1}·kg^{-1}, respectively, in mesoectomorphs 33,6±1,43 kg-m·min^{-1}·kg^{-1} and 29,0±1,01 kg-m·min^{-1}·kg^{-1}, respectively. The presence of the fat component in males is inefficient for the performance of work in the anaerobic energy mode, as evidenced by low relative indicators $WAnT_{10}$, $WAnT_{30}$, MK3P in endomesomorphs, compared to males of other somatotype groups. Thus, the lowest anaerobic productivity according to the indicator $WAnT_{10\ rel.,}$ $WAnT_{30\ rel.}$ i $MK3P_{rel.}$ was recorded in young male endomesomorphs from lowland (50,3±1,18 kg-m·min^{-1}·kg^{-1}, 50,1±1,48 kg-m·min^{-1}·kg^{-1} and 22,6±0,77 kg-m·min^{-1}·kg^{-1}) and mountainous ($PPO_{rel.}$ 26,7±0,8 kg-m·min^{-1}·kg^{-1}) districts, tables III – IV.

DISCUSSION

The absolute value Vo_{2max} is directly dependent on body weight [1, 2, 6]. In males, this dependence is manifested to a greater extent than in females [11, 12]. Moreover, the dominant value belongs to the muscle component of body mass [3]. The fat component does not affect the absolute value $Vo_{2\,max}$ [2]. However, an increase in body weight due to the fat component negatively affects the relative Vo_{2max} value [2, 3, 9].

Aerobic productivity is determined by age and gender factors. There is contradictory information about the dynamics of age-related changes in absolute and relative Vo_{2max} value.

Some researchers indicate an increase in the absolute Vo_{2max} up to age 25, stabilization from age 25 to age 33, and a gradual decline after age 38 [5]. There is evidence that absolute Vo_{2max} value increases before full puberty [18]. The largest increase in this indicator is observed at 13-14 years of age in males (by 28%) and at 12-13 years of age in females. However, from the age of 16 in males and from 14 in females, the increase in $Vo_{2max\ abs.}$ is not observed [1]. Moreover, it is slightly lower in females than in males, and is 90.2% in males at 12-15 years of age, 82.5% at 16-20 years of age, and 82.1% at 21-24 years of age. [1, 7].

As for age-related changes in the relative Vo_{2max} value, some authors note its constancy, while others note its decrease. Concerning the age dynamics of $Vo_{2max\ rel.}$ Yu. Furman and S. Drachuk [4, 5] indicate its stability up to

17 years, whereas J. Astrand et al. [18] up to 35-40 years. W. Larry Kenney [8] claim that the relative value of Vo_{2max} practically does not change from 6 to 25 years and is on average 50 $ml \times min^{-1} \times kg^{-1}$. If we accept that Vo2 max is 100% at the age of 20-30, it will be 82.5% at 40-50 years of age, and 65% at 60-70 years of age according to V. Miroshnichenko [6]. A similar age-related decrease in the relative Vo_{2max} value is assumed according to Ya.P. Pyarnat's [4] and L. Astrand's [18] assessment criteria. Research results of O.O. Bekas [1] indicate a significant decrease in the Vo_{2max} value starting from the age of 16, both in males and females, whose body weight does not exceed the norm. Moreover, in the period from 16 to 20 years of age, there are no gender differences in the average $Vo_{2\ max\ rel.}$ value.

The data on the age-related dynamics of the body's anaerobic productivity are contradictory. There are data that indicate the growth of anaerobic alactic and lactic productivity up to 18 years and its stability up to 30 years. In persons younger than 18 and older than 30 years, anaerobic productivity decreases on average by 1-2% per year [19, 20]. A uniform age-related decrease in anaerobic productivity is indicated by Pałka MJ et al. [19]. According to their data, such a decrease reaches approximately 6% per decade. Moreover, the dynamics of the decrease does not depend on gender [13]. According to other authors, in adolescents aged 10-14, the value of anaerobic lactic productivity, which was determined by the relative indicator of external mechanical work in 30 seconds, does not differ from that of adults. At the same time, no significant gender difference of this indicator was found [19, 20]. However, the results of a research by S.A. Gaul et al. [10] demonstrate that the lactic and alactic productivity of children before the end of puberty is significantly lower than in adults.

The study of somatotypological characteristics has not only theoretical, but also practical significance, therefore it was studied by many researchers [2, 3, 6, 11, 12]. Thus, some studies highlight a strong correlation between dysplasia of connective tissue in patients with atopic dermatitis with the somatotype [23], as well as the dependence of the course of insulin-dependent diabetes upon anthropometric indicators and somatotype [22]. In addition, there are studies on somatotypological features of males with psoriasis [23], features of the course of schizophrenia [21]. There are also studies that characteristics features of the muscular system of boys and girls of different ages and somatotypes [9, 10]. Anthropometry is widely used to restore standards and indices for assessing the health of the younger generation [14, 15, 16]. Thus, it was widely used in the 18th century to assess the suitability of recruits for military service and it continues to be actively used to this day.

CONCLUSIONS

In females from lowland districts with normal fat content, normal and high muscle content, and a normal body mass index, the level of aerobic productivity is "excellent" according Ya.P. Pyarnat's criteria. Females from mountainous districts with high percentage of fat component have an "average" level of aerobic productivity, which does not provide a "safe health level" according to H.L. Apanasenko. Among all examined males, no individuals with "excellent" and "good" level of aerobic productivity of the body were found. In males, regardless of the area of residence, the increase in the fat component has a negative effect on the aerobic and anaerobic energy supply of the body. On the contrary, the growth of the muscle component of body mass helps to increase the aerobic and anaerobic capacity of the body.

The determined values of aerobic and anaerobic productivity of the body's energy supply in healthy young males and females make it possible to further develop an individual and population health forecast, to form groups of increased risk of pathology and to implement a program of medical and social rehabilitation.

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ORIGINAL ARTICLE

RECIPROCAL CLICKING LOCATION ANALYSIS IN THE INTRAARTICULAR TEMPOROMANDIBULAR DISORDERS AFTER AXIOGRAPHY INVESTIGATION

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ABSTRACT

The aim: To investigate the peculiarities of hinge axis trajectories in patients with condyle-disc complex intraarticular Temporomandibular Disorders (TMD) and determine the average coordinates of the reciprocal clicking location by axiography.

Materials and methods: The results of axiographic examination of 151 patients (108 females and 43 males) with TMD confirmed by MRI were analyzed. This population included 44 persons with disc displacement with reduction (DDR), 45 persons with disc displacement with reduction and intermittent locking (DDRI), 62 persons with disc displacement without reduction (DDWR). Axiographic examination was carried out using CADIAX diagnostic device. Analysis of hinge axis movements was performed and the coordinates of articular disc reduction were determined.

Results: The quality of hinge axis trajectories in persons with DDR, DDRI was defined mainly as average and in patients with DDWR as poor. Quantitative indicators of trajectories during protrusion-retrusion movements were not beyond the average level. The length of the mouth opening-closing trajectory in patients with DDRI and DDWR has shown a tendency to decrease. We found that on average the reciprocal closing clicking (disc reduction) occurs at a distance of 0-1.4 mm on the X-axis, 0.1-2.9 mm on the Z-axis, and 0-0.85 mm on the Y-axis.

Conclusions: The obtained wide range of reciprocal clicking location parameters indicates the priority of a personalized approach when planning preliminary treatment in order to restore the disc-condylar complex of TMJ.

KEY WORDS: disc displacement, condylar position, axiography, intracapsular derangement

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INTRODUCTION

One of the most important and difficult approaches in the noninvasive treatment of TMD is the correction of articular disc position. In the pathogenesis of disc displacement, the main factors are adjacent structures influencing the changes in morphology and function of the retrodiscal zone and articular disc. Disorders of the disc-condylar complex are characterized by a number of symptoms, including clicking, popping, or crunching in the temporo-mandibular joint (TMJ), deviation, and deflection during opening and closing movements of the mandible. Limited mouth opening and pain symptoms in TMJ can be an indicator of some intra-articular pathology [1, 2].

Magnetic resonance imaging is usually used to confirm the presence and type of intra-articular disorders [3]. Axiographic examination of mandibular movement trajectories is useful in determining muscle discoordination, asymmetry of mandibular movements, hyper- and hypomobility of condyles and helps to assess the mechanisms of circumvention of occlusal obstructions and clarify the type of pathology of the disc-condylar complex. In comparison to other methods of TMJ functional examination, the axiography has some advantages: it's a non-invasive procedure, and it doesn't use any factors of pathological influence like radiation. The obtained results allow us to determine the functional state of the TMJ in real-time, use the data for analysis in various computer programs, and for adjusting the articulators to an individual function according to recorded parameters of jaw movements. The obtained data analysis significantly improves the differential diagnosis of both intra-articular and extra-articular disorders of TMJ based on the analysis of static and dynamic indicators of the trajectories of the mandible movements [4-6]. The high level of sensitivity and specificity of axiographic examination has been proved by several scientific studies and its capabilities can be compared with MRI, which is currently the main method for detecting morphological changes in the TMJ [7].

The recovery of the disc-condylar complex can be achieved by using repositioning and distraction occlusal splints [8, 9]. Thanks to the coordinates obtained by axiographic examination, the therapeutic position of

the mandible can be established while maintaining the disc-condylar interrelations on the custom-made splint, keeping the mandible in the therapeutic position, and preventing displacement of the articular disc [10].

The significant prevalence of intra-articular disorders of TMJ forms a need to determine the average values of reciprocal clicking coordinates in order to increase the efficiency of distraction and repositioning occlusal splints that confirm the relevance of this study.

THE AIM

The aim of the study was to investigate the peculiarities of hinge axis trajectories in patients with condyle-disc complex intraarticular TMD and determine the average coordinates of the reciprocal clicking location by axiography.

MATERIALS AND METHODS

The retrospective study was conducted at the Dental Medical Center of Bogomolets National Medical University and covered the period from 2016 to 2020. The case histories of 573 patients (389 females and 182 males) who complained of pain in the TMJ, clicking, crunching in the TMJ, and limited mouth opening were analyzed. Considering the purpose of the study, the case histories and results of axiographic examination of 151 (108 females and 43 males; mean age 38.7±12.9 years) patients with condyle-disc complex intraarticular TMD confirmed by MRI were selected for further analysis.

The study excluded people with no signs of pathological changes in the TMJ, with signs of inflammation in the TMJ, patients with complete teeth loss, patients during splint therapy, psychologically unstable patients, patients during treatment of somatic pathology, and patients who underwent the specific treatment of TMD.

The selected population was divided into three groups according to The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) [2]. The first group (n=44) included patients with disc displacement with reduction (DDR). The second group (n=45) included patients with disc displacement with reduction and intermittent locking (DDRI). The third group (n=62) included patients with disc displacement without reduction (DDWR). The third group included individuals with and without limitation of mandibular movements due to certain problems of differentiating these conditions in a retrospective context.

Axiographic examination was carried out using CADIAX diagnostic device and GAMMA Dental Software Version 7.7.14 (GAMMA Medizinisch-wissenschaftliche Fortbildungs-GmbH, Austria). Analysis of hinge axis movements during symmetrical mandibular movements (opening-closing and protrusion-retrusion) was performed in three-dimensional space in the sagittal, transversal and cranial planes. The trajectories were analyzed from top to bottom in sagittal (x-z), frontal (y-z), and cranial (x-y) planes. Also, the coordinates of articular disc reduction were determined.

Statistical analysis of the results was performed by EZR v. 1.54 package (graphical user interface for R statistical software version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) [11]. For quantitative indicators in the case of normal distribution, the mean value of the indicator ± standard deviation (SD) was calculated, in the case of a distribution other than normal the median value of the indicator and the interquartile range (IQR) were calculated. The distribution was checked for normality by the Shapiro-Wilk test. The critical value for statistical hypotheses testing was taken at $p<0.05$.

The study was approved by the Bioethics Commission of Bogomolets National Medical University. All participants have signed informed consent for diagnostic and therapeutic procedures as well as for observation in accordance with the World Medical Association Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects.

RESULTS

The analysis of hinge axis movement trajectories in the first group has determined that 36 patients (81.8%) had the intersections of trajectories during opening-closing and protrusion-retrusion movements, which are signs of bilateral displacement of the articular disc with reposition. In 8 patients (18.1%) the intersections of the trajectories were found unilaterally. Lateral translation during symmetrical mandibular movements was determined mainly in unilateral DDR. The average value of the trajectory length (Quantity) in patients with DDR was 12.9$\pm$1.6 mm during opening-closing movements and 10.3$\pm$1.7 mm during protrusion-retrusion movements. The Quality of trajectories values in most cases was average, in some patients with unilateral DDR a combination of poor and average values was observed. The shapes of the trajectories were variable with changing characteristics from convex to concave and with the intersection of lines. Hinge axis movement trajectories showed strong sagittal and transversal asymmetry in volume and direction of displacement during all symmetrical mandibular movements with different degrees of manifestations. The disc reduction clicking at the beginning of mouth opening and the reciprocal clicking at the end of mouth closing differed in amplitude and coordinates of the formation (Fig. 1).

Concerning the peculiarities of distribution in the population with DDR, the average indicators of the statistical analysis were presented by Me and IQR (Q_I-Q_{III}). During retrusion, according to the "X" axis, the displacement was 0.5 mm on the right and 0.7 mm on the left with IQR (Q_I-Q_{III}) 0.0-1.25 mm in right TMJ and 0.05-1.3 mm in left TMJ without statistically significant difference ($p>0.05$) in parameters of trajectories of hinge axis movements of the condyles outside the disc at the stage of jaws closing. During retrusion in the "Z" direction, Me was 1.45 mm on the right and 1.4 mm on the left with IQR (Q_I-Q_{III}) 0.0-2.0 mm on the right and 0.0-1.9 mm on the left without statistically significant difference ($p> 0.05$) between the

Table I. Comparative analysis of hinge axis movements parameters of TMJ condyles at the level of reciprocal clicking in patients with DDR according to the results of axiography (mm, Me (Q_I – Q_{III}))

Parameter	Right TMJ (n=44)	Left TMJ (n=44)	Level of significance of the difference, p
Retrusion (X)	0.5 (0.0-1.25)	0.7 (0.05-1.3)	0.2
Retrusion (Z)	1.45 (0.0-2.0)	1.4 (0.0-1.9)	0.441
Retrusion (Y)	0.35 (0.0-0.8)	0.25 (0.0-0.8)	0.381
Closing (X)	1.0 (0.6-1.4)	1.0 (0.25-1.4)	0.456
Closing (Z)	1.8 (1.2-2.9)	1.9 (1.0-2.4)	0.456
Closing (Y)	0.45 (0.2-0.85)	0.4 (0.0-0.7)	**0.016**

Note:
1. T-Wilcoxon criterion for related samples was used for comparison.
2. The directions of movements of the hinge axis are presented in coordinate system: "X" – forward-backward direction; "Z" – top-bottom direction; "Y" – left-right direction.

Table II. Comparative analysis of hinge axis movements parameters of TMJ condyles at the level of reciprocal clicking in patients with DDRI according to the results of axiography (mm, Me (QI – QIII))

Parameter	Right TMJ (n=45)	Left TMJ (n=45)	Level of significance of the difference, p
Retrusion (X)	0.7 (0.0-1.025)	0.7 (0,175-1.325)	0.295
Retrusion (Z)	1.0 (0.0-1.7)	1.2 (0,275-2,0)	0.555
Retrusion (Y)	0.3 (0.0-0.675)	0.3 (0.075-0.625)	0.939
Closing (X)	0.8 (0.3-1.3)	0.9 (0.2-1.425)	0.341
Closing (Z)	1.5 (0.925-2.275)	1.5 (1.0-2.4)	0.414
Closing (Y)	0.35 (0.15-0.65)	0.4 (0.075-0.825)	0.846

Note:
1. T-Wilcoxon criterion for related samples was used for comparison.
2. The directions of movements of the hinge axis are presented in coordinate system: "X" – forward-backward direction; "Z" – top-bottom direction; "Y" – left-right direction.

Table III. Comparative analysis of hinge axis movements parameters of TMJ condyles at the level of reciprocal clicking in patients with DDWR according to the results of axiography (mm, Me (QI – QIII))

Parameter	Right TMJ (n=62)	Left TMJ (n=62)	Level of significance of the difference, p
Retrusion (X)	0.25 (0.0-0.9)	0.15 (0.0-0.6)	0.695
Retrusion (Z)	0.8 (0.0-1.725)	0.35 (0.0-1.4)	0.823
Retrusion (Y)	0.05 (0.0-0.6)	0.0 (0.0-0.6)	0.27
Closing (X)	0.74 (0.2-1.4)	0.85 (0.1-1.5)	0.711
Closing (Z)	1.75 (1.0-2.5)	1.95 (0.66-2.8)	0.573
Closing (Y)	0.45 (0.2-0.8)	0.4 (0.1-0.6)	**0.037**

Note:
1. T-Wilcoxon criterion for related samples was used for comparison.
2. The directions of movements of the hinge axis are presented in coordinate system: "X" – forward-backward direction; "Z" – top-bottom direction; "Y" – left-right direction.

parameters in right and left TMJ. In the "Y" direction Me was 0.35 mm on the right and 0.25 mm on the left with IQR (Q_I-Q_{III}) 0.0-0.8 mm on the right and left without a statistically significant difference (p>0.05) between the parameters.

At the end of the mouth closing in the "X" direction Me was 1.0 mm on the right and left with IQR (Q_I-Q_{III}) 0.6-1.4 mm on the right and 0.250-1.4 mm on the left without statistically significant difference (p>0.05) between the parameters. In the "Z" direction Me was 1.8 mm on the right and 1.9 mm on the left with IQR (Q_I-Q_{III}) 1.2-2.9 mm on the right and 1.0-2.4 mm on the left without statistically significant difference (p>0.05) between the parameters. In the "Y" direction Me was 0.45 mm on the right and 0.4 mm on the left with IQR (Q_I-Q_{III}) 0.2-0.85 mm on the right and 0.0-0.7 mm on the left with statistically significant

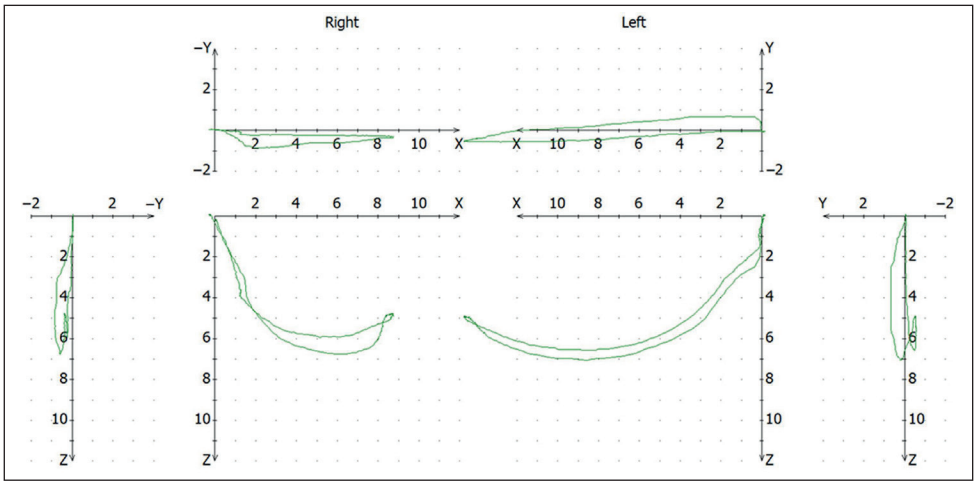

Fig. 1. Hinge axis movement trajectories at the axiogram of patient with DDR

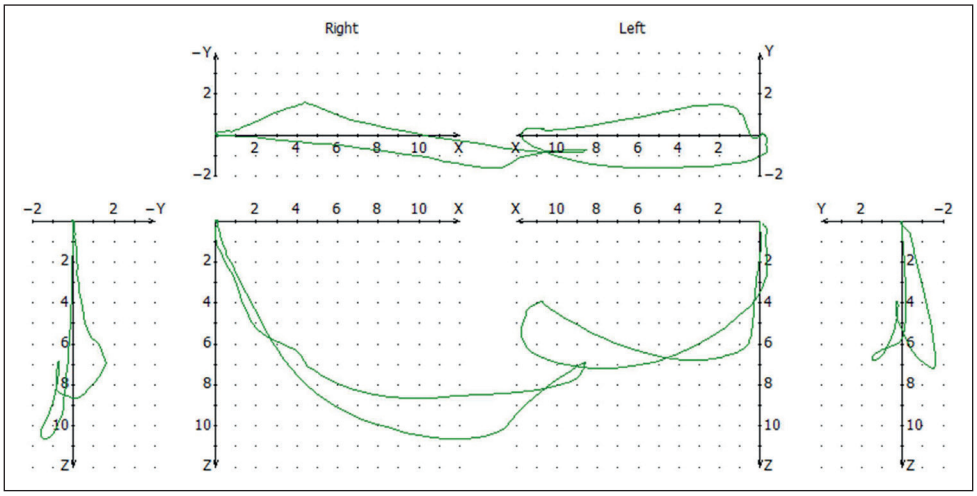

Fig. 2. Hinge axis movement trajectories at the axiogram of patient with DDRI

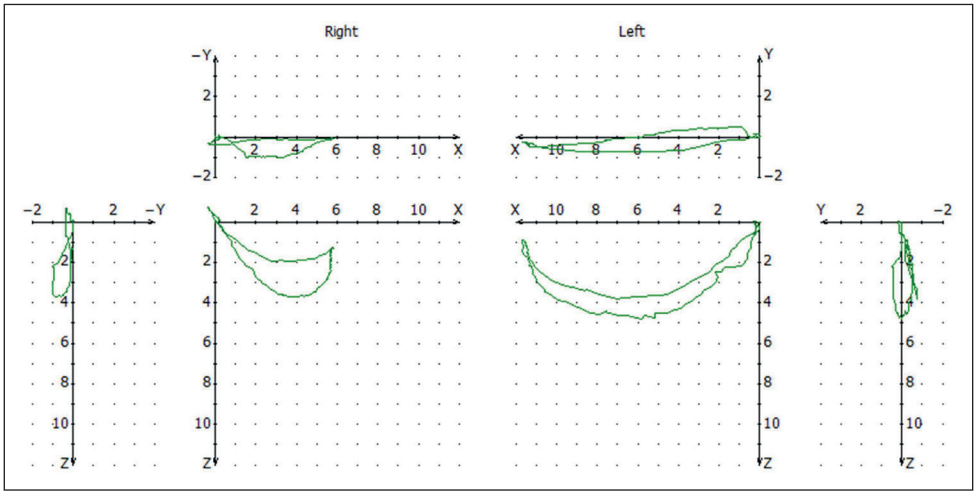

Fig. 3. Hinge axis movement trajectories at the axiogram of the patient with DDWR

(p=0.016) difference between ranges of movements on the right and left sides (Table I).

The main peculiarities of DDRI are intermittent limitations of condyles movements in TMJ during mouth opening and closing. The analysis of hinge axis displacement during mouth opening-closing and protrusion-retrusion movements has shown bilaterally asynchronous and asymmetric trajectories with different lengths and angulations in 45 patients with DDRI. The average length of the trajectory (Quantity) was 9.5±1.2 mm during mouth opening-closing and 10.1±1.3 mm during protrusion-retrusion movements. The signs of DDRI were detected unilaterally with pronounced changes in hinge axis trajectories of the opposite joint and lateral translation during symmetrical mandibular movements in 17 (37.8%) patients. In 28 (62.2%) patients with bilateral DDRI, hinge axis movement was accompanied by asymmetric intersections of traces during mouth opening-closing and protrusion-retrusion movements of the jaw, its shapes varied from convex to concave. The quality of trajectories was average, the dis-

placements and intersections of the trajectories during clicking on the left and right were formed asynchronously in time. The reciprocal clicks at the end of mouth closing differed in amplitude and coordinates of formation (Fig. 2).

Concerning the peculiarities of distribution in the population with DDRI, the average indicators of the statistical analysis were presented by Me and IQR (Q_I-Q_{III}). During retrusion, according to the "X" axis, the displacement was 0.7 mm on the right and left with IQR (Q_I-Q_{III}) 0.0-1.025 mm in right TMJ and 0.175-1.325 mm in left TMJ without statistically significant difference (p>0.05) between the parameters of right and left TMJ. During retrusion in the "Z" direction Me was 1.0 mm on the right and 1.2 mm on the left with IQR (Q_I-Q_{III}) 0.0-1.7 mm on the right and 0.275-2.0 mm on the left without statistically significant difference (p> 0.05) between the parameters. In the "Y" direction Me was 0.3 mm on the right and left with IQR (Q_I-Q_{III}) 0.0-0.675 mm on the right and 0.075-0.625 mm on the left mm without a statistically significant difference (p> 0.05) between the parameters.

At the end of the mouth closing in the "X" direction Me was 0.8 mm on the right and 0.9 mm on the left with IQR (Q_I-Q_{III}) 0.3-1.3 mm on the right and 0.2-1.425 mm on the left without statistically significant difference (p>0.05) between the parameters. In the "Z" direction Me was 1.5 mm on the right and left with IQR (Q_I-Q_{III}) 0.925-2.275 mm on the right and 1.0-2.4 mm on the left without a statistically significant difference (p>0.05) between the parameters. In the "Y" direction Me was 0.35 mm on the right and 0.4 mm on the left with IQR (Q_I-Q_{III}) 0.15-0.65 mm on the right and 0.075-0.825 mm on the left without statistically significant difference (p>0.05) between the parameters (Table II).

The analysis of hinge axis movements trajectories in the group with DDWR has shown a reduction of movement trajectories parameters in 42 (67.7%) patients. The typical trajectories of hinge axis movements were found in 30 (48.4%) patients bilaterally and in 32 (51.6%) patients unilaterally. Qualitative characteristics of hinge axis trajectories were evaluated as poor. In all cases, an asymmetry, intersections of trajectories in the vertical, sagittal, and transversal directions were observed, as well as no coincidence of the lines and extreme differences between the right and left sides during mouth opening-closing were found. The average length of the trajectory (Quantity) was 9.8±11.6 mm during mouth opening-closing and 9.3±1.4 mm during protrusion-retrusion movements of the jaw (Fig. 3).

Concerning the peculiarities of distribution in the population with DDWR, the average indicators of the statistical analysis were presented by Me and IQR (Q_I-Q_{III}). During retrusion, according to the "X" axis, the displacement was 0.25 mm on the right and 0.15 mm on the left with IQR (Q_I-Q_{III}) 0.0-0.9 mm in right TMJ and 0.0-0.6 mm in left TMJ without statistically significant difference (p>0.05) in parameters of trajectories of hinge axis movements. During retrusion in the "Z" direction Me was 0.8 mm on the right and 0.35 mm on the left with IQR (Q_I-Q_{III}) 0.0-1.725 mm on the right and 0.0-1.4 mm on the left without statistically significant difference (p> 0.05) between the parameters in right and left TMJ. In the "Y" direction Me was 0.05 mm on the right and 0.0 mm on the left with IQR (Q_I-Q_{III}) 0.0-0.6 mm on the right and left without statistically significant difference (p>0.05) between the parameters.

At the end of the mouth closing in the "X" direction Me was 0.74 mm on the right and 0.85 mm on the left with IQR (Q_I-Q_{III}) 0.2-1.4 mm on the right and 0.1-1.5 mm on the left without statistically significant difference (p>0.05) between the parameters. In the "Z" direction Me was 1.75 mm on the right and 1.95 mm on the left with IQR (Q_I-Q_{III}) 1.0-2.5 mm on the right and 0.66-2.8 mm on the left without statistically significant difference (p>0.05) between the parameters. In the "Y" direction Me was 0.45 mm on the right and 0.4 mm on the left with IQR (Q_I-Q_{III}) 0.2-0.8 mm on the right and 0.1-0.6 mm on the left with statistically significant (p=0.037) difference between ranges of movements on the right and left sides (Table III).

DISCUSSION

Qualitative assessment of hinge axis trajectories in the study in patients with DDR and DDRI has shown mainly average and in some cases poor values. Various deviations and intersections of lines were observed along the entire path of hinge axis movements. The number of deviations and intersections was determined from one to four. Such results may emphasize the changes in disc-condyles complex of TMJ. Qualitative characteristics of patients with DDWR were defined as poor.

The study included more female patients than male and bilateral manifestations of TMJ disorders were observed in $^4/_5$ of the first group, $^2/_3$ of the second group and ½ of the third group. The obtained data confirm the typical for women bilateral manifestations of TMJ pathology revealed in previous studies [12]. However, possibility to determine certain peculiarities of hinge axis trajectories is an advantage of axiography during early preventive and treatment procedures [13].

In the majority of patients (81.8%) we identified the signs of bilateral DDR with strong sagittal and transversal asymmetry in volume and direction of displacement during symmetrical movements of the mandible and varying degrees of manifestation. In contrast, the prevalence of unilateral manifestations in patients with DDRI was 37.8% compared to 18.2% in patients with DDR. Also, the disc reduction clicking and reciprocal clicking differed significantly in the coordinates of formation.

The signs of asymmetry during symmetrical movements of the mandible has been widely discussed in the literature. And as it has been already proven it can be observed in a significant amount even if the person has no TMJ pathology [13]. According to our observations, asymmetric trajectories can be formed due to both morphological peculiarities and translations in the sagittal, transversal, and vertical directions in patients with the condyle-disc complex intraarticular TMD. In our study, the transversal

asymmetry and, especially, its initial component (lateral translation) during symmetrical mandibular movements prevailed in patients with unilateral DDR and DDRI. Sadao Sato et al. suggested that the lateral translation of the condyle occurs in the lower joint when the lower joint is loosened with disk displacement, and the analysis of condylar tracking is probably useful for the early detection of dysfunction [14].

Quantitative parameters of trajectories during protrusion-retrusion movement in all study groups were within the average level. The length of the mouth opening-closing trajectories in patients with DDRI and DDWR has shown a tendency to decrease, which can be the result of condyle movement blocking. The possibility to determine the peculiarities of condyle movement trajectories confirms the benefit of axiography for the diagnostics of certain types of TMJ pathology [5].

Intra-articular disorders DDR and DDRI, which are characterized by certain clinical symptoms and morphological changes, have been described by numerous MRI studies [4]. When the jaws are closed, the disc occurs in an altered position, in most cases being displaced forward and medially. During the mouth opening movement, as well as during protrusion and mediatrusion, the restoration of normal disc-condyle interrelation occurs. DDWR clinically manifests itself by limitation of jaw movement, often without any noise. But among typical manifestations, there are always some changes in jaw movement trajectories during mouth opening-closing, protrusion, and mediotrusion which can be assessed by axiography. According to the recommendations of several authors, the therapeutic position of the mandible should be achieved before reaching the closing clicking and then fixed by occlusal splint [15]. Common pivoting splints for the distraction of the TMJ condyles are made with flat stops in the area of upper second molars which have 5 mm in diameter with a height of 1.5 mm [16, 17].

The analysis of obtained parameters of reciprocal clicking during symmetrical movements of the mandible (retrusion, mouth closing) shows that Me of reciprocal clicking coordinates are not significantly different in all groups of patients. There were no statistically significant differences between the movements in right and left TMJs, except for the transversal shift in "Y" direction in the first and third groups. With some limitations, it can be suggested that the average coordinate of reciprocal clicking in the "Z" direction is slightly increased during mouth closing movements in all groups of patients in the range from 1 to 2 mm. In the "X" direction during mouth closing movements the average displacement of the hinge axis was determined within 1 mm. Considering the IQR values in majority of all patients the average reciprocal closing click occurs at the distance of 0-1.4 mm on the "X"-axis, 0.1-2.9 mm on the "Z"-axis and 0-0.85 mm on the "Y"-axis. The determined values of reciprocal clicking coordinates significantly differ from the recommended average distraction parameters, which are used in the pivoting splints for condyle distraction. In his recommendations for the pretreatment of patients with TMJ disorders, Meyer suggested the use of individual parameters recorded by axiography as the best option for the formation of personalized approach in the rehabilitation of such patients [10]. At the same time, considering our average reciprocal clicking coordinates, it is possible to improve the characteristics of distraction splints and increase the efficiency of preliminary treatment of disc pathology.

CONCLUSIONS

The study of peculiarities of hinge axis trajectories in patients with disc-condylar disorders has shown qualitative and quantitative changes. The obtained wide range of reciprocal clicking location parameters indicates the priority of a personalized approach in planning the parameters of distraction occlusal splints. Common in the recommendations average parameters of distraction need to be revised in order to establish the optimal therapeutic position of the mandible considering the displacements in the vertical, sagittal, and transversal directions. Further research is required.

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ORIGINAL ARTICLE

HORMONAL STATUS OF PATIENTS WITH A PREDICTED WEAK RESPONSE OF THE OVARIES TO GONADOTROPIN STIMULATION

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ABSTRACT

The aim: To assess the hormonal status of patients with weak ovarian response to stimulation with various gonadotropins.

Materials and methods: The hormonal examination recommended before infertility treatment with the use of assisted reproductive techniques consisted of determining basal serum concentrations of FSH, LH, estradiol (E2), AMH, thyroid hormone, prolactin on day 3 to 5 of the spontaneous menstrual cycle. The study was carried out by radioimmune and enzyme immunoassay methods. The concentration of serum STH and growth factors, such as IGF-I and IGFBP-3, was measured on day 2 to 3 of the spontaneous menstrual cycle and on the day of transvaginal puncture of follicles (TPV).

Results: During hormonal examination, signs of restricted ovarian reserve associated with a basal FSH increase to 10-15 IU were detected in 61 patients (43.6%). Signs of ovarian reserve reduction associated with a decrease in AMH to values less than 1 ng/ml were found in 110 women (78.5%). The STH concentration in and serum on the day of TPO in the main group was significantly higher than that in the comparison group, while the IGF BP-3 concentration in the main group was significantly lower than that in the comparison group.

Conclusions: In patients in the main group, stimulation of superovulation with urinary gonadotropins leads to an increase in serum STH concentration, a decrease in IGFBP-activity on the day of TPO compared to day 2 to 3 of menstrual cycle, while in patients in the second group, the concentration of these indicators remains unchanged.

KEY WORDS: assisted reproductive technologies, controlled ovarian stimulation, urinary and recombinant gonadotropins, hormonal status

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INTRODUCTION

Currently, to predict the ovarian response in IVF programs, it is advisable to use indicators such as the basal FSH concentration, the level of anti-Müllerian hormone (AMH) in the blood serum, as well as the number of antral follicles in the ovaries according to ultrasound) [1-3].

The optimal ovarian response depends on the molecular structure of FSH and its receptors, as well as the factors involved in their interaction [4]. The specificity of FSH as a predictor of a "weak" ovarian response to gonadotropic stimulation reaches 83 – 100%, while the sensitivity of this parameter is 10 – 80% and decreases with increasing FSH control points [5]. According to a number of authors, there is a strong variability in serum FSH levels in different menstrual cycles. According to modern concepts, high levels of FSH in women under the age of 40 cannot be used as the only marker for predicting a "weak" response of the ovaries to gonadotropic stimulation and the onset of clinical pregnancy in IVF programs [6, 7]. FSH molecular structure and FSH receptor polymorphism can lead to the development of the phenomenon of resistant ovaries and plays a fundamental role in determining the ovarian response to stimulation [1-3].

Adequate folliculogenesis and steroidogenesis are dependent on luteinizing hormone (LH) levels and are essential for successful fertilization and implantation. For optimal follicle growth and oocyte maturation, LH values are unknown [8, 9]. Adequate steroidogenesis occurs when less than 1% of follicular LH receptors are recruited, so the basal LH level should be sufficient to ensure maximum stimulation of the theca cells [10, 11].

Serum AMH concentration is associated with age, FSH level and follicular pool size [11-16]. In addition, the level of AMH most reflects the number of antral follicles in the ovaries, compared with other known hormonal markers of ovarian reserve [1, 3, 17]. As a predictor of insufficient ovarian response in IVF programs, an AMH value of less than 1 ng / ml has a high sensitivity and specificity [1]. It should be noted that the concentration of AMG in the blood serum is an informative predictor of the number, but not the quality of oocytes. A number of researchers suggest considering the AMH level as a marker of the possibility of obtaining oocytes in DRT programs and live births [18-22]. Therefore, the study of hormonal status in ART programs is appropriate and relevant.

THE AIM

To assess the hormonal status of patients with weak ovarian response to stimulation with various gonadotropins.

Table I. Hormonal status of examined patients (M±m)

Indicator	Study groups		p
	I n=75	II n=65	
FSH, IU / l	11,5±2,4	6,5±2,6	0,0001
LH, IU / l	4,9±2,1	5,2±2,7	0,9618
AMG, ng / ml	0,71 ±0,1	0,85±0,1	0,0001
Estradiol, pg / ml	174,1±104,1	178,1±91,4	0,4736
Prolactin, mME / ml	336,9±147,8	352,5±166,6	0,4455
TSH ME / l	1,9±0,8	1,7±0,9	0,9903

Note: p> 0.05 - significance of differences between groups I and II

MATHERIALS AND METHODS

The materials for this study were clinical and laboratory data obtained from a survey of patients treated at the Ukrainian State Institute of Reproductology of the National University of Health of Ukraine named after P.L. Shupyk, for the period from 2018 to 2021. According to the purpose of the study We selected 140 women with infertility of various origins who met the inclusion criteria and signed a voluntary informed consent to participate in the study. Prognostic analysis of "weak" ovarian response to gonadotropin stimulation was performed based on the Bologna criteria [12] under two of the following conditions: – two episodes of "weak" ovarian response to superovulation stimulation in previous IVF protocols; – the presence of a history of one cycle of superovulation stimulation with a "weak" ovarian response, as evidenced by the fact that in previous IVF programs received 3 oocyte-cumulus complexes (without assessing oocyte maturity) at a daily dose of recombinant FSH at least 150 IU; – risk of "weak" response to stimulation of superovulation (shortening of the menstrual cycle, endometrioid cysts of the ovaries, history of ovarian surgery); – the concentration of AMG in the serum less than 0.5 – 1.0 ng / ml regardless of the day of the menstrual cycle and / or the presence in both ovaries less than 5 – 7 antral follicles with a diameter of less than 10 mm on 2 – 3 days of spontaneous menstrual cycle.

Depending on hormone therapy in IVF (ICF / ICSI) in a subsequent study, 140 patients with a predicted "weak response" were divided into the following groups: Group I – 75 women aged 25-42 years, controlled stimulation of superovulation, in which urinary gonadotropins, group II – 65 women aged 25-42 years, controlled stimulation of superovulation (CSSO) in which was performed with recombinant gonadotropins,

The hormonal examination recommended before infertility treatment with the use of assisted reproductive technology consisted of determining basal serum concentrations of FSH, LH, estradiol (E2), AMH, thyrotropic hormone, prolactin on day 3 to 5 of the spontaneous menstrual cycle. The study was conducted by radioimmune and enzyme immunoassay methods.

Serum concentrations of hGH and growth factors, such as IGF-I and IGFBP-3, were measured on day 2 to 3 of the spontaneous menstrual cycle and on the day of transvaginal puncture of follicles (TPV) in 16 first-group women and 14 first-group patients. The level of hGH, IGF-I, IGFBP-3 was determined by enzyme immunoassay (hGH, IGF-I, IGFBP-3 ELISA, Mediagnost (Germany)), which was performed in the medical laboratory of Dila in Kiev. The results were calculated using methods accepted by medical and biological statistics and the classical Kolmogorov-Smirnov criteria, as specified by Glantz [23, 24]. Data were processed using the Stat Soft Statistica 8.0 software package.

RESULTS

The results of hormonal examination of women with predicted poor ovarian response to stimulation in DRT programmes showed that basal gonadotropin levels, serum estradiol and prolactin concentrations on days 3 to 5 of the spontaneous menstrual cycle were within the reference values. AMH levels demonstrated a decrease in ovarian reserve in this category of patients, with a serum concentration of 0.71±0.1 ng/ml and 0.85±0.1 ng/ml (Table I).

The analysis of the initial hormonal status revealed a tendency for the serum FSH concentration to increase on the 3rd to 5th day of the spontaneous menstrual cycle in the patients of the main group. The level of FSH in the main group was found to be significantly higher compared to the comparison group.

The examination revealed that there were no significant differences in the estimation of AMH levels between the main group and the comparison group. Although the established intergroup differences were statistically insignificant, extremely low ovarian reserve values were detected in the women of the main group. This fact suggested that the use of another criterion of non-parametric statistical methods would establish the reliability of differences. Using the Kolmogorov-Smirnov test [30], we found that the serum AMH concentration on days 3 to 5 of the menstrual cycle was significantly lower in the study group compared to comparison group I (p<0.001). During hormonal examination, signs of restricted ovarian reserve associated with a basal FSH increase to 10-15 IU were detected in 61 patients (43.6%) (Table II). Signs of ovarian reserve reduction associated with a decrease in AMH to less than 1 ng/ml were found in 110 women (78, %).

The laboratory examination of women with a predicted poor ovarian response to stimulation in IVF programmes

Table II. Hormonal markers of ovarian reserve decrease (abs.h., %)

Hormonal markers	Number of patients	
	abs.	%
Basal FSH (10-15 IU / l)	61	43,6
AMG < 1 ng / mL	110	78,5

Table III. Concentration of hormonal and growth factors in the examined women (M±m)

Indicator	Study groups		p
	I n=16	II n=14	
1 day CSR			
STG ng / ml	1,78±0,4	2,11 ±0,4	0,115
IGF-I ng / ml	139,76±78,1	141,31 ±82,1	0,056
IGFBP-3 ng / mL	3689,8±1361,2	2407,8±1322,4	0,849
TVP Day			
STG ng / ml	3,78 ±0,6	2,71 ±0,6	0,022
IGF-I ng / ml	164,68 ±98,1	144,67 ±96,1	0,008
IGFBP-3 ng / mL	2198,6±1221,1	2740,4±1347,2	0,057

Note: p> 0.05 - significance of differences between groups I and II

revealed serum concentrations of STH, IGF-I and IGFBP-3 on day 2 to 3 of the spontaneous menstrual cycle and on the day of transvaginal follicle puncture (Table 3). The evaluation of the dynamics of changes in STH, IGF-I and IGFBP-3 during IVF in women with a weak ovarian response showed that the concentration of STH and IGF-I in both serum during the ovarian stimulation increases and the concentration of IGFBP-3 decreases, but the changes were not statistically significant.

Comparative characteristics of hormonal and growth factors in blood serum and follicular fluid in women of the groups examined are presented in Table III.

There were no significant differences in the serum levels of STH, IGF-I and IGFBP-3 on day 2-3 of menstruation in the studied groups. The concentration of STH in and serum on the day of TPO in the study group was significantly higher than that in the comparison group, while the concentration of IGF BP-3 in the study group was significantly lower than that in the comparison group. In addition, the serum IGF-I concentration on the day of TEF in the study group was significantly higher than in the comparison group.

DISCUSSION

While the necessity of prescribing FSH+LH-containing preparations instead of FSH monotherapy in patients with an expected poor response is not in the slightest doubt today, the choice of specific types of combined gonadotropins for this purpose taking into account their origin (human or recombinant) has not yet been argued and is in fact an unsolved problem. This is evidenced by directly opposite expert opinions, some of which recommend a combination of urinary gonadotropins (hMG preparations) for patients with a predicted impaired response [25, 26], while others recommend a combination of recombinant FSH and LH administered separately (rFSH and rLH) or as a single preparation (rFSH+rLH) [27].

From the literature review, it does not yet appear that the clinical outcomes of HRT in patients at high risk of poor response depend on the origin (source) of the FSH+LH-containing gonadotropins used. Obviously, in order to make a final judgment on this issue, it is advisable to continue collecting evidence to provide an objective comparative assessment of the therapeutic effects of combined human and recombinant gonadotropins in groups of patients classified as poor-response patients according to the ESHRE Bologna criteria. The need to address this problem motivated our own research.

CONCLUSIONS

The examination revealed that the AMH concentration in the main group was significantly lower compared to the comparison group. Although the established intergroup differences were not statistically significant, extremely low ovarian reserve values were detected in the women of the main group. This fact suggested that the use of another criterion of non-parametric statistical methods would establish the validity of the differences. Using the Kolmogorov-Smirnov test, we found that the serum AMH concentration on day 3 to 5 of the menstrual cycle in the study group was significantly lower compared to the comparison group (p<0,001).

Normogonadotropic failure of ovarian function was observed in the majority of patients with a reduced response to gonadotropin stimulation in ART programmes (78.5%).

In women with a "weak" ovarian response to stimulation in IVF/ICSI programmes, serum concentrations of TSH,

IGF-I and IGFBP-3 on day 2 to 3 of the spontaneous menstrual cycle and on the day of transvaginal follicle puncture are within reference values.

In the main group patients, stimulation of superovulation with urinary gonadotropins leads to an increase in serum hTG concentration on the day of MBP (3.78±0.6 ng/ml) vs. the 2nd-3rd day of menstruation (1.78±0.4 ng/ml p=0.015); Decrease of IGFBP-3 activity in blood serum on the day of FFT (2198,6±1221,1 ng/ml p=0,022) in comparison with day 2 – 3 of menstrual cycle (3689,8±1361,2 ng/ml), while in group II patients' cycles, this indicator remains unchanged.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

ANALYSES OF STRUCTURE AND INCIDENCE OF EXTRAGENITAL PATHOLOGY OF PREGNANT (2011 TO 2020 YEARS)

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ABSTRACT

The aim: To conduct analyses of structure and incidence of extragenital pathology, course of pregnancy and labour in pregnant from 2011 to 2020 years.

Materials and methods: Clinical and statistical analysis of 159,367 births over 2011-2020 years in Transcarpathian region was conducted. All complications of pregnancy were divided into 6 subgroups depending on the available obstetric pathology and extragenital pathology.

Results: The incidence of extragenital pathology among women born in the Transcarpathian region over the past 10 years has increased by an average of 6-10%. The incidence of placental dysfunction on the background of somatic morbidity in the maternity hospital in Uzhgorod increased during the study period from 6.1% (2011) to 10.9% (2020). A significant reduction in the number of births from 18,168,000 in 2011 to 13,150,000 in 2020 was noted. The incidence of combined somatic pathology increased from 10.4% in 2011 to 23.8% in 2020. ($p < 0.001$).

Conclusions: It is necessary to develop comprehensive modern measures to prevent obstetric and perinatal complications in this group of pregnant women.

KEY WORDS: great obstetrical syndromes, placental dysfunction, obstetrical and perinatal complications

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INTRODUCTION

An idea that came up a few years ago about the common pathogenetic processes, that are associated with appearance of the most typical and in this case the most dangerous from the perspective of perinatology, set a new vector in the study of the fundamental foundations of ontogenesis, forced a new look at the role of provisional organs, in particular, the placenta, in the genesis of the so-called "great obstetrical syndromes", which include preeclampsia, placental insufficiency, accompanied by fetal growth retardation, premature birth and miscarriage pregnancy in general [1, 2]. The listed pathology gives a vast majority of perinatal loss, maternal and perinatal morbidity and mortality [3-13].

Ukraine is the largest country in Europe and ranks fifth on the continent in terms of population. However, our country is currently experiencing a deep economic crisis that has negatively affected all spheres of society life. The demographic situation in Ukraine in the last decade is considered by most experts to be critical. [14-19]. Complex environmental and social problems, the progressive decline in living standards of the majority of the population, the shift in concepts of life priorities, the lack of real social protection of families and children have led to a number of negative trends. The main one is the decline in fertility [16-18]. In 2020 the birth rate was 9.1 per 1,000 population, which is 31.6% lower than in 2011 [14].

The current birth rate is the lowest, compared to all «post-Soviet» countries, and the lowest in the history of Ukraine [14]. In Ukraine, the birth rate decrease limit has been exceeded, which leads to a loss of favorable demographic prospects. Decrease in birth rate is accompanied by a fairly high level of perinatal mortality, which is more than twice the corresponding figure in economically developed countriesax [14, 16, 17].

One of the reasons for the critical demographic balance, as noted by many domestic and foreign researchers [14, 16-18, 20, 21], is the deteriorating health of women of reproductive age. Meanwhile, the end of the last century is characterized by a decline in the general health of women, even in countries with highly developed economy. In Ukraine, this trend is particularly pronounced, including among pregnant women. The incidence of extragenital diseases in general is about 40 per 100 pregnant women, and there is a clear trend towards its growth. In the last decade, the incidence of anemia (almost 6 times), cardiovascular pathology, pathology of the kidneys and endocrine system has increased significantly. This situation has led to increased complications of pregnancy and childbirth, a large increase in the number of surgical interventions in childbirth, which influences the level of perinatal loss, because it is known that stillbirth and infant mortality in most cases are due to negative influence of mother's health on the state of fetus [16-18, 20, 21].

In the issue of The Journal of Maternal and Fetal Medicine [1], G.C. Di Renzo stated that the main obstetric conditions that cause maternal and perinatal morbidity

and mortality should be reconsidered and treated not as independent diseases but as syndromes. Here he cited the main characteristics of the «great obstetric syndromes», which have been repeatedly cited in various articles: (1) multiple etiologies; (2) a long preclinical period; (3) adaptive in nature; (4) fetal involvement and (5) the result of complex interac- tions between the maternal and fetal genome and the environment . The idea is that the basis of etiopathogenesis in these syndromes is common, but the reasons that trigger it can be quite different [1].

Thus prognostication and prophylaxis of great obstetrical syndromes and perinatal loss on the background of extragenital pathology is an essential part of reducing the indexes of reproduction of the population. Many aspects of this problem now need in-depth analysis and study.

THE AIM

The aim was to conduct analyses of structure and incidence of extragenital pathology in pregnant, of Transcarpathian region from 2011 to 2020 years and to analyze the course of pregnancy and labour in this group of patients.

MATERIALS AND METHODS

To address the goals and objectives of the study the later was phased. Thus, at the first stage a clinical and statistical analysis of 159,367 births was conducted, including 473 cases of perinatal loss according to the data of the last 10 years (2011-2020) in Transcarpathian region. Data for this stage of the study were taken from the Center for Medical Statistics of the Ministry of Health of Ukraine and the Center for Medical Statistics of Uzhgorod, namely the data form №21 – Report on medical care for pregnant women, parturient and postpartum women from 2011 to 2020. All complications of pregnancy were divided into 6 subgroups depending on the available obstetric pathology (preeclampsia, placental dysfunction and intrauterine growth retardation, premature birth, fetal distress, gestational anemia) and extragenital pathology. Extragenital pathology had the highest incidence – 85,528 cases (53.6%), every second pregnant woman in the Transcarpathian region had somatic pathology. Analyzing the main features of perinatal losses in women with extragenital pathology, a methodological approach was used, according to which a group of women with combined somatic disease and placental dysfunction was singled out. In our opinion, this approach allows us to establish a number of patterns and relationships in pathogenesis of great obstetrical syndromes.

When calculating the results, the methods accepted by biomedical statistics, described in the Glanz manual [22] were used. Data processing was performed using the software package StatSoft Statistica 8.0.

RESULTS

According to Fig. 1, the incidence of extragenital pathology among women born in the Transcarpathian region over the past 10 years has increased over the years, by an average of 6-10%. The biggest rise was in the period 2017-2018 (from 53.2% in 2011 to 57.5% in 2018 and 62.2% in 2018). In the Transcarpathian region (Fig. 1) the increase in the level of extragenital pathology was pronounced, but in some periods the growth rate was almost the same.

As evidenced by the data of Fig. 2 the incidence of extragenital pathology in the years from 2011 to 2020 in the maternity hospital in Uzhgorod increased by an average of 10%. The highest frequency of extragenital pathology was observed from 2013 to 2019 (from 43.2% in 2013 to 46.4% in 2019).

The dynamics of the incidence of placental dysfunction on the background of somatic morbidity in the maternity hospital in Uzhgorod (Fig. 3) increased during the study period from 6.1% (2011) to 10.9% (2020).

In contrast, the dynamics of changes of the studied index in the Transcarpathian region (Fig. 4) had a steady upward trend, especially in the last 4 years, when its value was 13.8% in 2017 to 16.0% in 2020.

Summarizing the above data, we can note a steady trend of increasing incidence of extragenital pathology in pregnant women, including an increase in the incidence of placental dysfunction on the background of somatic pathology. At the same time, in our opinion, in a particular area it is easier to address the diagnosis and tactics of management of pregnant women with extragenital pathology, in order to reduce their incidence of placental dysfunction. Of course, data on the structure of extragenital pathology are of considerable interest. According to Table I, we observe significant changes over the past 10 years in pregnant women in the Transcarpathian region. First of all, the gradual significant reduction in the number of births from 18,168,000 in 2011 to 13,150,000 in 2020 and a significant increase in combined somatic pathology from 10.4% in 2011 to 23.8% in 2020 ($p < 0.001$) should be noted. Among other fluctuations it is worth noting a significant increase over 10 years of the incidence of: circulatory diseases from 3.3% to 7.2% ($p < 0.01$), varicose veins from 3.4% to 4.3% ($p < 0.05$), diseases of the gastrointestinal tract from 7.3% to 17.8% ($p < 0.01$), with a simultaneous decrease in the level of endocrine pathology from 34.7% to 23.7% ($p < 0.01$) and anemia from 34.6% to 28.8%; $p < 0.05$). Among the more stable indicators of the last decade, kidney disease should be noted (12.2% -11.4%; $p > 0.05$). All other nosological forms occurred in isolated cases and without significant fluctuations ($p > 0.05$).

The structure of extragenital pathology in the maternity hospital of Uzhgorod city from 2011 to 2020 years are presented in Table II.

The obtained data indicate a significant increase in combined pathology in pregnant women from 9.5% to 18.3% ($p < 0.01$), urogenital infections from 11.9% to 14.0% ($p < 0.05$), diseases circulatory system from 5.6% to 6.8% ($p < 0.05$) against the background of a simultaneous decrease in the incidence of varicose veins and a stable high incidence of anemia (38.6% and 40.1%) and thyroid pathology (33.7 and 30.3%). The incidence of lung and gastrointestinal diseases was without significant differences ($p > 0.05$).

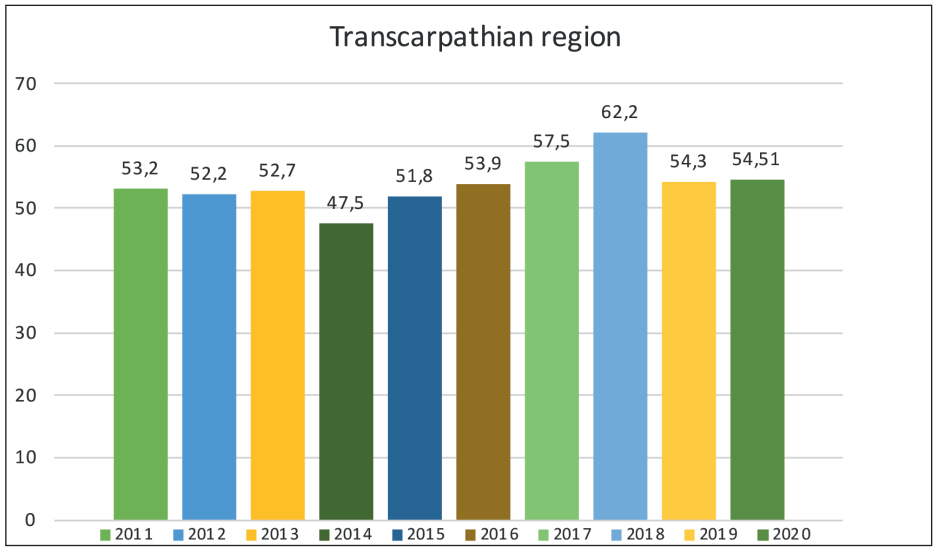

Fig. 1. Incidence of extragenital pathology in the Transcarpathian region from 2011 to 2020 (%)

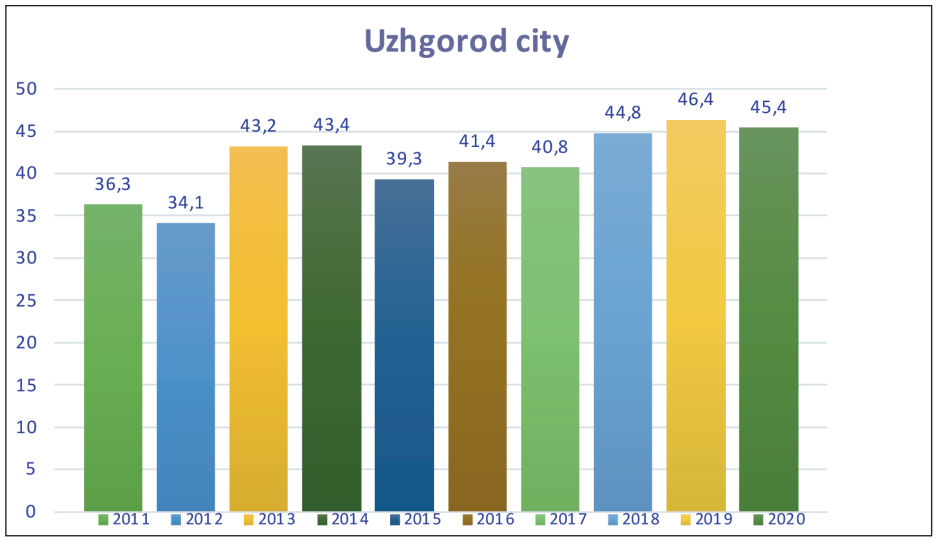

Fig. 2. Frequency of extragenital pathology in the maternity hospital in Uzhgorod from 2011-2020 (%)

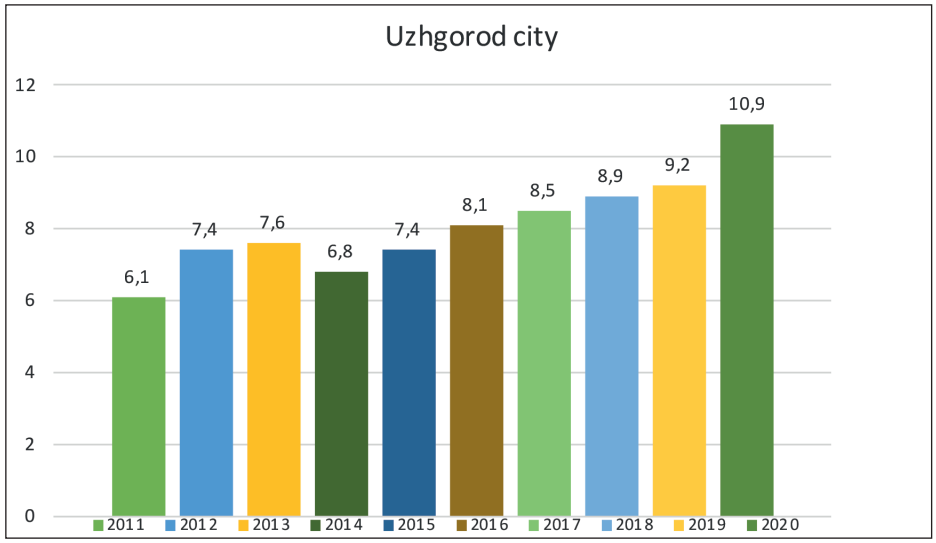

Fig. 3. Incidence of placental dysfunction on the background of extragenital pathology in maternity hospital of Uzhgorod (%)

In the statistical analysis of the structure of extragenital pathology in pregnant women on the background of placental dysfunction in the maternity hospital in Uzhgorod (Table III) draws attention the lack of significant changes in the combined pathology (20.5% -20.6%).

The main feature here is the increase in the proportion of cardiovascular disease from 29.5% to 35.8% ($p < 0.05$) and anemia from 30.7% to 32.9% ($p < 0.05$) on the background of development placental dysfunction, endocrine pathology, on the contrary, significantly decreased on the background of

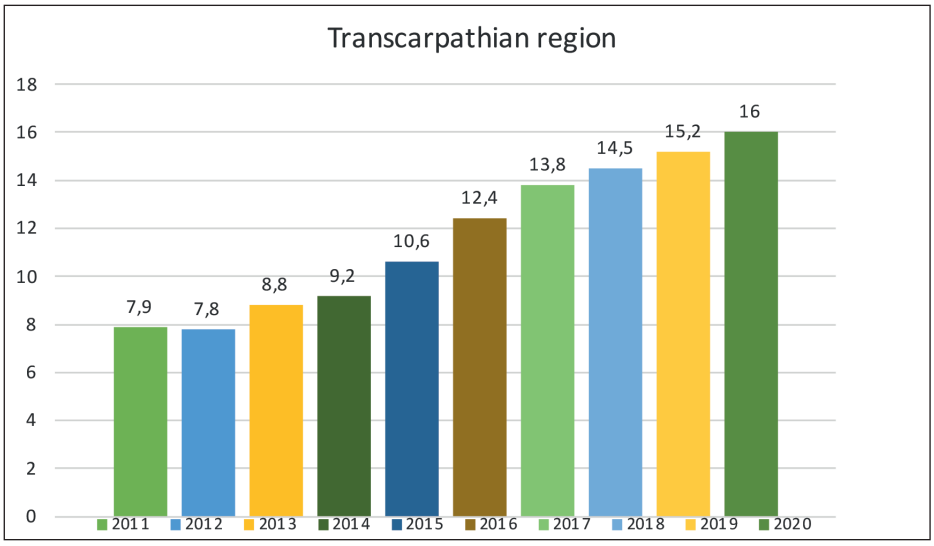

Fig. 4. Incidence of placental dysfunction on the background of extragenital pathology in Transcarpathian region (%)

Table I. Structure of extragenital pathology in Transcarpathian region from 2011 till 2020 years (absolute numbers, %)

Pathology	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Number of deliveries	18168	18737	18222	18127	16424	15628	14467	13680	12764	13150
Urinary tract infection	1180 (12,2)	970 (9,9)	1181 (12,3)	963 (11,2)	1088 (12,8)	1127 (13,3)	1207 (14,5)	936 (10,9)	832 (11,9)	815 (11,4)
Circulatory diseases	318 (3,3)	391 (3,9)	552 (5,7)	481 (5,6)	448 (5,3)	535 (6,3)*	486 (5,8)*	614 (7,2)**	474 (6,8)**	401 (5,6)*
Diabetes mellitus	12 (0,1)	20 (0,2)	16 0,2)	31 (0,4)	27 (0,3)	28 (0,3)	21 (0,3)	26 (0,3)	19 (0,3)	37 (0,5)
Thyroid gland diseases	3338 (34,6)	3212 (32,8)	3170 (33,1)	2283 (26,5)	2212 (25,9) *	2124 (25,2) *	1974 (23,7) **	2136 (25,1)	1624 (23,4) **	1666 (23,2) **
Anemia	3335 (34,6)	3572 (36,4)	2936 (30,5)	2967 (34,5)	2987 (35,1)	2759 (32,7)	2729 (32,8)	2763 (32,5)	2038 (29,4) *	2064 (28,8) *
Varicose veins	328 (3,4)	382 (3,9)	328 (3,4)	430 (4,9)	372 (4,4)	467 (5,5)*	445 (5,4)*	422 (4,9)*	309 (4,5)*	289 (4,3) *
Gastrointestinal tract diseases	712 (7,3)	812 (8,3)	921 (9,6)	943 (10,9)	898 (10,5)	912 (10,8) *	948 (11,4) *	1012 (11,9) **	1026 (14,8) **	1276 (17,8) **
Lung diseases	411 (4,3)	432 (4,4)	495 (5,1)	512 (5,9)	489 (5,7)	486 (5,8)	512 (6,2)	601 (7,1)	612 (8,8)	621 (8,7)
Combined pathology	1006 (10,4)	13601 (13,9)	1452 (15,1) *	1587 (18,4) *	1831 (21,4) **	1786 (21,1) **	1894 (22,7) **	1911 (22,4) **	1699 (24,5) **	1712 (23,8) **
Total	9634 (53,2)	9791 (52,2)	9599 (52,7)	8610 (47,5)	8521 (51,8	8438 53,9)	8322 (57,5)	8510 (62,2)	6934 (54,3)	7169 (54,51)

p-value relative to 2011 * <0.05 ** <0.01

PD from 19.2% to 9.5% (p <0.05). The rate of renal pathology was in the range of 15.3% to 15.6% during the study period (p> 0.05) and isolated cases of placental dysfunction were observed against the background of varicose veins, diseases of the gastrointestinal tract and lungs (p> 0.05).

In the analysis of the structure of extragenital pathology, against which the development of placental dysfunction was observed according to the data of the Transcarpathian region, there is a significant increase in the incidence of cardiovascular diseases from 22.1% in 2011 to 29.8% in 2020 (p <0.05), the incidence of anemia increased from 38.5% to 42.6% (p <0.05), also significantly increased the incidence endocrine pathology (thyroid pathology and diabetes) from 12.1% in 2011 to 23.6% in 2020 (p <0.05). The rate of renal pathology ranged from 21.5% to 23.6% during the study period (p> 0.05) and isolated cases of placental dysfunction were observed against the background of varicose veins, diseases of the gastrointestinal tract and lungs (p> 0.05). The increase in the level of combined pathology from 10.5% (2011) to 20.6% (2020) (p <0.05) is noteworthy (Table IV).

In addition to the above features, we studied the frequency of major complications of pregnancy in women with extragenital pathology from 2011 to 2020. The results show

Table II. Structure of extragenital pathology in maternity hospital of Uzhgorod city from 2011 till 2020 years (absolute numbers, %)

Pathology	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Number of deliveries	3546	3919	1599	4018	3831	3838	3771	3633	3555	3581
Urinary tract infection	154 (11,9)	172 (12,8)	85 (12,3)	257 (14,7)	196 (12,9)	204 (12,8)	221 (14,3)*	216 (13,4)	236 (14,2)*	228 (14,0)*
Circulatory diseases	72 (5,6)	86 (6,4)	39 (5,7)	102 (5,8)	83 (5,5)	101 (6,3)*	106 (6,8)*	108 (6,7)*	104 (6,3)*	102 (6,3)*
Diabetes mellitus	8 (0,6)	10 (0,7)	12 (1,7)	18 (1,1)	16 (1,1)	19 (1,2)	21 (1,3)	24 (1,5)	18 (1,1)	34 (2,1)
Thyroid gland diseases	435 (33,7)	468 (34,9)	235 (33,9)	591 (33,8)	505 (33,4)	462 (29,1)	458 (29,8)	471 (29,3)	483 (29,3)	494 (30,3)
Anemia	498 (38,6)	501 (37,4)	267 (38,5)	645 (36,9)	580 (38,4)	602 (37,8)	645 (41,9)	637 (39,5)	646 (39,1)	653 (40,1)
Varicose veins	48 (3,7)	51 (3,8)	21 (3,0)	56 (4,9)	51 (3,4)	87 (5,4)*	35 (2,4)*	66 (4,1)*	70 (4,2)*	27 (1,7) *
Gastrointestinal tract diseases	43 (3,4)	39 (2,9)	22 (3,2)	52 (2,9)	53 (3,5)	79 (5,0)	29 (1,9)	61 (3,8)	59 (3,6)	58 (3,6)
Lung diseases	31 (2,4)	12 (0,9)	11 (1,6)	24 (1,4)	25 (1,7)	38 (2,4)	24 (1,6)	28 (1,7)	36 (2,2)	32 (1,9)
Combined pathology	123 (9,5)	159 (11,8)	103 (14,8) *	279 (15,9) *	246 (16,3) **	267 (16,8) **	271 (17,6) **	289 (17,9) **	295 (17,8) **	299 (18,3) **
Total	1289 (36,3)	1339 (34,1)	692 (43,2)	1745 (43,4)	1509 (39,3)	1592 (41,4)	1539 (40,8)	1611 (44,3)	1652 (46,4)	1628 (45,4)

p-value relative to 2011 * <0.05 ** <0.01

Table III. Structure of extragenital pathology on the background of placental dysfunction in the maternity hospital of Uzhgorod (%)

Pathology	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Cardio-vascular diseases	29,5	31,3	33,9	33,1	34,2	32,6*	35,1*	36,4*	36,8*	35,8*
Endocrine pathology	19,2	18,2	17,8	17,0	17,2	16,7	11,6*	9,8*	13,2*	9,5*
Kidney diseases	15,3	14,1	15,1	15,3	14,4	13,1	14,5	16,7	13,8	15,6
Pathology of gastro-intestinal tract	2,5	4,1	3,7	4,2	3,6	2,3	3,1	2,1	1,3	3,9
Lung diseases	-	2,0	-	0,8	-	2,0	2,1	2,1	-	1,1
Anemia	30,7	28,3	28,3	27,9	27,9	30,2	32,1	30,2	33,6*	32,9*
Varicose veins	2,8	2,0	1,9	1,7	2,7	3,1	1,5	0,7	1,3	1,1
Combined pathology	20,5	18,2	15,1	17,8	18,0	17,8	18,3	18,1	19,7	20,6

p-value relative to 2011 * <0.05.

that the level of major complications of pregnancy, which are due to the development of great obstetrical syndromes on the background of existing extragenital pathology, increased significantly (p <0,05). (Table V)

The obtained data show that for 10 years in pregnant women with extragenital pathology, residents of the Transcarpathian region significantly increased the incidence of the threat of premature birth from 8.9% to 18.1% (p <0.05); placental dysfunction with fetal growth retardation syndrome (IUGR) from 7.8% to 16.0% (p <0.05); gestational anemia from 33.9% – 57.9% (p <0.05) and preeclampsia from 11.9% – 16.9% (p <0.01). All these complications of pregnancy are due to one pathogenetic factor, namely, they are all a manifestation of the development of great obstetrical syndromes. The obtained results coincide with general tendency of increase of incidence of GOS over the last decade in the country as a whole.

DISCUSSION

Analyzing the structure and incidence of complications in women with extragenital pathology, residents of the Transcarpathian region, for the period 2011-2020 can be seen a significant increase in somatic morbidity, on average, by 10.0%, which is also pointed out in the works of many researchers worldwide [23, 24]. The analysis of the structure of extragenital pathology, against which the development of placental dysfunction was observed in pregnant women, residents of the Transcarpathian region, there is a significant increase in cardiovascular disease, anemia and a significant increase in endocrine pathology (thyroid disease and diabetes).

Table IV. Structure of extragenital pathology on the background of placental dysfunction in Transcarpathian region (%)

Pathology	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Cardiovascular diseases	22,1	22,9	24,5	23,2	22,9	24,3	25,2*	26,4*	28,0*	29,8*
Endocrine pathology	12,1	14,5	13,3	14,6	15,5	14,9	17,9*	21,2*	22,7*	23,6*
Kidney diseases	21,5	21,2	20,4	21,3	21,1	22,7	22,8	22,2	23,8	23,6
Pathology of gastrointestinal tract	2,6	4,5	4,2	3,5	3,5	3,6	3,7	4,1	6,5	6,2
Lung diseases	1,1	0,9	0,7	1,1	1,2	1,3	1,3	1,4	1,1	1,4
Anemia	38,5	36,0	39,1	38,4	39,9	41,3	42,2*	41,9*	41,6*	42,6*
Varicose veins	2,1	1,9	2,1	2,0	1,9	1,8	1,8	1,5	1,7	1,8
Combined pathology	10,5	10,7	13,0	12,3	10,7	13,9	15,5	17,5	19,2*	20,6*

p-value relative to 2011 * <0.05.

Table V. Major complications of pregnancy in women with extragenital pathology (%)

Clinical manifestation	2011-2020 years.
	Transcarpathian region
Threat of preterm labour	8,9% - 18,1%*
Placental dysfunction, intrauterine growth retardation	7,8% - 16,0%*
Fetal distress	5,6% - 12,1%*
Preeclamsia	11,9% - 16,9%**
Gestational anemia	33,9% - 57,9%*

p-value relative to 2011 * <0.05 ** <0.01

Among the main gestational complications in women with extragenital pathology, the threat of premature birth, placental dysfunction with fetal growth retardation syndrome, gestational anemia, fetal distress and preeclampsia were more common than others. Based on the results, we can agree with the opinion of many domestic and foreign scientists [25-27] that solving the problem of reducing the risk of great obstetrical syndromes in women with extragenital pathology requires a comprehensive approach based on improving organizational and treatment measures.

CONCLUSIONS

1. It should be noted a gradual significant reduction in the number of births from 18,168 thousand in 2011 to 13,150 thousand in 2020.
2. The frequency of extragenital pathology among women born in the Transcarpathian region over the past 10 years has increased over the years, by an average of 6-10%. The biggest rise was in the period 2017-2018 (from 53.2% in 2011 to 57.5% in 2018 and 62.2% in 2018).
3. It is necessary to note a significant increase in combined somatic pathology from 10.4% in 2011 to 23.8% in 2020. ($p < 0.001$), a significant increase over 10 years, the frequency of diseases of the circulatory system from 3.3% to 7.2% ($p < 0.01$), diseases of the gastrointestinal tract from 7.3% to 17.8% ($p < 0.01$); with a simultaneous decrease in the level of endocrine pathology from 34.7% to 23.7% ($p < 0.01$) and anemia from 34.6% to 28.8%; $p < 0.05$).
4. The analysis of the structure of extragenital pathology, against which there was the development of placental dysfunction in pregnant women, residents of the Transcarpathian region, there is a significant increase in the incidence of cardiovascular disease from 22.1% in 2011 to 29.8% in 2020 ($p < 0.05$), the incidence of anemia increased from 38.5% to 42.6% ($p < 0.05$), also significantly increased the incidence of endocrine pathology (thyroid pathology and diabetes) from 12.1% in 2011 to 23.6% in 2020 ($p < 0.05$).
5. In pregnant women with extragenital pathology, residents of the Transcarpathian region, the incidence of threat of premature birth ($p < 0.05$), placental dysfunction with fetal growth retardation syndrome (IUGR) ($p < 0.05$), gestational anemia ($p < 0.05$) and preeclampsia ($p < 0.01$) increased significantly.

Thus, as shown by statistical analysis of the frequency and structure of extragenital pathology in pregnant women, residents of the Transcarpathian region for 10 years (from 2011 to 2020) modern measures should be developed to prevent obstetric and perinatal complications in this group of pregnant women, which will significantly reduce the frequency and severity of placental dysfunction, which is the basis for the development of GOS, and most importantly – will reduce perinatal loss in women with high risk of obstetric and perinatal complications.

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ORIGINAL ARTICLE

CORRECTION OF AUTONOMIC DYSFUNCTION IN OVERWEIGHT CHILDREN BY NORMALIZING BODY COMPOSITION

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ABSTRACT

The aim: To investigated the effect of a 3-month body weight correction program on the functional state of the ANS in children of primary school age who had an increased body mass index and signs of autonomic dysfunction.

Materials and methods: 82 children aged 9 to 11 were examined. During 3 months, all examinees underwent a body weight correction course. Body composition was measured by the bioimpedance method using the body composition analyzer «TANITA-BC-601» (Japan). The functional state of autonomic regulation was assessed using heart rate variability (HRV) indicators obtained by recording standard 5-minute ECG intervals using the computer hardware and software complex "CARDIOLAB" (XAI-MEDICA, Ukraine).

Results: Statistical processing of HRV indicators showed that 51 children (62.2%) had signs of autonomic dysfunction. In the first group, there was a statistically significant decrease in body weight (from 47.33±4.62 to 44.12±3.96), BMI (from 28.15±2.64 to 26.63±2.87), TFC (from 33.54±3.68 to 30.89±2.81), VF (from 7.056±1.814 to 4.817±2.017) with a simultaneous statistically probable increase in the FFM index (from 60.27±2.47 to 63.15±2,38). According to the time domain indicators of HRV, children in first group have increased the TP of autonomous heart rhythm regulation, as indicated by a statistically significant increase in SDNN from 38.43±6.39 ms to 51.65±7.19 ms ($p<0.05$); the activity of the sympathetic link of the ANS decreased according to AMo from 41.23±6.17% to 34.29±5.83% ($p<0.05$) and the intensity of autonomic regulation according to IS, which decreased from 116.3±31,6 units to 81.2±29.1 units ($p<0.05$).

Conclusions: 3-month body weight correction program led to the elimination of signs of autonomic dysfunction in 43.9% of the examined persons.

KEY WORDS: autonomic dysfunction, body composition, overweight children, heart rate variability

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INTRODUCTION

Obesity among school-aged children has reached the scale of a global epidemic both in our country and abroad [1], and its prevalence remains high, despite the enormous efforts made by doctors and educators to stabilize the situation [2]. It is known that obesity in childhood is associated with a number of metabolic, cardiovascular and other disorders, which include dyslipidemia, type 2 diabetes, lung disorders, blood system pathology [3]. Since dysfunction of the autonomic nervous system (ANS) can contribute to the development or stabilization of obesity and is associated with cardiovascular mortality [4], studying the functional state of the ANS in obesity is of significant clinical interest. The majority of studies of autonomic dysfunction in children with obesity relate to the assessment of autonomic regulation of heart function by analyzing heart rate variability (HRV), which is considered a kind of diagnostic window into the functional state of the ANS as a whole. These studies generally found a decrease in parasympathetic activity. However, it remains unclear how significant the changes in the sympathetic chain of the ANS are in overweight and obese children and adolescents. It is considered proven that autonomic dysfunction increases the load on the cardiovascular system, aggravates hemodynamic stress, serious heart rhythm disorders and other cardiac pathology. Thus, cardiac autonomic imbalance may also be an important link between obesity and increased morbidity and mortality.

THE AIM

It was established that autonomic disorders in overweight adults are subject to reverse development under the condition of weight loss. Because autonomic imbalance is a marker of adverse risk, improvements derived from weight loss should also benefit the health of overweight and obese children. To test this assumption, we investigated the effect of a 3-month body weight correction program on the functional state of the ANS, assessed by heart rate variability, in children of primary school age who had an increased body mass index and signs of autonomic dysfunction.

MATERIALS AND METHODS

82 children aged 9 to 11 were examined, of which 38 were boys and 43 were girls. All examined children were in the pre-pubescent period of development without clinical signs of pathology according to physical examination

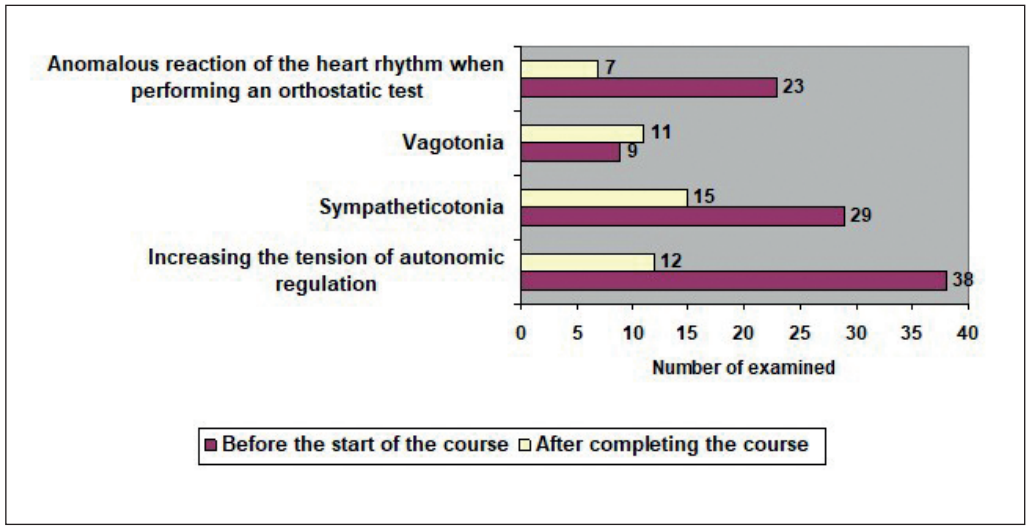

Fig. 1. Dinamics of the number of eximinees with sings of autonomic dysfunction under the influence of a 3-months course of body weight correction

and laboratory tests (general blood and urine analysis, biochemical blood analysis, blood pressure indicators). The criterion for inclusion in the study was the presence of excess body weight according to the criterion of body mass index (BMI) in the range of 25.0-29.9 kg/m^2. Individuals with clinical signs of obesity or metabolic syndrome were excluded from the study.

During the next 3 months, all examinees, under the guidance of an instructor, underwent a body weight correction course, which included the formation of healthy eating skills with the selection of individual caloric content of the diet and physical activity of a high-speed and strength nature (dance and gymnastic exercises, sports games) with a frequency of 3 training sessions per week lasting 45-60 minutes.

The examination was carried out before the beginning and at the end of the course and included the assessment of body composition by the bioimpedance method using the body composition analyzer «TANITA-BC-601» (Japan). In particular, the following were determined: body weight (W, kg.), body mass index (BMI, kg/m^2), total fat content (TFC, %), visceral fat rating (VF, units), fat-free mass content (FFM, %). The functional state of autonomic regulation was assessed using heart rate variability (HRV) indicators obtained by recording standard 5-minute ECG intervals using the computer hardware and software complex «CARDIOLAB» (XAI-MEDICA, Ukraine) according to the generally accepted method [5]. In particular, the time characteristics of the heart rhythm were determined: indicators of the general variability of the heart rate: SDNN, ms – standard deviation of all RR intervals of a 5-minute ECG interval, indicators of parasympathetic ANS activity (RMSSD, ms – square root of the average value of the squares of the differences in the lengths of consecutive RR intervals, pNN50, % is the percentage of adjacent RR intervals, the difference between which exceeds 50 ms.). In the spectral analysis of HRV, the following parameters were used: TP, ms^2 – the total power of the heart rhythm spectrum; VLF, ms^2 – the power of the spectrum of very low frequencies (central neurohumoral influences); LF, ms^2 – the power of the spectrum of low frequencies (reflecting the activity of the sympathetic link of the ANS); HF, ms^2 – the power of spectral high frequencies (reflect the activity of the parasympathetic link of the ANS); LF/HF – an indicator of sympatho-vagal balance (sympatho-parasympathetic index). In addition, the percentage contribution of frequency components of the spectrum to TR (VLF%, LF%, HF%) was calculated. The reactivity of the peripheral link of the ANS was evaluated based on the results of an orthostatic test with the determination of the reaction coefficient (K 30:15), which is calculated as the ratio of the maximum value of the R-R interval (usually around the 30th contraction of the heart after the transition to a vertical position) to the shortest R – R-interval corresponding to the 15th cardiac contraction.

In addition to standard indicators, the following were also determined: the index of centralization (IC), which reflects the relationship between the autonomous and central circuits of heart rhythm regulation, the index of tension of regulatory systems (IS), which characterizes the degree of centralization of heart rhythm control. MS Excel statistical package was used for statistical processing of the research results. The difference between the studied samples was evaluated using non-parametric methods (ANOVA) and the Student's t-test for two independent samples.

RESULTS

Statistical processing of HRV indicators in the entire sample of the examined showed that 51 children (62.2%) had signs of autonomic dysfunction (Table I). These signs included: an increase in the intensity of autonomic regulation, the criterion of which was the total power of the heart rhythm spectrum (TP) and the standard deviation of all RR intervals of a 5-minute ECG interval (SDNN) output beyond the lower limit of the norm for this age category; sympathicotonia or vagotonia according to the deviation from the norm of the sympatho-vagal balance indicator (LF/HF); anomalous reaction of the heart rhythm when performing an orthostatic test, estimated by the reaction coefficient (K 30:15). The sum

Table I. The distribution of examined children depending on the presence of autonomic dysfunction

№	A type of autonomic dysfunction	Absolute number	Percentage of all examined
1	Increasing the tension of autonomic regulation	38	46,3
2	Sympatheticotonia	29	35,4
3	Vagotonia	9	11,0
4	Anomalous reaction of the heart rhythm when performing an orthostatic test	23	28,0
5	Absent	31	37,8
6	All examined	82	100

Table II. The dynamics of indicators of the component composition of the body of the examined persons under the influence of a 3-month course of body weight correction (M+m)

Indicators of the component composition of the body	Group 1 (n=51)		Group (n=31)	
	Before the start of the course	After completing the course	Before the start of the course	After completing the course
BMI, kg/m^2	28,15±2,64	26,63±2,87*	27,96±2,82	25,94±2,66**
TFC, %	33,54±3,68	30,89±2,81*	32,81±3,75	29,99±2,76*
VF, units	7,056±1,814	4,817±2,017**	6,573±1,722	3,832±2,118**
FFM, %	60,27±2,47	63,15±2,38*	61,03±2,24	63,34±2,19*
Body weight, kg	47,33±4,62	44,12±3,96*	46,98±4,71	43,32±4,06*

Note: Differences are statistically significant at level * - p≤0,05; ** p≤0,01

Table III. The dynamics of indicators of the component composition of the body of the examined persons under the influence of a 3-month course of body weight correction (M+m)

HRV indicators	Group 1 (n=51)		Group 2 (n=31)	
	Before the start of the course	After completing the course	Before the start of the course	After completing the course
SDNN, ms	38,43±6,39	51,65±7,19*	50,82±14,37	55,53±16,87
TP, ms^2	3122±695	3959±675*	3099±1034	3867±1445
LF, ms^2	1305±264	1033±218*	705±364	956±418
AMo, %	41,23±6,17	34,29±5,83	40,55±10,07	37,67±6,83
RMSSD, ms	17,95±2,15	31,22±3,81**	35,19±4,15	41,28±4,82*
pNN50, %	6,79±2,45	15,28±4,11	16,82±6,55	25,09±7,12*
HF, ms^2	878±288	1236±345	803±281	1045±448
VLF, ms^2	939±351	1690±448	1591±752	1866±748
LF/HF	1,49±0,74	0,84±0,48**	0,88±0,77	0,91±0,58
IC	4,39±2,81	4,56±3,15	4,56±2,84	4,23±3,16
IS	116,3±31,6	81,2±29,1*	119,1±42,5	88,4±32,4*
VLF %	30,08±5,74	42,69±6,71**	51,34±11,21	48,25±10,35
LF, %	41,89±7,12	26,09±5,79**	22,75±10,98	24,72±5,09
HF, %	28,12±4,02	31,22±5,70	25,91±4,77	27,02±6,76

Note: Differences are statistically significant at level * - p≤0,05; ** p≤0,01

of all types of autonomic disorders in the table exceeds the total number of persons with these disorders, as some of them combined 2-3 of the identified signs of autonomic dysfunction. In this regard, all examinees were divided into two groups: group 1, which included 51 overweight individuals with signs of autonomic dysfunction, and group 2, which included 31 overweight individuals without signs of autonomic dysfunction according to HRV.

In the table II shows the dynamics of indicators of the component composition of the body in the examined children of both groups under the influence of the 3-month body weight correction program. In both groups, there were significant changes in body weight, BMI, TFC, VF, and FFM. In the first group, there was a statistically significant decrease in body weight (from 47.33±4.62 to 44.12±3.96), BMI (from 28.15±2.64 to 26.63±2.87), TFC

(from 33.54±3.68 to 30.89±2.81), VF (from 7.056±1.814 to 4.817±2.017) with a simultaneous statistically probable increase in the FFM index (from 60.27±2.47 to 63.15±2 ,38). Similar changes occurred in the examined children of the 2nd group. Thus, their body weight decreased from 46.98±4.71 to 43.32±4.06; BMI from 27.96±2.82 to 25.94±2.66; TFC from 32.81±3.75 to 29.99±2.76; VF from 6.573±1.722 to 3.832±2.118 with a simultaneous statistically probable increase in the FFM indicator from 61.03±2.24 to 63.34±2.19. It is worth noting that even after the positive dynamics of the body composition indicators of the subjects in both groups, they did not reach the normative values for children of the corresponding age and sex.

The dynamics of HRV indicators under the influence of a 3-month course of body weight correction is presented in Table III. Statistical processing of the obtained data showed that similar changes in the functional state of the ANS occurred in both groups of subjects. However, these changes were more pronounced in children of the 1st group. Thus, according to the time domain indicators of HRV, they have increased the TP of autonomous heart rhythm regulation, as indicated by a statistically significant increase in SDNN from 38.43±6.39 ms to 51.65±7.19 ms ($p<0.05$); the activity of the sympathetic link of the ANS decreased according to AMo from 41.23±6.17% to 34.29±5.83% ($p<0.05$) and the intensity of autonomic regulation according to IS, which decreased from 116.3±31,6 units to 81.2±29.1 units ($p<0.05$). At the same time, indicators characterizing the activity of the parasympathetic part of the ANS significantly increased. This applies to RMSSD, which increased from 17.95±2.15 ms to 31.22±3.81 ms ($p<0.01$) and pNN50, which increased from 6.79±2.45% to 15.28± 4.11% ($p<0.01$).

This nature of changes in the functional state of the ANS is also confirmed by the dynamics of the HRV spectral parameters. In particular, the total power of autonomous heart rhythm regulation according to TP increased from 3122±695 ms^2 to 3959±675 ms^2 ($p<0.05$); the power of low-frequency LF waves decreased from 1305±264 ms^2 to 1033±218 ms^2 ($p<0.05$); the power of very low frequency VLF waves increased from 939±351 ms^2 to 1690±448 ms^2 ($p<0.05$). The absolute value of the indicator of the activity of the parasympathetic link of the HF did not change statistically reliably, although the indicator of the sympatho-parasympathetic balance LF/HF decreased from 1.49±0.74 to 0.84±0.48. The most vivid redistribution of the activity of the peripheral part of the ANS in favor of the parasympathetic link was manifested in the dynamics of the relative contribution of the indicators of the sympathetic link (LF%) and the range of segmental levels of regulation (VLF%) to the total power of the wave spectrum of the heart rhythm (TR). Thus, LF% decreased from 41.89±7.12% to 26.09±5.79% ($p<0.01$), while VLF% increased from 30.08±5.74% to 42 .69±6.71% ($p<0.01$).

In the examined subjects of the 2nd group, the dynamics of changes in HRV indicators was similar in direction to similar changes in the 1st group, but for most parameters it was not statistically reliable. The exception was the time indicators characterizing the activity of the parasympathetic link of the ANS and the stress index of autonomic regulation (IS). In particular, the RMSSD in the examinees of this group increased from 35.19±4.15 ms to 41.28±4.82 ms ($p<0.05$); pNN50 increased from 16.82±6.55% to 25.09±7.12% ($p<0.05$), and IS decreased from 119.1±42.5 to 88.4±32.4 ($p <0.05$).

As a result of the redistribution of the functional activity of various links of the ANS in the examined persons of the 1st group under the influence of the course of body weight correction, the total number of children with autonomic dysfunction decreased from 51 to 15 persons, or in relative figures from 62.2% to 18.3% of all examined (Fig. 1). The biggest changes occurred in the number of children with increased tension of autonomic regulation (from 38 to 12) and with an abnormal heart rate response during the orthostatic test (from 23 to 7).

DISCUSSION

Childhood obesity is a complex syndrome that is ultimately the result of the interaction of many factors, including genetics, prenatal experiences, family and cultural traditions, emotional factors, and levels of physical activity [6-9]. In a number of studies of obese adults, the presence of autonomic nervous system dysfunction is noted [10-12]. However, the connection between obesity and the function of the ANS cannot yet be considered completely clarified. Studies of the functional state of the ANS in overweight and obese children compared to studies of adults are few. That is why clarifying the relationship between indicators of the component composition of the body and autonomous regulation in children of primary school age with excessive body weight is an urgent scientific problem. From the data we obtained, it follows that about 60% of such children have signs of autonomic dysfunction. The most frequent forms of such dysfunction were an increase in the intensity of autonomic regulation, which was expressed in a decrease in the heart rate variability according to the mean square deviation of the ECG cardio intervals (SDNN) and the total power of the heart rate spectrum (TP), as well as abnormal reactivity of the ANS to the orthostatic test.

A detailed analysis of the HRV indicators of the studied contingent revealed a change in the activity of both the sympathetic and parasympathetic links of the ANS. In general, the results obtained by us indicate a tendency towards excessive activation of the sympathetic link of the ANS and simultaneous suppression of the parasympathetic link. To the best of our knowledge, no previous similar studies have been conducted in elementary school-age children who are overweight but without clinical signs of obesity. Studies of ANS in obese adults report conflicting findings. Some of them demonstrate hypoactivity of the parasympathetic nervous system [9,10], which was also found in our study. Some others have demonstrated dysfunction of both the sympathetic and parasympathetic branches of the ANS, or only dysfunction of the sympathetic branch [11,12]. These discrepancies may result from the use of different methods

in different studies.

In several studies, the authors provided evidence of autonomic dysfunction in obese children. In particular, there were signs of a decrease in vagal activity of heart rate variability [13-15,18] with some reports of a simultaneous decrease in sympathetic activity [17,19]. The ratio of low-frequency to high-frequency waves may also be increased in obese children [14, 15], which is a marker of sympathovagal imbalance [17]. These data coincide with the results of our study. In addition, a decrease in baroreflex sensitivity was also reported [21]. Given that the baroreflex is important for blood pressure regulation, assessment of cardiac baroreceptor sensitivity includes both afferent and efferent signaling in cardiac vagal activity and may be more sensitive than heart rate variability for detecting autonomic dysfunction in children.

Based on the hypothesis of a close relationship between the accumulation of fat in the body and autonomic disorders, it is logical to assume that the normalization of body composition can contribute to the elimination of these disorders. A proven method of correcting the component composition of the body in overweight children is a healthy diet and dosed physical aerobic activity. It is known that overeating and eating food with a high glycemic index is the main cause of obesity [5]. The centers of appetite and satiety in the hypothalamus play a key role in the regulation of eating behavior [2,5]. On the other hand, it is known that the hypothalamus controls the functions of the ANS. Therefore, we believe that teaching a child healthy eating skills eliminates a possible pathogenetic mechanism of the formation of autonomic dysfunction. This is evidenced by the dynamics of autonomic disorders in the group of children who underwent a 3-month body weight correction course. In particular, the percentage of children with signs of autonomic dysfunction decreased from 62.2% to 18.3%.

Physical activity is a key element in the prevention and treatment of obesity and diabetes in children. Regular physical activity effectively supports weight loss achieved through a healthy diet, improves glycemic control, and can prevent or delay the diagnosis of type 2 diabetes. In addition, physical activity has a positive effect on the lipid profile, blood pressure, reduces the frequency of cardiovascular disorders and related mortality, and also restores the quality of life in type 2 diabetes [22]. Obesity in combination with diabetes is characterized by hyperactivity of the sympathetic link of the ANS and a progressive decrease in parasympathetic control of the heart. They manifest through various pathogenetic mechanisms, including hyperinsulinemia, visceral obesity, subclinical inflammation, and increased thrombosis. That is why we consider it necessary to include in the body weight correction program and regular aerobic exercises in the form of dance and gymnastic exercises and sports games.

CONCLUSIONS

1. Among elementary school-aged children with excess body weight (BMI in the range of 25.0-29.9 kg/m^2), 62.2% had signs of autonomic dysfunction in the form of increased tension of autonomic regulation, sympathicotonia or vagotonia according to deviations from the norm an indicator of sympatho-vagal balance, an abnormal reaction of the heart rhythm when performing an orthostatic test.
2. The application of a 3-month body weight correction program (teaching healthy eating skills and regular physical activity in the form of dancing and gymnastic exercises and sports games) led to the elimination of signs of autonomic dysfunction in 43.9% of the examined persons.

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ORIGINAL ARTICLE

DYNAMICS OF FIBROTIC CHANGES IN THE LIVER AFTER THE SUCCESSFUL ERADICATION OF HEPATITIS C VIRUS IN PATIENTS WHIT NAFLD

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ABSTRACT

The aim: To assess the dynamics of serum levels of angiopoietin-2 and transforming growth factor-β1 in patients with chronic hepatitis C (CHC) with concomitant nonalcoholic fatty liver disease (NAFLD) after successful DAAs.

Materials and methods: 82 patients with CHC were examined, of which 56 were diagnosed with NAFLD and increased body weight. Ang-2, TGF-β1, leptin, adiponectin, and the degree of liver fibrosis were determined for all participants. The patients were divided into groups: 1 gr. (n=23) – CHC + increased body weight + hepatic steatosis, 2 gr. (n=33) – CHC + increased body weight + nonalcoholic steatohepatitis, 3rd gr. (n=26) – CHC. All patients received DAAs for 12 weeks.

Results: From 82 patients F_{3-4} had 31 people, F_{1-2} – 25, F_{0-1} – 11, F_0 -15 patients. F_{3-4} and steatosis S2-3 ($p<0.05$) was more common in patients of 2 gr.. Serum Ang-2 levels were higher ($p<0.05$) in patients of 2 gr. with F_{3-4}, than in patients with F_{0-2}. Fibrosis regression occurred more often in patients with 1 and 3 gr. with F_{1-2} than in patients 2 gr. and F_{3-4} and was accompanied by a decrease in Ang-2 and TGF-β1 levels.

Conclusions: High levels of Ang-2 and TGF-β1 are registered in patients with CHC+NAFLD, which correlate with the degree of liver fibrosis and significantly decrease after successful DAAs in patients with low initial stages of liver fibrosis and normal body weight.

KEY WORDS: chronic hepatitis C, NAFLD, increased body weight, fibrosis, regression, angiopoietin-2, transforming growth factor-β1

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INTRODUCTION

In recent years, the treatment of chronic hepatitis C (HCV) has undergone significant progress [1]. Direct-acting antiviral agents (DAAs) have made a breakthrough in the treatment of CHC with the possibility of sustained virological response (SVR) in more than 95% of patients [2,3]. Most patients who achieve SVR have a reduction in the degree of liver fibrosis and have a lower risk of developing hepatocellular carcinoma (HCC). However, some patients may experience progression of liver fibrosis and/or development of HCC after successful HSV eradication with DAAs. [4]. Long-term persistence of HCV in the liver tissue, followed by inflammation, leads to angiogenesis, fibrosis, cirrhosis and HCC [5]. The rate of progression of fibrosis has been linked to various factors, in particular other liver diseases, including alcoholic and nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), obesity, hepatitis B virus infection, and HIV infection. The process of fibrogenesis in CHC is an appropriate reaction of the body to liver damage, which is initiated and maintained by a chronic inflammatory process [6, 7]. Cytokines are involved in the regulation of the development of the inflammatory reaction of liver tissue, apoptosis and necrosis of liver cells, the development of cholestasis and fibrosis [8]. The progression of liver fibrosis is accompanied by angiogenesis, regardless of the etiology of the liver disease [9,10]. One of the key factors in the development of fibrogenesis is transforming growth factor β (TGF-β1), which is the main profibrogenic cytokine that promotes the activation of liver myofibroblasts [11]. TGF-β also has proangiogenic ability and regulates the differentiation, proliferation and migration of pericytes [12]. Angiogenesis in liver damage is associated with increased levels of vascular endothelial growth factor (VEGF) and angiopoietins [13]. Angiopoietins are a group of vascular growth factors, and the most well-studied are angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) [14]. Ang-1 helps maintain the vasculature by acting as an endothelial preservation factor. Ang-2 is a biological antagonist of Ang-1, which is highly expressed at sites of vascular remodeling. It reduces vascular stability and makes VEGF more accessible to endothelial cells [15]. Prediction of fibrotic changes in the liver after HCV treatment is a crucial clinical problem [16].

Since the issue of NAFLD progression in CHC patients who have completed treatment with DAAs has not been definitively studied, and the data of scientific studies are

contradictory, this determined the relevance of our research.

THE AIM

To assess the dynamics of serum levels of angiopoietin-2 (Ang-2) and transforming growth factor-β1 (TGF-β1) in patients with chronic hepatitis C (CHC) with concomitant nonalcoholic fatty liver disease (NAFLD) after successful DAAs.

MATERIALS AND METHODS

The study was conducted at the Department of Faculty Therapy with the consent of the patients, and the methodology was in accordance with the Declaration of Helsinki of 1975 and its revision of 1983. The study was approved by the local ethics committee (protocol No. 6/2 dated 09/07/2021), and the participants read and signed the consent form , the structure of which corresponded to the officially accepted one.

Criteria for inclusion in the study: patients with a verified diagnosis of CHC genotype 1b with and without NAFLD, who agreed to follow-up.

Criteria for the exclusion of patients from the study: the presence of markers of infection with other hepatitis viruses (A, B, D), markers of autoimmune hepatitis/cross syndrome (anti-LKM-1, anti-SLA and anti-LC-1) and HIV infection, use of corticosteroids, nonsteroidal anti-inflammatory and immunosuppressive drugs, and the patient's decision to stop participating in the study.

Taking into account the specified criteria, only 82 patients with a verified diagnosis of CHC were included in the study, of which 56 had CHC combined with NAFLD and 26 patients with CHC without NAFLD. There were 53.7% (44) men, 46.3% (38) women. The average age of patients is 58.5±1.5 years. All patients received specific antiviral therapy: sofosbuvir 400 mg + daclatasvir 60 mg once a day for 12 weeks. The control group (n=25, average age 33.2±1.5 years) consisted of practically healthy individuals.

The diagnosis of HCV was established according to the International Classification of Diseases of the 10th revision and confirmed by the detection of RNA-HCV in the blood of patients by the method of polymerase chain reaction (PCR) in real time (RT-PCR) with determination of viral load and genotyping. The degree of activity of the pathological process was determined by the level of increased activity of ALT, according to the international classification of liver diseases (Los Angeles, 1994). The diagnosis of NAFLD was established according to the unified clinical protocol "Non-alcoholic steatohepatitis" (2014) and the adapted evidence-based clinical guideline "Non-alcoholic fatty liver disease" (2012), according to the recommendations of the European Association for the Study of the Liver (EASL).

In the work, Enzyme-Immuno-Sorbent-Assay (ELISA) was used to determine the levels of serum Angiopoietin-2 (Ang-2), transforming growth factor – β1 (TGF-β1), and leptin and adiponectin, according to the instructions attached to the kits Diagnostics Biochem Canada and DRG (USA) reagents. Indicators of biochemical blood analysis – total bilirubin, total protein, activity of serum cytolytic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), activity of cholestatic enzymes alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (GGT) were carried out in certified laboratories ("Dila" and "Synevo").

The degree of fibrosis and steatosis of the liver was determined by a non-invasive diagnostic method – FibroMax, which includes: FibroTest, ActiTest, SteatoTest, AshTest, NashTest and is carried out by BioPredictive (Paris, France) in commercial laboratories "Dila" and "Synevo" (BioPredictive, Paris). All participants underwent abdominal ultrasound and the amount of HCV RNA, angiopoietin-2, TGF-β1, leptin, and adiponectin was determined. The degree of liver fibrosis was assessed before and 24 and 48 weeks after the end of treatment. Body mass index (BMI) was determined for all patients. A BMI of 18.5-24.9 kg/m2 was considered normal body weight. A BMI > 24.9 kg/m2 was considered overweight.

The analysis and processing of the results of the examination of patients was carried out with the help of the Statistics for Windows v.7.0 computer program (StatSoft Inc, USA) using parametric and non-parametric methods for evaluating the obtained results. The difference was considered to be significant at $p<0.05$.

RESULTS

82 patients with CHC were examined, of which 56 (68,3%) were diagnosed with various degrees of NAFLD and increased body weight. According to the set tasks, patients were divided into groups: 1 gr. (n=23) – CHC + increased body weight + hepatic steatosis, 2 gr. (n=33) – CHC + increased body weight + nonalcoholic steatohepatitis, 3rd gr. (n=26) – CHC + normal body weight. The groups were representative by age and gender. All patients received DAAs for 12 weeks.

Of the 82 patients, 31 (37.8%) had progressive liver fibrosis (F_{3-4}), 25 (30.5%) had moderate fibrosis (F1-2), 11 (13.4%) had minimal fibrosis (F_{0-1}), and 15 people (18.3%) did not have fibrosis (F_0). Comparing groups of patients, it should be noted that progressive liver fibrosis F_{3-4} is more often registered in patients with CHC combined with NASH. It was also established that patients of group 2 (CHC+NASH) significantly more often than patients of groups 1 and 3 had pronounced steatosis of the liver S 2-3 (45.5% versus 30.4% and 3.9% of patients; $p< 0.05$) (Table I).

During the study of serum level of TGF-β1 in patients with CHC, an elevated level was found in 60 (73.2%) patients, a decreased level in 8 (9.8%) and a normal level in 14 (17.0%) patients. Serum Ang-2 levels were significantly higher in patients with CHC + NASH + increased body weight than in patients with CHC + steatosis + increased body weight and CHC without steatosis (by 1.8 and 2.3 times, respectively; $p<0$,05). It should be noted that se-

Table I. Data of the non-invasive FIBROMAX method before treatment

Indicator		Groups of patients		
		1	2	3
		CHC + increased body weight + hepatic steatosis (n=23) abs/%	CHC + increased body weight + NASH (n=33) abs/%	CHC + normal body weight (n=26) abs/%
Fibrosis degrees FibroTest	F_0 (n=15)	3/13.0	5/15.2	7/26.9
	F_{0-1} (n=11)	3/13.0	3/9.1	5/19.2
	F_2 (n=25)	10/43.5	9/27.2	6/23.1
	F_{3-4} (n=31)	7/30.4	16/48.5*	8/30.8
Activity of the necro-inflammatory process ActiTest	A_0 (n=19)	6/26,1	5/15.2	8/30.8
	A_1 (n=20)	7/30.4	7/21.2	6/23.1
	A_2 (n=23)	6/26.1	10/30.3	7/26.9
	A_3 (n=20)	4/17.4	11/33.3*	5/19.2
Steatosis degrees SteatoTest	S_{0-1} (n=37)	10/34.8	7/21.2	20/76.9
	$S_{>1}$ (n=22)	6/26.1	11/33.3	5/19.2
	$S_{>2}$ (n=23)	7/30.4	15/45.5*	1/3.9
Inflammation in metabolic disorders NashTest	N_0	0	0	0
	N_1 (n=17)	0	17/51.5	0
	N_2 (n=16)	0	16/48.5	0

Notes: * – significant difference in degrees of fibrosis, steatosis, and inflammation between groups (p<0,05)

Table II. Levels of fibrogenesis and angiogenesis cytokines in the examined patients

Group	Indicator			
	TGF-β1, pg/ml	Ang-2, pg/ml	Leptin (ng/ml)	Adiponectin (mcg/ml)
1 (n=23)	224,3±36,3*	325,4±22,5*	19,4±1,7*‥	52,4±12,3*‥
2 (n=33)	457,2±28,7*‥	573,2±45,8*‥	27,5±2,2*‥	30,5±2,7*‥
3 (n=26)	176,2±15,3*	254,6±27,5*	12,3±1,5	68,5±7,2
Control (n=20)	134,0±14,5	128,5,0±5,2	6,5±0,7	77,4±9,5

Note. Significance of the difference: * – with the control group; •• – with group 3 (the indicator was calculated according to the Mann-Whitney test, p<0.05).

rum levels of Ang-2 were significantly higher (p<0.05) in patients with CHC + NASH with BMI > 24.9 kg/m2 and progressive degrees of fibrosis (F_{3-4}), than in patients with a degree of fibrosis to F_2 and normal body weight.

The average values of Ang-2 and TGF-β1 were increased in all CHC patients with the highest values in group 2, which was significantly (p<0.01) different from the corresponding values of patients in groups 1 and 3. IAs blood leptin levels increased, the degree of hepatic steatosis increased, corresponding to higher levels of Ang-2. Serum levels of leptin and adiponectin were significantly higher in patients with CHC + NAFLD than in patients with CHC. The concentration of leptin in patients with CHC + NASH was increased by 4.2 times, and in patients with CHC with simple steatosis – by 2.9 times, compared to the control group. At the same time, the serum level of adiponectin in patients of groups 2 and 1 was reduced by 2.5 times and 1.4 times, respectively, in comparison with patients of group 3 (Table II).

Based on the results of Fibromax, 24 weeks after the end of successful antiviral therapy (DAAs), regression of liver fibrosis stages was registered in 65.6% (54/82) of patients. Liver fibrosis regression was defined as a decrease in fibrosis by more than one stage for patients with data from F_2 to F_4, and for patients with liver fibrosis F_{0-1}, if the stage of liver fibrosis did not worsen.

DISCUSSION

12 weeks after the successful elimination of the hepatitis C virus, 97.6% (80/82) of patients with NAFLD had normalization of markers of cytolysis (ALT, AST) and cholestasis (bilirubin, ALP, GGT). Similar data were obtained by a group of scientists led by Van der Meer AJ [17], who found that ALT, AST and alkaline phosphatase significantly decreased 12 weeks after successful treatment with DAAs.

24 weeks after HCV eradication, a significant decrease in the activity of the necroinflammatory process was estab-

lished in 96.3% (79/82) of patients. It was found that the regression of liver fibrosis was significantly more frequent ($p<0.001$) in patients with CHC without steatosis and with lower stages of fibrosis before treatment than in patients with CHC combined with steatosis or NASH.

The study of the dynamics of the Ang-2 level in patients with CHC after treatment with DAAs showed a significant decrease (value $p<0.001$) in persons who underwent regression of liver fibrosis, and a slight decrease in patients without regression of fibrosis (value $p=0.072$). These data overlap with the data obtained by Makhlouf MM. etc. [18]. In patients with CHC + NASH + increased body weight who had higher initial stages of liver fibrosis, serum Ang-2 levels did not decrease significantly after treatment with DAAs, and no regression of liver fibrosis was registered. Our results are consistent with the data of Osawa et al., who found a significant decrease in Ang-2 among F_{0-3} patients ($p <0.001$), and a slight decrease (p 0.136) in F_4 patients [19]. Similar data were obtained by Lefere et al. [20] who found that serum Ang-2 levels are significantly higher in patients with NASH than in patients with simple hepatic steatosis but without CHC.

A positive correlation of leptin and Ang-2 values ($r=0.49$; $p<0.05$) with the degree of fatty infiltration of the liver was revealed, while a similar relationship between the adiponectin/leptin ratio was negative ($r=-0.34$; $p <0.05$). As blood leptin levels increased and the adiponectin/leptin ratio decreased, the degree of hepatic steatosis increased, corresponding to higher Ang-2 levels. It is obvious that angiogenesis is influenced by cytokines involved in the formation of NAFLD. Leptin is an adipokine that regulates satiety, has a key role in obesity and stimulates angiogenesis [21].

In CHC patients with low stages of fibrosis ($\leq F_2$) after treatment, a significant decrease in TGF-β1 levels was registered against the background of regression of fibrosis and a decrease in the necroinflammatory activity of the process according to Fibromax data. However, in 10 out of 16 (62.5%) patients with CHC+NASH with fibrosis stage F_{3-4} after successful DAAs, regression of liver fibrosis was not registered, and TGF-β1 levels remained high, which confirms the involvement of TGF-β1 in fibrogenesis. A high level of TGF-β1 in patients with CHC is associated with the risk of developing liver cirrhosis and hepatocellular carcinoma, as reported by Radwan M.I. et al. [22].

CONCLUSIONS

1. High serum levels of angiopoietin-2 and transforming growth factor – β1 are registered in patients with CHC+NAFLD, which correlate positively with the stage of fatty infiltration of the liver and the degree of liver fibrosis.
2. In patients with CHC + NAFLD, a decrease in the levels of angiopoietin-2 and transforming growth factor – β1 after successful eradication of HCV and low stages of liver fibrosis before treatment are predictors of regression of liver fibrosis.
3. Increased body weight, high leptin level, higher initial degree of liver fibrosis before treatment can be negative predictors of regression of liver fibrosis in patients with CHC + NAFLD after successful DAAs, which must be taken into account during further observation of such patients.
4. High serum levels of angiopoietin-2 and transforming growth factor-β1 may be an important biomarker of liver angiogenesis and fibrogenesis in patients with CHC on the background of NAFLD.

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ORIGINAL ARTICLE

THE CLINICAL EXPERIENCE OF THE EFFECTIVE USE OF DAPAGLIFLOZIN IN COMORBID CARDIAC PATIENTS WITH CONCOMITANT TYPE 2 DIABETES MELLITUS AND ARTERIAL HYPERTENSION ON THE BACKGROUND OF OVERWEIGHT IN OUTPATIENT SETTING

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ABSTRACT

The aim: To assess the efficacy and safety of dapagliflozin in the treatment of comorbid cardiac patients with type 2 diabetes mellitus (T2DM) in combination with arterial hypertension (AH) and overweight in outpatient setting.

Materials and methods: Under observation were 19 patients who were treated in outpatient setting during 2019-2021 for AH and had T2DM, overweight or obesity. As part of complex treatment, patients received dapagliflozin 10 mg once a day for 12 months.

Results: The normalization of blood pressure, elimination of heart failure symptoms on the background of increased ejection fraction, improved indicators of the functional capacity of the kidneys, and a decrease in the degree of proteinuria/albuminuria were noted after treatment. The patients had an easier time losing weight (body mass index and waist circumference decreased; $p<0.05$) and decreased levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). None of the monitored patients had cases of hypoglycemia or urinary tract infection. The number and/or doses of antihypertensive, hypouricemic and diuretic drugs were gradually reduced.

Conclusions: Using dapagliflozin in a standard dose of 10 mg/day in the complex therapy of patients with T2DM in combination with arterial hypertension and overweight contributes not only to the normalization of blood pressure, but also to a reduction in body weight and waist circumference. The proposed therapy can be an alternative for the treatment of patients with T2DM with concomitant overweight or obesity, arterial hypertension, with or without heart and/or renal failure as a first-line antidiabetic drug.

KEY WORDS: arterial hypertension, type 2 diabetes mellitus, body weight, dapagliflozin

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INTRODUCTION

The cardiovascular disease (CVD) remains the leading cause of death and disability worldwide. However, Ukraine, where the mortality from CVD is 64.3% [1], is a region with a very high cardiovascular risk [2] for various, primarily socio-economic, environmental and mental reasons. The main risk factors for cardiovascular mortality in Ukraine include smoking, unhealthy diet, low physical activity, alcohol abuse, obesity, and air pollution [1]. An additional risk factor has become daily life problems, burdened by "covid" restrictions and stresses, which often lead to AH, atherogenic dyslipidemia, T2DM, and their complications. That is why comorbid patients with various combinations of cardiometabolic syndrome (obesity, arterial hypertension, dyslipidemia, hyperuricemia, impaired glucose tolerance or diabetes mellitus) dominate today among cardiac patients. This leads to long-term prescribing of a large number of medications by various specialists, often without taking into account possible drug interactions. Therefore, the search for drugs with combined mechanisms of action and physiological effects that would have a positive effect on various links of the pathogenesis of cardiometabolic syndrome is extremely relevant.

From this point of view, a relatively new group of oral drugs for the treatment of T2DM – sodium-glucose co-transporter-2 inhibitors (SGLT-2 inhibitors) is considered promising. SGLT-2 ensures tubular reabsorption of up to 90% of glucose from the ultrafiltrate, and their inhibitors, due to the reduction of glucose reabsorption and, accordingly, glucosuria, have a hypoglycemic effect. Along with the hypoglycemic effect, SGLT-2 inhibitors have natriuretic and diuretic, and therefore hypotensive effects, and due to glucosuria, they contribute to a decrease in body weight [3]. The number of randomized studies of the effectiveness of SGLT-2 inhibitors in the treatment of T2DM revealed a positive effect on the cardiovascular system and kidneys even in patients without established atherosclerotic CVD and chronic kidney disease [4,5]. Further studies of SGLT-2 inhibitors revealed their effectiveness in reducing the risk of cardiovascular and renal complications both in patients with T2DM and heart failure (HF), and without them [6,7]. Since all the mechanisms of favorable cardioprotective effects of SGLT-2 inhibitors have not been fully established, the study of this issue is relevant.

THE AIM

The aim was to assess the efficacy and safety of dapagliflozin in the treatment of comorbid cardiac patients with T2DM in combination with AH and overweight in outpatient setting.

MATERIALS AND METHODS

The studies were conducted with the informed consent of the patients, and their methodology was in line with the Declaration of Helsinki of 1975 and its revision of 1983 and was approved by the local bioethics commission of UzhNU (Protocol No. 1 dated 10.01.2020), and its participants read and signed the consent letter, the structure of which corresponded officially accepted. There were 19 comorbid patients under observation who were treated in outpatient setting by a cardiologist during 2019-2021 for hypertension and had various combinations of cardiometabolic syndrome, overweight or obesity, and T2DM. All patients were consulted by an endocrinologist and received dapagliflozin 10 mg once a day as part of complex treatment, as a new antidiabetic drug.

Among the patients were 5 people with newly diagnosed T2DM (1 patient with estimated glomerular filtration rate (eGFR) of 48 ml/min, 4 patients with existing cardiovascular and renal pathology), who received dapagliflozin as the first and only antidiabetic drug; 6 patients received metformin 1000 mg + dapagliflozin due to insufficient effectiveness of metformin; 3 patients were prescribed dapagliflozin instead of sulfonylurea derivatives; 5 patients received dapagliflozin to replace the combination of metformin with sulfonylurea derivatives due to eGFR less than 60 ml/min (2 patients) or the presence of cardiac and renal pathology (3 patients).

Only patients who received dapagliflozin 10 mg for more than 12 months were included in the study. Among them were 17 men and 2 women, aged from 42 to 63 years.

All patients underwent a general clinical examination and special examination methods, which included: ECG, echocardioscopy, ultrasound examination of extracranial vessels, eGFR, general urinalysis, fasting blood glucose, glycated hemoglobin, blood insulin and insulin resistance index, total cholesterol, low and high density lipoproteins, triglycerides, uric acid, and potassium level in the blood. All studies were carried out in certified laboratories. Also, body mass index (BMI) was calculated and waist circumference (WC) was determined for all patients.

Due to quarantine restrictions, the current control was carried out online, laboratory tests were carried out at the place of residence on an outpatient basis, taking into account the need once every 3-6 months, ECG and echocardioscopy – once every 6-12 months.

At the same time, patients continued to receive basic therapy, which included the standard prescription of lisinopril and losartan, amlodipine and verapamil, spironolactone or eplerenone, and torasemide (furosemide if there is a risk of hyperkalemia). Beta-blockers were prescribed only in case of direct indications, preference was given to metabolically neutral nebivolol. When antiatherothrombotic therapy was indicated, statins (atorvastatin, rosuvastatin) and an antiplatelet agent were prescribed (taking into account the frequent presence of hyperuricemia, clopidogrel was preferred). In case of hyperuricemia (uric acid over 360 μmol/l in patients with gout and over 400 μmol/l in patients without gout), allopurinol was prescribed (if eGFR is less than 60 ml/min – flebuxostat).

The criteria for the effectiveness of the therapy were the normalization of blood pressure ((BP) 120/70-130/80 mm Hg) and heart rate (HR) (60-80 bpm), carbohydrates (glycated hemoglobin 6-7%), lipid (LDL-C < 2.4 mmol/l), electrolyte (blood potassium 3.5-5.0 mmol/l) and purine (blood uric acid 200-360 μmol/l) exchanges. The ultimate aim of therapy was the reduction or absence of symptoms of heart failure: shortness of breath and edema against the background of increased left ventricular ejection fraction (EF), signs of kidney damage (proteinuria or albuminuria) and renal failure (decrease in urine albumin/creatinine index and increase in eGFR). The analysis and processing of the results of the examination of patients was carried out using the Statistics for Windows v.7.0 computer program (StatSoft Inc, USA) using parametric and non-parametric methods of evaluating the obtained results. The difference was considered probable at $p<0.05$.

RESULTS

After the treatment, a gradual improvement of the cardiovascular system was observed in all patients, which consisted in a decrease in shortness of breath, leg's edema, and after 12 months of treatment, shortness of breath remained only in 3 patients, and none of the patients had leg's edema. BP normalization was noted (on average from 176/103 mm Hg to 135/84 mm Hg, $p<0.05$) with a gradual reduction in the total number of antihypertensive drugs; elimination of HF symptoms against the background of an increase in EF on average from 56±2.4 to 57±1.3% (only 3 patients had HF symptoms with moderately reduced HF). Indicators of the functional ability of the kidneys improved, in particular, eGFR increased from 72±2.6 to 81±3.8 ml/min/1.73 m2 on average, $p<0.05$, and the degree of proteinuria/albuminuria decreased. Patients noted that it was easier for them to lose weight than before, as evidenced by the dynamics of the degree of obesity (BMI decreased from 36±1.6 to 31±1.2 kg/m2, WC – from 144±3.2 to 126±2.2 cm, respectively; $p<0.05$). A positive effect of dapagliflozin on lipid metabolism was noted, as the levels of total cholesterol and LDL-C significantly decreased (from 6.4 mmol/l to 5.2 mmol/l, and from 4.2 mmol/l to 2.6 mmol/l, respectively; $p<0.05$) (Table I).

Were established that the appointment of dapagliflozin leads to a reduction in the need for diuretics. Thus, the number of patients taking diuretics decreased from 8 to 4. In four patients without atherosclerotic CVD, temporarily, under the control of the lipid profile, statins were discontinued. None of the monitored patients had cases of hypoglycemia or urinary tract infection.

Table I. Dynamics of clinical and laboratory indicators on the background of taking dapagliflozin

Indicators	Before treatment (n=19)	After 6 months of treatment (n=19)	After 12 months. treatment (n=19)
BMI (kg/ m2) (M±m)	36±1,6	33±1,6	31±1,2*
WC (cm) (M±m)	144±3,2	134±3,6	126±2,2*
Overweight (number of the patient)	5	7	7
Obesity class I	8	7	8
Obesity class II	6	5	4
Obesity class III	0	0	0
HR (bpm.) (M±m)	86±1,8	74±1,3	72±1,3
BP systolic (mm Hg.) (M±m)	176±3,4	136±1,9	135±1,8*
BP diastolic (mm Hg.) (M±m)	103±2,3	85±1,4	84±1,2
Normal (number of the patients)	0	4	4
High normal (number of the patients)	0	11*	12*
Grade 1 hypertension (number of the patients)	6	4	3
Grade 2 hypertension (number of the patients)	10	0	0
Grade 3 hypertension (number of the patients)	3	0	0
EF (%): (M±m)	56±2,4	56±1,8	57±1,3
Preserved (number of the patient)	12	13	14
Moderately reduced (number of the patients)	6	6	5
Reduced (number of the patients)	1	0	0
Symptoms of HF:			
Shortness of breath (number of the patients)	18	8*	3*
Edema of the lower legs (number of the patients)	12	2*	0
Fasting blood glucose (mmol/l)	8,6±0,4	7,8±0,3	6,8±0,4*
Glycated hemoglobin (%)	7,4±0,2	6,6±0,3	6,4±0,3
Insulin (μIU/ml)	28±1,2	34±2,2	24±1,8
Index of insulin resistance	12,5±0,8	14,4±	7,8±0,6*
Total blood cholesterol (mmol/l)	6,4±0,5	5,4±0,4	5,2±0,4
LDL-C (mmol/l)	4,2±0,2	3,0±0,3*	2,6±0,2*
Uric acid (μmol/l)	398±12	286±8*	234±11*
Blood potassium (mmol/l)	4,2±0,08	4,5±0,1	4,4±0,1
Blood creatinine (μmol/l)	112±4,8	98±3,6	96±4,2
eGFR (ml/min/1.73 m2)	72±2,6	80±4,4	81±3,8
Albuminuria (number of the patients)	11	9	7
Proteinuria (number of the patients)	6	4	3
Albumin/creatinine index (mg/mmol) (number of the patients)			
< 3.4 - normal	6	9	12
3.4 - 33.9 - abnormal	9	7	6
>33.9 - high abnormal	4	3	1

Note: The significance of the difference:* – with the indicator before treatment (the indicator is calculated according to the Mann-Whitney test, $p<0.05$).

DISCUSSION

In the observed patients the cardioprotective effect of dapagliflozin was manifested in the reduction of the number of persons with shortness of breath from 19 to 3, the disappearance of edema on the lower legs in all patients, and the increase of the ejection fraction. The mechanisms of favorable cardioprotective effects of SGLT-2 inhibitors have not been fully established, but it is believed that they are based on the reduction of pre- and afterload on the heart due to natriuresis and diuresis, a positive effect on energy

metabolism in the myocardium, prevention of its fibrosis and remodeling [8]. The improvement of indicators of the functional capacity of the kidneys, in particular, an increase in eGFR and a decrease in the degree of proteinuria/albuminuria, may be one of the factors in reducing the further need for antihypertensive, hypouricemic, and diuretic drugs. The decrease in body weight registered by us in all patients is obviously caused by glucosuria, due to a decrease in glucose reabsorption, which is a characteristic feature of SGLT-2 inhibitors and coincides with the data of other researchers [3].

The fact that there were no patients with decompensated T2DM among the patients, and no sharp improvement in the indicators of carbohydrate metabolism was observed. Nevertheless, a year after the appointment of dapagliflozin, only five patients were also taking metformin, and one, with contraindications to it (eGFR less than 60 ml/min/1.73 m2) – a sulfonylurea derivative (glurenorm). At the same time, the improvement of health indicators occurred against the background of a gradual decrease in the number and/or dose of antihypertensive, hypouricemic, and diuretic drugs.

That why, can be talked about the pleiotropic effects of dapagliflozin, which are not directly related to its effect on carbohydrate metabolism. A temporary increase in insulin resistance and compensatory hyperinsulinemia in those patients who were prescribed dapagliflozin to replace metformin deserves additional study.

At the end of the study, all patients continued to take dapagliflozin 10 mg, as there was no case of a decrease in the functional capacity of the kidneys or the development of hypoglycemia.

The data was obtained confirm the positive effect of dapagliflozin both on the components of the cardiometabolic syndrome (obesity, hypertension, T2DM), and the prevention of cardiovascular complications, in particular, heart and kidney failure. Thanks to these properties, dapagliflozin is included in the European and American guidelines not only for the treatment of T2DM [9,10], but also for the prevention of cardiovascular pathology in general [2].

Analyzing the obtained data, we the conclusion that dapagliflozin is effective and safe and can be an alternative for the treatment of patients with T2DM with overweight or obesity and arterial hypertension, with or without heart and/or renal failure.

CONCLUSIONS

Using dapagliflozin in a standard dose of 10 mg/day in the complex therapy of patients with T2DM in combination with arterial hypertension on the background of overweight or obesity contributes not only to the normalization of blood pressure, but also to a reduction in body weight and waist circumference. The absence of unwanted effects of the therapy makes it possible to use it widely and for a long time in outpatient clinical practice. The proposed therapy can be an alternative for the treatment of patients with T2DM with concomitant overweight or obesity, arterial hypertension with or without heart and/or renal failure as a first-line antidiabetic drug.

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ORIGINAL ARTICLE

MORPHOLOGICAL RESEARCH OF ADHESIONS IN PATIENTS WITH TUBOPERITONEAL INFERTILITY

DOI: 10.36740/WLek202210115

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ABSTRACT

The aim: To study history, clinical manifestations and histological structure of adhesions in patients with tuboperitoneal infertility.

Materials and methods: 66 women with tuboperitoneal infertility and 30 healthy women were studied. The criterion for inclusion in the study was the presence of adhesions of the 2nd and 3rd degrees by J. Hulka et al. classification. During laparoscopy adhesions were sampled. Serial histological sections after preparation were stained with hematoxylin and eosin, picrofuxin according to van Gizon and fuxelin according to Hart.

Results: The study showed that patients with tuboperitoneal infertility, unlike the control group, had surgery on the abdominal cavity and pelvic organs much more often, as well as inflammatory diseases of the reproductive organs. The majority of women in the control group had childbirth in history, whereas among the patients with infertility ectopic pregnancies and abortions prevailed. All examined women had adhesions that were confirmed during laparoscopy. The study showed that ultrasound is not an informative method to confirm this pathology. A histological study of adhesions revealed the presence of differences in their structure depending on the etiological factor (surgery or inflammation).

Conclusions: Necessary to take into account the presence or absence of a chronic inflammatory process while developing approaches for the secondary prevention of the formation of adhesions in women with tuboperitoneal infertility at the stage of postoperative rehabilitation and infertility treatment.

KEY WORDS: adhesions, tuboperitoneal infertility, histological examination

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INTRODUCTION

In gynecological practice, the problem of adhesions in the pelvis is quite common [1-3]. According to the data from many authors, the presence of adhesions has a negative impact on the health of patients [4]. This is due to the fact that the presence of even small adhesions leads to dysfunction of the fallopian tubes, resulting in the preconditions for the development of tuboperitoneal infertility or ectopic pregnancy [5]. The adhesion process can disrupt the anatomical relations of the pelvic organs, uterus, uterine appendages, the function of adjacent organs – rectum, bladder leading to the development of intestinal obstruction [6].

While studying the anamnesis of women with adhesions of the pelvic organs, it was found that up to 60% of them suffer from infertility [2, 7] and noncarrying of pregnancy [8]. Most of them have inflammatory processes of the genitals and various forms of menstrual disorders [9].

THE AIM

The aim of this study was to study the history, clinical manifestations and histology in patients with tuboperitoneal infertility.

MATHERIALS AND METHODS

66 women with tuboperitoneal infertility and 30 healthy women were examined. Patients with infertility were randomly divided into 2 groups: main (1 group, 34 women) and comparison (2 group, 32 women). Healthy women formed a control group (group 3). All examined patients aged 25 to 42 years. That relates to the criteria for selecting them for the study. Surgery is the last stage of detection and treatment of women with infertility. This is due to the fact that the objective criteria for the presence or absence of adhesions in the abdominal cavity is their visualization, which is possible by laparotomy or laparoscopy. Women in the control group were selected on the case-control study basis, where the selection criterion was age.

The women were studied by taking anamnesis, evaluation of clinical manifestations and undertaking of additional examinations.

There are a significant number of classifications of the adhesion process. We have chosen the classification of adhesion process of pelvic organs by J. Hulka et al. [10]. In this classification there are 4 stages of adhesion process and obstruction of fallopian tubes is taken into account:

1st degree – adhesions are minimal, fallopian tubes are passable, visible most of the ovary;

2nd degree – more than 50% of ovarian surface is free, ampullary occlusion with preservation of folds;

3rd degree – less than 50% of ovarian surface is free, ampullary occlusion with destruction of folds;

4th degree – the surface of ovary is not visible, bilateral hydrosalpinx [11].

The criterion for inclusion in the study was presence of adhesions of 2nd and 3rd degree. Women with the 1st degree were excluded due to tubal patency and the possibility of natural pregnancy. Women with the 4th degree were excluded because hydrosalpinx reduces the possibility of pregnancy and requires removal. This leads to direct indications for in vitro fertilization.

All patients underwent ultrasound scan of pelvic organs, which was performed on the 5th-10th of menstrual cycle by a endovaginal transducer with a frequency of 7.5 MHz on the device Aloka SSD-680 (Japan). The shape and size of uterus, ovaries and the presence of adhesions' signs were assessed on the echograms.

Adhesions of pelvic cavity were obtained with the help of laparoscopy by the following method: pelvic adhesion is pulled through the trocar, washed in saline (0.9% sodium chloride),preserved in solution of formalin (50 ml) for 24 hours and then in 70% ethyl alcohol until the study is performed. After dehydration, the pieces were poured into paraffin according to standard methods. On a rotary microtome Microm HM325 with STS slice transfer system (Carl Zeiss, Germany) serial histological sections 3-4 μm thick were made. Then they were stained with hematoxylin and eosin according to standard methods, picrofuxin according to van Gizon, and fuxelin according to Hart in order to determine elastic fibers. Microscopy of the samples was performed on an Olympus AX70 Provis microscope (Olympus, Japan) using image analysis program the Analysis 3.2 Pro (Soft Imaging, Germany) according to the software manufacturer's recommendations.

Data processing was performed using the methods of variation statistics, $\chi 2$-criterion and Fisher's exact test.

RESULTS

The average age of the examined women was 33.25 ± 2.68; 35.18 ± 1.73 and 32.43 ± 2.59 years, accordingly by groups. About half of the patients aged 30-35 years, and after 40 years – only one woman in the main group and two women in the comparison group. There was no significant difference in the studied groups in terms of age structure and average age (p> 0.05).

According to social status, women were distributed in the following way: the majority of the examined were residents of the city (73.53%; 68.75% and 70.00%, respectively, by groups) with secondary (23.53%; 21.88% and 10.00%) or higher education (52.94%; 46.88% and 53.33%). No significant difference was found between groups by place of residence and education (p> 0.05).

Women with tuboperitoneal infertility did not differ in the frequency of somatic pathology. Most commonly they had gastrointestinal (20.59% and 15.63% in the 1st and 2nd group, respectively, p> 0.05), urinary tract diseases (17.65% and 21.88%, p> 0.05) and various types of allergies (14.71% and 18.75%, p> 0.05). The absence of somatic diseases in women in the control group was related to the selection criteria.

Analysis of anamnesis for surgical interventions showed that healthy women of reproductive age usually had tonsillectomy (6.67%) and appendectomy (3.33%) in the past. While patients with tuboperitoneal infertility in every third case had surgery on the pelvic organs (32.35% and 28.13%, respectively, in groups, p> 0.05). It should be noted that some women in the main and comparison groups had repeated operations on the pelvic organs (36.36% and 22.22% among all the operated on the pelvic organs, p> 0.05). The leading cause of surgery in women with tuboperitoneal infertility were ectopic pregnancy and inflammation in the area of the uterine appendages. According to other researchers, women with peritoneal infertility in 30-40% of cases had surgery on the pelvic organs [12,13].

The age of menarche of all the examined women did not differ significantly and was 12.33 ± 0.42; 12.45 ± 0.37 years and 12.58 ± 0.51 years (p> 0.05). The duration of menstruation and the menstrual cycle were also comparable to groups (p> 0.05). While in the nature of menstrual function some differences between women with tuboperitoneal infertility and without it were revealed. Women with tuboperitoneal infertility were more likely to have profuse (23.53% and 18.75% compared with 0% in the control, p <0 , 05) and painful (32.35% and 21.87% compared with 6.67%, p <0.05) menses.

The study of gynecological history of the examined women did not reveal a difference between the main and the comparison group (p> 0.05). Due to the selection criterio there was no history of gynecological pathology in the control group (women had to be gynecologically healthy). Two thirds of women in the main and comparison groups had a history of inflammatory diseases of the genital organs (73.53% and 65.62%, p> 0.05), and in half of them they were recurrent (41.17% and 31.25% of the total number of the examined, p> 0,05).

The results of studies of other authors showed that almost all (90%) patients with tuboperitoneal infertility have a history of inflammatory processes of the uterine appendages, and a third of them – frequent exacerbations [7,14-16]. Many researchers point to the frequent occurrence of tuboperitoneal infertility after salpingo-oophoritis (33-70.0%) [7, 15, 17]. It is considered that the body responds with series of protective specific or nonspecific reactions to certain bacteria [18-21].

None of the women had endometriosis because the study included women with tuboperitoneal infertility and endometriosis is a separate factor of infertility. According to the criteria of inclusion in the study, all the examined women had infertility. In large part of them it was secondary (67.65% and 71.88%, respectively, by groups, p> 0.05). 5 women (14.71%) from the main group and 3 women (9.38%) from the comparison group had surgery for ovarian cysts (p> 0.05). An additional adverse factor was that in most cases operations were performed in connection with cyst apoplexy. The cause of the intervention was ectopic pregnancy in some of the operated (4 and 3 or 11.76% and 9.38%, respectively, by groups, p> 0.05). Almost all the patients with infertility had cervical pathology in the past (73.53% and 81.25%, p> 0.05), and in most cases it was cervicitis or mild dysplasia.

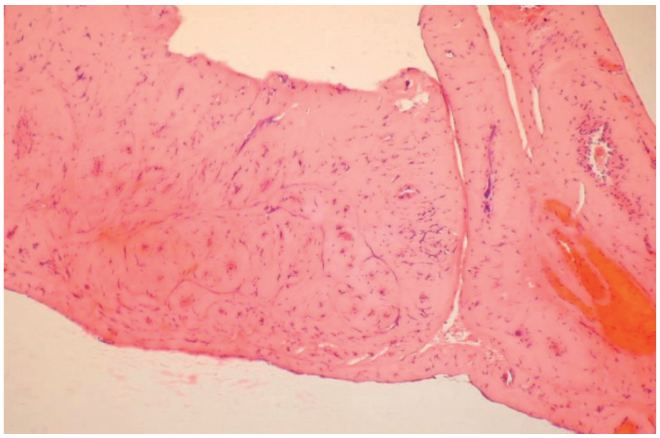

Fig. 1. Formation of scar. Hematoxylin and Eosin stain (x100 magnification)

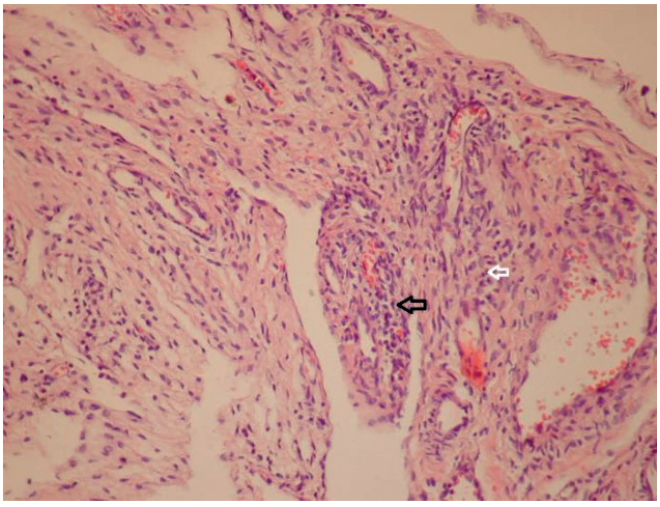

Fig. 2. Focal lymphoplasmocytic infiltration around vessels with a large number of plasma cells (indicated by arrows). Hematoxylin and Eosin stain (x100 magnification)

Analysis of reproductive history of the patients showed that a significant number of them had pregnancies in their lifetime (67.65; 71.88% and 90.0%, respectively, by groups), but there was a considerable difference in their structure. The majority of women in the control group had childbirth (70.0% compared with 20.59% and 28.13% in the 1st and 2nd groups, p <0.05), while the studied women with infertility mostly had ectopic pregnancies (11.76% and 9.36% compared, p <0.05) and abortions – spontaneous – 14.71% and 21.88%, medical – 26.47% and 25.00%, p <0, 05).

All the studied women underwent an ultrasound examination to detect signs of the adhesion process. All indications were divided into two categories: absolute and relative. The absolute indications were those that allow to visualize or locate adhesions: the presence of point or linear echopositive shadows on projection of the pelvic organs during ultrasonographic examination [22,23]; palpatory localization of connective tissue strands during bimanual gynecological examination. Relative indications included a displacement of the internal genitalia from standard anatomical terms of location, which was recorded during gynecological or ultrasound examination.

Thus, linear (64.71% and 78.13%) and small-point (79.41% and 75.0%) adhesions were visualized during the operation in most cases; A third of the women were revealed severe paraovarian fibrosis (32.35% and 43.75 %), whereas due to ultrasound examination adhesions were found 3-5 times less often (p <0,05). Regarding such sign as a displacement of the pelvic organs, the ultrasound was quite informative and we did not recorded a significant variation according to ultrasound and laparoscopy (p> 0.05).

The number of women with 2nd and 3rd degree of the adhesion process was almost the same in both groups, but there was a slight increase of patients with the 3rd degree of the adhesion process. (55.88% compared to 44.12% ; 62.50% compared to 37.50%, respectively, in groups, p> 0.05).

During laparoscopy, andhesions' samples were taken and histologically examined. It should be noted that we found some differences in the histological structure of the adhesions in women with history of surgery and without such.

Thus, in women with surgery on pelvic organs, adhesions were represented by dense or very dense connective tissue (Fig 1) with foci of excess collagen fibers in form of bundles going in one direction and a small number of fibroblasts. The presence of elastic fibers in the places of collagen accumulation was also noted.

The studied women without surgical interventions in the past were characterized by the presence of infiltration foci, which consisted of lymphocytes, plasma cells, and a small number of segmented neutrophils (Fig 2). In addition, clusters of fibroblasts were noticed, connective tissue was loose, collagen fibers went in different directions, elastin fibers were absent.

DISCUSSION

Bases on the analysis, the patients in the main and the comparison groups differed from the control group by several characteristics, which were determined by:

1) Chronic processes of the pelvic organs that play significant role in the pathogenesis of formation and progression of adhesive disease.
2) The presence of surgical interventions on the organs of the abdominal cavity and pelvis, a significant frequency of repeat operations, as well as inflammatory diseases of the reproductive organs.
3) Difference in the frequency of detection of the adhesion process by ultrasound and laparoscopy. According to literature, in order to visualize an adhesion during ultrasonographic examination, its thickness should be at least 5-6 mm, otherwise there is no refraction of the ultrasonic wave in the tissues [22, 23]. Adhesions in the pelvic cavity with such characteristics are quite rare.
4) Adhesion process, which was confirmed by laparoscopy, while ultrasound was an uninformative method to confirm this pathology.
5) Histology of the adhesions that revealed differences in their structure depending on factor that caused their formation (surgery or adhesion disease), as well as the presence of inflammation signs in women with the lack of clinical signs of inflammatory process and no surgery in the past.

CONCLUSIONS

The study showed that women with tuboperitoneal infertility have a history of surgical interventions on the pelvic organs, which are often repeated. Almost all suffered one or more episodes of inflammation of the reproductive organs. The structure of adhesions differs depending on the etiological factor. Due to histological study, the inflammatory process is detected even in the absence of its clinical signs and treatment in the past.

PROSPECTS FOR FURTHER RESEARCH

The data indicates the need to take into account the presence or absence of chronic inflammation in the development of approaches to secondary prevention of adhesions in women with tuboperitoneal infertility at the stage of postoperative rehabilitation and infertility treatment. Further research is needed to study the effectiveness of tuboperitoneal infertility treatment depending on the factor of the adhesion process in the pelvic cavity.

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ORIGINAL ARTICLE

EFFECTIVENESS OF LISINOPRIL AND AMLODIPINE COMBINATION AT HYPERTENSION WITH COMORBIDITY OF ARTERIOSCLEROSIS OBLITERANS IN GENERAL PRACTICE

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ABSTRACT

The aim: To analyze the dynamics of daily monitoring of blood pressure, intracardiac (according to echocardiography), peripheral hemodynamics (according to ultrasound of the vessels of the lower extremity), the thickness of the intima-media complex (according to carotid sonography) in patients with hypertension the effect of treatment with a combination of lisinopril and amlodipine.

Materials and methods: The study included 40 patients with hypertension with 2 (29 patients) and 3 (11 patients) degrees of hypertension in combination with AOLE with I-III stages of chronic insufficiency of the lower extremity, which revealed hyperkinetic, eukinetic, and hypokinetic types of hypertension with a predominance of the sympathetic nervous system. The groups are comparable in age, sex, duration of hypertension, and medications received in the previous stages. For antihypertensive therapy, the most common drugs for use were selected – lisinopril + amplodipine in fixed doses of 10 and 5 mg, respectively. If after 2 weeks we did not reduce the mean level of SBP and DBP by 10% or more from baseline, we doubled the dose of lisinopril without changing the dose of amlodipine.

Results: After 6 months of treatment, in particular, an increase in the pulse index – by 24.8%, a decrease in the resistance index – by 21.1%, an increase in linear and volumetric blood velocity – by 25.6% and 27.4%, respectively, while achieving the target blood pressure.

Conclusions: It is proved that in the absence of individual contraindications the combination of lisinopril and amlodipine is optimal and universal for effective treatment of patients with hypertension in combination with AOLE in all types of central hemodynamics.

KEY WORDS: arteriosclerosis obliterans, hypertension, lisinopril, amlodipine

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INTRODUCTION

Hypertension is a serious medical and social problem due to high mortality, and disability, as well as high morbidity [1-4]. At the same time, the incidence of diseases of the arteries of the lower extremity, which include arteriosclerosis obliterans of the lower extremity (AOLE), is about 3% in patients under 40 years and more than 6% in elderly patients [5, 6]. According to the latest recommendations of 2016, experts from the AHA \ ACC (American Heart Association / American College of Cardiology) identify among the risk factors for AOLE that are similar to coronary heart disease and atherosclerosis in general: smoking, dyslipidemia, diabetes, and hypertension. The presence of hypertension increases the relative risk of AOLE by 2.8 times [7]. Early detection of AOLE, as well as quality management of patients with comorbidity of hypertension and AOLE, especially after undergoing reconstructive surgery for occlusions of the arteries of the lower extremity, is an important component of family physicians [8]. Therefore, a study on the effectiveness of different combinations of basic antihypertensive drugs in the comorbidity of hypertension and AOLE was considered relevant.

The effectiveness of the combination of an angiotensin-converting enzyme inhibitor (ACEI) and calcium channel antagonist (CCA) in the treatment of hypertension has been confirmed by ASCOT-BPLA studies [9]. This combination is included in the recommendations for the treatment of hypertension ESH/ESC (2018) as one of the best combinations for the treatment of elderly patients, as well as patients at high risk of cardiovascular complications, target lesions, and metabolic syndrome. Also, this combination is attractive because there is a "cross" effect of drugs on the pathogenetic mechanisms of the disease: decreased activity of renin-angiotensin and indirectly sympathoadrenal system for ACEI inhibitors and direct vasodilating effect of calcium antagonists. In addition, to date, a significant number of indirect pleiotropic effects of drugs of both groups, the synergy of which also plays a significant role in achieving not only antihypertensive but also organ protective effects [10].

THE AIM

The aim of the study was to analyze the dynamics of daily monitoring of blood pressure, intracardiac (according to echocardiography), peripheral hemodynamics (according to ultrasound of the vessels of the lower extremity), the

thickness of the intima-media complex (according to carotid sonography) in patients with hypertension the effect of treatment with a combination of lisinopril and amlodipine.

MATERIALS AND METHODS

The study included 40 patients with hypertension with 2 (29 patients) and 3 (11 patients) degrees of hypertension in combination with AOLE with I-III stages of chronic insufficiency of the lower extremity, which revealed hyperkinetic, eukinetic, and hypokinetic types of hypertension with a predominance of the sympathetic nervous system. The groups are comparable in age, sex, duration of hypertension, and medications received in the previous stages. Control group – 20 healthy people of the same age and sex. The diagnosis of hypertension was made according to the criteria of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) in 2018 and according to the guidelines of the AHA\ACC in 2017, and the diagnosis of AOLE – according to the ESH Recommendations for the diagnosis and treatment of peripheral arterial diseases in 2011. Blood pressure was measured by the Korotkov method with a mercury sphygmomanometer. The ECG was performed in 12 standard leads using the software and hardware complex of automated ECG analysis USEKG-01 CARDIO. Daily monitoring of blood pressure was performed with the device "Holter blood pressure measurement system" AVR-01. Structural and functional features of the left ventricle and the mass of the left ventricular myocardium (LVMM) were determined using a two-dimensional echocardiographic Doppler on BIOMEDICA (USA). The size of the left atrium (LA), end-diastolic size (EDS) and end-systolic size (ESS), left ventricular size (LV), and interventricular septal thickness (IVST) during diastole and ventricular posterior ventricular wall (LVPV) were determined. According to standard formulas (Teicholtza formula), end-diastolic (EDV) and end-systolic (ESV) volume, LV volume, and LV ejection fraction (EF) were calculated as a percentage. The LVMM and the LVMM index were calculated according to the Penn-Convention method.

Ultrasound of the vessels of the lower extremity was performed using the LODGIQ device (USA) using the Doppler effect. Blood flow was assessed by the aorto-femoral-popliteal-tibial segment by peak systolic velocity – (Vps-peak systolic velocity) – maximum blood flow velocity during systole; maximum end diastolic velocity (Ved – end diastolic velocity) – maximum blood flow velocity at the end of diastole; systolic-diastolic ratio, which characterizes the elasticity of the arterial wall, according to RI – peripheral resistance index, IP (pulsation index) – the ratio of the difference between peak systolic and maximum end-diastolic blood flow velocities to the average maximum blood flow velocity, Vv.

The state of the intima-media complex was assessed by its thickness (IMT) on the posterior wall of the common carotid artery 1 cm proximal to its bifurcation: TIM <0.9 mm – normal, IMT ≥ 1.0, but <1.3 mm – thickening, TIM ≥ 1.3 was regarded as atherosclerotic plaque.

For antihypertensive therapy, the most common drugs for use were selected – lisinopril + amplodipine in fixed doses of 10 and 5 mg, respectively. If after 2 weeks we did not reduce the mean level of SBP and DBP by 10% or more from baseline, we doubled the dose of lisinopril without changing the dose of amlodipine. The effective dose of lisinopril in patients with moderate and severe hypertension was 20 mg/day when combined with amlodipine at a daily dose of 5 mg. The antihypertensive effect of this combination of drugs occurred in most cases for 2-3 days, when blood pressure began to decline gradually, and in the case of selection of an effective dose for patients – for 10-12 days blood pressure reached the target level.

Statistical processing of the results was performed in Microsoft Excel XP using the paired Student's t-test to assess differences in indicators in the comparison groups, where data with $p < 0.05$ were considered reliable.

RESULTS

In the table I presents the obtained data Dynamics of daily blood pressure monitoring under the influence of treatment with the combination of lisinopril + amlodipine in patients with hypertension + AOLE. After 6 months of antihypertensive therapy (Table I) with the combination of lisinopril + amlodipine, 69% of patients reached the target level of office blood pressure, in 24% – a satisfactory antihypertensive effect – SBP decreased by 11 mm Hg. Art., DBP – 7 mm Hg. Art.

Analysis of the dynamics of daily monitoring indicators shows that long-term therapy with this combination was significantly effective in lowering blood pressure during the day, and especially at night. Also, after 1 month of lisinopril + amlodipine, the average daily heart rate decreased by 6.2% ($p < 0.05$), and after 6 months – the average daily heart rate decreased by 12.0% ($p < 0.01$). There was a significant difference in treatment before and after treatment with the combination of lisinopril + amlodipine.

Analysis of structural and functional changes in the myocardium in patients with the combination of lisinopril + amlodipine (Table II) after 6 months of treatment showed a tendency to reduce LVPV by 16.2% ($p < 0.05$), IVST – by 7.3% $p < 0.05$), LVMM – by 3.2% ($p < 0.05$) and ILVMM – by 3.2% ($p > 0.05$). This made it possible to improve hemodynamic parameters. Thus, EDV and ESV decreased by 6.4% ($p < 0.05$) and 11.9% ($p < 0.05$), respectively, and the emission fraction increased by 12.0% ($p < 0.05$).

Improvement in the structural and functional state of the heart muscle had a positive effect on central hemodynamic (CH) parameters (Table III).

Thus, there was an increase in Shock volume, Minute blood volume, Shock index, Cardiac index by 15.4% ($p < 0.05$), 17.4% ($p < 0.05$), 8.4% ($p < 0.05$) and 32, 3% ($p < 0.01$). At the same time, there is a decrease in Total peripheral vascular resistance and Specific peripheral vascular resistance – by 8.4% ($p < 0.05$) and 17.7% ($p < 0.05$).

It was noted that patients after the treatment increased the distance of 6-minute walk from 153.2 meters to 290.7 meters, which is almost 1.9 times.

Table I. Dynamics of daily monitoring of blood pressure under the influence of lisinopril and amlodipine in patients with hypertension + AOLE (n = 40)

Indicator, the measurement unit	The magnitude of the indicator (M + m)			p		
	Before treatment	in 1 month	in 6 months	p_{1-2}	p_{1-3}	p_{2-3}
The average daily SBP mmHg. Art.	169.9±3.1	142.4±2.1	121.9±1.3	<0.01	<0.01	<0.01
The average daily DBP mmHg. Art.	105.4±3.2	83.9±1.7	77.8±1.5	<0.01	<0.01	<0.05
The average daily heart rate in 1 minute	83.5±2.8	78.3±2.3	73.5±1.8	<0.05	<0.01	<0.05
Average daily SBP mmHg Art.	168.7±2.3	145.3±1.4	125.4±1.2	<0.01	<0.01	<0.01
The average daily DBP mmHg. Art.	102.4±2.4	93.2±2.1	81.7±1.5	<0.05	<0.01	<0.01
The average daily heart rate in 1 minute	86.8±2.7	81.1±1.9	75.5±2.1	<0.05	<0.01	<0.05
Average night SBP mmHg. Art.	154.9±2.4	141.6±3.6	116.9±1.3	<0.05	<0.01	<0.01
Average night DBP mmHg. Art.	104.1±3.0	96.4±2.7	84.3±2.7	<0.05	<0.01	<0.01
Average night heart rate in 1 min.	80.2±2.5	74.7±2.2	71.1±2.1	<0.05	<0.01	>0.05

Note: p_{1-2} – the reliability of the difference between the indicators of the main group before treatment and in 1 month after treatment;
p_{1-3} – the reliability of the difference between the indicators of the main group before treatment and in 6 months after treatment;
p_{2-3} – the reliability of the difference between the main group after 1 month and in 6 months after treatment.

Table II. Dynamics of intracardiac hemodynamics in patients with hypertension + AOLE after treatment with the combination of lisinopril + amlodipine (n = 40)

Indicator of intracardiac hemodynamics	The value of the indicator in the study group	
	Before treatment	6 months after treatment
EDV, ml	138.2±1.2	129.3±2.9*
ESV, ml	68.2±1.9	60.1±2.1*
EDS, ml	46.3±0.8	41.9±0.2*
ESS, ml	31.4±0.6	24.1±0.7*
EF, %	51.7±1.3	57.9±1.4*
LVPV, cm	1.36±0.1	1.14±0.1*
IVST, cm	1.23±0.1	1.14±0.1*
LVMM, g	182.2±3.2	176.4±3.7
ILVMM, g/m2	91.1±3.4	88.2±2.4

Note: * – the reliability of the difference in indicators after 6 months of treatment compared with indicators before treatment (p<0.05).

Table III. Dynamics of CH of patients with hypertesion + AOLE when prescribing a combination of lisinopril + amlodipine (n = 40)

CH indicator	Before treatment	In 1 month	In 6 months	p	
				p1-2	p1-3
Shock volume, ml	68.64±2.58	79.23±2.04	84±2.36	<0.05	<0.05
Minute blood volume, l/min.	5.97±0.24	7.01±0.13	8.6±0.15	<0.05	<0.05
Shock index, ml/m2	41.56±1.19	45.05±1.13	49±1.18	>0.05	<0.05
Cardiac index, l/min×m2	3.72±0.15	4.92±0.54	4.96±0.36	>0.05	<0.05
Total peripheral vascular resistance, kPa×s/l	166.15±4.24	152.25±4.15	142.36±4.20	<0.05	<0.05
Specific peripheral vascular resistance, kPa×s/(l×m2)	92.53±6.59	76.15±5.87	72.24±4.25	<0.05	<0.05

Note: p1-2 – the reliability of the difference in indicators before treatment and after 1 month of treatment;
p1-3 – the reliability of the difference in indicators before treatment and after 6 months of treatment.

Analysis of peripheral hemodynamic parameters (PH) (Table IV) shows that the combination of lisinopril + amlodipine significantly improves them, which is a positive aspect in the treatment of this category of patients. Thus, PH in the main arteries of the lower extremity affected by atherosclerotic process is improved due to the increase in RI, LSKmach cm × s-1, Vvol ml/min. respectively by 2.7% (p> 0.05), 22.2% (p <0.05) and 5.5% (p> 0.05) after 1 month of treatment and 24.8% (0.05), 27.3% (p <0.01), 23.6% (p <0.01) – after 6 months. Decrease in resistance index (RI) – respectively by 22.2% (p> 0.05) after 1 month of treatment and by 23.6% (p <0.05) – after 6 months from the start of treatment.

Analysis of the results of duplex scanning of the carotid arteries in the group of patients treated with the combination of lisinopril + amlodipine (Table V) for 6 months showed

Table IV. PH dynamics of patients with hypertension + AOLE when prescribing a combination of lisinopril + amlodipine (n = 40)

Indicator	The magnitude of the indicator (M±m)			p		
	Output data	In 1 month	In 6 months	p_{1-2}	p_{1-3}	p_{2-3}
Ripple index (PI)	2.26±0.29	2.32±0.21	2.82±0.23	>0.05	<0.05	>0.05
Resistance index (RI)	0.71±0.01	0.68±0.02	0.56±0.02	>0.05	<0.05	<0.05
Linear blood flow velocity, $cm \times s^{-1}$	0.18±0.03	0.22±0.02	0.28±0.05	>0.05	<0.05	<0.05
Volumetric velocity of blood flow, ml/min.	4.73±1.55	4.99±1.8	6.17±1.54	>0.05	<0.05	<0.05

Note: p_{1-2} – the reliability of the difference between baseline and 1 month after treatment;
p_{1-3} – the reliability of the difference between baseline and after 6 months of treatment;
p_{2-3} – the reliability of the difference between 1 month and 6 months of treatment.

Table V. Changes in TIM in patients with hypertension + OANK when prescribing lisinopril and amlodipine (n = 40)

IMT indicator	Before treatment	6 months after treatment
The thickness of the intima-media complex, mm	1.421±0.08	1.144±0.07*

Note: * – the reliability of the difference in indicators before treatment and after 6 months of treatment (p<0.05).

that the thickness of the complex "intima-media" decreased from (1,421 ± 0,08) to (1,144 ± 0,07)), ie by 19.5% (p <0.05).

Thus, the analysis of the results of the use of lisinopril + amlodipine showed that such a combination of drugs has a stable antihypertensive effect with a gradual decrease in blood pressure. A positive effect of this combination on the structural and functional state of the heart muscle was also found, which directly affected the improvement of BP. It is important to establish a significant improvement in CH and organoprotective effect of drugs on the vascular wall, as evidenced by a decrease in IMT after 6 months of treatment.

DISCUSSION

The issue of treatment of hypertension in the background of atherosclerotic lesions of the main arteries of the lower extremity remains unresolved and insufficiently clarified. After all, the peculiarities of the state of central and peripheral hemodynamics in this category of patients require an individual approach to the choice of antihypertensive drugs and their combinations [11, 12]. Moreover, the performance of reconstructive surgical interventions in the occlusion of the main arteries, especially in arteries of large diameter, can change the parameters of central and peripheral hemodynamics. Underestimation of this fact in the appointment of antihypertensive drugs can cause complications of the cardiovascular system and the progression of limb ischemia [13-15]. Therefore, it was considered relevant to investigate the effect of antihypertensive drugs of different first-line groups on central, peripheral, and intracardiac hemodynamics in order to select the optimal combination of these drugs for the treatment of hypertension with peripheral arteries of the lower extremity for predictable effective and safe patients in primary care.

CONCLUSIONS

It is proved that in the absence of individual contraindications the combination of ACEI inhibitor lisinopril and calcium antagonist amlodipine is optimal and universal for effective treatment of patients with hypertension in combination with AOLE in all types of central hemodynamics, because after 6 months of treatment, in particular, an increase in the pulse index – by 24.8%, a decrease in the resistance index – by 21.1%, an increase in linear and volumetric blood velocity – by 25.6% and 27.4%, respectively, while achieving the target blood pressure.

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ORIGINAL ARTICLE

OPTIMIZATION OF PARARECTAL FISTULA SURGICAL TREATMENT

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ABSTRACT

The aim: To improve the results of treatment of complex PF by the ligation of the intersphincteric fistula tract (LIFT).

Materials and methods: 27 patients with transsphincteric fistulas of the rectum of different complexity have been operated by two methods: by ligature method ("cutting seton") and by the ligation of the intersphincteric fistula tract (LIFT).

Results: No early complications were noticed in patients who had been applied the technique of fistula ligation in the postoperative period. The pain syndrome was expressed insignificantly. The rehabilitation period was less than 12 days. Having analyzed the long-term results of the observation period lasting up to 26 months, we arrived at the conclusion that the choice of surgical treatment had little effect on the recurrence rate of pararectal fistula (21.4 and 15.38%, respectively). However, one LIFT patient had gas incontinence within 1 year of surgery in contrast to 4 patients who had had a cutting ligature method having anal incontinence for 1 year and 1 patient – during the observation period.

Conclusions: Ligation of the fistula in the intersphincter tract is an effective sphincter-preserving operation, does not require additional equipment and expensive consumables, is characterized by minimal damage to the anal sphincter and a high percentage of closure of PF (84.6%). The recurrence rate does not exceed 15.38%.

KEY WORDS: pararectal fistula, LIFT operation (intersphincter ligation)

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INTRODUCTION

Pararectal fistula (PF) occupies a special place in the structure of rectum diseases with a prevalence of 8 to 23 cases per 100 thousand population. Rectal fistulas account for 15.45% of patients with colorectal pathology. The most problematic group for surgical treatment in 30% are patients with complex (extrasphincteric and high transsphincteric) PF, which are complicated by the formation of infiltrative changes, continuous course and frequent exacerbations of the inflammatory process [1, 2]. This most often causes the development of severe local changes that cause deformation of the anal canal and perineum, scarring of the muscles that compress the anus, resulting in, primarily, external sphincter insufficiency. Frequent exacerbations of the purulent process in the perineum are accompanied by the spread of infection leading to the formation of new fistulous branches with breakthroughs through skin in the form of additional external holes. Violation of the outflow of fistula from its outer hole ends with exacerbation of chronic paraproctitis, which requires urgent surgical care. The ongoing chronic inflammatory process in the perianal area creates the conditions for the appearance of pectenosis [3]. Pectenosis is a change in the smooth muscle elements of the anal canal due to inflammatory and dystrophic-degenerative changes, which is usually accompanied by the presence of anal incontinence of different degrees. Pectenosis is found in 47.9% patients with extrasphincteric fistulas, in 23.2% with transsphincteric fistulas and in 4% with horseshoe fistulas. Cicatricial changes in the anal canal complicate the course of the disease, significantly increasing the technical difficulties in performing radical surgical interventions for recurrent paraproctitis and create conditions for persistent anal incontinence in the postoperative period [3-7]. In spite of the progress made in recent years in the treatment of patients with chronic paraproctitis, the frequency of unsatisfactory treatment outcomes remains quite high. Recurrences of rectal fistulas reach 40.2%. 17-36% of patients have discomfort in the anus, and the appearance of persistent anal incontinence of varying degrees is observed in 29% of patients [2,6-8]. The main cause of recurrence of rectal fistula is its not eliminated inner hole, and its not diagnosed branches in the pararectal tissue during surgery [4,5]. The existing significant number of different methods of surgical treatment of recurrent chronic paraproctitis so far does not guarantee complete elimination of fistula and does not exclude recurrence of the disease when using radical methods of surgical treatment [5,9-11]. In each case, coloproctologists are faced with the task of choosing the optimal method of surgical treatment in order to avoid a high percentage of anal incontinence and recurrence, which is from 9 to 50% in the treatment of complex pararectal fistulas. The number of recurrences of pararectal fistulas using the ligature method ranges from 0 to 43 [4,12-15]. The technique of dissection of extrasphincteric fistula into the lumen of the rectum with the restoration of sphincter fibers has been the subject of discussion by proctologists for several decades. In this regard, most authors prefer the ligature method at

Table I. Early postoperative complications

Category of postoperative complication	Clinical group			
	1 group (n = 14)		2 group (n = 13)	
Bleeding	1	7,14%	1	7,7%
Postoperative wound suppuration	3	21,43%	-	-
Acute paraproctitis	1	7,14%	-	-
Hemorrhoidal thrombosis	1	7,14%	1	7,7%
Hematoma of the perineum	1	7,14%	-	-
Pain	12	85,7%	6	46,15%

Table II. Late postoperative complications

Category of postoperative complication	Clinical group			
	1 group (n=14)		2 group (n=13)	
Recurrence of pararectal fistula	3	21,4%	2	15,38%
Anal incontinence 1st d.	4	28,6%	1	7,14%
Anal incontinence 2st d.	1	7,14%	-	-

IV degree, or various plastic methods at I-III degrees of fistula complexity.

THE AIM

The aim was to improve the results of treatment of complex PF by the ligation of the intersphincteric fistula tract (LIFT).

MATERIALS AND METHODS

27 patients with transsphincteric fistulas of the rectum of different degrees of complexity have been operated in the surgical department. They were operated by two methods: 1 group was represented by 14 patients, operated by ligature method ("cutting seton"); the second group consisted of 13 patients who were operated by a new method, i.e., the ligation of the intersphincteric fistula tract (LIFT). The method used was proposed by A. Rojanasakul in 2007. [16] The main stages of the procedure include incision in the intersphincteric groove, identification of the intersphincteric tract, ligation of the intersphincteric tract near the internal hole and removal of the intersphincteric tract, scraping off all granulation tissue in the rest of the fistula and suturing. All operations were performed under spinal anesthesia. The average age was 46 ± 0.7 years. The duration of the disease was from 6 months up to 7 years. Anal sphincter insufficiency was not observed in any patient before the surgery. For the sake of purity of comparison, both groups were comparable in sex, age, severity of the pathological process. Regardless of the method used, both groups used a single approach to preoperative preparation and postoperative symptomatic treatment.

RESULTS

In the course of analysis of the early postoperative period complications (table I), it has been found that 3 patients of group 1 had postoperative wound suppuration, which amounted up to 21.43% of cases in contrast to the absence of suppuration in patients of group 2. This was more likely to affect the type of postoperative wound healing and development of recurrence in the future. Twelve patients in group 1 required adequate analgesia, including narcotic analgesics, and 8 of them required more than one analgesic injection in the early postoperative period. In contrast to it, only 6 patients required single drugs injection in group 2.

Thus, no early complications were noticed in patients who had been applied the technique of fistula ligation in the postoperative period lasting from 3 to 5 days. The pain syndrome was expressed insignificantly due to the low trauma of the technique. The rehabilitation period was less than 12 days, whereas the period of rehabilitation of patients who had undergone ligature surgery ranged from 21 days to 78 days, accompanied by pain, discomfort and reduced quality of life.

Having analyzed the long-term results of the observation period lasting up to 26 months, we arrived at the conclusion that the choice of surgical treatment had little effect on the recurrence rate of pararectal fistula (21.4 and 15.38%, respectively).

However, one LIFT patient had gas incontinence within 1 year of surgery. While in group 1 gas incontinence disappeared in 3 patients within 1 year after the intervention and in 1 patient grade 1 incontinence was observed within 26 months after treatment. 1 patient who had been applied the method of cutting ligature noted incontinence of gases and feces during the entire observation period.

The average duration of hospital stay in the first group was 13.1 ± 2.1 days, while in the second group the period of hospital stay averaged 8.7 ± 2.3 days, due to the minimization of surgical trauma and lower incidence of early postoperative complications. The period of full recovery in the first group averaged 33.4 ± 4.2 days, in group 2 it decreased significantly to the average of 16.2 ± 2.9 days.

DISCUSSION

Simple pararectal fistulas cause no difficulty to be diagnosed and treated. They are accompanied by a small percentage of postoperative complications, whereas complicated fistulas are a frequently discussed issue in clinical practice. Many surgical techniques have been described for the treatment of such fistulas, including Setontechnique, fibrin glue, collagen closures, fistulotomy with sphincter regeneration, and diversion of the fistula tract. However, treatment outcomes vary, and no particular procedure is believed to be "the gold standard". Notably, the goal of any treatment of this type is to destroy the fistula passage and reduce the frequency of relapses, maintaining the full functionality of the anal mass complex. The most reliable method of surgical treatment of complex fistulas is their excision or dissection into the lumen of the rectum. Sphincterotomy is an effective way to treat anal fistulas. However, if the fistula extends to most of the sphincter complex, the operation may contribute to the failure of the anal sphincter in the postoperative period. During the surgical approach to fistula dissection/excision, some authors take into account the degree of involvement of the sphincter apparatus by no more than 10-20%, while others consider it to be no more than 33%. Therefore, this operation requires appropriate selection of patients. In 2007, Rojanasakul et al. described a new surgical option for such cases with very good initial results. LIFT has been used as a technique to interrupt the fistula passage with satisfactory results since then. Currently, there are more than 6 variants of LIFT. Nevertheless, the success rate ranges from 47 to 95%. It should also be noted that excision of the fistula in the intersphincteric space reduces the risk of anal sphincter insufficiency. We are convinced that the success of the given operation depends on the correct identification of the fistula passage and the treatment of its distal part without damage, as well as on the reliable treatment of the internal opening of the fistula. Our study has registered 4 cases of anal sphincter insufficiency, using fistulotomy and 3 cases of fistula recurrence after these interventions at different periods after surgery. The LIFT technique is associated with insufficiency of the anal sphincter of the 1st stage in 1 patient, whereas 15.38% of recurrent fistulas were observed in these patients. Having analyzed the results, we determined the main causes of recurrence and failure of the anal sphincter. The first group includes errors related to the preoperative diagnostics. Incomplete contrast of the fistula contributes to the incorrect estimation of the fistula way to the fibers of the anal sphincter and the presence of undiagnosed additional purulent cavities or passages. Therefore, the use of preoperative MRI or ultrasound diagnostics may be recommended. This will help to identify purulent pararectal cavities or passages, as well as to obtain entire information about the state of the anal sphincter complex and guarantee the correct choice of surgical intervention. We have marked two main technical errors. The first mistake is an excessive excision of the tissue of the anal sphincter during the fistula removal. The second one is suppuration of wounds, which contributes to the failure of sutures and secondary wound healing. These factors lead to the formation of a rough postoperative scar, which reduces the functional capacity of the sphincter. It is necessary to continue the research of various modifications of the LIFT technique, which will help to identify shortcomings, and contribute to the improvement of surgical treatment methods of complex transsphincter rectal fistulas.

CONCLUSIONS

Ligation of the fistula in the intersphincter tract is an effective sphincter-preserving operation, which should be used in complex anatomical variants of PF, does not require additional equipment and expensive consumables, is characterized by minimal damage to the anal sphincter and a high percentage of closure of PF (84.6%). The recurrence rate does not exceed 15.38%.

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ORIGINAL ARTICLE

SAFETY OF USING DURAL PUNCTURE EPIDURAL ANALGESIA AS A METHOD OF LABOR ANALGESIA

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ABSTRACT

The aim: To evaluate the clinical characteristics of complications and side effects of CSE and DPE as a method of analgesia.

Materials and methods: The study included 137 patients who had a vaginal birth using one of two, CSE or DPE methods of analgesia. All of them were divided into two groups: Group I – 54 women (DPE group) and Group II – 83 women (CSE group). In group I, an epidural kit with a Tuohy G18 needle, G20 catheter, and a Whitacre G25 x 120 mm spinal needle was passed through the epidural needle for puncture of dura mater and removed after cerebrospinal fluid receiving, the epidural catheter was conducted on 3-4 cm. The initial dose of anesthetic was: 3 ml of Naropin 0.12% – test dose and 17 ml of working solution (Naropin 0.12% + Fentanyl 2 μg / ml) – main dose. In group II, a spinal-epidural kit with Tuohy G18 needle, catheter G20, spinal needle "Whitacre" G27 x 132 mm for dura mater puncture was used. Bupivacaine 1.5 mg + Fentanyl 15 mcg, 1 ml solution was administered spinally. To maintain analgesia in both groups – the patient-controlled analgesia with a working solution (Naropin 0.12% + Fentanyl 2 μg / ml) with a bolus of 8 – 10 ml, lockout 15 minutes.

Results: The higher frequency of hypotension in childbirth when using CSE – 4 women (4.8%) vs 1 woman (1.9%) in the DPE group. Inadequate or insufficient analgesia in group I was found in 2 women (3.7%), and in group II in 4 women (4.8%). The severity of monolateral block in group I was not high and did not cause significant discomfort in women. The higher incidence of monolateral blockade was in group II, in three cases there was a need for additional anesthesiologist interventions and catheter manipulations. In the CSE group there were two cases (2.4%) of severe itching in women, in group I such an adverse reaction was absent. No complication such as PDPH was documented in either group.

Conclusions: 1. The use of the DPE technique showed a lower frequency of complications compared to CSE. 2. The use of a G 25 spinal needle for puncture of the dura mater does not lead to an increase in the frequency of PDPH. 3. DPE technique using G25 spinal needles reduces the need for additional manipulations with the epidural catheter to overcome unilateral blockades.

KEY WORDS: dural puncture, epidural, labor analgesia, combined spinal-epidural, post dural puncture headache, monolateral block

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INTRODUCTION

Childbirth is a physiological process accompanied by severe pain, which the vast majority of women describe as unbearable and the most pronounced that they could feel in their lives [1,2]. The pain is visceral, characterized as diffuse, and difficult to localize. The pain impulse is transmitted through thin myelin-free C-fibers through the uterine-vaginal, aortic, subperitoneal plexus, and then through the white connecting branches through the T10-L1 segments to the posterior horns of the spinal cord. In the second period of childbirth, the type of pain changes, it becomes somatic due to stretching of the vaginal walls, and pelvic floor muscles, as well as the pressure caused by the fetus on the perineum. Pain impulses come from the pelvic region mainly through Aδ fibers through segments T10 – S4, but pudendal nerves (segments S2 – S4) and spinal nerves L1 – L3 are more involved in the pain response [3,4]. From the spinal cord, pain impulses are transmitted along the spinothalamic tract to the thalamus and reach the posterior central gyrus of the sensory zone of the cerebral cortex [4].

At the current stage of medicine development, there are many pharmacological and non-pharmacological methods of analgesia. Each of the methods has its advantages and disadvantages, as well as limitations in application. Today, the leading positions in the structure of methods of analgesia are occupied by neuraxial techniques: epidural analgesia (EA), combined spinal-epidural analgesia (CSE), and the recently proposed technique of dural puncture epidural analgesia (DPE). Epidural analgesia is the gold standard for relieving labor pain and is used in 60-70% of cases. In general, given current trends in EA, the method is effective and safe for mother and fetus, but EA is an invasive technique and carries a certain risk of complications and adverse reactions [2,3]. Inadequate block (insufficient analgesia on 30-40 minutes) and monolateral block are some of the most common complications of EA, which significantly impair the quality of analgesia and may require additional anesthesiologist intervention and catheter manipulation – their frequency reaches 23% [5,6]. In an effort to improve the quality of analgesia in the practice of obstetric anesthesiologists combined spinal-epidural analgesia has emerged. Using a dura mater puncture with a spinal needle to

administer a local anesthetic, alone or with opioids, to increase patient satisfaction (within 3-5 min) and lower frequency of monolateral blockades compared to traditional EA [5]. But at the same time the frequency of side effects and complications increased – when using the initial spinal injection of a local anesthetic with an opioid: more often there is a motor block, hypotension, fetal bradycardia, itching [5,7]. Therefore, it is important to find the middle ground by improving the quality of analgesia without increasing the risk of complications and side effects. Now the DPE modification is gaining popularity, which uses dura mater puncture with a spinal needle without medication into the spinal canal. This hole is required for the gradual translocation of the anesthetic solution into the spinal canal. It is slow and gradual distribution of the anesthetic solution that is intended to improve the quality of EA, and should not cause potential complications and side effects when using CSE. Puncture of the dura mater with a spinal needle creates the preconditions for post dural puncture headache (PDPH), and pushing in the second period of childbirth increase the risk of this complication [7,8]. Therefore, questions arise as to whether the use of neuroaxial anesthesia techniques in the technique of which uses dura mater puncture (CSE and DPE) causes an increase in the frequency of complications and side effects, and what are their clinical characteristics?

THE AIM

To evaluate the clinical characteristics of complications and side effects of CSE and DPE as a method of analgesia.

MATERIALS AND METHODS

We studied the birth history of the maternity hospital "Leleka" for 8 months from January 2021 – to August 2021. The study included 137 patients who had a vaginal birth using one of two, CSE or DPE, methods of analgesia where the technique dura mater puncture was used. All of them were divided into two groups: Group I – 54 women (DPE group) and Group II – 83 women (CSE group). In group I, an epidural kit with a Tuohy G18 needle, G20 catheter, and a Whitacre G25 x 120 mm spinal needle was passed through the epidural needle for puncture of dura mater and removed after cerebrospinal fluid receiving, the epidural catheter was conducted on 3-4 cm. The initial dose of anesthetic was: 3 ml of Naropin 0.12% – test dose and 17 ml of working solution (Naropin 0.12% + Fentanyl 2 μg / ml) – main dose, maintenance – patient-controlled analgesia with a working solution with a bolus of 8 – 10 ml, lockout 15 minutes. In group II, a spinal-epidural kit with Tuohy G18 needle, catheter G20, spinal needle "Whitacre" G27 x 132 mm for dura mater puncture was used. Bupivacaine 1.5 mg + Fentanyl 15 mcg, 1 ml solution was administered spinally. To maintain analgesia – the patient-controlled analgesia with a working solution (Naropin 0.12% + Fentanyl 2 μg / ml) with a bolus of 8 – 10 ml, lockout 15 minutes. Based on the obtained data, the assessment of complications, and side effects of using these analgesic methods was performed.

RESULTS

The received data (see Table I) show a higher frequency of hypotension in childbirth when using CSE – 4 women (4.8%) against 1 woman (1.9%) in the DPE group. Inadequate or insufficient analgesia in the form of monolateral block in group I was found in 2 women (3.7%), and in group II in 4 women (4.8%). The severity of monolateral block in group I was not high and did not cause significant discomfort in women, a sufficient method of correction was to change body position and use an additional bolus of working solution. It is worth noting the higher incidence of monolateral blockade in group II, but different correction options – in three cases there was a need for additional anesthesiologist interventions and catheter manipulations, in one case a catheter pull with an additional bolus of working solution, and in two cases re-catheterization of epidural space. In the CSE group there were two cases (2.4%) of severe itching in women, in group I such an adverse reaction was absent. No complication such as PDPH was documented in either group.

DISCUSSION

Neuroaxial methods of analgesia are considered to be quite safe and effective methods of analgesia, so their use is an integral part of most births [3-5]. However, each of the neuroaxial techniques can cause both general and individual complications specific to each of the methods of analgesia. Side effects include: hypotension, itching, nausea and vomiting, urinary retention, chills and hyperthermia. The use of epidural anesthesia can lead to complications such as systemic toxicity of local anesthetics, catheter migration, high spinal block, motor block and post-puncture headache, fetal bradycardia, complications such as epidural or spinal hematoma occur, fortunately, extremely rare [6].

A clinical assessment of complications and adverse reactions when using CSE and DPE showed 2.5 times the greater frequency of hypotension when using CSE compared to the DPE group. The monolateral block was observed in both groups. Still, more often in the CSE group, 4.8% vs. 3.7%, and the severity of this complication was higher in the CSE group, which ultimately led to additional attention of the anesthesiologist and manipulation of the catheter, even with re-catheterization of the epidural space. In our opinion, this can be explained by the larger diameter of the spinal needle when performing DPE and better distribution of the anesthetic working solution into the spinal canal. Although a larger diameter of the spinal needle has a higher risk of PDPH during dura mater puncture in labor, the success of analgesia may depend on the diameter of the needle. To reduce the risk of PDPH in obstetrics, using spinal needles of minimum diameter (G25 – G27) with an atraumatic tip is recommended. Using the DPE technique and based on the available data, even a minimal difference in the diameter of the spinal needle is essential. In studies that used the minimum diameter of the G27 needle, there was either no difference between the DPE and EA groups in the studied parameters, including the frequency of unilateral blockades, or it was insignificant [9,10]. When using the G25 needle diame-

Table I. Clinical characteristics of complications

Complication	I group (n=54)	II group (n=83)
Hypotension	1 (1,9%)	4 (4,8%)
Monolateral block	2 (3,7%)	4 (4,8%)
PDPH	-	-
Itching	-	2 (2,4%)

Note: *Statistical significance of differences relative to the 1st group; $p < 0.05$

ter, a lower frequency of unilateral and inadequate blockades and a higher frequency of the coverage of the S1-S2 segments were demonstrated [11-13]. Chau et al. note a 7-minute faster achievement of <1 on VAS in the DPE group compared to EA and a lower frequency of hypotension and pruritus compared to CSE [13]. In our study, G25 spinal needles were used, but PDPH did not manifest itself and we did not record a single case of this complication in both groups. In the CSE group, we found two cases of side effects of opioids when administered spinally – itching, in the DPE group no case was documented, which can be explained by a slower and more gradual translocation of the local anesthetic with an opioid.

CONCLUSIONS

1. The use of the DPE technique showed a lower frequency of complications compared to CSE.
2. The use of a G 25 spinal needle for puncture of the dura mater does not lead to an increase in the frequency of PDPH.
3. DPE technique using G25 spinal needles reduces the need for additional manipulations with the epidural catheter to overcome unilateral blockades.

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ORIGINAL ARTICLE

THE ROLE OF ENTEROVIRUS IN THE DEVELOPMENT OF ISCHEMIC STROKE AND ITS OUTCOMES

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ABSTRACT

The aim: To study the role of enteroviruses (EV) in the development of ischemic stroke and its outcome.

Materials and methods: The main group (MG) included 72 patients with acute cerebrovascular disorders were examined using the National Institutes of Health Stroke Scale and Barthel Index. The comparison group (CG) included 35 patients without cerebrovascular disease. Viruses were isolated from patients' sera and identified in neutralization test. EV genomes were detected in polymerase chain reaction (PCR). Serological diagnosis was performed by enzyme-linked immunosorbent assay.

Results: EV genomes were more frequently detected in the patients' sera in MG than in CG (23.6 ± 5.9% and 2.9 ± 2.8%, $p < 0.05$). The greater level of neurological deficits was in patients with positive PCR test results comparatively with patients with negative PCR test results (11.76 ± 0.31 and 10.97 ± 0, 27, $p = 0.040$). The regression of neurological deficit during the treatment was a worse in patients with positive PCR test results and presence of specific IgG compared with patients with positive PCR test results and absence of specific IgG (11.2 ± 2.6% and 19.6 ± 2.4%, $p = 0.031$).

Conclusions: The trigger role of EV in the development of IS is established. PCR is recommended for diagnosis of EV in patients with IS.

KEY WORDS: ischemic stroke, neurological deficit, enteroviruses

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INTRODUCTION

Acute cerebrovascular accident (ACM) is the second leading cause of disability and death in the world [1]. Nearly 50% of patients have disability after ishemic stroke (IS) [2]. A second IS develops in 25-30% of cases in a year after the first IS, and only 10% of patients return to work. IS is the cause of permanent disability in 53% of patients [3, 4].

The most common etiology of ischemic stroke in adults is atherosclerosis (AS). There are a number of hypotheses about the emergence, development and progression of AS that complement each other (lipid-infiltrative, inflammatory with free radicals, lower nitric oxide, peroxide, «response to damage» to vascular walls, chronic endothelial damage and dysfunction, autoimmune and bacterial infections, etc.) [2, 4-6]. The cause of IS remains unclear in about 40% of cases. This necessitates research on risk factors (RF) of AS and its cardiovascular and cerebrovascular complications [7]. Infectious can initiate the inflammatory process with subsequent damage of vascular endothelium, which leads to endothelial dysfunction as an early sign of AS. It is associated with severity of IS and determines the development of complications [2, 7, 8].

Inflammatory changes in AS can be initiated by human herpesviruses (HSV-1, HSV-2, EBV, CMV), human T-cell lymphoma virus type 1, Chlamydia pneumoniae, Helicobacter pylori, because these pathogens were found in affected blood vessels and atherosclerotic plaques [5, 10, 11]. The simultaneous persistence of several infectious agents in patients with severe immunoreactivity on the background of genetic predisposition in the presence of other RF can lead to AS. It can be confirmed by the detection of Ig G simultaneously to several infectious agents in the serum of patients with AS [4]. Therefore, the study of the role of infectious agents in the development of IS is important.

THE AIM

Study of the role of enteroviruses in the development of ischemic stroke and its consequences.

MATERIALS AND METHODS

A total of 107 patients who were hospitalized in the Neurological department and the Department of Cerebrovascular Pathology of the Oleksandrivska Clinical Hospital in Kyiv from 2009 to 2015 were enrolled in the study. The study was approved by the Bioethic Commission of the O.O. Bogomolets National Medical University. All patients gave voluntary written consent to participate in the study.

MG consisted of 72 patients with ACVD who were examined using the NIHSS stroke severity scale (the National Institutes of Health Stroke Scale) and Barthel Index (IB). Verification of the diagnosis was performed using Doppler ultrasound (DU), computed tomography (CT) or magnetic resonance imaging (MRI).

Inclusion criteria were the following: age of the patient over 18 years, confirmed diagnosis of ACVD (ischemic stroke or transient ischemic attack (TIA)), and absence of exclusion criteria. Exclusion criteria were: length of hospital stay less than 2 weeks, inability to collect serum at intervals of two weeks.

The control group (35 people) consisted of patients who were treated at the hospital in case of neurological diseases not related to the vascular pathology (13 patients with peripheral nerve neuropathy and polyneuropathy, 8 – with radiculopathy and ganglionitis, 9 – with hereditary diseases of the nervous system).

The age of the examined patients of MG ranged from 31 to 86 years and the average age was 62.6 ± 12.0 years. The sample included 41 women (56.9%) and 31 men (43.1%). CG included 35 patients aged from 16 to 86 years, the average age was 56.3 ± 19.3 years. The sample included 19 women (63.3%) and 11 men (36.7%).

Clinical and neurological parameters were studied using modern neurological scales: the dynamics of neurological disorders was determined by the NIHSS stroke severity assessment scale; functional stroke recovery was assessed using BI. The pathogenetic subtype of stroke was determined using TOAST criteria.

All patients underwent ultrasound and transcranial Doppler (TCD) examination of the brachiocephalic arteries using a Medison ACCUVIX V10 with a 2-4 MHz phased array sensor to determine the severity of the stenosis, the thickness of the intima-media complex (IMT) of the common carotid artery (CCA), internal carotid arteries, middle cerebral, anterior cerebral arteries (respectively ICA, MCA, ACA), subclavian, extracranial parts of vertebral, basilar and posterior cerebral arteries (respectively SCA, VA, BA, PCA). Examination of the main vessels of the head in the extracranial region was performed using an ultrasound Doppler "Multigon 500M" (MultigonIndustriesInc, USA). The analysis of cerebral hemodynamics parameters was performed with the determination of average indicators of the maximum and mean velocity in ICA and VA. The generally accepted method provided blood flow determination in CCA, ICA, ACA, VA, BA, PCA by qualitative (audiovisual) and quantitative characteristics.

Magnetic resonance imaging (MRI) of the brain was performed on a device "FLEXATAR" (Toshiba) with a field strength of 1.5 T.

Isolation of viruses from blood sera and their identification was performed by micromethod on cell cultures (RD, HEp-2 and HeLa) with 100% cytopathic effect, followed by identification in the virus neutralization test. The genomes of EV were determined in reverse transcriptase-polymerase chain reaction (RT-PCR) using the AmpliSens test system [12]. Serological testing was performed in the paired sera of patients of MG and CG by enzyme-linked immunosorbent assay (ELISA) using the test system for the determination of Ig G and Ig M to EV "Ig G Teskit / Ig A Teskit / Ig M Teskit", manufactured by Sekisui Virotech GmbH, Germany. The results were recorded using the ELISA HumaReader (Human GmbH, Germany). All calculations were performed using the statistical data analysis package IBM SPPS Statistics 22.

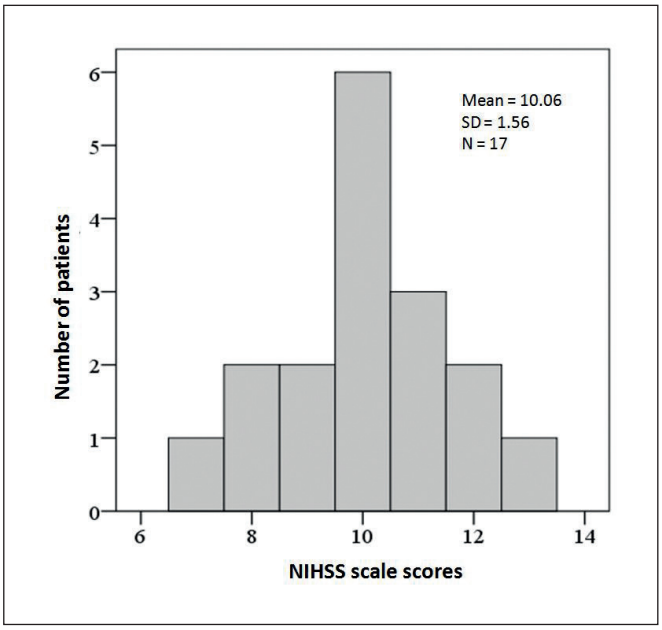

Fig.1. Distribution of patients in the main group by NIHSS score

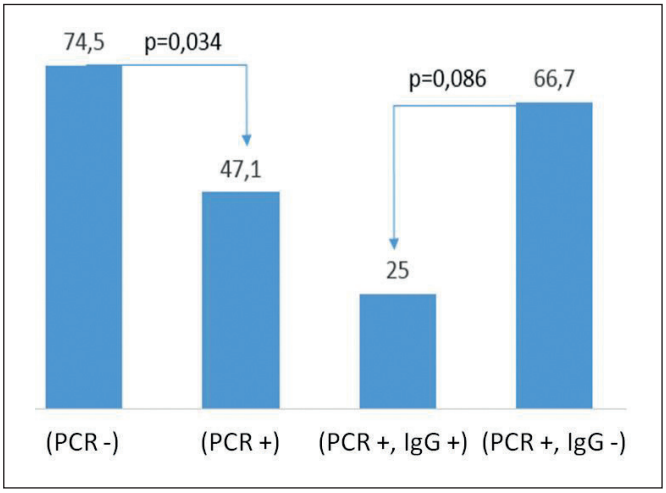

Fig. 2. Frequency of minimal functional dependence of ≥ 75 points according to the BI three months after stroke

RESULTS

It was proved that EV genomes were detected in 17 of 72 sera of patients with MG (23.6 ± 5.9%) and in the serum of one patient of 35 patients in CG (2.9 ± 2.8%). EV were isolated on cell cultures from 11 sera of 17 PCR-positive sera of patients in MG. There were identified 8 isolated strains as Coxsackie B viruses (serotypes 2, 3, 4) and ECHO viruses (serotypes 6, 9, 27 (two strains), 29), however other 3 isolated strains were not identified. Virus was not isolated from one PCR-positive serum of a patient in GP. Detection of EV genomes in the sera of examined patients indicates the presence of enterovirus infection [13].

The paired sera of patients were studied by ELISA to detect specific IgM and IgG to EV. IgM to EV were not detected in any serum of patients in MG and CG. IgG to EV were detected in both sera of 17 patients in MG (23.6 ± 5.1%). IgG to EV were detected in 8 of 17 PCR-positive

Table I. Indicators of neurological deficit scores according to the NIHSS scale for different values of the PCR test results and IgG

NIHSS, points	PCR-test		p	PCR + IgG +	PCR + IgG -	p
	+	-				
Admission	11,8±0,3	10,9±0,3	0,040	12,3±0,3*	11,3±0,5	0,153
Discharge	10,1±1,6	7,07±2,1	0,001	10,9±0,4*	9,3±0,5*	0,046
Dynamics of points, %	15,6±8,2	34,6±1,6	0,001	11,2±2,6*	19,6±2,4*	0,031

Note. * - significant difference (p <0.05) compared to patients with negative PCR test results.

Table II. Characteristics of risk factors in patients of the main and comparison groups

Evaluation Criteria	MG (n=72)	CG (n=35)	P
	Absolute value (%) M±m	Absolute value (%) M±m	
Age of patients, years	63,0±13,0	56,4±19,3	p> 0,05
Male, %	31 (43,1%)	13 (37,1%)	p> 0,05
Female, %	41 (56,3%)	22 (62,9%)	p> 0,05
Smoking, %	16 (22,2%)	5 (14,3%)	p> 0,05
Alcohol abuse, %	11 (15,3%)	1 (2,9%)	p> 0,05
Hypertension, %	63 (87,5%)	24 (68,6%)	p> 0,05
Overweight, %	11 (15,3%)	1 (2,9%)	p> 0,05
Blood cholesterol (mmol/l)	5,3±1,0	4,74±0,8	p> 0,05

patients in MG, and only in 2 patients in CG who were PCR-negative.

It was found that the genomes of EV were more common detected in patients aged 51 to 55 years old (58.3 ± 14.8%). The lowest incidence of EV genomes was observed in patients under 60 years old (9.7 ± 5.3%). Detection of EV in patients in MG was significantly higher than in CG (p<0.05).

The frequency of detection of structural and morphological changes in cerebral vessels in patients with ACVD was high. In all patients of MG relative to CG significant changes in the inner vascular wall of the carotid arteries during ultrasound examination – an increase IMT: in CG – 0.62 ± 0.09 mm (p <0.001), in patients of MG – 1.03 ± 0.07 mm (p <0.001) were detected. The high risk of IMT increase may be caused by an association with a viral infection. Of the 72 patients of MG, cerebral stenosis was found in 64: 24 patients had minor ICA stenosis > 25%, which was accompanied by an asymmetry of blood flow velocity, 30 had minor VA stenosis <50%, and 10 had moderate ICA stenosis > 50%. A cerebral hemodynamic parameters analysis revealed that in patients with ACVD, the average linear and mean blood flow velocities in ICA relative to CG are much lower. According to CT or MRI data, the MG patients had confirmed changes typical for stoke foci; the TIA patient over 50 had occasional foci of encephalomyelitis. At the time of hospitalization, the mean value of neurological deficit according to the NIHSS scale was 10.06 ± 0.38 points (7 to 13 points), Fig. 1.

According to the mean NIHSS scores at the time of admission to the hospital in the subgroup of patients with positive PCR test results, the severity of neurological deficit was higher and differed significantly compared with patients who had negative PCR test results (11.76 ± 0.31 vs. 10.97 ± 0.27 points, p = 0.040, respectively).

PCR-positive patients who had IgG to EV in serum did not differ in severity of neurological manifestations from PCR-positive patients who did not have IgG to EV in serum (12.25 ± 0.31 points and 11.33 ± 0.51 points, respectively, p = 0,153).

During treatment in patients with a positive PCR test result and the presence of IgG a slower regression of neurological deficit was observed and at the time of discharge from the hospital and was on average 11.2 ± 2.6% compared to patients with the positive PCR test results and no IgG presence – 19.6 ± 2.4%, p = 0.031. Slow recovery of neurological functions led to significantly higher values of the neurological scores at the time of discharge: 10.88 ± 0.39 points compared with 9.33 ± 0.53 in the case of seronegative results for IgG, p = 0.046, table I.

The presence of enterovirus infection signs in patients was reflected in a functional dependence for three months after stroke, as assessed according to BI. In particular, in patients that have the enterovirus's genome the recovery to the level of minimal functional dependence of ≥ 75 points on the BI scale occurred in 8 (47.1%) patients; in the case of RNA virus genome absence, 41 (74.5%) patients, p = 0.034.

The combination of the positive enteroviruses genome RNA and IgG was associated with poorer functional recovery of <75 points on the BI in 6 (75.0%) patients compared with the 3 PCR-negative patients (33.3%), but the data did not reach statistical significance, p = 0.086, fig. 2.

Clinical and laboratory patient data of MG and CG was analyzed to assess the impact of enterovirus infection on

the course of the disease and to determine the role of enteroviruses in ischemic stroke occurrence (Table 2). We did not find a significant difference between the data on the proportion of smokers in the MG and the CG. The portion of heavy alcohol users in the MG was higher than in the CG (p> 0.05). At the same time, 63 (87.5%) of 72 patients in the MG were diagnosed with hypertension (blood pressure higher than 140/90 mm Hg), while in the CG only 24 (68.6%) of 35 patients were diagnosed with hypertension. Also 11 (15.3%) of 72 patients of the MG were overweight, while in the CG only 1 (2.9%) of 35 patients was overweight. A higher level of cholesterol in blood was found in the MG patients – 5.3 ± 1.0 mmol / l compared with the CG patients (4.74 ± 0.84 mmol / l), but these differences in indicators were not statistically significant (p> 0,05).

DISCUSSION

The results of experimental studies confirm the initiation of atherogenesis by existing viral infection. At the heart of the initial stage of AS are foci of endothelial cell damage, which occur due to changes in the vascular wall under the influence of hypertension, viral infection, accompanied by increased endothelial permeability [10, 11]. Under conditions of hypertension, the increase in vascular pressure narrows, the autoregulation of vascular tone changes in the direction of promoting further vasodilation with a decrease in muscle tone of unstriated muscles. This mechanism changes the state of the vascular wall endothelium, plasma cells impregnate the latter, which leads to the development of perivascular edema, which leads to diapedetic hemorrhage, which causes edema and dystrophic changes in nerve cells [2, 7].

Numerous studies suggest that latent infections may be predictors of IS. The accumulation of infectious agents that can act as triggers of the inflammatory process is obvious. In most cases, the development of CVD is influenced by the association of viral infection and other RF [7, 9, 11, 14]. Recent studies confirm the similarity of the process of atherogenesis with the typical inflammatory response.

Enterovirus infection is laboratory confirmed by the isolation of EV or detection of EV RNA in sterile clinical material. Molecular methods based on nucleic acid in vitro amplification is the gold standard for diagnosing EV infections [15]. Reverse transcriptase PCR (RT-PCR) targeting the 5'noncoding regions (5'NCR) is recommended for diagnosis of EV because of their sensitivity, specificity and short turnaround time [13]. Sequencing of part of the VP1 capsid protein gene is used for EV type identification [15]. Virus isolation including neutralization assays is a classical method, but should not be used in primary routine diagnostics due to their known insensitivity and slowness. The European Non-Polio Enterovirus Network (ENPEN) (the network collaboration of clinical and molecular virologists, clinicians, epidemiologists and public health experts functions) was created to develop and share knowledge on diagnostic techniques for EV and parechoviruses detection and characterization, disease presentations and prognosis, virus evolution and pathogenesis [15].

According to our study laboratory markers of EV infection (isolated EV or EV genome) were not detected in 9 of 72 patients in MG (12.5 ± 3.9%), but specific Ig G to EV were detected in paired sera of these patients in ELISA. These results indicate that such patients have suffered from enterovirus infections in the past, resulting in antibodies to EV that remain in diagnostic titers.

Thus, we determined the presence of laboratory markers of EV infection in 26 patients of 72 patients (36.1%) in MG: laboratory markers of acute EV infection were detected in 6 patients (EV were detected by PCR and / or virological method and specific Ig M were detected in ELISA); laboratory markers of chronic persistent EV infection in the acute stage were detected in 8 patients (EV were detectted by PCR and / or virological method, and specific Ig G or both Ig M and Ig G were detected in ELISA); laboratory markers of EV infection were detected in 9 patients (no EV were detected in serum by PCR and / or virological method, but specific Ig G in ELISA were detected); laboratory markers of persistent EV infection were detected in 3 patients (PCR revealed EV RNA, but no specific Ig M and Ig G were detected). No laboratory markers of EV infection were detected in 46 patients in CG.

We found that 33 patients (45.8%) in MG had acute respiratory disease 1-14 days before hospitalization for IS. This explains the detection of laboratory signs of EV infection in these patients on the first day of hospitalization and confirms the possible role of EV as a trigger in the development of IS.

When testing the patients with atherothrombotic (AT) ischemic stroke subtype for the presence of EV, a poorer functional recovery was observed in patients with the positive PCR test results and the presence of IgG to viruses associated with the functional recovery; <75 points by BI, p = 0.086.

We studied the effect of viral infection on the condition of cerebral vessels, the course and consequences of IS. The functional recovery in patients with confirmed EV persistence was significantly worse one year after IS, than in patients without one. Recovery of neurological function one year after ischemic stroke was significantly worse in patients in MG than in patients in CG. This was reflected in a lower mean score of IB in patients in MG. These data support the hypothesis regarding the triggering effect of EV infection on the development of structural changes in atherosclerotic plaques.

According to the literature, the study of pathogenetic mechanisms of the origin and development of AS, which confirms the participation of viruses in its development, opens new perspectives for the use of complex anti-viral therapy in the complex therapy of ACD / IS.

This study demonstrates the potential of using PCR to detect EV in patients with IS as a more sensitive, rapid and specific method than virological and allows to detect EV that are not isolated in cell culture. This will adequately adjust the therapy and improve the course of the disease and prognosis [16, 17]. Nesting RT-PCR, which involves

amplification of the genomic region encoding the viral structural protein VP1, has been developed for direct identification of EV in clinical specimens. It allows to detect EV group B, including relatively rare viruses ECHO and ECHO 15, ECHO, as well as enteroviruses A71 (EV-A71), that can be used for direct identification of EV in clinical material with low viral load [18]. Further research will focus on the etiopathogenetic role of viral associations in the onset and development of IS.

CONCLUSIONS

EV genomes were isolated from serum of patients with IS in 23.6 ± 5.9%, that is significantly higher than in patients in CG: 2.9 ± 2.8% ($p < 0.05$). EV were isolated on cell cultures in 11 cases of 17 PCR-positive sera of patients from the main group and identified as Coxsackie B viruses (serotypes 2, 3, 4), ECHO viruses (serotypes 6, 9, 27 (two strains), 29), but in three samples the isolated viruses were not identified.

Thus, studies have found an association between the presence of EV RNA genome and the severity of developed IS, as well as a positive correlation between the effectiveness of neurological recovery and the presence of EV in the blood, especially in presence of IgG in serum. The presence of viral infection predicted a negative regression of neurological deficit for next three years after IS. The functional recovery was significantly worse, which was reflected in a lower average score of IB and a lower percentage of patients with minimal limitation of function.

The use of PCR to detect enteroviruses in patients with IS in the future will complement the arsenal of diagnostic methods. Expanding knowledge about the pathogenetic processes of IS and confirming the possible role of EV in the development of atherosclerotic changes opens new perspectives for improving existing and new diagnostic methods, as well complex therapy and prevention.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

CLINICAL AND IMAGING FEATURES OF MEDIAL MEDULLARY INFARCTION: RESULTS OF A PROSPECTIVE HOSPITAL-BASED COHORT STUDY ILLUSTRATED WITH A CASE REPORT IN A WHITE EUROPEAN ADULT

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ABSTRACT

The aim: This study aims in a prospective hospital-based cohort study to determine clinical and imaging features of medial medullary infarction and report a relevant clinical case in a white European adult.

Materials and methods: We have prospectively enrolled one hundred twenty adult patients with acute posterior circulation stroke. All patients were admitted and enrolled in the study within 6 to 24 hours from the onset of the stroke symptoms. Study subjects were recruited from the hospital's wards and emergency departments from 2011 to 2020. Comprehensive clinical, MRI, ultrasound, and laboratory examinations were performed on all patients.

Results: 68 men and 52 women aged 28 to 89 years (average age 60.7 ± 12.1 years) with an acute ischemic posterior circulation stroke were enrolled in the study. Out of these 120 patients, 22 (18.3%) had acute medulla oblongata infarctions. Clinical and imaging features of medial medullary infarction are analyzed and illustrated with a clinical case presentation in a white European adult.

Conclusions: Specific features of medial medullary infarction were determined, analyzed, described, and illustrated with a clinical case.

KEY WORDS: posterior circulation stroke; medial medullary infarction; stroke; imaging; prospective study; case report

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INTRODUCTION

Posterior circulation stroke (PCS) is a life-threatening condition with a more severe clinical course and is more difficult to diagnose than anterior circulation stroke [1-7]. Consequently, misdiagnosing posterior circulation stroke accounts for 30-60%, leading to the highest mortality [4, 8, 9].

The medial medullary infarction (MMI) is an uncommon stroke resulting from the occlusion of a vertebral artery or its branch to the anterior spinal artery. It is often misdiagnosed or missed. Failure to rapidly diagnose PCS postpones lifesaving treatment and results in higher disability and mortality [10-12]. That is why recognizing and diagnosing MMI promptly prevents its severe consequences.

THE AIM

We aimed in a prospective hospital-based cohort study to determine clinical and imaging features of MMI, illustrated with a clinical case presentation in a white European adult.

MATERIALS AND METHODS

The study of MMI is a part of the research project on PCS patients [13, 14]. Materials and methods of the study, exclusion and inclusion criteria, ethical approval, and features of statistical analysis were reported in detail previously [4].

Briefly, only adult patients with MRI-proven PCS were included in the study. All patients were enrolled in the study within 6 to 24 hours from the onset of the stroke symptoms at the University Hospital named Oleksandrivska Clinical Hospital (hereinafter, Hospital) in Kyiv, Ukraine. Since established in 1875, the Hospital became the highest scientific and pedagogical institution with 27 specialized departments and a catchment population of approximately two million. The Neurological Center of the Hospital consists of an admission department, a clinical department of neurology, a department of cerebrovascular pathology with an intensive care/stroke unit, and a research department of neurology. The study was approved by the Institutional Ethics Board and written informed consent was obtained from all participants or legally authorized representatives.

Stroke in the study was interpreted in agreement with the World Health Organization and American Heart Association/American Stroke Association guidelines [15-17]. The etiology of the stroke was defined in concord with the TOAST criteria [18-22]. Secondary stroke prevention was prescribed immediately after the stroke diagnosis was made [23-28]. Stroke educational programs were provided to all study participants [29-31].

RESULTS

STUDY POPULATION DEMOGRAPHY

Between 2011 and 2020, we examined 120 consecutive patients aged 28 to 89 years (average age 60.7 ± 12.1 years) with an acute ischemic MRI/CT-proven PCS. The breakdown for these patients by sex was as follows: 68 men and 52 women.

POSTERIOR CIRCULATION STROKE LOCALIZATION

Among 120 study patients, 10.9% (n=13) were diagnosed with acute midbrain infarctions, 18.3% (n=22) had acute medulla oblongata infarctions, 18.3% (n=22) developed acute thalamic infarctions, 20.8% (n=25) were diagnosed with acute cerebellar infarctions, and 31.7% (n=38) had a proven diagnosis of acute pontine infarctions.

Isolated medullary infarcts were identified in 14 (63.6%) examined patients, combined – in eight (36.4%) [32]. MMI has been identified in five (22.7%) out of 22 patients with acute medulla oblongata infarctions. Two (9.1%) patients were diagnosed with combined lesions of the medial and lateral parts of the medulla oblongata. Another 15 (68.2%) patients were diagnosed with lateral medullary infarctions.

MEDIAL MEDULLARY INFARCTION: CLINICAL FEATURES

Unilateral MMI in one patient showed a clinical picture of purely motor hemiplegia due to a lesion in the pyramidal pathway located in the medulla oblongata medially. In another patient, unilateral MMI manifested with sensorimotor stroke with the development of contralateral hemiparesis and contralateral loss of deep sensation.

Bilateral MMI was registered in 3 patients. It presented with impaired consciousness, respiratory issues, bulbar syndrome, and flaccid tetraparesis. The baseline neurological deficit by the NIHSS scale was 16.0 ± 0.8 points, and by the B. Hoffenberth scale – 25.2 ± 0.5 points, which corresponded to a severe stroke.

A rare combination of medial and lateral infarction of the medulla oblongata was observed in 2 cases. These patients developed an alternating brainstem syndrome and presented with severe systemic dizziness, nausea, repeated vomiting, and impaired swallowing. The neurological status revealed horizontal nystagmus, Bernard-Horner syndrome, segmental dissociated type of sensory impairment, bulbar and cerebellar symptoms with contralateral hemiparesis and pain, temperature, and proprioceptive sensitivity impairment.

MEDIAL MEDULLARY INFARCTION: IMAGING FEATURES

Brain MRI was done on all study patients within 12-24 hours from the onset of the symptoms. It revealed ischemic foci in patients with medullary infarcts were mainly localized in the medulla oblongata middle part (65%), less often – in the upper (20%) and lower (15%) parts. These foci have a rounded or cubic shape and were sized an average of 52.7 mm^3. In one patient, no significant signs of acute ischemia in the medullar oblongata were visualized (false-negative result). An acute ischemic lesion measuring 64.8 mm3 in the middle part of the medulla oblongata was detected 32 hours after the onset of the disease in two patients with Babinski-Nageotte syndrome that develops in the case of occlusion of the vertebral artery (VA).

MEDIAL MEDULLARY INFARCTION: AUTOPSY FEATURES

All clinical cases of bilateral MMI became fatal within the first 4 days. During the autopsy, bilateral foci of ischemia were found in the middle part of the medulla oblongata, located medially; in 1 patient they were combined with thalamic lesions; in another – an additional ischemic focus was localized at the level of the leg of the brain.

CLINICAL CASE

We present a clinical observation of patient O., 56 years old. The patient was hospitalized at the Neurological Center of the Oleksandrivska Clinical Hospital in Kyiv on October 8, 2007, with complaints of severe weakness in the left extremities. Symptoms developed acutely after sleep. Elevated to 160/80 mm Hg blood pressure was noticed. For the last 8 years, the patient has been suffering from hypertension, and coronary heart disease with a constant form of atrial fibrillation but did not take antihypertensive therapy systematically.

Findings: pulse – 78 beats/min, arrhythmic, blood pressure – 150/80 mm Hg. Pronounced left hemiparesis, tendon reflexes from the upper and lower extremities – S> D, abdominal reflexes – S <D, bilateral Strumpel's symptom, positive Babinski reflex on the left. Slight increase in muscle tone in the left extremities. No issues in sensitivity and coordination were detected. The neurological deficit on the NIHSS scale was 6 points, which corresponds to a mild stroke, on the scale of B. Hoffenberth and co-authors – 12 points (neurological disorders of moderate severity).

Ultrasound of carotid arteries and Transcranial Doppler ultrasound revealed hemodynamically significant stenosis of the right middle cerebral artery (80%), left middle cerebral artery (65%), and right VA (55%). MRI image of the brain is shown in Figure 1.

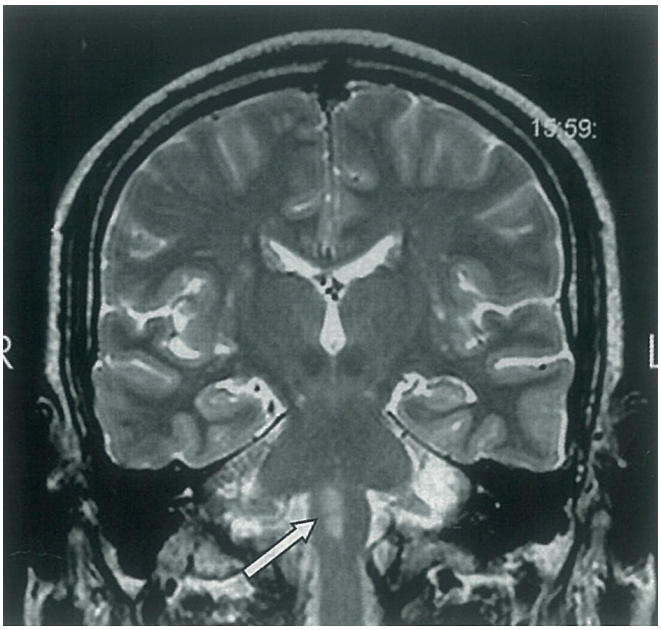

Fig. 1. DWI MRI imaging of the brain of patient O., 56 years old was performed 36 hours after the onset
Note*In the presented axial projection in the medial region of the medulla oblongata on the right, the focus of acute ischemia (arrow) was revealed.

Diagnosis: medullary medial ischemic infarction (cardioembolic subtype) in a patient with subcortical arteriosclerotic encephalopathy of III stages.

DISCUSSION

MMI is a rare variant of PCS. Our study identified MMI in five (4.2%) out of 120 PCS patients. MMI incidence among all ischemic strokes is 0.25% and among PCS – is less than 1.0% [33]. The low frequency of MMI is explained by the bilateral blood supply from the anterior spinal artery that arose from VA as well as by the compensation of blood flow through the "bulbar arterial ring".

MMI occurs in the case of ischemic lesions in the structures of the ventromedial part of the medulla oblongata. The most common reason for MMI is an occlusion of VA, anterior spinal artery, or lower parts of the basilar artery [34].

First described over a century ago, the clinical manifestation of MMI has a classic triad of symptoms [35]: contralateral hemiplegia sparing the face; contralateral loss of deep sensation; ipsilateral hypoglossal paralysis. These symptoms were presented in MMI patients in our study.

Complete MMI syndrome is a type of alternating hemiplegia also known as hypoglossal alternating hemiplegia, inferior alternating syndrome, lower alternating hemiplegia, or Dejerine syndrome. It includes ipsilateral hypoglossal palsy, contralateral hemiparesis, and lemniscal sensory loss [36]. Ipsilateral hypoglossal palsy results from damage to the nucleus and root of the sublingual nerve. Contralateral hemiparesis and lemniscal sensory loss appear due to damage to the corticospinal tract and medial loop. Incomplete MMI syndromes are characterized by ipsilateral hypoglossal palsy and contralateral central hemiparesis.

Patients in our study were presented with unilateral and bilateral MMI. Bilateral MMI is characterized by more severe clinical characteristics and poor prognosis compared to unilateral MMI [37]. This statement was proved by our prospective cohort study results, where all the patients with bilateral MMI deceased within four days after stroke development.

We provided a complex clinical, imaging, and laboratory analysis of MMI illustrated with a clinical case presentation. MMI's specific clinical and imaging features were determined, analyzed, compared, and described.

CONCLUSIONS

1. MMI is a rare and dangerous form of PCS with the highest incidence of fatality. Our prospective study found that MMI occurred three times less often than lateral medullary infarction. Three out of five patients with MMI in our study died during the first 4 days since the first stroke symptoms occurred.
2. MMI must be promptly diagnosed and treated to avoid high morbidity and mortality associated with it.
3. We have described the clinical-imaging correlation of bilateral and unilateral MMI as well as a combination of medial and lateral infarctions in the medulla oblongata.
4. The results of our study showed that MMI is mostly characterized by severe and very severe neurological deficits. MMI combined with lesions in other parts of the brain and bilateral MMI have an even more severe course and adverse effects.
5. Bilateral MMI has the poorest clinical outcome (100% mortality in our study).
6. Knowledge of the features of the neurological clinical course and imaging features of MMI is important, helping to diagnose this type of PCS promptly to select and choose the correct methods of therapy to improve prognosis. We have presented a clinical case of the cardioembolic subtype of MMI in a white adult patient with atrial fibrillation.

PROSPECTS FOR FURTHER RESEARCH

Future studies are needed on a larger number of patients to determine clinical and imaging features of MMI; to promptly increase diagnosing and treatment of such patients to avoid high morbidity and mortality. It is also important to promote awareness of stroke prevention programs and key MMI clinical and imaging correlations among patients and medical personnel.

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ORIGINAL ARTICLE

PECULIARITIES OF OBESITY EFFECTS ON THE QUALITY OF LIFE AND PSYCHOEMOTIONAL STATE OF PATIENTS WITH BRONCHIAL ASTHMA

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ABSTRACT

The aim: To study the effect of concomitant obesity in patients with bronchial asthma on quality of life and psychoemotional state depending on the phase of the disease.

Materials and methods: 176 patients with bronchial asthma in different phases of the disease with normal weight, pre-obesity and obesity were examined. The quality of life and psycho-emotional state of the patients was determined by the «Sent George Respiratory Question» and the Spielberger-Hanin and Beck tests

Results: All studied patients, showed significant violations of the psychoemotional sphere, a decrease in quality of life compared to healthy individuals ($p<0.05$). The remission phase revealed a deterioration in the quality of life of patients with overweight and obesity compared to patients with normal weight ($p<0.05$), in the exacerbation phase – with obesity and normal body weight ($p < 0.05$). Exacerbation negatively affected the psycho-emotional sphere in patients with normal body weight and obesity ($p<0.05$).

Conclusions: The quality of life was reduced in all studied patients, regardless of body mass index($p<0.05$), and the exacerbation of the disease worsened it ($p < 0.05$), increased depressive tendencies in patients with normal body weight and obesity ($p<0.05$). In patients with obesity, the worst quality of life indicators were found in the remission phase ($p<0.05$) and more pronounced depressive tendencies in the exacerbation phase than in the pre-obesity group ($p<0.05$). The most important indicators determining the course of bronchial asthma are quality of life and body mass index.

KEY WORDS: bronchial asthma, obesity, quality of life

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INTRODUCTION

Quality of life (QOL) is an integral indicator reflecting the degree of adaptation of a person to the disease and the possibility of performing his usual functions corresponding to his socio-economic situation [1]. The study of QOL using standardized methods makes it possible to assess the level of adaptive capabilities of the individual and to understand the nature of the disease more deeply [2]. Changes in QOL occur in all chronic diseases of internal organs, which include bronchial asthma (BA) [3]. The main manifestation of BA is suffocation attacks, which also affect the emotional and personal sphere of patients [4]. Meanwhile, manifestations of the psychoemotional state are not only the result of the main clinical syndrome. Attachment of Concomitant pathology can also provoke psychoemotional deviations. Obesity should also be considered among diseases with a significant spread and expressed impact on the psycho-emotional sphere of the patient [5, 6]. It is known that mental disorders increase the severity of somatic diseases, reducing the ability to work and quality of life often to a greater extent than diseases of internal organs [7].

THE AIM

The aim of our work was to assess the effect of concomitant obesity on QOL and psychoemotional state in BA patients at different periods of the disease course.

MATERIALS AND METHODS

176 patients with BA were examined, including 143 patients in the remission phase, 33 in the exacerbation phase, of which 54 were men and 122 were women. The average age of the patients was (45.19 ± 0.89) years. 3 groups were formed: with normal weight (NW) – 57 patients with body mass index (BMI) (21,79±0,25) kg/m^2 (1st group), including 47 patients in remission (1-A) and 10 in exacerbation (1-B); with overweight – preobesity – (PO) – 60 with BMI (27,15±0,18) kg/m^2 (2nd group), including 45 in remission (2-A), 15 in exacerbation (2-B); with obesity (OB) – 59 with BMI (34,14±0,48) kg/m^2 (3rd group), including 51 in remission (3-A) and 8 in exacerbation (3-B). The control group consisted of 30 practically healthy persons with normal body weight, men – 11, women – 19, with an average age (42.4 ± 2.0) years. Examination and treatment of BA patients was carried out in accordance with the current regulatory documents and recommendations of the GINA (Global Initiative for Asthma) 2022 [8]. Body mass index (BMI) was calculated using the formula: BMI = body weight (kg)/height (m^2). According to WHO, overweight is a condition in which the BMI is equal to or greater than 25kg/m^2 and obesity is a BMI level equal to or greater than 30kg/m^2 [9]. To determine the QOL of patients, the Saint George Respiratory Questionnaire (SGRQ) [10] was used, which consisted of 76 questions divided into

Table I. Quality of life indicators in patients with bronchial asthma depending on body mass index

Period of disease	Groups	Quality of life parameters, %			
		Symptoms	Activity	Impact	Final assessment
Remission	1-A	51,43±3,73*,4	34,11±3,28*,4	31,04±2,84*,4	35,35±2,69*,4
	2-A	59,72±3,33*	46,34±3,07*,2	35,15±2,67*	42,58±2,45*,2
	3-A	58,05±3,39*,4	52,19±2,93*2,4	44,25±2,95*2,3	48,82±2,64*2,4
	All studied patients	54,4±2,02*,4	44,41±1,88*,4	37,05±1,69*,4	42,43±1,57*,4
Exacerbation	1-B	72,58±2,29*	62,38±5,99*	58,13±3,73*	61,79±3,89*
	2-B	62,26±5,92*	56,46±5,55*	42,93±5,06*,2	49,91±4,54*
	3-B	81,58±5,84*,3	71,29±7,2*	60,84±8,01*	67,39±6,61*,3
	All studied patients	70,07±3,34*	61,85±3,61*	51,88±3,44*	57,75±3,07*
Control group		9,54±4,39	12,38±3,58	3,13±1,27	7,26±2,16

Notes:

* - differences are statistically significant relative to the control group ($p < 0.05$);

[2] - differences are statistically significant relative to the group with normal mass ($p < 0.05$);

[3] - differences are statistically significant relative to the overweight group ($p < 0.05$).

[4] - differences are statistically significant relative to the group with asthma exacerbation ($p < 0.05$).

3 parts. The first part "symptoms" measured the degree of anxiety caused by respiratory symptoms. The second part "activity" – measured the limitation of mobility and physical activity. The third part "influence" – studied the psychosocial impact of the disease. In addition, the final score of QOL was calculated. The sum of the scores when evaluating responses to this questionnaire ranged from 0 to 100%, with 0 being the best possible value. As BA patients are prone to anxiety and depressive tendencies [11], we additionally used Spielberg-Khanin tests for determining personal anxiety and tests to determine Beck's depression with the two subscales – cognitive-affective and somatic manifestations of depression. The survey was conducted at the permission of the Bioethics Commission of the Faculty of Medicine of the Uzhhorod National University (Minutes No. 4 dated February 26, 2019).

Statistical processing of the data was carried out using the programs Microsoft Office Excell 2016 and Statistica v 13.3.

RESULTS

All patients suffering from BA showed significant changes in QOL parameters, and the state of the psychoemotional sphere compared to the control group. This refers to increased personal anxiety, the level of depressive trends and a decrease in QOL according to all scales – "symptoms," "activity," "impact," "final assessment" ($p<0.05$). In patients of different weight categories, certain features were found in the indicators of QOL and in the psycho-emotional state.

In patients with normal body weight in the exacerbation phase, a higher level of manifestations of depression was found, mainly due to the second subscale ($p<0.05$), than in remission. The level of anxiety did not depend on the phase of the disease course, unlike to QOL, which was reduced during exacerbation ($p<0.05$).

In patients with PO, compared with normal weight, it was found that during remission, the level of depressive tendencies was slightly higher, and QOL was lower due to the "activity" and "total" scales ($p<0.05$). An inverse pattern was observed during exacerbation – a lower level of depressive manifestations due to the subscale II ($p<0.05$) and better QOL indicators ("impact," $p<0.05$) than in patients with normal weight. In the exacerbation phase of BA, individuals with PO had a tendency to decrease QOL compared to remission.

When comparing the QOL parameters of patients with OB with patients with normal weight, the following features were found: with OB in remission, all QOL indicators were reduced ($p<0.05$) with the same symptoms of the disease, in contrast to the exacerbation phase, where they did not differ statistically from each other. During exacerbation QOL in persons with OB, was more reduced due to the scales «symptoms,» «activity» and «total» than during remission ($p<0.05$). When comparing QOL in patients with OB and PO, it was found that in the remission phase there were more pronounced changes in the «impact» scale ($p<0.05$), in the exacerbation – «symptoms» and «total» ($p<0.05$).

The level of depression in OB was differed depending on the phase of the course of the disease: during exacerbation, the indicators of depression were higher ($p<0.05$), due to the I subscale of cognitive-affective disorders ($p<0.05$) than during remission. In the exacerbation phase, the level of depression in patients with OB was higher than in patients with PO ($p<0.05$). In patients with OB, there was a tendency to increase anxiety compared to patients with normal weight.

When conducting a correlation analysis in patients with normal weight, links were established between the severity of the disease and depression ($r = 0.39$), QOL scales ($r = 0.36$); between anxiety and depression ($r = 0.62$), QOL scales ($r = 0.4$); between the level of depressive manifestations and QOL scales ($r = 0.51$). In patients with PO, an average degree of correlation was found: between anxiety level and gender is negative ($r = -0.35$), depressive

Table II. Indicators of psychoemotional state of patients with bronchial asthma depending on body mass index

Period of disease	Groups	Anxiety, scores	Depression, scores	Depression subscales, scores	
				I	II
Remission	1-A	47,81±1,35*	8,21±0,91*,4	4,17±0,55*	4,68±0,69*,4
	2-A	49,24±1,42*	10,78±1,23*	5,49±0,88*	5,29±0,52*
	3-A	50,37±1,34*	10,33±1,03*,4	5,09±0,68*,4	5,24±0,48*
	All studied patients	49,17±0,79*	9,78±0,62*,4	4,92±0,41*	5,07±0,33*,4
Exacerbation	1-B	46,9±3,26*	17,6±2,83*	7,8±2,18*	9,7±0,98*
	2-B	51,13±2,58*	9,93±1,63*,2	5,2±1,04*	4,73±0,79*,2
	3-B	55,5±2,95*	14,75±1,18*,3	8,38±1,28*	6,38±0,68*,2
	All studied patients	50,91±1,74*	13,42±1,28*	6,76±0,88*	6,64±0,61*
Control group		39,69±1,32	4,07±0,79	2,03±0,46	2,03±0,45

Notes:

* - differences are statistically significant relative to the control group ($p < 0.05$);

[2] - differences are statistically significant relative to the group with normal mass ($p < 0.05$);

[3] - differences are statistically significant relative to the overweight group ($p < 0.05$).

[4] - differences are statistically significant relative to the group with asthma exacerbation ($p < 0.05$).

tendencies (r = 0.66), QOL (r = 0.34); between the level of depressive manifestations and QOL scales (r = 0.34). In patients with OB, an average degree of correlation was established: between the severity of the disease and the level of anxiety (r = 0.46), QOL scales (r = 0.46); between the level of anxiety and depression (r = 0.62), QOL scales (r = 0.39); between the level of depressive tendencies and QOL scales (r = 0.4).

Using the method of multivariate analysis, the factors that are the most typical for the studied groups: QOL ("final assessment") and body mass index have been identified.

DISCUSSION

Overweight and obesity are multifactorial conditions. They can be risk factors or a comorbid condition with somatic diseases. Overweight and obesity themselves can cause changes in the physical and psycho-emotional state of the patient and cause a decrease in QOL [5]. A comprehensive assessment of the condition of a patient with BA is the determination of QOL [2].

We made an attempt to establish the characteristics of the psycho-emotional state and QOL depending on BMI in patients with BA in the phase of remission and exacerbation.

In conducting our research, we found probable deterioration of all indicators of quality of life and psycho-emotional state during remission and exacerbation of BA compared to healthy individuals. The obtained results confirm the value of negative emotions from the disease in reducing QOL and controlling BA [11]. In our patients, exacerbation of BA had a negative effect on QOL. The total score increased in all studied groups, probably in patients with NW and OB, and in the group with PO – had a tendency. In patients with excessive BMI, there is a decrease in physical activity, which in turn contributes to an increase in body weight [9]. In the remission phase of the disease, the worst QOL indicators were observed in groups of patients with PO and OB. On the "Activity" and "Final assessment" scale, these groups had a statistically significant difference compared to the with NW. It is interesting to note that the exacerbation of BA led to possible QOL violations in patients with NW and OB, but leveled the differences between the studied groups.

Our studies have confirmed that the chronic course of the disease, periodic exacerbations, the need for long-term treatment, fear of a suffocation attack form a state of chronic psycho-emotional overstrain, stress in a patient with BA and have a significant impact on the formation of anxiety and depression [3].

The «Anxiety» scores in all studied groups were probably worse than the group of healthy individuals and did not depend on the phase of BA and BMI. Indicators of «Depression» were also probably higher in all groups of studied patients during remission and exacerbation of BA compared to healthy individuals. Exacerbation of BA probably increased depression in the groups with NW and OB and practically did not affect patients with PO. Such changes led to the fact that during the period of exacerbation of BA in the PO group, the value of depression was statistically significantly less than the groups of patients with NW and OB.

CONCLUSIONS

The following changes in quality of life and psycho-emotional sphere were found in BA patients:

1. With bronchial asthma in all patients, regardless of body mass index, there was a decrease in quality of life indicators on the scales "symptoms", "activity", "impact", "final assessment", increased level of anxiety and depressive tendencies, compared with healthy individuals ($p<0.05$).
2. Exacerbation of BA significantly reduced QOL in all patients ($p<0.05$) and increased depressive tendencies in patients with normal weight and OB ($p<0.05$).
3. In patients with obesity, there was a decrease in QOL ($p<0.05$) and an increased tendency to anxiety than in

other patients with the same symptoms of the underlying disease.
4. The most significant factors associated with the course of BA were indicators of QOL and body mass index.

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ORIGINAL ARTICLE

ASSOCIATION BETWEEN SERUM ZINC, COPPER AND SELENIUM LEVELS AND THE DEGREE OF LIVER DAMAGE IN PATIENTS WITH CHRONIC HEPATITIS C

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ABSTRACT

The aim: To evaluate the content of trace elements Zn, Cu and Se in blood serum and their relationship with viral load and the degree of liver fibrosis according to the results of the FibroMax test in patients with CHC.

Materials and methods: 62 outpatients with a verified diagnosis of CHC were under observation, in which serum Zn, Cu and Se levels, viral load and degree of liver fibrosis were determined according to the FibroMax test.

Results: HCV 1b genotype was detected in all patients. The proportion of patients with a high viral load was 32%, with a low viral load – 68%. In 19% of patients, the level of Zn was below normal, and the levels of Cu and Se were within the reference values. The proportion of patients without fibrosis was 32%, 16% had minimal fibrosis, 40% had moderate fibrosis, 8% had progressive fibrosis, and 3% had severe fibrosis. 68% of patients had active inflammation of various degrees, liver steatosis – 65%, non-alcoholic steatohepatitis – 48%, inflammation caused by alcohol consumption was absent. No statistically significant difference was found in serum trace element levels and viral load ($p>0.05$). A weak negative correlation between the level of Zn and the degree of fibrosis ($\rho=-0.340$, $p=0.007$) and a negligible negative correlation between the level of Zn and inflammation activity ($\rho=-0.286$, $p=0.024$) were revealed. Patients with fibrosis grade ≥F2 had lower Zn levels compared to patients with fibrosis ≤F1 (0.607 (0.540, 0.691) mg/l vs. 0.716 (0.593, 0.875) mg/l, $p=0.01$), and when comparing there was no difference in Cu and Se levels ($p>0.05$).

Conclusions: Thus, there is a relationship between the level of Zn in blood serum and the degree of liver damage in patients with CHC, which indicates the prospects for further research.

KEY WORDS: chronic hepatitis C, trace elements, zinc, liver fibrosis, FibroMax

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INTRODUCTION

According to the latest global estimates published in the Global Hepatitis Report (2017), more than 71 million people had chronic HCV infection in 2015, extrapolating to 1% of the population. The main clinical form of HCV infection is chronic hepatitis C (CHC), which develops in an average of 70% of infected individuals, for 15-30% of whom there is a risk of liver cirrhosis within 20 years [1]. The chronic course of the disease definitely leads to changes in the entire metabolism, including the exchange of trace elements. Zinc (Zn), copper (Cu) and selenium (Se) are essential for the normal functioning of the whole human organism, including the immune system and antioxidant defense, and their basic metabolism takes place in the liver [2]. In general, researches show that in HCV, as a result of HCV-mediated mitochondrial dysfunction, Zn deficiency occurs [3]. A decrease in the level of Zn can also be a consequence of liver fibrosis, which includes various mechanisms. The metabolism of Cu is also disturbed in patients with CHC at various stages of the disease, which usually leads to an increase in its level in the blood [4]. HCV infection is associated with low levels of antioxidants, including Se, and increased levels of oxidative stress [5]. Disruption of Zn, Se, and Cu homeostasis associated with oxidative stress and inflammation may enhance HCV replication and liver fibrosis and reduce the effectiveness of antiviral treatment [6]. Therefore, the question of the association of the content of Zn and other trace elements in the blood with the course of CHC remains relevant.

THE AIM

To evaluate the content of trace elements Zn, Cu and Se in blood serum and their relationship with viral load and the degree of liver fibrosis according to the results of the FibroMax test in patients with CHC.

MATERIALS AND METHODS

62 outpatients with a diagnosis of CHC were under observation. Criteria for inclusion in the study: patients with a verified diagnosis of CHC who agreed to follow-up. Exclusion criteria were: alcoholic, autoimmune, and toxic liver damage, liver cirrhosis, myocardial infarction in the first 4 months, diseases

of the respiratory and gastrointestinal tract in the acute phase, decompensated diseases, diseases of the nervous system, psycho-emotional and mental disorders that prevent conducting this study and the patient's decision to stop participating in the study. The studied patients had no markers of infection with other hepatitis viruses (A, B, D, G, TT), highly specific markers of autoimmune hepatitis/ cross syndrome (anti-LKM-1, anti-SLA and anti-LC-1) and HIV infection. All patients denied the use of corticosteroids, non-steroidal anti-inflammatory and immunosuppressive drugs.

All patients underwent clinical and laboratory examinations according to the standard of medical care for hepatitis C in adults (2021). HCV was performed according to the 10th revision of the ICD and verified by the detection of total antibodies of the IgG class to the structural and non-structural proteins of HCV (antiHCV IgG +) by the serological ELISA method, as well as by the indication of the investigated RNA HCV + in the blood by the PCR method with viral load (VL) and genotyping. Testing was performed on a thermal cycler with a real-time PCR product detection system "iQ 5", Bio-Rad, USA. Laboratory studies were performed in the accredited private laboratory "Dila". The level of Zn, Cu and Se in the blood serum of the patients was determined. The degree of liver fibrosis was analyzed according to the data of the non-invasive diagnostic method FibroMax according to the criteria proposed by the developers of the method. Data included: FibroTest, ActiTest, SteatoTest, NashTest, AshTest. FibroMax is manufactured by BioPredictive (Paris, France). FibroMax results are calculated using a special patented algorithm depending on the patient's sex, age, height and body weight and 10 biochemical indicators: haptoglobin, α-2-macroglobulin, apolipoprotein-A1, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), total bilirubin, glucose, total cholesterol and triglycerides.

To determine the duration of CHC, a thorough collection and analysis of the epidemiological history was carried out, taking into account the ways and factors contributing to infection. The most frequent ways of infection were surgical interventions and dental manipulations (23.5% and 21.4%, respectively), parenteral manipulations and blood transfusions in the anamnesis were indicated by 19.2% and 17.8%, respectively. The number of persons who indicated infection during the performance of their professional duties was 4.3% and 3.7% of patients believed that they were infected during unprotected sexual acts. In 10.1% of patients, it was not possible to establish the ways of infection. The duration of CHC in 78.0% of patients was an average of 10.5±0.3 years, and in 22.0% of patients it was detected for the first time.

The assessment of body shape was carried out according to generally accepted anthropometric indicators. Body mass index (BMI) was considered anthropometric criteria of obesity. BMI in the range of 18.5-24.9 kg/m^2 was considered as normal body weight, 25.0-29.9 kg/m^2 as overweight, ≥30.0 kg/m^2 as obesity.

Statistical analysis was performed in the jamovi 1.6 program using the Mann-Whitney U test, the Kruskal-Wallis test, and the Spearman correlation coefficient. The normality of the distribution of interval variables was assessed by the Shapiro-Wilk test. The assessment of the strength of the relationship between the variables was evaluated according to the Chaddock scale. Mean values were described as Me (Q_1; Q_3). The critical level of significance was α=0.05.

The research was carried out with the personal signed consent of the patients and in accordance with the methodological recommendations of the Declaration of Helsinki (1975) with redrafting, the International Code of Medical Ethics (1983), the laws of Ukraine, the relevant provisions of the WHO, and was approved by the local ethics commission of the Uzhhorod National University (protocol №6/4 dated 09/07/2021), and all those who participated were informed and, as a result, gave their consent in the consent letter, the structure of which corresponded to the officially agreed one.

RESULTS

Among the examined patients, the proportion of men was 56%, women – 44%, the average age was 41.7±10.9 years. The distribution depending on BMI was as follows: 31% had normal weight, 45% had overweight, and 24% had varying degrees of obesity.

The examined patients had a latent course of CHC with the following clinical syndromes and symptoms: asthenovegetative, dyspeptic, arthralgias, general weakness, reduced work capacity, periodic heaviness in the right hypochondrium and itching of the skin, and with varying degrees of activity of liver enzymes.

HCV 1b genotype was detected in all patients. The criteria for dividing patients depending on the VL were: with a high viral load – HCV RNA ≥6x10^5 IU/ml and with a low VL – HCV RNA ≤5x10^5 IU/ml. The proportion of patients with high VL was 32%, with low VL – 68%. Laboratory data are shown in Table I.

The proportion of patients in whom the Zn level was below normal was 19% (the lowest value was 0.405 mg/l), Cu and Se levels in all patients were within the reference values.

The distribution of patients according to FibroMax results is shown in Figure 1. The proportion of patients without fibrosis (FibroTest) was 32%, minimal fibrosis was 16%, moderate fibrosis was 40%, progressive fibrosis was 8% and severe fibrosis was 3%. 68% of patients had active inflammation of various degrees (ActiTest), liver steatosis (SteatoTest) – 65%, non-alcoholic steatohepatitis (NashTest) – 48%, inflammation caused by alcohol consumption (AshTest) was absent.

No statistically significant difference was found in the levels of trace elements in blood serum depending on sex, BMI and VL, and there was no correlation with age (p>0.05). During the analysis of the relationship between the level of trace elements and indicators of the components of the FibroMax test (Table II), a weak negative correlation between the level of Zn and the degree of fibrosis (ρ=-0.340, p=0.007) was revealed, a negligible negative correlation between the level of Zn and inflammation activity (ρ=-0.286, p=0.024) and a negligible negative correlation between Zn and Cu levels (ρ=-0.271, p=0.033). Also, the level of Zn was negatively correlated with the levels of α-2-macroglobulin (ρ=-0.273, p=0.032) and ALT (ρ=-0.251, p=0.049).

Additionally, patients were divided into two 2 groups depending on the degree of fibrosis: Group I (48% of pa-

Table I. Results of laboratory examination of patients

Indicator	Result	Reference values
Zn	0,649 (0,569; 0,739)	0,553-1,046 mg/l
Cu	1,04 (0,883; 1,23)	0,7-1,4 mg/l
Se	0,0775 (0,0622; 0,0958)	0,046-0,14 mg/l
α-2-macroglobulin	2,27 (1,89; 3,0)	1,3-3,0 g/l
Haptoglobin	1,03 (0,7; 1,33)	0,4-2,4 g/l
Apolipoprotein-A1	1,43 (1,27; 1,58)	0,79-1,69 g/l
Total bilirubin	12,0 (9,0; 15,0)	5,0-21,0 μmol/l
GGT	29,5 (20,3; 44,0)	8-61 U/l
ALT	42,0 (28,0; 80,8)	0-55 U/l
AST	31,5 (26,0; 44,0)	13-40 U/l
Glucose	5,3 (5,0; 5,9)	4,1-6,0 mmol/l
Total cholesterol	4,43 (3,91; 5,02)	<5 mmol/l
Triglycerides	1,05 (0,765; 1,45)	<1,7 mmol/l

Table II. Correlations between trace element levels and FibroMax data

		Zn	Cu	Se	FibroTest	ActiTest	SteatoTest	NashTest	AshTest
Zn	ρ	—							
	p	—							
Cu	ρ	-0.271	—						
	p	0.033	—						
Se	ρ	-0.016	0.077	—					
	p	0.899	0.551	—					
FibroTest	ρ	-0.340	0.140	-0.016	—				
	p	0.007	0.276	0.904	—				
ActiTest	ρ	-0.286	0.080	-0.080	0.479	—			
	p	0.024	0.535	0.538	<0.001	—			
SteatoTest	ρ	-0.158	0.065	-0.035	0.101	0.331	—		
	p	0.221	0.613	0.784	0.435	0.009	—		
NashTest	ρ	-0.133	0.132	0.023	0.050	0.351	0.780	—	
	p	0.303	0.307	0.856	0.699	0.005	<0.001	—	
AshTest	ρ	-0.113	-0.010	0.123	0.175	-0.211	0.147	0.039	—
	p	0.381	0.937	0.342	0.174	0.100	0.255	0.764	—

tients) – no fibrosis or minimal fibrosis (≤F1), Group II (52% of patients) – moderate, progressive or severe fibrosis (≥F2). A statistically significant difference was found in Zn levels depending on the degree of fibrosis (U=296, p=0.01), which was lower in the group of patients with more pronounced liver fibrosis (0.607 (0.540; 0.691) mg/l vs. 0.716 (0.593; 0.875) mg/l). Regarding the levels of Cu and Se, no difference was found (p>0.05).

DISCUSSION

There are conflicting data regarding the relationship of Zn level with HCV infection. Some studies indicate a decrease in its level in CHC [6, 7], while others do not confirm this connection [8]. This may be due to eating habits, antiviral therapy and other factors [7]. Liver disease affects the digestion, assimilation, storage and metabolism of nutrients, which can lead to vitamin and micronutrient deficiencies and protein-energy insufficiency. There is no gold standard for the diagnosis of nutritional deficiency in patients with chronic liver disease, including insufficient studies of the nutritional status of HCV patients without cirrhosis [9]. In a study by Gottschall et al. 2015 [9] insufficient intake of Zn and other nutrients (Ca, Na, K, vitamin C) was found in more than half of patients with CHC (but not cirrhosis). According to the results of the study by Pourhassan et al. 2015 [7], serum Zn and haptoglobin levels were significantly lower in patients with CHC (but not cirrhosis) compared to controls. In a study using bioelectrical impedance of body composition, the level of Zn was reduced in 6% of examined patients with HCV infection, however, the disease was in the stage of cirrhosis [8]. According

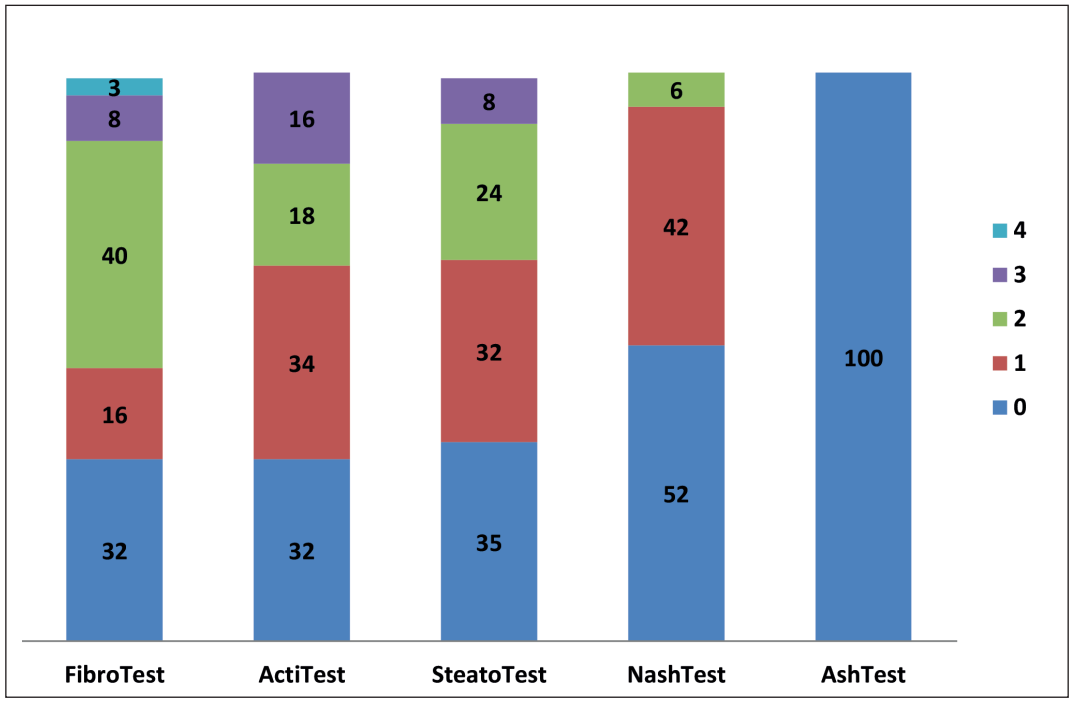

Fig. 1. Distribution of patients (in %) according to FibroMax data

to the results of other studies, the average level of Zn decreases with the progression of fibrosis, cirrhosis and was associated with the presence of varicose veins of the esophagus [10]. However, in a study by Suda et al. 2019 [11] Zn deficiency was observed in 27 (87.1%) patients with CHC, despite a good functional state of the liver. In our study, a decrease in the level of Zn was observed in 19% of patients. Such a small proportion of examined patients with hypozincemia may be due to the absence of pronounced cirrhotic liver changes and decompensation in them, as well as the relative compliance of patients with a healthy lifestyle, and probably a small sample size.

Persistent viral replication also results in a strong inflammatory response, characterized by an abundance of activated immune cells in the liver, as well as elevated levels of serum transaminases and proinflammatory cytokines such as IL-6 and TNF-α. As a result, chronic liver damage mediated by ineffective innate and adaptive immune responses promotes liver fibrosis, ultimately leading to cirrhosis and hepatocellular carcinoma [12]. It was shown that the serum Zn level is an independent prognostic factor of the overall survival of patients with CHC, as well as an indicator of the functional state of the liver and the degree of fibrosis. The concentration of Zn in serum and hepatocytes is reduced in patients with chronic liver diseases, and the depletion of Zn reserves is believed to accelerate the processes of fibrogenesis [13]. Zn deficiency can promote activation of hepatic stellate cells and collagen production, increasing fibrosis [14]. Zn inhibits the proliferation and synthesis of type IV collagen in hepatic stellate cells by increasing matrix metalloproteinase 13 [15]. Zn also promotes apoptosis of hepatic stellate cells. In addition, Zn can inhibit liver fibrosis by reducing the activity of lysyl oxidase [14].

A sufficient level of Zn in the liver stimulates the induction of metallothioneins, which are powerful antioxidants due to binding and release of Zn, but also have a moderate antiviral effect precisely due to the modulation of intracellular Zn homeostasis [2, 12]. Patients with CHC have low serum Zn levels and low metallothionein expression in the liver. Low metallothionein expression is associated with increased liver fibrosis, increased inflammation, and histological activity index (HAI), suggesting a protective role of metallothioneins in chronic inflammation [16].

In our study, a negative correlation was found between the level of Zn and the degree of liver fibrosis and the activity of the inflammatory process, as well as the levels of α-2-macroglobulin and ALT. Also, patients with fibrosis grade ≥F2 had lower Zn levels compared to patients with fibrosis ≤F1 (0.607 (0.540, 0.691) mg/l vs. 0.716 (0.593, 0.875) mg/l, p=0.01). Such data are consistent with the results of research by Omran et al. 2017 [13], where the level of serum Zn in patients with CHC was negatively correlated with the degree of liver fibrosis and was significantly lower as fibrosis progressed. This indicates the connection of Zn deficiency with the severity of liver damage.

The metabolism of Cu and Zn is closely related in the liver. Excessive Zn intake can lead to Cu deficiency due to metallothionein-mediated inhibition of intestinal Cu absorption [2]. In our study, a negative correlation of these trace elements was found, which indicates their antagonism in certain metabolic pathways both in normal and liver diseases. In addition, there is a certain indicative Cu/Zn ratio, the norm of which should be 0.8-1.2 μg/dL [5].

Regarding the trace elements Cu and Se, there are much fewer clinical studies, compared to Zn, regarding their association with chronic HCV infection [2]. In our study, no connection of these trace elements with liver damage was found, and their levels were within the reference values.

CONCLUSIONS

It was found that 19% of the examined patients had a Zn deficiency, while the levels of Cu and Se in all patients were within the reference values. There was no statistically significant differ-

ence in the levels of trace elements in blood serum depending on sex, BMI and VL, and there was no correlation with age (p>0.05). A negligible negative correlation was found between the levels of Zn and Cu (ρ=-0.271, p=0.033), as well as the level of Zn and α-2-macroglobulin (ρ=-0.273, p=0.032) and ALT (ρ=-0.251, p =0.049). It was established that the serum Zn level was negatively correlated with the degree of liver fibrosis (ρ=-0.340, p=0.007) and the activity of the inflammatory process (ρ=-0.286, p=0.024). A statistically significantly lower level of Zn was found in patients with a degree of fibrosis ≥F2, compared to patients with a degree of fibrosis ≤F1 (0.607 (0.540; 0.691) mg/l vs. 0.716 (0.593; 0.875) mg/l, p=0.01), and when comparing the levels of Cu and Se, no difference was found (p>0.05). Thus, there is a relationship between the level of Zn in blood serum and the degree of liver damage in patients with CHC.

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ORIGINAL ARTICLE

UNRAVELING THE CLINICO-GENETIC ASSOCIATION OF CATECHOL-O-METHYLTRANSFERASE-RS4680 G>A GENE POLYMORPHISM IN WOMEN WITH FIBROMYALGIA SYNDROME

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ABSTRACT

The aim: To determine the clinical and the genetic association of the COMT rs4680 SNP in women with FMS.

Materials and methods: Extracted DNA from peripheral blood samples were utilized as template for the PCR and RFLP analysis.

Results: A significant difference was found in the distribution of the COMT genotype between FMS patients and controls (P<0.05). The frequency of GG, AG, AA genotypes were 12%, 72%, 21% in FMS patients and 32%, 62%, 11% in controls. The clinical features of FMS reveal that FIQR and the severity of pain measured by VAS were significantly associated with the COMT rs4680 SNP (P=0.042; P=0.016). The co-dominant model for GG verse v. AG genotype (P=0.004) and AG v. AA genotype (P=0.002) has shown to be high risk for FMS. An increased risk of FMS in the dominant model for (AG+AA) v. GG genotype (P=0.001) and no significant difference was found between (GG+AG) v. AA genotype (P=0.08) in the recessive model. The result indicated that A allele considerably increase the risk of FMS (P=0.004) in comparison to the G allele.

Conclusions: AA genotype and A allele of the COMT rs4680 SNP were significantly associated with severity in FMS patients and also plays a significant role in the clinical manifestation of this disease.

KEY WORDS: Fibromyalgia Syndrome, FIQR, Polymorphism, COMT

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INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic pain condition caused by abnormal central sensory processing of pain signals. The interaction between different neurotransmitters, psychological factors, external stressors, hormones, and the Central Nervous System (CNS) dysfunction is thought to be the cause [1]. FMS is characterized by muscle pain, fatigue, stiffness, anxiety, depression, headache, sleep disturbance, and digestive problems [2]. The prevalence of FMS in the general population is between 0.2 to 6.6% and among women between 2.4 to 6.8% [3]. The etiology and pathophysiology of FMS is completely unknown, both genetic and environmental variables are involved in development of FMS [4]. Significant familial aggregation, along with conclusive evidence of genetic linkages and associations, suggest an underlying genetic cause of FMS [5]. Therefore, number of studies has turned into genetics in order to better understand some of the variation in FMS pain. Many studies have been conducted to investigate the potential role of candidate gene polymorphisms in FMS susceptibility and the results of these studies are diverse [6, 7].

Various studies have shown that FMS patients have altered pain processing inside the CNS, resulting in an amplified perception of pain. Increased nerve impulse transmission from the periphery to the CNS causes this amplification [8]. Monoamine system are associated with central sensitization [9]. Therefore, polymorphisms in the Catechol-O-methyltransferase (COMT) gene have also been studied in FMS which may represent that genetic factor may be the cause associated with the symptoms of FMS. The COMT gene is assumed to be implicated in central pain processing via dopaminergic pathway regulation, resulting in compensatory changes in opioidergic activity in the pain perception (9). COMT is an enzyme that inhibit the activity of catechol-amine and drugs containing catechol-amine. The COMT is found in the CNS, and the COMT gene is present on chromosome-22q11 (10). Several alterations in the COMT gene cause enzyme dysfunction [10]. As a result, COMT gene polymorphisms that result in high catecholamine levels may contribute to the development of chronic pain by triggering adrenergic receptors in the peripheral nerve and CNS [11]. Polymorphism in the COMT gene is associated with enhanced sensitivity to pain stimuli [12]. The COMT gene has Single Nucleotide Polymorphism (SNP) at 158 codons (rs4680) that change Valine (Val) to Methionine (Met) by substituting guanine as adenine [13]. SNPs in the COMT gene have been implicated in FMS susceptibility and symptom severity [14]. Therefore, research

Table I. Primer sequences used for COMT gene polymorphism.

Primer		Sequence
COMT-rs4680	Forward	5′- GGAGCTGGGGGCCTACTGTG-3′
	Reverse	5′-GGCCCTTTTTCCAGGTCTGACA-3′

Table II. Genotype and allele frequency of COMT polymorphism in FMS patients and control.

Subjects	GG	AG	AA	χ2	df	G	A	P-value
Patients (n=105)	12(11.4%)	72(68.8%)	21(20%)	12.96	2	96(45.7%)	114(54.3%)	**0.001**
Controls (n=105)	32(30.5%)	62(59%)	11(10.5%)			126(60%)	84(40%)	

Table III. Association between COMT rs4680 SNP with the clinical characteristics of FMS patients

Characteristics	Total (n=105)	GG(n=12)	AG(n=72)	AA(n=21)	P-value
Age, Mean±SD	35.9±11.1	37.8±10.5	35.7±11.1	35.6±11.8	0.826
Weight, Mean±SD	58.1±9.8	52.5±7.8	59±9.9	56.9±9.6	0.063
Height, Mean±SD	153.4±6.1	153±9	153.2±6.3	154.2±3.3	0.774
BMI, Mean±SD	24.6±4.1	22.8±3.7	25.1±4.2	23.8±3.9	0.143
FIQR, Mean±SD	75.2±4.7	72.1±8.2	75.2±4.2	76.8±2.5	0.024
VAS, Mean±SD	4.0±0.8	4.3±1.1	3.9±0.5	4.4±1.1	0.016
BDI, Mean±SD	21.2±11.1	18.1±8.8	21.4±11.6	22.2±10.9	0.579
BAI, Mean±SD	17.8±4.0	16.6±2.4	17.8±4.1	18.3±4.2	0.497
Weight loss, n (%)	23/105(21.9%)	2(8.7%)	14(60.9%)	7(30.4%)	0.358
Jaw pain, n (%)	32/105(30.5%)	5(15.6%)	20(62.5%)	7(21.9%)	0.595
Frequent awakening, n(%)	95/105(90.5%)	9(9.5%)	67(70.5%)	19(20%)	0.142
Family history, n (%)	60/105(57.1%)	7(11.7%)	42(70%)	11(18.3%)	0.885
Headache, n (%)	47/105(44.8%)	4(8.5%)	33(70.2%)	10(21.3%)	0.691
Feeling of fever, n (%)	90/105(85.7%)	8(8.9%)	64(71.1%)	18(20%)	0.125
Lack of energy, n (%)	78/105(74.3%)	7(9%)	8(74.4%)	13(16.7%)	0.092
Abdominal pain, n (%)	89/105(84.8%)	10(11.2%)	63(70.8%)	16(18%)	0.442
Disequilibrium in stairs climbing, n (%)	82/105(78.1%)	8(9.8%)	59(72%)	15(18.3%)	0.352
Irritable bowel syndrome, n (%)	69/105(65.7%)	6(8.7%)	52(75.4%)	11(15.9%)	0.115

Table IV. Association of COMT rs4680 gene variation with FMS patients

Genotype	Patients (n=105)	Controls (n=105)	OR (95% CI)	Risk Ratio (RR)	P-value
Co-dominant Model					
GG	12(11.4%)	32(30.5%)	1 (ref.)	1 (ref.)	
AG	72(68.8%)	62(59%)	0.32(0.153-0.63)	0.50(0.30-0.84)	0.004
AA	21(20%)	11(10.5%)	0.19(0.07-0.52)	0.41(0.24-0.71)	0.002
Dominant Model					
GG	12(11.4%)	32(30.5%)	1 (ref.)	1 (ref.)	
AG+AA	93(88.6%)	73(69.5%)	0.29(0.14-0.61)	0.48(0.29-0.80)	0.001
Recessive Model					
GG+AG	84(80%)	94(89.5%)	1 (ref.)	1 (ref.)	
AA	21(20%)	11(10.5%)	0.46(0.21-1.02)	0.71(0.53-0.96)	0.08
Allele					
G	96(45.7%)	126(60%)	1 (ref.)	1 (ref.)	
A	114(54.3%)	84(40%)	0.56(0.38-0.82)	0.75(0.61-0.91)	0.004

on the COMT rs4680 gene polymorphism in association with pain sensitivity in FMS is still unclear. To the best of our knowledge, this is the first study investigating the clinical and the genetic association of the COMT rs4680 SNP in North Indian (Uttar Pradesh) women with FMS.

THE AIM

The aim of the study was to determine the clinical and the genetic association of the COMT rs4680 SNP in women with FMS.

MATERIALS AND METHODS

STUDY POPULATION

A total number of 105 FMS patients and 105 controls participants from Era's Lucknow Medical College and Hospital (ELMCH), Era University, Lucknow, India was involved in this case control study. The ethics committee of the ELMCH approved this study. All the procedures including human subjects were performed in accordance with the ethical standards of ELMCH.

PATIENTS AND CONTROLS SELECTION CRITERIA

All the FMS patients and controls were female and came from the same ethnic group and geographical region. Patients were participants of the ELMCH, Lucknow those who attended OPD from Department of Rheumatology. The study includes only those patients with FMS who will fulfil the American College of Rheumatology criteria 2016 [15]. The patients with diabetes, rheumatoid arthritis, systematic lupus erythematosus and multiple myeloma or any other endocrinology disease were excluded from the study. The mean time for the patients suffering with fibromyalgia was 19.5±2.5 weeks. Mean age of FMS patients was 36.1±11.1 years and controls were 34.6±10.3 years. The controls were participants of the ELMCH, Lucknow those are visiting for routine check-up. The controls were defined as those without FMS and no past history of rheumatic disease and none of them receiving any medicine at the time of enrolment in the study will be included.

DATA AND SAMPLE COLLECTION

During the time of enrolment, the patients and controls were provided with questionnaires to be filled out and the questionnaire inquired about the duration of symptoms, age, weight, height, Body Mass Index (BMI), Fibromyalgia Impact Questionnaire Revised (FIQR), Beck Depression Inventory (BDI), present pain on Visual Analogue Scale (VAS), Beck anxiety Inventory (BAI), weight loss, jaw pain, frequent awakening, family history, headache, feeling of fever, lack of energy, abdominal pain, disequilibrium in stairs in climbing and irritable bowel syndrome After signing the informed consent form, the blood samples were collected form the patients and controls in EDTA-tubes and stored at 20^0C for genetic analysis.

COMT GENOTYPING

The peripheral blood was taken in a blood collection tube from the FMS patients and controls after taking written consent. Salting out method was used for the DNA isolation from the blood samples. Extracted DNA was used for the amplification of the COMT-rs4680 gene polymorphism by PCR-RFLP (Polymerase chain reaction-Restriction fragment length polymerase) method. The primer details for the COMT gene are given in the Table II. PCR was performed in a final volume of 25µl consisting of 150-200ng genomic DNA, 10pmol of each primer and 2x master mix (Takara) per tube using a gradient Master-Cycler (BIO-RAD). The PCR protocol: initial denaturation at 94^oC for 5 min, followed by 30 cycles of denaturation were carried out at 94^oC for 40 sec, annealing was carried out at 68^oC for 40 sec, extension was carried out at 72^oC for 40 sec, followed by final extension at 72^oC for 5 min. PCR products were run on agarose gel (4%) containing ethidium bromide and visualized by gel documentation apparatus (EZ BIO-RAD California), which allows for the identification of PCR product of 185 bp. The 185 bp PCR products were digested with NIaIII restriction enzyme (New England Biolabs INC, Ipswich, MA, USA), for 3 hours at 37^0C. Then, 10µl of PCR products were run on agarose gel (4%) containing ethidium bromide and visualized by gel documentation apparatus (EZ BIO-RAD California). The COMT-AA (Met/Met) genotype generated three bands of 114bp, 36bp, and 35bp, COMT-AG (Val/Met) genotype generated five bands of 114bp, 96bp, 36bp, 35bp and 18bp, COMT-GG (Val/Val) generated four bands of 96bp, 36bp, 35bp, and 18bp. To visualize the bands of 36bp, 35bp, and 18bp were difficult because of their small size and comigration with the similarly sized primer residue.

STATISTICAL ANALYSIS

FMS patients and controls were compared using statistical analysis performed with sufficient post hoc analysis using SPSS statics 28.0 software (IBM). The chi-square (χ^2) test or Fisher's exact test were used to compare the genotyping data between FMS patients and controls. Odds Ratio (OR), Risk Ratio (RR), and 95% Confidence Interval (CI) were used to assess the risk factors. χ^2 test was used to evaluate the Hardy-Weinberg Equilibrium (HWE) for the genotype distribution of the patients and controls. The value was considered to be significant when $P<0.05$.

RESULTS

CASE-CONTROL GENOTYPE DISTRIBUTION

A significant difference was found in genotype distribution between the FMS patients and controls ($P<0.05$) (Table II). The frequency of occurrence of GG, AG, AA genotypes in FMS patients was 12%, 72%, and 21% compared to 32%, 62%, and 11% in controls. The distribution of the COMT genotypes was consistent with HWE. FMS patients had a

higher prevalence of AG genotype than controls. In comparison to controls, the frequency of the A allele was found to be higher in FMS patients (114 vs. 84). Furthermore, FMS patients had a lower frequency of the G allele than controls (96 vs. 126).

Association of genotype frequency of COMT rs4680 SNP with respect to the clinical characteristics of FMS patients (Table III). The COMT rs4680 SNP was significantly associated with FIQR (p= 0.042) and VAS (P=0.016). The frequency of AA genotype presented a high FIQR score in FMS patients. A non-significant correlation was observed with other clinical symptoms such as age, weight, height, BMI, BDI, BAI, weight loss, jaw pain, frequent awakening, family history, headache, feeling of fever, lack of energy, abdominal pain, disequilibrium in stairs in climbing and irritable bowel syndrome (P>0.05).

ASSOCIATION OF COMT RS4680 SNP VARIATION WITH FMS PATIENTS

In order to investigate the association between the COMT rs4680 SNP and the risk of FMS in North Indian women, a multivariant analysis by logistic regression was performed with OR, RR, and 95% CI calculated for patients and controls Table IV. The COMT rs4680 SNP is associated with increased risk of FMS in North Indian women, according to our findings. In the co-dominant model, a significant association was observed between the GG and AG genotype (OR=0.32, 95% CI=0.153-0.63; RR=0.50, 95% CI=0.30-0.84; P=0.004). Moreover, in the co-dominant model, a significant association was reported between AG and AA genotype (OR=0.19, 95% CI=0.07-0.52; RR=0.41, 95% CI=0.24-0.71; P=0.002). In the dominant model, (AG+AA) vs. GG genotype had high risk of FMS (OR= 0.29, 95% CI=0.14-0.61; RR=0.48, 95% CI=0.29-0.80; P=0.001), whereas in the recessive model, (GG+AG) and AA genotype had a non-significant correlation (OR=0.46, 95% CI=0.21-1.02; RR=0.71, 95% CI=0.53-0.96; P=0.08). When comparing to the G allele, the frequency of occurrence of the A allele associated with an increased risk of FMS (OR=0.56, 95% CI=0.38-0.82; RR=0.75, 95% CI=0.61-0.91; P=0.004). As a result, the COMT rs4680 SNP is associated with FMS susceptibility, offering new insight into the genetic underlying aetiology and biology of this disease.

DISCUSSION

COMT enzymes breakdown the monoamine neuro-transmitters such as dopamine, serotonin, and norepinephrine. The enzymatic coding region has SNP rs4680 at codon 158 which changed Val to Met, causing an alteration in the enzyme. The enzymatic activity of Met-allele is three to four times less, which results in high amount of prefrontal dopamine and reduced threshold for pain. The Val-allele has high enzymatic activity and contains low amounts of prefrontal dopamine, resulting in a higher pain threshold [16]. To the best of our knowledge, this is the first study exploring the influence of COMT rs4680 SNP in North Indian women with FMS.

We found a significant association between COMT rs4680 SNP genotypes in FMS patients. Two recent meta-analysis on the COMT rs4680 SNP have been published. However, one of this meta-analysis reported an association between the COMT rs4680 SNP and FMS as similar to our results, but another meta-analysis reported no association between the COMT rs4680 and FMS [6,7]. Lee at al. meta-analysis consist of five different studies including five hundred twenty-two FMS patients and four hundred fifty-three controls from distinct geographic (Israeli, Turkish, Canadian, Spanish, and Mexican). However, this meta-analysis showed no correlation between COMT rs4680 SNP and FMS but some of these include studies found association [6]. Another, the meta-analyses by Tammimaki et al. consisted of eight different studies and found relation between the COMT rs4680 and FMS. According to their results, the A allele was found to be a risk factor for FMS (OR=1.23, 95% Cl=1.06-1.55, P=0.01) [7. These results are consistence with our finding that the A allele is significantly related with an increased risk to FMS (OR=0.56; 95% CI=0.38-0.82; P=0.004).

Two further case-control have been published [17,18]. One of this research showed an association between the COMT rs4680 SNP and FMS including one hundred-thirteen FMS patients and sixty-five controls (18), while the other study found no association in one ninety-eight FMS patients and ninety-nine controls [17]. The polymorphism in the COMT gene associated with FMS has been found in a small sample of the Turkish population [10,19]. Tander et al. found no relation between the COMT rs4680 SNP and FMS including eighty FMS patients and ninety-one controls [19]. Gursoy et al. reported that AA and AG genotypes together were more common in sixty-one FMS patients than sixty-one controls (P=0.024). These results are similar to our finding showing that AA and AG genotypes together were high in one hundred-five FMS patients compared to one hundred-five controls (P=0.001) (10).

FMS patients with AA genotype exhibited higher FIQR scores than patients with GG genotype in our study. Several studies have found that FMS patients with AA genotype score significantly high on the FIQ compared to those with GG and AG genotypes, which support our finding [20-22]. In contrast to our results, Inanir et al. found that FIQ scores were lower in FMS patients with Met allele carriers than those with GG genotype [23].

COMT is involved in the pain modulation [24]. According to Zubieta et al. healthy controls with the GG genotype have higher threshold pain. FMS Patients with the AA genotype have lower tolerance for pain [9]. These results are supported by our finding. In our study of 105 FMS patients, we found significant correlation between the COMT rs4680 SNP and VAS (P=0.016). Patients with FMS who had AA genotype were more susceptible to pain. In contrast to our results, Inanir et al. found no association between the COMT rs4680 SNP and VAS [23]. Finan et al. reported similar to our results that AA genotype per-

ceived more pain compared to AG or GG genotype and the COMT genotype altered the everyday relations between maladaptive behavior and pain [25].

FMS patients with AA genotype had high BDI and BAI scores compared to GG genotype, although the differences were not statistically significant in our study. In agreement with our results, Inanir et al. and Desmeules et al. reported that FMS patients with AA genotype had high psychological scores in comparison to GG genotype, however no statistical difference was found [23, 17]. In FMS patients, the COMT gene polymorphism had reported a significant impact on depression (P=0.001) and anxiety (P=0.004) [21].

Our study suggests that the COMT rs4680 SNP may change the function or expression of protein which may influence the susceptibility and severity in FMS patients. Therefore, it is possible that the genetic variation in the COMT gene moderates the pain in the sample of FMS patients. These finding contribute to the growing body of research and explore into new territory, further improve our understanding on the role of COMT in FMS.

CONCLUSIONS

Our study tested the association of COMT rs4680 SNP in North Indian women with FMS and found that COMT rs4680 SNP is associated with an increased risk of FMS. Furthermore, the results revealed that AA genotype and A allele are significantly implicated in the pathogenesis of FMS.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

MONITORING ASSESSMENT OF THE EARLY PROCESS ON THE BACKGROUND OF TES THERAPY

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ABSTRACT

The aim: To investigate and evaluate the effect of TEC therapy on the wound process.

Materials and methods: On the models of clean, purulent and purulent-necrotic wounds in a comparative aspect, the wound process in the dynamics of wound healing in dental patients was studied in 233 patients, of which 105 were treated with TES therapy and 128 were treated with traditional treatment. A monitoring evaluation of the wound process was carried out based on the screening of the cytological picture of the wound contents, the study of the types of cytograms of smears-imprints from the wound on the 3rd, 6th and 9th days after surgical interventions.

Results: It was established that against the background of TEC therapy, compared to traditional therapy, a positive trend of reparative processes in the wound was noted starting from the 3rd day. Destructive forms of granulocytes were significantly reduced with a simultaneous increase in the quantitative and qualitative composition of macrophages and an increase in the number of fibroblasts. The transition of the inflammatory phase to the regeneration phase was observed in the smear-imprints.

Conclusions: The positive effect of TEC therapy on regenerative processes, both on clean and purulent and purulent-necrotic wounds at all stages of healing, has been established. The cytological picture of the wound contents, the type of cytogram of smears-imprints are sensitive markers of regenerative processes in the wound, regardless of its type. These criteria for evaluating the course of the wound process can be successfully used for prognostic purposes.

KEY WORDS: wounded process, tes therapy, cytograms

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INTRODUCTION

The wound process is accompanied by a complex of complex molecular and cellular changes that occur in the wound after injury and are aimed at wound regeneration and healing [1-5].

It is believed that the speed of wound healing is not only a function of time, but also a reflection of the ability of tissues to regenerate [6, 7]. This process involves both molecular and cellular components, which can be used to evaluate regenerative changes [8-12].

Given the key role of cellular elements at different phases of wound healing, the type of cytogram and the cytological picture of the wound contents can play an important role in the monitoring assessment of the course of the wound process against the background of TES therapy [14].

THE AIM

The aim of this work was to investigate and evaluate the effect of TEC therapy on the wound process.

MATERIALS AND METHODS

On the models of clean, purulent and purulent-necrotic wounds in a comparative aspect, the wound process in dynamics was studied in representative groups of dental patients in terms of age, social status and pathology in 233 patients, of which 105 were treated with TES therapy and 128 – with traditional treatment. A monitoring evaluation of the wound process was carried out based on the screening of the cytological picture of the wound contents, the study of the types of cytograms of smears-imprints from the wound on the 3rd, 6th and 9th days after surgical interventions.

Statistical analysis was carried out using the Excel program (Microsoft Office 2010, Microsoft USA) and Statistica 6.0 (Statsoft , USA).

Differences of indicators at significance level $p<0.05$ were considered statistically significant.

RESULTS

It was established that already on the third day of treatment with the use of TES therapy, positive dynamics of the course of the wound process were observed in all the studied main groups, as evidenced by the cytological picture of the wound contents (Table I).

Analysis of the cytological pattern of smears – prints from wounds from patients of the studied groups indicates a more significant decrease compared to traditional therapy in the number of neutrophil granulocytes in the second group by 1.1 times, the third – by 1.2 times,

Table I. Cytological picture of wound contents on the 3rd day after TES therapy (M ± m)

Indicators	Groups of patients					
	The main one			Comparison		
	And the group (n=27)	II group (n=37)	III group (n=41)	And the group (n=21	II group (n=56)	III group (n=51)
Neutrophil granulocytes,%	51.86 ± 1.81	86.35 ± 2.04	80.12 ± 2.25	56.43 ± 1.81	92.17 ± 2.14	92.26 ± 2.84
Destructive forms,%	4.73 ± 0.94	68.24 ± 2.11	60.23 ± 2.16	9.74 ± 0.35	74.35 ± 2.34	69.77 ± 2.24
Phagocytic forms,%	38.6 ± 1.34	31.73 ± 1.54	39.65 ± 1.82	31.12 ± 1.45	12.86 ± 1.95	14.48 ± 1.65
Macrophages,%	14.21 ± 0.26	8.72 ± 0.15	10.11 ± 0.82	1 3.85 ± 0.38	6.45 ± 0.16	7.25 ± 0.14
Fibroblasts,%	16.34 ± 0.58	3.16 ± 0.46	4.21 ± 0.81	15.72 ± 0.86	1.96 ± 0.08	2.78 ± 0.13
Lymphocytes,%	11.42 ± 0.45	6.41 ± 0.94	7.32 ± 0.87	8.91 ± 0.34	4.23 ± 0.56	5.13 ± 0.68
F,%	52.12 ± 1.53	49.18 ± 3.42	50.24 ± 3.01	51.94 ± 1.43	48.85 ± 2.42	49.1 ± 2.65
FC	8.12 ± 0.42	6.42 ± 0.53	6.12 ± 0.86	6.62 ± 0.73	5.98 ± 0.85	5.51 ± 0.46

Note: P < 0.05 – compared between the main and comparison groups.

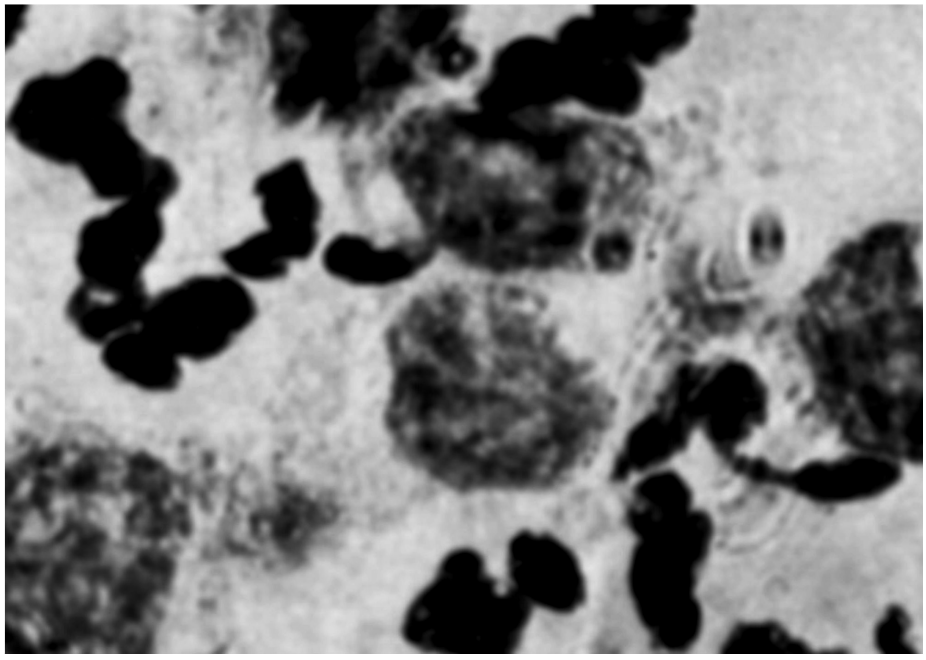

Fig. 1. Regeneration – inflammatory type of cytogram. The transition from the inflammatory phase to the regeneration phase (a group of young polyblasts is among the remnants of neutrophils). Hematoxylin eosin staining. Collection: volume x40.x10

of which the destructive forms were composed (68,24 ±2.11% and 60.23±2.16%), phagocytic – (31.73±1.54% and 39.65±1.82%). The number of macrophages increased to (8.72±0.15% and 10.11±0.82%), lymphocytes – to (6.41±0.94% and 7.32±0.87%). An increase in FA by (0.33% and 1.1%) and FC by (0.44 and 0.61) was recorded. In the patients of the first group, the studied indicators were as follows: the number of neutrophilic granulocytes decreased to (51.86±1.81%), of which phagocytic forms were (38.64±1.34%), destructive (4.73±0.94 %), which is 2.1 times less than the indicator of the comparison group.

On the sixth day of complex therapy with the use of TES – therapy, positive dynamics were observed, which are more pronounced in the main groups compared to patients on the background of traditional treatment. A decrease in the number of neutrophil granulocytes was observed in the first group to (56.41±0.34%), in the second to (78.54±2.46%) and in the third to (72.53±2.45%), with whose destructive forms accounted for (9.74±0.35%) in the first group and (56.52±2.83% and 42.36±1.83%) in the second and third. The phagocytic forms were 32.11±1.42%, 42.45±1.84% and 58.51±2.14%, respectively. The number of macrophages increased to (13.82±0.34, 10.43±0.36 and 12.83±0.96)%, fibroblasts – to (15.71±0.84, 3.17±0, 46 and 7.92±0.72)%, lymphocytes – up to (8.91±0.36%, 6.94±0.26% and 8.63±0.42%).

An increase in FA to (51.92±1.43%) in the first group and to (51.85±1.94% and 54.31±1.34%) in the second and third groups was also recorded.

The average indicators of the phagocytic number (PF) were (6.62±0.71, 6.51±0.24 and 6.96±0.21), respectively.

This is also confirmed by the analysis of the cytological pattern of smears – prints from the wounds of patients of the examined groups, which indicates the favorable effect of TES – therapy on the dynamics of regeneration

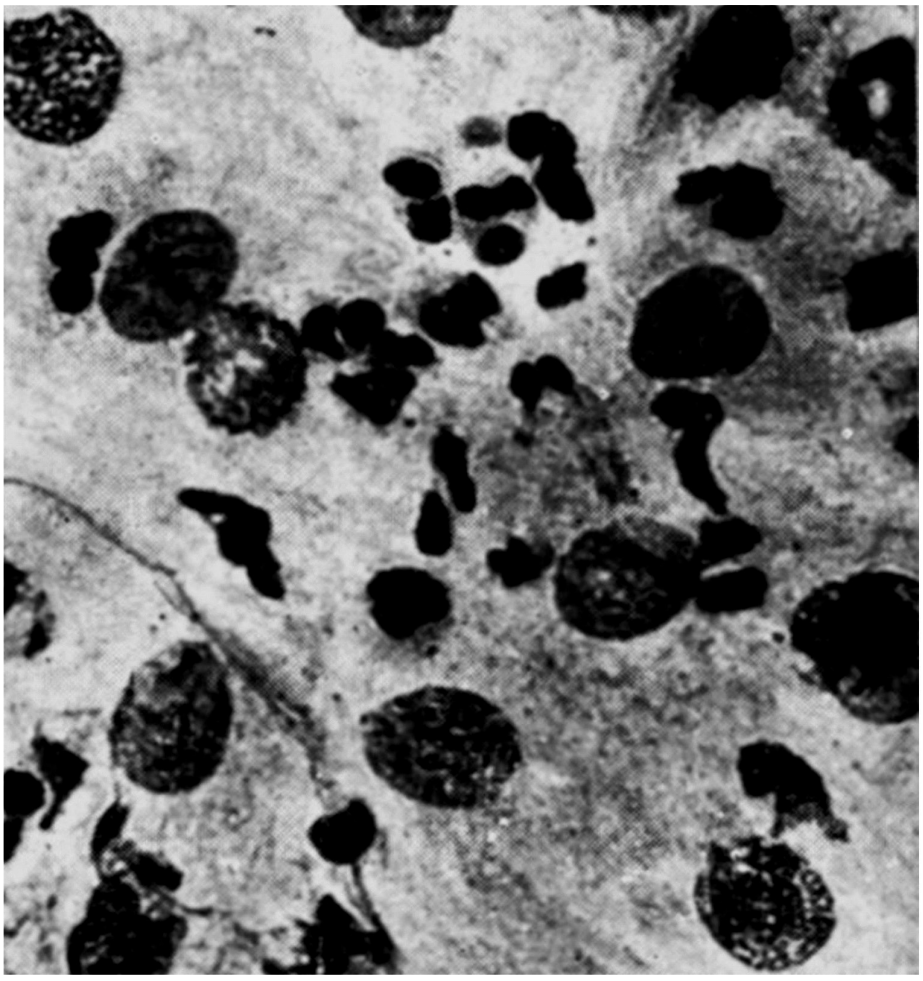

Fig. 2. Wound after wisdom tooth extraction. Epithelialization (V-th type of cytogram – layers of flat non-healing young epithelium)

processes. In smears – impressions, a regenerative – inflammatory (Fig. 1) or regenerative type of cytogram (Fig. 2) was observed.

We found this type of smear-imprints in 70.4% of the 1st main group and in 46.7% of the similar comparison group. In the second and third groups, this indicator was 35.1% and 46.3%, respectively, against 26.7% and 40% in the comparison group.

It should be noted that with chronic periodontitis, the course of the wound process was delayed by an average of 3.5±1.3 days, despite the positive trend towards changes in cytological smears – imprints in dynamics.

DISCUSSION

The results of complex studies of the wound process against the background of the use of TES therapy [14] in the complex treatment of wounds show that it is more effective than traditional therapy. According to the conducted studies, it was established that already on the 3rd day of the postoperative period, with clean wounds in smears-prints, 55.6% of the IV type of cytogram is noted, against 40.0% in the comparison group. In the 2nd main group, this indicator was 24.3% against 20.0% and the third, respectively, 41.5% and 33.3%, which is 4.3% and 8.2% higher than the comparison group. On the 9th day, the V – th type of cytogram in patients of the 1st main group was 7.6% higher than in the comparison group. A similar regularity was observed in the 2nd and 3rd main groups, which indicates a greater effectiveness of TES therapy compared to traditional therapy [14].

In this regard, it should be noted that, since it is observed in patients during the wound process that the cytomorphological picture of one phase of wound healing is superimposed on another, it is advisable to determine the cytological picture in dynamics in a comparative aspect.

So, as our research shows, starting from the third day against the background of the use of TES – therapy in the complex treatment of the wound process in dental patients, more pronounced positive trends in reparation processes are observed. A more significant decrease in the number of destructive forms of neutrophil granulocytes, an increase in their phagocytic forms, lymphocytes, macrophages, fibroblasts, FA and PF compared to groups of patients against the background of traditional therapy is noted.

CONCLUSIONS

1. The positive effect of TEC therapy on regenerative processes, both on clean and purulent and purulent-necrotic wounds at all stages of healing, has been established.

2. The cytological picture of the wound contents, the type of cytogram of smears-imprints are sensitive markers of regenerative processes in the wound, regardless of its type.
3. These criteria for evaluating the course of the wound process can be successfully used for prognostic purposes.

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ORIGINAL ARTICLE

ANTIPSEUDOMONAL ACTIVITY OF METABOLIC COMPLEXES OF L. RHAMNOSUS GG AND S. BOULARDII AGAINST THE POLYRESISTENT PATHOGEN IN IN VITRO AND IN VIVO TESTS

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ABSTRACT

The aim: Explore the antimicrobial properties of lactobacilli's metabolites and combination of lactobacilli's and saccharomycetes' metabolites with different concentrations *(in vitro)* and to test the effectiveness of samples with minimum inhibitory concentration on infected polyresistant strain *P. aeruginosa* skin wounds *(in vivo)* for the possibility of creating prophylactic antimicrobial agents.

Materials and methods: Metabolic complexes *(L. rhamnosus* GG *and S. boulardi)* were obtained by culturing lactobacilli or lactobacilli and saccharomycetes in lactobacilli disintegrates. The sensitivity of *Pseudomonas aeruginosa* PR *(in vitro)* to them was determined by the microtechnique of serial dilutions in a liquid nutrient medium. In vivo, 0.9 % sodium chloride solution (control) or lactobacillus metabolic complex (experiment, treatment group) was applied to infected skin wounds or, in addition, immediately before the infection, to the wound and then to infected wounds (experiment, prophylactic-treatment group).

Results: There was observed the decrease of the infectious process of skin wounds in the prophylactic-treatment group (3.25-3.4 times; p=0.01 related to control samples) compared with the treatment group (2.05-2.25 times; p=0.02) by the wound healing rate (day 5). The healing rate of control wounds (day 11) coincided with the rates of experimental wounds in the prophylactic-treatment group (day 8), indicating that the use of lactobacilli metabolites promotes the acceleration of healing by almost three days.

Conclusions: Metabolic complexes of probiotic microorganisms are promising for construction on their new class of antimicrobials for the effective pharmacoprophylaxis and pharmacotherapy.

KEY WORDS: infected wounds, planimetric parameters, minimum inhibitory concentration

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INTRODUCTION

Obtaining substances with multifunctional properties for the design of new preventive-therapeutic antimicrobial agents is becoming relevant due to a number of reasons. First, the emergence and spread of antibiotic resistant strains of microorganisms, especially polyresistant, is significant [1]. Second, there is an increase in the number of patients with multivalent allergic reactions to antibiotics [2, 3]. And third, there are existing disadvantages of modern antimicrobial drugs, in particular wound healing agents [4].

The product of the vital activity of *L. reuteri* (2×10^7 CFU) accelerates wound healing compared with untreated wounds or wounds treated with *L. reuteri* cells [5]. *L. rhamnosus* GG lysate stimulates the re-epithelialization of damaged keratinocytes by activating cell migration and increases the wound healing rate [6]. Nisin (a polypeptide antibiotic produced by *L. lactis*) reduces the number of viable *S. aureus* cells (4.3×10^2 CFU/wound) compared to control wounds (2.2×10^7 CFU/wound) and stimulates wound closure on experimental models of each mouse infection *(in vivo)* [7].

In our previous *in vitro* experiments a wide range of antimicrobial and anti-biofilm (for the process of formation and pre-formed biofilms) activity of lactobacilli's and saccharomyces metabolites and their combinations obtained by the author's method (without the use of traditional nutrient media) was proved against the pathogens and toxigenic strains of *Corynebacterium* spp. tox + [8, 9].

THE AIM

Explore the antimicrobial properties of lactobacilli's metabolites and combination of lactobacilli's and saccharomycetes' metabolites with different concentrations *(in vitro)* and to test the effectiveness of samples with minimum inhibitory concentration on infected polyresistant strain *P. aeruginosa* skin wounds *(in vivo)* for the possibility of creating prophylactic antimicrobial agents.

MATERIALS AND METHODS

For the study, two samples were taken: the metabolic complex of *Lactobacillus rhamnosus* GG (ML) obtained

by culturing lactobacilli in its own ultrasonic disintegrates, and the combination of the metabolic complexes of *L. rhamnosus* GG and *Saccharomyces boulardii* obtained by the cultivation of co-cultures of lactobacilli and saccharomycetes in ultrasonic lactobacillus disintegrates (MLS) [10]. The test culture was an antibiotic-resistant strain of *Pseudomonas aeruginosa (P. aeruginosa* PR*)* (to cefoperazone, cefepime, imipenem, etc.), obtained from the collection of the microorganism museum of the SI "IMI NAMS", Kharkiv.

Sensitivity determination of *P. aeruginosa* PR (optical density of suspensions corresponded to 0.5 units on a McFarland scale (Densi-La-Meter instrument (PLIVA-Lachema Diagnostika, Czech Republic)) to metabolic complexes *(in vitro)* was performed by microtechnique of serial dilutions in liquid nutrient medium in 96 well plates produced by EXIMCARGOTRADE LLC (Ukraine) [11] The optical density of the samples was measured using a Lisa Scan™ EM (Erba Mannheim, Czech Republic) analyzer at a wavelength of 630 nm. ML concentrations were from 1.1 mg/ml to 0.03 mg/ml) and MLS – from 0.83 mg/ml to 0.02 mg/ml of total protein, determined by the Lowry method.

Modeling of infected skin wounds *(in vivo)* was performed on guinea pigs weighing 250-260 g. Control group was consisted of animals treated with 0.9 % sodium chloride solution with the addition of polyethylene oxide (PEO) 1500 and PEO 400, treatment group – animals treated with ML on infected wounds with the addition of PEO 1500 and PEO 400 and prophylactic-treatment group (P) – animals, in which ML was additionally applied on the wounds immediately before infection, and then it was used as in the treatment group (daily, twice a day). Wounds were infected of *P. aruginosa* PR at a concentration of $\geq 10^9$ CFU/ml.

Microbiological methods involved the collection of smears from the surface of infected wounds with identification of the pathogen and determination of the number of colony-forming units (CFU) of bacteria (expressed in decimal logarithm (lg)).

The size of the wounds was determined at 1, 5, 8 and 11 days after infection with the subsequent calculation of the total wound area in cm^2 [12]. The wound healing area was calculated by the formula: $S=S_0-S_X$, where S_X is the mean value of the wound area at the time of study, cm^2; S_0 is the initial mean value of the wound area, cm^2 [13]. The wound healing rate over a certain period was calculated by the formula: $V=(S_0-S_X)/n$, where S_X is the average value of the wound area at the time of the study, cm^2; S_0 is the initial mean value of wound area, cm^2, n is the day of treatment [13]. The coefficient of wound healing rate over a certain period was calculated by the formula: $V_k=(S_0-S_X)/S_0$, where S_X is the average value of the wound area at the time of study cm^2; S_0 is the initial mean value of the wound area, cm^2 [13]. The reparative effect (RE) was calculated by the formula: $RE=(S_C-S_E)/S_C\times100$ %, where S_E is the value of the wound area in the experimental group, cm^2; S_C is the value of the wound area in the control group, cm^2 [13].

All animal experiments were carried out in accordance with the Law of Ukraine "On the Protection of Animals from Cruelty" (No 3447-IV of 21.02.2006) in accordance with the requirements of the Institute's Bioethics Committee and the provisions of "European Convention for the Protection of Vertebrate Animals Used for Experimental and other scientific purposes" (Strasbourg, 1986).

Statistical processing of the results was performed using Microsoft Office Excel 2007 and Statistica 10.0 (StatSoft Inc., USA). The experimental data are presented as mean value (x) with the indication of standard deviation (SD). Statistical comparisons between the groups were performed using one-way analysis of variance (ANOVA) with the Bonferroni correction. Correlation data analysis was performed using nonparametric Spearman's correlation coefficient (r). Differences were considered statistically significant at $p<0.05$ relative to control.

RESULTS

Minimum inhibitory concentrations (MIC) of ML and MLS for inhibiting the growth of *P. aeruginosa* PR showed similar results (Fig. 1). MIC of the ML and MLS samples relative to the selected polyresistant strain was 0.27 mg/ml and 0.21 mg/ml of total protein respectively. The absence of statistically significant difference in the concentrations of ML and MLS obtained in in vitro tests contributed to further study *in vivo* of the antimicrobial activity of concentrations of ML (0.27 mg/ml (I) and 0.55 mg/ml (II) of total protein).

The CFU values of the pathogen on the first day of the experiment were lower in the prophylactic-treatment group (lg 6.1 ± 0.45 CFU/ml and lg 6.7 ± 0.3 CFU/ml at the concentrations of ML 0.55 mg/ml and 0,27 mg/ml of total protein, respectively) compared to control (lg 8.5 ± 0.1 CFU/ml; p=0.04) and therapeutic (lg 8.36 ± 0.25 CFU/ml and lg 8.4 ± 0.23 CFU/ml; p=0.04 at ML concentrations of 0.55 mg/ml and 0.27 mg/ml protein, respectively) by groups (Fig. 2A). Microbiological examination of the smears taken from the infected wounds on day 8 of the experiment also showed the superior efficacy of ML with its additional prophylactic use (lg 0.8 ± 0.26 CFU/ml regardless of the ML concentration) unlike the test samples without pre-treatment of wounds (lg 2.7 ± 0.36-3.46 ± 0.34 CFU/ml; p=0.05 depending on concentration) and control samples (lg 5.1 ± 0.3 CFU/ml; p=0.003). On the day 11 of the experiment, healing of infected wounds was observed in all experimental animals and there were no growth of the pathogen's microbial cells, except for the treatment group with a concentration of ML of 0.27 mg/ml of total protein (lg 0.66 ± 0.58 CFU/ml; p=0,05) and control animals (lg 2.23 ± 0.35 CFU/ml). A direct correlation between the antimicrobial activity of ML (concentration of 0.27 mg/ml of total protein) and the method of its application (r=0.94; p=0.04). was established.

Slow reduction of the total area of the control wound (from 6.46 ± 0.22 cm^2 to 5.16 ± 0.34 cm^2; 3.41 ± 0.28 cm^2; 1.36 ± 0.36 cm^2 on the days 1, 5, 8, 11, respectively) differed from the area of wounds of the prophylactic-treatment group (2.02 ± 0.09-2.15 ± 0.2 cm^2; p=0.01 and 0.6 ± 0.08-0.8 ± 0.1 cm^2; p=0.03 on the days 5 and 8, respectively, depending on the concentration of ML) and the area of wounds of the

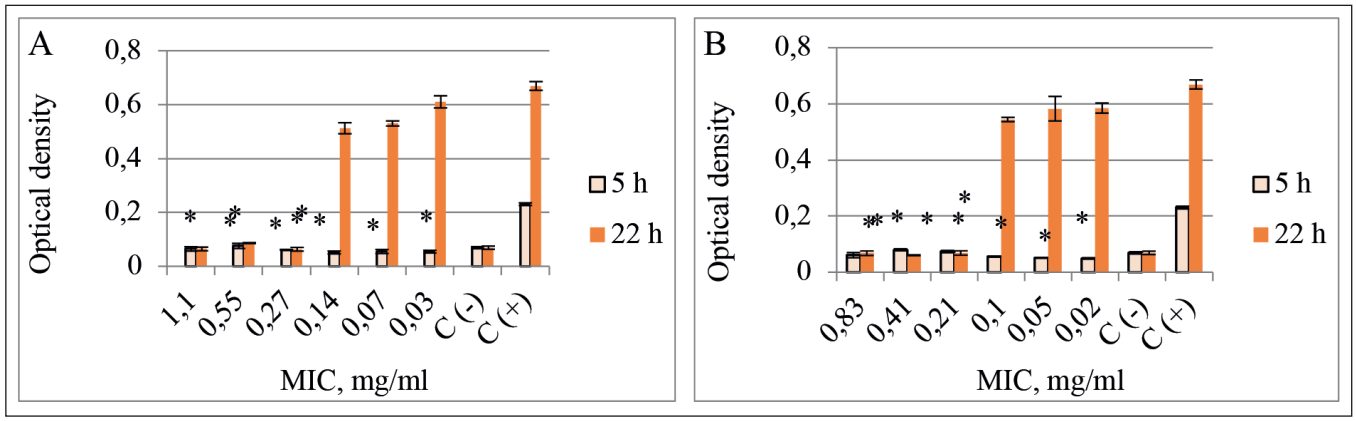

Fig. 1. Values of the minimum inhibitory concentration (MIC, mg/ml) for the polyresistant strain of P. aeruginosa of the metabolic complex of L. rhamnosus GG obtained by cultivation of lactobacilli in own disintegrates (ML) (A) and combinations of the metabolic complex of L. rhamnosus GG and S. boulardii, obtained by cultivation of co-cultures of lactobacilli and saccharomycetes in lactobacilli' desintegrates (MLS) (B), of negative control C (-) – nutrient medium with test substances, of positive control C (+) – nutrient medium with test culture. (x±SD).
Note. * – the probability of discrepancies as compared to the control C (+) ($p<0.05$).

treatment group (3.3 ± 0.15-3.6 ± 0.6 cm^2; p=0.03 and 1.06 ± 0.06-1.5 ± 0.15 cm^2; p=0.03 on the days 5 and 8, respectively, depending on the concentration of ML, and also on the day 11 0.1 ± 0.009 cm^2; p=0.001 with a lower concentration of ML) (Fig. 2B).

Regarding baseline indicators, the most intensive wound healing in the prophylactic-treatment group occurred in the first 5 days of the experiment, in the treatment group – from 1 to 8 days, in the control group – after 8 days (Fig. 2C). The calculation of the healing rate made it possible to determine the greatest decrease in 1.96-3.38 times (p=0.02) in the experimental wounds compared to the control ones on the fifth day irrespective of the concentration of ML (Fig. 2D). The value of the healing rate of control wounds at day 11 (0.18) corresponded to the experimental wounds with the additional preventive application of ML on day 8 of the experiment (0.17-0.16), which implies the acceleration of healing by almost three days. The coefficient of healing rate of experimental wounds on the day 5 of the experiment exceeded the control in 3.25-3.4 times, p=0.01 (prophylactic-treatment group) and in 2.05-2.25 times, p=0.02 (treatment group) (Fig. 2F). Statistically significant wound reduction efficiency with respect to the rate factor was established with the additional prophylactic use of ML on the day 5 (p=0.014) and day 8 (p=0.018) compared with the treatment alone. The results of the analysis of the reparative effect are slightly different: no significant acceleration of reparative processes in the prophylactic-treatment group, unlike the treatment group, is observed on the day 5 of the experiment (p=0.01), and on the days 8 and 11 there is no significant difference (p=0.7 and p=0.5 respectively) (Fig. 2F).

DISCUSSION

The positive dynamics of prophylaxis and treatment of those infected with a persistent pathogen due to the local influence of the complex of lactobacilli's metabolites are likely due to their antimicrobial and anti-biofilm activity. This assumption is based on the high antimicrobial and antibiolamina properties of ML, established in vitro, in relation to the process of formation and preformed biolamina of polyresistant opportunistic and pathogenic bacteria [8, 9]. As well as data from other authors on the antimicrobial effect of Lactobacillus metabolites on pathogens of infectious diseases [16-18]; antimicrobial and antibiolamina effects of L. rhamnosus substances on preformed biolamina of antibiotic-resistant strains of A. baumannii, E. coli, S. aureus [19]; antibiolamina properties of metabolites against microbial cells of Staphylococcus and Pseudomonas [20-22].

Although the results of in vitro tests are not always reproduced in in vivo models, Jabés D. and co-authors have shown the effectiveness of microbisporicin (products of the bacterium Microbispora corallina), which was equal to or exceeded vancomycin and linezolid, in acute lethal infections in mice and rats caused by methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, and penicillin-resistant Streptococcus pneumonia [23]. Other researchers have found a reduction in low-grade bandages on the nanofibers of staphylococcal wound load and stimulating the closure of infected wounds [7]. Confirmation of the antibacterial activity of metabolic complexes of L. rhamnosus GG, under conditions of in vivo use, is relevant and promising.

These results have practical, scientific value: according to the list of priority pathogens for research and development of new antibacterial drugs, published by the WHO, P. aeruginosa belongs to the first priority category: critically high level [1]. It is known that 80-90 % of postoperative wounds are contaminated with bacterial pathogens, where 25 % of nosocomial infections. Complications of wounds in surgical infections are accompanied (in 75 % of cases) by changes in the species composition of pathogens as follows: *Streptococcus* spp. → *Staphylococcus* spp. → *Enterobacteriaceae* spp. → *Pseudomonas* spp. [14]. In recent years, there has been an increase in the

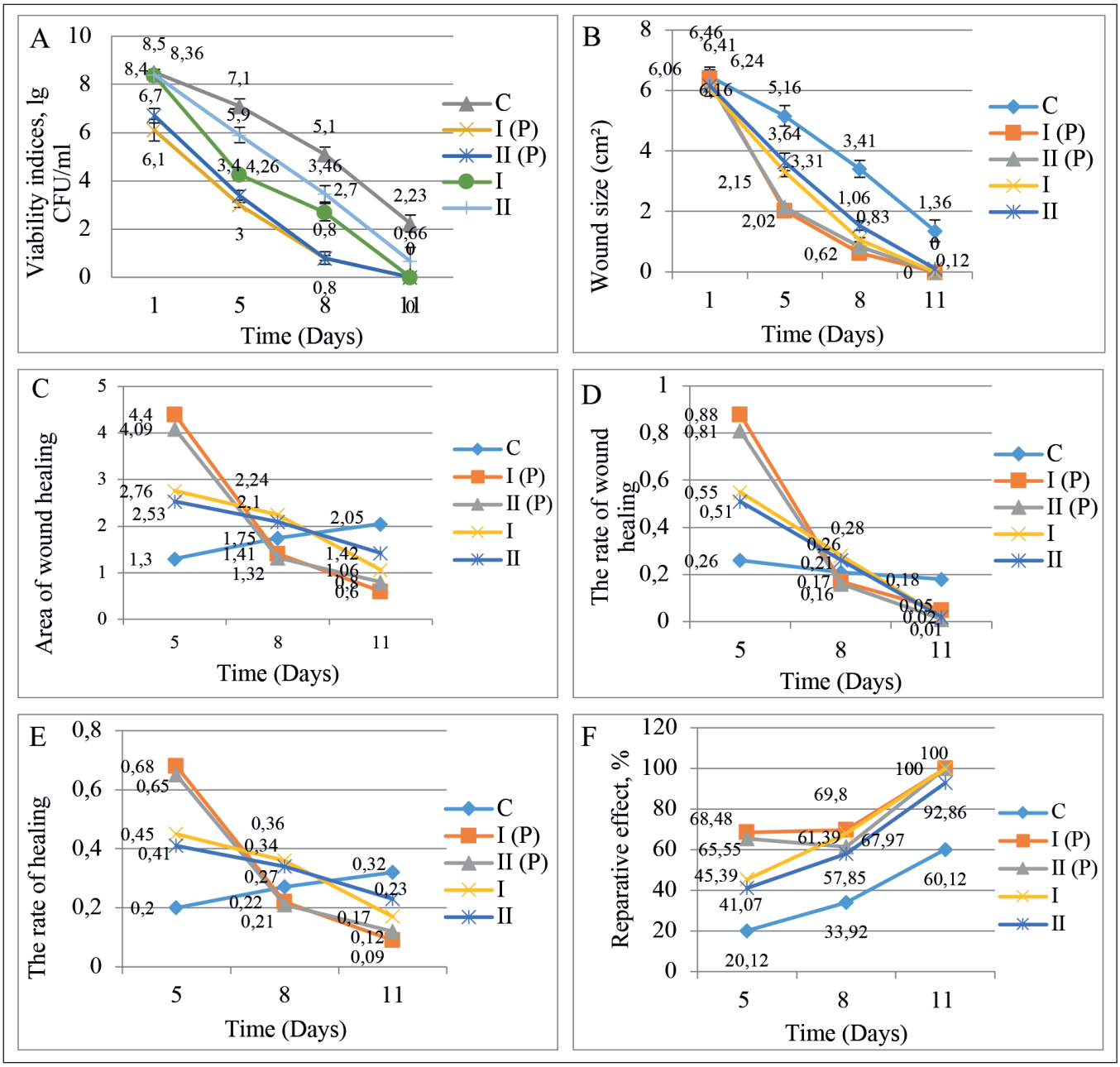

Fig. 2. Dynamics of changes in the population level of the polyresistant strain of P. aeruginosa by determining the number of colony forming units in the material of control (C) and test specimens of infected wounds at 1, 5, 8, 11 days after exposure to the metabolic complex of L. rhamnosus GG obtained by cultivation of lactobacilli in its own disintegrates at concentrations of 0.55 mg/ml (I) and 0.27 mg/ml (II) of total protein, (A). Dynamics of changes in planimetric parameters: total area of wounds (B), area of wound healing (C), wound healing rate (D), coefficient of wound healing rate (E), reparative effect of wounds (F) infected with polyresistant strain of P. aeruginosa at 5, 8, 11 days after exposure to the metabolic complex of L. rhamnosus GG obtained by cultivation of lactobacilli in their own disintegrates at concentrations of 0.55 mg/ml (I) and 0.27 mg/ml (II) of total protein). P – method involves additional direct application of the metabolic complex of lactobacilli before infection of the wound (prevention of development or reduction of the degree of infectious process), (x±SD).

frequency of detection of non-fermenting gram-negative bacteria from infectious wounds, in particular P. aeruginosa [15]. Infectious wounds caused by polyresistant microorganisms are especially dangerous [13]. Therefore, the effectiveness of the use of lactobacilli metabolites for the treatment of infected wounds in the absence of antibiotics, preventing the formation of suppurations or reducing the likelihood of infection, as well as eliminating the development of the wound as its own microflora and environmental microflora, is relevant.

CONCLUSIONS

1. The minimum inhibitory concentrations of ML and MLS relative to the polyresistant strain of *P. aeruginosa* was 0.27 mg/ml and 0.21 mg/ml of total protein.

2. The most effect (of infected *P. aeruginosa* wounds, *in vivo*) in terms of rapid healing relative to control samples was observed in the prophylactic and therapeutic use of ML: (3.25-3.4 times; p=0.01) in difference from the therapeutic (2.05-2.25 times; p=0.02) on the 5th day of the experiment. A strong direct correlation was established between methods of using ML (concentration of 0.27 mg/ml of total protein) to obtain CFU of the pathogen (r=0.94; p=0.04).
3. The value of the healing rate of control wounds at day 11 (0.18) corresponded to the experimental wounds with the additional preventive application of ML on day 8 of the experiment (0.17-0.16), which implies the acceleration of healing by almost three days.
4. Metabolic complexes of probiotic microorganisms are promising for construction on their new class of antimicrobials for the effective pharmacoprophylaxis and pharmacotherapy when used in infected wounds, as well as when antibacterial products cannot be used.

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ORIGINAL ARTICLE

THE NEED FOR IMPROVEMENT OF FUNGICIDES RESIDUAL QUANTITIES CONTROL METHODS IN THE CONDITIONS OF THE DOMESTIC REGULATORY BASE HARMONIZATION

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ABSTRACT

The aim: To develop highly sensitive analytical methods for the determination of the systemic phenylamide class fungicide – Metalaxyl-M residues in watermelons and grapes to reduce the risk of hazardous effects on workers' and public health.

Materials and methods: Conditions for Metalaxyl-M detection by gas-liquid chromatography (GLC) using a chromatographic capillary column SH-Rxi-5ms (length – 30 m, inner diameter – 0.25 mm, layer thickness – 0.25 μm) were determined. The optimal conditions for chromatography of Metalaxyl-M were established: column thermostat temperature – 220°C, evaporator temperature – 260 °C, detector temperature – 280 °C. The retention time under these conditions was 3,384 ± 0.1 minutes. The linear detection range is 0.01 to 0.05 mg / kg. The calibration dependence of the tested substance peak area on its concentration was established and described by the linear regression equation.

Results: We found that the most sensitive method for chromatography of Metalaxyl-M is the method of using a capillary column SH-Rxi-5ms on a gas chromatograph Shimadzu Nexis 2030.

Conclusions: The developed GC methods correspond to modern requirements, are selective and allow to control the Metalaxyl-M content in the matrices of the studied crops and can be used as a marker of the safety of agricultural products grown with fungicides containing Metalaxyl-M application. We found that the most sensitive method for Metalaxyl-M chromatography detection is the method with usage of a capillary column SH-Rxi-5ms on a gas chromatograph Shimadzu Nexis 2030.

KEY WORDS: metalaxyl-M, gas-liquid chromatography, fungicides, phenylamides, berry crops

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INTRODUCTION

As preventive measures aimed at preventing the negative impact of pesticides on human health and the environment, at the stage of pre-registration testing, it is mandatory to optimize and improve the methods of analytical determination of their residual amounts in the studied crops.

As of 2021, fungicides occupy a leading place in the list of the State Register of Pesticides and Agrochemicals Allowed for Application in Ukraine, including about 30 formulations based on phenylamide compounds and about 10 with the active substance Metalaxyl-M [1, 2].

Today high-performance liquid and gas-liquid types of chromatography are used in Ukraine to determine the residual amounts of pesticides in agricultural raw materials [3-5].

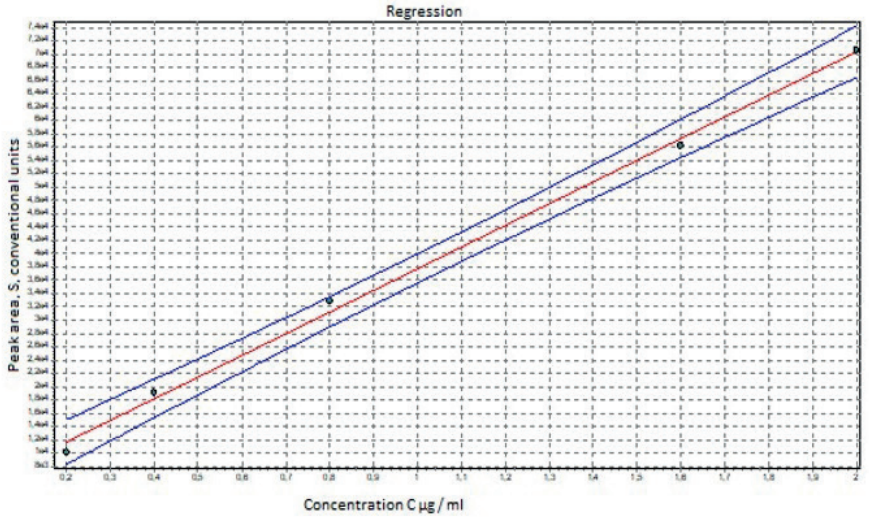
In particular, modern sensitive and effective methods for quantification of Metalaxyl-M residual amounts have been developed, involving the usage of gas chromatography with Nitrogen-Phosphorus Detector (NTD) and gas chromatography with mass spectrometry (GC-MS) [6].

Methods for detecting Metalaxyl-M residual amounts in grapes and watermelons approved in Ukraine were developed in 2000 and 2014, respectively.

The importation into the EU of agricultural products containing pesticide residues above 0.01 mg/kg will be prohibited since May 2020, according to the EU decision on reduce the maximum allowable levels of certain pesticides in agricultural and food products, and establishment of new standards that will apply to both food products produced in the EU and imports [7].

In Ukraine, the Commission on Integrated Hygienic Standardization and Regulation of Pesticides and Agrochemicals of the State Enterprise «Committee on Hygienic Regulation of the Ministry of Health of Ukraine» examines materials on the scientific substantiation of hygienic standards and regulations for safe pesticides application under the requirements of Resolution 04.03.1996 №295 «On approval of the Procedure for conducting state tests, state registration and re-registration, publication of lists of pesticides and agrochemicals permitted for usage in Ukraine». Institutions of the toxicological and hygienic profile of the Ministry of Health and the National Academy of Medical Sciences of Ukraine accredited for the right to carry out work in the field of hygienic regulation of pesticides in industrial and environmental facilities substantiate hygienic standards [8].

Concerning hygienic standards, particularly maximum allowable levels (MALs) of pesticide content in products, such standards are substantiated and approved in the man-



Executant	Hygiene and Ecology Institute affiliated to O.O. Bogomolets National Medical University
Analysis	Calibration schedule for Metalaxyl-M
Regression type	Standart
Target function	A +bx
a=	5152,51 (95% confidence interval a+3,85E3)
b=	32617,1 (95%confidence interval a+3,16E3
Standard deviation met. (Sxo=S y/b)	0,04720601
Residual standard deviation (Sy)	1539,721
Coefficient of variation, Vxo, %	5,900751
Xd(Ccbeta), Xc(Ccalfa)	
Significance of regression	Satisf. {Sreg/Drem=1,08E3>F(1;3)=10,1}
Data linearity	Satisf. {PG=0,5671;F(1;3;0,95)=17,44}
Homogeneity of dispersions	Satisf. {PG=9,963;X2(4;0,95)=11,14}

Fig 1. Diagram of the dependence of the Metalaxyl-M chromatographic peak height (conventional units) from the concentration of Metalaxyl-M in the calibration solution (µg/ml)

ner prescribed by applicable law, methods of their control are developed, and the risk of residues is assessed.

However, the approved maximum residue levels of these active substances in some crops significantly exceed the standard recommended by the European Commission at the level of 0.01 mg/kg.

Therefore, it is possible to limit the content of Metalaxyl-M residues in products from 0.04 mg/kg to the level of 0.01 mg/kg only if the existing standards in Ukraine are revised and (if necessary) the MALs is approved at the level of 0.01 mg/kg, which provides for an increase sensitivity of the method [9].

This issue can be resolved only in compliance with the procedure of approval of hygienic standards and regulations in the manner prescribed by applicable law, in compliance with the requirements of Law №86 / 95-VR, Resolution of the Cabinet of Ministers of Ukraine № 420 of 13.06.1995 and other regulation documents, regulating the safety of pesticides at the stage of their post-registration usage [10, 11].

That is why as the purpose of our work we have chosen the development of analytical methods for the determination of Metalaxyl-M in berry crops to improve the quality of control and safety of consumption of products grown with usage of fungicides based on compounds of the phenylamide class.

THE AIM

Aim of the work: the development of highly sensitive analytical methods for the determination of residues levels of the phenylamide class systemic fungicide – Metalaxyl-M in watermelons and grapes to reduce the risk of dangerous effects on the workers' and public health.

MATERIALS AND METHODS

To establish the optimal conditions for chromatographic detection of Metalaxyl-M, we conducted a series of experiments. Selection of optimal gas-liquid chromatography conditions was performed using Shimadzu Nexis GC-2030 and GC-2014 gas chromatographs equipped with SH-Rxi-5ms capillary columns. The study was performed at different column temperatures in the range of 220-260 °C. Data on the physicochemical properties of Metalaxyl-M are shown in table I.

RESULTS

To establish the optimal conditions for chromatography detection of Metalaxyl-M, shown in table II, a series of experiments were performed at the previous stage. Selection of optimal conditions for gas-liquid chromatography was performed using the above-mentioned Shimadzu

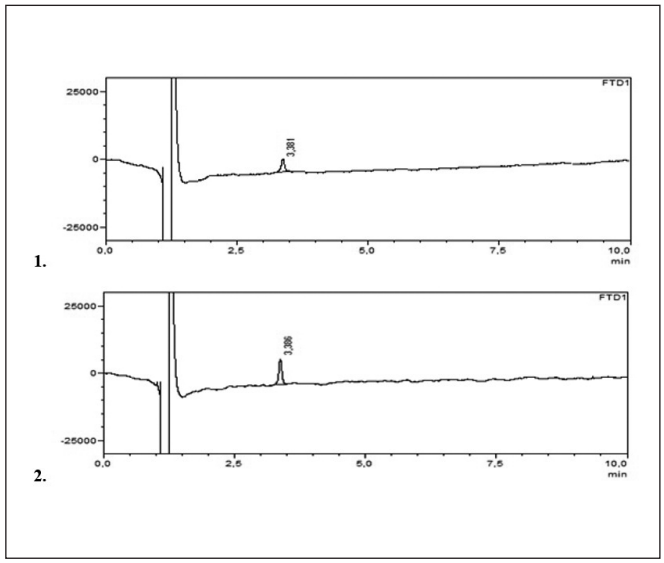


Fig 2. Chromatograms of Metalaxyl-M calibration solutions with concentrations:
1 – 0.4 µg/ml
2 – 0.8 µg/ml

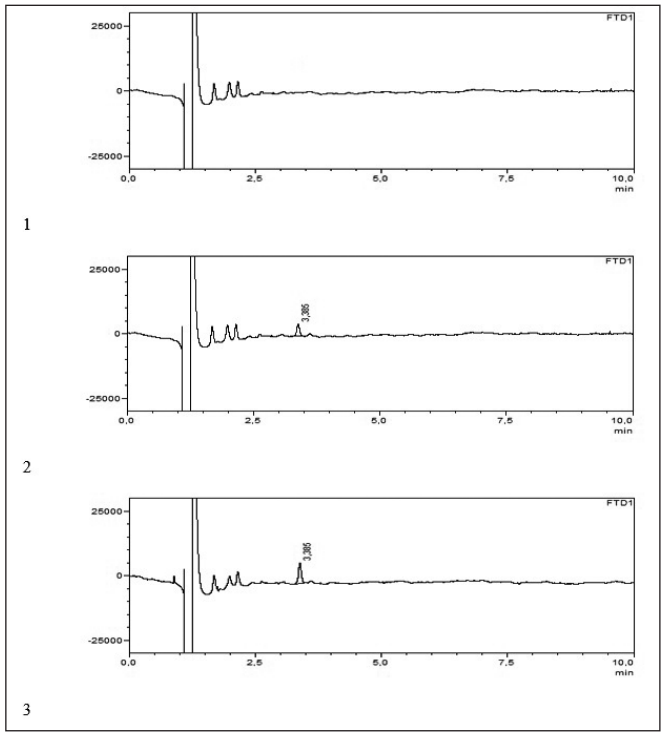


Fig. 4. Chromatograms of grape sample extracts
1 – control sample (1 µg/ 1ml / 40g);
2 – model test with the introduction of Metalaxyl-M 0.01mg / kg (1 µg/ 1 ml / 40g)
3 – model test with the introduction of Metalaxyl-M 0.02mg / kg (1 µg/ 1 ml / 40g)

gas chromatographs. Each time the work began with the construction of a calibration diagram, according to the international standard [12], which revealed the relationship between the peak area and the Metalaxyl-M concentration.

The next stage of the laboratory experiment was the selection of reagents for Metalaxyl- M extraction from

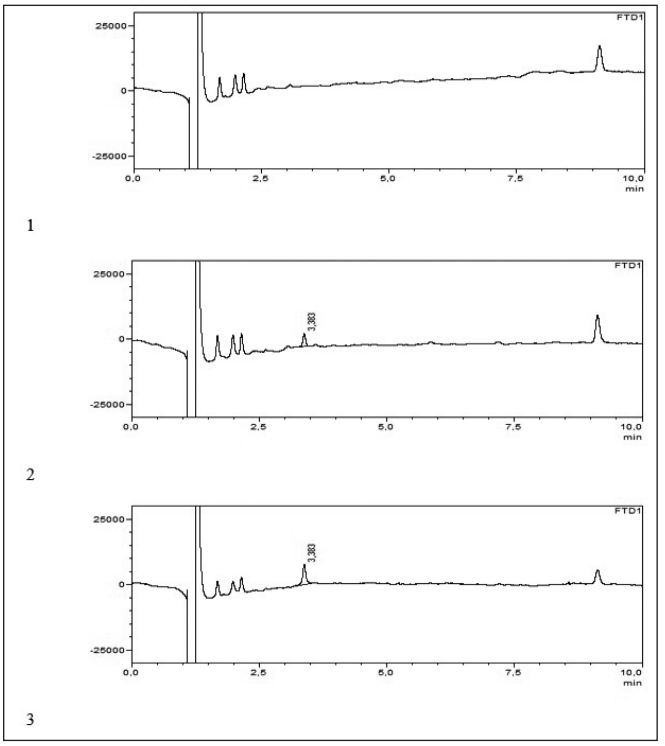


Fig 3. Chromatograms of watermelon samples extracts
1 – control sample (1 µg/ 1ml / 40g);
2 – model test with the introduction of Metalaxyl-M 0.01mg / kg (1 µg/ 1 ml / 40g)
3 – model test with the introduction of Metalaxyl-M 0.02mg / kg (1 µg/ 1 ml / 40g)

samples of the studied crops, as well as sequential purification of samples of the obtained extract by redistribution in the liquid-liquid system and purification by solid phase extraction (SPE). When choosing extractants for the Metalaxyl-M determination in watermelons and grapes, the best result was achieved using an extraction mixture of hexane + acetone (1 + 1, volume + volume). Also, at the stage of extractants selection, hydrochloric acid, sodium hydroxide, chloroform, a mixture of hexane + diethyl ether (1 + 1, volume + volume) were used.

The studies allowed to establish the optimal conditions of extraction and purification, which provided a selective Metalaxyl-M determination from matrices without impurities, which did not interfere with its chromatographic determination.

Before chromatography detection, the obtained extracts were filtered through a filter "blue tape" into a 250 ml volumetric flask. The extraction was repeated twice. The residue on the filter was washed with 10 ml of hexane + acetone extraction mixture. The combined filtrate for distilling off the solvents was transferred to a 250 ml pear-shaped flask and evaporated on a rotary evaporator at a water bath temperature not exceeding 40° C to the aqueous residue.

The aqueous residue of watermelon and grape samples was transferred to a separating funnel with a capacity of 250 ml. The flask was washed with 10 ml of acetone and transferred to a separatory funnel. There was added 20 ml of hydrochloric acid (0.1 mol), mixed thoroughly and

Table I. Physicochemical properties of Metalaxyl-M

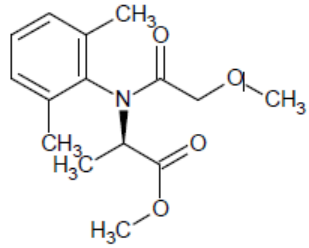
Index	Value	
Chemical name (IUPAC)	(R)-2[(2,6-dimethylphenyl)-methoxy-acetylamino]-propionic acid methyl ester	
CAS RN	70630-17-0	
Empirical formula	C15H21NO4	
Relative molecular mass	279.3	
Structure formula		
Vapor pressure, mPa (20 °C)	3,3×10-3	
Solubility in water, mg / dm3 (25 °C)	26	
Solubility in organic solvents, g / dm3 (20 ° C)	n-hexane	59
Partition coefficient Log Po/w (25°C)	1,71	

Table II. Conditions for chromatography detection of Metalaxyl-M

Characteristics of the method for determining	Metalaxyl-M
	GC
Chromatograph	Gas-liquid chromatograph «Nexis GC-2030», «Shimadzu»
Detector	thermoionic detector
Column	capillary column SH-Rxi-5ms, length - 30 m, inner diameter - 0.25 mm, layer thickness - 0.25 μm
Volumetric flow rate of carrier gas (helium), ml/min	20.6±1
Column thermostat temperature, °C	220±1
Evaporator temperature, °C	260±1
Detector thermostat temperature, °C	280±1
Liquid chromatograph injector loop volume, μl	1
Retention time under these conditions, minutes	3.384±0.1
Linear detection range, μg / cm3	0.2-2
Dependence of the area of the chromatographic peak (S) of metalaxyl-M (units) on its concentration (ρ) in the calibration solution (μg/cm3)	S Metalaxyl-M = 5152,51+32617.1×ρ

the pH of the solution was adjusted to 5-6 with sodium hydroxide (1 mol). It was then extracted three times with chloroform in 20 ml portions and shaken for (1-2) minutes. After phase separation, the lower (chloroform) layer was collected in a 250 ml volumetric flask and dried by infusion over 20-25 g of anhydrous sodium sulfate, stirring periodically for 20 minutes. The extract separated from the precipitate by decantation was then poured into a 100 ml pear-shaped solvent distillation flask and evaporated on a rotary evaporator at a water bath temperature of not more than 40 °C to a volume of ~ 0.5 ml. The solvent was evaporated to dryness by a stream of dry air.

The dry residue obtained after evaporation was washed with 5 ml of hexane + diethyl ether and passed through a Strata®NH2 cartridge using a vacuum solid phase extraction system. The filtrate was collected in a 25 ml pear-shaped flask. The speed of passing the sample through the cartridge was 5-7 ml/min (preventing drying of the cartridge surface!). The cartridge was washed with 5 ml of a mixture of hexane + diethyl ether, adding the solvent to the main extract. The combined filtrate was evaporated on a rotary evaporator at a water bath temperature not exceeding 40 °C to a volume of ~ 0.5 ml. The solvent was evaporated to dryness by a stream of dry air. The resulting

Table III. Metrological characteristics of Metalaxyl-M determination in grapes

Object of analysis		Grapes			
Sample, grams		40			
Added Metalaxyl-M, mg/kg	Detected Metalaxyl-M, Xij, mg/kg	Detected Metalaxyl-M, Rij, %	Detected, Rij, %	Standard deviation of single concentration, (n=6), Sij, %	Confidence interval of single concentration, ± %
0.4	0.0089	88.6	92.1	3.28	3.44
	0.0096	96.2			
	0.0093	92.5			
	0.0089	88.8			
	0.0094	94.4			
	0.0093	92.6			
0.8	0.0175	87.5	86.0	3.16	3.,32
	0.0166	83.2			
	0.0177	88.7			
	0.0178	89.2			
	0.0169	84.4			
	0.0167	83.,4			
The average value of the definition, R, %				88.9	
Standard deviation (n=12), S, %				4.7	
Confidence interval (p=0,95), ± %				3.0	
Limit of determination, mg / kg				0.4	

Table IV. Metrological characteristics of determination of Metalaxyl-M in watermelon

Object of analysis		Watermelon			
Sample, grams		40			
Added Metalaxyl-M, mg/kg	Detected Metalaxyl-M, Xij, mg/kg	Detected Metalaxyl-M, Rij, %	Detected, Rij, %	Standard deviation of single concentration, (n=6), Sij, %	Confidence interval of single concentration, ± %
0.4	0.0091	91.1	92.7	1.45	1.52
	0.0094	94.0			
	0.0094	93.6			
	0.0092	92.4			
	0.0094	94.1			
	0.0091	91.3			
0.8	0.0181	90.5	90.0	1.60	1.68
	0.0179	89.5			
	0.0178	89.0			
	0.0183	91.7			
	0.0176	88.0			
	0.0183	91.4			
The average value of the definition, R, %				91.3	
Standard deviation (n=12), S, %				2.1	
Confidence interval (P=0,95), ± %				1.33	
Limit of determination, mg / kg				0.4	

dry residue was transferred to a 10 ml graduated tube with acetone (final sample extract volume 1 ml). A parallel sample was prepared similarly. The schedule of the dependence of the Metalaxyl-M chromatographic peak height on the concentration in the calibration solution is shown in Fig.1.

Metrological characteristics of the Metalaxyl-M determination in agricultural raw materials, like watermelons and grapes are given in tables III, IV.

Chromatograms of Metalaxyl-M standard solutions, sample extracts with the introduction of Metalaxyl-M in watermelons and grapes are shown in Figure 2,3,4.

According to the data shown in tables III and IV, the average value of the Metalaxyl-M determined concentrations in different matrices was not less than 70 %, which corresponds to modern requirements [13].

DISCUSSION

We conducted a study of literary data and scientific works regarding the conditions of chromatography, extraction and methods of analysis of materials for Metalaxyl-M. Unlike our sample preparation the extraction in the case of European colleagues for high moisture content crops like grapes and watermelons looks different. For example, on the first steps of preparation: they took 25g of the finely chopped sample and added 250 ml of 20 % water+methanol and blended the sample for 10 minutes on slow speed. At the same time, we took 40 grams of the sample and found the best results with extraction mixture of hexane + acetone.

Their next step was to filter the extract through a Whatman 2V filter paper into a 16-oz. bottle. In our case the obtained extracts were filtered through a filter "blue tape" into a 250ml volumetric flask. After that they transferred a 54 ml aliquot (5 g equivalent) and concentrated to a small volume (approximately 10 ml) using evaporator (bath temperature 40 degrees). After that 100 ml of 85% phosphoric acid, approximately 1 g of cobalt chloride hexahydrate and 2-3 boiling chips were added to the flask containing the sample. The flask was boiled to the point 170 degrees. We avoided the step with boiling and instead after the evaporation phase of preparation after the transfer with acetone to the separators funnel was added 20 ml of hydrochloride acid and mixed with sodium hydroxide to adjust the pH.

Then their description of following steps includes cooling and adding distilled water, adding sodium hydroxide solution, rinsing the condenser with water, steam distillation and alumina column cleanup which is perfectly described in the materials. And after that samples are ready for GC analysis.

In general, to describe the methods and sample preparation stages, we should admit that EU variant contains more stages and our is more simplified. The proportions and reagents we were using has some differences. But in the end, we can see the result that corresponding.

In their results plant samples fortified at 0.05 to 0.40 ppm showed recoveries ranging from 53 to 95% with an average recovery of 72 + 11% (n = 18). While our results had shown that the average value of the Metalaxyl-M determined concentrations in different matrices (watermelons and grapes) was 88.9- 91.3 %, which corresponds to modern requirements and the same studies in other countries of EU.

Gas chromatographic method was used for the determination of total residues of Metalaxyl-M in crops in both cases. They were using Tracor 200 GC-AFID analysis (with alkali flame ionization detector) and Finnigan Model 3200 GC-MS analysis while we were using Shimadzu Nexis GC-2030 and GC-2014 with flame thermionic detector (FTD) with suitable temperatures and settings [14, 15].

CONCLUSIONS

The developed GC methods correspond to modern requirements, are selective and allow to control the Metalaxyl-M content in the matrices of the studied crops and can be used as a marker of the safety of agricultural products grown with fungicides containing Metalaxyl-M application. We found that the most sensitive method for Metalaxyl-M chromatography detection is the method with usage of a capillary column SH-Rxi-5ms on a gas chromatograph Shimadzu Nexis 2030.

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ORIGINAL ARTICLE

EXPERIENCE OF THE TREATMENT OF PATIENTS WITH ACUTE PANCREATITIS

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ABSTRACT

The aim: To improve the results of treatment of patients diagnosed with acute pancreatitis.

Materials and methods: The materials of the work are based on the clinical examination and treatment of 301 patients with acute pancreatitis, in the treatment of which, along with classical treatment, a therapeutic and diagnostic complex was used, which allows predicting and preventing the development of abdominal compartment syndrome (ACS).

Results: Managed to reduce the number of cases of infected pancreatic necrosis, effectively predict and prevent the development of abdominal compartment syndrome (ACS), reduce the average length of stay of patients in the hospital.

Conclusions: The use of the proposed management algorithm for patients with acute pancreatitis allows to shorten the treatment period by effectively predicting and preventing the development of pancreatic necrosis, its septic complications and abdominal compartment syndrome.

KEY WORDS: acute pancreatitis, pancreatic necrosis, abdominal compartment syndrome

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INTRODUCTION

Acute pancreatitis (AP) is one of the most serious acute diseases of the abdominal cavity organs. According to the frequency of treatment, it ranks third among acute diseases of the organs of abdominal cavity after acute appendicitis and acute cholecystitis [1]. According to the latest data, the frequency of diagnosis of AP in different countries ranges from 4.9-73.4 cases per 100,000 population, and in Ukraine 102 cases [1,2]. The overall mortality varies from 4% to 15%, and with the necrotic form it is 24-60%, postoperative mortality reaches 70-80%.It is also worth noting socially significant factors: a significant deterioration in the quality of life of patients if the process is chronic [1-3].

Over the past decade, pancreatologist surgeons have revised the key points of the pathogenesis of acute pancreatitis, the phasic nature of its course, the basic principles of medical and surgical treatment, which significantly changed the approaches to providing medical care to patients of this group and improved the results of treatment [4,5].

Despite the introduction of new diagnostic methods, the use of prognostic programs for the severity of the course of the disease, the development of numerous treatment protocols and recommendations, and the introduction of the latest conservative, interventional endoscopic, radiological and surgical treatment methods, the results of the treatment of this contingent of patients are close to the satisfactory [6].

THE AIM

To improve the results of treatment of patients diagnosed with acute pancreatitis.

MATERIALS AND METHODS

The study included 301 patients with a diagnosis of AP, who were treated in the surgical hospital of the KNP «URKL» URR in the period from 2018 to 2021.There were 207 men (68.8%), 94 women (31.2%). The age range was from 21 to 78 years.The average age of the statistical population was 41.5 years.A clinical diagnosis was made based on the presence of at least 2 of 3 generally accepted criteria:

- clinical picture (spinning pain in the upper abdomen);
- increased levels of amylase and lipase (>3 above the normal limit);
- results of imaging methods of examination (ultrasound examination (USE), computed tomography (CT), magnetic resonance imaging (MRI)) that correspond to acute pancreatitis.

We assessed the severity of the course of AP using the Atlanta classification, 2012. According to it, 191 (63.5%) patients had a mild course of AP, 101 (33.5%) had a moderate course, 9 (3.0%) had a severe course of AP.In 4 patients with signs of severe AP, phenomena of peritonitis were detected, which became the reason for emergency surgical intervention. Other patients, due to the severity of the condition and the need to support the work of the main body systems, are hospitalized in the DAIC. These 9 patients dropped out of our study.

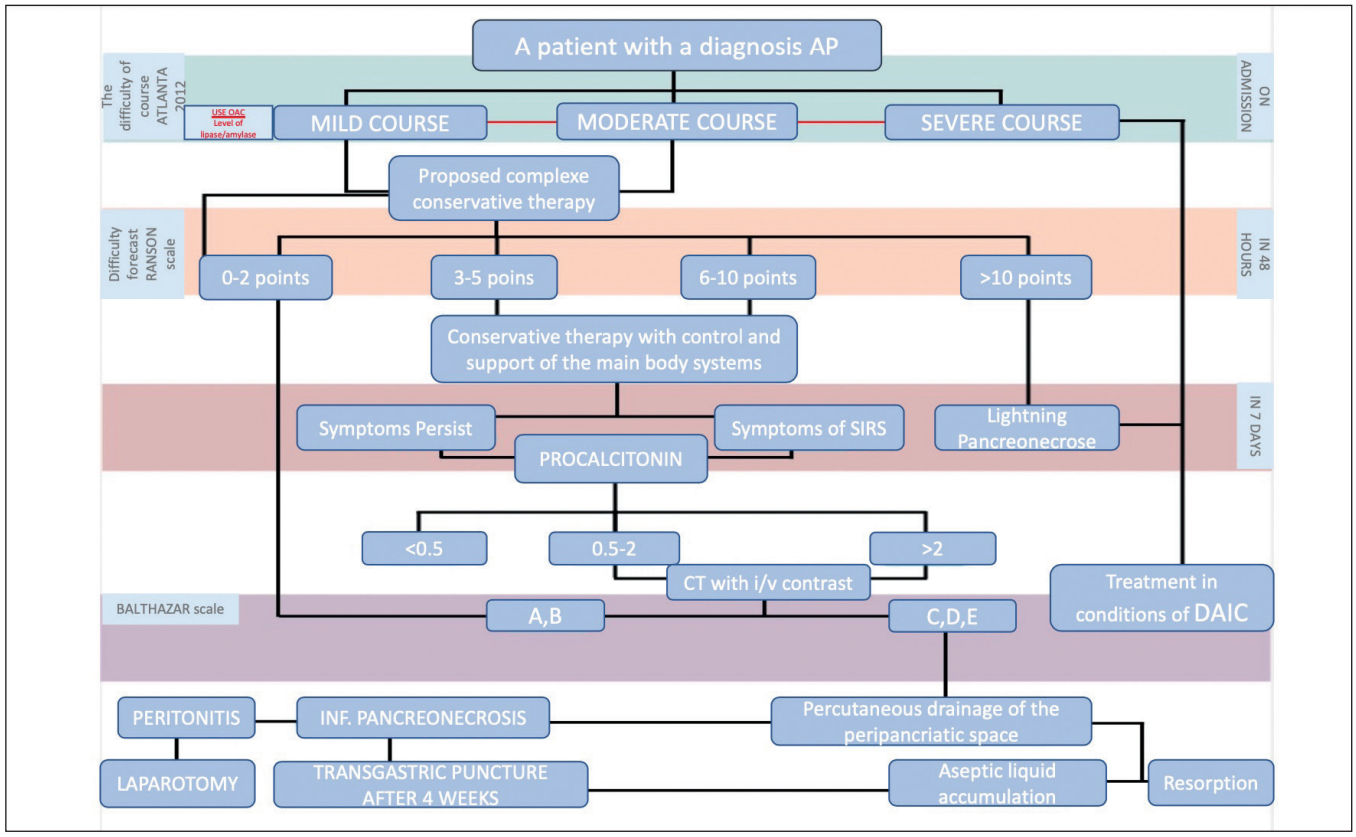

Fig.1. Management algorithm for patients with AP

All 292 patients were divided into two groups: group A (145 patients) – control, in which treatment was carried out according to approved protocols for the treatment of acute pancreatitis, and group B (147 patients) – study, in which the treatment algorithm developed by us was applied .

We used the Ranson scale to predict the severity of the course of AP [6,7]. For this purpose, all patients were assigned to one of two etiological groups based on complaints, medical history, USE, and the dynamics of laboratory parameters within 48 hours: biliary and alcoholic AP. 11.03% of patients in the control group and 10.2% of the study group, according to USE and medical history, met the criteria of «idiopathic pancreatitis» and were evaluated according to the scale for miliary pancreatitis.

0-2 points in the control group were scored by 86 (59.3%) patients, in the study group this indicator reached 68.7% (101 patients);

3-5 points in the control group scored 49 (33.85%) patients , and 42 (28.5%) in the study group;

6-11 points in the control group were scored by 10 (6.9%) patients. In group B, this indicator was 2.7% (4 patients).

All patients of the study group underwent complex conservative treatment. For decompression of the alimentary canal and enteral tube feeding, patients were fitted with naso-gastric tubes.Patients consumed food to prevent complications such as infected peripancreatic necrosis by reducing bacterial translocation, contrary to previous practice that recommended keeping the «bowel calmness» to prevent prolongation of inflammation of the pancreas.

In the future, depending on the dynamics of clinical symptoms and laboratory indicators, patients were transferred to enteral nutrition. In the case of significant clinical improvement, even with the maintenance of laboratory indicators above the norm, we transferred patients to fractional enteral nutrition.

All patients receivedadequate analgesia. In cases of a mild course, NAIDs were used, while in severe pain syndrome, which was more often noted in the course of moderate severity, narcotic analgesics were used (morphine 0.1% – 1.0 i/m x 2-3t/d).

Infusion therapy has also become an integral part of the treatment algorithm.

Considering the indicator of hematocrit and electrolytes, infusion therapy was carried out at the rate of 1-2 ml/kg/h. On average, the amount of transfused fluid reached 2.5-3 liters in the first day. We also took into account concomitant cardiac and renal insufficiency: in these cases, infusion volumes were reduced. The infusion was carried out mainly with solutions of blood substitutes of the crystalloid group.

An important component of conservative therapy was the technique of forced diuresis, which was aimed at reducing of concentration of enzymes in blood and related manifestations of SIRS.

To create a functional rest of the digestive system, in the case of a mild course of AP, we used proton pump inhibitors (PPI). If according to the prediction of the Ranson scale, the patients scored more than 3 points, or the course of AP was initially of medium severity, we used synthetic octapeptides in the standard administrationmode.

The electrolyte composition was corrected on the basis of laboratory indicators. To eliminate hypocalcemia, we used calcium preparations. Administration of magnesium was mandatory.

With pronounced nausea and intensive vomiting, ondasetrom or metoclopramide intravenously jetand KCl drug were used to eliminate hypokalemia and metabolic acidosis.

The use of disaggregants to preserve the rheological properties of blood and antioxidants, the purpose of which was to eliminate free radicals and interrupt the development of oxidant stress, became an integral part of conservative therapy.

Glycemia indicators were actively monitored. With the help of simple insulin, the indicator was kept within the limits of no higher than 7 – 7.5 mmol/l.

All patients with clinical symptoms persisting for more than 1 week or patients with deterioration in the form of hyperthermia above 38°C, leukocytosis ≥12 with a significant shift to the left were shown to determine the level of procalcitonin as a marker of pancreatic necrosis.An indicator above 2ng/ml was an indication for conducting a CT scan with i/v contrast (in the case of kidney pathology, MRI) followed by a CT determination of the AP severity index using the Balthazar scale.Patients with stage B, C, D according to this classification were subject to active tactics: percutaneous drainage of the para-pancreatic zone was used.4 weeks after demarcation of the zone of destruction and formation of cysts, they were drained through the skin followed by obliteration. Peritonitis was the indication for open intervention.

In cases of increased procalcitonin level above 1.0 ng/ml, or persistence of symptoms for more than 1 week, we added antibacterial agents from the group of fluoroquinolones and metronidazole to conservative therapy.

In the case of biliary pancreatitis with mild and moderate degrees of severity of the course of AP, laparoscopic cholecystectomy was performed after clinical improvement. In case of a severe course of AP, or in the presence of liquid septic or aseptic accumulations, surgical intervention was performed after resorption of the accumulations, or after performing minimally invasive interventions (puncture methods), not earlier than 6 weeks. In the presence of choledocholithiasis without wedging or signs of cholangitis, endoretrograde cholangiopancreatography (ERCP) with papillosphincterotomy was performed after clinical improvement. In cases of wedging or cholangitis – as a matter of urgency. In our study, there were 2 such cases.

According to the results of our past studies, we also took into account the possible development of abdominal compartment syndrome (ACS), which can complicate the course of AP in 8-15% of cases. In patients with an increased in volume, distended abdomen, unstable hemodynamics (BP ≤ 90/60 mm Hg), respiratory failure (FRM ≥ 20), oliguria (daily urine ≤500 ml), among other diagnostic measures, intra-abdominal pressure (IAP) using the intravesical method of indirect manometry.In 6.2% of patients of group A and 6.8% of subjects of group B, the indicator reached above 12 mm m/c. Regarding these patients, we applied a set of measures to prevent the occurrence of ACS in the treatment process.

In order to radiologically confirm aseptic and septic complications in persons with a corresponding clinical picture, an increased level of procalcitonin above 2 ng/ml and the absence of the desired response to the treatment, we used CT of the abdominal cavity with intravenous contrast according to the recommendations of the American College of Radiology in 2013 th year [8-11].

RESULTS

According to proposed conservative treatment in group B according to the Ranson prognostic scale, the total number of stocks with a predicted mild course is 68.7%, which is significantly higher than in group A (59.3%). Also, in the study group B, the number of patients with a predicted severe course was only 4 (2.7%) patients, among whom in 2 cases there were signs of biliary pancreatitis, choledocholithiasis with wedging and signs of cholangitis, which required emergency ERCP with papillosphincterotomy, while in the control group, this indicator was as much as 6.9%.

The study of the level of procalcitonin, as a marker of pancreatic necrosis, made it possible to timely add antibacterial agents to the therapy and conduct CT with contrast in order to determine the expediency of percutaneous drainage of the pancreatic space vapor.In the study group, the number of such patients was 7.48% (11 patients). The 1st (0.67%) of them subsequently developed the phenomenon of infected pancreatic necrosis, which was isolated over time, and after 4 weeks a percutaneous puncture was successfully performed.

In the control group, the total number of cases of infected pancreatic necrosis reached 3.44%.

It should be noted that in the control group, ACS phenomena were observed in 4.5% of cases, while in the study group such phenomena were not observed.

The average length of stay in the hospital of patients in the control group reached 9.3 days, while in the patients of the study group this indicator was at the level of 6.7 days.

In the 1st case of the study group, phenomena of peritonitis were noted, which required emergency open surgical intervention. Such cases were not observed in group B.

DISCUSSION

The relevance of the problem of acute pancreatitis today is based on the increase in the frequency of its diagnosis, the severity of complications and the threatening increase in mortality. The diagnostic algorithm of acute pancreatitis requires improvement, taking into account the rational, combined use of modern methods of diagnosing the pathology of the abdominal organs, with the aim of effective forecasting and prevention of its complications. [12]. The proposed diagnostic algorithm and treatment technique allows predicting and preventing the development of

abdominal compartment syndrome, the development of septic complications and pancreatic necrosis, which significantly improves the results of treatment and rehabilitation of this contingent of patients and it can be used in the conditions of specialized departments of the surgical profile at the district, city and regional levels hospitals [13, 14].

The effectiveness of complex conservative therapy in acute pancreatitis is directly related to its use already in the first hours of the disease, the pathogenesis of which is characterized by a rapid cascading course. That is why, precisely this problem often appears before surgeons – patients seek help late and often in a difficult condition. In such cases, conducting intensive complex therapy makes it possible to bring patients in the early stages of the disease out of shock, which in the recent past was the main cause of the patient's serious condition and death. The possibilities of modern intensive therapy make it possible to overcome severe intoxication and shock in the enzyme phase, to provide favorable conditions for operations at a later date [14, 15].

But the results of treatment of acute pancreatitis are still far from being resolved. Indeed, the number of patients who die or are operated on in the early period of the disease has decreased. However, against the background of conservative therapy, they pass into the category of patients with retroperitoneal purulent processes and the most severe manifestations of sepsis. Therefore, the solution of intensive care aspects led to the appearance of problems of septic surgery, which did not exist before due to the inoperability, and even the incurability of patients with severe pancreatic necrosis. This is the reason why the authors' conclusions are not very optimistic and sound like a call to find new effective methods of diagnosis and treatment of acute pancreatitis [15, 16].

CONCLUSIONS

In this way, the algorithm proposed by us for the management of patients with HP allows:

1) Significantly reduce the number of patients with a predicted severe course according to the Ranson scale. In the study group, this indicator was only 2.7%, while in the control group, this indicator was as much as 6.9%;
2) Reduce the length of stay in the hospital: 9.3 days in the control group, while this indicator was 6.7 days in the patients of the study group.
3) With the help of procalcitonin as a marker of pancreatic necrosis and a CT scan with intravenous contrast, it is possible to supplement conservative treatment with antibacterial agents and skin drainage of the pancreatic space, which significantly reduced the number of cases of infected pancreatic necrosis in the study group (0.67%) in compared to the control (3.44%).
4) The algorithm provides for taking into account the possibility of the occurrence and prevention of the development of ACS. In the control group, ACS phenomena were noted in 4.5% of cases, while such phenomena were not observed in the study group.

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ORIGINAL ARTICLE

MORPHOFUNCTIONAL PECULIARITIES OF THE PLACENTA IN WOMEN WITH UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA SYNDROME

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ABSTRACT

The aim: The impact of undifferentiated connective tissue dysplasia on the formation of the placenta.

Materials and methods: The morphostructure of 50 placentas with the undifferentiated connective tissue syndrome and 50 placentas of women with physiological pregnancy and absence of connective tissue pathology was studied.

Results: The results of morphological studies have shown that the main pathogenetic link of placental dysfunction with highly resistant blood flow in the umbilical arteries in pregnant women with undifferentiated connective tissue dysplasia syndrome is a disorder of functional differentiation of the villous tree.In these cases the dominats were large and medium-sized villi with narrowed lumen in arterial, venular and capillary vessels and arterial spasm and venous plethora, as well as with numerous chaotically sclerosed villi, indicating stage I and II of placental. There is a large amount of fibrins in intervillous space which narrows it and leads to violation of microcirculation and placenta tissue hypoxia.

Conclusions: The morphological basis of high flow resistance in the umbilical artery with the undifferentiated connective tissue dysplasia syndrome in pregnant women is a pathological immaturity of the placental villous tree. Morphological study of the architecture of the stem and intermediate placental villi revealed a violation of the structure of collagen fibers in the form of lack of crosslinks of bundles of collagen fibers.

KEY WORDS: placenta, pregnancy, undifferentiated connective tissue dysplasia syndrome, fibrin

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INTRODUCTION

Undifferentiated forms of connective tissue dysplasia (UDCTD) in women of reproductive age reach from 28% to 86% of cases in different populations. The negative influence of connective tissue pathology on gestational process, prenatal morbidity and infant mortality has been proved [1-4].

Violation of the stroma and vascular component of the endometrium affects not only the nidation and implantation, but also the differentiation of the villous tree of the placenta fetal part of the placenta in women with UDCTD [5,6].

THE AIM

The impact of undifferentiated connective tissue dysplasia on the formation of the placenta

MATERIALS AND METHODS

Morphological features of gestational placental transformation in two representative groups of 50 patients with premature birth with undifferentiated connective tissue dysplasia syndrome (group I) and 50 patients with physiological childbirth and absence of UDCTD (group II) were studied.

HISTOLOGY

For morphological study of the placental tissue in the form of a piece was fixed in10% formaldehyde solution for 24 hour, followed by passing through alcohols of increasing concentration and pouring in paraffin, made sections of 5-6 μm thick, sections stained with hemotoxylin and eosin(H&E), *picrofuxin* on Van Gieson`s.

MORPHOMETRY

Morphometrically using Stefanova SB N3 / 16 scoring grid, determined the relative areas of the main structural components of the placenta on an area of 625 μm^2. Microphotography of the structural components of the placenta was performed on a digital Sony DSH-57.2MpS camera).

STATISTICAL ANALYSIS

The results were calculated and analyzed by using standard statistical analysis programs In Vivo Stat V.3.0 Sofa Stat V.1,4.6 and Hiber Office Calc V.5.2,2.2 using the distribution normality check. Pearson Chi-square criteria were used to compare the significance of the difference between groups in terms of frequency of manifestation.

Table I. Variants of pathological immaturity of the placental villi from women with undifferentiated connective tissue dysplasia syndrome (absolute number, %)

Variants of pathological immaturity of the placental villi	I group (n=50)		II group (n=50)	
	abs.	%	abs.	%
Intermediate villi	5	10	9	18
Immature intermediate villi	21	42	3	6
Chaotic sclerosed villi	19	38	1	2

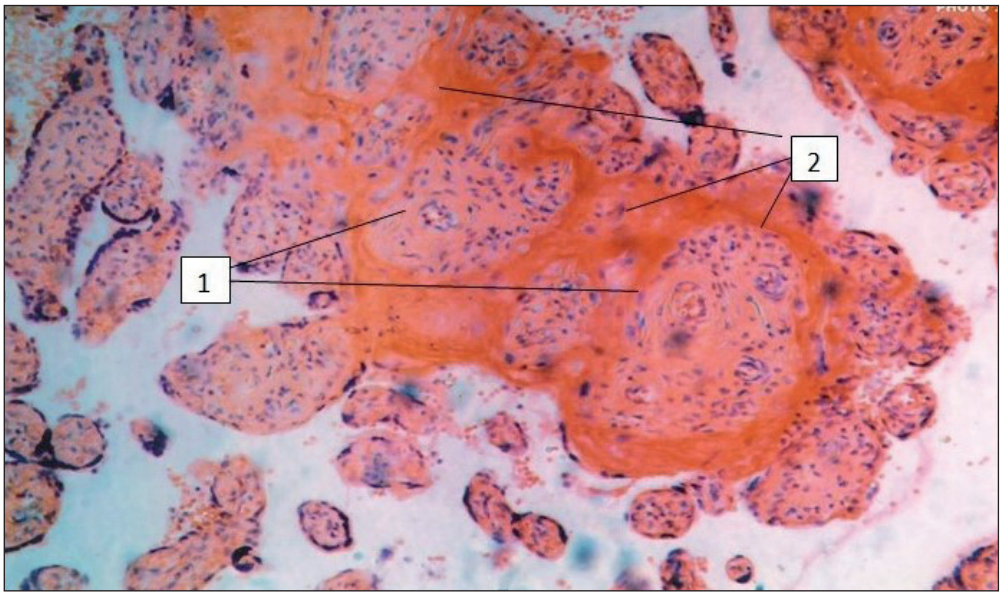

Fig. 1. Intermediate villus with narrowed lumen of ventricular and capillary types of vessels (1) and fibrinoid in the intervillous space (2). Stained with hematoxylin and eosin (H&E)

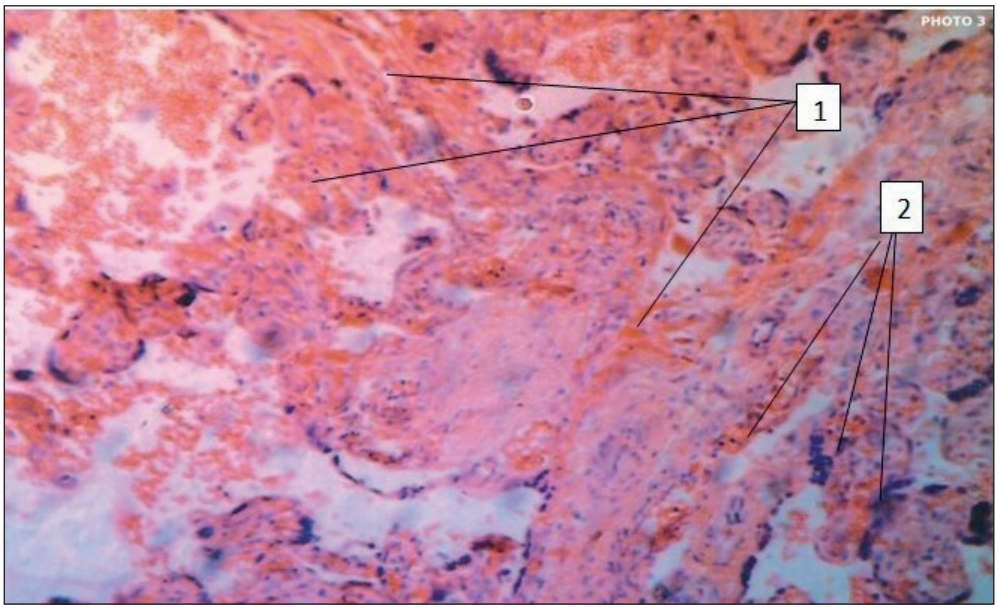

Fig. 2. Intermediate villus with arterial spasm (1) and full vein (2).Highly resistant blood flow was recorded in the artery of the umbilical cord doplemetry (IP 0.65). Stained with hematoxylin and eosin (H&E)

Results $p < 0.05$(probability of difference more than 95%) were considered relevant.

RESULTS

In a comparative aspect, the morphofunctional peculiarities of the placental and fetal blood circulation in 50 patients with undifferentiated connective tissue dysplasia syndrome (group I) and 50 patients in physiological pregnancy with no UDCTD markers (group II).

According to the results of our research, 15 (30%) placentas from mothers of group 1 revealed circulatory infarctions in the diameter from 1 cm to 3. Where in women of group II infarctions were occurred in less than 4 (8%) placentas. In 30 (60%) cases of patients with undifferentiated connective tissue dysplasia syn-

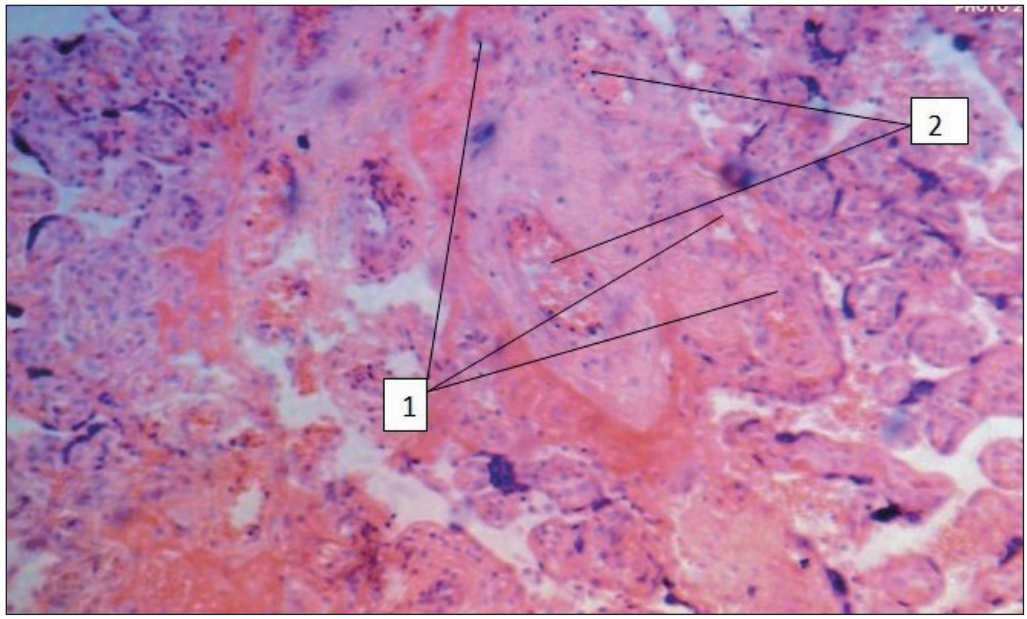

Fig. 3. Stem villus with chaotic growth of connective tissue (1) and varicose veins (2).
Highly resistant blood flow was recorded in the artery of the umbilical cord doplemetry (IP 0.69). Stained with hematoxylin and eosin (H&E)

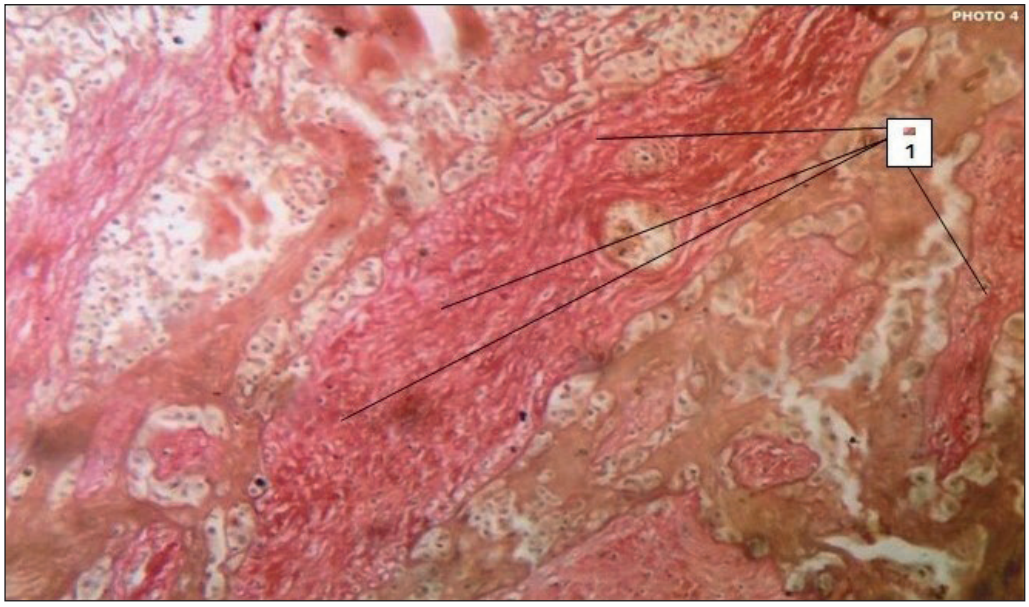

Fig. 4. Disorder of the structural organization of collagen fibers in the stemvillus.Insufficient cross linking of collagen fibers (increasing gaps between collagen fibers) (1).Stained with Van Gieson`s

drome, signs of abnormal fetal part of the placenta were detected (Table I).

A distinctive histological peculiarity of the immature intermediate villi, which is 2.3 times more frequent in the placenta of patients with undifferentiated connective tissue dysplasia syndrome is the dominance of large and medium-sized villi with a narrowed lumen in the arterial, venular and capillary vessels, as well as the accumulation of fibrinoid in the intervillous space .

The spasm of arterial vessels and venous plethora were marked in all immature intermediate villi with highly resistant blood flow in umbilical artery which is a characteristic morphological sign of stage 1 of chronic placental hypertension [7].

While studying the morphology of the stem villi it was found that, compared to the norm, they are reduced in size with the chaotic growth of fibrous tissue and the presence of enlarged intraplacental veins which is a characteristic morphological feature of stage 2 of chronic placental hypertension [8].

However, it is noted that in these cases there is an increase in the gaps between the beams of collagen fibers in the stem and intermediate villi, which is a morphological sign of decreased oxygenation of the connective tussiue [9].

DISCUSSION

In the present study, we performed an analysis morphological features of gestational placental transformation in two representative groups with premature delivery with syndrome of undifferentiated connective tissue dysplasia and with physiological delivery and no markers(UDCTD). According to the results of our research, 15 (30%) placentas from mothers with (UDCTD) revealed circulatory infarctions in the diameter from 1 cm to 3. Where in women without signs of (UDCTD) infarctions were occurred in

less than 4 (8%) placentas. All placentas from mothers with (UDCTD) has immature intermediate villi with highly resistant blood flow in umbilical artery. All this characteristics morphological sign of chronic placental hypertension. Chronic placental hypertension increasing risk of placental abruption,preeclampsia and fetal growth restriction (FGR) [10,11].

To reduce fetal death rate in women with UDCTD diagnostic and prophylactic measures should be aimed at correcting disorders of uterine-placental circulation [12].

CONCLUSIONS

The morphological basis of highly resistant blood flow in the umbilical artery with the undifferentiated connective tissue dysplasia syndrome in pregnant women is the pathological immaturity of the placenta villous tree.Morphological study of the architectonics of the stem and intermediate placental villi revealed a violation of the structure of collagen fibers in the form of lack of crosslinks of bundles of collagen fibers. Morphological signs of chronic placental hypertension with undifferentiated connective tissue dysplasia syndrome in mother is a reduction of blood flow in the microcirculatory system in villous tree of the placenta.

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ORIGINAL ARTICLE

POINT-OF-CARE ULTRASOUND IN THE EARLY DIAGNOSIS OF NECROTIZING FASCIITIS

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ABSTRACT

The aim: To detect the ultrasonographic signs of necrotizing fasciitis (NF) suitable for its early diagnosis.

Materials and methods: Eigty two patients with soft tissue infection, including 14 with necrotizing faciitis, were examined by ultrasonography at the admission. Ultrasonografic features were compared to intraoperative findings by the same surgeon.

Results: The thickening of subcutaneous tissue had high sensitivity (100%), but low specificity (5.8%). The hypoechoic and hyperechoic zones had the shape of "cobblestone" with sensitivity – 78.5%, specificity – 33.8%. Higher specificity (69.1%) had sign of "cobblestone separation" on two layers. The presence of fluid above the fascia (sensitivity – 71.4%; specificity – 69.1%), thickening of the fascia (sensitivity – 85.7%; specificity – 58.8%), indistinctness of the fascia edges (sensitivity – 85.7%; specificity – 66.1%) and loss of fascial homogeneity (sensitivity – 71.4%, specificity – 66.1%) were noted in early stages of NF. Advanced cases of NF were accompanied by the dissection of thickened fascia with a strip of fluid (sensitivity – 57.1%, specificity – 92.6%) and accumulation of a fluid under the fascia (sensitivity – 28.5%, specificity – 95.5%). The muscles thickening (sensitivity – 28.5%; specificity – 67.6%), skin thickening (sensitivity – 57.1%; specificity – 58.8%), and loss of the skin's lower edge clarity (sensitivity – 57.1%; specificity – 63.2%) don't have diagnostic value without other signs of NF.

Conclusions: Point-of-care ultrasonography allows visualization of soft tissue changes that may be hidden in the initial stages of necrotizing fasciitis and should be recommended for implementation as mandatory method of examination in patients with suspected surgical soft tissue infection.

KEY WORDS: soft tissue infection, necrotizing fasciitis, ultrasound, early diagnosis

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INTRODUCTION

Necrotizing fasciitis is a life-threatening surgical infection of soft tissues. The primary pathological process develops in the depth of the tissues, between the deep and superficial fascia, and gradually spreads horizontally along these structures without involving the overlying skin at an early stage. Due to this feature, the manifestation of external skin evidence of necrotizing fasciitis lags in time from the actual course of the destructive process in the thickness of soft tissues. Even with the appearance of the first skin symptoms, their visual evaluation is very subjective to establish this threatening diagnosis. Only with the appearance of late markers, blisters with cloudy contents, and skin necrosis, which are combined with systemic dysfunction, the diagnosis of necrotizing fasciitis become evident. Unfortunately, the diagnosis of necrotizing fasciitis at this late stage is far too late for effective surgical treatment. It has been proven that when surgical intervention is performed later than 24 hours after the onset of the disease, mortality due to necrotizing fasciitis significantly increases [1].

Therefore, the key to the successful treatment of necrotizing fasciitis is its early diagnosis.

Modern medical technologies offer several methods that allow the doctor to see the deep layers of subcutaneous fat and fascia, where the initial destructive changes occur in necrotizing fasciitis, from ultrasonography to computer tomography (CT) and magnetic resonance imaging (MRI).

Today, CT and MRI allow us to visualize any hidden to the naked eye pathological process in the human body, including necrotizing fasciitis [2].

However, the cost of this examination, the ability to perform it only in specially equipped rooms, waiting for the interpretation of the results, and side effects (irradiation, a significant magnetic field) substantially narrow the possibilities for using these methods for a quick, early, and screening examination of patients with suspected necrotizing fasciitis.

Until recently, ultrasonography had the same limitations regarding its use for necrotizing fasciitis diagnosis. Although a quarter of a century has passed since the first publication analyzing the possibility of using ultrasound diagnostics for the early detection of signs of necrotizing fasciitis, this idea did not gain popularity for a long time [3]. It was due to the considerable cost and dimensions of ultrasonography devices, which occupied separate, specially equipped rooms and the examinations were performed and interpreted by a radiologist.

The appearance of portable, mobile, and even pocket ultrasonography devices changed the monopoly of radiologists on their use.

It led to the development of a separate direction in medicine: point-of-care ultrasound (POCUS), which means performing ultrasound diagnostics by a doctor of any specialty at any stage of providing medical care: from the ambulance to intraoperative use. As a natural result, the number of scientific publications devoted to ultrasonographic characteristics of soft tissue infections has increased in the past five years [4-6].

At the same time, performing ultrasonography in patients with necrotizing fasciitis by a surgeon and comparing the detected changes with ultrasonographic findings may be useful for identifying previously unnoticed additional criteria for early ultrasonographic diagnosis of necrotizing fasciitis.

THE AIM

To detect the ultrasonographic signs of necrotizing fasciitis suitable for early diagnosis, based on the comparison of ultrasonographic, local clinical, and intraoperative signs of necrotizing fasciitis.

MATERIALS AND METHODS

The study was carried out in the surgical clinics of the Danylo Halytsky Lviv National Medical University for 12 months from August 2021 to July 2022.

Point-of-care ultrasound (POCUS) was performed in patients with suspected surgical soft tissue infection using portable ultrasound devices with 12-MHz linear probe.

In all patients, the examinations were performed personally by surgeons with ultrasonographic examination skills, who later participated in the surgical intervention and were able to compare the ultrasonographic and intraoperative findings.

Results of ultrasonography, external local clinical signs, and intraoperative findings of the patients were recorded in a database and later analyzed retrospectively.

The medical data of 82 patients who consented to processing their medical and graphic data were enrolled in the analysis, including 14 patients with necrotizing fasciitis and 68 patients with other forms of surgical soft tissue infection who underwent surgery, and their diagnosis was confirmed intraoperatively. Patients with demarcated accumulations of fluid in soft tissues in the form of an abscess were not included in the study.

For each ultrasonographic sign, sensitivity and specificity were calculated using an online calculator (medcalc.org).

RESULTS

After analyzing the ultrasonographic changes in patients with necrotizing fasciitis and comparing them with preoperative visually noticeable signs of the skin and intraoperative findings, we identified a few characteristic features in different anatomical layers of soft tissues.

For surgical soft tissue infection, one of the earliest clinical symptoms is local swelling or infiltrate. Ultrasonographically, it is manifested by thickening of the subcutaneous tissue, which we observed in all 14 patients with necrotizing fasciitis (sensitivity – 100%). However, this symptom is not unique to necrotizing fasciitis and can occur in cellulitis, lymphostasis, anasarca, allergic edema, and many other conditions not associated with surgical infection. Despite the detected low specificity (5.8%), this symptom should not be neglected. Thickening of the subcutaneous tissue should pay attention to the area of the potential problem and encourage the physician to look for other ultrasonographic signs in that anatomic area.

In patients with initial manifestations of necrotizing fasciitis, one of the very characteristic ultrasonographic signs was the appearance of the "cobblestone" symptom. This name is caused by the graphic similarity of the ultrasonographic image with hypoechoic zones that pass between hyperechoic zones of the subcutaneous tissue with the contours of irregularly shaped stones (Fig.1).

In our study, we found the "cobblestone" sign in 11 (78.5%) patients with necrotizing fasciitis (sensitivity – 78.5%, specificity – 33.8%). In the literature, this ultrasonographic sign is considered more characteristic of cellulitis [7].

However, in contrast to cellulitis, in the initial stage of necrotizing fasciitis, we found other regularities.

In particular, with necrotizing fasciitis, the hypoechoic zone prevails in the lower half of the subcutaneous tissue, which, in our opinion, is more characteristic of necrotizing fasciitis, in contrast to cellulitis and swelling of the subcutaneous tissue. We suggest paying attention to such a feature as a separate symptom of the "separation of cobblestone" into two layers. The sensitivity of this symptom was 78.5%, and the specificity – 69.1%.

It should be noted that with the progression of necrotizing fasciitis and the formation of visually noticeable signs of skin necrosis, the symptom of "cobblestone" and "dissection" may disappear around necrotic changes, at the same time, they can be detected along the perimeter, on the border with undamaged soft tissues.

The progression of necrotizing fasciitis and the fluid accumulation in the lower layers of the subcutaneous tissue finally led to the formation of a well-visible (>2 mm) layer of fluid over the deep fascia. This feature is very important for the diagnosis of necrotizing fasciitis because it is accompanied by enough high indicators of both sensitivity (71.4%) and specificity (69.1%). These data are very close to the data described in the literature (75.0% and 70.2%, respectively) [8].

Of course, in patients with necrotizing fasciitis, ultrasonographic changes in the fascia deserve the most attention.

The early stage of necrotizing fasciitis is characterized by swelling and thickening of the fascia >2mm, which has enough high sensitivity (85.7%), but insufficient specificity (58.8%). Usually, swelling of the deep fascia is combined with indistinctness and unevenness of the fascia edges (sensitivity – 85.7%, specificity – 66.1%) and loss of homogeneity (sensitivity – 71.4%, specificity – 66.1%).

With the progression of colliquative necrosis, two more ultrasonographic signs are added, which we consider be-

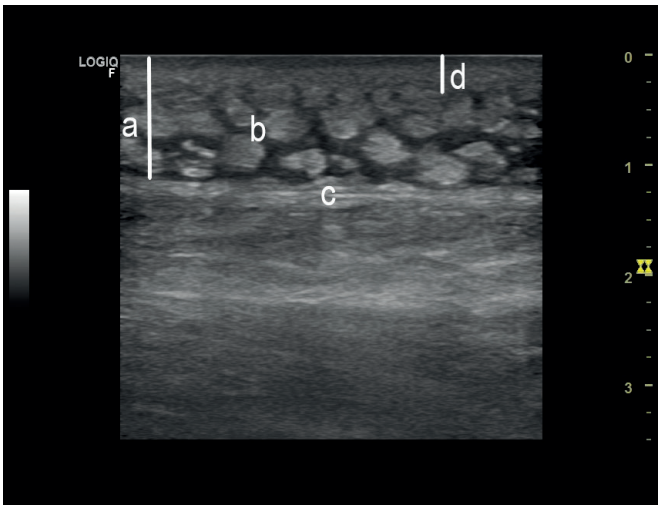

Fig. 1. Ultrasonographic sign of necrotizing fasciitis at the initial stage with early skin manifestation
a. thickening of the subcutaneous tissue
b. "cobblestoning" and its separation into two layers
c. fascial thickening, loss of homogenity, indistinctness of the fascia edge,
d. thickening of the skin and indistinctness of the skin lower edge.

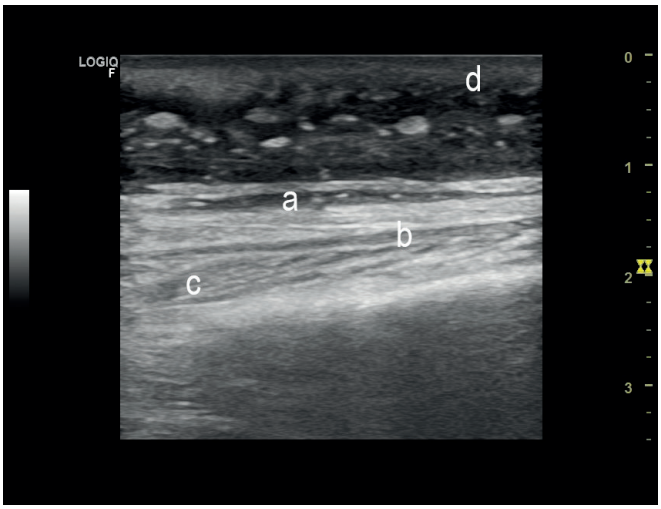

Fig. 2. Ultrasonographic sign of the advanced stage of necrotizing fasciitis.
a. dissection, swelling and heterogeneity of the deep fascia,
b. hypoechoic shadow under the fascia (fluid strip),
c. thickening and hypoechoic zones of muscle tissue
d. thickening of the skin and unevenness of its lower edge.

ing very important criteria in the diagnosis of necrotizing fasciitis – a dissection of thickened fascia with a strip of fluid (sensitivity – 57.1%, specificity – 92.6%) and accumulation of a fluid layer under the fascia (sensitivity – 28.5%, specificity – 95.5%) (Fig.2).

These findings are primarily valuable due to their high specificity, which is the highest among other ultrasonographic signs we were able to detect in this study. In our opinion, these symptoms arise due to the fascia losing its barrier function and resistance. In such patients, during surgical intervention, the fascia is easily dissected under the surgeon's finger, which has received the name of the well-known "finger test" [9]. At the same time, a cloudy exudate in the form of "dishwater fluid" is released. For a long time, these clinical tests were the only method to confirm or deny necrotizing fasciitis. For this purpose, it was proposed to make a small diagnostic incision under local anesthesia and by finger or surgical clamp to dissect the soft tissues at the level of the fascia. The disadvantage of this manipulation is its invasive nature.

Therefore, we interpret such ultrasonographic findings as a dissection of the thickened fascia with a strip of fluid and/or the presence of fluid under the fascia as a non-invasive analog of the "finger test".

When the fluid penetrates under the deep fascia, we also noted certain ultrasonographic changes in the muscle layer – thickening of the muscles and changes in the echogenicity of the muscle. However, both signs were accompanied by low sensitivity (28.5%) and insufficient specificity (67.6%).

In patients with necrotizing fasciitis, the skin changes are secondary to the underlying pathological process in the deeper layers of the soft tissues.

In patients with necrotizing fasciitis, ultrasonographic skin changes may be accompanied by skin thickening and loss of clarity of the skin's lower edge. We observed these symptoms only in combination with other above-described changes in the subcutaneous tissue. Skin thickening had a sensitivity of 57.1% and a specificity of 58.8%, and loss of clarity of the skin's lower edge was 57.1% and 63.2%, respectively. We do not consider these ultrasonographic signs characteristic for the diagnosis of necrotizing fasciitis. However, in combination with other signs, we suggest considering them because they can be an addition to the early manifestations of necrotizing fasciitis. We always noted them in areas of changed skin in the form of "lemon peel".

As we observed, in necrotizing fasciitis, ultrasonographic changes were not uniform on all surfaces. Usually, the area with the largest number of ultrasonographic signs was noted, around which excentrically extended zones with less expressed signs or their smaller number. In our opinion, changes in these peripheral areas, almost at the border with healthy skin, can provide valuable information for the analysis of tissue changes inherent in the early stage of necrotizing fasciitis.

DISCUSSION

For the first time, the idea of using ultrasonography for the early diagnosis of necrotizing fasciitis was described in the literature by Tsai CC et al. in 1996. He described ultrasonographic changes in five patients and suggested relying on such ultrasonographic signs as 1) irregularity of the fascia; 2) abnormal fluid collections along the fascia plane; and 3) diffuse thickening of the fascia when compared with the control site in the normal limb [3].

Despite this, the idea did not have a general application for a long time. At the same time, the diagnostic capabilities of computed tomography and magnetic resonance

imaging for visualization of hidden to the eye changes in soft tissues in patients with necrotizing fasciitis are being described [2,10,11].

However, these methods were also not useful for the early diagnosis of necrotizing fasciitis due to inaccessibility for routine use by doctors in the emergency department, high cost, and considerable waiting time for the description of the examination results.

Only after the appearance on the market of more portable ultrasonography devices, tenfold decrease in their price for the last decades, opened new opportunities in the use of point-of-care ultrasonography by emergency physicians and general surgeons. Developers of pocket devices that have appeared on the market in the last three years claim that soon insonation will be considered as important a component of the initial examination of the patient as palpation, percussion, auscultation, and the ultrasound device is called the "stethoscope of the 21st century" [12-14].

Evidence of this is the introduction of numerous point-of-care ultrasonography protocols: FAST, RUSH, BLUE, CAUSE, etc. [7]. Naturally, the idea about the possibilities of ultrasonographic diagnosis of soft tissue infections, in particular, necrotizing fasciitis, was revived [15-18].

In our opinion, performing point-of-care ultrasonography personally by a surgeon at the stage of preoperative diagnosis and comparing the findings with clinical manifestations and intraoperative signs, gives a much better chance of detecting changes that may seem unimportant to a radiologist.

During ultrasonography of soft tissues, it is important to compare the detected signs with a similar area in a symmetrical part of the body. It will allow reducing the number of false positive signs.

We understand that the small study group of our study may have influenced the calculated sensitivity and specificity of each sign. At the same time, we hope that our study made it possible to pay attention to other ultrasonographic signs that were not previously described. For example, separation of the "cobblestone" into two layers in the subcutaneous tissue, thickening and loss of clarity of the dermis lower edge.

It should be noted, that in any of the clinical cases, we did not find described in the literature hypoechoic inclusions with an acoustic shadow, which are characteristic of the air accumulation in the subcutaneous tissue and anaerobic forms of necrotizing fasciitis [19].

Ultrasonographic symptoms with high specificity – the dissection of the fascia with fluid and the presence of a fluid layer under the deep fascia, should be interpreted as "severe" ultrasonographic criteria of necrotizing fasciitis. Additional signs can be the symptom of a cobblestoning with dissection on two layer and a fluid layer over the fascia with a specificity of 69.1%. In doubtful cases, if there is a fluid layer over the fascia, a puncture and aspiration of the fluid can be performed under the control of ultrasonography for visual assessment and bacteriological examination. We are convinced that this additional manipulation under ultrasound control will be able to significantly increase the accuracy of the preoperative examination when necrotizing fasciitis is suspected.

CONCLUSIONS

Point-of-care ultrasonography allows visualization of changes in soft tissues that may be hidden in the initial stages of necrotizing fasciitis and should be recommended for implementation as mandatory method of examination in patients with suspected surgical infection of soft tissues.

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ORIGINAL ARTICLE

MARKER DIAGNOSTIC HEART FAILURE PROGRESSION IN THE POST-INFARCTION PERIOD

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ABSTRACT

The aim: To study the relationship between the concentration of copeptin, NT-proBNP, ST2 and indicators of myocardial remodeling, the dynamics of these indicators in order to predict the occurrence of decompensated heart failure (HF) in patients with acute myocardial infarction (AMI).

Materials and methods: The study is based on the results of the examination of 160 patients with MI, including 120 patients with decompensated CHF II A-B stage according to Vasylenko-Strazhesko classification of (FC) III-IV (according to NYHA) and 40 patients with MI without signs of decompensated CHF, as well as 20 medically healthy individuals. The level of copeptin, NT-proBNP, ST2 were determined.

Results: In patients with signs of decompensated HF there were significantly higher levels of NT-proBNP in the blood serum that amounted to (950.38±3.15) pg/ml, in patients without decompensated HF after MI (580.15±3.03) pg/ml compared to healthy individuals (111.20±3.47) pg/ml ($p<0.05$). The mean value of copeptin concentration in patients with decompensated CHF was recorded (18.11±0.12) pg/ml, compared to (12.03±0.14) pg/ml in patients with MI without signs of CHF decompensation.

Conclusions: The most significant for clinical and prognostic assessment of the post-infarction period complicated by decompensated HF is the response of the patient's body to dosed physical exertion and the levels of NT-prpBNP, copeptin and ST2.

KEY WORDS: decompensated heart failure, postinfarction cardiosclerosis, NT-proBNP, sST2, copeptin

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INTRODUCTION

Heart failure (HF) is a syndrome that develops due to changes in the structure and function of the myocardium as a result of its damage or hemodynamic overload, which ultimately leads to insufficient pumping and filling of the heart with blood [1,2]. Chronic HF (CHF) develops due to the inability of the heart to produce sufficient blood output to ensure the body's metabolism with normal venous return and its filling pressure [3,4]. The decompensation of HF is based on a cascade of pathological reactions involving many mechanisms of interaction, such as hemodynamic overload, venous stasis, inflammation, renal dysfunction, endothelial dysfunction, oxidative stress and its effect on cardiac remodeling and vascular wall [5].

Acute myocardial infarction (AMI) is the most severe manifestation of coronary heart disease (CHD) and is the cause of more than 2.4 million deaths in the United States, more than 4 million deaths in Europe and North Asia and more than a third in the developed countries of the world annually [6].

HF is a major public health problem affecting more than 23 million patients worldwide [7]. Current projections show that the prevalence of HF will increase from approximately six million to more than eight million patients by 2030 [8]. As the life expectancy of patients after MI is increasing, the incidence and prevalence of HF in the post-infarction period grow [9]. Prediction of HF development can be difficult due to the unpredictable trajectory of the syndrome from exacerbation to partial remission [10]. Decompensated HF in the post-infarction period is a clinical syndrome associated with poor quality of life, significant use of health care resources and premature mortality [11]. Decompensated HF remains one of the urgent problems of modern cardiology. In patients with CHF (FC) IV, mortality within six months reaches 44 % [12].

The disclosure of pathogenetic links from new theoretical positions and the identification of non-traditional risk factors for HF that affect the clinical picture and its prognosis stimulate the search for new effective areas in cardiology related to early diagnosis, prevention and treatment of cardiac decompensation [13].

The NP system is a group of hormones circulating in the blood that regulate water-salt homeostasis and blood pressure and play an important role in the regulation of the structural and functional state of the cardiovascular system, both in physiological conditions and in the formation of cardiovascular pathology [14]. BNP, a peptide secreted mainly by the LV when the heart is unable to perform its main pumping function, is released in equimolar amounts with NT-proBNP in response to an increase in ventricular filling pressure [15].

Determination of BNP and NT-proBNP levels provides only one view of the biological landscape in patients with HF, which led to the need to develop other biomarkers that provide "orthogonal" biological information of the pathogenetic appearance of this syndrome.

Copeptin and ST2 are novel markers of biomechanical cardiac stress. Copeptin is a predictor of total, cardiovascular

and CHF-dependent death, and re-hospitalization in acute or decompensated CHF [16]. Copeptin is a stable C-terminal part of the prohormone vasopressin (precursor of arginine vasopressin); it is very stable in plasma ex vivo at room temperature and is easy and reliable to measure. Copeptin is secreted in an amount equimolar to vasopressin [17]. Its determination is important in assessing the severity of the disease and stratification of patients with favorable or unfavorable outcomes in sepsis, lower respiratory tract infection, stroke, myocardial infarction, and is a possible predictor of the occurrence and death in CHF and its decompensation [18].

The influence of the ST2 system in the human body is complex, and its role in the development of HF is insufficiently studied. ST2 is a member of the Toll/like/interleukin-1 receptor superfamily. The ST2 gene, located on chromosome 2q12, is expressed in 4 isoforms, 2 of which include a transmembrane receptor (ST2 ligand or ST2L) and a soluble serum circulating receptor (sST2) that can be detected in blood plasma [19,20]. Elevated levels of sST2 in blood plasma are associated with the presence and progression of cardiac fibrosis and remodeling [21,22]. This biomarker has a prognostic value, regardless of NP, although the appearance of both of them is due to a single mechanism – cardiac strain [23].

THE AIM

To study the relationship between the concentration of copeptin, NT-proBNP, ST2 and indicators of myocardial remodeling, the dynamics of these indicators in order to predict the occurrence of decompensated HF in patients with AMI.

MATERIALS AND METHODS

The study was conducted on the basis of Regional Clinical Cardiology Center, infarction department No.2 and rehabilitation.

The members of the Ethics Commission at the Ivano-Frankivsk National Medical University decided that this study would not contradict the main provisions of the GCP, Convention Council of Europe on human rights and biomedicine, the Helsinki Declaration of the World Medical Association on ethical principles for the conduct of scientific medical research with the participation of man and the Law of Ukraine «On Medicines». All patients signed an informed consent to participate in a clinical trial.

The study is based on the results of the examination of 160 patients with MI, including 120 patients with decompensated CHF II A-B stage according to Vasylenko-Strazhesko classification of (FC) III-IV (according to NYHA) and 40 patients with MI without signs of decompensated CHF, as well as 20 medically healthy individuals.

Inclusion criteria were prior Q-QS and non-Q MI which happened not earlier than 24-28 days before the study, complicated in the post-infarction period by decompensated HF.

All patients with Q-QS and non-Q MI were divided into 2 groups depending on the presence of decompensated HF: Group I: patients diagnosed with Q-QS and non-Q MI with decompensated HF (n=120) Group II: patients diagnosed with Q-QS and non-Q MI without decompensated HF (n=40). Study groups were homogeneous by age, sex, severity of the disease, duration of the post-infarction period, and the presence of clinical manifestations of decompensation. The level of copeptin in the blood serum was studied using the kit EK 065-32, EIA Copeptine (RayBiotech, Inc. USA). The concentration of NT-proBNP in blood serum was determined using reagents of the ELISA Kit for Human NT-proBNP (BIOMEDICA Slovakia s.r.o., Slovakia). To determine ST-2 in blood serum, the Presage ST-2 kit (Critical Diagnostics, USA) was used. The level of ST2 was determined in ng/ml.

In order to determine the functional class of CHF, to assess the tolerance to physical exertion and the effectiveness of treatment and rehabilitation measures, the 6MWT (6-minute walk test) was performed. The test was performed in the hospital corridor, 30-50 m long. Before the start of the walk, the heart rate and blood pressure were recorded, and a standard 12-lead ECG was performed.

RESULTS

As a result of 6MWT analysis, it was found that the presence of decompensated HF significantly worsened the test results (Table I).

Thus, the distance covered by the patients of the third group was considerably lower and amounted to (174.32±2.65) m ($p<0.05$) compared to the patients of the second and first groups, where this figure was (383.75±5.75) m ($p<0.05$) and (573.97±4.51) m, respectively.

The decrease in the proper distance covered was accompanied by an inadequate hemodynamic response to physical exertion, which was reflected in the disproportionate increase in heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP).

The heart rate of post-infarction patients with signs of decompensated HF before the exercise test was (88.2±3.18) beats/min ($p<0.05$), in patients with MI without signs of decompensated HF – (75.32±3.41) beats/min ($p<0.05$) and in medically healthy individuals – (77.73±3.02) beats/min.

The level of SBP at rest in the third group was (161.21±7.02) mm Hg ($p<0.05$), which was significantly higher than that of the second and first groups – (132.00±8.14) mm Hg ($p<0.05$) and (122.03±8.11) mm Hg, respectively.

After performing 6MWT, the value of SBP increased in the third group of subjects to (179.43±6.02) mm Hg ($p<0.05$) and in the second and first groups – (150.38±6.24) mm Hg ($p<0.05$) and (129.03±7.34) mm Hg.

The increase in these indicators after a six-minute walk was 11.30, 13.92 and 5.74, respectively.

Similar patterns of increase in the level of DBP were observed, especially after physical exertion.

During the study, promising biomarkers of HF decompensation in the post-infarction period were studied.

For this purpose, the mean values of NT-proBNP, copeptin and ST-2 levels in the blood serum of the examined patients were analyzed.

The levels of biomarkers in patients after MI, depending on the severity of decompensated HF, are presented in Table II.

NT-proBNP in the group of patients with MI and decompensated HF was (950.38±3.15) pmol/L ($p<0.05$), in patients with

Table I. 6MWT results in the post-infarction period depending on the presence of decompensated HF

Indicator, unit of measurement	Healthy Individuals (n=40)	Patients with MI without decompensated HF (n=40)	Patients with MI and decompensated HF (n=120)
1	2	3	4
Proper distance, m	574,25±6,25	565,00±6,88 p_1<0,05	545,95±5,62 p_1<0,05 p_2<0,05
Distance covered, m	573,97±4,51 Δ-0,05	383,75±5,75 p_1<0,05 Δ-32,07	174,32±2,65 p_1<0,05 p_2<0,05 Δ-68,07
Heart rate in the state of at rest, beats/min	70,23±6,37	75,32±3,41 p_1<0,05	88,20±3,18 p_1<0,05 p_2<0,05
Heart rate after physical exertion, beats / min	77,73±3,02 Δ+10,68	89,82±2,98 p_1<0,05 Δ+19,25	105,37±2,82 p_1<0,05 p_2<0,05 Δ+19,46
SBP in a state of rest, mmHg	122,03±8,11	132,00±8,14 p_1<0,05	161,21±7,02 p_1<0,05 p_2<0,05
SBP after physical exertion, mmHg	129,03±7,34 Δ+5,74	150,38±6,24 p_1<0,05 Δ+13,92	179,43±6,02 p_1<0,05 p_2<0,05 Δ+11,30
DBP in a state of rest, mmHg	78,57±3,65	91,6±3,59 p_1<0,05	92,78±2,18 p_1<0,05 p_2<0,05
DBP after physical exertion, mmHg	84,22±2,2 Δ+7,19	101,83±2,11 p_1<0,05 Δ+11,17	103,08±2,05 p_1<0,05 p_2<0,05 Δ+11,10
Consumed O2, ml/min/m^2	22,93±0,48	16,09±0,44 p_1<0,05	11,59±0,15 p_1<0,05 p_2<0,05

Notes. p_1 – probability of difference in indicators comparing with medically healthy individuals; p_2 – probability of difference in indicators comparing with patients with MI without decompensated HF

MI without signs of decompensated HF – (580.15±3.03) pmol/L ($p<0.05$) and in medically healthy individuals – (111.20±3.47) pmol/L. The mean value of copeptin concentration in patients with decompensated CHF was recorded (18.11±0.12) pg/ml, compared to (12.03±0.14) pg/ml in patients with MI without signs of CHF decompensation and (5.17±0.12) pg/ml in healthy individuals ($p<0.05$).

The ST2 indicator in patients of the third group was (49.22±1.40) ng/ml, in patients of the second group it was (36.00±1.43) ng/ml, and in the practically healthy individuals – (14.80±1 .61) ng/ml ($p<0.05$).

In patients with signs of decompensated HF there were significantly higher levels of NT-proBNP in the blood serum (Table II) that amounted to (950.38±3.15) pg/ml, in patients without decompensated HF after MI (580.15±3.03) pg/ml compared to healthy individuals (111.20±3.47) pg/ml ($p<0.05$) (Table III). Moreover, in patients of the third group with an inadequate response to physical exertion, the level of NT-proBNP was significantly increased and amounted to (1048.06±4.83) pg/ml, in patients of the second group – (619.03±4.70) pg/ml ml and in healthy individuals – (116.20±4.83) pg/ml ($p<0.05$).

DISCUSSION

Several strategies to address the risks of adverse events in patients with HF in the post-infarction period have been developed, but they are significantly limited from the perspective of physicians who make decisions about hospitalization of such patients, emergency and family doctors and cardiologists. In fact, the diagnosis of HF and its decompensation is still

Table II. Levels of biomarkers in patients after myocardial infarction depending on the presence of decompensated heart failure

Indicator, unit of measurement	Medically healthy individuals (n=20)	Patients with MI without decompensated HF (n=40)	Patients with MI and decompensated HF (n=120)
1	2	3	4
NT–proBNP, pg/ml	111,20±3,47	580,15±3,03 p_1<0,05	950,38±3,15 p_1<0,05 p_2<0,05
Copeptine, pmol/L	5,17±0,12	12,03±0,14 p_1<0,05	18,11±0,12 p_1<0,05 p_2<0,05
ST-2 ng/ml	14,80±1,61	36,00±1,43 p_1<0,05	49,22±1,40 p_1<0,05 p_2<0,05

Notes. p_1 – probability of difference in indicators comparing with medically healthy individuals; p_2 – probability of difference in indicators comparing with patients with MI without decompensated HF

Table III. NT-proBNP level in the post-infarction period depending on the presence of decompensated HF

Indicator, unit of measurement	Medically healthy individuals (n=20)	Patients with MI without decompensated HF (n=40)	Patients with MI and decompensated HF (n=120)
NT–proBNP pg/ml, before physical exertion	111,20±3,47	580,15±3,03 p_1<0,05	950,38±3,15 p_1<0,05 p_2<0,05
NT–proBNP pg/ml, after physical exertion	116,20±4,83 Δ+4,49	619,03±4,70 p_1<0,05 Δ+6,70	1048,06±4,83 p_1<0,05 p_2<0,05 Δ+10,28

Notes.: p_1 – probability of difference in indicators in comparison with healthy individuals; p_2 – probability of difference in indicators in comparison with patients without signs of decompensated HF; Δ increase (+) or decrease (-) of the indicator in percentage to the values of medically healthy individuals

based on a set of clinical symptoms supported by objective evidence of cardiac dysfunction. Patients who develop HF decompensation in the post-infarction period have to go through a number of stages before its onset [24].

According to current recommendations, the detection of BNP level is an invariable criterion for the diagnosis and assessment of the severity of HF. The obtained data prove the high prognostic value of MNUP in assessing the risk of death and myocardial dysfunction in patients with acute MI. However, the diagnostic potential of BNP in the development of clinical complications in MI is not sufficiently covered, so it is of interest for further research [25]. Today, the question is raised about a certain prospect of using NT-proBNP level for monitoring the effectiveness of CHF therapy and stratification of patients according to the risk of adverse clinical events.

Alteration of neuroendocrine activation may reduce the consequences of adverse LV remodeling and improve the prognosis for such patients. Foreign studies have shown that plasma copeptin levels in patients with HF correlate with the severity and stage of its development [26]. According to these studies, in patients with HF, the assessment of clinical symptoms such as shortness of breath, cardiac asthma, echocardiographic findings are less prognostic than the increase of sST2 in plasma concentration. However, the final value of sST2 in each of the above pathways and the point of application of its prognostic value in conditions of inflammation or necrosis of the heart muscle and its remodeling are currently unknown.

The level of increased tolerance to physical exertion after myocardial infarction and increased levels of B-type natriuretic propeptide in blood serum depend not only on the duration of rehabilitation treatment, but also on the presence of signs of decompensated heart failure.

CONCLUSIONS

1. The most significant for clinical and prognostic assessment of the post-infarction period complicated by decompensated HF is the response of the patient's body to dosed physical exertion and the levels of NT-prpBNP, copeptin and ST2.
2. Most patients with HF have reduced tolerance to physical exertion. That is why 6MWT is used to determine the degree of changes in myocardial contractility.
3. High levels of NP, copeptin and ST2 indicate an unfavorable prognosis. Therefore, an inadequate response to dosed physical exertion and increased immunological indicators as quantitative markers of HF can be useful not only for diagnosis, but also for risk stratification, decision-making on optimization of treatment of such patients and decision on discharge.

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ORIGINAL ARTICLE

AMBULATORY BLOOD PRESSURE VARIABILITY IN YOUNG ADULTS WITH LONG-COVID SYNDROME

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ABSTRACT

The aim: To perform an overall assessment of BP and BP variability using ambulatory measurements in young adults with long COVID syndrome.

Materials and methods: We enrolled young patients with diagnosed long-COVID syndrome (n = 58, mean age 23.07 ± 1.54 years), compared with an age-matched healthy subjects who had not suffered from COVID-19 (n = 57, mean age 22.9 ± 1.83 years). Patients with long-COVID syndrome had recovered from mild/moderate illness and none had required hospitalization. Ambulatory 24 hours blood pressure (AMBP) parameters (mean BP, daytime BP, nighttime BP, pulse pressure, nocturnal systolic BP dipping, dipper status) were measured in all participants. The variability of systolic BP (SBP) and diastolic BP (DBP) values was assessed by the following common metrics, including the average real variability (ARV), the coefficient of variation (CV), the standard deviation (SD), and the weighed SD of SBP and DBP.

Results: The average values of 24-hour ambulatory blood pressure, mean BP, daytime and nighttime systolic BP, diastolic BP and pulse pressure were found to be significantly different among patients with long COVID syndrome and control group. Group analyses showed that this difference was in SBP mean values (127.1 ± 6.65 mmHg and 115.93 ± 6.24 mmHg respectively) and DBP mean values (73.31 ± 5.30 mmHg and 68.79 ± 5.5 mmHg respectively) mainly at night. PP values at daytime were almost similar among groups, but PP values at nighttime were higher in patients with long-COVID syndrome (53.8 (52.44- 55.14) mmHg and 47.14 (46.45 – 47.88) mmHg respectively). Nocturnal SBP dipping was better in control group than in patients with long-COVID syndrome (5.3 ± 5.68 and 3.1 ± 3.79 mmHg respectively). Only 13 (22.4%) patients with long-COVID syndrome had normal dip-per status while more than half – 38 (66.7%) in healthy subjects. The values of ARV of SBP and DBP over 24-hour, awake, and asleep time frames were found to be greater in patients with long COVID syndrome than healthy controls ($p < 0.05$).

Conclusions: Patients with long- COVID syndrome have higher BP mean values of 24-hour ABPM particularly at nightime, significant blood pressure BP variability, which increases the risk of cardiovascular events in future. Nevertheless, the further prospective investigations is warranted to investigate the potential mechanisms and causality associations.

KEY WORDS: long COVID syndrome, 24-hour ambulatory blood pressure measurements, BP variability

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INTRODUCTION

Long COVID syndrome or post-acute sequelae of SARS-CoV-2 (PASC) is a major health issue in patients with previous SARS-CoV-2 infection.

The term "long COVID" has been officially accepted by the National Institutes of Health to describe the persistence of symptoms or development of sequelae beyond 3 weeks from the onset of acute symptoms of SARS-CoV-2 infection [1].

The most commonly reported symptom among young subjects with previous COVID-19 infection is fatigue, which has been associated with a high prevalence of anxiety [2].

Hypertension is recognized as one of the most fatal comorbidities, which is associated with the severity of COVID-19 symptoms and increased mortality rate [3].

Persistently elevated BP in previously healthy individuals or poor BP control in patients with a pre-existing controlled hypertension is an often findings during routine medical check-up after recovery from COVID-19 [4,5].

While the mechanisms of association between hypertension and COVID-19 remains unclear, on the one hand, it has been proposed that the SARS-CoV-2 virus enters not only cells in the lung via ACE2 (angiotensin-converting enzyme 2) receptors but also neuronalcells (nACE2). The presence of nACE2 may play a facilitatory role in the neurotropism of SARS-CoV-2 [6]. However, it remains to be determined whether the neuroinvasive and neurotropic capabilities of SARS-CoV-2 contribute to the neural control of hypertension.

On the other hand, endothelial dysfunction due to oxidative stress and inflammation is a major phenotype underlying both the pathogenesis and progression of hypertension.

The epidemiological and clinical data from COVID-19 suggests that both may have common inflammatory pathways. There is a lot of evidence supports the hypothesis that hypertension is associated with immune activation and oxidative stress [7].

The innate (macrophages, microglia, monocytes, dendritic cells, and myeloid-derived suppressor cells) and adaptive immune cells (CD8+ T cells, CD4+ cells [Th1, Th17 and Treg cells], T cells and B cells) have been shown to play a role in hypertension [8].

Moreover, the dysregulation of adaptive immune CD4+ and CD8+ T cells plays a critical role in the development of hypertension [9]. A particular immunologic profile of CD8+ CD8+ T cells makes them less efficient in antiviral defense and lead to the overproduction of cytokines, which results in development of hypertension-mediated organ damage [10].

The experimental and clinical studies have revealed the link between hypertension and activation of several cytokines. Thus, IL (interleukin)-6 is one of the major cytokines regulating immunoinflammatory responses in hypertension [11,12].

High level of immunomodulatory proteins such as IL2, IL6, IL10, MCP1, and TNF-α in plasma has been observed in COVID-19 patients [13].

It has been noted that SARS-CoV-2-induced immune dysregulation with immunosuppressive and inflammatory monocytes/macrophages, with an IL-6-driven inflammatory status directly correlates with progression to severe forms of COVID-19 and mortality [14].

In addition, a recent observational and genetic analyses demonstrate a concordant, positive and potentially causal relationship of lymphocyte count with systolic and diastolic BP suggesting a loss of lymphocytes in hypertension.

Concurrently with hypertension, loss of lymphocytes is also a major feature of COVID-19 [15].

Although it has not yet been proven whether inflammation in humans is related to hypertension or represents a secondary effect of hypertension, it is nevertheless clear that inflammation and the dysregulated immune system are closely linked, and that immunoinflammation plays an important role in hypertension.

However, the effect of COVID-19 on blood pressure (BP) has not yet been elucidated.

THE AIM

The aim of the study was to perform an overall assessment of BP and BP variability using ambulatory measurements in young adults with long COVID syndrome.

MATERIALS AND METHODS

We enrolled young patients with diagnosed long-COVID syndrome (n = 58, mean age 23.07 ± 1.54 years), compared with an age-matched healthy subjects who had not suffered from COVID-19 (n = 57, mean age 22.9 ± 1.83 years).

All long-COVID-19 patients had recovered from mild / moderate illness and none had required hospitalization.

The subjects in the study group were infected on average 1.68 ± 1.2 months earlier, with symptoms of the infection persisting on average for 17.04 ± 8.62 days, and the feeling of fatigue persisting on average for 2.75 ± 2.34 weeks

There was no statistically significant difference between the two groups regarding age, gender, body mass index or smoking.

Exclusion criteria were patients with diagnosis of hypertension, intolerance for the 24 hours ABPM and BP reading success rate < 70%, congestive heart failure, presence of bundle branch block on ECG, usage of antiarrhythmic medications, moderate to severe mitral and/or tricuspid regurgitation, active infections, hyperparathyroidism, hipo- or hyperthyroidism, and autoimmune diseases.

Ambulatory BP was measured in all participants.

Participants were instructed to perform normal daily activities without any moderate-vigorous physical activity during the 24-h period.

Ambulatory BP readings were automatically taken and recorded every 15 min during waking hours and every 30 min during sleeping hours for 24 h.

The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated for the 24-h period and separately for daytime (awake) and night-time (sleep) periods, defined by subjects' diary reports of actual asleep and awake times.

Elevated ambulatory BPs were defined as follows: elevated 24-h ABP as mean 24-h SBP ≥130 mmHg and/or DBP ≥80 mmHg; elevated daytime ABP as mean daytime SBP ≥135 mmHg and/or DBP ≥85 mmHg; and elevated night-time ABP as mean night-time SBP ≥120 mmHg and/or DBP ≥70 mmHg.

Pulse pressure (PP) was measured as the difference between SBP and DBP. Nocturnal SBP dipping was calculated as follows: (diurnal SBP-nocturnal SBP) × 100/diurnal SBP. Based on the nocturnal fall in BP, we classified participants into two groups: non-dippers (nocturnal BP fall < 10%) and dippers (nocturnal BP fall ≥ 10%).

The variability of SBP and DBP values was measured by the following common metrics, including the average real variability (ARV), the coefficient of variation (CV), the standard deviation (SD), and the weighed SD of SBP and DBP.

ARV is the mean of absolute changes between successive blood pressure readings and was calculated using the following formula:

$$ARV = \frac{1}{N-1} \sum_{k=1}^{N-1} |BP_{k+1} - BP_k|$$

where N is the total valid numbers of BP readings, and Bp*k* and Bp*k*+1 denote two adjacent BP measurements. Data were extracted to calculate SD, which measures the dispersion of a data set around the mean values. Weighed SD over 24 hours was calculated with the following formula: Weighed SD = (SD of diurnal BP × daytime + SD of nocturnal BP × nighttime)/Total recording lenght. CV was calculated as 100 × SD/mean blood pressure of SBP and DBP.

Statistical analyses were carried out in SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, Illinois).

Continuous variables were presented as the mean ± standard deviation (SD) and were compared using an independent samples t test. The differences between groups were checked by Chi-square test for categorical variables and by independent t-test for continuous variables.

Table I. The characteristics of 24-h ambulatory blood pressure in patients with long -COVID syndrome and control group

Parameter	Post-COVID-19 group (n=58) Mean±SD	Control group (n=57) Mean±SD
Systolic BP, mmHg		
24-h systolic mean	129.13 ± 9.06*	119.21 ± 10.3 *
Day systolic mean	131.16 ± 6.83 *	122.48 ± 7.02 *
Night systolic mean	127.1 ± 6.65 *	115.93 ± 6.24 *
Diastolic BP, mmHg		
24-h diastolic mean	77.73 ± 9.03 *	70.41 ± 7.19*
Day diastolic mean	82.14 ± 4.62*	72.04 ± 5.20*
Night diastolic mean	73.31 ± 5.30*	68.79 ± 5.5*
Pulse pressure (PP), mm Hg		
24-h PP	51.4 (51.43 -51.37) *	48.8 (45.69 - 51.91) *
Day PP	49.02 (46.81- 51.2) *	50.44 (48.62 -51.90) *
Night PP	53.8 (52.44- 55.14)*	47.14 (46.45 - 47.88) *
Nocturnal SBP dipping, mm Hg	3.1 ± 3.79 *	5.3 ± 5.68 *
Dipper status (%)	13 (22.4)	38 (66.7)

*: $p < 0.05$ compared to the control group

Table II. The characteristics of 24-h blood pressure variability in patients with long-COVID syndrome and control group

Parameter	Long-COVID syndrome group (n=58) Mean±SD	Control group (n=57) Mean±SD
Average real variability (ARV), mmHg		
24-h SBP	21.3 (18.6-23.9) *	11.8 (10.4-13.1)*
24-h DBP	14.1 (11.9-16.3) *	7.7 (6.1-9.3) *
Day SBP	22.4 (19.8-24.9) *	13.5 (9.5-17.4) *
Day DBP	15.7 (11.7-19.6)*	8.2 (6.1-10.2)*
Night SBP	20.1 (14.5-25.6)*	9.6 (7.0-12.1)*
Night DBP	12.6 (9.0-16.1)*	7.3 (5.1- 9.5)*
Coefficient of variation (CV), mmHg		
24-h SBP	13.5 (11.2-15.7) *	10.4 (8.3-12.4) *
24-h DBP	12.9 (10.7-15.0) *	11.2 (9.3-13.1) *
Day SBP	14.1 (11.7-16.4) *	10.9 (8.1-13.7) *
Day DBP	13.5 (10.2-16.8) *	11.8 (9.7-13.9) *
Night SBP	11.5 (8.6-14.3) *	9.6 (7.5-11.5) *
Night DBP	12.4 (8.8-15.9) *	10.5 (8.2-12.8) *
Standard deviation (SD), mmHg		
24-h SBP	17.2 (12.8-21.6) *	13.6 (11.4-15.7) *
24-h DBP	11.0 (9.2 -12.8) *	10.2 (7.8-12.5) *
Day SBP	16.5 (12.4-20.6) *	12.6 (9.1-16.1) *
Day DBP	10.9 (8.2-13.5) *	8.4 (6.5-10.3) *
Night SBP	15.4 (11.4-19.3) *	11.7 (9.3-14.0) *
Night DBP	11.4 (7.0-15.7) *	8.3 (6.2-10.3) *
Weighed SD, mm Hg		
Weighed systolic SD	16.3 (12.8-19.7)*	12.4 (9.7-15.1)*
Weighed diastolic SD	9.2 (7.5-10.8)*	7.1 (5.7-8.5)*

*: $p < 0.05$ compare with the control group

The results were analyzed with a 95% confidence interval at a significance level of $p < 0.05$ or with a 99% confidence interval at a high significance level of $p < 0.01$.

RESULTS

The average values of 24-hour ambulatory blood pressure, mean BP, daytime and nighttime systolic BP, diastolic BP and pulse pressure were found to be significantly different among patients with long COVID syndrome and control group (Table I).

There was higher average of SBP and DBP in patients with long COVID syndrome as compared with healthy subjects.

Group analyses showed that this difference was in SBP mean values (127.1 ± 6.65 mmHg and 115.93 ± 6.24 mmHg respectively) and DBP mean values (73.31 ± 5.30 mmHg and 68.79 ± 5.5 mmHg respectively) mainly at night.

Elevated night-time SBP and DBP measured by ABPM is associated with an increased risk of subclinical cerebrovascular disease, independent of traditional risk factors and echocardiographic changes related to hypertension and stroke [12].

PP values at daytime were almost similar among groups, but PP values at nighttime were higher in patients with long-COVID syndrome (53.8 (52.44- 55.14) mmHg and 47.14 (46.45 – 47.88) mmHg respectively).

However, nocturnal SBP dipping and dip-per status significantly differ among groups ($p < 0.05$).

Thus, nocturnal SBP dipping was better in control group than in patients with long-COVID syndrome (5.3 ± 5.68 and 3.1 ± 3.79 mmHg respectively).

Only 13 (22.4%) patients with long-COVID syndrome had normal dip-per status while more than half – 38 (66.7%) in healthy subjects.

Similar results were obtained for the overall blood pressure variability ($p < 0.05$ for all).

The overall magnitudes of blood pressure variability, including ARV, CV, SD, and weighed SD, were significantly different among groups (Table II).

The values of ARV of SBP and DBP over 24-hour, awake, and asleep time frames were found to be greater in patients with long COVID syndrome than healthy controls ($p < 0.05$).

With regard to CV and SD over 24 hours, daytime, and particularly nighttime, the significant differences were detected among study group and healthy subjects ($p < 0.05$).

A significant increased of weighed systolic (16.3 (12.8-19.7) and 12.4 (9.7-15.1) respectively) and diastolic SD (9.2 (7.5-10.8) and 7.1 (5.7-8.5) respectively) was observed in patients with long-COVID syndrome as compared to controls ($p < 0.05$).

DISCUSSION

Nowadays, we still do not know all of the long-term consequences of SARS-CoV-2 infection, despite the advancing research related to this disease.

Many patients who had recovered from COVID-19 may suffer from lasting impairments, including those related to the nervous system [16].

Recent studies suggest that SARS-CoV-2 infection may affect the autonomic nervous system causing dysautonomia in patients with long COVID syndrome or with post-acute COVID sequalae [17].

However, the autonomic symptoms may also be present in patients recovered from mild/moderate COVID-19, and they may well correlate with fatigue or postural/orthostatic intolerance [18].

Three possible conditions by which SARS-CoV-2 may induce dysautonomia, have been proposed and gained support from preliminary evidence: hypovolemia, brainstem involvement, and autoimmunity [19].

Moreover, the neurotropism of SARS-CoV-2 has recently been proved by demonstrating the presence of viral particles in brain tissues and cerebrospinal fluid of COVID-19 patients.

There is a lot of evidence to suggest that hypothalamic pituitary adrenal axis is beeing affected by SARS-CoV-2 and could lead to dysautonomia [20].

Neuroinvasion by SARS-CoV-2 causes neuronal degeneration and sub-sequently activates astrocytes and microglial cells, results in cellular immune deficiency, generates dysfunction within the cardiovascular center in the brain and leads to the development of hypertension [21].

In this settings, an alteration of the autonomic nervous system has already been associated with COVID-19 severity, and BP circadian rhythm variability has been indicated as a non-invasive predictor for clinical outcomes.

CONCLUSIONS

Patients with long- COVID syndrome have higher BP mean values of 24-hour ABPM particularly at nightime, significant blood pressure variability, which increase the risk of cardiovascular events in future.

Nevertheless, further prospective investigations is warranted to investigate the potential mechanisms and causality associations.

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ORIGINAL ARTICLE

OPTIMIZATION OF THE FREQUENCY AND STRUCTURE OF CESAREAN SECTIONS BASED ON ROBSON'S QUALIFICATION SYSTEM

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ABSTRACT

The aim: Analyze the frequency and structure of indications for cesarean section in municipal non-profit enterprise "Uzhgorod city maternity hospital" of Uzhgorod city council to determine promising ways to optimize the tactics of childbirth.

Materials and methods: A comparative clinical and statistical analysis of the frequency and indications for caesarean section for 2011-2015 (first group) and 2016-2020 (second group) years according to the Robson system classification was conducted.

Results: The increase in caesarean section had no effect on overall perinatal mortality. The main reserve for reducing the incidence of cesarean section is the primi- and secundipara women with full-term singleton pregnancy, the cephalic presentation of the fetus. Increasing the proportion of vaginal births in women with a scar on the uterus is possible through careful selection of patients for vaginal birth. The high frequency of cesarean section in groups of women with premature births, multiple pregnancies, pelvic preterm births or abnormal preterm births is justified by modern obstetric approaches and does not significantly affect the overall frequency of cesarean section due to the small number of these groups.

Conclusions: The reserve for reducing the frequency of cesarean sections is the standardization of medical care in obstetrics and also in social and legal protection of an obstetrician and gynecologist.

KEY WORDS: cesarean section, Robson qualification system

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INTRODUCTION

Cesarean section (CS) is done in case of maternal and fetal indications, that not always alows to conduct an appropriate analyses concerning the evaluation of factors, that objectively influence the indicence of performing CS. [1]. It is now veryfied that C-section, performed in the absence of medical indications, is a more dangerous method of delivery for both mother and fetus than delivery through the natural birth canal. The role of C-section in reducing perinatal morbidity and mortality remains unresolved [2]. Due to cesarean section, the reproductive potential, both individual and population, is reduced. Doctors lose obstetric professionalism. A generation with a lack of perinatal memory is formed. In addition, the incidence of distant complications after one or more C-section incfreases, it includes pathology of placenta attachment, retained placenta and uterine rupture with possible subsequent hysterectomy [3]. According to the WHO, it is almost impossible to statistically determine and analyze the reasons for the increase in the proportion of C-section. The determinants of this phenomenon in each region, in each obstetric team – are different. To identify a reserve for improving the quality of obstetric care in 2014, the WHO recommended that the C-section incidence should be analyzed using the method proposed by Robson [4]. This is an easy-to-perform method that divides all births into 10 groups and calculates the C-section incidence in each group separately and provides factual material for working out a strategy to reduce the frequency of cesarean sections [5,6,7]. The ratio of groups in different institutions may differ, but the frequency of C-section within groups is comparable.

THE AIM

The aim of this wark was to analyse the structure and incidence of indications for CS municipal non-profit enterprise "Uzhhorod city maternity hospital" of Uzhhorod city council for determination of perspective ways of optimizing labour management.

MATERIALS AND METHODS

This wark was based on a comparative clinical and statistical analysis of the incidence and indications for C-section surgery for 2011-2015 (first group) and 2016-2020 (second group) from the standpoint of the ICD 10 classification and the Robson system was conducted. Statistical analysis of the results of the study was performed using the computer

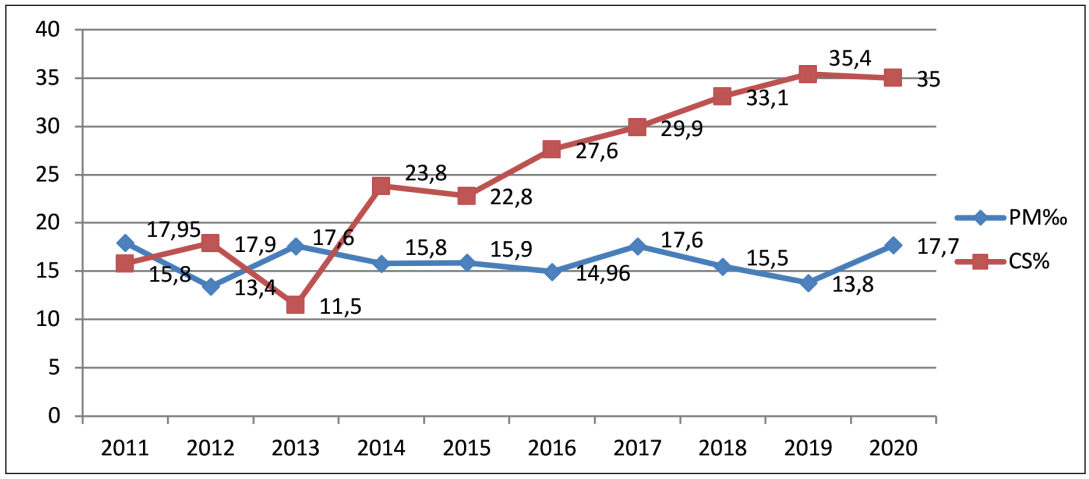

Fig. 1. Dynamics of cesarean section frequency and perinatal mortality rates 2011-2020
*PM – perinatal mortality, CS – cesarean section

program Statistica 6.0 (StatSoft, USA) and the method of t- Student's test.

RESULTS

During 2011-2015 there were 19307, 3551 of which were completed by caesarean section, which amounted to 18.4%. In the period 2016-2020 there were 18,378, 5,897 of which were completed by caesarean section, which amounted to 32.1%. The increase in C-section frequency did not affect the overall perinatal mortality rate (p> 0.05), as illustrated in Fig 1.

At the same time, adaptability disorders and the incidence of children morbidity after C-section are three times higher than those born through the natural birth canal (p <0.05). Analysis of the structure of indications for caesarean section in the first and second groups on the basis of the classification of ICD 10 showed that the following were dominant: scar on the uterus – 25.1% vs. 23.6%; fetal distress – 19.7% vs. 20.6%; anomalies of labour activity – 15.9% against 17.1%; extragenital pathology in the mother – 4.5% vs. 5.3%; pelvic presentation of the fetus – 3.5% vs. 5.2%, but this difference was not statistically significant (p> 0.05). Among the factors contributing to the increase in the frequency of C-section, we should highlight, above all, the increase in the average age of pregnant women and the growth of extragenital pathology. Analyzing the structure of C-section, it is noteworthy to increase the number of elective and decrease the number of urgent operations (p <0.05). The most important indications for elective C-section are scar on uterus, pelvic presentation, multiple pregnancy and abnormal fetal presentation, and for emergency cesarean section – fetal distress in the absence of conditions for rapid delivery through natural birth canal, albour actuvuty abnormalities, failure of labour indcution.

The general structure of childbirth was dominated by primipara women with full-term singleton pregnancy, cephlalic presentation of the fetus, spontaneous labor activity (28.0% in group I and 29.8% in group II, p> 0.05). In 2.9% of women of group I and in 16.8% of group II childbirth occurred by C-section due to urgent indications (p <0.05), which further required primary resuscitation of newborns and subsequent observation or treatment in intensive care unit. The analysis of the peculiarities of the course of pregnancy in women of group II allowed to identify factors that could contribute to the increase in the frequency of C-section: increase in the average age of mothers; obesity and other somatic and gynecological pathology; fetal distress; anomalies of labor activity that are not amenable to drug correction and obstructied labor. We noticed a certain arbitrariness of different physicians' approaches to determining the indications and contraindications to these manipulations, oxytocin doses, evaluating the effectiveness and deciding on the need for C-section in case of failure of delivery or interpretation of cardiotocography.

A significant share in the overall structure of childbirth was made by primipara patients with a full-term singletone pregnancy and the cephalic presentation of the fetus, in which induction of labor or planned C-section was planned (12.5% in group I and 15.5% in group II, p. > 0.05). 22.3% of births in group I and 53.6% of births in group II ended in cesarean section either in accordance with the planned delivery or due to their unsuccessful induction (p <0.05). Multipara patients, singleton pregnancy, cephalic presentation, at ≥37 weeks, spontaneous delivery accounted for 27.4% of the total birth structure in group I and 25.5% in group II (p> 0.005). 1.4% of women in group I and 3.9% in group II gave birth by caesarean section due to emergency indications (p <0.05), which is probably due to problems in complying with the protocols of preterm rupture of amniotic membranes, induction of labour and physicians' skills to evaluate the results of cardiotocography, etc. Multipara patients with singleton pregnancies, cephalic presentation of the fetus at ≥37 weeks, in which induction of labor or elective caesarean section was planned were 9.4% in group I and 71% in group II (p> 0.05). 10.0% of births in group I and 31.0% of births in group II ended with a C-section either in accordance with the planned delivery, or due to their unsuccessful induction (p <0.05). The main contingent of pregnant women who were scheduled to give birth or planned C-section, regardless of whether they were primi- or multipara, were pregnant women with diabetes mellitus,

Table I. Distribution of the frequency of childbirth and cesarean section in the first and second groups.

Groups of women according to the Robson qualification system		The number of C-sections in the group / total number of births in the group		The relative size of the group from the total number of births,%		Frequency of C-section relative to group size,%		Frequency of C-section in relation to all genera,%		Frequency of C-section in relation to all C-section,%	
		I	II	I	II	I	II	I	II	I	II
1	Newborn women, singleton pregnancy, main presentation, ≥37 weeks, spontaneous delivery	159/5406	919/5476	28,0	29,8	2,9	16,8	0,8	5,0	4,5	15,6
2	Newborn women, singleton pregnancy, main presentation, ≥37 weeks A. Induced childbirth B. C-section before childbirth	538/2413	1199/2849	12,5	15,5	22,3	53,6	2,8	8,3	15,2	20,3
3	Reborn, singleton pregnancy, main presentation, ≥37 weeks, spontaneous delivery	74/5290	183/4685	27,4	25,5	1,4	3,9	0,4	1,0	2,1	3,1
4	Reborn, singleton pregnancy, main presentation, ≥37 weeks A. Induced childbirth B. C-section before childbirth	181/1816	405/1305	9,4	7,1	10,0	31,0	0,9	2,2	5,1	6,9
5	Previous C-section, singleton pregnancy, main presentation, ≥37 weeks *	1878/2433	1965/2040	12,6	11,1	77,2	96,3	9,7	10,7	52,8	33,4
6	All newborns, pelvic presentation *	320/637	341/400	3,3	2,5	50,2	85,3	1,7	1,9	9,0	5,9
7	All reborn, pelvic presentation (including previous C-section) *	117/309	203/276	1,6	1,5	38,0	73,5	0,6	1,1	3,3	3,4
8	All multiple pregnancies (including previous C-section) *	160/367	333/404	1,9	2,2	44,0	82,5	0,8	1,8	4,5	5,6
9	All abnormal presentation (except pelvic, including previous C-section) *	37/37	55/55	0,2	0,3	100	100	0,2	0,3	1,0	0,9
10	All singleton pregnancies, main presentation, ≤36 weeks *	87/599	294/827	3,1	4,5	14,5	35,5	0,5	1,6	2,5	4,9

* this category includes: a. spontaneous childbirth, b. induced childbirth, c. C-section before childbirth

including gestational diabetes; hypertensive disorders; intrauterine growth retardation, as well as other high-risk conditions that required delivery after full-term pregnancy. In our opinion, the increase in the share of C-section in group II is due to problems in the implementation of labor protocols, skills to assess the maturity of the cervix according to the Bishop scale, cardiotocography data and more. Analysis of C-section incidence in these groups should be performed continuously together with the assessment and review of protocols for complications that require planned delivery or labour induction.

The main contribution to the structure of cesarean section is made by women with a history of C-section (every 10th woman in the sample), with a singleton pregnancy, cephalic presentation of the fetus at ≥37 weeks (12.6% in group I and 11.1% in group II group, $p > 0.05$). 77.2% of women of group I and 96.3% of women of group II ($p < 0.05$) gave birth by caesarean section. The incidence of CS in relation to all surgical interventions in group I was 52.8%, and in group II – 33.4% ($p < 0.05$). We analyzed the type of delivery with one scar on the uterus and found that 32.8% of women in group I gave birth through the

natural birth canal, while in group II such women were only 6.2% (p <0.05), which, in our opinion, may be due to active implementation since 2011 in practice of obstetric protocol on vaginal delivery after C-section and the gradual loss of obstetricians practical skills in managing delivery of women with a scar on uterus, which requires sufficient diagnostic capabilities and highly qualified doctors from the medical institution. Increasing the proportion of vaginal births in women with uterine scar is possible through careful selection of patients taking into account the state of the lower segment, indications for previous C-section surgery, age, estimated fetal weight, body mass index, etc. Thus, approaches to the delivery of women with a scar on the uterus after a single caesarean section are discussed, but everyone agrees that the main direction in the prevention of C-section is the prevention of the first surgery.

One of the indications for C-section is a disagreement of patient from vaginal delivery in case of breeh presentation. Pregnant women recently use this right actively that doesn't allow obstetricians and gynecologists choose the tactics of vagiinal delivery in case of breech presenttion even in case of presence of conditions for natural delivery, thus the dynamics of this index is explained by medical and legal causes. All primipara patients in breech presentation made up in the overall structure of delivery 3.3% in I group and 2.5% in II group (p>0,005). 50,2% of deliveries in I group and 85,3% in II group were conducted my means of C-section (p<0,05). All multipara patients, in breech presentation (including previous C-section) made up 1.6% in the overall structure of I group and 1.5% in II group (p> 0,05). 38,0% deliveries in I group and 73.5% of deliveries in II group were conducted by means of Cesarean section (p<0,05). Number patients in groups with breech presentation can be decreased by exterenal cephalic version and by transfering patients to groups with cephalic presentation, where much higher probability of successful outcome of labour by vaginal delivery is observed. It's also, in our opinion, may be some reserve of decresing the incidence of abdominal deliveries.

All multiple pregnancies (inclulding previous C-section) made up 44.0% ni I group and 82.5% in II group in overall structure (p <0,05).

Of course, for modern maternal hospitals 100% C-sections in case of abnormal presentations (excluding breech, including previous CS) is a standart of providing health care for partutient. In structure of all deliveries in both groups of these women it was 0.2% relatively.

All singletone pregnancies with cephalic presentaion in gestational term of ≤36 weeks made up 3.1% in I group and 4.5% in II group (p>0,05). Operative delivery was conducted in 14.5% of women in of I group and in 35.5% of patients of II group (p<0,05), that is first of all due to modern resources of neonatal health care.

High incidence of C-section in group of patients with preterm deliveries, breech presentation , multiple pregnancies or abnormal presentations justified by modern obstetric approaches and does not significantly affect the overall frequency of cesarean section due to the small number of patients of these groups (total 10.1% in general structure, in I group with incidence of CS concerning CS 20.3% in all operative intervensions – 20.3%, in II group relatively 11.0% and 20.7% (p>0,05). Though, it must be remembered that in pretern neonates the incidence of morbidity and mortality is much higher. It is possible to decrease the incidence of CS in these patients, but not always expedient, due to extra increase of incidence of fetal and maternal complication risks in case of vaginal delivery especially in case of presence of extra risks. Natural delivery in these patients requires extra technical measures, that are not always justifies and available in practical medicine.

The main reserve in order to decrease the incidence of CS are primi- and miltipara patients with at term pregnancy, cephalic presentation, proportion of which is in the general structure of l;abour in I group is 77.3% total, the incidence of CS relatively to all surgeries 27.2%, in II group 77.9% and 45.9% relatively (p<0,05).

In majority of cases C-section was conducted in patients due to complications of labour or new data of delivery compication risks. Quite frequent indication for and urgent CS in these patients were abnormalities of labour activity or fetal distress. This contingent of women requires special attention. On the one hand, it is a reserve for decreasing the incidence of CS, on the other hand – in some cases CS is done too late, that cases deplesion of parturient, total depression of uterine contractile activity with absence of oxytocin sensivity and severe hypoxic-ischemic complications of fetus. We consider, this is a real contingent to work with in order to improve quality of maternal health case and for self-realization of a specialist

DISSCUSSION

The research topic is relevant and has a certain scientific novelty. The set goal was fully achieved and appropriate conclusions were drawn. The results of the work are reliable and original. Factors that objectively affect the frequency of cesarean sections remain undefined [1]. The question of the role of cesarean section in reducing perinatal morbidity and mortality remains unresolved [2]. In addition, we agree with the opinion of many authors that today it is practically impossible to statistically determine and analyze the reasons for the increase of incidence of cesarean sections [3, 4]. Nevertheless, we are sure that the main direction in the prevention of cesarean section is the prevention of the first surgery. Further research will be devoted to ways of reducing the rate of caesarean sections in Transcarpathian region.

CONCLUSIONS

The main reserve for reducing the incidence of cesarean section is the first and second birth of women with full-term singleton pregnancy and the cephalic presentation of the fetus. The way to reduce the frequency of cesarean sections is to plan the optimal tactics of childbirth in these women based on the identification of risk factors

and determine the contingent of women in whom a set of preventive and curative measures is appropriate. The reserve for reducing the frequency of cesarean sections is the standardization of medical care in obstetrics, as well as the social and legal protection of obstetricians and gynecologists.

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ORIGINAL ARTICLE

DEVELOPMENT AND FORMATION OF THE TOPOGRAPHY OF THE INFERIOR VENA CAVA AND PULMONARY VEINS DURING THE EIGHTH MONTH OF PRENATAL HUMAN ONTOGENESIS

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ABSTRACT

The aim: To determine the topographic features and morphometric parameters of the pulmonary veins and inferior vena cava in human fetuses during the eighth month of intrauterine development.

Materials and methods: A morphometric and histological research of 25 human fetuses in the eighth month of prenatal ontogenesis (271.0 – 310.0 mm parietal-coccygeal length) was conducted. The topographic features of the inferior vena cava and pulmonary veins during the eighth month of intrauterine development were established, and their length and diameter, as well as the change in the angle of their formation, were morphometrically determined. The formation of the topography of these veins is due to the formation of the chest and abdominal organs and continues throughout the entire fetal period of development.

Results: The inferior vena cava is formed at the level of the body of the IV lumbar vertebra in the eighth month of the intrauterine period of human development. The initial part of the trunk of the inferior vena cava obliquely "crosses" the common iliac artery from the left to the right. At this level, the vein is located to the right and slightly behind the aorta. In fetuses of the given age group, the right adrenal gland borders the inferior vena cava only at the level of the lower 2/3 of its medial edge. At the level of the subhepatic section of the inferior vena cava, 4-5 pairs of lumbar veins flow into it. In most cases, the ductus venosus flowed into the inferior vena cava independently between the middle and left hepatic veins. Compared to other sections of the inferior vena cava, the lumen of its diaphragmatic section, which passes through the opening in the dorsal part of the tendinous center of the diaphragm on the right, increases. During this period, it was established that the pulmonary veins lie completely in the heart cavity and are surrounded by a serous membrane. In all fetuses, two pulmonary veins flow from each lung into the left atrium. The level of confluence of the venous ducts of the pulmonary veins and their number varies individually. Pulmonary veins and their ducts lie more superficially and do not repeat the passage of the corresponding bronchi and arteries, lying, as a rule, within the limits of interlobular, intersegmental, and intersubsegmental connective tissue membranes.

Conclusions: In this age group, changes in venous vessels and complications in the structure of their walls and their ducts continue. The passage and branching of the bronchial tree and arterial branches (starting with the segmental branches) are almost completely identical. A significant increase in the number of small ducts was found in the system of pulmonary veins. There is an increase in the morphometric indicators of the size of the inferior vena cava in comparison with its other parts. In the wall of the pulmonary veins and inferior vena cava, all three tunics are clearly visible, which in structure are close to the definitive one.

KEY WORDS: human fetuses, pulmonary veins, inferior vena cava, parietal-coccygeal length, prenatal ontogenesis

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INTRODUCTION

Establishing the morphological regularities of human ontogenesis has not only theoretical value, but also important practical significance. The research of the peculiarities of the development of venous vessels is a morphological basis for understanding the mechanisms of the occurrence of variants, anomalies and malformations, as well as for the development of methods of antenatal prevention of some congenital diseases [1-8]. There are many scientific works that describe the morphological features of venous vessels in the age aspect [9-11]. However, despite the significant functional value of the inferior vena cava and pulmonary veins, their detailed and comprehensive morphological research in prenatal ontogeny was not conducted.

THE AIM

To determine the topographic features and morphometric parameters of the inferior vena cava and pulmonary veins in human fetuses during the eighth month of intrauterine development.

MATERIALS AND METHODS

The study of the pulmonary veins and inferior vena cava and also adjacent organs and structures was performed in compliance with the "Rules of Ethical Principles of Conducting Scientific Medical Research with Human Participation", approved by the Declaration of Helsinki (1964-2013), ICH GCP (1996), EU Directive No. 609 (from 24.11.1986), order of the Ministry of Health of Ukraine No. 680 from 23.09.2009.

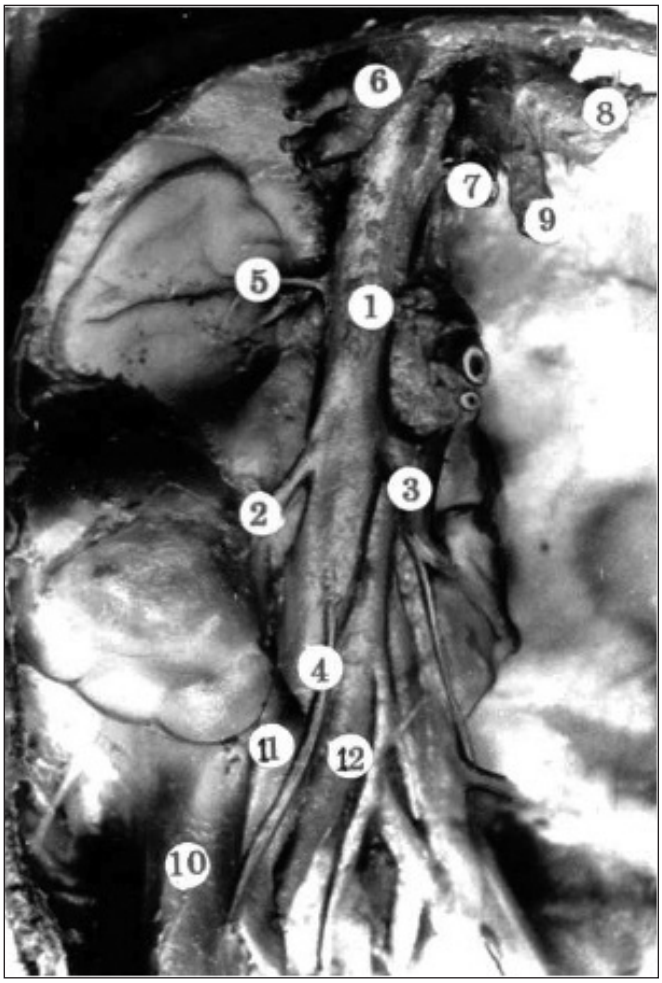

Fig. 1. Complex of organs of the abdominal cavity of a human fetus 348.0 mm parietal-coccygeal length (intestine and liver are removed). Macro photo. The photo is 2 times enlarged.
1 – inferior vena cava; 2 – right renal vein; 3 – left renal vein; 4 – right gonadal vein; 5 – central vein of the right adrenal gland; 6 – right hepatic vein; 7 – middle hepatic vein; 8 – left hepatic vein; 9 – venous duct; 10 – large lumbar muscle; 11 – right ureter; 12 – aorta.

The research was conducted on 25 corpses of human fetuses from 271.0 to 310.0 mm parietal-coccygeal length (PCL), which corresponds to the eighth month of prenatal ontogenesis. We also used histological preparations of fetuses from the archive of the department of human anatomy named after M.G. Turkevych, as well as the graphic reconstruction method used. The age of the object was determined according to the appropriate tables [12]. The length of the fetuses was measured after they were fixed in a 5% solution of neutral formalin for a day, which ensured the constancy of the shape of the gelatinous body and avoided mistakes in determining the age. Serial histological sections of fetuses with a thickness of 25 μm were made in three planes – sagittal, frontal and horizontal, stained with hematoxylin-eosin. Morphometrically, the length and diameter of the pulmonary veins and inferior vena cava were determined on histological sections and graphic reconstructions. The obtained morphometric parameters were processed statistically [13].

RESULTS

The morphogenesis and formation of the topography of the inferior vena cava and pulmonary veins and their ducts during the eighth month of intrauterine development were studied on the preparations of 25 fetuses 271.0 – 310.0 mm parietal-coccygeal length (PCL).

The end of the fetal period is characterized by a relative increase in morphometric indicators mainly in the diaphragmatic and intrapericardial sections of the inferior vena cava in comparison with its other sections and, thus, the vein acquires its final appearance. The inferior vena cava is formed at the level of the body of the IV lumbar vertebra. The left and right common iliac veins, with a diameter of 2.56±0.11 mm and 3.13±0.34 mm, respectively, in fetuses of the eighth month of development, merge at an angle of 47.63±0 ,40°. The initial part of the trunk of the inferior vena cava obliquely "crosses" from left to right the common iliac artery. At this level, the vein is located to the right and slightly behind the aorta. The right ureter is closely adjacent to it on the right, and the large lumbar muscle is attached to the back surface (Fig. 1).

The subrenal section of the inferior vena cava has an oval shape on cross-section, its transverse size is 4.49±0.02 mm in fetuses of the eighth month of development.

At the level of the lower pole of the right kidney, the inferior vena cava is slightly more distant from the kidney, which is connected with the final formation of the position of the kidneys in the retroperitoneal space. On the left, the aorta closely adjoins the vein. Starting from the level of the kidney gate, the aorta takes a dorsal position in relation to the vein. The upper pole of the right kidney is separated from the inferior vena cava by the right adrenal gland, the caudal sections of which cover the anterior-medial surface of the upper third of the kidney. The renal section of the inferior vena cava has a rounded shape on cross-section, its diameter in eight-month-old fetuses is 4.69±0.39 mm, and its length is 20.19±0.32 mm, respectively.

The right renal vein, the diameter of which is 2.86±0.11 mm, flows into the inferior vena cava at an angle of 60.0±1.14°. Its length in fetuses of the eighth month of development reaches 3.72±0.08 mm. 3.0 mm below it, the right gonadal vein with a diameter of 2.17±0.14 mm flows into the right anterior-lateral surface of the inferior vena cava.

The left renal vein flows into the inferior vena cava 3.0 mm above the level of the right renal vein. It has a tortuous passage, its diameter is 3.41±0.07 mm, and at the point of confluence with the inferior vena cava it increases to 4.29±0.05 mm. The central vein of the left adrenal gland with a diameter of 2.20±0.14 mm flows into its upper semicircle. Lateral from it, the left gonadal vein with a diameter of 2.08±0.12 mm flows into the lower semicircle of the left renal vein.

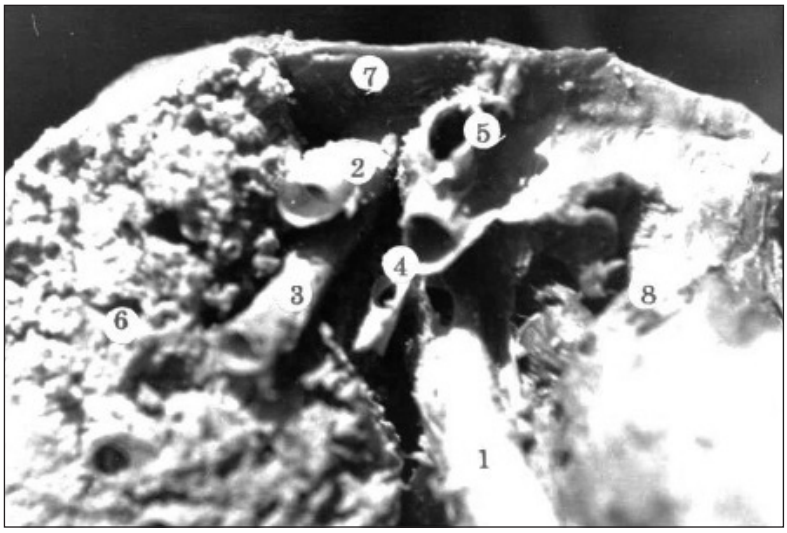

Fig. 2. Complex of organs of the upper part of the abdominal cavity (a part of the liver is removed) of a human fetus 320.0 mm parietal-coccygeal length (view from below). Macro photo. The photo is 4 times enlarged.
1 – inferior vena cava; 2 – right hepatic vein; 3 – middle hepatic vein; 4 – venous duct; 5 – left hepatic vein; 6 – liver; 7 – diaphragm; 8 – stomach.

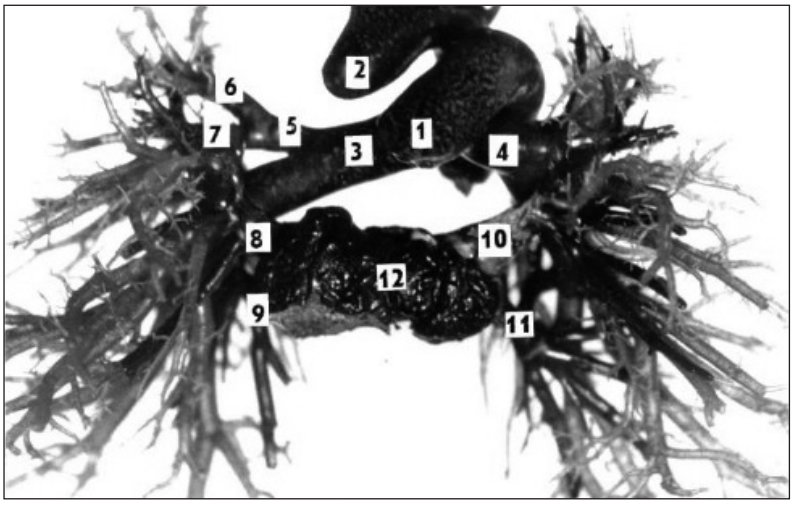

Fig. 3. Corrosive preparation of the pulmonary vessels of the fetus 280.0 mm parietal-coccygeal length. Front view. 36. x 2.4.
1 – pulmonary trunk, 2 – aorta, 3 – right pulmonary artery, 4 – left pulmonary artery, 5 – upper lobe branch of the right pulmonary artery, 6 – apical segmental artery, 7 – anterior segmental artery, 8 – right superior pulmonary vein, 9 – right lower pulmonary vein, 10 – left upper pulmonary vein, 11 – left lower pulmonary vein, 12 – left atrium.

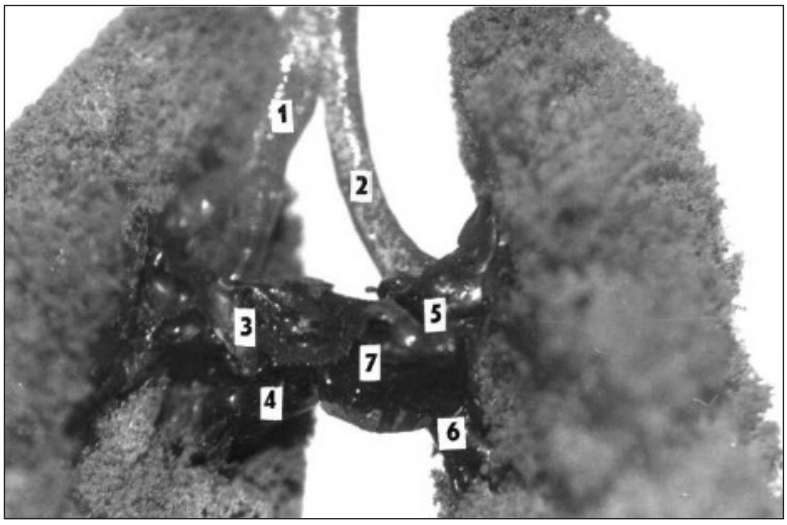

Fig. 4. Corrosive preparation of the bronchi and pulmonary vessels of the fetus 300.0 mm parietal-coccygeal length. Macro photo. Front view. 36. x 2.4.
1 – right main bronchus, 2 – left main bronchus, 3 – right upper pulmonary vein, 4 – right lower pulmonary vein, 5 – left upper pulmonary vein, 6 – left lower pulmonary vein, 7 – left atrium.

Fetuses of this age group, the right adrenal gland borders the inferior vena cava only at the level of the lower 2/3 of its medial edge. Within its upper third, the vein deviates ventrally and enters the liver parenchyma. At the level of the adrenal gland, the inferior vena cava borders the posterolateral surface of the descending part of the duodenum. The diameter of the suprarenal vein in fetuses of the eighth month is 5.03±0.06 mm of development, the length is 11.06±0.39 mm. The central vein of the right adrenal gland, which emerges from the anterior surface of the gland near its medial edge, flows into the inferior vena cava. Its diameter is 2.33±0.11 mm.

At the level of the subhepatic section of the inferior vena cava, 4-5 pairs of lumbar veins with a diameter of 1.58±0.16

mm flow into it. The lower lumbar veins fall 2.0 mm above the place of formation of the trunk of the inferior vena cava, and the upper ones – at the level of the upper third of the right adrenal gland. The left lumbar veins are located slightly higher than the right. Lumbar veins in fetuses of the eighth month are at a distance of 6.8 – 7.1 mm from each other.

In the liver, the inferior vena cava lies in its sulcus. Adjacent to the posterior surface of the vein is the right adrenal gland and the right crus of the diaphragm. At the level of the liver, the vein is slightly compressed from the sides, its transverse size in fetuses of the eighth month of development is 4.41±0.09 mm. The length of the hepatic part of the inferior vena cava during this period increases by 1.83±0.03 mm. When the vein comes out the sulcus, the three main hepatic

The right and middle hepatic veins, which head to the inferior vena cava from the side of the right lobe of the liver, are the same in diameter on almost all preparations, which is 2.94±0.13 mm in fetuses of the eighth month of development. The diameter of the left hepatic vein during this period increases from 2.5±0.54 mm to 3.1±0.38 mm. The ductus venosus, which connects the umbilical vein to the inferior vena cava, flew into the left hepatic vein in one case (340.0 mm parietal-coccygeal length in a fetus), and in all other cases it flew into the inferior vena cava independently between the middle and left hepatic veins. The length of the ductus venosus increases during the eighth month of fetal development, and its diameter increases until the ninth month. The length of the venous duct gradually increases in eight-month-old fetuses. During this period, the diameter of the duct at the level of the umbilical opening decreases from 3.7±0.48 mm to 2.1±0.24 mm, and the diameter of its caval opening remains almost unchanged (between 4.0 and 4.2 mm). This fact is explained by the gradual exclusion of the venous duct from the circulatory system.

Compared to other sections of the inferior vena cava, the lumen of its diaphragmatic section, which passes through the opening in the dorsal part of the tendinous center of the diaphragm on the right, increases. During this period, the length of the diaphragmatic vein reaches 11.21 ± 1.40 mm.

The heart cavity at the end of the fetal period is already clearly formed. The diameter of the intra-pericardial part of the vein in its expanded part in fetuses of the eighth month of development is 6.01±0.07 mm [14].

Pulmonary veins in fetuses of this age group lie completely in the cavity of the heart and are surrounded by a serous membrane. In all these fetuses, four pulmonary veins flow into the left atrium (two from each lung). However, the number of venous ducts that form the pulmonary veins, as well as the level of confluence of these ducts varies individually (Fig. 3).

Therefore, in twenty-two preparations (88.0%), the right upper pulmonary vein (length – 3.1 ± 0.64 mm, diameter – 2.92 ± 1.02 mm) is formed by the fusion of the apical branch and the branch of the middle lobe. In sixteen cases (64.0%), the apical branch of the right upper pulmonary vein is formed from two branches – intrasegmental and intersegmental. The length of the apical branch of the vein is 2.6 ± 0.09 mm, the diameter is 1.78 ± 0.17 mm. It is located in front of the right pulmonary artery and bronchus. The ducts of the apical branch lie superficially and are clearly visible on the medial surface of the lungs. The diameter of intersegmental branches is 1.4 ± 0.18 mm, intersubsegmental – 0.57 ± 0.12 mm.

The vein of the middle lobe, as a rule, is formed as a result of the fusion of two trunks – lateral and anterior branches. In three cases (12.0%), the named trunks flow into the apical branch separately. In these cases, the branch of the middle lobe does not exist as an independent trunk. The length of the branch of the middle lobe is 2.34 ± 0.15 mm, the diameter is 1.41 ± 0.08 mm. It is located below and medial to the artery and bronchus of the same name. Its passage is directed somewhat in the upward direction, where it merges at an acute angle with the apical branch [15-16].

The right lower pulmonary vein collects blood from the lobe of the lung of the same name and is formed in 50% of cases from two or three (42.5%) of venous trunks.

In the first version, it is formed by the upper branch and the common main vein, in the second – by the upper venous branch and two intersegmental veins. In five cases (20.0%), the upper branch flows not into the lower one, as usual, but into the upper pulmonary vein, "crossing" its back wall near the point of confluence of the latter into the left atrium. The right lower pulmonary vein in these cases is a direct continuation of the common main vein and flows into the left atrium in the area of its right lower lateral corner.

The length of the right lower pulmonary vein at this stage of development is 3.0 ± 0.09 mm, the diameter is 3.19 ± 0.08 mm; upper branch – 3.88 ± 0.2 mm and 2.07 ± 0.13 mm, respectively; the common main vein – 3.82 ± 0.16 mm and 3.09 ± 0.87 mm, respectively. The diameter of the intersegmental veins is 2.07 ± 0.11 mm.

The left upper pulmonary vein collects blood from the lobe of the lung of the same name and is formed as a result of the fusion of three (50%), two (25%), and sometimes four (5.8%) of venous trunks.

The length of the left superior pulmonary vein is 4.77 ± 0.21 mm, and its diameter is 3.07 ± 0.12 mm. In the first case, it is formed by apical-posterior, anterior and lingual branches, in the second – by apical-posterior and lingual branches, in the third – by apico-posterior and anterior branches.

The length of the apical-posterior branch is 2.41 ± 0.17 mm, the diameter is 2.0 ± 0.2 mm, the lingual branch is 3.72 ± 0.26 mm and 1.69 ± 0.14 mm, respectively. The diameter of the intersegmental ducts of the above-mentioned veins is 1.71 ± 0.08 mm and 1.39 ± 0.12 mm. Their passage and relation to the bronchial and arterial branches are the same as in fetuses of the previously described age groups.

The lower pulmonary vein collects blood from the lobe of the lung of the same name. Its length is 3.88 ± 0.11 mm, its diameter is 3.17 ± 0.14 mm, and in most cases this vein is formed as a result of the fusion of two veins (upper branch and common main vein). The principle of formation, pas-

sage and topography of veins are similar to those of fetuses of 6-7 months of prenatal development [17-18].

The length of the upper branch is 2.92 ± 0.04 mm, the diameter is 1.91 ± 0.07 mm, the common main vein is 4.22 ± 0.16 mm and 2.35 ± 0.13 mm, respectively.

In three fetuses (12.0%), the left lower pulmonary vein as a separate trunk is almost absent, because the trunks that form it merge with each other near the wall of the atrium, opening into its cavity through one common mouth (Fig. 4).

DISCUSSION

Scientific works that would discuss the development and formation of the lower vena cava and pulmonary veins during the eighth month of prenatal embryogenesis are not found. Ji Hyun Kim1 (2014) emphasizes that the variants of formation of the topography of the lower vena cava do not always depend on the period of development, but partly on the individual differences [18]. Blom N.A. (2001) indicates that the common pulmonary vein develops in segments of the venous sinus, and later – between the venous sinus in the right atrium [19]. Some authors confirm such a formation of pulmonary veins [20].

According to the results of our research, it was established that the eighth month of the fetus ontogenesis of a person is characterized by a change in the morphometric indicators of veins, both in thoracic and also abdominal cavities. During this period, the length, diameter, and angle of formation of the inferior vena cava relatively increase in the diaphragmatic and intrapericardial sections. A gradual distance of the lower vena cava from the lower pole of the right is observed. In fetuses of this age group, this vein partially borders the adrenal gland from the medial edge and the descending part of the duodenum. The length of the hepatic section of the inferior vena cava increases significantly. The ductus venosus is gradually excluded from the circulatory system.

Two pulmonary veins from each lung flow into the left atrium in all fetuses of this age group. At the same time, they lie completely in the cavity of the heart. Changes in morphometric parameters are characterized by some increase in both the length and diameter of the pulmonary veins, but not as pronounced as in the inferior vena cava. In the wall of the veins, all three membranes are almost completely formed, which in terms of histological structure are close to the definitive ones.

CONCLUSIONS

During the eighth month of the fetal period of human ontogenesis, the inferior vena cava and its tributaries undergo significant changes that lead to the formation of its final state. This concerns the level and indicators of the angle of formation of the inferior vena cava, its length and diameter. The passage and branching of the bronchial tree and arterial branches (starting with the segmental branches) are almost completely identical. Veins and their branches lie more superficially and do not repeat the passage of the corresponding bronchi and arteries, lying, as a rule, within the limits of intersegmental, intersegmental, and intersubsegmental connective tissue membrane.

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ORIGINAL ARTICLE

CHANGES IN PROSTAGLANDIN LEVELS IN BLOOD SERUM OF PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE ON THE BACKGROUND OF THE OSTEOCHONDROSIS OF THE SPINE AND OBESITY

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ABSTRACT

The aim: To study the features of changes in the level of prostaglandins (I_2 and $F_{2\alpha}$) in blood serum of patients GERD on the background of OH of the cervical and thoracic spine and obesity.

Materials and methods: The examined patients included 56 patients with GERD and OH of the cervical and thoracic spine. All patients had their blood serum prostaglandin (Pg) $F_{2\alpha}$ and 6-keto prostaglandin $F_{1\alpha}$ (blood prostacyclin – Pg I_2) levels examined using the method of immunoassay analysis.

Results: In all patients with GERD and OH an excessive body weight or obesity of varying degrees was found while analyzing anthropometric study results. The determination of prostaglandin $F_{2\alpha}$ and prostacyclin (Pg I_2) levels in blood serum in patients with GERD and OH and healthy individuals was performed. A more pronounced increase of Pg I_2 and Pg $F_{2\alpha}$ in blood serum in patients with GERD and OH with III degree obese was found and the smallest concentration of prostaglandines in blood serum was diagnosed in patients with excessive weight ($p<0.05$).

Conclusions: 1. In patients with GERD and OH, an increase in levels of prostaglandins $F_{2\alpha}$ and I_2 in blood serum has been established. 2. The relationship between the duration of excess body weigh, obesity and the dynamics of the level of prostaglandin Pg I_2 and $F_{2\alpha}$ in blood serum in patients with GERD on the background of OH has been established.

KEY WORDS: gastroesophageal reflux disease, osteochondrosis, prostaglandin(I_2, prostaglandin $F_{2\alpha}$

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INTRODUCTION

The increased interest towards gastro-esophageal reflux disease (GERD) is caused by the high prevalence of this disease with a permanent upward trend (~5% annual increase). Moreover, in some cases, extra-esophageal manifestations may come to the foreground in clinical findings. In addition, in 25% of cases, GERD occurs along with extra-esophageal symptoms: bronchopulmonary, cardiac, otorhinolaryngopharyngeal, and dental [1-4].

As it is known, the etiopathogenesis of GERD is based on the imbalance between the protection factors (barrier function of the lower esophageal sphincter, effective esophageal clearance, normal resistance of the esophagus mucosa) and aggression (hydrochloric acid, pepsin, bile, pancreatic enzymes, etc.) [5-7]. Many hormones and biologically active substances (BAS) in the body (estrogen, progesterone, prostaglandins, somatostatin, cholecystokinin, etc.) affect the tension of the lower esophageal sphincter [8].

The search for new factors that play a role in the formation of GERD is especially relevant in patients with polymorbid pathology, the treatment of which requires medications that may adversely affect the condition of the mucous membrane of the upper gastrointestinal tract, as well as its functional activity.

Osteochondrosis (OH) of spine is also one of the most common diseases among the adult population, which affects from 40 to 80% of the world's inhabitants. Manifestations of OH are back pain, headaches, which are seen in 25-30% of patients after 30 years old [9, 10]. According to modern recommendations, patients are prescribed non-steroidal anti-inflammatory drugs (NSAIDs) to reduce pain and improve the quality of life in case of the musculoskeletal system damage. Side effects of NSAIDs are very often observed during treatment with this group of drugs. The main negative property of all NSAIDs is a high risk of digestive tract disorders. Thus, dyspepsia is observed in 30-40% of patients receiving NSAIDs, in 10-20% – erosions and ulcers of the stomach and duodenum, in 2-5% – bleeding and perforation. Dyspepsia is the main reason for discontinuation of NSAIDs in more than 50% of cases. Most often, this symptom is noted in patients with a history of digestive tract pathology [11].

Therefore, the study of the clinical course, as well as factors and levels of various biologically active substances that may play an important role in the pathogenetic mechanism of

GERD in patients with combined pathology, including OH, is an extremely relevant problem of modern clinical medicine.

THE AIM

To study the features of changes in the level of prostaglandins (I_2 and $F_{2\alpha}$) in blood serum of patients GERD on the background of OH of the cervical and thoracic spine and obesity.

MATERIALS AND METHODS

At the clinical base of the Department of Internal Diseases Propaedeutics of the Medical Faculty of the SHEI "Uzh-NU" (gastroenterological, endocrinological, neurological department of the KNP "ZOKL named after A. Novak" TRC and patients who were under outpatient observation by a family doctor at their residence place) during 2019-2022 years, 56 patients with GERD and OH of the cervical and thoracic spine were examined. Among the examined patients, there were 32 (57.1%) men, 24 (42.9%) women. The average age was 43.6±4.2 years. The control group included 20 practically healthy people (12 men (60.0%), 8 women (40.0%)). The average age was 44.1±5.2 years.

All studies were performed with the consent of the subjects, and the methodology of their conduct was in accordance with the Helsinki Declaration of Human Rights of 1975 and its revision of 1983, the Convention of the Council of Europe on Human Rights and Biomedicine, and the legislation of Ukraine. All examined patients were subjected to anthropometric, general clinical, laboratory and instrumental methods of examination. During the anthropometric investigation the body mass index (BMI), waist circumference (WC), hips circumference (HC) were measured and the waist/hip index (WHI = WC/HC) was calculated. According to the obtained data, in compliance to WHO recommendations, patients were distributed according to their BMI in the following way: BMI 16.0 and less corresponded to the expressed deficient body weight; 16.0-18.5 – insufficient body weight; 18.0-24.9 – normal weight; 25.0-29.9 – excessive weight; 30.0-34.9 – I degree obesity; 35,0-39,9 – II degree obesity; 40.0 and more – III degree obesity (morbid obesity).

Osteochondrosis of the cervical and thoracic spine was diagnosed based on physical, general clinical examination methods, as well as the results of computed tomography of the spine.

The diagnosis of GERD was established according to the criteria of the unified clinical protocol (order of the Ministry of Health of Ukraine dated 31.10.2013 № 943) taking into account complaints, endoscopic examination data, etc. To confirm the diagnosis, the examined patients underwent fibroesophagogastroduodenoscopy (FEGDS) using endoscopy equipment Pentax ERM-3300 video processor and flexible fiber endoscopes Pentax E-2430, GIF-K20. Also, 24-hour pH monitoring according to Prof. V.N .Chernobrovy's method was performed.

The Los Angeles (LA) classification (1998) was used for endoscopic assessment of the degree of damage to the esophagus: grade A – single erosion ≤5 mm; grade B – ≥1 erosion> 5 mm long that does not occupy the entire space between 2 adjacent folds of the esophagus; grade C – ≥1 erosion that occupies the entire space between ≥2 folds of the esophagus and ≤75% of the perimeter of the esophagus; grade D – erosions or ulcers occupying ≥75% of the esophageal perimeter [10].

In the examined patients, HP-infection was diagnosed using a rapid urease test (CLO-test) before the comprehensive treatment. The effectiveness of eradication therapy was assessed 4 weeks after treatment using the ^{13}C-urea breath test (^{13}C-UBT) (IZINTA, Hungary).

All patients had their blood serum prostaglandin (Pg) $F_{2\alpha}$ and 6-keto prostaglandin $F_{1\alpha}$ (blood prostacyclin – Pg I_2) levels examined using the method of immunoassay analysis with the help of the test system Enzo Life Sciences, "BCM Diagnostics" (USA).

The analysis and processing of the results of the examination of patients was carried out using the Statistics for Windows v.10.0 computer program (StatSoft Inc, USA) using parametric and non-parametric methods of evaluating the obtained results.

RESULTS

In all patients with GERD and OH an excessive body weight or obesity of varying degrees was found while analyzing anthropometric study results – Table I.

The determination of prostaglandin $F_{2\alpha}$ and prostacyclin (Pg I_2) levels in blood serum in patients with GERD and OH and healthy individuals was performed. The results are presented in Table II.

Increased levels of prostaglandins of examined patients with GERD and OH were established. Attention is called to a more significant increase in Pg I_2 concentration compared with Pg $F_{2\alpha}$, in blood serum.

An estimation of change in prostaglandin levels in the examined patients was performed depending on the violation of BMI (Table III).

A more pronounced increase of Pg I_2 and Pg $F_{2\alpha}$ in blood serum in patients with GERD and OH with III degree obese was found and the smallest concentration of prostaglandines in blood serum was diagnosed in patients with excessive weight ($p<0.05$).

The obtained data indicate that in case of the combination of several pathological states (GERD, OH, increased BMI), a more pronounced increase in the concentration of prostacyclin is observed.

DISCUSSION

We have not found any scientific works that discuss the role of prostaglandins in patients with the combination of GERD, OH and obesity. Takeuchi K. (2010) highlights the role of prostaglandins, predominantly type E, in GERD and chronic gastritis. At the same time, the authors have proven that Pg E_2 protects the esophagus from acid reflux and provides cytoprotection of the stomach [12].

Table I. Distribution of examined patients according to their BMI

Indicator	Examined patients with GERD and OH (n=56)
BMI, kg/m^2	38.96 ± 4.61
Excessive body weight	30. 3 %
I degree obesity	42.9 %
II degree obesity	21.4 %
III degree obesity	5.4 %

Table II. Levels of prostaglandins in blood serum in the examined patients

Examined patients	Indicator	
	Pg I_2 (pg/ml)	Pg $F_{2\alpha}$ (pg/ml)
Control group (n=20)	51.14 ± 3.23	72.25 ± 2.31
Patients with GERD and OH (n=56)	141.22 ± 5.64*	136.22 ± 4.71*

Note: the difference in indicators between the control group and groups of patients with GERD and OH - * $p<0.01$.

Table III. Change in prostaglandin levels in the examined patients depending on nutrition status

Indicator	Examined patients with with GERD and OH I group (n=56)	
	Pg I_2 (pg/ml)	Pg $F_{2\alpha}$ (pg/ml)
Excessive weight	116.23 ± 8.98	104.12 ± 6.15
I degree obesity	132.14 ± 4.16	128.15 ± 4.12
II degree obesity	148.20 ± 7.75^	141.17 ± 8.91^
III degree obesity	152.23 ± 10.15*	162.00 ± 5.11*

Note: ^ $p<0.05$ – the difference in the indicators in patients with excessive weight and II degree obesity is reliable; * $p<0.05$ – the difference in the indicators in patients with excessive weight and III degree obesity is reliable.

We have studied the levels of class I_2 and $F_{2\alpha}$ prostaglandins, which have a divergent effect on the body, namely: Pg I_2 exhibits a relaxing effect, while prostaglandin $F_{2\alpha}$, on the contrary, has constrictive properties. According to the results of our study, increased levels of blood serum prostaglandins $F_{2\alpha}$ and I_2 in patients with GERD and OH of spine were determined. When characterizing the change in prostaglandins by classes, a predominant increase in prostacyclin in the blood serum was detected. Prevalence of prostaglandin, which has a relaxing effect on smooth muscles, including the digestive system, suggests its effect on the formation of GERD, especially on the background of OH. It is plausible that the loss of the physiological balance between prostaglandins, which have opposite effects on the internal organs on the background of metabolic disorders in obesity, may be considered as one of the components affecting the lower esophageal sphincter, leading to its relaxation and the formation of GERD manifestations. The obtained data require further investigation and analysis of changes in prostaglandins in OH of spine and their probable effect on the formation of GERD in these patients.

CONCLUSIONS

1. In patients with GERD and OH, an increase in levels of prostaglandins F2α and I2 in blood serum has been established.
2. The relationship between the duration of excess body weigh, obesity and the dynamics of the level of prostaglandin Pg I_2 and $F_{2\alpha}$ in blood serum in patients with GERD on the background of OH has been established.

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REVIEW ARTICLE

APELIN IN HEART FAILURE

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ABSTRACT

Apelin is a biologically active protein encoded by the APLN gene. It was first isolated in 1998 as a ligand for the APJ receptor. It exists in several isoforms differing in polypeptide chain length and biological activity. It is secreted by white adipose tissue, and its expression has been identified in many body tissues, including the cardiovascular system, kidneys, lungs, CNS (especially the hypothalamus, suprachiasmatic and ventricular nuclei), skeletal muscle, mammary glands, adrenal glands, ovaries, stomach, liver cells, placenta, and breast milk. However, the highest concentrations were observed in the endocardium and endothelium of vascular smooth muscle cells. In myocardial tissue, apelin has a positive inotropic effect and exerts an opposing effect to the RAA (renin-angiotensin-aldosterone) system, lowering blood pressure. Therefore, its positive role in early stages of heart failure, in patients with hypertension and ischemic heart disease is emphasized. The synthesis and secretion of apelin by adipocytes makes it possible to classify this peptide as an adipokine. Therefore, its production in adipose tissue is enhanced in obesity. Furthermore, apelin has been shown to increase cellular sensitivity to insulin and improve glucose tolerance in the onset of type 2 diabetes, and therefore appears to play a significant role in the pathogenesis of metabolic disease. An accurate assessment of the importance of apelin in cardiovascular disease requires further studies, which may contribute to the use of apelin in the treatment of heart failure.

KEY WORDS: cardiovascular system, heart failure, apelin, APJ receptor

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INTRODUCTION

Heart failure (HF) is a serious problem in cardiology due to its steadily increasing incidence and unfavorable prognosis, despite advances in its treatment. HF is a clinical syndrome characterized by inappropriate myocardial remodeling and impaired left ventricular systolic and diastolic function [1]. HF is not a disease but a syndrome, a combination of signs and symptoms caused by a structural and/or functional abnormality of the heart and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. Left ventricular failure causes blood return and stasis in the pulmonary circulation, giving respiratory symptoms: shortness of breath, especially on exertion and when lying down. Right ventricular failure causes blood stasis in the venous vessels, leading to edema, especially in the lower extremities, as well as abdominal pain and liver enlargement. [2]. According to the World Health Organization (WHO), the leading cause of mortality worldwide is cardiovascular disease. Also in Poland cardiovascular diseases are the leading cause of death (about 45%), and HF has the highest mortality rate of all these diseases. The number of HF patients in 2018 exceeded 70 million worldwide, 10 million in the European Union, and as many as 1.24 million in Poland. Also in the same year (2018), 142,000 people with HF died, accounting for more than one-third of all deaths during that time. In Poland, more than 40% of patients with heart failure do not survive five years after diagnosis [3, 4]. Early diagnosis of HF is difficult due to the absence of clinical symptoms, despite the abnormalities of myocardial structure or function already present. Detection of these changes and early implementation of appropriate treatment can prolong the life of patients with HF. Recent studies point to the key role of specific biomarkers that reflect the severity of cardiovascular disease and therefore allow early diagnosis of heart failure, monitoring of treatment and accurate assessment of prognosis [5].

A promising contemporary marker is the apelin protein, which, due to its functions, can be used to improve the diagnosis and treatment of both HF and hypertension. Apelin is a newly discovered peptide hormone and ligand for the APJ receptor with proven positive effects in the early stages of HF. This is primarily due to its vasodilator and positive inotropic effects. In addition, it has been shown to have a hypotensive effect in patients with primary hypertension, due to its apparent antagonistic effect on the renin-angiotensin-aldosterone system. Understanding its mechanism of action requires further research, which may contribute to therapeutic advances in cardiovascular disease [6, 7].

THE AIM

The aim of this study is to analyze the available literature on the effects of apelin on the cardiovascular system and to evaluate its potential as a therapeutic agent in patients with HF.

REVIEW AND DISCUSSION

APELIN

Apelin is an endogenous ligand for the G-protein-coupled receptor APJ. The gene encoding apelin is located on the short arm of the X chromosome at position q25 - 26.1 and encodes a sequence of 77 amino acids called preproapelin. Under the influence of endopeptidases, preproapelin is cleaved into several C-terminal fragments with different polypeptide chain lengths, which are classified based on the number of amino acids [8, 9]. Accordingly, the following active isoforms are distinguished: apelin-36, apelin-17, apelin-16, apelin-13 and exogenously synthesized apelin-12. Other shorter fragments have no biological activity [10]. It follows that 12 C-terminal amino acids are required for receptor binding, while the N-terminal sequence modulates interaction with the APJ receptor. The different isoforms differ in their potency, and so apelin-36 is a precursor with limited biological activity. As its chain length is shortened, by post-translational modification, this activity increases. Another factor that distinguishes the isoforms from each other is the duration of action, which depends on the duration of APJ receptor internalization. It has been shown that the gradual cutting off of the N-terminal amino acids, thus reducing the length of the polypeptide chain of the individual apelin isoforms, accelerates the dissociation of the substrate from the receptor reducing the duration of internalization, i.e. the duration of action of the substance. Accordingly, apelin-36 is characterized by a longer duration of activity, as a result of a longer duration of receptor internalization, and apelin-13 by a shorter duration [11].

In healthy humans, the presence of mRNA for apelin and its receptor has been confirmed in most tissues of the body. Apelin-like immunoreactivity has been detected in cardiomyocytes, endocardial vascular endothelial cells, internal mammary arteries, pulmonary arteries, pericardial coronary arteries, small intracardiac coronary arteries, intrarenal vessels, adrenal resistance arteries and saphenous veins [7]. However, the highest concentration of apelin is found in endothelial cells and vascular smooth muscle cells. In addition, it has also been detected in the kidneys, white adipose tissue, lungs, CNS (especially in the hypothalamus, suprachiasmatic and paraventricular nucleus), where it is involved in regulating the secretion of tropic hormones and vasopressin in the hypothalamic-pituitary axis, as well as in skeletal muscle, mammary gland, adrenal gland, testes, ovaries, placenta, lining cells and glandular epithelium of the gastric fundus, Kupffer cells of the liver and in breast milk [12-14]. It is believed that high concentrations of apelin can be found in adipocytes, or fat cells, and is therefore released by adipose tissue as a hormone belonging to the adipokine family.

Such widespread occurrence of the apelin/APJ-receptor system, known as the apelinergic system, indicates its involvement in many physiological processes, such as regulation of blood pressure, body fluid homeostasis, cardiac contractility, angiogenesis, stress response and energy metabolism [15, 16].

THE APJ RECEPTOR

The APJ receptor was discovered in 1993, and the isolation of its ligand, apelin, occurred in 1998. The gene encoding the APJ receptor is located on the short arm of chromosome XI [8]. APJ is a receptor composed of 377 amino acids and conjugated to G protein, with a trans-membrane domain of 7. When it binds to apelin, the G protein complex is broken down, resulting in the release of α GTP, β and γ subunits, activating secondary messengers responsible for such cell biological effects as activation of ion channels, contraction, diastole, and alteration of metabolism, including gene expression and protein synthesis [17].

APJ shows striking similarity, in structure as well as distribution, to the angiotensin II type 1 receptor (AT1R) and has 30% identical amino acid residues to it (54% within the transmembrane regions), while it has a lack of affinity for angiotensin II (AngII). This fact implies that apelin is involved in the regulation of the cardiovascular system via the renin-angiotensin-aldosterone (RAA) system [18]. APJ receptor activity is dependent on the form of attached apelin. Shorter fragments stimulate APJ for a short time, as it is rapidly internalized and within an hour returns to the cell membrane surface becoming available for reactivation. On the other hand, longer-chain apelin isoforms dissociate slowly from the receptor, locking it in an active state for a longer period of time [19].

FUNCTIONS OF APELIN

INOTROPIC EFFECTS OF APELIN

The apelinergic system provides important beneficial effects in the cardiovascular system under pathological conditions due to its ability to regulate such functions as blood pressure, cardiac contractility and body fluid balance. Several studies have shown a positive effect of apelin on the strength of cardiac contraction, resulting from the induction of an increase in the sensitivity of the intracellular contractile apparatus to Ca_2+ ions. This is due to the activation of phospholipase C and protein kinase C, resulting in an increase in Na+/H+ ion exchange in the sarcolemma, an increase in Na+ concentration in the cell with subsequent activation of the Na+/Ca_2+ pump [7, 20]. Apelin is ranked among some of the most potent endogenous substances with positive inotropic effects. However, it does not affect myocardial mass and hypertrophy like other substances with a similar action profile, which is due to apelin's simultaneous reduction of myocardial preload and afterload, due to its vasodilatory effect [21]. Parikh et al. demonstrated that fiber stretch is mediated by the myocardial APJ and that the APJ receptor is essential for stretch-induced increases in cardiac contractility, and that a novel inotropic mechanism of the apelin/APJ system involves increased Ca_2+ sensitization in the muscle layer. These data highlight the unique potential of apelin as a therapeutic agent to promote cardiac function on the one hand and protect against myocardial hypertrophy in HF patients on the other [22].

It has also been observed that the main groups of drugs used in HF patients, namely β-blockers and angiotensin II receptor antagonists (ARBs), do not attenuate apelin-induced inotropy, which is of great importance if apelin were implemented in HF therapy [15].

HYPOTENSIVE EFFECT OF APELIN

Studies emphasize the role of apelin in lowering blood pressure due to its vasodilatory effect, which consequently leads to a reduction in systemic vascular resistance, lowering LV preload and afterload, and improving LV filling. Vasodilatation may be due to the direct effect of apelin on vascular smooth muscle cells (as a result of activation of phospholipase C and protein kinase C) or result from the indirect action of apelin, which mediates the phosphorylation and activation of nitric oxide synthase (NOS) [23]. Jia et al. confirmed that apelin administration in isolated rat aorta, increases the synthesis and release of nitric oxide (NO) and its uptake by endothelial cells, as a result of an increase in NO synthase activity. In this way, apelin causes an increase in cGMP and vascular smooth muscle cell relaxation [24]. The hypotensive effect of apelin was demonstrated in healthy rats, in which both systolic and diastolic blood pressures were immediately reduced after intravenous apelin administration [25]. On the other hand, this phenomenon did not occur in mice intentionally lacking the APJ gene, confirming that this response is mediated by the APJ receptor. In healthy people, apelin infusion lowers both mean arterial pressure and systemic vascular resistance, while cardiac index is increased [26].

The hypothesis of a dual effect of apelin depending on endothelial status also seems correct. Han et al. observed that apelin has a vasoconstrictive effect on blood vessels with asymmetric endothelial dysfunction induced by dimethylglargin, while it dilates vessels having an intact, healthy endothelium in a control sample. It follows that apelin binding to APJ in normal endothelium is associated with vasodilation and APJ binding in vascular smooth muscle is associated with vasoconstriction [27]. Thus, although apelin exhibits vasodilatory effects, it is also a potent vasoconstrictor when endothelium is deprived.

ROLE IN FLUID HOMEOSTASIS

In a study by De Mota, apelin was found to be a potent diuretic neuropeptide with antivasopressin (AVP) effects, due to inhibition of vasopressin activity and release. Injection of apelin into the ventricles of the brain, in healthy mice, has been shown to reduce plasma AVP concentrations and increase diuresis. On the other hand, dehydration, which leads to increased vasopressin release and depletes hypothalamic AVP stores, simultaneously decreases blood apelin concentrations due to its accumulation in the hypothalamus, indicating that AVP and apelin act in opposition to each other on fluid homeostasis [28]. Hus-Citharel et al. also demonstrated that intravenous boluses of apelin increased urinary excretion in healthy rats, while apelin-deficient HF mice had 2-fold higher blood AVP concentrations than controls [29]. It seems logical that a similar antagonistic relationship exists in humans. Reducing the amount of water in the body and thus increasing plasma osmolality in a healthy population leads to an increase in circulating AVP concentration, while apelin concentration is reduced. In turn, a decrease in plasma osmolality decreases the concentration of circulating AVP, causing a sharp increase in apelin concentration [7].

ROLE OF APELIN IN HF

There are many studies that confirm the beneficial effects of apelin on cardiac function in patients with HF. In ischemic HF, injection of apelin into rats resulted in: increased sarcomere shortening, increased conduction velocity in ventricular myocytes and increased Na+/H+ exchanger. This resulted in increased contractility of the failing heart muscle and a significant increase in left ventricular stroke volume [30]. Jia et al. demonstrated that the use of apelin both improved the performance of damaged myocardium and attenuated the development of HF caused by left ventricular (LV) pressure overload in a group of apelin-treated rats, in which the degree of LV systolic dysfunction was significantly reduced, compared to untreated rats also exposed to LV pressure overload [31]. Ma et al. showed a negative correlation between plasma apelin levels and the prognosis of patients with HF. They observed that apelin levels mainly increase in patients with mild to moderate HF, while they decrease with the transition from moderate to severe HF [32]. Therefore, a study by Jia et al. concluded that the amount of endogenously synthesized apelin was insufficient during severe HF and supplementation with exogenous apelin is more effective [31]. The above fact prompts the use of apelin in the treatment of HF.

The apelin/APJ system shows similar expression to elements of the RAA system and counteracts it by antagonizing AngII activity. Apelin induces a direct interaction between APJ and ATR1 receptors and increases the density of APJ compared to ATR1, resulting in a decrease in ATR1 affinity, thus reducing its interaction with AngII [33]. This may explain the development of cardiovascular disease when the apelinergic system is dysfunctional, unable to counterbalance the deleterious, over-activated RAA system [34].

Apelin, like angiotensin I and II, are substrates for angiotensin-converting enzyme 2 (ACE2), which is a carboxypeptidase that cuts off the terminal fragments of its peptide substrates [35]. There is a relationship between apelin and ACE2, characterized by increased activity and expression of ACE2 in failing hearts in response to apelin treatment [34]. Zhon et al. showed that ACE2 is a major negative regulator of apelin in the blood vessels and heart, as it enhances the degradation of apelin-13 and apelin-17 by cleaving their C-terminal phenylalanine, resulting in the formation of apelin-12 and apelin-16 with negligible cardioprotective effects [36]. Hence, it follows that reduced apelin concentrations are observed in HF, which adversely

affects the effect of treatment, due to its important role in cardiovascular homeostasis.

It is not only the shortening of apelin peptides, by cleaving off the C-terminal fragments, that has a negative effect on the cardiac system. Disruption of the hydrophobic interaction between the C-terminal phenylalanine and the aromatic residues of APJ through chain shortening, alanine substitution or mutagenesis of the receptor's aromatic residues significantly reduces receptor internalization and thus cardioprotective effects. This was demonstrated by Ceraudo in his study [37]. Therefore, the conserved C-terminal 12-amino acid fragment of apelin is essential for proper interaction with the receptor and proper physiological activity [36]. In a recent study, McKinnie et al. identified an enzyme that degrades and inactivates apelin peptides by proteolysis. This is neprilysin metalloprotease (NEP), which represents a new research target in establishing and understanding the mechanisms of NEP inhibition in cardiovascular disease [38]. There are many more studies confirming the positive role of apelin in cardiovascular disease.

THERAPEUTIC APPLICATION

A recent study by Ouyang et al. demonstrated that deterioration of LV mechanoenergetics (mechanical efficiency and ventriculo-arterial coupling) in rats with HF can be improved by apelin treatment. Such an effect is partly due to: inhibition of cardiac fibrosis and LV myocardial necrosis, reduction of collagen deposition in the aorta, and dilation of resistance vessels [21]. The stiffness of the arterial system is characterized by our Ea index, which includes peripheral vascular resistance and arterial compliance, among others, which is an important determinant of LV function and coronary flow. Elevated Ea may result from peripheral vasoconstriction or decreased arterial compliance, or both may occur simultaneously. The same study showed that increased Ea in rats with HF was reversed by apelin treatment. At the same time, higher collagen deposition was observed in the aorta in the untreated HF group, which is consistent with lower arterial compliance determined by the collagen and elastic fiber system. It was found that this condition could also be alleviated by apelin treatment. In addition, it has been confirmed that SW (external mechanical work performed by the LV during one cardiac cycle) increases during apelin treatment, and there is virtually no change in PVA (the index of total LV energy consumption, related to myocardial oxygen consumption), indicating that apelin increases cardiac contractility without significantly altering metabolic demands. We can conclude that apelin is a potentially innovative treatment for patients with HF [39].

Zhang, on the other hand, studied the role of exogenous apelin in rats with myocardial infarction and demonstrated an excellent effect of apelin on microcirculation and angiogenesis as a result of stimulating endothelial cell migration to areas of ischemia, accelerating healing and new vessel formation. In addition, apelin reduces swelling and inflammation in the ischemic area, as a result of reducing vascular permeability. The above data can be translated to ischemic heart disease with subsequent HF, indicating a potential benefit of apelin treatment [40].

The study by Pang et al. further confirms the importance of apelin and its receptor in the development of HF and the potentially beneficial effect of treatment with exogenous apelin in patients with systolic dysfunction. This is because apelin's potent inotropic and vasodilatory effects lead to an increase in cardiac minute volume and a decrease in systemic vascular resistance without significant hypotension and tachycardia [30].

CONCLUSIONS

Apelin was first isolated in 1998, serving as a ligand for the APJ receptor. It is secreted by white adipose tissue, and its expression has been identified in many tissues of the body including the cardiovascular system, kidney, lung, CNS, skeletal muscle, mammary gland, adrenal gland, ovary, stomach, liver cells, placenta and breast milk. However, it is found in the highest concentrations in the endocardium and endothelium of vascular smooth muscle, including the aorta and coronary arteries, which - due to its structural similarity to elements of the RAA system - may suggest its involvement in cardiovascular regulation. Apelin acts in opposition to the RAA system and thus keeps its activation in balance, preventing the harmful effects of AngII on the myocardium. Intense and prolonged activation of RAA deprives apelin of its cardioprotective effect. Many studies emphasize the role of apelin in increasing contractility of the failing myocardium and lowering blood pressure. Apelin is one of the most potent endogenous substances that have a positive inotropic effect on the myocardium, and exhibits a hypotensive effect by affecting vascular wall tone as a result of increased synthesis and release of NO from endothelial cells. In addition, apelin regulates body fluid homeostasis and thus exerts a central hypotensive effect by inhibiting vasopressin synthesis in the suprachiasmatic and paraventricular nuclei. The combined potent inotropic effect and reduction in afterload with vasodilation and increased diuresis suggest that apelin could serve as a great therapeutic option in patients with HF. The benefits that could be derived from apelin include slowing the progression of the disease, reducing complications that occur, and reducing the incidence of hospitalization for uncompensated HF. Previous studies provide evidence that apelin and its receptor are downregulated during the process of myocardial remodeling (ischemia, hypertension), resulting in reduced inotropic, hypotensive and cytoprotective effects. Apelin treatment restores the position of the APJ in the membrane and restores the inotropic mechanism, both in failing and normal hearts. The apelin/APJ system plays a key role in protecting the heart from LV pressure overload injury or structural damage, thereby preventing the development of HF. In addition, apelin has many other beneficial functions in pathological processes. All these facts provide a rationale for the potential benefit of apelin in the treatment of HF, but further studies are needed.

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ORIGINAL ARTICLE

IMPROVEMENT OF THE HEALTH SERVICES FOR THE PREVENTION OF HIV TRANSMISSION FROM MOTHER TO CHILD AT THE LEVEL OF PRIMARY HEALTH CARE

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ABSTRACT

The aim: To analyze the problems of PMTCT of HIV and to clarify the ways for their solving through the increasing their obstetrical and gynecological services at the primary health care level.

Materials and methods: Bibliosemantic, statistical and method of structural and logical analysis. The research materials are the data of the statistical reports for the period 2016-2020.

Conclusions: The analysis of the problems of PMTCT for HIV demonstrated that in Ukraine there is insufficient availability of pregnant women for HIV testing, the excessive duration of the existing algorithm for testing pregnant women for HIV, the imperfect system of referrals of pregnant women for timely diagnosis, as a result, late and therefore less effective the prophylactic antiretroviral therapy (ART), defects in the effectiveness of standardization of health care for the prevention of mother-to-child transmission (PMTCT) of HIV with the participation of primary healthcare specialists, the main representative of which is a general practitioner – family medicine (GP-FD).

KEY WORDS: prevention of HIV transmission from mother to child, HIV infection, pregnant woman, newborn

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INTRODUCTION

The article deals with the relevance of perinatal HIV infection as a solution of its problematic components. In particular, in Ukraine there is an insufficient availability for pregnant women for HIV testing, the excessive duration of the existing algorithm for testing of pregnant women for HIV, the imperfect system of referrals of pregnant women for timely diagnosis, as a result, the late and therefore less effective prophylactic antiretroviral therapy (ART), defects in the effectiveness of standardization of health care for the prevention of mother-to-child transmission (PMTCT) of HIV with the participation of primary healthcare specialists, the main representative of which is a general practitioner – family doctor (GP-FD). The article focuses on the increasing the functions of a family doctor in the organization of obstetric and gynecological services to carry out the prevention of perinatal HIV infection, in particular, testing pregnant women for HIV as early as possible using available methods. The early detection of HIV in pregnant women will lead to earlier starting of antiretroviral therapy (ART), which is much more effective for PMTCT. Such approaches, according to scientists, will bring the achievement of elimination of mother-to-child transmission of HIV according to the WHO Initiative 2014, in which the Global Community committed the elimination of mother-to-child transmission of HIV by 2030 as one of the priorities of the public health system [1].

The problem of human immunodeficiency virus (HIV) infection remains relevant in the society for more than 30 years, the scale of HIV spread has acquired a global aspect and is a real threat to the social and economic developments of the most countries in the world. The epidemic of HIV is one of the most severe among the countries of the Eastern Europe. According to the definition of the World Health Organization (WHO), the results of HIV testing in pregnant women are the proxy indicator of the pathogen spread among the general population [2].

In 2020, the average national indicator of the HIV infection among pregnant women was 0.67 %, according to the results of primary testing, a decrease in HIV infection level among pregnant women was determined from 0.32 % in 2016 to 0.21 % in 2020. The rate of mother-to-child transmission (MTCT) of HIV, based on early diagnosis of HIV infection in newborns, decreased from 2.6 % in 2016 to 1.3 % in 2020. However, according to the results of the cohort analysis in 2020, which is being conducted rate of MTCT in the cohort of children born from HIV-positive women in 2018 was 3.0 %, which is the criterion for not

fully achievement of the level for the elimination of mother-to-child transmission (EMTCT) of HIV in accordance with the WHO Initiative 2014. According to the international recommendations, the achievement of EMTCT validation is based on ensuring universal access to prophylactic, diagnostic and therapeutic measures to prevent perinatal transmission of HIV [1].

Among the main problems of PMTCT of HIV in Ukraine there are an insufficient level of the initiation of antiretroviral prophylaxis (12 %) on the background of the high rate of early registration of pregnant women for the antenatal care (87 %). This can be due, in particular, to the problems with the primary testing of the pregnant women for HIV and the algorithm of informing of pregnant women with the results and the delay of the decision to start ART. Therefore, the availability and the good organization of algorithm of HIV diagnosis in pregnant women is relevant and need to be improved in Ukraine.

THE AIM

The aim of the study is to analyze the problems of PMTCT of HIV and to clarify the ways for their solving through the increasing their obstetrical and gynecological services at the primary health care level.

MATERIALS AND METHODS

Such research methods were used: bibliosemantic, statistical and method of structural and logical analysis. The research materials are the data of the statistical reports for the period 2016-2020.

REVIEW

The analysis based on the statistics data for the period 2016-2020 indicated a high level of rate of mother-to-child transmission of HIV. Thus, the indicator of the MTCT rate of HIV on the background of a decrease remains high and in 2021, according to the results of a cohort analysis, is amounted 2.6 %, which requires increasing the availability of pregnant women to HIV testing through the use of rapid double tests by the family doctor during the first visit on antenatal care.

The problem of perinatal HIV infection in Ukraine is an actual one because of the high index of MTCT rate. During the last years based of the results of polymerase chain reaction (PCR) the implementation of PMTCT measures lead to decrease of MTCT rate of HIV to 2.6 % (2016), 2.2 % (2017), 2.0 % (2018), and 1.6 % (2019), 1.3 % (2020). However, despite of the high coverage of the pregnant women with HIV testing (more than 97 % since 2003), antiretroviral therapy (more than 95 % since 2007), prolongation of ART after childbirth (98 % of women), use of antiretroviral prevention by children which were born from the HIV-positive women (98 %) and artificial feeding of such newborns (99 %), the final index of MTCT rate (at the age of `18 months of the child) in 2020 is high and amounts to 3.0 % [3, 4]. In 2021 (tab. 1) 98.73 % of pregnant women were examined for HIV, HIV infection was diagnosed in 0.52 %, and the incidence of HIV infection in newborns was 28.7 % [5].

According to the general conclusions of WHO, the awareness of the staff of the antenatal health services about HIV status, which was not determined previously or was hidden by a woman from the medical staff, is a necessary condition for the decreasing of MTCT rate of HIV to the level less than 1 %. In addition, it is an important moment to start treatment and provide health care to HIV-positive pregnant women and their children. The aim of the antenatal screening for HIV is the detection of all HIV-positive pregnant women as early as possible for providing the measures for PMTCT and to minimize the risk of transmission of the virus to the child during pregnancy, childbirth and postpartum period [6, 7], namely, the early diagnosis of HIV infection is provided by the optimal time for this – the first trimester of pregnancy [8].

Today, with a much higher level of effectiveness, WHO recommends rapid testing for HIV with simultaneous rapid testing for syphilis as two perinatal infections (HIV/syphilis) as the first test in the strategy and algorithm of HIV testing during pregnancy monitoring. The use of dual rapid tests for the simultaneous diagnosis of HIV and syphilis provides an opportunity to immediately reduce the difference between the coverage of HIV and syphilis testing among pregnant women in order to eliminate adverse consequences. The use of dual tests allows to test for both infections with a single finger prick. The results are ready quickly, it allows women to start treatment in time.

It was determined that in both high- and low HIV epidemic countries the dual testing for HIV/syphilis allows to save the costs for congenital syphilis prevention and has no negative influence on HIV testing coverage, helps to reduce the storage and transporting costs of the samples. According to the results of many researches the dual HIV/syphilis tests have a sensitivity more than 99 % and a specificity of 100 %, the treponema component has a sensitivity more than 90 % and a specificity more than 96 % [9].

In Ukraine, the analysis of the effectiveness of the dual rapid tests for express testing for HIV and syphilis in female dispensaries and obstetrical hospitals as a pilot project was carried out with our participation.

The study of the feasibility of implementation in Ukraine the use of the dual rapid (express) tests for HIV and syphilis diagnosis in the ambulance obstetrical health care institutions was provided because of the constant different rate between the coverage of testing for HIV and syphilis among pregnant women (in 2020 – 99.1 % and 92.3 %, respectively). However, over the last 10 years 40 000 new cases of syphilis have been registered in the country. The majority of patients were diagnosed late and unspecified forms of syphilis, the frequency of such patients increased from 70 % in 2010 to 85 % in 2020; the 4th generation test systems (Ag+Ab) are used for the screening for HIV in the pregnant women in the country in accordance with the order No 794 of the Ministry of Health of Ukraine dated

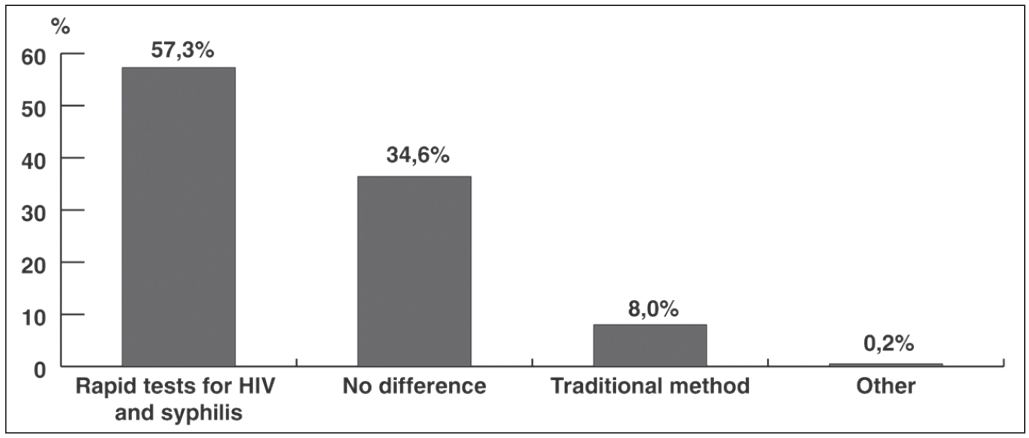

Fig. 1. The distribution of the participants' answers to the question "By which method would you like to be tested in the future – traditional laboratory method (blood from the vein) or rapid test?"

Table I. HIV screening of pregnant women and newborns in Ukraine, 2021 year

Indicator	Number of persons who were examined for HIV									
	The total number		Including twins		Persons with positive HIV-status		Number of persons who had childbirth			
							Ill newborns		Healthy newborns	
	abs. number	per 100 pregnant women	abs. number	per 100 pregnant women	abs. number	per 100 pregnant women	abs. number	per 100 pregnant women with HIV+status	abs. number	per 100 pregnant women with HIV+status
Ukraine	247020	98.73	239099	95.56	1292	0.52	371	28.72	647	50.08

Table II. The detection of HIV infection and syphilis based on the testing with instrumental method

Pathogen	Number of negative results	Number of positive results	Detected, %	95% CI
HIV (n=1496)	1493	3	0.2	0.04 – 0.58
Syphilis (n=1488)	1485	3	0.2	0.04 – 0.59

Table III. Evaluation of the effectiveness of HIV testing with the use of rapid tests for HIV/syphilis

Accuracy of tests results with the use of rapid tests for HIV/syphilis	Reference result (true HIV status)		Total
	Positive	Negative	
Positive	3 (a – true positive)	0 (b - false positive)	3
Negative	0 (c – false negative)	1493 (d – true negative)	1493
Total	3	1493	1496

Notes: Sensitivity = a/(a+c) = 3 / (3 +0) *100 = 100 % (95 % CI 0.292- 1.00)
Specificity = d/(b+d) =1493 / (0 + 1493)*100 = 100 % (95 % CI 0.998 – 1.00)
PPV = a/(a+b) = 3 / (3 + 0)*100= 100% (95 % CI 0.292 – 1.00)
NPV = d/(c+d) = 1493 / (0 + 1493)*100 = 100 % (95 % CI 0.998 – 1.00)

Table IV. Evaluation of the effectiveness of syphilis testing with the use of rapid tests for HIV/syphilis

Accuracy of tests results with the use of rapid tests for HIV/syphilis	Reference result (true syphilis status)		Total
	Positive	Positive	
Positive	2 (a – true positive)	1 (b - false positive)	3
Negative	1 (c – false negative)	1484 (d – true negative)	1485
Total	3	1485	1488

Notes: Sensitivity = a / (a+c) = 2 / (2 + 1)*100 =66,7 % (95% CI 0.094 – 0.992)
Specificity = d / (b+d) =1484 / (1 + 1484)*100 = 99,9 % (95% CI 0.996 – 1.00)
PPV = a / (a+b) = 2 (2 + 1)*100= 66.7 % (95% CI 0.094 – 0.992)
NPV = d / (c+d) = 1484 / (1 + 1484)*100 = 99.9 % (95% CI 0.996 – 1.00)

05.04.2019 which makes impossible to standardize the use of dual rapid tests for HIV and syphilis during the first visit of the pregnant women for the pregnancy monitoring according the WHO recommendations.

According to the Project program, the medical specialists had a one-day training how to use rapid tests, explained in detail to pregnant women about the rapid testing and its benefits, and the majority of pregnant women (57 %) after screening testing with rapid tests for HIV and syphilis indicated the comfort of the method. And only 8 % of the women preferred the routine method of laboratory examination (Fig. 1).

The specialists determined that rapid tests are easy to use, as well as a reduction of the time and number of the necessary examinations in the cases with negative results.

The performance indicators of the screening test for HIV and syphilis with the use of the rapid dual teats for HIV/syphilis and the routing testing with instrumental method (IM) were calculated among women who were tested both with IM and rapid tests: HIV – 1496 women, syphilis – 1488 women. The final result is considered with the IM use.

The prevalence rates were: HIV – 0.2 % (95 % CI 0.04 – 0.58) and syphilis 0.2% (95 % CI 0.04 – 0.59 (Table II).

The indicators of the sensivity, specificity and significance of the positive and negative predictive values (PPV and NPV, respectively) of the screening testing results with rapid tests for HIV/syphilis are presented in tab. III for HIV and tab. IV for syphilis.

Thus, the corresponding indicators of screening testing for HIV with the use of rapid tests for HIV/syphilis were: sensitivity – 100 % (95 % CI 0.292-1.00), specificity – 100 % (95 % CI 0.998 – 1.00), PPV – 100 % (95 % CI 0.292 – 1.00) and NPV – 100 % (95 % CI 0.998 – 1.00).

Thus, the corresponding indicators of screening testing for syphilis with the use of rapid tests for HIV/syphilis were: sensitivity – 66.7 % (95 % CI 0.094 – 0.992), specificity – 99.9 % (95 % CI 0.996 – 1.00), PPV – 66.7 % (95 % CI 0.094 – 0.992), NPV – 99.9 % (95 % CI 0.996 – 1.00) (table IV).

Thus, the obtained results of the study allow to use the rapid tests for HIV/syphilis for the diagnosis of these diseases by the doctor during the first visit of the pregnant women and pregnancy monitoring, in particular, by a family doctor. The use of the rapid tests for HIV/syphilis improves the availability of pregnant women to high-quality examination, which lead to effective screening of pregnant women for these infections and prescribe the treatment in more early terms of pregnancy, this approach decreases the rate of perinatal infection, in particular, HIV-infection.

WHO recommended the screening for all pregnant women for HIV and syphilis during the first antenatal visit which is provided almost in all countries in the world. WHO has published new recommendations to help countries to reach coverage for testing of 8.1 million people with non-diagnosed HIV infection and persons who do not have an access to life-saving treatment. HIV testing is very important for early diagnosis and early treatment. Quality HIV testing services also involves to provide the effective services for HIV-negative patients for prevention facilities as a primary health care servicers by a family doctor as a doctor of the first visit of the pregnant woman during pregnancy monitoring. This will help to reduce the number of new HIV-infected individuals, which is amounted 1.7 million persons per years worldwide. In particular, the use of combined express-tests for HIV/syphilis as the first test for HIV during antenatal care can help the countries to eliminate the mother-to-child transmission of these infections. This can help to reduce the defects in the diagnosis and treatment and to stop the second leading cause of the reason of stillbirth in the world [10].

Although the HIV-testing should be voluntary, it is clear that the standardization of HIV-testing as an important part of prenatal care and health care of medical services of HIV-infected women, has a significant meaning for the improvement the assess for health care [3]. HIV-positive pregnant women must have an assess to professional antenatal care during pregnancy and the use of effective medical technologies of PMTCT.

Taking into account the need to standardize the health care for the prevention of mother-to-child transmission of HIV, Medical Care Standards "Prevention of Mother-to-Child HIV Transmission", which standardizes HIV screening with dual rapid tests, namely, rapid tests for HIV/syphilis, were developed in Ukraine [11]. The standards provide global approaches to PMTCT that HIV-positive pregnant women should have an access to high-quality prenatal medical care during pregnancy monitoring and to the use of effective PMTCT medical technologies. The most important component of the prevention of vertical transmission of HIV is to ensure the involvement of women in health care, that involves the use of medical interventions based on a multidisciplinary approach and the provision of complex complete support that prevents the transmission of HIV from mother to child.

Early diagnosis of HIV infection in pregnant women will help to prevent the transmission of HIV from mother to child. Unified and standardized algorithms of HIV testing services for pregnant women will contribute to expanding access to HIV testing by medical institutions and increasing the coverage of pregnant women with such services. All pregnant women are tested for HIV during their first antenatal care visit (screening). HIV testing with a rapid test as a screening for the simultaneous detection of serological markers of HIV and syphilis are performed.

In the case of the negative result of the second HIV test in pregnant women with high risk for HIV infection, namely, a woman from a serological discordant couple (HIV-negative pregnant woman, HIV-positive partner); persons who inject grugs; a woman who has a new sexual partner with unknown HIV-status; a woman with sexually transmitted infections is tested for the third time to identify the serological markers of HIV in 32-36 weeks of pregnancy or during childbirth by instrumental methods or rapid (express) tests.

Pregnant women with unknown HIV-status or who are HIV-negative from serological discordant couple, if the HIV-positive partner is not virologically suppressed and/or

does not receive ART, the HIV-testing is performed during the third trimester of pregnancy. If HIV is diagnosed, ART is prescribed to pregnant woman for HIV treatment and prevention of the vertical HIV transmission.

DISCUSSION

Thus, the standardization of PMTCT for HIV according to world best practices will contribute to overcoming the spread of HIV infection among the general population as well. According to the estimated data of the Joint Program of the United Nations Organization on HIV/AIDS (UNAIDS), the total number of people with HIV in the world at the beginning of 2020 reached 38.0 million people, of which – 36.2 million adults and 1.8 million children under 15 years of age. 73 % of women, 85 % of pregnant women with HIV and 53 % of children living with HIV have access to ART. PMTCT interventions have contributed to the prevention of 1.6 million new cases of HIV infection among children since 2000 [16-18].

The region of Eastern Europe and Central Asia (EECA), to which Ukraine belongs, is one of the three regions in the world where the HIV epidemic continues to grow. The increase in cases of HIV infection by sexual transmission and the active involvement of women of childbearing age in the epidemic process are a serious risk for perinatal HIV infection in EECA [18, 19].

According to the WHO definition, the results of HIV testing of pregnant women are a proxy indicator of the spread of the pathogen among the general population. In the conditions of the concentrated stage of the epidemic, the spread of HIV among pregnant women from 1.0 % and above is considered high and indicates a tendency towards the generalization of the epidemic [18, 20].

The PMTCT program has become one of the most successful programs to counter the HIV epidemic in Ukraine due to the coverage of pregnant women with HIV testing at the level 97 %, antiretroviral treatment – more than 95 %, prolongation of ART after childbirth – in 98 % cases, antiretroviral prophylaxis – 98 %, and the organization of artificial feeding of children born from the HIV-positive women – 99 % [21, 22]. The principles of the four-pronged strategy for PMTCT and reducing child mortality, proposed by WHO/UNICEF/Population Fund in 2001, are still relevant today. The widespread implementation of the PMTCT program on a global scale has proven that this is facilitated by: i) primary prevention of HIV infection; ii) the prevention of unwanted pregnancies among women living with HIV; iii) the access to testing, counseling, ART, safe birth practices and appropriate newborn feeding practices and iv) in the case of the birth of a child who inherited the virus, providing care and support to HIV-positive mothers, their children and their families [21, 23].

The screening of all pregnant women for HIV and syphilis at the first prenatal visit, recommended by WHO, is carried out in almost all countries of the world. The use of tests for the simultaneous diagnosis of HIV and syphilis makes possible to immediately close the gap between HIV and syphilis testing coverage among pregnant women in order to eliminate adverse consequences. Using double tests makes possible to test for both infections with one finger prick. The results are ready quickly, which allows women to start treatment for HIV infection and syphilis in a timely manner [24, 25].

The World Health Organization has published new guidelines to help countries to reach the 8.1 million people living with undiagnosed HIV infection who lack access to life-saving treatment. HIV testing is very important to ensure early diagnosis and early treatment [26, 27]. Quality HIV testing services also involve providing HIV-negative patients with effective prevention services. This will help to reduce the number of new cases of HIV infection, which today is 1.7 million per year. WHO's "Consolidated Guide to HIV Testing Services" provides recommendations for innovative approaches to meet current needs [28, 30], in particular, the use of combined rapid HIV/syphilis tests as the first HIV test within antenatal care can help countries to eliminate mother-to-child transmission of these infections. This could close the gap in diagnosis and treatment and eliminate the second leading cause of stillbirth worldwide [29, 31].

CONCLUSIONS

The analysis of the problems of PMTCT for HIV demonstrated that in Ukraine there is insufficient availability of pregnant women for HIV testing, the excessive duration of the existing algorithm for testing pregnant women for HIV, the imperfect system of referrals of pregnant women for timely diagnosis, as a result, late and therefore less effective the prophylactic antiretroviral therapy (ART), defects in the effectiveness of standardization of health care for the prevention of mother-to-child transmission (PMTCT) of HIV with the participation of primary healthcare specialists, the main representative of which is a general practitioner – family medicine (GP-FD).

The increasing the family doctor's functions in obstetrics and gynecology services for the prevention of perinatal HIV infection through HIV screening of pregnant women with the use of rapid dual tests for HIV/syphilis during the first visit to the doctor for pregnancy care. This makes a possibility to reduce the time for examination as early as possible and, in case of detection of HIV infection, to use prophylactic ART, which increases the effectiveness of PMTCT and the elimination of cases of perinatal HIV infection in Ukraine.

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ORIGINAL ARTICLE

REPERFUSION INJURY IN ACUTE PERIOD OF MYOCARDIAL INFARCTION – WAYS OF PREVENTION AND CORRECTION

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ABSTRACT

The aim: To identify pathophysiological peculiarities of myocardial reperfusion injury and ways of its reduction based on the literature data analysis.

Materials and methots: This literature review was made by searching the PubMed database using key words . Additional data were sought in the Google search engine by entering key words: " risk factors, ischemic heart disease, arrhythmia, sudden cardiac death, heart rhythm, heart failure." in the Polish, English, Russian and Ukrainian language versions

Conclusions: Considering conducted data analysis, provided data indicate the prospects of phosphocreatine usage in treatment scheme of heart rhythm disorders and heart failure on the background of myocardial ischemia and elimination of reperfusion injury and myocardial remodeling consequences.

KEY WORDS: risk factors, ischemic heart disease, arrhythmia, sudden cardiac death, heart rhythm, heart failure

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INTRODUCTION

The most common reason of sudden cardiac death (SCD) is the acute coronary syndrome (ACS), and in 25% of patients with IHD, who died suddenly, SCD was the first and only manifestation of the disease [1,2]. SCD takes 40-50% of death cases in patients with cardiovascular insufficiency [3]. In postinfarction patients with high risk (EMIAT, CAMIAT, TRACE, SWORD, DINAMIT trials data), total arrhythmic mortality reaches nearly 5% during a year and during two years, while non-arrhythmic cardiac mortality equals 4% and 7% correspondingly [4-6]. One of the main predictors of SCD is acute heart failure (AHF) [7]. Despite all successes, achieved in the treatment of chronic HF, annually in the USA, the diagnosis of AHF while discharging from the hospital is registered in almost 1 million cases and in 3 million cases – as the concomitant diagnosis [7, 8]. Frequency of early rehospitalizations due to HF decompensation is still high and is near 20% during 30 days after discharge, and almost 50% – during 6 months [9, 10]. Also, during last two decades, 30-day mortality because of AHF is still unchanged and equals >10% [3]. Nowadays, intrahospital mortality in case of acute decompensated heart failure is 4-8%, and in 6 months – is almost 25-30%. Mean duration of treatment lasts for 4-6 days [11]. These date are confirmed by large Registries, such as Acute Decompensate Heart Failure National registry (ADHERE, 2014), Euro Heart Survey Program, 2014 [12, 13].

THE AIM

The aim of this work was to identify pathophysiological peculiarities of myocardial reperfusion injury and ways of its reduction based on the literature data analysis.

MATERIALS AND METHOTS

This literature review was made by searching the PubMed database using key words. Additional data were sought in the Google search engine by entering key words: "risk factors, ischemic heart disease, arrhythmia, sudden cardiac death, heart rhythm, heart failure." in the Polish, English, Russian and Ukrainian language versions

REVIEW AND DISCUSSION

Despite the essential improvements of the myocardial reperfusion techniques (transradial access, implementation of drug-eluting stents, development of biodegradable stents, usage of novel antithrombotic drugs), it was established, that the restoration of the coronary bloodflow itself for the myocardial salvage, can paradoxically launch the process of myocardial injury, enlarging the lesion site in the meantime – so called reperfusion injury phenomenon [14, 15]. Main pathogenetic reason of mortality in case of IHD is the myocardial reperfusion injury (MRI) [16]. MRI manifests itself as: myocardial contractile dysfunction (stunned myocardium); lac of bloodflow restoration on the tissue level (no-reflow syndrome); reperfusion arrhythmias; accelerated cardiomyocyte necrosis, function of which was impaired [16]. According to data, the reperfusion injury itself provokes nearly 50% of the final necrosis area in case of acute MI [17]. Insufficient supplement of myocardium with oxygen leads to the depletion of endogenous adenosine triphosphate (ATP), what is crucial for maintaining cellular homeostasis. Energetic methabolsim of cardiomyocytes depends on the acetyl coenzyme A, which is generated via aerobic/anaerobic glycolysis of β-oxidation of fatty acids and then is

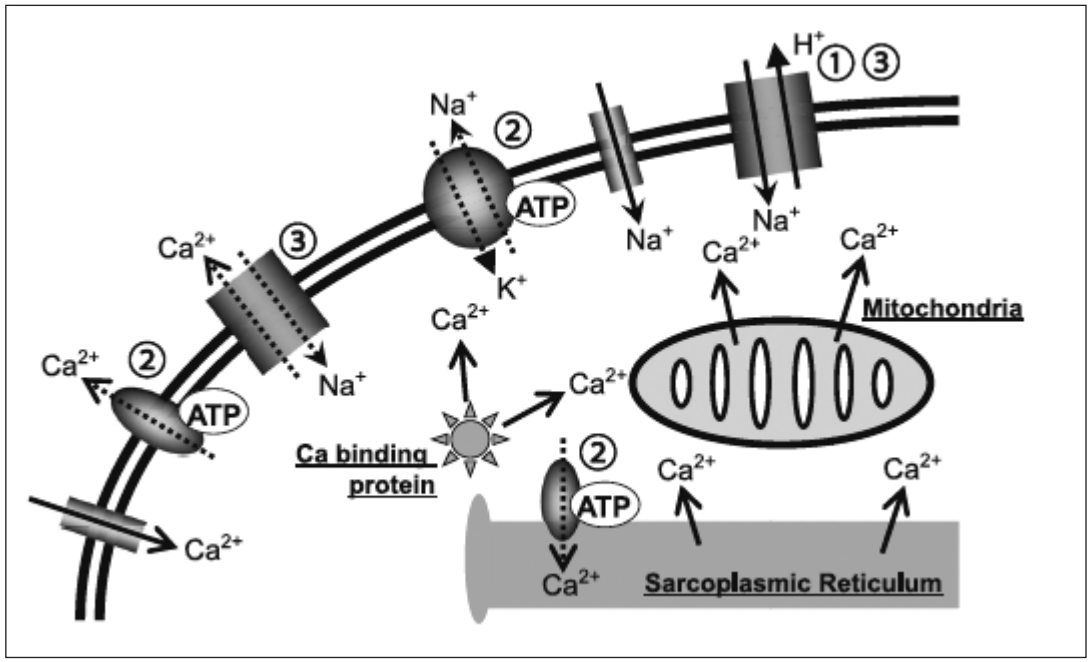

Fig.1. Schematic picture of ion movement while myocardial ischemia. 1) Excretion of the H+ due to decrease of pH; 2) deactivation of ion movement due to ATP depletion 3) decrease of Na+/Ca++ transition due to lowered extracellular pH and intercellular accumulation of Na+ (adapted by S. Sanada, I. Komuro, M. Kitakaze, 2011) [24].

metabolized in the Krebs cycle [18]. Cardiomyocytes are incredibly rich with mitochondria, because of high consumption of endogenous ATP. In the meantime, myocardial demand in ATP completely can be fulfilled only via aerobic glycolysis [19]. Decrease of oxygen supply in the ischemic myocardium leads to fast depletion of the endogenous ATP stockpiles, what makes myocardium even more exposed to ischemia [20]. In the basis of the MRI development, there are following connected mechanisms, so called paradoxes. Unfavorable effects of reoxygenation of ischemic tissue are connected with the free oxygen radicals' formation («oxygen paradox»). There is sufficient scientific base, which proves that restoration of the passage via occluded artery leads to the intensification of superoxide anion O_2^- formation, which damages the myocardial fibers alongside with other active oxygen form, that are already affected by the ischemia [21].

Hence, these products induce the apoptosis process, and their interaction with the nitrogen oxide (NO) leads to formation of the peroxynitrite-anion ($ONOO^-$), which worsens the negative influence on the myocardium [22]. From the other side, it is proved, that superoxide-associated injury can be leveled with the help of conversion of superoxide-anion into hydrogen peroxide H_2O_2 (via superoxide dismutase) [23]. But, in presence of Fe^{++} and Cu^{++} ions, H_2O_2 can transform into hydroxyl-anion (HO^-), which is more toxic, than O_2^- or H_2O_2, and can also worsen the toxic influence on the myocardium [24]. Further activation of the anaerobic glycolysis leads to the production and stockpiling of the lactate that leads to the decrease of extra- and intracellular pH. For the correction of such violation, Na^+ ions move inside the cell, whilst H^+ ions move outside from the cell. Increase of the intracellular concentration of Na+ (which is normally extracellular ion) is also corrected endogenously via transport of Ca^{++} ions inside the cell, and extraction of the Na^+ ions in the intercellular space [25]

The other, but not less important moment of the reperfusion injury phenomenon, is the so called «Calcium paradox» [26]. It is proved, that immediately after the ischemia beginning, so called calcium overload of cardiomyocytes appears, that worsens while the reperfusion. Calcium overload leads to an increase of intracellular osmolality, what causes the cardiomyocite swelling as the result. Hence, the excess of the Ca^{++} ions results in an increase of proapoptic factors expression by mitochondria [27]. It is worth noting, that violation of the transmembrane movement of Ca^{++} ions may lead to the structural «fragility» of cardiomyocytes, their excessive contractility [28]. Literature describes the data about Ca++ overload of cardiomyocytes may play significant role in apoptosis launch, and this happens because procaspase-8 converting into active caspase-8, activation of the Bax-protein (BLC2- associated X apoptosis regulator), what leads to the release of apoptosis-inducing factor (Smac-protein) and, as a result, cytochrome C from the mitochondria [29]. Noted apoptosis-inducing factor translocates inside the cardiomyocyte nucleus, where mediates non-specific DNA fragmentation. Herewith, Smac-protein inactivates connected with the X-chromosome protein-inhibitor of the apoptosis, which in turn inactivates caspase-3. Finally, cytochrome C forms an apoptosomic complex with the procaspase-9 and apoptic protease-activating factor-1, that binds the caspase-9 [30]. Mechanic injury of the cardiomyocytes in case of invasive procedures increases in 3 times (so called «mechanical paradox») [31].

Together, all noted mechanisms and reactions lead to inevitable cellular dysfunction. Result of the continuous ischemia is stockpiling of the toxic metabolites, increase of cytoplasmic calcium concentration, cardiomyocyte swelling. These factors in the end lead to mitochondrial pores opening, which regulate the permeability of the mitochondrial internal membrane (mitochondrial permeability transition pore, mPTP), that results in proapoptic factors release, which trigger programmed cellular death. Together with existing oxygen radicals, which worsen inflammatory response, this entire complex worsens myocardial injury [32]. All noted mechanisms and leukocyte/

thrombocyte adhesion to the endothelium surface can cause one more phenomenon – «no-reflow» [33].

Main pathogenetic mechanism of cardiomyocyte apoptosis in case of ischemia is the opening of mPTP that results in mitochondrial dysfunction [34]. Mitochondrial PTP is formed by the protein complex of internal and external mitochondrial membrane. Its opening happens during certain cases that are followed by energetic deficit (stroke, MI, muscular dystrophy, hepatic encephalopathy, cranial trauma) [35]. It was identified, that on the area of cytotoxic damage of the heart muscle, ultrastructural changes occur in the biggest part of the neural fibers [36]. Destruction of the neural terminals, enlightening of the cytoplasm, mitochondrial swelling, decrease of the number of the mediator vesicles in the synaptic structures, loss of the membrane contour clearness were observed [37]. Alongside noted changes, cardiogenic depressor reflexes from the injured heart side weakened, such as Bezold-Jarisch reflex, what led to depressor reaction of the vagal nerves and reflective bradycardia, significant decrease of the antifibrillatory activity of the vegetative nervous system [38]. So, the cardoimyocyte destiny depends on the stage and duration of the mPTP opening and ATP pool restoration [39]. While ischemia lasts, mPTP is closed, and opens as soon as tissue bloodflow restores. In case of internal membrane opening, fall of the potential between external and internal environment is observed, fluid admission into the mitochondrial matrix, mitochondrial swelling and external membrane rupture [40]. This, in turn, leads to the malfunction of the «breathing chain», release of the cytochrome C, apoptic factors, and ATP hydrolysis is overwhelming over synthesis, that results in cell death [41].

Researches from the last years give the basis to think that the whole specter of biologically active substances that conduct specific regulative functions in organism can serve as endogenous cardioprotectors [11, 23, 40, 42]. They include insulin – main regulator of the carbohydrate metabolism; sodium uretic peptides, that regulate renal function and fluid volume in the organism; big family of heat shock proteins and phosphocreatine (PC) [42]. PC acts as energy transporter in the myocardium and skeletal muscles and is used for ATP synthesis that provides energetics for muscular contractions [40]. Providing normal myocardial function in case of slowed oxidative processes (metabolism) is the focal point of PC action in myocardial cells damage in hypoxic conditions (insufficient tissues supply with oxygen and disorders of its assimilation) and ischemia (disparity between oxygen delivery and demand) [6, 32].

According to the numerous multicenter studies, PC inhibits whole specter of enzymes (5-nucleotidase, phosphatases), which participate in ATP splitting [25]. This promotes preserving of the membrane ATP pool in plasmatic membrane and preserving functions of membranotropic enzymes (Na/K-ATP-ase, Ca-ATP-ase), what, in turn, normalizes transmembrane processes while myocardial ischemia [44]. Secondly, PC acts as inhibitor of catabolic enzymes, such as phospholipase, interrupting the deposition of fatty acids and such arrhythmogenic substances as lysophospholipids [14]. PC has expressed antiischemic, antiarrhythmic and antioxidant action [43]. Moreover, PC has antiagregant activity, increases oxygen capacity of blood, has mild diuretic action [31]. So, PC influences onto the main pathogenetic mechanisms of myocardial ischemia development – spasm, thrombosis, and reduced endotheliocytes swelling (what makes it stand out of other antiischemic, antiarrhythmic drugs), reduces spasm of coronary arteries, enhances the bloodflow of the heart conduction system [45]. In case of systemic hypoxia, PC acts as renal protector, enhances microcirculation [20]. PC significantly decreases activity of such pathogenic substances as leukotrienes, which have vasoconstrictive, proagregant and chemotactive abilities that promote neutrophils accumulation in the heart damage site [17]. Since lipooxigenases activation, as neutrophils accumulation are powerful pro-oxidant mechanisms, there is a basis to state, that PC has antioxidant effect and stops peroxidation of the lipids, including membrane phospholipids [44].

Among the most significant effects of exogenous PC should be noted:

- antiplatelet effect – is realized in the systemic bloodstream by inhibiting the degradation of ATP with the formation of a strong proaggregator ADP;
- improves microcirculation by increasing the plasticity of erythrocytes and their ability to penetrate into thin capillaries;
- antiarrhythmic effect associated with inhibition of phospholipid degradation of cell membranes and accumulation of lysophosphoglycerides (substances with arrhythmogenic potential) in the myocardium;
- positive indirect action (not related to the role of FC as a direct source of energy for muscle contractions) effect on the contractile function of the heart, is realized through the preservation of adenine cellular reserves during ischemia due to blockade of the enzyme sarcolemma 5-nuclease and associated processes of ADP degradation to adenine and excretion of adenine from cells [32, 40].

Thus, it should be assumed that the cardioprotective potential of phosphocreatine is due to inhibition of catabolic enzymes (phospholipases, lipoxygenases, 5-nucleotidases and others), which, firstly, helps to maintain or reduce disturbances in the structure, function of membranes, prevents uncontrolled intracontrol formation of hypercontractures of the myofibrillar apparatus, secondly, reduces the formation of coronary constrictor, arrhythmogenic, proaggregative and chemoactive neutrophils, biologically active substances (leukotrienes and lysophospholipids), thirdly, also inhibits the formation of free radicals. , fourthly, it preserves the functions of the endothelium, which determines the possibility of compensatory reactions due to the preservation of nitric oxide production (dilation of blood vessels, antiplatelet effect) [44, 45].

A number of studies have shown that exogenous PC has antiarrhythmic activity, prevents the development of ventricular fibrillation in experimental acute myocardial ischemia [32, 40, 42]. It is known that in acute ischemia the rate of excitation is reduced, and there is a significant heterogeneity of the refractory periods of the heart muscle, which leads to the formation of foci of excitation circulation. According to scientific studies, PC in acute coronary occlusion increases the rate of propagation of excitation in the ischemia and thus prevents the occurrence of the re-entry foci [47]. In a series of experiments to study the electrophysiological mechanisms of antiarrhythmic action

of exogenous PC investigated the membrane-ionic effect of the drug on myocardial cells. It was found that it inhibits fast sodium input current and slow calcium current input through the cardiomyocyte membrane and therefore has an original electrophysiological effect that combines the properties of class I and IV antiarrhythmic drugs [24].

A number of clinical domestic and foreign studies have confirmed the possibility of using PC as an effective treatment for myocardial infarction to reduce the incidence of life-threatening arrhythmias, heart failure, heart failure with a tendency to reduce mortality [6, 8, 42, 44]. It is shown that the use of PC no later than 6 hours after the onset of acute coronary syndrome has a powerful antiarrhythmic effect on both ischemic and reperfusion arrhythmias [47]. The results of a multicenter study of Italian scientists on the use of FC in acute myocardial infarction confirmed the rapid normalization of the ST segment and a significant reduction in the complexity of ventricular arrhythmias in patients receiving PC within the first hour after symptoms of acute myocardial infarction [32].

CONCLUSIONS

Considering conducted data analysis, provided data indicate the prospects of phosphocreatine usage in treatment scheme of heart rhythm disorders and heart failure on the background of myocardial ischemia and elimination of reperfusion injury and myocardial remodeling consequences. These data indicate both the prospects for the use of PC in the treatment of patients with cardiac arrhythmias on the background of myocardial ischemia, and the need for further research to determine its place among other cardiac pharmacological drugs.

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ORIGINAL ARTICLE

THE HUMAN RIGHT TO TRANSPLANTATION OF ORGANS AND TISSUES: MEDICINE, ETHICS AND LAW

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ABSTRACT

The aim: To study the combination of medical, legal, ethical principles and regulations in the field of transplantology, as one of the key problems of bioethics.

Materials and methods: Formal-logical methods of analysis and synthesis allowed to reveal the content of the concepts that make up the subject of research, to classify them, as well as to formulate intermediate and general conclusions. The systematic method allowed to study the role and significance of human right to transplantation among other somatic human and civil rights and freedoms. Using the historical method, the doctrinal basis of the study was analyzed, and the main stages of the formation of human right to transplantation were identified.

Conclusions: The level of modern development of the Institute of Transplantology depends primarily on the tolerance of the society itself regarding the concept of brain death. The actual normalization of the concept of death in one or another state determines the level of realization of the human right to organ and tissue transplantation. Regarding the reform of the current legislation in the field of transplantology, as one of the key problems of bioethics, first of all, moral principles should be taken into account (at the same time, today morality in its development is even slightly ahead of the development of international law, although progressive principles of legal regulation of transplantation processes have been distinguished at the international level). Therefore, during the development of norms of both international and national law regarding transplantology, existing moral principles should be taken as a basis. At the same time, one should not forget that a necessary factor is the presentation of a number of issues for public discussion, as well as their discussion at scientific and practical conferences not only of doctors and lawyers, but also of theologians and philosophers.

KEY WORDS: human rights and freedoms, fourth generation human rights, somatic human rights, medicine, ethical principles, transplantology

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INTRODUCTION

The sphere of health care is a paradigm that connects all countries of the world, is established in international standards and is reflected in various legal systems and legislation. According to statistics, in Ukraine, more than 90,000 people of various ages need transplant surgery, the vast majority will die without timely help. There are qualified doctors in Ukraine, there are potential donors, but this branch of medicine is developing very slowly. Modern needs in the transplantation of anatomical materials to a person, legal support and prevention of crimes in this area require comprehensive scientific and practical research. In addition, the right to life and health, which can be ensured by transplanting the recipient of anatomical materials, borders on the ethical norms related to donation, especially in relation to a cadaver donor. The balance between medicine, law and ethical norms is quite sensitive. The complexity of the combination of medical, legal, ethical, social and other issues along with different approaches of legal regulation in the field of transplantology increases the relevance of this research [1].

THE AIM

The aim was to study the combination of medical, legal, ethical principles and regulations in the field of transplantology, as one of the key problems of bioethics.

MATERIALS AND METHODS

Formal-logical methods of analysis and synthesis allowed to reveal the content of the concepts that make up the subject of research, to classify them, as well as to formulate intermediate and general conclusions. The systematic method allowed to study the role and significance of human right to transplantation among other somatic human and civil rights and freedoms. Using the historical method, the doctrinal basis of the study was analyzed, and the main stages of the formation of human right to transplantation were identified.

REVIEW AND DISCUSSION

Somatic rights also include the right to transplant organs, which at the same time is one of the key issues of bioethics. Transplantology as a science is a progressive section of medicine that is developing significantly and which inevitably poses a new volume of ethical, medical and legal issues to the world community. At the same time, if other key issues of bioethics (euthanasia, abortion) have been devoted to a significant number of scientific works, sociological surveys and public discussions, then the issue of transplantation, in our opinion, is given rather insignificant attention.

In the course of the medical reform on May 17, 2018, V. Pishta notes, the Verkhovna Rada of Ukraine adopted the Law "On the Application of Transplantation of Anatomic Materials to Humans". The adoption of the new law, the scientist notes, is due to the inefficiency and actual absence of transplantation as a systemic phenomenon in Ukraine, as indicated by the ratio between the need for organ transplants and the actual number of transplants carried out in Ukraine. Therefore, the new law should contribute to the improvement of the transplantation system in Ukraine and create appropriate legal conditions for its full functioning. Thus, V. Pishta points out, among the innovations of the Law of Ukraine "On the Application of Transplantation of Human Anatomical Materials", it is worth highlighting such as: the introduction of cross-donation, the introduction of the Unified Transplantation Information System, the introduction of the Institute of the Authorized Representative, and the definition of the list of subjects of state administration in the field of transplantation [2].

Transplantology is a branch of medicine that studies not only the problems of organ and tissue transplantation, but also the development of methods of organ preservation, as well as the creation and use in practical medicine of various artificial organs and tissues, the use of which allows to weaken, and sometimes solve the problem of the shortage of donor organs [3]. Thus, scientists L. Sharkov, A. Kupchenko, V. Stanovenko write, transplantology has become a branch of medicine that has concentrated the latest achievements of surgery, anesthesiology, resuscitation, immunology, pharmacology and other medical and biological sciences. Thanks to this, in transplantology, the latest medical technologies of the highest category of complexity have been developed, which at the same time have found wide application in other fields of practical medicine [4].

However, there are many more problems in transplantology, first of all, ethical ones, which arise as a result of manipulations with the human body, both living and dead. When transplanting organs and tissues, two very important moments of a person's life are inextricably linked: it is the probable death of the patient in the absence of the possibility of replacing a viable organ, or the death of a person whose body can become a donor or the threat of losing the physical health of a living donor [4]. The further development of transplantology has certain limitations, both of a medical and ethical and legal nature. The successes of biomedicine in organ transplantation do not relieve the moral and ethical tension surrounding this type of medical activity.

Transplantology, V. Pishta rightly notes, at the current stage of development is one of the leading branches of medicine, which relies on the achievements of modern science in various fields. The connection of transplantology with experimental and clinical surgery, conservation of donor organs, genetic engineering, immunogenetics, transplant immunology, biomechanics, cardiac surgery is most closely traced. Thanks to organ transplantation, more than one human life can be saved. This is confirmed by the statistical data of one of the leading countries in the field of transplantation – the USA. For example, in 2016, 33611 operations were performed in the United States of America. This fact indicates the demand for transplantation in modern society. Some modern scientists call transplantation a symbol of the XXI century [2].

Transplantation as a treatment method is indicated for a large number of various diseases, often it is the only way to save human life. At the same time, the development of this branch of medicine, increasing the need for the necessary organs, creates certain moral problems and can pose a danger to society. From the very beginning, transplantology has posed a number of legal, medical and ethical questions to society, a large part of which has not been resolved even now [5].

In world society today, there are a number of issues regarding the legal regulation of the procedure for the removal and use of donor organs. All these issues are combined into three main blocks: moral problems of the organ harvesting procedure (principles of informed consent, presumption of consent and routine harvesting); the problem of justice in the distribution between potential recipients of scarce resources (organs and tissues) of transplantology; ethical problems related to trade in human organs and tissues in transplant practice [6].

The right to transplantation in general and from a deceased donor in particular, as a personal non-property right, should first of all be determined by the norms of civil legislation [7]. At the same time, the Civil Code of Ukraine does not contain any separate article regarding the content of the recipient's right to transplantation. But, according to the correct statement of M. Tikhonova and M. Kryvorodko, it can be determined by analyzing the content of those personal non-property rights, which may include the right to transplantation as a constituent factor:

1) the human right to life (Article 27 of the Constitution of Ukraine, Article 283 of the Civil Code of Ukraine). The right to life is a personal non-property good of a higher level and natural nature protected by law, which belongs to a person and is expressed in the natural ability of the human body to maintain physiological functions that ensure its vital activity. For a person who needs a transplant, the content of the right to life is primarily manifested in the fact that he has the right to demand from the state and other legal entities and individuals not to prevent the exercise of the right to transplantation, to ensure its exercise in accordance with the law (for example, to demand from the state, from bodies of state power to adopt legislation regarding the possibility of exercising, exercising the right to transplantation), she has the right to demand the performance of specific duties from obligated persons (for example, such a person must have a real inviolable non-declaratory right, the right guaranteed by the state to demand the performance of the duty from the Ministry of Health will review within the period specified by the regulatory legal act the petition regarding the need to send a citizen of Ukraine for treatment, including transplantation,

abroad, to pay the Ministry of Health for the treatment of the citizen, including transplantation abroad, within the limits of budget allocations [8];

2) the right to health. The current legislation does not contain such a separate right as the "right to health". The right to health also consists of a number of personal non-property rights – the right to eliminate danger that threatens life and health (Article 282 of the Civil Code of Ukraine), the right to health care (Article 283 of the Civil Code of Ukraine), the right to medical assistance (Article 284 of the Civil Code of Ukraine), the right to information about one's state of health (Article 285 of the Civil Code of Ukraine), the right to secrecy about the state of health (Article 286 of the Civil Code of Ukraine), etc. The content of the right to health consists of the rights of an individual regarding the possession, use and disposal of his health. Powers regarding the possession and use of one's health are exercised almost always and are manifested in special situations and in case of health impairment. Thus, scientists M. Tikhonova and M. Kryvorodko note with reference to M. Maleina "... a citizen has the opportunity to contact a medical institution and conclude a contract with it for the provision of medical assistance. A citizen becomes the owner of relative subjective rights (to qualified medical care, the choice of a doctor, information about the state of health, holding a consultation, etc.), which specify the content of the right to health and determine its limits. [9]. Transplantation, both from a living and a deceased donor, belongs to the powers of use and disposal of one's own health of an individual who needs a donor or an individual acting as a donor. After all, donation can lead to adverse consequences both for an individual who needs a donor (for example, a kidney transplant from an incompletely compatible donor), and for the person who acted as a donor – further life with one kidney, or submission of consent for posthumous donation [8].

At the same time, despite the huge number of both national and international sources of legal regulation of human organ transplantation, there remains an array of ambiguous and unsettled issues. As S. Stetsenko notes, "... to date, legislation mainly regulates activities related to organ transplantation, and the specifics of tissue and cell transplantation are not taken into account. In addition, there are no comprehensive mechanisms for ensuring the proper quality of transplant care, proper control over the use of transplantation of organs, tissues, and cells" [10]. At the same time, Y. Brych points out, we do not have clear criteria for the same selection of donors and recipients, ensuring their post-operative status, especially when it is related to their loss of working capacity. International cooperation in this field is also ineffective, as there are no close ties with the leading transplant centers in Europe [11].

To date, there are several options for the classification of types of transplantation. So, for example, N. Gashina and O. Zaitseva distinguish several types of transplantation depending on the basis:

1) by type of donors: *ex vivo* transplantation – the transplant is taken from a living donor; *ex mortuo* transplantation – a transplant is taken from a deceased person;
2) by type of transplants: transplantation of organs (or complex organs: heart-lung); tissue and cell culture transplantation;
3) by object type: transplantation of regenerative objects (blood, bone marrow, reproductive tissues); transplantation of non-generative objects (even – lungs, kidneys; single – liver, heart);
4) according to the classification of types of various transplants: autotransplantation (autologous transplantation) – the donor and recipient are the same person (for example, in case of severe burns, patients' own skin is transplanted from unaffected areas to damaged ones); isotransplantation – an organ or tissue is transplanted, taken from organisms, genetically completely (monozygotic twins) or to a greater extent identical (blood relatives) (this is the only possible method of ex vivo transplantation (the exception is bone marrow, it can be transplanted even in the absence of a genetic link) ligament from a living donor); allotransplantation (homotransplantation) – the donor and recipient are organs of the same species; xenotransplantation (heterotransplantation) – transplantation of organs from a donor of another species, for example, transplantation of organs and tissues of animals and humans [12].

At the same time, modern medical practice prefers in most cases to extract organs or tissues from a corpse rather than from a living donor. Today, the absolute majority of all transplant operations are transplants of cadaveric organs. The necessity and validity of extracting organs or tissues from a corpse is caused by the following circumstances: it is the only possibility to obtain an odd organ; even when choosing a paired or regenerative transplant in a living donor, it is impossible to completely exclude the risk to his life and health.

In order for the removal and transplantation of an organ and (or) tissue from a corpse to be legal, it is necessary to fulfill the legal and medical conditions for these operations. Current legal norms provide for the following legal conditions for extracting and transplanting organs or tissues from a corpse: 1) the death of the donor must be established in a specified manner; 2) availability of permits from the chief physician of the health care institution to remove organs and tissues from the corpse; 3) it is necessary to secure the will of the parties when conducting these operations [12].

At the same time, from the point of view of bioethics, it is the establishment of the death of the donor. Confirmation of death – preparation for organ removal is necessary. Today, under the influence of the goals and tasks of transplantology, the concept of "brain death" is being formed. At the same time, among specialists, its interpretation is ambiguous, but taking into account the experience of most countries of the world, brain death is considered the death of the entire brain (with the cortex, hemispheres and sections, including the trunk). Brain death is an iatrogenic disease, as it develops due to the intervention of medical personnel in the natural process of death. Although the criterion of brain death is accepted in

medicine, its improvement in public knowledge is related to the contradiction of the traditional idea of people about the heart as the basis of human life [4].

The concept of brain death is a thorough examination of the notion of legitimacy of a new concept of death. Behind the concept of legitimacy is the problem of the sociocultural and legal status of death. The idea of a methodologically correct definition of death must meet certain conditions and fundamental grounds [13]. Yu. Sergeev and S. Pospelova, referring to the Polish researcher M. Wihrovsky, single out two reasons: 1) cultural agreement of the definition of death; 2) irreversibility of death. Therefore, culture inevitably leaves an imprint on the theoretical understanding of the concept of brain death. As M. Vihrovsky writes, scientists note, the question "why is there a dead human body?" should be consistent with the beliefs accepted in this culture, which are not local superstitions, but are deeply rooted in the mentality. The problem of brain death articulates the problem of a possible value conflict both in the development of new technologies and in the expansion of theoretical knowledge of medicine. The conflict between innovation and tradition can take two extreme forms: 1) conservative, which implies the protection of the values of human corporeality, primarily its integrity and naturalness (including supporting "natural death" in accordance with traditional death criteria and demanding the prohibition of any methods of modification, for example, with the help of genetic engineering or by transplanting human organs and tissues (the so-called ecology of corporeality); 2) innovative, which is manifested in the requirement to remove any form of ban on manipulation of the human body, for example, bans on human cloning, manipulation of embryos, moral and legal restrictions related to organ transplantation [14].

From the point of view of philosopher and bioethicist A. Ivanyushkin, "human death is an unobservable object. From the point of view of common sense, such a person is alive, hence the initial definition of the condition of a patient with brain death – "external coma". Brain death is a clinical condition when the border between life and death has been "erased", truly: a person is "partly alive", "partly dead". Secondly, the death of a person here is an artifact, that is, an iatrogenic condition that persists while resuscitation is carried out. Thirdly, the interpretation of this fact depends on the social context [15].

A condition for an ethically impeccable diagnosis of brain death is compliance with at least three conditions or ethical principles:

1) the principle of a single approach: the same approach to diagnosis regardless of whether the patient becomes a potential donor;

2) the principle of collegiality: mandatory participation of several doctors in the diagnosis (at least three) – this allows to significantly reduce the risk of premature diagnosis and the likelihood of abuse;

3) the principle of organizational and financial independence of teams participating in transplantation. The first team only ascertains "brain death", the second only carries out the removal of organs and the third – a team of transplant specialists carries out organ transplants. Funding of these brigades is carried out from parallel sources that never intersect. It is unacceptable that in transplantology, doctors are encouraged depending on the number of patients diagnosed with brain death. All participants in the procedure must be clearly aware that until the moment of ascertaining the death of the donor's brain, none of the intended "donor-recipient" pair has a predominant right to life. It is unacceptable to extend the life of some patients at the expense of shortening the life of others [16].

Within the scope of our research, we cannot fail to note that informed consent for organ donation is an important point in transplantation [17].

In modern science, there are two ways to solve this ethical issue: "presumption of consent" – assumes that every person who did not leave written consent during his lifetime to the use of his body organs for transplantation, after his death can be used as a donor for those who need it ; "presumption of non-consent" for the removal of organs, tissues and anatomical material – means that every competent person who has reached the age of 18 has the right to write an informed consent to become an organ, tissue or anatomical material donor after his death [18].

At the same time, L. Bachynska notes, the possibility of changing modern Ukrainian legislation regarding informed consent for donation from the deceased has provoked a heated debate in recent years in academic circles. Therefore, modern legislation of Ukraine follows the path of presumption of disagreement regarding the possibility of transplanting organs or other anatomical materials to another person. Today, it is proposed to replace the specified presumption of disagreement with the presumption of consent for organ transplantation from a dead donor, which will actually provide an opportunity to increase the amount of anatomical materials that are necessary for many patients in our country [18].

But not all scientists share the opinion regarding the need to change the legislation, which concerns the presumption of consent for organ transplantation from a dead donor. Bioethicists point out that this practice should be implemented with caution. In particular, it is necessary to interpret the so-called presumptive consent, according to which the state considers everyone as a potential donor except those who declare their disagreement. This ethical line is unacceptable because it lacks a valid expression of personal will [19]. From an ethical point of view, the "presumption of consent" is considered unacceptable, since it is believed that a person should consciously express his opinion freely during his lifetime about the possibility of potentially becoming a donor. In fact, the best option for solving this moral problem would be the introduction of an effective institution of mandatory declaration of the will of every adult regarding the disposal of the body after his death, correctly notes L. Bachynska [18].

The specialist in the field of medical law I. Senyuta, analyzing the transplantation legislation, also notes that it is still too early to talk about reform. Ukraine is in difficult

socio-economic conditions, there is an increase in the number of socially vulnerable segments of the population, which can serve to commercialize this sphere. And the human body and its parts as such should not be a source of financial gain, which is clearly provided for in Art. 21 of the Convention on Human Rights and Biomedicine. In addition, mentally and psychologically, the Ukrainian people are not ready for radical steps. It should be a step-by-step weighted state program, which will be directed, among other things, to legal education, highlighting the positives of this method of treatment, which in some cases is the only way to save a life, in particular a child (this problem is well known, understood only by people who have met "face to face" with a disease that can be cured precisely thanks to transplantation). It is not yet time to analyze the changes to the "transplantation" legislation, in particular, in the aspect of transformation of presumptions, because we should wait for the project, which must undergo professional discussion, including public [20].

CONCLUSIONS

Thus, as we can see, the level of modern development of the Institute of Transplantology depends primarily on the tolerance of the society itself regarding the concept of brain death. The actual normalization of the concept of death in one or another state determines the level of realization of the human right to organ and tissue transplantation.

Regarding the reform of the current legislation in the field of transplantology, as one of the key problems of bioethics, first of all, moral principles should be taken into account (at the same time, today morality in its development is even slightly ahead of the development of international law, although progressive principles of legal regulation of transplantation processes have been distinguished at the international level). Therefore, during the development of norms of both international and national law regarding transplantology, existing moral principles should be taken as a basis. At the same time, one should not forget that a necessary factor is the presentation of a number of issues for public discussion, as well as their discussion at scientific and practical conferences not only of doctors and lawyers, but also of theologians and philosophers.

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ORIGINAL ARTICLE

INTERNATIONAL YEAR OF MEDICAL AND SOCIAL WORKERS IN UKRAINE: RECOGNITION OF THE ROLE IN THE FIGHT AGAINST THE COVID-19 PANDEMIC AND PROTECTING HEALTH AND WELL-BEING

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ABSTRACT

The aim: Defining the role of health workers and problems in combating the COVID-19 pandemic, outlining ways to protect health and safety in the workplace.

Materials and methods: The following methods were used: content analysis of international and domestic legal documents of state and sectoral level on the problem of functioning and social protection of medical and social workers in the COVID-19 pandemic and statistical reporting on the dynamics of their number and wages.

Conclusions: With the advent of COVID-19, tensions in the work of medical staff have increased, which has contributed to a reduction in the number of health workers in Ukraine due to death, permanent disability, termination / change of professional activity and migration of medical personnel. It has been found that the slow growth of wages is inadequate to carry out socially necessary activities with a risk to life and health.

Fair pay for health and social workers is a necessary but not sufficient component of measures to combat the COVID-19 pandemic at the present stage. The International Year of Health and Social Workers should be an opportunity to draw attention to the need to increase investment in education, training and social protection of these professionals and to minimize the risks posed by the pandemic to the economy and development of countries and people's lives.

KEY WORDS: COVID-19, health, safety for health workers

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INTRODUCTION

During a pandemic, the demand for medical services is growing sharply, especially in the field of care for people with coronavirus disease. However, the growth of needs is not limited to this contingent. This causes a progressive increase in the workload of medical staff. Medical workers are people of different ages and health conditions. They do not receive an indulgence for the disease together with their diploma, even if they are equipped with the necessary means of protection and special knowledge and skills to work in dangerous conditions (and the first and second, especially at the beginning of the pandemic, were catastrophically lacking). In the process of performing professional activities, the fact of infection inevitably led to the temporary (more or less long-term) withdrawal of some specialists from the care process, and in the most tragic cases – and the final. This applies to both deaths of medical workers and the onset of permanent disability. At the same time, prolonged stress and overtime work beyond the capabilities of the older human body prompted some working retirees to stop working (as a result, the burden on those who remained increased even more). Proper care of patients, especially those on ventilators, is important in the management of severe COVID-19. For example, the need for frequent turning of the patient requires regular physical effort for more than one day, which places a significant burden on junior medical staff, most of whom in Ukraine are traditionally women [1, p. 228]. An open letter on behalf of 80 health experts, known as the John Snow Memorandum, noted that the spread of the pandemic placed an unacceptably heavy burden on the economy and health workers, many of whom died of COVID-19 or suffered injuries as a result of that they had to practice «disaster medicine» «an unacceptable burden on the economy and health-care workers, many of whom have died from COVID-19 or experienced trauma as a result of having to practice disaster medicine» [2].

THE AIM

The aim of the work was to highlight the role of health workers in countering the pandemic, to identify problems that have arisen during and as a result of their duties, and to identify ways to protect health and well-being and safety in the workplace.

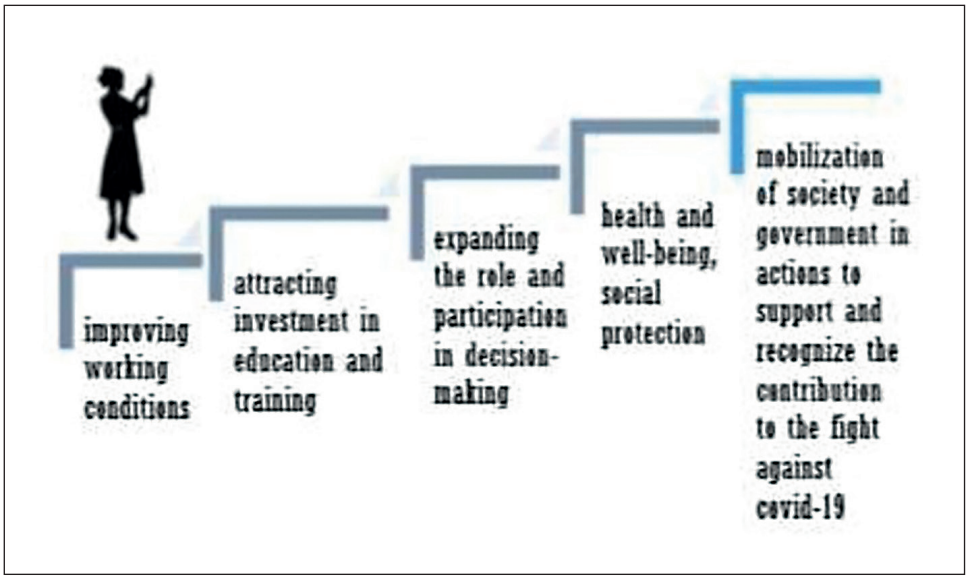

Fig. 1. Scheme of step-by-step investment in health, education, well-being and fair remuneration of medical and social workers

MATERIALS AND METHODS

The following methods were used: statistical, content analysis of international documents (including WHO operational materials and the Seventy-third session of the World Health Assembly), and domestic legal documents of state and sectoral level on the functioning and social protection of medical and social workers in a COVID-19 pandemic; as well as statistical reporting on the dynamics of the number of medical and social workers and their remuneration.

REVIEW

The publication on the UN website published the views of Ukrainian doctors on the unpreparedness for the situation with COVID-19 (due to rapid developments, lack of necessary recommendations and tested standards, lack of knowledge, skills and experience, equipment and oxygen and protection).. The risk of infecting doctors is much higher than the rest of the population, and the salaries of Ukrainian doctors and nurses are lower than the average salary in the country. Doctors also complained about the inefficiency of trade unions and the lack of psychological support. At the same time, 83% of health workers in Ukraine are women who have been working for wear since the beginning of the pandemic, trying to provide assistance to all those who need it in difficult and dangerous conditions. According to the UN Monitoring Mission in Ukraine, due to low salaries and overwork, some health workers resigned: if at the beginning of 2020 777 thousand people worked in hospitals and clinics, at the end of the same year – less than 735 thousand [3]. According to the official website of the State Statistics Service of Ukraine, the average number of full-time health care workers from January to December 2020 decreased from 777.6 to 734.9 thousand people. As of June 2021, the number of full-time employees at the end of the month, who were paid 50% or more of the working time established per month, amounted to 641.2 thousand people in health care (according to similar reports in June 2020 were 690.1 thousand people, in June 2019 – 750.3 thousand people, respectively). If we analyze the changes during 2021, then only in eight months of 2021 the number of full-time health care workers decreased by almost 17 thousand people (Table I). As can be seen, the number of specialists is declining and, consequently, the ability of Ukrainian society to resist the spread of the pandemic is decreasing.

Data exclude the temporarily occupied territory of the Autonomous Republic of Crimea, the city of Sevastopol and a part of temporarily occupied territories in the Donetsk and Luhansk regions.

In our opinion, despite the declaration of gratitude to doctors for selfless work, which is proclaimed in Ukraine starting from the highest level, the return on professional activity is reflected in the amount of wages, really reflects the inconsistency with the important role of health professionals that they have in modern society (especially more during a pandemic). In particular, the increase in wages declared by the government is happening very much low rate and does not correspond to rising prices, and its average monthly size is less than that in industry, but also the national average (Table II).

If we analyze the distribution of the number of full-time employees by the amount of their accrued wages, it turns out that 44.4% receive a salary of less than 8000 hryvnia (Table III), and in industry – 34.5%, and in financial and insurance activities, this share is only 23.7%.

The website of the Ministry of Health of Ukraine compared the incidence of COVID-19 among health workers in Ukraine and the world, in particular, it was stated that as of May 2020, the share of health workers among all patients, the average in the world was 3.9% , in Ukraine it was much higher – 19.5%. As of the end of March 2021 in the United States, according to the US Centers for Disease Control and Prevention (CDC) – the federal agency of the Ministry of Health / CDC, this figure was 1.5% in Ukraine , according to official data – about 4%. Thus, as of October 21, 2021, 95,286 medical workers became ill in Ukraine during the entire pandemic, and 955 cases of the disease became fatal [4]. According to statistics, the situation has improved (a significant decrease in the share of health workers among all infected), but personal communication between

Table I. Average number of regular workers by type of economic activity (monthly information), 2021 / thsd.

Activity	The month of the year							
	January	February	March	April	May	June	July	August
Total	7075,0	7103,6	7145,9	7155,2	7134	7115,4	7091	7078,9
Health care and social assistance	814,6	813,9	800,1	805,5	803,1	800,5	796,6	796,9
Of which health care	737,5	737,6	723,7	729,7	727,8	724,4	720,5	720,7

Source: State Statistics Service of Ukraine [Official site] http://www.ukrstat.gov.ua/ Access date: 25.10.2021

Table II. Average monthly wages of regular employees by types of economic activity, 2010-2020, wage accruals per pay-roll, UA)

Year Type of activity	2010	2013	2015	2017	2019	2020
On average for an economy	2250	3282	4195	7104	10497	11591
Manufacturing	2578	3774	4789	7631	11788	12759
Human health and social work activities	1616	2351	2829	4977	7020	8848
of which human health	1624	2374	2853	5023	7087	8995

Source: State Statistics Service of Ukraine [Official site] http://www.ukrstat.gov.ua/ Access date: 24.10.2021

Table III. Distribution of the number of full-time employees by the size of their accrued wages, by type of economic activity in June 2021, %

Activity	Share of employees to whom the wages have been charged within the following limits, %												
	up to 6000 UAH	6000,01-7000 UAH	7000,01-8000 UAH	8000,01 - 9000 UAH	9000,01 – 10000 UAH	10000,01 – 11000 UAH	11000,01 до 12000 UAH	12000,01 до 13000 UAH	13000,01 - 14000 UAH	14000,01 - 15000 UAH	15000,01 - 20000 UAH	20000,01 - 25000 UAH	over 25000 UAH
Total	16,3	17,1	7,7	6,1	5,5	4,9	4,4	4,2	3,6	3,3	11,7	6,1	9,1
Manufacturing	13,3	14,1	7,1	6,1	5,7	5,3	5,0	4,9	4,3	3,9	13,8	7,1	9,4
Human health and social work activities	20,3	15,5	9,8	8,2	6,9	5,7	4,6	3,9	3,1	2,6	8,8	4,6	6,0
Of which human health	19,6	15,2	9,6	8,1	6,8	5,7	4,6	4,0	3,2	2,7	9,2	4,9	6,4

Note. The information is formed on legal entities with the number of employees of 10 or more persons according to the register of insured persons of the State Register of Compulsory State Social Insurance.

authors and colleagues, especially practitioners, shows the lack of registration of even confirmed test cases of mild infection (both for industrial and personal reasons) , and sometimes even the refusal to conduct a laboratory test due to the argument of the management «And who will work then?».

The Ukrainian authorities have made a number of attempts to address the issue of rewarding health workers for participating in the pandemic: certain surcharges and compensations have been introduced, for example in the case of illness [5]. In Ukraine, in the event of the death of a medical worker as a result of his infection with acute respiratory disease COVID-19 caused by the coronavirus SARS-CoV-2, while performing professional duties in conditions of increased risk of infection, family members, parents, dependents of a deceased medical worker (persons entitled to payment) is paid in the amount of 750 times the subsistence level for able-bodied persons, established on January 1 of the calendar year in which the medical worker died. The Government has regulated the procedure for investigating the deaths of health care workers who provide care to patients with COVID-19 due to the disease, in January 2021 adopted a resolution of the Cabinet of Ministers of Ukraine «Some issues of investigation of deaths of certain categories of health workers» [6].

According to the Social Insurance Fund of Ukraine, in January-June 2021, for 100 insured events, the families of medical workers who died as a result of infection with acute respiratory disease COVID-19 were paid a one-time allowance of 750 times the subsistence level for able-bodied persons. , established on January 1 of the calendar year. The amount of payments for cases that occurred in 2020 amounted to UAH 1,576.5 thousand, and for cases from January 1, 2021 – UAH 1,702.5 thousand per family. The total amount of payments for the first half. in 2021 it amounted to 161,682 thousand hryvnias. Two medical workers with disabilities were provided with a one-time allowance of UAH 1,425.1 thousand, of which one medical worker with a disability group II was paid a one-time benefit in the amount of UAH 794.5 thousand, and one employee who was diagnosed with a disability. established III group of disability – one-time assistance in the amount of 630.6 thousand UAH [7].

However, the experts of the UN Monitoring Mission in Ukraine stressed that the allowances introduced by the government were provided only to those who work in medical institutions where patients with COVID-19 were treated. Thus, many health workers who had to come into contact with and provide care for people infected with coronavirus were not entitled to additional remuneration. Moreover, only a small number of coronavirus infections have been officially declared work-related, and many doctors and nurses have not been able to receive adequate compensation. It is concluded that Ukraine should significantly increase investment in the health sector to improve the working conditions of health workers [8].

Order of the Ministry of Health №1614 [9] in Ukraine introduces a new approach to combating the emergence and spread of infectious diseases associated with the provision of medical care (IPNMD), as health care facilities are the first line to detect, respond to and prevent the spread of infectious diseases. Systematic monitoring of the rules of safe medical care can prevent and / or reduce the spread of infectious agents, IPNMD is included in the list of occupational infections of health care workers, but it is also a problem of morbidity of patients and visitors to health care facilities.

Being at the forefront of the fight against COVID-19, doctors are exposed to various dangers in addition to the action of SARS-CoV-2 – heavy workload, prolonged use of protective equipment, stress at work and more. The WHO has issued a special document outlining specific measures to protect the occupational health and safety of health workers, their rights and responsibilities for health and safety at work in the context of COVID-19 [10].

WHO has declared 2021 the International Year of Health and Social Workers, in recognition of their willingness to provide assistance in the face of the COVID-19 pandemic, which has challenged health systems around the world. These include all health and public health workers, workers in related fields (doctors, nurses, midwives, pharmacists, physiotherapists, mental health professionals, social workers, occupational health professionals, engineers and technicians , laboratory assistants and others). The COVID-19 pandemic has proven the importance of all health and social workers without exception and reaffirmed their important role in emergencies in ensuring the readiness and sustainability of health systems [11].

In Ukraine, the contingent of medical workers is more likely to get COVID-19 than the general population. In one of the smallest regions of Ukraine with the most favorable age structure of the population and a smaller percentage of the population over 65 years old – Zakarpatska, by the end of 2020 3579 doctors fell ill with COVID-19 (including doctors – 578, nurses – 1884, junior nurses – 716, the other – 401 people). Of these, 26 doctors died. For example, if we take into account that as of the beginning of 2020 there were 3.9 thousand doctors in the region, it turns out that more than every tenth person has contracted COVID-19 in a year. Instead, the corresponding percentage for the whole population was much lower – less than 5% of the region's residents. According to statistics, as of 1.01.2020, wages in the area of «Health care and social assistance» amounted to 156.7% of the minimum wage and 90.3% of the average level in the region. The latest available data on 01.08.2021 showed the dynamics from 9402 to 10716 UAH, ie up to 87.7% of the average regional level [12].

There is also some gender inequality. Up to 70% of the world's health and social workers are women, and they are at the forefront of the pandemic. In the Organization for Economic Co-operation and Development (OECD), every tenth worker is employed in the health sector, and three quarters of them are women [13], and a similar situation is found in Ukraine in terms of employment and sex distribution. According to data from Germany, Spain and Italy, the proportion of confirmed cases of COVID-19 among female health workers is two to three times higher than among their male counterparts [14].

Funding and delivery of public health services (disease prevention, health promotion and health care) is now becoming a combined responsibility of central and local government. The outbreak of the new coronavirus pandemic (COVID-19) has posed major public health challenges to national and local governments, hampering full reform. [15]

The health and well-being of medical and social workers has now become truly crucial to the very existence of the state. In times of pandemic confrontation, power and life are not connected to preventing the effects of severe stress and long-term overload of these workers, and creating concrete next steps to invest in maintaining their health, education, well-being and fair compensation for work and real risks to life and health associated with the implementation of professional mandatory relationships (Fig. 1). They should be rewarded for their work in ensuring the coverage of health services, providing protection for a large number of people from health emergencies (both related to the spread of coronavirus disease and a huge range of other services, and with pleasure needs due to various existing health problems), aimed at strengthening and well-being for all and at any age – not only deserved words of gratitude, but also concrete measures.

DISCUSSION

Considering the above, the role of medical workers in combating the pandemic is undeniable [16], because it is not limited to the provision of medical services to persons with the coronavirus disease, but also ensures the satisfaction of the sharp increase in demand for medical services in the field of providing assis-

tance to the entire population. Thus, the COVID-19 pandemic had a significant impact on the spread and complications of non-communicable diseases (NIDs) among patients. This is due to the complex nature of NID risk factors, which combine social, economic, political and environmental aspects of everyday life [17]. At the same time, the problems of the ability to maintain a high and fair level of coverage of routine immunization at each subnational and regional level remain unresolved, in particular with regard to ensuring full coverage of the population with vaccination against COVID-19 [18]. The main obstacles to the implementation of the planned immunization project are also a number of complex factors: political will, efficient and effective management and financing programs, supply of vaccines and their management within the framework of ensuring their quality, material and technical support through appropriate implementation and monitoring strategies, effective data registration and reporting for appropriate action, public accountability and positive attitudes towards vaccination and, most importantly, effective service delivery with adequate human resources. Thus, it is the provision of medical personnel that is the basis for tracking the progress of achieving the scope of coverage of health care services, including vaccination, and is evidence of the stability of the personnel of the health care system of any country. It is medical workers who bear the burden of preventing and containing the spread of COVID-19 in Ukraine and the world and overcoming the consequences of the pandemic for patients, and therefore the population of the country as a whole [19].

In addition, against the background of the COVID-19 pandemic, most health workers are facing the problem of exhaustion and a drop in morale. Given that 2021 has been declared the International Year of Medical Workers, all interested institutions and individuals involved in political decision-making in Ukraine should continue to take measures and implement policies to improve the working conditions of medical workers, preserve their health and well-being, attract investments in their education, providing them with rights and opportunities for full application of their knowledge [20].

Along with this, it should be taken into account that any humanitarian crises, including natural disasters and conflicts, can rapidly destroy the health care infrastructure and cause a long-term shortage of qualified medical personnel, which threatens to disrupt the provision of services not only for population immunization, but for the entire field provision of medical plows. At the same time, the discrepancy between the needs of the population in health care services and the demand in the labor market can also lead to the emergence of unsatisfied needs, irrational distribution of human resources and unfair differences in access to health services. Therefore, the responsibility of medical and social workers for the fulfillment of tasks to achieve comprehensive coverage of the population with health care services and protection of the population in emergency situations, which includes work with corona virus patients, deserves not only recognition, but also requires more tangible financial gratitude. In the absence of prospects for material remuneration, medical workers will leave the field of health care in the future, and young people will choose other professions.

A number of identified problems that arose during and as a result of the performance of the duties of medical and social workers (this is a significant reduction in the number of medical and social workers in the health care sector, and the discrepancy between the amount of wages and the performed duties with a risk to life and health, as well as the unacceptably large burden on medical workers and the economy, which is imposed by the spread of the pandemic, etc.), needs a more detailed and in-depth study from the point of view of the importance of the role of medical and social workers in countering the pandemic in modern conditions, in particular at the regional level.

CONCLUSIONS

The health and well-being of health and social workers today play a crucial role in human survival. Efforts to ensure the health, well-being and social protection of health and social workers are perhaps the most important contribution to overcoming the COVID-19 pandemic in the world in specific countries. Fair pay for health and social workers is a necessary but not sufficient component of pandemic response at the present stage and in the long run to ensure sustainable development.

In Ukraine, there is a reduction in the number of health workers (both due to direct losses (death or permanent disability) and due to the cessation (change) of professional activity, as well as the migration of medical personnel and the share of tension in the work of medical staff. 19 «flowed out»), and the slow growth of wages is inadequate to carry out socially necessary activities at risk to life and health.

The International Year of Health and Social Workers should be an opportunity to draw attention to the need to increase investment in education and training (social skills) and social protection of these professionals in order to increase their capacity and preparedness to respond to the pandemic and its consequences, to carry out comprehensive vaccination against COVID -19, and ultimately – to minimize the risks posed by the pandemic to the economy and development of countries and actually to the lives of the people who inhabit them.

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ORIGINAL ARTICLE

REPRODUCTIVE RIGHTS AND IMPLEMENTATION OF THE RIGHT TO HUMAN LIFE

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ABSTRACT

The aim: To find out the peculiarities of citizens' implementation of their reproductive rights, while combining the basic principles of medicine and law.

Materials and methods: Formal-logical methods of analysis and synthesis allowed to reveal the content of the concepts that make up the subject of research, to classify them, as well as to formulate intermediate and general conclusions. The systematic method allowed to study the role and significance of human reproductive right among other somatic human rights and freedoms. Using the historical method, the doctrinal basis of the study was analyzed, and the main stages of the formation of human right to transplantation were identified. The application of the above-mentioned methods necessitates the inclusion of an activity method in the research methodology. This method, becoming a logical continuation of the integral structural-functional method, involves the study of relevant reproductive rights through the development of medical technologies.

Conclusions: The modern development of biotechnology has caused a number of serious threats to the possibility of realizing the human right to life. The modern understanding of the content of the right to life concerns a number of bioethical aspects, primarily related to the development of scientific and technological progress in both biology and medicine. The content of the human right to life in the context of the achievements of reproductive rights is significantly expanding, which leads to a new concept of it, not only as a fundamental human right, but also as a set of rights that relate to human life, taking into account the principles of bioethics. Therefore, the need to compare the goal and the means in biological and medical manipulations with human life, their consideration of the ethical and moral aspect is extremely important for the further development of the entire legal array regarding biomedicine.

KEY WORDS: human rights and freedoms, fourth generation human rights, somatic human rights, medicine, law, ethical principles, reproductive rights

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INTRODUCTION

According to the views of the ancient Greek philosopher Epicurus, the state and law arise when people enter into an agreement with each other to ensure mutual benefit – mutual security. Therefore, the main purpose of the state is the safe existence of society [1].

The modern approach with the declared principles of democracy is somewhat outdated and the whole world needs to rethink the acquired and search for new approaches to understanding equality, justice, protection, etc. The necessary stability of the concept of protection of human rights is achieved by relying on a system of principles tested by science and practice. The viability and progressiveness of this concept consists of a combination of legal, moral, traditional, and other social and regulatory norms [2].

The relevance of the research subject of this scientific work is determined by the fact that, in accordance with the rapid development of medical technologies, a problem arises in determining the role of reproductive rights, which are included in somatic rights. In the international legal documents, in which the basic principles of the development of biomedicine are established, considerable attention is paid to the legal regulation of somatic human rights. Somatic rights are increasingly becoming an object of study in legal science, because the separation of these rights into a separate category is a logical process that arises as a result of the development of the subjective rights of a person. A number of domestic and foreign scientists were engaged in the study of certain aspects of reproductive rights. However, usually reproductive rights are considered by scholars either in the context of the right to life, or in the context of the right to health, or in the sense of a general constitutional right.

THE AIM

The aim was to find out the peculiarities of citizens' implementation of their reproductive rights, while combining the basic principles of medicine and law.

MATERIALS AND METHODS

Formal-logical methods of analysis and synthesis allowed to reveal the content of the concepts that make up the subject of research, to classify them, as well as to formulate intermediate and general conclusions. The systematic

method allowed to study the role and significance of human reproductive right among other somatic human rights and freedoms. Using the historical method, the doctrinal basis of the study was analyzed, and the main stages of the formation of human right to transplantation were identified. The application of the above-mentioned methods necessitates the inclusion of an activity method in the research methodology. This method, becoming a logical continuation of the integral structural-functional method, involves the study of relevant reproductive rights through the development of medical technologies.

REVIEW AND DISCUSSION

The modern concept of reproductive rights, notes D. Rashidkhanova, includes the right of married couples and individuals to achieve the highest possible level of reproductive health, the right to freely and responsibly make decisions regarding the reproduction of offspring without any discrimination, coercion and violence, to place for this necessary information and have access to the most effective and safe methods of family planning and methods of overcoming infertility [3].

Determining the legal nature of reproductive rights, it should be noted that they have a complex nature and include a number of personal rights that are enshrined in international legal documents on human rights and freedoms, as well as in the Constitution. Yes, every person's right to life, the right to health care, physical integrity, privacy, personal and family secrets, as well as the right to protection of personal dignity and the principle of equality between men and women, are directly related to reproductive rights, believes Ye. Solovyov [4].

K. Wichterich claims that the formation of the paradigm of sexual and reproductive rights arose in response to the activities of women's movements around the world, which fought for freedom from male violence against the female body, from patriarchal control over their sexuality with various manifestations: from marital rape to sexual violence in war, from humiliating practices such as virginity and pregnancy testing to pre-sex selection and infanticide [5].

Article 3 of the Constitution of Ukraine stipulates: "a person, his life and health, honor and dignity, inviolability and security are recognized as the highest social value in Ukraine". At the same time, as of today, there is no separate regulatory act in Ukraine that would enshrine exactly reproductive rights. These rights derive from the content of a person's right to motherhood (Article 49 of the Family Code of Ukraine) and fatherhood (Article 50 of the Family Code of Ukraine). Among scientists, it is customary to divide reproductive rights into rights of a positive nature – the right to artificial insemination, and rights of a negative nature – sterilization, abortion. This classification is characterized by the presence of positive and negative aspects of freedom [6].

Positive human rights record the obligations of the state, individuals and organizations to provide citizens with certain benefits and perform certain actions. The implementation of positive rights is impossible without the availability of sufficient resources in the state, their specific fulfillment directly depends on the wealth of the country and the democracy of its political system [7].

A. Dutko and M. Zabolotna note that the sphere of a person's reproductive activity concerns his private life, the non-interference in which is guaranteed by the Constitution of Ukraine and the norms of international legal acts. The content of the constitutional right to inviolability of personal and family life is very dynamic. It is constantly changing, and therefore, with the development of legal relations that arise in the exercise of reproductive rights, the possibility to freely make decisions in the exercise of reproductive activity should be attributed to the private life of a person, in addition to other aspects, thus realizing the right to freedom of reproductive choice. In view of this, scientists believe that the absence of an own concept of reproductive rights in Ukraine, which would take into account the interests of the state and the nation as a whole and would establish mechanisms for the constitutional protection and realization of reproductive rights, is unacceptable [8].

At the same time, A. Dutko and M. Zabolotna point out, there are isolated attempts to interpret the concept of reproductive personal non-property rights of natural persons in European law enforcement practice, where they mean the right of a female and male person to have a genetically native child, and for a female person – also the right to bear a child on your own (the right to conceive and be pregnant) and the right to a physiological birth [8]. However, in particular, the scientist N. Tyukhtiy believes that such a definition is quite limited – reproductive rights have many more components, for example, the right to prevention, treatment of infertility, artificial insemination, surrogate motherhood, etc. [9]. Despite the lack of clear wording and principled positions in international legislation regarding the implementation of reproductive rights, which states primarily focus on when creating national law, some foreign countries have consolidated their understanding of these rights [10].

From the point of view of our research, the dissertation work of V. Checherskyi is interesting. The research provides an author's definition of the human right to reproduction (reproduction) – this is a fundamental personal non-property right to free, voluntary, personal decision-making regarding the implementation of the reproductive function, which consists in the birth or refusal to give birth to genetically native children, their number and the intervals between their births, as well as the use of available reproductive technologies to achieve this goal. The scientists indicated the relationship of the specified right with other rights and stated that it should be distinguished from other externally similar rights, as well as such generalizing definitions as "rights related to the human right to reproduction" and "reproductive rights". Rights related to a person's right to reproduction (reproduction) are those rights that are directly intended to facilitate the realization by a person of his fundamental right to reproduction (reproduction), and

human reproductive rights are a set of rights that a person possesses in the reproductive sphere [11].

In his work, V. Checherskyi presents modern approaches to understanding reproductive rights: the first, according to the scientist, is based on the fact that the term "reproductive rights" has a conditional character, which is used mostly in sociology and demography than in jurisprudence; the second direction – on a certain connection between international sources and the need to implement the ideas expressed in these sources in domestic legislation; the third direction is that reproductive rights have their own special nature in basic human rights and freedoms. It was established that when studying the human right to reproduction (reproduction), it is appropriate to use the definition "reproduction" and not the similar in meaning "procreation", since the latter is reduced more to the biological essence of reproduction, although this process is a biosocial phenomenon. During human reproduction, the following takes place: 1) biological reproduction – reproduction of individuals and, accordingly, reproduction of the biosphere; 2) social reproduction – reproduction of personality, social structure and relevant social relations; 3) psychological reproduction – reproduction of consciousness, mentality and mechanisms. The modern understanding of instinct, innate need, their influence on the behavior of a living being and the peculiarities of the influence on the behavior of a person as a biosocial being, including on reproductive behavior, are considered. The researcher argued that the right to reproduction is a natural human right, as it is determined by the innate need to continue one's own kind. It is proposed to divide the fundamental rights of a person into those that are laid down by the biological essence of a person, including those that are due to innate needs, and those that are recognized as basic or fundamental in society at a specific stage of its development. The first are unchanged, the second are gradually evolving [11].

Determining the legal nature of reproductive rights, A. Dutko and M. Zabolotna believe that they should be interpreted as a type of so-called personal rights, which are a subtype of personal human rights. According to scientists, these rights have a complex nature and cover a whole range of personal rights, which are enshrined in international legal documents on human rights and freedoms, in laws and other legal acts. The norms that form the basic conditions for the realization of reproductive rights include articles 27-29 of the Constitution of Ukraine, which enshrine the right to life, respect for dignity, freedom and personal integrity, article 24 of the Constitution of Ukraine, which proclaims the principle of equality, and others [8].

At the international level, writes T. Dlugopolska, the issue of reproductive rights has been little studied, although the problem of their legal definition is given significant importance. The concept of reproductive rights, the scientist believes, was first enshrined in clause 7.2 of the Action Program of the International Conference on Population and Development (Cairo, September 5-13, 1994) and was further developed in clause 95 of the Platform of Action (PlatformofAction), which was approved according to the results of the Fourth World Conference on the Status of Women (Beijing, September 4-15, 1995). In this act, it is recorded that reproductive rights are based on a set of fundamental rights, namely: all married couples and individuals are free to make a responsible decision regarding the number of their children, the intervals between their births, the time of their births and the necessary information and means for this; to achieve the highest possible level of sexual and reproductive health; make decisions on issues related to reproductive behavior in the absence of discrimination, coercion to violence; the right to information, access to safe, effective family planning methods and the right to access appropriate health care services. However, the researcher writes, in international legal documents related to human rights and which are basic in this area, in particular the Universal Declaration of Human Rights, the International Covenant on Civil and Political Rights, the International Covenant on Economic, Social and Cultural Rights, the Convention on the Protection of human rights and fundamental freedoms, nothing is mentioned about the above rights [12].

It should be noted, T. Dlugopolska points out, that all these documents do not provide clear wording and definitions and do not have a principled position on this issue. They do not contain precise recommendations for states to implement reproductive rights. They consider reproductive possibilities as part of inalienable human rights. At the same time, as T. Dlugopolska rightly points out, as far as international judicial practice is concerned, there is no clear position here either. According to the scientist, the reason is the same: lack of definition of reproductive rights both at the international level and in the national legislation of many countries. In solving such specific issues, the European Court of Human Rights gives freedom of choice for the settlement of such issues to individual states whose parties have appealed to the international institution. However, there are separate attempts to interpret the concept of "reproductive personal non-property rights of natural persons". In European law enforcement practice, they mean the right of a female or male person to have a genetically native child, and for a female person, reproductive rights also include the right to bear a child on her own (the right to conceive and be pregnant) and the right to physiological childbirth. At the same time, according to the scientist, it is difficult to agree with such a definition, since it is too narrow, because it does not reflect all its components [12].

According to the above-cited scientist, the system of reproductive rights should include: the right to reproductive choice; the right to reproductive health; a woman's right to abortion; the right to artificial insemination and the transfer of an embryo into a woman's body; the right to donation and preservation of reproductive cells; the right to use the surrogate motherhood method; the right to sterilization; the right to use contraception; the right to prevention and treatment of infertility; the right to information about reproductive rights; the right to confidentiality of information regarding the implementation of reproductive rights; the right to protection of reproductive rights [12].

The problem of reproductive rights or individual reproductive capabilities has been discussed quite a lot precisely in civil science. Thus, the issue of legal regulation of birth rate was raised by M. Maleina even in Soviet times. However, the scientist does not use the term "reproductive rights" in her works. For example, in the study "Man and medicine in modern law" she uses the term "regulation of reproductive activity". It is through this concept that such rights as the right to artificial termination of pregnancy, artificial insemination, medical assistance in case of infertility, etc. are considered [13]. That is, reproductive rights as an independent category of personal rights of an individual, E. Muhamedova points out, were not recognized, since it was mostly about methods of state influence on one of the spheres of human activity [14].

According to R. Stefanchuk, the interpretation of reproductive rights exclusively as a component of the right to life, accepted by the Central Committee of Ukraine, is inadmissible, since the right to life has its own clearly defined structure. These rights are limited by object. So, if the object of the right to life is a personal non-property good – the life of the bearer of this right, then the object of reproductive rights is the implementation of the reproductive function aimed at conceiving the life of other persons. Understanding reproductive rights exclusively as a component of the right to health care is also considered by scientists to be a rather narrow understanding, since these rights are also characterized by a number of positive powers. Reproductive rights should be considered as a system of separate personal non-property rights of individuals that ensure their natural existence and are aimed at the implementation of the reproductive function of individuals [15].

According to E. Muhamedova, reproductive rights should be understood as rights related to human reproduction, aimed at achieving a state of complete physical, mental and social well-being in the field of reproductive opportunities (reproductive health) by freely resolving issues of childbearing and family planning and consist in the possibility of a woman freely carrying out an artificial termination of pregnancy, carrying out sterilization at the will of a woman or a man, using auxiliary reproductive technologies only for medical reasons, and are also characterized by the properties of the personal non-property right of an individual to health, which includes, or an integral element of which they act [14].

At the same time, one cannot fail to note that the concept of human reproductive rights is based, first of all, on the human right to life [16]. With the development of scientific and technical progress in biology and medicine, writes B. Ostrovska, its content is expanding, which prompts the transformation of the idea of the right to life, not only as the main fundamental human right, but also as a set of rights that relate to human life (directly related to the physical existence of a person as a biological being) through the prism of bioethics and international law. As a result, the issues of protection of the human genome from illegal interventions, protection of the right to life at the prenatal stage of human development, violation of the principle of informed consent in matters of donation and transplantation, protection from involuntary biomedical intervention in the human body, etc. arise. The right to life as a fundamental natural human right is inextricably linked to the concept of human dignity and permeates all areas of research in biomedicine, in which the question of the moral admissibility of their application to humans is raised [17].

V. Kozhan fills the content of the right to life with two groups of rights. At the same time, the first group of rights, which he calls reproductive, include the right to artificial termination of pregnancy, the right to sterilization, the right to artificial insemination and the transfer of an embryo into a woman's body [7].

CONCLUSIONS

Within the scope of our research, we consider it necessary to focus on the following. The modern development of biotechnology has caused a number of serious threats to the possibility of realizing the human right to life. The modern understanding of the content of the right to life concerns a number of bioethical aspects, primarily related to the development of scientific and technological progress in both biology and medicine. The content of the human right to life in the context of the achievements of reproductive rights is significantly expanding, which leads to a new concept of it, not only as a fundamental human right, but also as a set of rights that relate to human life, taking into account the principles of bioethics. Therefore, the need to compare the goal and the means in biological and medical manipulations with human life, their consideration of the ethical and moral aspect is extremely important for the further development of the entire legal array regarding biomedicine.

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CASE STUDY

LIVER CIRRHOSIS WITH CRYPTOGENIC GENESES. CLINICAL CASE

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ABSTRACT

The article presents clinical observation of a patient with cryptogenic cirrhosis of the liver, a chronic diffuse progressive liver disease, which is manifested by structural rearrangement of its parenchyma. Cryptogenic cirrhosis is cirrhosis of uncertain etiology that lacks definitive clinical and histological criteria for a specific disease. Cryptogenic cirrhosis accounts for nearly 5% to 30% of cases of cirrhosis and nearly 10% of liver transplants. The problem of cirrhosis of the liver is extremely relevant, because this pathology is observed mainly in young and able-bodied people. In addition, it takes the first place among the causes of mortality from diseases of the digestive system.

To clarify the diagnosis, laboratory and instrumental diagnostic methods of investigation were performed. Due to severe thrombocytopenia and minor leukopenia, myelodysplastic syndrome was suspected. Metabolic disorders that can be considered as probable in the occurrence of the above-mentioned changes in the liver parenchyma had been ruled out.

KEY WORDS: Cryptogenic liver cirrhosis, varicose veins of the esophagus, patient

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INTRODUCTION

Cirrhosis of the liver (CL) is a chronic, diffuse, progressive disease of the liver, which is manifested by restructuring of its parenchyma in the form of nodular transformation and fibrosis due to necrosis of hepatocytes, the appearance of shunts between the portal and central veins bypassing hepatocytes with the development of portal hypertension and increasing liver failure.

Cirrhosis of the liver takes the first place among the causes of mortality from diseases of the digestive system. In economically developed countries, CL is among the six main causes of death in patients aged 35 to 60 years. According to the World Health Organization (WHO), over the past 20 years, there has been a continuous increase in mortality rates from this disease [1]. Over the last decade, the prevalence of liver diseases in Ukraine has increased significantly, especially among young people: chronic hepatitis – by 2,2 times, and cirrhosis of the liver – by 60%.

Therefore, the problem of CL is extremely relevant, because this pathology is observed mainly in people of young and working age [2]. Despite the absence of clear clinical manifestations, CL is dangerous due to the tendency to progress. The main causes of the development of CL are as follows: alcoholic liver disease (33%), viral hepatitis and non-alcoholic steatohepatitis, others occur less often due to the rarity of the pathology itself – hemochromatosis, Wilson's disease and Budd-Chiari disease, medicinal and cryptogenic hepatitis, etc. The proportion of patients with chronic HCV infection who develop CL within 20 years after infection varies from 2-4% in children to 20-30% in middle-aged patients, with an average of 10-15%.

The leading pathogenetic factor in CL is the development of bridge-like necrosis in the parenchyma, which leads to the death of hepatocytes. The development of connective tissue causes formation of false lobules with subsequent shunting of blood flow to bypass hepatocytes, hypoxia occurs on the background of a chronic inflammatory process. Regenerative cirrhotic nodes compress the terminal branches of the hepatic veins and branches of the portal vein in the portal tracts, which is the main reason for the development of portal hypertension. There are arteriovenous anastomoses between the branches of the hepatic artery and the portal vein in the fibrous septa, and in the late stages of the disease, portal blood outflow is blocked, blood circulation slows down, and in some cases, reverse blood circulation in the portal vein occurs. Immunological disorders and an increase in the level of pro-inflammatory cytokines are observed [3,4].

Clinical manifestations of cirrhosis are quite diverse. In about 20% of patients, the initial stages of the disease are asymptomatic [5]. Depending on the stage of the disease, the following symptoms may be observed: liver enlargement in the early stages, which is replaced by significant decrease in sizes; spleen enlargement; pain of a distending nature, localized in the right hypochondrium; asthenic syndrome; increase in body temperature; dyspeptic manifestations; decrease in body weight; signs of cholestasis; portal hypertension, varicose veins of the esophagus, rectum and stomach; edema; ascites; telangiectasias; hemorrhagic syndrome, manifested by bleeding of the mucous membranes, development of petechiae, hematomas; «hepatic» smell from the mouth; palmar erythema; hepatic encephalopathy; gynecomastia; xanthomas and xanthelasmas [6];

Classification of CL is carried out according to various parameters [7].

1. Morphology classification: morphologically, cirrhosis may be micronodular, macronodular, or mixed. This classification is not as clinically useful as etiologic classification.

Micronodular cirrhosis (uniform nodules less than 3 mm in diameter) is mostlu due to due to alcohol, hemochromatosis, hepatic venous outflow obstruction, chronic biliary obstruction, jejunoileal bypass, and Indian childhood cirrhosis.

Macronodular cirrhosis (irregular nodules with a variation greater than 3 mm in diameter) is the result of hepatitis B and C, alpha-1 antitrypsin deficiency, and primary biliary cholangitis.

Mixed cirrhosis (when features of both micronodular and macronodular cirrhosis are present) usually progresses into macronodular cirrhosis over time.

2. Etiology Classification. Based on the cause of cirrhosis it is sub-classified as follows:

Viral – hepatitis B, C, and D; Toxins – alcohol, drugs; Autoimmune – autoimmune hepatitis; Cholestatic – primary biliary cholangitis, primary sclerosing cholangitis; Vascular – Budd-Chiari syndrome, sinusoidal obstruction syndrome, cardiac cirrhosis; Metabolic – hemochromatosis, NASH, Wilson disease, alpha-1 antitrypsin deficiency, cryptogenic cirrhosis.

Also, the Child-Pugh classification of this disease is now used all over the world, which makes it possible to determine the degree of severity of cirrhosis (initial, moderately expressed and terminal) [8,9]. According to this classification, 5 signs are distinguished, each of which can be evaluated from 1 to 3 points. Then these points are added up, and depending on the number obtained, a class is determined: A, B or C, each of which corresponds to a certain degree of severity of cirrhosis.

- Cirrhosis stage according to Child – Pugh A – 5-8 points;
- Cirrhosis stage according to Child – Pugh B – 7-9 points;
- Cirrhosis stage according to Child – Pugh C – 10-15 points.

In the compensation phase of liver cirrhosis, differential diagnosis with other chronic diseases should be carried out [10]. With decompensation, differentiation is required by certain symptoms of the disease, depending on the clinical manifestation, including jaundice, portal hypertension, and hepatic encephalopathy.

The Model For End-Stage Liver Disease (MELD) score is a calculation aimed to determine the severity of end-stage liver disease and the need for transplantation. The components of the MELD score include creatinine, bilirubin, INR, and sodium [11].

Complications of liver cirrhosis are: hepatic coma (or precoma); bleeding from varicose veins of the esophagus and stomach, hemorrhoidal veins; portal vein thrombosis; bacterial peritonitis; cirrhosis – cancer [12,13].

Mortality is influenced mainly by age at diagnosis and Child's class [14].

CASE REPORT

The patient Mykola S. (25 y.o.): clinical-anamnestic examination, laboratory and instrumental methods of investigation, molecular-genetic study), born in 1997, sought medical help with complaints of general weakness, fatigue, pain in the right hypochondrium, discomfort in the epigastric area, nausea. Considers himself sick for a long time, when icterus of the sclera and skin first appeared. The patient was consulted by a gastroenterologist.

From the anamnesis, it is known that since the age of 17, he periodically noted stool disorders, flatulence. No significant childhood or adult illness in the history, no medication or alcohol use preceding the current complaints.

Objective status: the general condition is of moderate severity, consciousness and cognitive levels are normal, the patient is well-fed, afebrile, the skin and visible mucous membranes are pale pink. Peripheral lymph nodes are not enlarged. The constitution is normosthenic. The abdomen is soft, painful on palpation in the upper parts, the liver +3 cm below the right costal arch, dense.

To clarify the diagnosis, the following laboratory and instrumental diagnostic methods of investigation were performed:

General blood analysis (19.09.2017): ESR – 6 mm/h, hemoglobin – 152 g/l, hematocrit – 44,4, erythrocytes – 4,97×1012/l, leukocytes – 4,02×10^9/l (normal range 3,9-10×10^9/l), segmented granulocytes – 67,5%, eosinophils – 1,4%, basophils – 0,3%, lymphocytes – 22,9%, monocytes – 6,5%), platelets – 57 g/l (normal range 166-389 g/l).

Coagulogram (19.09.2017): international normalized ratio was (INR) 1,11; prothrombin according to Kwik – 76,8%; prothrombin time – 11,2 sec; activated partial thromboplastin time (APTT) – 28,9sec; fibrinogen – 264 mg/dL.

Biochemical blood analysis (19.09.2017) revealed slightly elevated total bilirubin – 22,1 μmol/l (normal range 5,0 – 21 μmol/l), elevated alanine aminotransferase – 69 U/l normal (4-41 U/l) and aspartate aminotransferase – 50 U/l (normal range (4-37 U/l), creatinine 74 – μmol/l, urea – 7,5 μmol/l, total protein – 80 g/l, cholesterol – 325 mmol/l.

Copper (Cu) content in urine by atomic absorption spectrometry with electrothermal atomization on the KAS-120.1 device: 84,7 μg/100 ml.

Copper (Cu) content in blood serum: 9,54 μmol/l (normal range 11,0 – 24,0 μmol/l).

Transferrin level – 251 mg/dL (normal range 200-300 mg/dL); ferritin – 50,8 ng/ml (normal range 28 – 365 ng/ml), ceruloplasmin – 55.6 mg/dL (normal range 22 – 61 mg/dL).

PCR (20.11.2017) was performed to detect cytomegalovirus (CMV DNA): not detected;

Epstein-Barr virus PCR (qualitative determination): detected.

IgM antibodies to HAV(20.11.2017): <0,02 (negative), antibodies to HCV (anti HCV IgG): <0,11 (negative), HBsAg (Australian antigen): 0,75 (negative).

We presented in Echographic changes of the liver and spleen of patient by date of Abdominal ultrasound investigation (06.10.2017) on figure 1. (fig. 1).

The images showed normal sized liver with heterogenous parenchyma of medium echogenicity contours are not even, parenchyma is unevenly compacted, the vascular pattern of the portal veins (left and right lobes) is intensified, enlarged; intrahepatic bile ducts are not dilated. V. portae expanded to 1,6 cm; The gallbladder is deformed, measuring 7,0*3,0 cm; the wall is not thickened, the content is homogeneous; choledoch 0,6 cm; Pancreas without echostructural changes. The spleen is enlarged, measuring 18,5*6,0 cm, homogeneous, with normal structure; v. lienalis expanded to 1,7 cm. Kidneys and bladder without pathological features. Conclusion: Echographic diffuse liver changes? Signs of biliary hypertension, splenomegaly

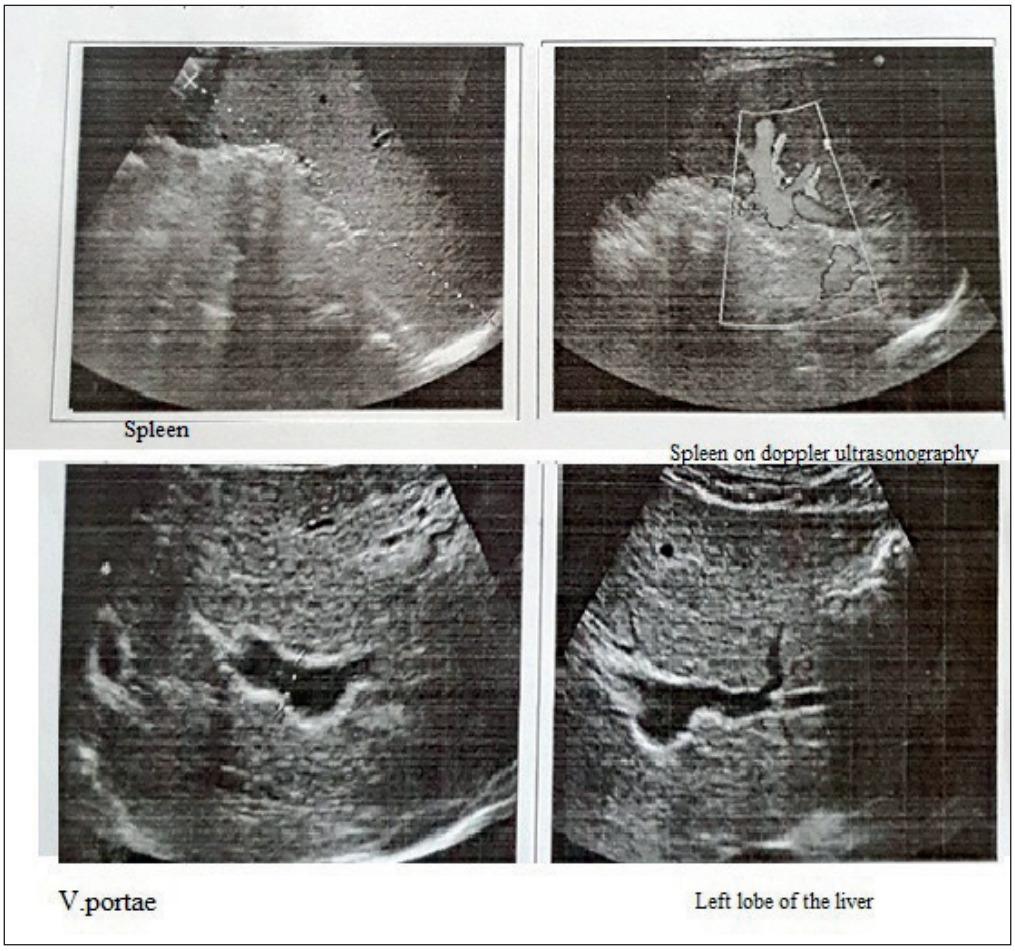

Fig. 1. Echographic changes of the liver and spleen

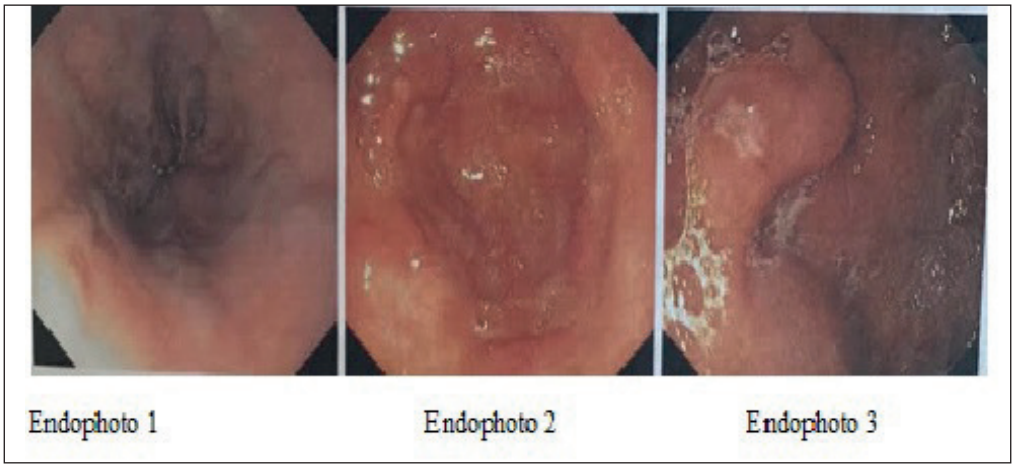

Fig. 2. Esophagogastrointestinal endoscopy

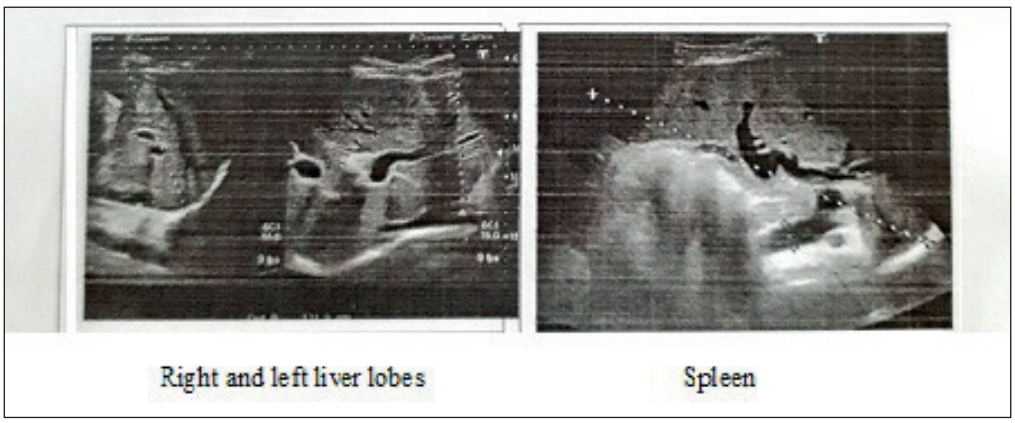

Fig. 3. Echographic dynamics of of the liver and spleen changes

Esophagogastrointestinal endoscopy data (12.10.2017) are presented on figure 2.

The esophagus is freely passable. The mucous membrane is pale pink, hyperemic in the lower third, at a distance of 30 cm from the incisors and to the hiatus, there are 4 varicose veins of the esophagus, which slightly protrude into the lumen by 3 mm. Endophoto 1. The hiatus is at the level of 42 cm from the incisors, it closes partially, it is freely passable, there is no CLE, palisade vessels are not expressed, there are no erosions in the area of the esophageal-gastric junction. With inversion – cardiac fold of 2nd degree.

The stomach is well expanded with air, freely permeable, on an empty stomach contains an increased amount of secretory fluid, bile. The folds of the mucous membrane are tortuous. The mucous membrane is focally hyperemic. In the lower third antral part of the stomach up to 20 small erosions of 2-3 mm in size are detected. Endophoto 2.

The pyorus closes completely, freely accessible for the endoscope. On the wall of the pylorus, on the hypertrophic fold, a rounded shape, 4*6 mm sized ulcer is determined. Endophoto 3.

The ampulla of the duodenum keeps its shape, freely accessible for the endoscope. The mucous membrane is focally hyperemic. The lumen of the postbulbar department is easily filled with air, there is a small amount of bile in the cavity. Peristalsis is preserved, circular folds are well expressed, villi are conical. Duodenal papillae were not visualized.

Conclusion of esophagogastrointestinal endoscopy: 1st stage varicose veins of the esophagus. Chronic esophagitis. Erythematous gastroduodenopathy. Duodeno-gastric bile reflux. Multiple small erosions of the stomach. Ulcer of the pylorus.

Magnetic resonance imaging (12.12.2017): MRI signs of diffuse changes in the liver according to the type of its cirrhotic deformation, appearance of signs of secondary hemochromatosis. Portal hypertension syndrome, splenomegaly. Vascular venous collaterals in the cardioesophageal region and in the region of the portae spleni.

Due to severe thrombocytopenia and minor leukopenia, myelodysplastic syndrome was suspected and the following examinations were performed:

Bone marrow puncture (27.09.2017): atypical mononuclear cells of various degrees of maturity are found in the preparation.

Cytomorphological method (16.10.2017): reduced cellularity in the bone marrow. Cells of the granulocytic series at various stages of maturation, cells of the erythroblastic series (mainly normoblasts), reduced number of megakaryocytes, lymphocytes – 23,0% are represented.

Cytochemical method (16.10.2017): chemical reactions for myeloperoxidase, acid phosphatase, acid non-specific esterase were carried out. Absence of histiocytes/macrophages with an intense reaction to acid phosphatase and acid nonspecific esterase, which is characteristic for myelodysplastic syndrome of refractory anemia (MDS RA).

Immunophenotyping (16.10.2017): 18,1% lymphocytes, 1,4% blasts were identified in the bone marrow. The ratio of T- and B-lymphocytes is within normal limits. Cytomorphological and cytochemical research: suspicion of chronic tautoimmune thrombocytopenia.

Trepan-biopsy of the iliac bone (06.11.2017): bone marrow is normal with signs of reticulin fibrosis, morphological changes are most consistent with myelodysplastic syndrome.

Data of immunohistochemical and morphological examination of bone marrow (15.11.2017) correspond to changes in myelodysplastic syndrome. Immunohistochemical examination: hypocellular bone marrow with markedly reduced megakaryopoiesis, activated erythropoiesis, reduced granulopoiesis and lymphocytosis without signs of atypia/cellular atypia. Histological criteria of dysplastic syndrome are not fulfilled. No signs of Gaucher's disease in the material.

The patient was consulted at the Center for Orphan Diseases «Okhmatdit» (11.12.2017) to rule out lysosomal storage diseases. Data in favor of a hereditary disorder of the metabolism of amino acids, acylcarnitines were not found, Gaucher disease and sphingomyelinase deficiency (Niemann-Pick disease) were excluded:

1. Tandem mass spectrometry of blood plasma: according to the results of the analysis, no violation of the concentration of amino acids and acylcarnitines in the blood was found.
2. Lactate: 1,54 mmol/l
3. Ammonium: 8,3 μmol/l
4. α-1 antitrypsin – 1,44
5. Research on the activity of lysosomal enzymes: B-glucosidase – 8,2 nmol/h/ml of plasma (normal 5,1 – 9,5 nmol/h/ml); chitotriosidase – 17 nmol/h/ml of plasma (norm 0 – 159 nmol/h/ml), acid sphingomyelinase – within reference values.

Molecular genetic study (16.10.2018) to detect the H1069Q mutation by PCR (BI-PASA): no mutation, which causes Wilson's disease, was detected in the ATP7B gene. Genotype, respectively, HGVS p.[=];[=]. However, it is known that Wilson's disease can be caused by more than 300 different mutations in the ATP7B gene, the most common of which is H1069Q.

Based on the results of a comprehensive examination, the diagnosis was established: Cirrhosis of the liver of cryptogenic etiology. Hepatocellular failure, class A according to Child-Pugh. Intrahepatic form of portal hypertension. Varicose veins of the esophagus 0-1 st. Portal gastropathy. Splenomegaly. Hypersplenism. PSE 0-1 st.

On control examination of the patient laboratory results (14.10.2020) showed normal ESR – 6 mm/h, hemoglobin – 151 g/l, hematocrit – 42,8, erythrocytes – 4,47×1012/l, leukocytes – 3,54×109/l (normal range 3,9-10 ,2), segmented granulocytes – 64,4%, eosinophils – 1,3%, basophils – 0,5%, lymphocytes – 25,8%, monocytes – 5,7%), platelets – 57 g/l (normal range 166-389), average hemoglobin content in one erythrocyte – 33,7 pg (normal range 27,0-33,5).

Abdominal ultrasound (16.10.2020) revealed liver enlargement due to the left lobe (left lobe – 10,0 cm, right slightly reduced – 13,0 cm), with uneven contours, unevenly compacted parenchyma of medium echogenicity, emphasized and enriched vascular pattern; intrahepatic bile ducts are not dilated. V. portae expanded to 1,6 cm; The gallbladder is deformed, slightly enlarged, measuring 7,2*3,4 cm; the wall is compacted, the contents in the cavity are heterogeneous; choledoch 0,6

cm; Pancreas without echostructural changes. The spleen is enlarged, measuring 20,0*6,8 cm, homogeneous, with slightly increased echogenicity; v. lienalis expanded to 1,6 cm, tortuous at the gate; parenchymatous veins are dilated. Kidneys and bladder without features. Conclusion: Echographic diffuse liver changes. Pronounced splenomegaly (figure.3).

Esophagogastroduonenoscopy (23.03.2021) showed passable esophagus with moderately hyperemic mucosa, 3 collaterals of varicose veins in the lower third part. The hiatus closes completely. Small amount of liquid in the stomach, moderately hyperemic mucous membrane. Multiple erosions in the prepyloric part of the stomach. The pylorus is rounded. The bulb of the duodenum is easily passable for the endoscope, and the mucous membrane is hyperemic. Postbulbar section without features. The result of the study: Varicose veins of the esophagus of I-II st. Multiple erosions of the stomach.

As it can be seen, there is a slow progression in the clinical course of the disease.

CONCLUSIONS

In this case, with the help of additional methods of examination, metabolic disorders that can be considered as probable in the occurrence of the above-mentioned changes in the liver parenchyma – Wilson-Konovalov disease, Gaucher disease, Niemann-Pick disease – have been ruled out. Cytopenia (thrombocytopenia, leukopenia) was presumably associated with the syndrome of hypersplenism.

Based on the results of a comprehensive examination, the diagnosis of cirrhosis of the liver of cryptogenic etiology was established with a slow progression of the clinical course.

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CASE STUDY

RARE COMPLICATION OF COVID -19 DISEASE TINU SYNDROME IN A 11-YEAR-OLD BOY, FEATURES AND MANAGMENT

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ABSTRACT

Tubulointerstitial nephritis and uveitis syndrome (TINU) is a rare disease defined by a combination of different abnormalities, tubulointerstitial nephritis and uveitis. We describe an 11-year-old boy who got sick with the Covid-19 disease with positive outcome and after 2 weeks developed a complication – tubulointerstitial nephritis with pain in the abdominal cavity, loss of appetite, weakness and low-grade fever with further subsequent attachment of anterior uveitis. Laboratory indicators corresponded to renal insufficiency of tubular origin. Ophthalmological examination conducted against the background of redness of both eyes, photophobia, pain in the eyeball area and decreased vision confirmed bilateral uveitis. Analysis showed high levels of La/SS-B, anti-SARS-CoV-2 IgG with confirmed the suspicion of post-covid TINU syndrome. This case showed a good response to steroid therapy with long-term remission of nephritis and less clinical efficacy in the treatment of uveitis. Special attention should be paid to the occurrence of such a rare syndrome at an early stage after recovery from the Covid-19 disease.

KEY WORDS: children, tubulointerstitial nephritis and uveitis syndrome

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INTRODUCTION

While Covid-19 is commonly associated with infection of the lungs and heart, a growing number of cases indicates that infection can also impact the eyes and others internal organs. Approximately 10% people exposed to Covid-19 have at least one eye problem, such as dryness, redness, blurred vision and sensitivity to light. Conjunctivitis, or "pink eye," may also appear in the early stages of infection, suggesting that it may be one the first markers of acute Covid-19 infection [1-3], another patients suffer from kidney damage [4]. Multi-organ involvelment is based on data from recent studies [5] which show that the angiotensin-converting-enzyme-2 receptor is expressed not only in lungs but in many another internal organs such as eyes (conjuctival, corneal cell, retina), vessels, nerves, enterocytes of the small gut, the kidney proximal tubules. Combined eye and kidney damage – TINU syndrome in the acute Covid-19 disease has recently been described as a result of SARS-Cov-2 infection [6], where the ocular and kidney manifestations have an independent outcome; for the first – bilateral anterior uveitis (in early phase of disease) then tubulointersticial nephritis – two weeks later. Treatment includes topical and oral corticosteroids, which were supplemented with anti-TNF-alfa treatment. At the same time, the occurrence of TINU syndrome in the early period after recovery from Covid-19 infection, which is the subject of our publication, is of interest.

CASE REPORT

An 11 – years old boy applied 21.12.2020 for an outpatient appointment with complaints for abdominal pain, subfebrile temperature, weakness, loss of appetite. From the anamnesis, it is known that 2 weeks ago he recovered from COVID – 19 disease (nasopharyngitis, pneumonia, conjunctivitis and diarrhea, with positive nasopharyngeal swab for SARS-CoV-2 infection). Patient was examined clinically and paraclinically, the following changes were established – blood tests revealed: erythrocyte sedimentation rate (ESR) 38 mm/h, C – reactive protein (CRP) 1.59 mg/dl (n.v. < 0,5), platelets – 459 ×10*9/l, creatinin 56.8 (mkmol/L), it was above the normal value(n.v < 59), cholesterol 5.86 (mmol/L). The examination of the urine shows the following: albuminuria 150 mg/L, glukosuria 148 mg/dl, protein trases, urine specific gravity – 1025, an ultrasound examination of the kidneys was performed (moderate swelling), also was find the high level of specific anti – SARS – CoV -2 IgG: 11,25 (>1.1 positive) and diagnosis of post COVID – 19 interstitial nephritis was confirmed. Patient was treated with steroids – prednisone 1,0 mg/kg/day for 2 month with a gradual tapering of the steroids. The control tests showed the normalization of the relevant blood and urine indicators.

However, during the third week from the moment of recovery from interstitial nephritis, the boy turned to an outpatient appointment (18.03.2021) of an ophthal-

mologist with complaints of bilateral red eyes, eye pain, photophobia. The optical computerized tomography was done and bilateral irido-capsular synechiae, papilla edema, makulo edema were found and the diagnosis of anterior bilateral uveitis was made. Futhermore, the relapse of nephitis occurred. In addition to the previous analysis autoimmune tests were made – Ro/SS-A52, dsDNA, MPO, AMA M2, HLA B27 – negative, but the La/SS-B was moderately increased up to 2.3 kU/L (<0.3 negative result). On this background the diagnosis was specified to tubulointersticial nephritis and uveitis syndrome. To the steroid treatment (prednisone 0,5 mg/kg/day) were added topic 0,1% dexamethasone and mydryatics. According to the control survey data on 13.05.2021 recovery was established, however, the boy continued to receive steroid therapy, with its withdrawal at the end of May (20.05.2021). A new recurrence of uveitis occurred 7 days after withdrawal of steroid therapy and this relapse was treated by intraocular steroids with mydriatics which led to the stabilization of the disease. The third exacerbation of uveitis occurred after 2 months of remission and was treated by topic dexamethasone for 10 days, then for 1 month with topical nonsteroidal agents with positive outcome.

Now the patient is under dynamic observation and the last analyzes (0.6.07.2022) show long-term normalization of laboratory parameters: white blood cels – $5{,}27\times10^{9}$/L, Hemoglobin 131 g/l, platelets $431\times10^{9/L}$, erythrocyte sedimentation rate – 9 mm/hour, creatinin 52.6 (mkmol/L), cholesterol 4.79 (mmol/L), urine tests: urine specific gravity – 1025, albuminuria < 30 mg/L, glucose – negative, creatinin- 8.8 mmol/L (normal level), the La/SS-B – 0,17 kU/L and the patient has no complaints.

TINU syndrome is present with combined kidney and eye damage and was described for the first time in 1975 by Dobrin R.S. [7]. More than 250 cases have now been reported including post Covid-19 TINU and 60% patients were children [6,7,8]. The majority of cases have been reported in the pediatric nephrology and ophthalmology literature in the form case reports and small cohort samples of patients. Kidneys and eyes involvement can persist as asymptomatic and can have an independent outcome. The clinical picture of renal disease shows as acute kidney injury and resolves spontaneously with full recovery of kidney function, in contrast to this uveitis can persist longer or it recurs years after its first presentation [9]. There are no specific serum markers that are unique to patients with TINU syndrome, findings include elevated erythrocyte sedimentation rate, C-reactive protein, leukocyturia, glycosuria, antinuclear antibody, an autoantibody directed against renal tubular cells [8, 10]. Further more, antibodies that react to both tubular and uveal cells have been identified in the case of TINU syndrome [11].

The clinical picture of our patient during one and half year of follow up showed the full recovery of the kidney function after steroids therapy and several relapses of uveitis after its initial presentation. In addition, this is the first pediatric case with TINU syndrome after recovery from SARS CoV 2 infection in the international literature.

CONCLUSIONS

This case of the TINU syndrome showed several features of the course of interstitial nephritis with uveitis – existence of a "latent" interval between recovery from Covid-19 disease and starting of complication, independent outcome of tubulointerstitial nephritis and uveitis, good response to the steroid treatment, a long period of remission after relapse of nephritis, severe course of uveitis with frequent relapses, bad response to uveitis treatment.

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Conflict of interest

The Authors declare no conflict of interest

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CASE STUDY

A CASE OF KAWASAKI DISEASE IN AN EIGHT-YEAR-OLD BOY

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ABSTRACT

Kawasaki disease is an acute systemic disease characterized by the predominant lesions of middle and small arteries, alongside destructive and proliferative vasculitis development. The aetiology is currently being discussed. Infectious factors are mostly preferred, in addition, autoimmune mechanisms and genetic heredity are considered. The diagnosis of Kawasaki disease is established by clinical signs; laboratory changes are usually taken into account as are ancillary criteria.

The article discusses the clinical case of Kawasaki disease in an 8-year-old boy. Given the variety and inconsistency of the clinical symptoms (the child had four of the five mandatory criteria together with prolonged fever), there was a late diagnosis, namely on day 10 of the disease.

Due to the high risk of cardiovascular complications in the differential diagnosis of children with fever lasting more than 3 days should be considered Kawasaki disease, followed by mandatory heart echocardiography during the first 10 days of the disease, especially if the fever is accompanied by the increase of acute phase reactants. When treating children with chronic fever without a specific source, the doctor should be wary of Kawasaki disease, as it can clinically simulate acute respiratory viral disease, the onset of diffuse connective tissue disease, and infectious endocarditis, and can have common features and require differential diagnostics with coronavirus associated multisystem inflammatory syndrome.

KEY WORDS: mucocutaneous lymph node syndrome, vasculitis, paediatrics

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INTRODUCTION

Kawasaki disease (KD), or mucocutaneous lymph node syndrome, is an acute systemic disease characterized by the predominant middle and small arteries lesion and the destructive proliferative vasculitis development. It is usually a self-limiting condition in which fever and inflammation last for about two weeks without treatment. However, KD can cause aneurysms and coronary artery stenosis. Thus, KD is one of the causes of acquired cardiovascular disease. The aetiology of the KD is currently being discussed. Most authors consider the infectious factor to be the most significant (mostly viral), which explains the peak incidence in spring and winter [1]. In addition, autoimmune mechanisms and genetic heredity are considered as factors in the development of KD. There are 11 known genetic loci associated with this disease [2]. KD is more common in Asia, where it was first described by T. Kawasaki in 1967. Thus, KD in Japan occurs with a frequency of 330 cases per 100,000 children. In contrast, in North America, Australia and Europe, there are only 19,7 to 29,8 cases per 100,000 children [3]. Children under 5 years get sick more often, but the disease is also registered in older children. It should be noted that all statistics on KD are usually understated due to significant difficulties in diagnosis and the exceeding presence of incomplete disease forms.

Attention to KD has recently increased significantly due to the COVID-19 pandemic. Some similarities between the immune response in multisystemic inflammatory syndrome in children, which occurs in the body in response to coronavirus, and the changes that are characteristic of KD complicate diagnostics [1,4,5].

KD is a clinical diagnosis, which means that there are no specific laboratory tests to confirm the diagnosis. Laboratory changes are usually considered as supportive criteria[6]. Thus, classic KD is characterized by: fever lasting more than 5 days without any other explanation, and the presence of at least 4 of the following 5 criteria: bilateral conjunctival injection; changes in the oral mucosa (redness and cracks of the lips, injection of the pharynx, or strawberry tongue); changes in the peripheral extremities (erythema of the palms and/or feet, swelling of the hands or feet – in the acute phase and desquamation – in the recovery phase); polymorphic rash (maculopapular or scarlet fever-like rash involving the extremities, torso, perineum); cervical lymphadenopathy (at least 1 lymph node ≥1.5 cm in diameter) [6].

The oral mucosa lesions are observed in approximately 90% of KD cases, polymorphic rash in – 70-90%, changes in the extremities – in 50-85%, ocular changes – in 75% and cervical lymphadenopathy – in 25-70%[4]. A significant difficulty in the diagnosis is that the KD manifestations do not occur simultaneously, but sequentially and do not have a typical occurrence order, making it difficult to combine separate symptoms into an overall picture of the disease. The number of incomplete disease forms is also increasing, in which in addition to fever there are not 4, but only 2-3 symptoms [7].

Brief description of the main manifestations. Fever is the most significant sign of this disease. It is pertinacious and resistant to antipyretics. The "diagnostic minimum" is 5 days, but it lasts much longer usually. The main symptoms tend to appear during the first 10 days amid fever. Conjunctivitis is always bilateral, non-exudative, and begins within a few days of the fever onset. Photophobia may occur. Mucositis often becomes apparent as KD progresses. There are cracked red lips and "strawberry tongue", which is the result of the filamentous papillae obstruction. The rash is often polymorphic, beginning within the first few days. Skin changes may also be manifested by redness or crusting at the Bacillus Calmette-Guérn vaccination site. Changes in extremities are the latest manifestation in the vast majority of cases. Swelling of hands and feet often occurs, as does diffuse of palms` and soles`. Noted can be leaf-like desquamation in the convalescence phase, which also begins with the arms and legs. As for lymphadenopathy, it is the least consistent sign of KD, which may be absent in half or even three-quarters of patients. Usually anterior cervical nodes are involved; one large node is often palpable, although ultrasound usually reveals numerous nodes located like a grape bunch [7-9].

Cardiovascular manifestations are not a part of the diagnostic criteria for KD, but they support the diagnosis. Gallop sounds and tachycardia may be observed during the first 10 days, which is proportional to the fever severity. These symptoms are the result of lymphocytic myocarditis, which usually occurs in KD. In addition, heart sounds may be muffled due to pericardial effusion, which occurs in approximately 30% of patients, but is usually small in volume. Among all the cardiovascular system manifestations the most dangerous ones are myocarditis, heart failure and coronary artery aneurysms, which usually develop within the first 7 to 10 days after the onset of the disease. The latter makes early diagnosis and treatment relevant. Therefore, echocardiography should be performed in all patients with KD as soon as there are suspicions of the diagnosis so that a benchmark for further monitoring of the dynamics and evaluation of the effectiveness of treatment could be set [10-12].

Arthritis is also not a diagnostic criterion, but it occurs in almost 25% of patients with KD. Large joints (knees, ankles and hips) are the first to be involved. Arthritis is usually limited and does not deform the joints [7-9].

Other manifestations, such as diarrhoea, vomiting, abdominal pain, cough, rhinorrhoea, and irritability prevail in the prodromal period [13]. Tonsillitis, pneumonia symptoms or urinary tract infections are also common at the onset of the disease. However, the persistence of fever after the antibiotic's treatment raises doubts about the diagnosis and gives reason to continue the diagnostic search.

Laboratory evaluation. Although laboratory criteria are not included in the classic diagnostic criteria, they can nevertheless support the diagnosis of KD in ambiguous cases, so they are useful in diagnostic algorithms. Typical manifestations include acute phase reactants increase, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR). Thrombocytosis usually develops after the seventh day of illness, leucocytosis and a left shift. Normochromic and normocytic anaemia are also common [7-9].

Intravenous immunoglobulin (IVIG) treatment during the first 10 days of illness reduces the coronary artery aneurysms incidence 5-fol compared to untreated children. Usually a single dose of IVIG is prescribed at the rate of 2 g/kg, which is administered within 8 to 12 hours. IVIG should be administered in cases of late diagnosis, even after 10 days, if the patient has signs of vasculitis or systemic inflammation (persistent fever, increase of the acute phase of inflammation). During the acute phase of the disease, it is also recommended to administer aspirin in a wide range of doses (30-100 mg/kg/day). The dose of aspirin should be reduced in 48 hours after fever cessation to 3-5 mg/kg/day and continued until laboratory inflammation signs (ESR, CRP, platelet count) return to normal, in the absence of coronary artery abnormalities according to echocardiography echocardiography [6,14,15].

CASE REPORT

An 8-year-old boy was hospitalized with complaints of prolonged fever up to 39˚-39.5˚C, skin rash on the torso, perineum and extremities, swelling of the hands and feet, general weakness, and catarrhal phenomena. Hospitalization took place on the 8th day of the disease; the child's general condition was assessed as moderately severe. After taking a medical history it was detected that the disease began acutely with a rise of body temperature to 39˚C, which couldn't be lowered with antipyretics. During the first three days the temperature ranged from 39 to 39.5˚C. Taking paracetamol and ibuprofen in doses appropriate to the age reduced the fever for a short interval of 2-3 hours by 0.5˚C.

At the end of the 3rd day of the disease there were symptoms of bilateral catarrhal conjunctivitis, changes in the oral cavity – "strawberry tongue", throat hyperaemia, and chapped lips; this was accompanied by growing fatigue. The child was examined by a paediatrician on an outpatient visit; the situation was considered as manifestations of acute viral infection. The patient was prescribed symptomatic therapy: nasal lavage, throat lozenges and antipyretics.

On the 4th day, a rash appeared in the perineum area. Subsequently, the rash spread to the limbs and torso (Figure 1, 2).

The rash was scarlatiniform and was not accompanied by itching. When the rash appeared, the child was examined by an infectious disease physician who found no reliable data in favour of any specific infectious pathology.

The blood count was performed on the 5th day of disease and revealed leucocytosis up to 13x10^{9}/L, increased ESR to 38 mm/h, and decreased haemoglobin to 109 g/l; the rest of the indicators were within normal limits. On the same day, after the doctor's examination, the mother made the decision to start antibacterial therapy with azithromycin by herself. In Ukraine, pharmacies are not forbidden to sell antibiotics without medical prescription. No outpatient

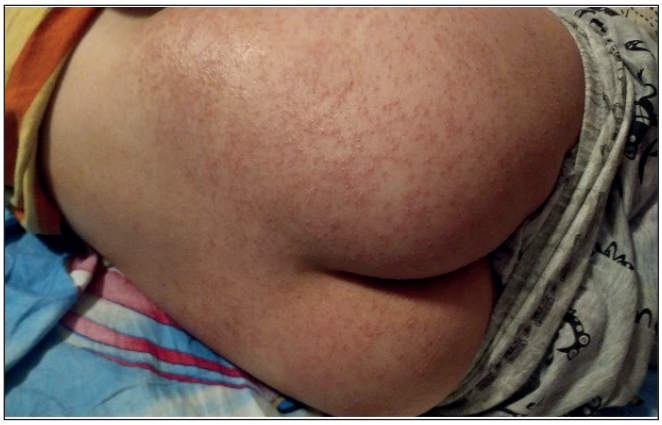

Fig. 1. Rash on the buttocks

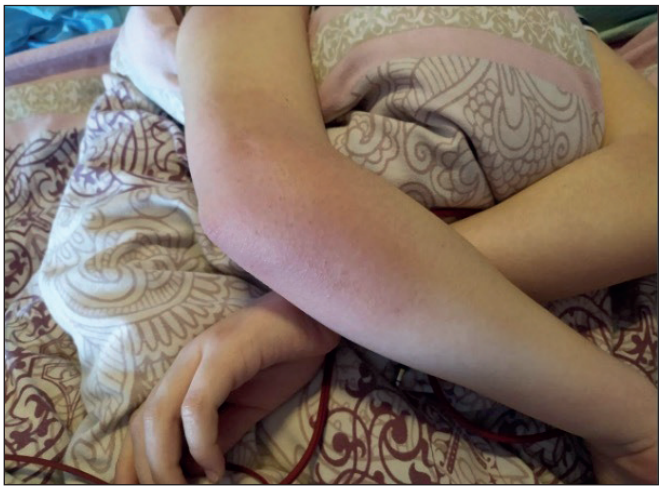

Fig. 2. Rash around the elbow joint

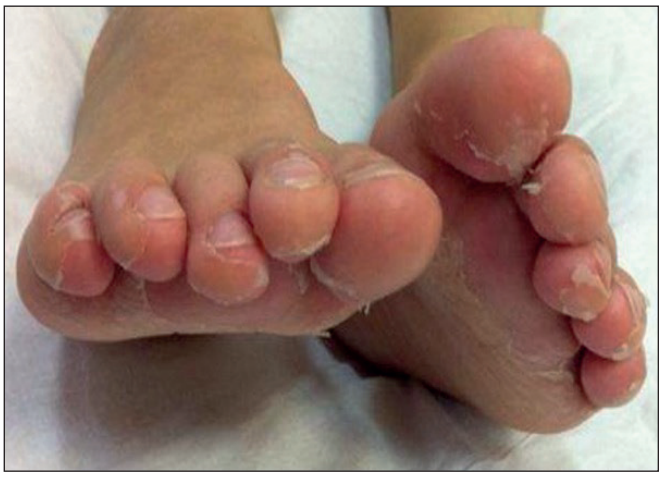

Fig. 3. Desquamation of the skin of the palms and sole

paediatric follow-up took place. The fever of 39°-39.5°C continued and the child was given antipyretics to relieve symptoms. No positive dynamics were observed during the disease.

Swelling of the extremities appeared on the 8th day after the disease onset. An ambulance was called and the child was admitted to the hospital. Blood count revealed: leucocytosis – $15x10^9$/L, increased ESR to 50 mm/h, thrombocytosis – $540x10^9$/L, increase in CRP – three times. After the hospital admission it was decided to start antibacterial therapy ex juvantibus, due to the increase in acute haematological parameters in the dynamics, duration of fever, prior inadequate antibacterial therapy and, consequently, the lack of response to it. Later a broad-spectrum antibiotic was prescribed from the 3rd generation cephalosporin group, namely ceftriaxone in the appropriate dosage according to the age and weight of the child. A diagnostic search was launched simultaneously with the start of therapy, which was aimed at identification of a possible infection source.

On the 9th day from the start of the disease (on the second hospitalisation day) the child developed pain in the knee joints without visual inflammation signs. Instrumental and laboratory data revealed the following: chest X-ray – without changes, blood culture for sterility, examination for typhoid-paratyphoid infection Taking into consideration the epidemiological situation was conducted an examination for COVID-19: PCR test (twice), IgM, IgG levels determination, which results were also negative, hence excluding both – the presence of atypical long-term coronavirus infection and the active stage of the disease (Differential diagnosis with multisystem inflammatory syndrome). Ultrasound examination of the abdominal cavity and joints did not reveal pathological changes. Tachycardia was found during auscultation, that correlated with the level of fever, the ECG revealed transient incomplete right bundle branch block. During the first two days of the child's hospital stay, the rash remained within the extremities, perineum and torso, there was no itching, the desquamation phenomenon increased over time (Figure 3).

Conjunctivitis and "strawberry tongue" regressed. The area of pain spread from the knees to the hips. The enlargement of peripheral lymph nodes was not observed during the entire period of the disease. Swelling of the extremities lasted for two days. After 48 hours of the ceftriaxone treatment, no response to antibacterial therapy was noted, the child continued to have a fever, and his general condition remained moderate.

From 10th of the disease, glucocorticosteroid therapy was prescribed at a dose of 2 mg/kg/day of prednisolone, which reduced joint pain and had a partial effect on fever level: the temperature dropped to subfebrile values and increased only twice a day. KD was suspected in a child after receiving the results of the abovementioned laboratory and instrumental studies and the analysis of the existing clinical symptoms (bilateral catarrhal conjunctivitis, changes in the oral mucosa in the form of cracked lips, redness, "strawberry tongue", changes in the extremities in the form of redness, swelling, and skin rash that was followed by desquamation) that were associated with prolonged fever.

Echocardioscopic transthoracic examination was performed on the 11th day of the onset. No ultrasound data in favour of coronary artery dilatation were detected. Thus, the child was diagnosed with KD due to the presence of 4 of the 5 mandatory criteria with the underlying prolonged fever.

Based on the fever regression on the 12th day from the disease onset and the absence of coronary artery disease, as

well as the stabilisation of the patient's general condition, intravenous immunoglobulin was not administered, the antibiotic was discontinued and aspirin was prescribed at 5mg/kg/day [6,14,15]. The child remained under observation in the hospital for another three days. There were observed improvements in general condition, body temperature normalisation, arthralgia, oedema of the extremities and skin rash regression, and the spread of desquamation. There was a positive trend in laboratory parameters: the total leukocytes count was $11x10^9$/L, total platelets count – $480x10^9$/L, ESR remained at 45 mm/h, CRP decreased by half. Biochemical parameters (kidney and liver tests, glucose, total protein levels) did not demonstrate abnormalities during the disease.

The child was discharged in good health with the following recommendations:

- To continue aspirin taking at a dose of 5 mg/kg/day until inflammatory markers stabilization;
- To monitor body temperature daily monitoring before taking aspirin;
- To perform echocardioscopy in 2 and 6 weeks under the cardiorheumatologist`s supervision.

We present a clinical case of KD in an 8-year-old child. The peculiarity of this case was the late diagnosis on the 11th day from the disease onset. Late diagnosis can be explained by the gradual onset of clinical symptoms, lack of adequate dynamic monitoring of the child's condition at the outpatient stage and delayed child`s hospitalization in the hospital. The clinical picture was characteristic of the full form of the KD and contained 4 of 5 mandatory symptoms together with prolonged fever: bilateral catarrhal conjunctivitis, changes in the oral mucosa in the form of chapped lips, redness and "strawberry tongue", changes in the extremities (in the form of hyperaemia and oedema, scarlatiniform rash followed by desquamation). Of the accessory symptoms, the child had arthralgias which is not of diagnostic value but may support the diagnosis. In this case, the disease was moderate and no cardiovascular complications were observed. IVIG was not administered due to diagnosis later than 10 days, no coronary artery disease, and regression of fever at the time of diagnosis. For prophylactic purposes, aspirin was prescribed and further monitoring of the echocardioscopic picture of the heart and coronary vessels was recommended [6,14,15].

CONCLUSIONS

1. There are significant difficulties in the early diagnosis of KD due to the variety and gradual symptoms onset, the lack of definitive diagnostic tests, the course of the disease in the form of atypical or incomplete forms.
2. Due to the high risk of cardiovascular complications, the diagnosis of KD should be considered in the differential diagnosis in children with fever lasting more than 5 days with mandatory echocardioscopy performed during the first ten days of the disease, especially if fever is accompanied by an increase in acute phase reactants.
3. Children who have KD need further careful cardiovascular system monitoring.
4. Paediatricians and family physicians should be suspicious about KD, because it can have a similar course to the acute respiratory disease, with the diffuse onset of connective tissue disease, infectious endocarditis, and have common features with multisystemic inflammatory syndrome in children with COVID-19 which determines the need for differential diagnosis.

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CASE STUDY

PYODERMA GANGRENOSUM AS THE ONLY MANIFESTATION OF ASYMPTOMATIC NEWLY DIAGNOSED NONSPECIFIC ULCERATIVE COLITIS. CLINICAL CASE

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ABSTRACT

The aim: To study the clinical case data for the feasibility of the obligatory inclusion of endoscopic methods of the gastrointestinal tract examination in patients with pyoderma gangrenosum of an unknown etiology.

Clinical case: A patient under our supervision was with a not previously treated pyoderma gangrenosum of the shin skin. In the process of differential diagnostics by colonoscopic examination, nonspecific ulcerative colitis was diagnosed without clinical intestinal manifestation. A prescribed pathogenetic treatment of nonspecific ulcerative colitis led to the healing of the ulcer on the leg and induction of colitis remission. Thus, the first manifestation of asymptomatic colitis was pyoderma gangrenosum.

Conclusions: Patients with pyoderma gangrenosum should be aware of the possibility of NUC, even in the absence of gastrointestinal symptoms, to get an early diagnosis and adequate treatment, to avoid disease manifestation and further complications. The inclusion of obligatory endoscopic examination of the gastrointestinal tract will increase the diagnosis of the etiology of severe skin lesions and increase the detection of asymptomatic nonspecific ulcerative colitis.

KEY WORDS: pyoderma gangrenosum, nonspecific ulcerative colitis, inflammatory bowel diseases

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INTRODUCTION

Pyoderma gangrenosum (PG) is a chronic, painful, aggressive, recurrent, ulcerative progressive skin disease of unknown etiology. According to the scientific data, up to 50% of cases of PG are of idiopathic origin. Louis-Anne-Jean Brocq, a French dermatologist, was the first to report about a group of patients with typical symptoms of PG in 1908, naming it "phagedenisme geometrique". Its relation to nonspecific ulcerative colitis (NUC) was recognized by L.A. Brunsting twenty years later in 1930 [1, 2]. However, the frequency of diagnosed inflammatory bowel diseases (IBD) on the background of PG remains extremely low nowadays. PG is a rare but serious peptic ulcer disease, the treatment of which is mainly empirical, often ineffective and long-term, which can delay timely diagnosis and have serious clinical consequences [3-5].

The average prevalence is 3-10 cases per 1 million population [2]. PG is most often observed in middle-aged people. The etiological factors of PG have not been established. The pathogenesis is insufficiently studied [1]. Some authors believe that the pathogenesis is based on a defect in neutrophils' chemotaxis and their impaired reactivity. Immune response disorders and cross-reactions of autoantibodies to antigens common to the skin, intestines or joints are also considered [1]. Pyoderma gangrenosum (PG) occurs in the practice of doctors of various specialties: surgeon, dermatologist, rheumatologist, gastroenterologist, as it is often associated with diseases of the internal organs. Most often PG goes hand in hand with such diseases as nonspecific ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis, Crohn's disease, myeloproliferative diseases. PG is also often associated with HIV, hepatitis, systemic lupus erythematosus, Takayasu's disease, and others. [2, 6-8].

During an active examination, NUC with equal frequency at men and women with a peak of age incidence between 25 and 54 years is diagnosed in 50% of patients with PG [3,4]. Conversely, 0.5 to 5% of patients with NUC have PG. 4 variants of pyoderma gangrenosum are described: ulcerative, pustular, bullous and vegetative. Ulcerative and pustular variant of PG are associated with inflammatory bowel disease. PG can occur before, during or after the onset of inflammatory bowel disease, and both diseases can occur independently of each other [2, 5, 9].

Ulceration begins as a follicular pustule with rapid growth, tissue necrosis, expansion of the affected area. Erythema with infiltration and swelling of the surrounding skin is observed. The edges of the ulcer are "eroded", of purple or bluish color. When a secondary infection joins, the ulcer is "covered" with pus and unpleasant odour [4].

The diagnosis of PG is a diagnosis of exclusion because of numerous causes of skin ulcers, including infections, tumors, vasculopathy, vasculitis, trauma, etc. [3,7]. Therefore, to improve the diagnosis of PG the diagnostic criteria by P. von den Driesh and later W.P. Su and others have been

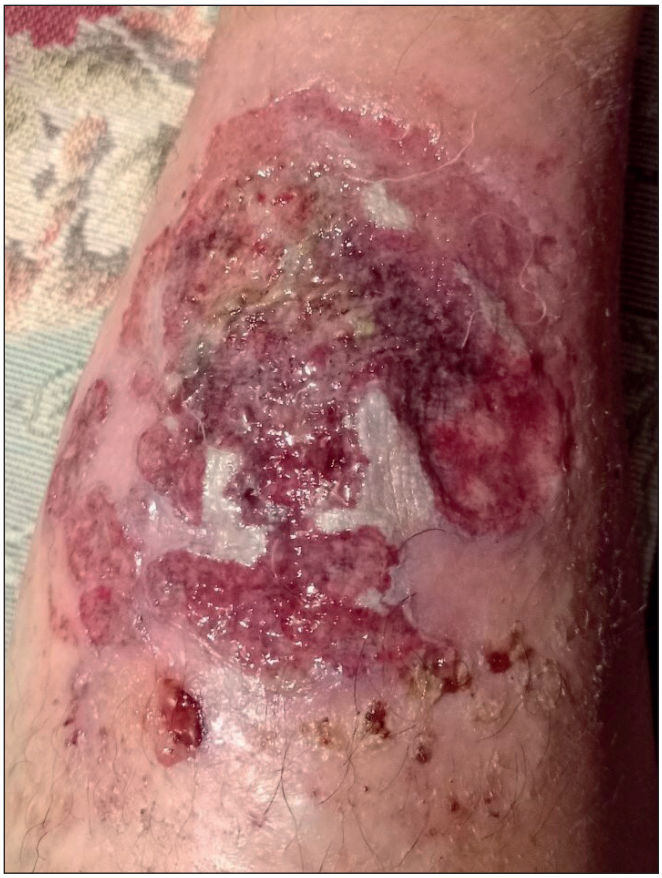

Fig. 1. Focus of pyoderma on the lower limb

offered [10, 11]. Two major diagnostic criteria are required to confirm the diagnosis of PG:

- rapid progression of painful, necrotizing skin ulcers with irregular, "eroded", raised edges;
- exclusion of other causes of skin ulcers;

and at least two minor criteria:

1) positive phenomenon of pathergy (appearance of painful ulcers due to minor injuries);
2) lattice scar;
3) systemic diseases associated with PG;
4) histopathological completion: "sterile" infiltration of the skin by neutrophils, +/- mixed inflammation, +/- lymphocytic vasculitis;
5) response to treatment (positive response to the use of systemic, immunosuppressive, steroid therapy) [2].

THE AIM

To study the clinical case data to assess the feasibility of obligatory inclusion of endoscopic methods of gastrointestinal examination in patients with pyoderma gangrenosum of an unknown etiology.

CLINICAL CASE

Patient M., 49 years old, was under our supervision. She had fallen ill 11 months ago with the appearance of pustular skin diseases in the form of paronychia of the fingers, boils, and foci of streptoderma on the face and neck. She was treated on an outpatient basis in another hospital of our region. 2 months ago, a lesion of skin up to 6 cm in diameter appeared on the shin, which progressively increased and ached, without the proper effect of local treatment. Given the latter, the recurrent nature of skin manifestations and the appearance of laboratory signs of moderate anemia, she consulted and was hospitalized. At the time of examination there was an ulcer defect up to 11 cm in diameter of dark cherry color with a red-black border, with eroded edges in some places and partial marginal epithelialization on the skin of the lower third of the right leg (Fig. 1). The vivid pain syndrome at the touch should be mentioned. The patient experienced general weakness and dizziness during exercise.

There is no pathology in the anamnesis of life. While being hospitalized it was objectively stated that the general condition of the patient is closer to the satisfactory one. Joints are visually unchanged, movements in the joints of the lower extremities are painless. The strength of the hands is preserved, the patient walks independently. Respiration is vesicular, with a hard tinge, wheezing is not heard. Heart tones are rhythmic, sonorous. Blood pressure is120/80 mm Hg. Art., heart rate is 68 beats / min. Abdomen is soft, neither painful, nor bloated. Pasternatskyi's symptom is negative on both sides. Physiological stools are regular.

Diagnosis at hospitalization was necrotic shin ulcer. There was suspicion for malignancy and moderate anemia.

The results of laboratory tests were:

General blood test: erythrocytes – 3.31 · 10 / l, hemoglobin – 90 g / l, platelets – 424 • 10 / l, leukocytes – 10.97 • 10 / l; leukocyte formula: rod-shaped – 5%, segment-nuclear – 68%, eosinophils – 3%, basophils – 0%, lymphocytes – 20%, monocytes – 4%, ESR – 38 mm / h.

Biochemical blood analysis: bilirubin – 10.5-0-10.5 microM / l, vol. etc. – 1.0, ALT – 0.25 mmol, AST – 0.25 mmol, total protein – 60.0 g / l, creatinine 76.0 micromol, urea – 4.3 mm / l. Ionogram: potassium – 3.5 mmol / l; sodium – 132 mmol / l.

Antibodies to: HIV1 / 2, HBsAg, hepatitis C, the causative agent of syphilis (Treponemae pallidi) – not detected. Glycosylated hemoglobin (HbA1c): 5.4 (4.5-6.2%).

Coagulogram: prothrombin time – 15.2sec; prothrombin index – 96%; total fibrinogen – 4.2g\l; fibrinogen B (-), ethanol test (-), INR 1.1.

General urine analysis: light yellow color, transparent, specific gravity – 1013, acid reaction, protein – 0.066, epithelium – 14-16 in p / s; leukocytes- 15-16 in p / z; mucus +; bacteria ++.

Electrocardiography was a variant of the norm.

Ultrasound examination of internal organs. The liver was slightly enlarged, due to the right lobe. The left lobe was 7.3 cm. Contours were clear, smooth. The parenchyma was homogeneous, medium echogenic. The bile ducts, portal veins and hepatic veins were not dilated. The gallbladder was elongated, with clear and smooth contours. The walls were compacted, not thickened, their filling was anechegenic bile. The pancreas

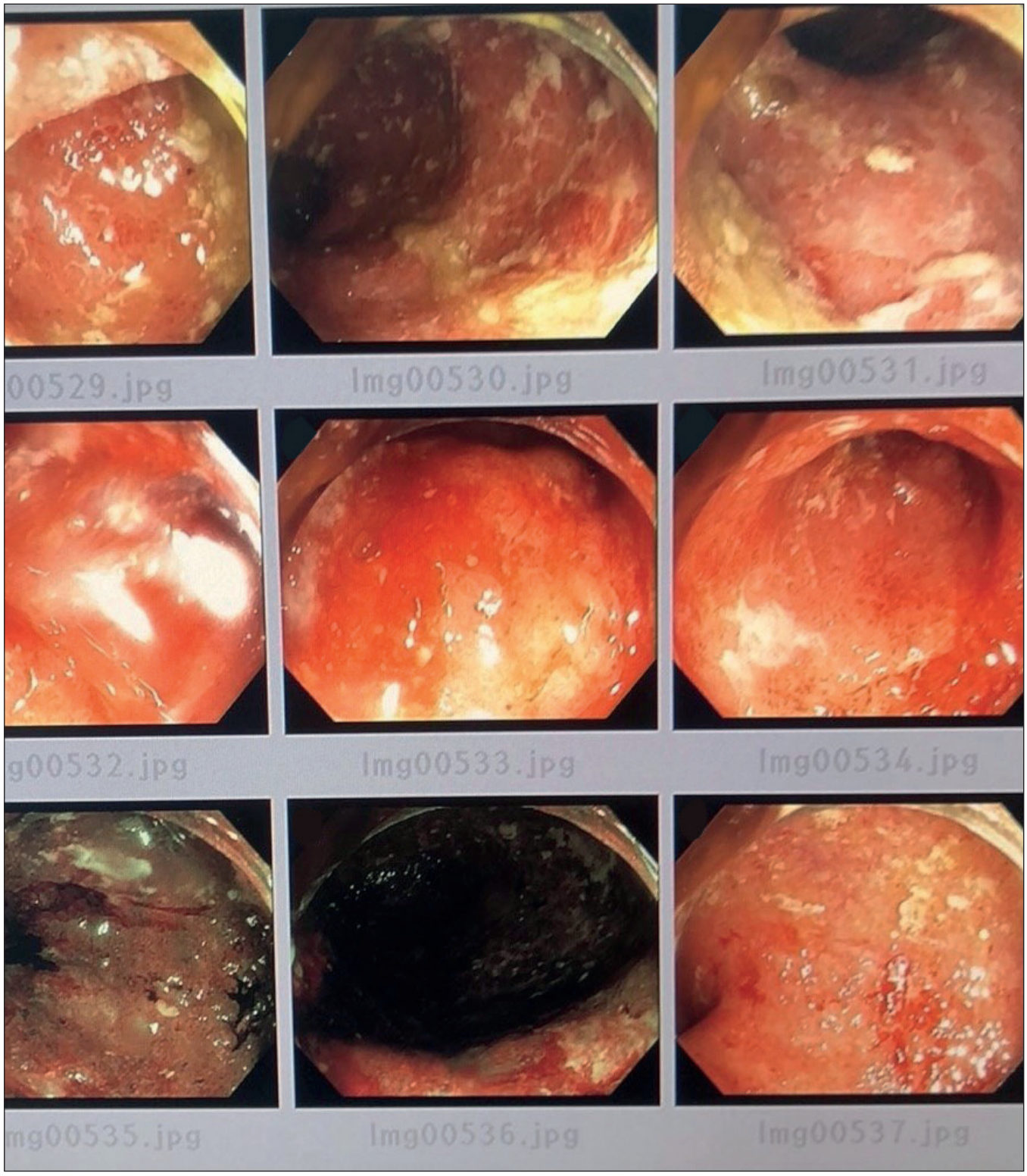

Fig. 2. Endoscopic picture of newly diagnosed non-specific ulcerative colitis

was of normal size. The structure was fine-grained, compacted. Echogenicity was average. Contours were clear, smooth. The spleen was not enlarged. The kidneys were of normal size, parenchyma was homogeneous, not thickened. There were salt inclusions in renal pelvis, more on the left side.

The duplex ultrasonographic examination of the vessels of the left lower extremity. No data on the violation of the main blood flow through the main arteries of the left lower extremity were found, as well as on deep vein thrombosis.

The results of the patohistological examination of the shin ulcer biopsy were as follows. Micro: connective tissue pieces with diffuse purulent infiltration, necrotic tissue, small, not numerous pieces of squamous epithelium. Pathohistological conclusion (diagnosis): inflammatory infiltrate.

During the period of hospitalization, comprehensive treatment was given, including antibacterial therapy (fluoroquinolone III generation – levofloxacin in combination with metronidazole), probiotics, fluconazole, nonsteroidal anti-inflammatory drugs, analgesic therapy (dexketoprofen intramuscularly in severe pain). Local care of the wound was also performed with a solution of betadine and Olasol. Occlusive hydrogel dressings were used to maintain a moist environment in the wound.

Given the anemia, fibrogastroduodenoscopy was performed. Erythematous gastropathy was observed without ulcerative and erosive defects.

Colonoscopy was performed. An endoscopic picture of nonspecific ulcerative colitis was diagnosed in the form of a smoothed vascular pattern, erosions and contact bleeding ulcers (Mayo index being 3 points) (Fig. 2).

A biopsy of the mucous membrane was performed. Micro: Nonspecific ulcerative colitis. Thus, the patient was diagnosed with nonspecific ulcerative colitis without clinical intestinal manifestation. The first sign of colitis was pyoderma gangrenosum.

The treatment was adjusted with 5-ASK (Salofalk) at a dose of 8g per day; Sorbifer 1 t 2 g per day.

After the 1st week of treatment, the patient's quality of life improved, which was marked with a significant decrease in the intensity of pain both when walking and when changing bandages. The wound surface also decreased. During the 2nd week the quality of granulation tissue improved and marginal epithelialization increased. On the 15th day the patient was discharged from the hospital for the further outpatient treatment. After 56 days (from the beginning of pathogenetic treatment) complete healing of the shin wound was noted.

After 2 months the control colonoscopy showed that Mayo index was 0 points. The dose of Salofalk was altered.

The given patient has been observed for 2 years. There was 1 recurrence of pyoderma which was successfully treated with Salofalk within 1.5 months at a dose of 3g per day. Intestinal manifestation of nonspecific ulcerative colitis was not observed during 2 years.

DISCUSSION

Pyoderma gangrenosum (PG) is considered to be a cutaneous manifestation of several systemic diseases. It is associated with: rheumatoid arthritis, myeloproliferative disorders, liver diseases, Wegener's granulomatosis, diabetes mellitus, and inflammatory bowel disease. In approximately 50% of cases, it is not possible to determine a concomitant disease, therefore it is called idiopathic pyoderma. Inflammatory bowel diseases are the commonest ones among systemic diseases, which accounts for 1/3 of the cases. Approximately 20% of patients who have skin lesions indicating pyoderma gangrenosum may have an inflammatory bowel disease.

The relationship between PG and the duration, the duration and severity of ulcerative colitis are controversial.

Pyoderma gangrenosum is believed to result from a reaction against intestinal disease antigens. The presence of bacterial antigens in the intestinal lumen and their absorption through the affected colonic mucosa can cause and prolong a local and systemic inflammatory response. It will result from the stimulation of cells of the immune system and the production of pro-inflammatory cytokines. The existence of an antigenic relationship between bacterial antigens and the mucosa of the colon, biliary tract, skin, and/or joints would make these organs real "antigens-targets" which would explain various manifestations.

Pyoderma gangrenosum manifests during an active intestinal disease in most of the cases described in the literature. It often coincides with an exacerbation of the previously diagnosed colitis. Intestinal symptoms precede or accompany pyoderma gangrenosum, and exacerbations can usually be associated with worse skin lesions. Nevertheless, pyoderma gangrenosum can occur at any stage of the disease without active inflammation, even after total colectomy. In the described clinical case, skin manifestations preceded the diagnosis of the initial ulcerative colitis. This fact confirms the importance to correlate both pathologies for active early diagnosis, even in the absence of clinical intestinal manifestations of the disease and early pathogenetic treatment.

The female patient has an ulcerative type of pyoderma gangrenosum, characterized by a deep and painful ulcer with a purple border and a necrotic purulent focus. This type generally affects legs, as in the patient under study.

When PG is associated with inflammatory bowel disease, therapy should be directed at the intestinal disease, the remission of which is accompanied by clinical improvement of skin lesions with mandatory local treatment aimed at preventing the development of secondary infectious lesions and complete healing of the wound.

In accord with the available literature, there are few descriptions of the occurrence of severe skin lesions in the manifestation of inflammatory bowel disease. This, together with the above presented clinical case, emphasizes the importance of the ratio of both pathologies for the purpose of early endoscopic diagnosis and pathogenetic treatment.

CONCLUSIONS

Patients with pyoderma gangrenosum should be aware of the possibility of NUC, even in the absence of gastrointestinal symptoms, to get an early diagnosis and adequate treatment, to avoid disease manifestation and further complications. The inclusion of obligatory endoscopic examination of the gastrointestinal tract will increase the diagnosis of the etiology of severe skin lesions and increase the detectability of asymptomatic nonspecific ulcerative colitis.

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ORIGINAL ARTICLE

MULTIPLE ACUTE POSTERIOR CIRCULATION STROKE WITH LESIONS IN THE PONS AND BOTH HEMISPHERES OF THE CEREBELLUM ASSOCIATED WITH OVARIAN HYPERSTIMULATION SYNDROME: A CASE REPORT OF A WHITE EUROPEAN ADULT IN UKRAINE

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ABSTRACT

We have presented a brief literature overview of the disease, supported by a clinical case of multiple acute posterior circulation strokes with lesions in the pons and both hemispheres of the cerebellum associated with ovarian hyperstimulation syndrome in a white young European adult in Ukraine. Specific features of posterior circulation stroke associated with ovarian hyperstimulation syndrome were determined, analyzed, and described.

Complex posterior circulation cerebral infarction in the pons and both hemispheres of the cerebellum associated with ovarian hyperstimulation syndrome has not been reported before but has devastating consequences for both mother and fetus. Strokes in patients with OHSS must be timely prevented, promptly diagnosed, and treated to avoid high morbidity and mortality associated with it.

KEY WORDS: stroke, in vitro fertilization, posterior circulation stroke, pons, cerebellum, ovarian hyperstimulation syndrome

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INTRODUCTION

Globally, fertility rates have dropped dramatically [1]. An estimated 15% of couples worldwide have trouble conceiving [2]. About 9% of men and 10% of women aged 15 to 44 reported infertility problems in the United States [3]. Infertility is a global health issue affecting over 186 million individuals of reproductive age worldwide and has an impact on their families and communities [4-6].

Ovarian hyperstimulation syndrome (OHSS) is one of the most serious and potentially fatal iatrogenic complications associated with ovulation induction during a complex series of procedures used to help with fertility or prevent genetic problems and assist with the conception of a child, in-vitro-fertilization (IVF). Serious OHSS complications include massive ascites, hydrothorax, thromboembolic events, and maternal death [7]. However, little to no data has been published on cerebral infarction associated with OHSS [8-11]. Moreover, no clinical cases of multiple acute posterior circulation strokes with lesions in the pons and both hemispheres of the cerebellum are reported on this topic.

Worldwide, stroke is a leading cause of death, long-term disability, and mortality [12-14]. Approximately a quarter of all strokes account for posterior circulation stroke (PCS) [15-18]. PCS has a more severe clinical course, higher mortality, and is more difficult to diagnose, compared to anterior circulation stroke [19-26]. Pontine infarctions (PI) are the most common among ischemic strokes of the brainstem, associated with high mortality and morbidity [27-29]. Clinical presentation of PI ranges from a classical crossed syndrome, less common pure motor or sensory stroke to severe respiratory and cardiac dysfunction [30, 31].

Around 3.7% of all strokes occurred in patients aged 15-45 years [32]. In women, pregnancy exposes a high risk for ischaemic events [35]. However, with growing infertility and expanding application of assisting conception of a child, should be growing awareness of stroke in young patients associated with OHSS [33, 34].

THE AIM

The aim of this study was to determine clinical and imaging features of posterior circulation stroke associated with ovarian hyperstimulation syndrome, illustrated with a clinical case presentation in a white European adult

CASE REPORT

Patient S., a 39-year-old white European woman, presented to the emergency room of the Neurological Center of the University Hospital (Oleksandrivska Clinical Hospital) in Kyiv, Ukraine, with complaints of severe headache, dizziness, nausea, vomiting, diplopia, ptosis of the right eye, slurred speech, numbness and weakness of the left half of her body, and lower abdominal pain. All symptoms developed suddenly. The patient has a previous history of infertility and underwent IVF five weeks before admission. Other history was unremarkable.

Findings Upon Admission: BP – 110/70 mm Hg, pulse rate – 90 beats/min. The patient was alert and oriented in space, time, and herself. Conciseness was impaired. Neurological deficit: slurred speech, right-sided ptosis, divergent strabismus, weakness of the left half of the body with brisk deep tendon reflexes, an extensor plantar response on both sides, ataxia. The neurological deficit on the neurological scores was as follows: NIH 10; Barthel Index 55; GCS 14.

Local Status: Mild abdominal distention, and marked diffuse tenderness with guarding and rebound.

Laboratory test results: WBC count 18300/μL, hematocrit 45,3%, AST 55 U/L, ALT 77/U/L, β hCG – 88,6 mIU/ml.

Ultrasonography showed that the patient is five weeks pregnant with twins, and has moderate ascites, and multicystic ovaries.

Because of fluid retention in the peritoneal cavity, an abdomen puncture was performed on the patient on the day of admission. Three liters of fluid were extracted with no compactions.

MRA – without abnormality and significant intracranial and extracranial arterial stenosis or occlusion.

MRI – posterior circulation infarction on both hemispheres of the cerebellum and the pons (Fig.1 a-l)

DIAGNOSIS

Acute posterior circulation ischemic stroke with lesions in the pons and both hemispheres of the cerebellum associated with ovarian hyperstimulation syndrome.

DISCUSSION

For the last 70 years, fertility has declined by 50% and keeps dropping [36]. Sub-Saharan Africa has the highest average fertility rate in the world while Southern Europe, Eastern Europe, and Eastern Asia witnessed the opposite [37]. Male infertility contributes to more than half of all cases of global childlessness [38].

The World Health Organization (WHO), defines infertility as a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse [39]. The WHO recognizes that infertility confers a disability, and it is now fifth on the international list of serious disabilities [40].

Infertility has devastating social and psychological impacts. Infertile individuals experience stigma, ostracism, shame, anxiety, depression, and low self-esteem. This burden is particularly strong in cultures where the birth of a child can secure a marriage, guarantee property and inheritance rights, offer a future source of household income, and provide social security in old age [41].

As millions of people have used fertility services in their lifetimes, the overall trend of infertility declines in high-income and developed countries and increases in other regions [36]. Assisted reproduction techniques have advanced considerably since the world's first baby was born through IVF in the UK in 1978. Each year, clinicians around the world perform more than 2.5 million IVF cycles, resulting in more than a half-million deliveries annually [42].

OHSS is a complication that affects women taking hormonal medications to stimulate oocyte development in the ovaries [43]. OHSS can cause serious psychological and physiological derangements and maternal death. Symptoms may develop as early as 4 to 5 days after oocyte retrieval [44].

The possible mechanisms of thromboembolism derived from OHSS are high serum estrogen concentration, hemoconcentration, and reduced circulating blood volume by exhaustion of intravascular volume. Also, OHSS can be associated with other hypercoagulable states, such as antiphospholipid antibody syndrome, antithrombin III deficiency, and activated protein C resistance.

Cerebral infarction seldom occurs as a complication of OHSS. The occurrence of progressive, multi-territorial infarctions, without atherosclerotic and cardioembolic source, suggest that hyperactivation of the hemostatic system likely plays a role in the development of thromboembolism. Although it may be related to the exaggerated response to gonadotropin in polycystic ovary syndrome.

We provided a complex clinical, neurological, laboratory, and instrumental analysis of posterior circulation stroke associated with ovarian hyperstimulation syndrome illustrated with a clinical case presentation in a white European adult. Specific clinical and imaging features were determined, analyzed, compared, and described.

CONCLUSIONS

Complex posterior circulation cerebral infarction in the pons and both hemispheres of the cerebellum associated with OHSS has not been reported before but has devastating consequences for both mother and fetus. Strokes in patients with OHSS must be timely prevented, promptly diagnosed, and treated to avoid high morbidity and mortality associated with it.

OHSS is a rare and serious complication of hormonal treatment for induction of ovulation. Haemoconcentration owing to the large fluid shift from the intravascular to the peritoneal cavity results in increased blood viscosity that leads to arterial and venous occlusion. That leads to thromboembolic stroke, cerebral venous thrombosis, and systemic arteriovenous thrombosis in patients with OHSS.

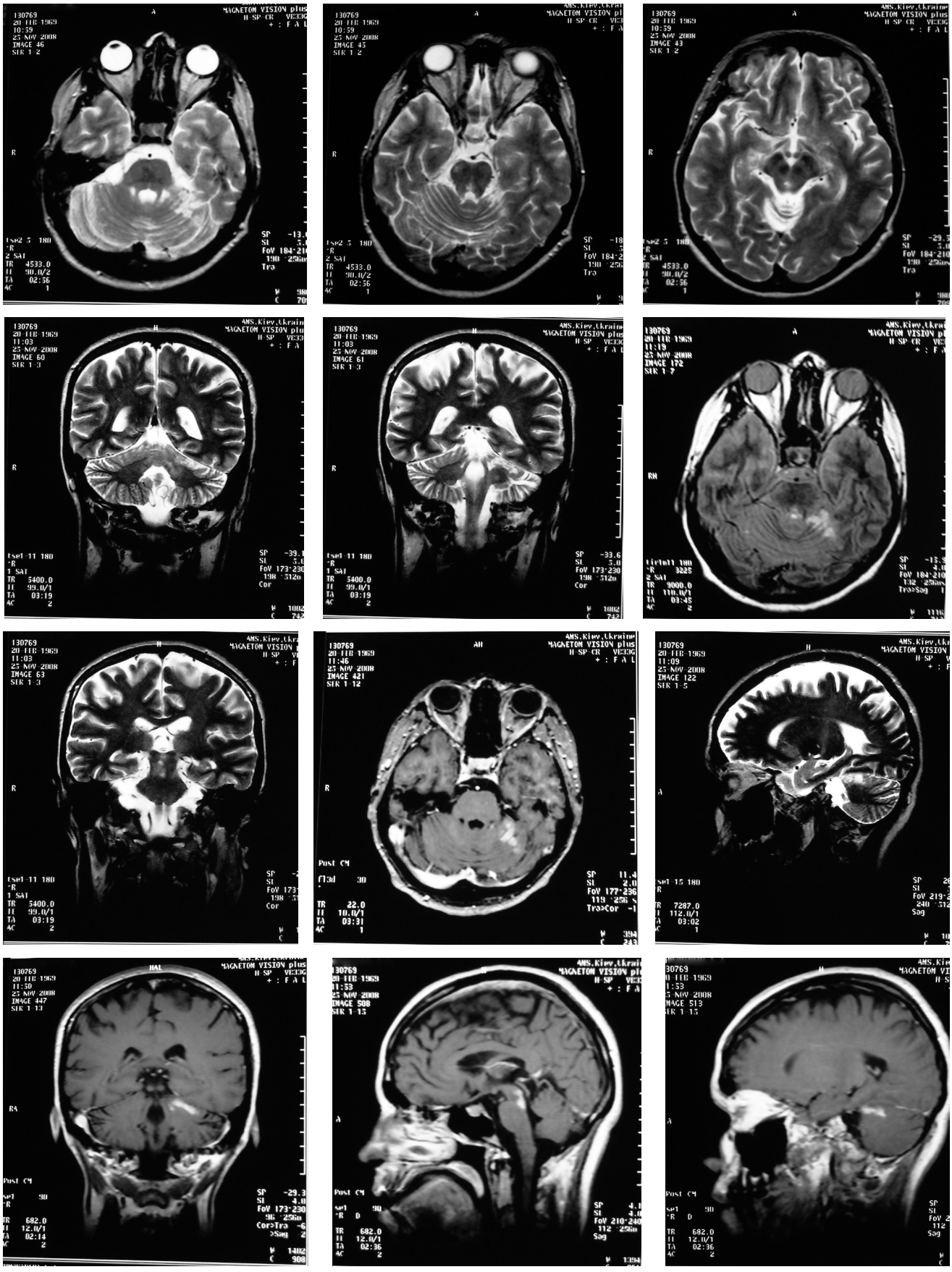

Fig. 1. MRI imaging of the brain of patient S., 39 years old. T2- (Fig. 1 a-f, h), FLAIR (Fig.1 g) shows bilateral foci of increased intensity of the MR signal in the parenchyma of the cerebellum and dorsolateral parts of the pons (basilar artery basin), which is on T1 + C (Fig.1 h-l) in the left cerebellar hemisphere demonstrates contrast enhancement.

PROSPECTS FOR FURTHER RESEARCH

It is important to promote awareness of stroke prevention programs in patients with OHHS and medical personnel.

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