CASE STUDY

# SARS-COVID-19 TRIGGERED WERNICKE'S ENCEPHALOPATHY (CLINICAL CASE)

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**ABSTRACT**
Patient P., born in 1956, was found by relatives in a state of confused consciousness, an act of involuntary urination and defecation, numbness and weakening of the strength of both lower limbs were recorded. He was taken by ambulance to the reception room of the Regional Clinical Center of Neurosurgery and Neurology. The following concomitant diseases are known from the life anamnesis: Atrial fibrillation, gout, hypertension and type II non-insulin-dependent diabetes mellitus. Objective status: general condition of medium severity, tophuses of small joints of hands and feet, knee and elbow joints. Pronounced deformity of hands and feet due to gouty lesions. Heart tones are weakened. Breath sounds are weakened. The abdomen is soft, not painful on palpation. Glasgow coma scale 14-15 points. Consciousness is confused, disoriented in time, space and own person. To clarify the diagnosis, clinical and laboratory and instrumental diagnostic methods were used.
Neurological complications, in particular, acute encephalopathy, on the background of coronavirus infection, may develop in patients with the presence of such risk factors as advanced age, cardiovascular diseases, hypertension, diabetes, gout. Most of the neurological complications in COVID-19 are probably not related to the direct penetration of the virus into the CNS, but are a trigger for the development of the pathology. Neuroimaging in such cases does not reveal pathological changes or reflects non-specific disorders.

**KEY WORDS:** acute encephalopathy, coronavirus infection, patient

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## INTRODUCTION

COVID-19 continues to remain an important medical and social problem [1, 2]. The number of reports of severe neurological damage, encephalitis/meningoencephalitis, encephalopathies, epileptic status, ischemic/hemorrhagic strokes, severe neuropathies, against the background of COVID-19 is increasing, which makes this problem particularly relevant.

There are reports of documented persistent damage to many organs and systems (lungs, heart, brain, kidneys and vascular system, etc.) in patients who have suffered from COVID-19 [3]. Among the main risk factors for the development of a severe course of COVID-19, the most important are advanced age, arterial hypertension, diabetes mellitus (DM), chronic obstructive pulmonary diseases, cardiovascular and cerebrovascular diseases [4,5].

The National Institute for Health and Care Improvement of Great Britain (NICE) offers the following terminology for COVID-19 [6]:

- acute COVID 19: signs and symptoms persisting for up to 4 weeks;
- prolonged symptomatic COVID 19: signs and symptoms persist from 4 to 12 weeks;
- post-COVID 19 syndrome: signs and symptoms that persist during and after the infectious disease (>12 weeks) and do not have an alternative diagnosis.

The Infectious Diseases Society of America (IDSA) distinguishes between «prolonged COVID», «post-COVID syndrome» and «post-acute COVID-19 syndrome».

Among the reasons that lead to the development of post-covid syndrome, the following are distinguished: persistent viremia due to a weak or absent antibody response, relapses or re-infection; inflammatory or other immune reactions; mental factors (post-traumatic stress); the presence of concomitant diseases.

The neurovirulence capacity of coronaviruses, including SARS-CoV-2, may contribute to the relatively high prevalence of neurological complications in patients with COVID-19, especially among hospitalized patients with severe or critical illness [7]. Early reports estimated the incidence of neurological complications to be approximately 37% [8,9].

Neurological manifestations arising from coronavirus infection can be divided into two categories: central and

peripheral [10]. Central manifestations include headache, dizziness, confusion, encephalopathy, delirium, syncope, seizures, difficulty walking, cerebrovascular events, encephalitis, and the development of postinfectious autoimmune disorders. Peripheral disorders include isolated cranial nerve dysfunction (impaired sense of smell and taste), Guillain-Barré syndrome, and myositis-like muscle damage. Although most neurological symptoms develop during the course of the disease, others, such as acute stroke, may be initial manifestations.

Encephalopathy with COVID-19 is quite common, especially in severe cases of the course of the disease. Encephalopathy is a collective concept of similar lesions of the brain with a violation of its function, which can be both a syndrome accompanying other diseases (secondary) and an independent nosological unit (primary). [11]. Symptoms and clinical course of this condition can be very heterogeneous.

Pathological mechanisms of encephalopathies caused by SARS-CoV-2 are: hypoxia, sepsis, severe systemic inflammation, renal failure, cytokine storm. The absence of an inflammatory reaction in the cerebrospinal fluid and affected brain tissue indicates that the disease is not inflammatory [12].

Hospitalized patients positive for SARS-CoV-2 show a characteristic form of encephalopathy associated with systemic hyperinflammation, mainly triggered by an abnormally excessive innate immune response. This kind of encephalopathy is characterized by generalized brain dysfunction with confused consciousness, often combined with hyperactive delirium and excitement or, conversely, depression and a catatonic state [13]. Manifestations are often more intense, neuropsychiatric signs are more pronounced (delusions, agitation, mood changes, and irritability) and, as a rule, are less amenable to correction with traditional antipsychotic drugs compared to the usual spectrum of encephalopathies in critical illness.

It is recommended to perform a cerebrospinal fluid analysis to rule out meningoencephalitis or detect destructive markers after hypoxia. It should be noted that the analysis of the cerebrospinal fluid in such cases is either within the reference values or indicates a moderate increase in the level of protein without pleocytosis. This suggests that most of the neurological complications associated with SARS-CoV-2 are probably not related to direct entry of the virus into the CNS.

With the help of computed tomography (CT) or magnetic resonance imaging (MRI), it is possible to detect structural lesions, brain edema, as well as hemorrhagic and necrotic changes. It is recommended to conduct an analysis of cerebrospinal fluid to rule out meningoencephalitis or detect destructive markers after hypoxia.

The combination of general and neurological examinations with appropriate diagnostic studies (serological, CMR, EEG and neuroimaging) allows to establish a diagnosis of this type of inflammatory encephalopathy caused by an enhanced innate immune response. Encephalopathy has been frequently reported in patients with acute respiratory distress syndrome (ARDS) associated with COVID-19, and its etiology remains unclear. These patients have a hypercatabolic state, weight loss, which are risk factors for thiamine deficiency. The diagnosis of Wernicke's encephalopathy (WE) is complex and is based on risk factors for thiamine depletion. There is information that thiamine deficiency may represent a relevant etiology of encephalopathy associated with COVID-19[14].

General recommendations for the examination and basic principles of care for patients with post-covid syndrome are described in the Stanford Hall Consensus (Stanford Hall Consensus, 2020) [15].

## CASE REPORT

For prepearing this article was used literature review and analysis of clinical, anamnestic, dynamic laboratory and instrumental methods of research of patient P. Analysis of disease course and treatment.

The article presents literature data and clinical observation of a patient with SARS-COVID-19 triggered Wernicke's encephalopathy. Hospitalized patients positive for SARS-COVID-19 show a characteristic form of encephalopathy associated with systemic hyperinflammation, mainly triggered by an abnormally excessive innate immune response. This kind of encephalopathy is characterized by generalized brain dysfunction with confused consciousness.

Patient P., 67 years old, was found by relatives in the morning of October 28th, 2022, in the condition of confused consciousness. Involuntary urination and defecation, numbness and weakening of the strength of both lower limbs were recorded. According to relatives, the patient was last seen healthy at 2.00 AM the same day. At 15:30 he was taken to the reception room of the Regional Clinical Center of Neurosurgery and Neurology by an ambulance. Multispiral computed tomography (MSCT) of the brain was urgently performed. No signs of hemorrhage were found. He was hospitalized outside the therapeutic window of systemic thrombolytic therapy (STLT).

Relatives reported the presence of the coronavirus infection in the family for the last 2 weeks, but the patient was not tested, did not seek medical help. They also noted the patient's refusal to eat for the last 2 weeks, the appearance of general weakness, general clinical tests had been performed.

The following concomitant diseases are known from the anamnesis of life: Atrial fibrillation, (cardioversion in 2017), gout, hypertension and non-insulin-dependent type II diabetes. Medications, taken on a regular basis are: nebivalol 5 mg/d, adenuric, metformin 500 mg/d;

Objective status: general condition moderately severe, the patient is well-fed. Blood pressure 170/100 mmHg, body temperature 36.7°C. The skin of the legs and hands is dry, with pronounced trophic changes. Tophus of small joints of hands and feet, knee and elbow joints are noted. Pronounced deformity of hands and feet due to gouty lesions. Cardiac activity is arrhythmic. Heart rate – within 80-100 bpm. Heart tones are weakened. Breathing is weakened. The abdomen is soft, not painful on palpation.

Neurological status: Glasgow Coma Scale is 14-15 points. Consciousness is confused, the patient is disorientated in time, space and his own person, he answers questions selectively, monosyllabically. Performs simple commands. Cranial nerves: isocoria, normal reaction of the pupils to light. Ophthalmodynamics in full. Nystagmus when looking to both sides. Surface sensitivity on the face cannot be assessed objectively. The face is symmetrical. Swallowing is not impaired. Tongue behind the midline. Tendon reflexes from arms and legs: reduced, distal-torpid. Pathological foot signs are negative. Muscle strength in all limbs up to 5 points, it is impossible to assess objectively due to the patient's uncooperativeness. Superficial and deep types of sensitivity cannot be assessed due to confusion of consciousness.

To clarify the diagnosis, the following laboratory and instrumental diagnostic methods were performed:

Multispiral computed tomography (MSCT) of the brain from 10.28.22: cerebral atherosclerosis with angiopathy phenomena.

Multispiral computed tomography of the chest from 10.28.22: according to the CT scan, bilateral polysegmental pneumonia is detected. Dilated cardiomyopathy. Coronarosclerosis

Magnetic resonance imaging of the brain from 10.28.22: magnetic resonance signs of focal parenchymal damage of both cerebral hemispheres of vascular character – cerebral microangiopathy, Fazekas 1. Mediated MR-signs of fluid dynamics disorders of moderate severity. Atrophic changes in the cortex of both cerebral hemispheres (CGA 3)-ddx with neurodegenerative diseases.

C-reactive protein: more than 100 ng/ml.

As of 10.29.22, the patient's condition has slightly improved regarding consciousness, however, the patient's body temperature has risen to 37.8 degrees. The maximum values are 38.6 degrees.

On October 29, 2022, detection of RNA for COVID-19 by the PCR method was performed – the result was positive.

Study of the hemostasis system: 856,0 ng/ml.

Blood electrolytes: sodium – 133 mmol/l, potassium – 3 mmol/l, chlorine – 94 mmol/l.

Uric acid: 422 μmol/l.

Based on the results of examination, the following diagnosis was established: G93.4 Acute encephalopathy against the background of coronavirus infection.

In connection with the positive results of the PCR – testing for Coronavirus infection, the patient was transferred to the «Pulmonary Disease Center» of Transcarpathian Regional Council, where the following laboratory results were obtained:

31.10.22 Complete blood count: ESR 70 mm/h, hemoglobin 95 g/l, erythrocytes 2.9 T/l, leukocytes 8.9 T/l (lymphocytes 12.6%, monocytes 2.2%, granulocytes 85.2%), platelets 231 T/l

31.10.22 Biochemical blood analysis ALT 15U/l, AST 16.3U/l, amylase 26.3U/l, albumin 33.1g/l, total protein 49.6g/l, urea 5.87mmol/l, creatinine 61.5mmol/l, total bilirubin 13.53 μmol/l, calcium 1.77 mmol/l, potassium 2.5 mmol/l, blood sugar 7.6 mmol/l, LDH 172.0 U/l. Blood sugar 12.00-14.00 -9.3-9.0 mmol/l.

01.11.22 Biochemical blood analysis: ALT-15.0 U/l, AST 17.5 U/l, amylase 23.9 U/l, albumin 53.1 g/l, total protein 53.7 g/l, urea 7.06 mmol/l, creatinine 63.9 mmol/l l, total bilirubin 12.00 μmol/l, calcium 1.91 mmol/l, potassium 3.3 mmol/l, blood sugar 8.5 mmol/l, LDH 224.5 U/l.

31.10.22 Coagulogram: prothrombin index 113% / 11.8sec, AChT- 27.6sec, thromb.time 12.6' INR-0.90, hematocrit 0.33 g/l, fibrinogen 5.52.

01.11.22 Coagulogram: prothrombin index 102% / 13.1sec, AChT-28.6 sec, thrombus time 14.0'INR- 0.98, hematocrit 0.32 g/l, fibrinogen 5.70. Blood group B(III)Rh(+).

Ultrasound examination of the heart (31.10.22): Mitral vlave – reg 1-2+, Aortal valve – reg+. Moderate left ventricular hypertrophy. Dilatation of the left ventricles. Contractile ability is slightly reduced due to diffuse hypokinesis. DR type 1. Slight pulmonary hypertension.

Ultrasound examination of the chest organs on 31.10.2022: During sonography of the front and lateral parts of both lungs – A-profile (normal). In the back parts of both lungs S6, S9, S10, the pleural line is unevenly thickened with shallow subpleural consolidations against the background of multiple diffuse B- lines – moderate interpleural interstitial syndrome with minimal amount of fluid. Conclusion: Signs of polysegmental bilateral pneumonia complicated by minimal bilateral pleurisy.

01.11.22 Retesting for SARS-CoV-2 (PCR) – «negative», in connection with which on 02.11.22 the patient was

transferred to the Regional Clinical Center of Neurosurgery and Neurology, to the Department of Cerebrovascular Pathology.

Ultrasound of extracranial vessels from 02.11.2022: Echo signs of atherosclerotic lesions of extracranial vessels of the neck, without hemodynamically significant stenoses. Hypoplasia of the right vertebral artery.

03.11.22 MRI of the brain 1.5 TL: in view of the obtained set of radiological data, there are more signs in proof of dysmetabolic damage of the supra- and infratentorial parenchima by type of Wernicke's encephalopathy. MR-signs of cerebral microangiopathy (Fazekas II), with changes in the brain parenchyma according to the ischemic-gliotic type, moderate liquefaction disorders in the form of replacement expansion of the external and internal CSF spaces. Phenomena of cerebral atrophy.

In order to further examine the patient, a lumbar puncture was performed (04.11.): cerebrospinal fluid samples were sent for general analysis, TORCH infection.

General analysis of liquor from 04.11.22: colorless, transparent, protein 1.61 g/l, glucose 4.5 mmol/l, erythrocytes 0-1 in the field of vision unchanged, cytosis – 0.

Cyanocobalamin level from 02.11.22: 343.0 (reference range 311.0-911.0 pg/ml), folic acid 20 ng/ml (3.0-17.0 pg/ml), estimated against the background of taking medications.

Diagnosis of TORCH infections in the cerebrospinal fluid by PCR (02.11.22): DNA of Toxoplasma gondii, DNA of cytomegalovirus, DNA of herpes simplex viruses types 1 and 2, DNA of Epstein-Barr virus – not detected.

Vitamin B1 in whole blood from 02.11.22: 11.5 μg/l (reference range 28-85 μg/l). Taking into account the previously detected anemia, additional blood tests were performed on 12.11.22: transferrin saturation 14.98% (reference range 8.00-45.00%), iron 7.10 μmol/l ( 11, 60-31.30 μmol/l), iron-binding capacity of serum 47.4 μmol/l (44.8-80.6 μmol/l).

Complete blood count from 11.11.22: ESR – 130 mm/h, hemoglobin 95 g/l, hematocrit 29.0%, erythrocytes 3.17×1012/l, leukocytes 14.0×109/l, platelets 436 ×109/l, thrombocrit 0.430%, average volume of erythrocytes 91.7 fL, average hemoglobin content in one erythrocyte 30.0 pg, average concentration of hemoglobin in erythrocytes 327 g/ l, red cell distribution width 17.2%, average volume of platelets is 9.8 fL; neutrophils 88.2%, lymphocytes 6.6%, monocytes 4%, eosinophils 0.2%, basophils 0.1%, large undifferentiated cells 0.8%, blasts – not detected, reactive lymphocytes – not detected, immature granulocytes – not detected, shift of the leukocyte formula to the left +, segmentation index 1.90, microcytes +, macrocytes – not detected, anisocytosis +, hypochromic erythrocytes +, hyperchromic erythrocytes – not detected, fragments of erythrocytes – not detected, shadows erythrocytes were not detected, large platelets were not detected.

Echocardioscopy from 12.11.2022: left ventricular hypertrophy, left and right ventricular dilatation. Slight expansion of the ascending aorta. Degenerative changes of the aortal and mitral valves. Moderate aortal and mitral insufficiency. 1-2nd stage pulmonary hypertension. Small amount of fluid in the pericardium with fibrin striations without signs of collapse of the right heart. Moderate hypokinesis of the interventricular septum, anterior-septal wall of the left ventricle. Moderate diffuse hypokinesis of other walls. Contractile ability is somewhat reduced. In dynamics – decrease in the amount of fluid in the pericardium.

On 12.11.22 the patient was consulted by a cardiologist with EchoCS, ECG data revision. A concomitant diagnosis of I30.8 Acute pericarditis was established.

Recommendations included: ibuprofen 600 mg every 8 hours for 1-2 weeks, with subsequent gradual dose reductions, colchicine 0.5 mg x 2/day with subsequent gradual dose reductions; complete blood count, C-reactive protein and EchoCS in dynamics, antibiotic therapy.

Echocardiogram control from 24.11.2022 found a decrease in the amount of fluid in the pericardium. Complete blood count control from 25.11.2022: reduction of ESR level (95 mm/h), treatment of anemia in outpatient settings was recommended.

The patient received the following treatment: infusion therapy with 0.9% NaCl 800 ml/d, KCL 7.5 20 ml/d, spironolactone 25 mg/d; amlodipine 5 mg/d, quetiapine 12.5 mg/d; Vitamin B1 10 ml/d; Vit B12 2.0 ml/d; Dexamethasone 4 mg/d; Enoxiparin 0.8 ml/d; Metformin 500 mg/d; Omeprazole 40 mg/d; Hepacef 2.0 ml/d; Rosuvastatin 20 mg/d; folic acid 3r/d; sorbifer 1 tab/d; adenuric 120 mg/d; nebivalol 5 mg/d; Lorista 25 mg/d; torasemide 10 mg/d; lactulose 45 ml/d; glycerin candles symptomatically.

At the time of discharge consciousness is confused, compared to previous days – improved communication with surrounding. Follows instructions. Nystagmus when looking to both sides. Tendon reflexes from arms and legs are reduced, distal reflexes – torpid. Muscle strength in all limbs – 5 scores. Pathological reflexes are negative. Meningeal signs are negative. Final diagnosis: SARS-COVID-19 triggered Wernicke's encephalopathy. Essential hypertension 2nd stage, cardiac insufficiency IIa with reduced left ventricular systolic function (EF 48%). Atrial fibrillation, permanent form, normosystole. Gout, rheumatoid-like form. Polyarthritic attack. Multiple tofuses. Diabetes type II, non-insulin dependent. Mild anemia. Dysphagia. Oculomotor disorders. Profound cognitive deficit.

We considered a clinical case of SARS-COVID-19 triggared Wernicke's Encephalopathy. Wernicke's Encephalopathy (WE) was described by Karl Wernicke in 1881 and is characterized by a clinical triad: encephalopathy,

ophthalmoparesis and ataxia, secondary to thiamine deficiency according to the literature, Thiamine deficiency is also observed in critical conditions, in particular, in patients with sepsis. Critically sick patients with COVID-19 have the same reasons for the development of toxic-metabolic encephalopathy. Examinations in patients with a severe course of COVID-19 demonstrate a hyper-inflammatory status (cytokine storm), a high catabolic state, intensive nutritional disorder with significant weight loss, frequent use of diuretics and dialysis therapy. An important component is the hyperactivity of the immune system, a high level of cytotoxicity, which contributes to adaptive and metabolic disorders. The occurrence of WE in three critically sick patients with COVID-19 and their positive response to thiamine therapy was first reported [14]. The clinical case described by us presents scientific information coherent with the general medical content

## CONCLUSIONS

Neurological complications, in particular, acute encephalopathy, on the background of coronavirus infection, may develop in patients with the presence of such risk factors as advanced age, cardiovascular diseases, hypertension, diabetes, gout. Most of the neurological complications in COVID-19 are probably not related to the direct penetration of the virus into the CNS, but are a trigger for the development of the pathology. Neuroimaging in such cases does not reveal pathological changes or reflects non-specific disorders.

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**Conflict of interest:**
*The Authors declare no conflict of interest.*

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