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ORIGINAL ARTICLE

IMMUNE-INFLAMMATORY-ENDOCRINE REGULATION DISORDERS IN CHILDREN WITH CORONAVIRUS INFECTION

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Olesya M. Horlenko, Khrystyna A. Hechko, Lyubomyra B. Prylypko, Olga Blaga, Fedir V. Horlenko, Oleksandr O. Kutsyn, Bohdan M. Halay
UZHHOROD NATIONAL UNIVERSITY, UZHHOROD, UKRAINE

ABSTRACT

The aim: To study the of homeostasis links desorder and indicators imbalance in children with Coronavirus infection.

Materials and methods: A clinical and laboratory study was conducted in children (50 persons) with Coronavirus infection. The children were used outpatient treatment.

Results: It was found that Direct bilirubin was increased in 3 times (10.55±7.67 vs. 3.63±0.49 μmol/l, p<0.01), Alanine aminotransferase – in 1.7 times (37,02±20.53 vs. 21.90±1.82 IU/l, p<0.01). An levels increassng of Ig G – in 12.3 times, Ig E – in 4.6 times, Ig M – in 3.4 times was observed. The CRP level was increased in 3.1 times (8.76 ± 2.16 vs. 2.54 ± 0.53 mg/l, p< 0.01), C-peptide (4.65±1.67 vs. 1.23±0.08 ng/ml, p<0.01) – in 3.8 times. Negative correlations of T3 with Procalcitonin (r=-0.30) and Creatinine (r=-34) were revealed. T4 values are correlated with Total cholesterol (r=-0.65) and Creatinine (r=0.29). Leptin was presented positive correlations with Alanine aminotransferase (r=0.48) and with C-peptide (r=0.39).

Conclusions: There was an increase in the Ig G levels in 12.3 times, Ig E – in 4.6 times, and the Ig M level - in 3.4 times. The Thyroid stimulating hormone level was significantly lower (in 4.7 times). An increase in the C-reactive protein levels (in 3.1 times) and C-peptide (in 3.8 times) was observed. It should be noted that the strongest negative correlation between T4 and Total cholesterol (r=-0.65) and the highest positive correlation between Leptin and Alanine aminotransferase (r=0.48) and C-peptide (r=0. 39).

KEY WORDS: Coronavirus infection, acute respiratory distress syndrome, pathogenesis, inflammatory immune response, children

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INTRODUCTION

In December 2019, an outbreak of a new infectious disease occurred in the city of Wuhan, Hubei Province, China. This is already the seventh coronavirus. On March 11, 2020, the World Health Organization (WHO) classified the outbreak as a pandemic. A number of studies have examined the symptoms and characteristics of adults with COVID-19. A smaller number of these studies cover the morbidity of children with COVID-19 [1]. To contain infection and develop effective systems to treat viral infections in an outbreak scenario, we must understand the nature of infection and the immune system's response about a new virus, and assess the similarities and differences of the new virus from viruses that have caused outbreaks in the past. Scientists focus on studying the reaction of the immune system against SARS-CoV-2 in comparison with cases of other CoVs (SARS and MERS) [2,3]. SARS-CoV-2 is a new infectious agent that has entered human civilization. As a rule, emerging and re-emerging viral infections belong to the RNA virus family, because these viruses have a high mutation rate, which allows them to adapt significantly to the environment with rapid evolution. We have a little and not inough about SARS-CoV-2 in children currently [4]. Also, the systemic landscape of immune responses in patients with COVID-19 is unclear. The mechanisms of development of the response reaction of the innate and adaptive immune system of the macroorganism to infection with the SARS-CoV-2 virus are described. Because the clinical features and immunopathogenesis of SARS-CoV-2 and SARS-CoV and MERS-CoV are somewhat similar, the knowledge gained from SARS-CoV and MERS-CoV has important implications for understanding [2,5]. Identification of characteristic clinical signs, understanding of the adaptive response of the child's organism to an infectious factor in the near future will be aimed at preventing the development and treatment of both acute respiratory distress syndrome and chronic conditions caused by damage to other target organs in the case of COVID-19 [3,6,7] .

Table I. Biochemical parameters in children

Laboratory indicators	Main group (n = 50) M ± m	Control group (n = 28) M ± m	Statistical significance (p)
Total protein (64-83, g/l)	67,31 ± 7,49	74,50 ± 3,39	< 0,01
Albumin (35-53, g/l)	45,38 ± 5,84	44,53 ± 2,32	0,46
Total bilirubin (<21,0, μmol/l)	18,37 ± 10,26	15,19 ± 0,84	0,11
Direct bilirubin (0-5,1, μmol/l)	10,55 ± 7,67	3,63 ± 0,49	< 0,01
Alanine aminotransferase (< 40,0, IU/l)	37,02 ± 20,53	21,90 ± 1,82	< 0,01, 1,7
Alkaline phosphatase (42-128, IU/l)	141,59 ± 99,44	52,02 ± 3,38	< 0,01 2,7
Creatinine (33-110, μmol/l	93,82 ± 34,63	61,21 ± 5,54	< 0,01 1,5
Urea (3,3-7,7, mmol/l)	6,84 ± 3,36	3,81 ± 0,32	< 0,01 1,8
Total cholesterol (3,1-5,0, mmol/l)	5,01 ± 1,71	4,31 ± 0,24	0,04 1,2
Glucose (3,3-6,1, mmol/l)	5,69 ± 2,37	4,75 ± 0,04	0,04 1,2
Potassium (3,5-5,1, mmol/l)	4,77 ± 0,47	4,21 ± 0,17	< 0,01 1,1
Sodium (135-155, mmol/l)	137,58 ± 4,91	143,71 ± 2,28	< 0,01
Chlorine (95-110, mmol/l)	102,47 ± 4,19	101,97 ± 2,82	0,58

THE AIM

To study the homeostasis links diorders and the indicators imbalance in children with Coronavirus infection

MATERIALS AND METHODS

Clinical and laboratory research was carried out in children with confirmed Coronavirus infection. The main group consisted of 50 children aged 14-16yy. (26 girls, 24 boys). The control group included healthy children (n=28), identical by the studied parameters. The children were used outpatient treatment of the City Multidisciplinary Clinical Hospital, Uzhhorod. Laboratory tests were performed on the 5th day of the disease and included biochemical and immunological examination, indicators of the pituitary-thyroid panel, markers of inflammatory-endocrine regulation.

RESULTS

The most common laboratory abnormalities associated with the new CoV include hypoalbuminemia, lymphopenia, decreased neutrophils, elevated C-reactive protein (CRP) and lactate dehydrogenase (LDH), and decreased CD8 counts; according to the researchers. The viral load of SARS-CoV-2 detected through the respiratory tract of patients was found to be positively related with the severity of lung disease. Albumin, lymphocytes, LDH, neutrophils, and CRP are highly correlated with acute lung injury. Age, viral load, lung injury score, blood biochemical parameters, albumin, CRP, LDH, lymphocytes (%) and neutrophils (%) can be disease severity predictors [8,9].

The obtained results are presented in the Table I.

There are no significant differences in the levels of albumin, total bilirubin, and chlorine in comparison with the results obtained in children of the control group (p=0.11-0.58), according to Table I. There is a significant predominance of Total protein in children of the control group in comparison with patients (74.50 ± 3.39 to 67.31 ± 7.49 g/l, p< 0.01) and Sodium level - (143.71 ± 2, 28 to 137.58 ± 4.91 mmol/l, p< 0.01). It should be noted that, the values were increased in sick children in all parameters, according to other indicators.

Table II. Immunogram of children with Coronavirus

Laboratory indicators	Main group (n = 50) M ± m	Control group (n = 28) M ± m	Statistical significance (p)
Ig M (0,31-1,79, g/l)	4,11 ± 1,74	1,20 ± 0,06	< 0,01 3,4
Ig G (6,98-15,49, g/l)	151,07 ± 39,77	12,29 ± 0,07	< 0,01 12,3
Ig E (till 120 IU/ml)	163,47 ± 43,29	35,60 ± 1,07	< 0,01 4,6

Table III. Results of the study of the homeostasis pituitary-thyroid link

Laboratory indicators	Main group (n = 50) M ± m	Control group (n = 28) M ± m	Statistical significance (p)
Thyroid stimulating hormone (0,4 - 4,0, mIU/ml)	0,40 ± 0,08	1,87 ± 0,46	< 0,01
Free triiodothyronine (1,2 - 2,8, nmol/l)	1,30 ± 0,24	1,39 ± 0,08	0,09
Free thyroxine (12,5 - 21,0, pmol/l)	15,25 ± 1,99	15,32 ± 0,49	0,86
Thyroid peroxidase antibody (< 35, IU/ml)	4,84 ± 3,56	5,69 ± 0,11	0,21

Table IV. Parameters of the levels of inflammatory endocrine regulation markers

Laboratory indicators	Main group (n = 50) M ± m	Control group (n = 28) M ± m	Statistical significance (p)
Ferritin (7-140, ng/ml)	79,32 ± 34,07	77,07 ± 10,40	0,73
C-reactive protein (<3, mg/l)	8,76 ± 2,16	2,54 ± 0,53	< 0,01
Procalcitonin (0-11, pg/ml)	9,27 ± 2,96	1,61 ± 0,23	< 0,01
Adiponectin (5-37, ng/ml)	27,92 ± 8,52	7,73 ± 0,86	< 0,01
Leptin (2,05-11,09, ng/ml)	10,44 ± 2,77	6,97 ± 0,32	< 0,01
C-peptide (0,81-3,85, ng/ml)	4,65 ± 1,67	1,23 ± 0,08	< 0,01

Table V. The correlations relationship of the pituitary-thyroid panel parameters

Laboratory indicators		Correlation coefficient (r)	Statistical significance (p)
Free triiodothyronine	Procalcitonin	-0,30	0,04
	Creatinine	-0,34	0,01
Free thyroxine	Total cholesterol	-0,65	< 0,01
	Creatinine	0,29	0,04
Thyroid stimulating hormone	Ig E	0,32	0,03
Thyroid peroxidase antibody	Albumin	0,28	0,05

Table VI. Correlationship of system of immune-inflammatory-endocrine regulation

Direct Bilirubin was increased in 3 times (10.55 ± 7.67 vs. 3.63 ± 0.49 μmol/l, p< 0.01) and exceeded the limits of reference values; Alanine aminotransferase - in 1.7 times (37, 02 ± 20.53 vs. 21.90 ± 1.82 IU/l, p< 0.01), Alkaline phosphatase – in 2.7 times (141.59 ± 99.44 vs. 52.02 ± 3.38 IU/ l, p< 0.01), Creatinine – in 1.5 times (93.82 ± 34.63 to 61.21 ± 5.54 μmol/l, p< 0.01), Urea – in 1.8 times (6.84 ± 3.36 vs. 3.81 ± 0.32 mmol/l, p< 0.01),

Laboratory indicators		Correlation coefficient (r)	Statistical significance (p)
Leptin	C-peptide	0,39	0,005
	Alanine aminotransferase	0,48	< 0,01
Adiponectin	Potassium	0,31	0,03
C-reactive protein	Direct bilirubin	0,38	0,007
	Albumin	-0,31	0,03
	Ferritin	-0,33	0,02
Procalcitonin	Free triiodothyronine	-0,30	0,04
Ig E	Thyroid stimulating hormone	0,32	0,03
	Albumin	-0,34	0,02
	Ig M	0,32	0,02
Ig G	Sodium	-0,33	0,02
	Total protein	-0,29	0,04

Total cholesterol, Glucose and Potassium – in 1.1-1,2 times within the reference values. That is, inflammatory markers are mainly increased compared to the control group against the background of a decrease in the level of total protein. Corresponding data were obtained by scientists too when have considered the laboratory examination of children with Coronavirus infection [8,9]

The immunogram of children with Coronavirus are presented in Table II.

Pathological increases in all Immunoglobulins beyond the reference values were observed in children with Coronavirus, according to the data in the table II. The highest comparative characteristic was the level of Ig G – in 12.3 times (151.07 ± 39.77 to 12.29 ± 0.07 g/l, p< 0.01). The level of Ig E with lower values of increase was observed – in 4.6 times (163.47 ± 43.29 to 35.60 ± 1.07 IU/ml, p< 0.01) and the level of Ig M – in 3.4 times (4.11 ± 1.74 to 1.20 ± 0.06 g/l, p< 0.01).

Consider the obtained results of the study of the homeostasis pituitary-thyroid link, which are presented in Table III.

As we can see by the data in Table III, all indicators are within the reference values and most have an unreliable difference, except of Thyroid stimulating hormone level, which is significantly lower (in 4.7 times) in patients (0.40 ± 0.08 to 1.87 ± 0.46 mIU/ml, p< 0.01).

The levels of inflammatory endocrine regulation markers are presented in table IV.

All obtained data are significantly different in patients and children of the control group (p<0.01), except for Ferritin values (p=0.73). An increase beyond the reference values is observed in the levels of C-reactive protein (8.76 ± 2.16 vs. 2.54 ± 0.53 mg/l, p< 0.01), the comparative ratio is 3.1 times and C-peptide (4.65 ± 1.67 to 1.23 ± 0.08 ng/ml, p< 0.01), which is increased in patients in 3.8 times.

Also, reliable correlation relationships between the studied parameters were found.

The correlations of the parameters of the pituitary-thyroid panel are shown in Table V.

The negative correlationships of T3 with Procalcitonin (r=-0.30) and Creatinine (r=-34) are observed, according to Table V. T4 values correlated with Total cholesterol (r=-0.65) and Creatinine (r=0.29). TSH presents positive correlationship with Ig E (r=0.32) and TPA level with Albumin (r=0.28). It should be noted about the highest negative correlation between T4 and Total cholesterol. As reported in viral infections, especially in immunocompromised patients, there is a two-way relationship between the Immune system and Thyroid hormones in both physiological and pathophysiological conditions. The Immune system and the Endocrine system interact with each other. Specifically involved in the relationship between inflammation and THS-related diseases, they can be considered not only as biomarkers but also as potential therapeutic targets [10].

The revealed correlations of indicators of immune-inflammatory-endocrine regulation are presented in Table VI.

According to the table VI, the most correlationship were found in the values of IgE with Thyroid Stimulating hormone(r=0.32), Ig M(r=-0.32) and Albumin(r=-0.34) and CRP with Direct bilirubin(r=0.38), Albumin(r=-0.31), Ferritin(r=-0.33). Leptin indicator presents positive relationships with inflammatory markers, in particular C-peptide (r=0.39) and Alanine Aminotransferase (r=0.48). C-peptide, formed as a result of proinsulin proteolysis, is not only an Insulin Chaperone in β-cells, but also a signaling molecule that regulates many physiological and biochemical processes through specific C-peptide receptors. The regulatory effects of

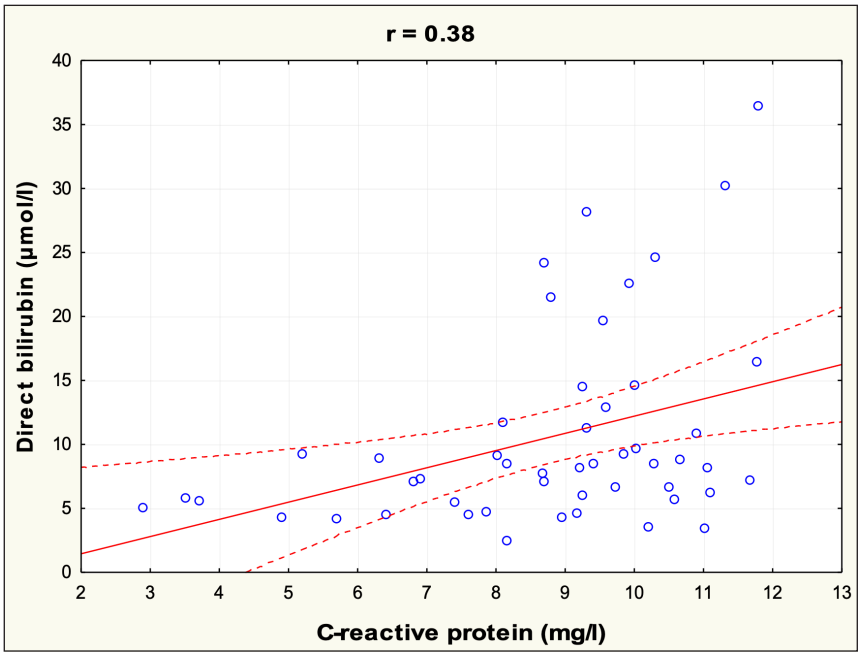

Fig. 1. Correlationship between CRP and Direct Bilirubin

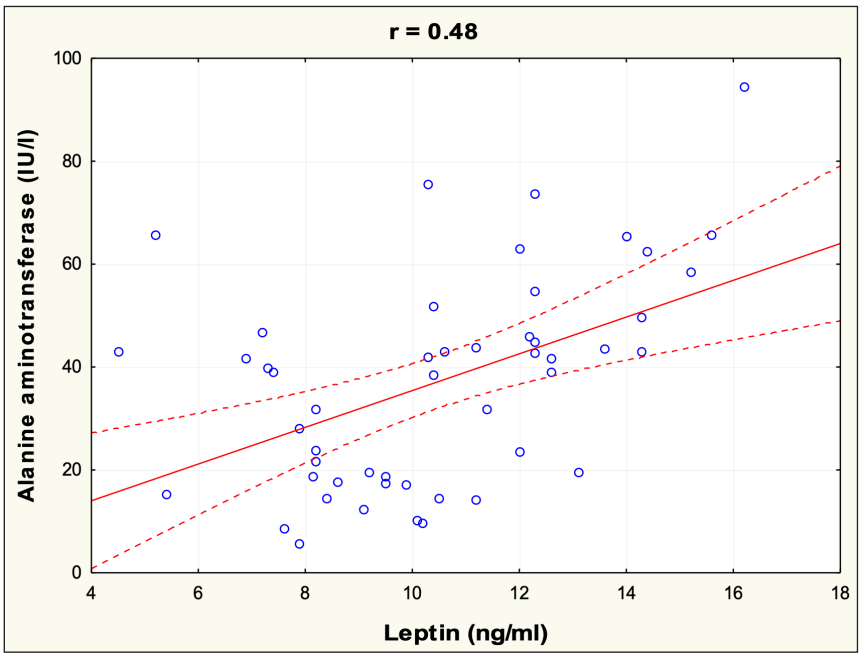

Fig. 2. Correlationship between Leptin and Alanine Aminotransferase

C-peptide are tissue-specific and largely depend on the physiological state of the organism, the concentration of C-peptide and its ability to form complexes. It was established that C-peptide is involved in the regulation of the synthesis and secretion of adipokines, which indicates its role in the control of energy homeostasis [11,12]. In addition to inflammatory diseases, it has been proven that some infectious diseases can be associated with the development of obesity. Mechanisms may include reprogramming of the host's metabolism, exchange of microbiota components, and adaptations of the host's immune and metabolic systems in the presence of chronic viral infection, which causes changes in cytokine and interferon levels that may play a role in the development of obesity. On the other hand, obesity has been found to be an important risk factor for the severity of some viral infections, such as severe acute respiratory syndrome, Coronavirus 2 (SARS-CoV-2). And leptin has also been suggested as a possible link [13-15].

The Procalcitonin (PCT) indicator correlates with the Free Triiodothyronine values (r=-0.30). Because of the low sensitivity of PCT for all outcomes, normal PCT levels should not be used to guide treatment decisions in patients with COVID-19. PCT is mainly used as a biomarker of bacterial infections. The results of the present study show a novel use of PCT in a specific group of

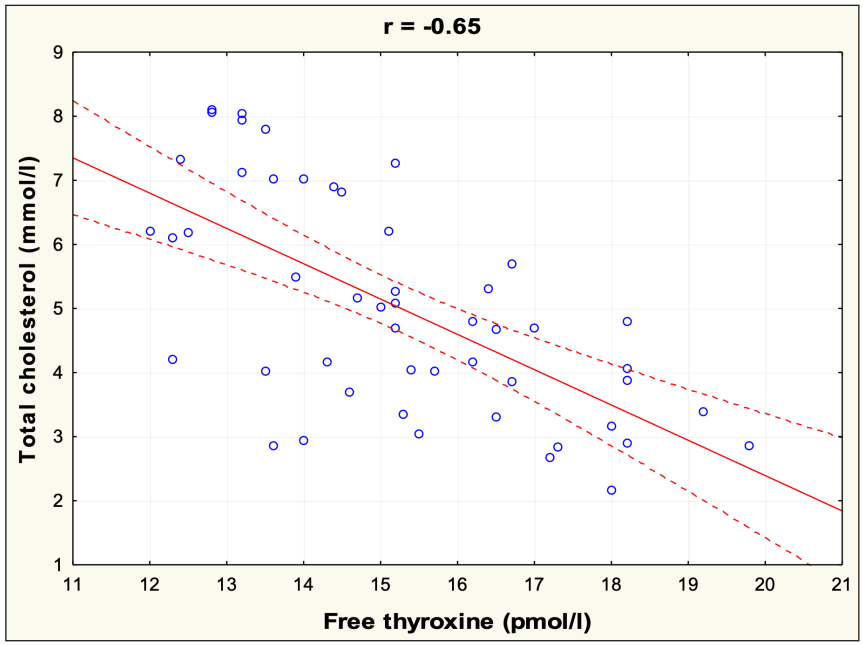

Fig. 3. Corelationship between Free T4 and Total Cholesterol

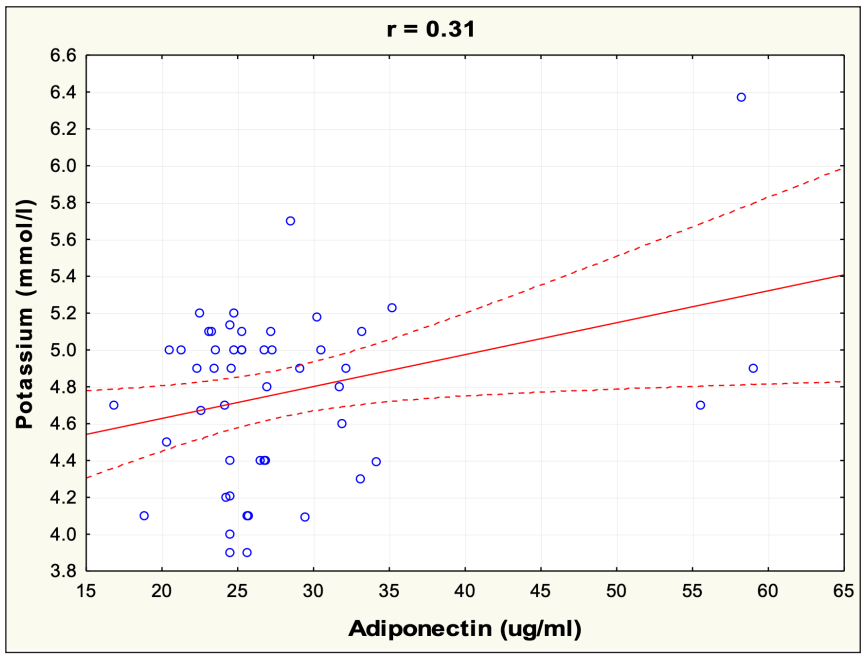

Fig. 4. Corelationship between Adiponectin and Potassium levels

patients with COVID-19 as a marker of disease severity. Even after adjusting for bacterial co-infections and the inflammatory markers CRP and d-dimer, elevated PCT levels remained associated with severe COVID-19 infection. Elevated PCT in severe COVID-19 infections can be explained by looking at the pathways of PCT synthesis, which is regulated by various cytokines such as Interleukin-6 and TNF-α. As hyperinflammation has been shown to be an important factor in the progression of COVID-19 infections, dysregulation of the immune response may also trigger the production of PCT[16]

The most representative correlogram of relationship, in particular the correlation between CRP and Direct Bilirubin is illustrated on Fig. 1.

There is growing evidence that Bilirubin, which is formed during the physiological breakdown of heme, has a powerful anti-inflammatory effect. Evidence suggests that Bilirubin can suppress inflammatory responses by preventing Leukocyte migration to target tissues through disruption of vascular cell adhesion molecule-1 (VCAM-1)-dependent cell signaling. Because VCAM-1 is an important mediator of tissue damage, in vitro experimental studies have shown significantly less tissue damage and reduced infiltration of inflammatory cells into tissues. The scientists' conclusions suggest that Bilirubin functions as an endogenous regulator of inflammatory reactions[17].

The correlogram of the relationship between Leptin and Alanine Transierase is represented on Fig.2.

In addition to the metabolic effect, the range of functional capabilities of the Leptin hormone includes the regulation of inflammatory processes, the effect on the Immune system and the synthesis of Thyroid hormones that regulate metabolism. Therefore, it is reasonable to interact with the inflammatory marker - ALT, the level of which increases due to the pathological destruction of cells and the release of the intracellular enzyme into the bloodstream [14,18]. The pronounced inflammatory process in the child's body was confirmed by the data of our survey and its correlation analysis the following correlogram of the relationship between Free T4 and Total Cholesterol is shown on Fig. 3.

The level of Cholesterol depends on the level of hormones, therefore, when diagnosing Hypothyroidism, it is so important to test Cholesterol and its fractions (HDL and LDL). Thyroxine is produced by the Thyroid gland, which transmute into the active form of Triiodothyronine and have affects on the level of Cholesterol in our organism. This means that the impaired action of both hormones will affect the level of Cholesterol in the same way [10]. In our research, a strong negative relationship between these parameters is observed.

Scientific information is provided by the correlogram about correlations between Adiponectin and Potassium levels and are illustrated on Fig. 4.

Consider the relationship between serum Potassium level - Adiponectin level and the risk of Metabolic syndrome development accordingly. The prevalence of Metabolic syndrome was 51.7% in participants with Hypokalemia and 37.7% in those who were Normokalemic. The level of Potassium in the blood serum significantly decreased with an increase in the number of components of the Metabolic syndrome. Low serum Potassium is significantly associated with the prevalence of Metabolic syndrome in middle-aged and elderly Chinese. That is, according to scientists, there are relationships between the level of potassium and the adipose tissue, hormones Adiponectin and Leptin, which is also proven in our research [19,20].

DISCUSSION

COVID-19 is either rare in children or undiagnosed, because this age group have asymptomatic course of disease. The proportion of children with COVID-19 with elevated inflammatory markers was reported as low. Severe cases of COVID-19 are associated with elevated PCT levels [16]. When patient have infected with COVID-19, the vast majority of homeostasis links were violated.

Activation of virus-specific B-cells leads to their differentiation into plasma cells, which successively produce specific IgM and IgG class antibodies. During the development of COVID-19, it is observed a gradual increase in the concentration of SARS-CoV-2-binding antibodies of IgM and IgG class in serum blood from the 7th to the 20th day of the disease. It has been demonstrated that SARS-CoV-2-specific antibodies of the IgM class disappear at the end of the 12th week from the moment of the onset of the disease, and the IgG class remains for a long period of time, determining the level of protection against re-infection[21]. There is a study that replacement therapy with C-peptide prevents the development of inflammation in the endothelial cells of vessels, and an excess of C-peptide, on the contrary, reveals its pro-inflammatory properties. It was established that C-peptide is involved in the regulation of the synthesis and secretion of Adipokines, which indicates its role in the control of energy homeostasis[11,12]. Clinically, the immune response induced by SARS-CoV-2 infection is biphasic. During the incubation and mild stages, a specific adaptive Immune response is required to eliminate the virus and prevent disease progression to severe stages. To develop an endogenous protective Immune response during the incubation and non-severe stages, the child must have good general health and an appropriate genetic background (eg, HLA) that cases specific antiviral immunity. However, when the protective Immune response is impaired, the virus will spread and massive destruction of affected tissues will occur, especially in organs that have high ACE2 expression, such as the intestine and kidney. Damaged cells induce innate inflammation in the lung, which is largely mediated by proinflammatory macrophages and granulocytes. [3,22]. Initiation of the development of the Inflammatory response of the child's organism, violation of the immune-inflammatory-endocrine regulation system, metabolic processes, requires the constant attention of doctors to identify markers of the pathological process and develop therapeutic treatment schemes.

CONCLUSIONS

1. The level of Direct bilirubin was increased in 3 times (10.55 ± 7.67 vs. 3.63 ± 0.49 μmol/l, p< 0.01) and exceeded the limits of reference values, Alanine aminotransferase - in 1.7 times (37.02 ± 20.53 vs. 21.90 ± 1.82 IU/l, p< 0.01), Alkaline phosphatase – in 2.7 times (141.59 ± 99.44 vs. 52.02 ± 3, 38 IU/l, p<0.01), Creatinine – in 1.5 times (93.82 ± 34.63 to 61.21 ± 5.54 μmol/l, p<0.01), Urea - in 1 .8 times (6.84 ± 3.36 vs. 3.81 ± 0.32 mmol/l, p< 0.01), Total cholesterol, Glucose and Potassium – in 1.1-1.2 times, but within the reference values . That is, inflammatory markers are mainly increased compared to the control group

against the background of a decrease in the level of Total Protein.

2. An increase in Ig G levels was observed – in 12.3 times (151.07 ± 39.77 to 12.29 ± 0.07 g/l, p< 0.01). With lower values of increase, the level of Ig E was observed – in 4.6 times (163.47 ± 43.29 to 35.60 ± 1.07 IU/ml, p< 0.01) and the level of Ig M - 3.4 times (4.11 ± 1.74 to 1.20 ± 0.06 g/l, p< 0.01).
3. All indicators of the Thyroid panel were within the reference values and most had an unreliable difference, except for the level of Thyroid Stimulating hormone, which is significantly lower (by 4.7 times) in patients (0.40 ± 0.08 to 1.87 ± 0 .46 mIU/ml, p< 0.01).
4. An increase beyond reference values was identified in the levels of CRP (8.76 ± 2.16 vs. 2.54 ± 0.53 mg/l, p< 0.01), the comparative ratio is 3.1 times and C -peptide (4.65 ± 1.67 to 1.23 ± 0.08 ng/ml, p< 0.01), which is increased in patients in 3.8 times.
5. Negative correlations of T3 with Procalcitonin (r=-0.30) and Creatinine levels (r=-34) were revealed. T4 values correlate with Total Cholesterol (r=-0.65) and Creatinine levels (r=0.29). TSH presents positive correlations with Ig E levels (r=0.32), Leptin with Alanine aminotransferase (r=0.48) and with C-peptide levels (r=0.39), TPA with Albumin indicator levels (r=0, 28). It should be noted that the highest negative correlationship of T4 with Total cholesterol levels and the highest positive correlation of Leptin with Alanine Aminotransferase levels were releaved

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ORCID and contributionship:
Olesya M. Horlenko: 0000-0002-2210-5503 [A,D,F]
Khrystyna A. Hechko: 0000-0003-4989-7659 [B,D]
Lyubomyra B. Prylypko: 0000-0002-4131-5450 [A,C]
Olga S. Blaga: 0000-0002-5627-1403 [B,D]
Fedir V. Horlenko: 0000-0002-0496-2069 [D,E]
Oleksandr O. Kutsyn: 0000-0001-7902-4598 [D,E]
Bohdan M. Halay: 0000-0002-7566-4982 [B,E]

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CORRESPONDING AUTHOR

Olesya M. Horlenko
Uzhhorod National University
46 Pidhirna st., 88000 Uzhhorod, Ukraine
tel: +38055269658
e-mail: ohorlenko@gmail.com

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