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МИАЛГИЧЕСКИЙ ЭНЦЕФАЛОМИЕЛИТ КАК ОСЛОЖНЕНИЕ COVID-19

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MYALGIC ENCEPHALOMYELITIS AS POST-COVID COMPLICATION

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Резюме. Нередко переболевшие COVID-19 сталкиваются с многочисленными осложнениями, некоторые из которых перекликаются с симптомами миалгического энцефаломиелита/синдрома хронической усталости. В данной работе рассматривается связь между постковидным синдромом и МЭ/СХУ и приводятся результаты исследования схожего клинического случая.

Ключевые слова: осложнения COVID-19, постковидный синдром, МЭ/СХУ.

Abstract. Patients with a history of COVID-19 frequently face numerous complications, sometimes resembling myalgic encephalomyelitis/chronic fatigue syndrome symptoms. This work focuses on analyzing the connection between the post-COVID syndrome and ME/CFS and shows results of a similar case study.

Keywords: COVID-19 long-hauler, the post-COVID syndrome, ME/CFS.

Relevance. Nowadays, a number of COVID-19 patients called *COVID-19 long-haulers* experience prolonged symptoms described by the common term of post-COVID syndrome and similar to those seen in *myalgic encephalomyelitis/chronic fatigue syndrome* (ME/CFS), including post-exertional malaise, sleep disturbances, fatigue and thermoregulation disorders. Additionally, a number of patients have suffered different forms of encephalopathy following COVID-19 infection, including acute necrotizing hemorrhagic encephalitis and acute dissemimated encephalomyelitis, it manifesting in loss of consciousness, generalized seizures, neck stiffness and other signs of neuroinflammation. Therefore, understanding the connection between these conditions could help to understand pathogenesis of the post-COVID syndrome and suggest some treatment measures.

Aim: to define the association between the history of COVID-19 and its possible complications in the form of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Objectives:

searching and analyzing available sources describing the symptoms of the post-COVID syndrome, diagnostic criteria for ME/CFS and its pathology;

investigating possible mechanisms leading to ME/CFS-like symptoms in the post-COVID syndrome;

studying a particular case of COVID-19 long-hauler to further develop and confirm the medical hypothesis.

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Materials and methods. In the course of study information from numerous internet sources and research papers has been analyzed and summarized. Additionally, one particular case of COVID-19 long-hauler has been investigated in order to confirm the medical hypothesis.

Results and discussion. As of now, there is no universally agreed-upon definition of ME/CFS. Therefore, 25 diagnostic criteria have been proposed so far, 5 of them being the major ones. Even though each criteria follow different approaches, there are some common symptoms, including persistent fatigue, pain, sleep disturbances, post-exertional malaise, cognitive changes, various visceral issues, thermostatic instability. Nevertheless, the diagnosisof ME/CFS cannot be made based on the post-COVID syndrome symptoms alone.

Pathology of ME/CFS is multifactorial. As there are no particular physical signs or biomarkers characteristic of ME/CFS, it is hard to identify its triggers. Potential risk factors include age, sex, psychiatric conditions (such as depression or anxiety disorder), genetic factors and a history of infection. Some of the most known infectious factors include Ross River Virus, Epstein-Barr Virus, and Q fever. Higher sickness rates of ME/CFS have been registered after 1918 influenza pandemic, 2009 H1N1 pandemic (the incidence rate was 2.08 per 100,000 person-months at risk) and *recent coronavirus outbreaks*, including severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012. A meta-analysis of post-infectious symptoms in MERS and SARS found that *19.3%* of patients experienced *ongoing fatigue* up to 39 months after infection. One common feature among these infections is that they act as a *severe physiological stressor*, causing intense inflammatory responses.

Thus it is suggested that SARS-CoV-2 infection could act as a factor in developing ME/CFS, for it manifests itself as a severe physiological stressor. It overwhelms the stress-integrator within the brain - *the hypothalamic paraventricular nucleus* (PVN), causing it to dysfunction. This leads to its hyper-sensitivity to normal otherwise physiological stressors and a higher risk of neuroinflammation and may manifest in fatigue, general malaise, anxiety, depression, ANS dysfunction, thermostatic problems and cognitive changes (see *Fig.1*).

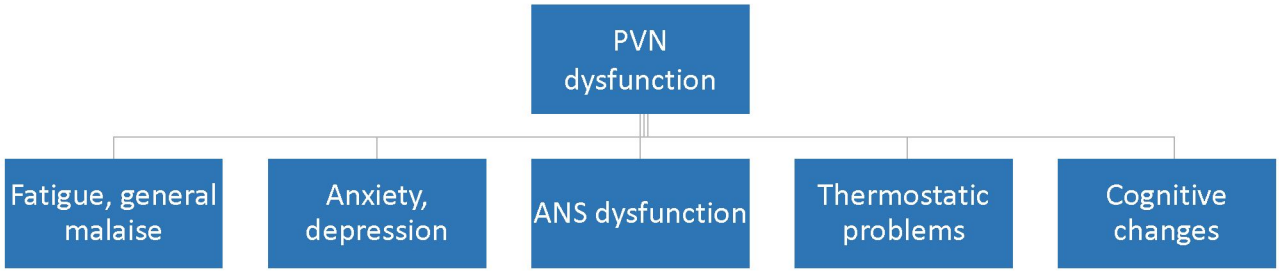

Fig. 1 – Symptoms caused by PVN dysfunction

Another study suggests that the post-COVID syndrome may develop due to an *increased level of autoantibodies against the autonomic nervous system* seen in COVID-19, which could be triggered by activation of auto-reactive bystander cells and molecular mimicry during acute infection. For example, receptor agonists antibodies against β2-

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adrenoceptor, α1-adrenoceptor, and angiotensin II receptor type 1 may be present, which could trigger neurological and cardiovascular disorders. Increased levels of anti-nuclear antibodies and rheumatic factor have been detected as well, presumably due to activation of auto-reactive B cells.

The *"hit-and-run" hypothesis* suggests that infective agents alter immune system function and cause persistent dysregulation of immune, neurologic and metabolic pathways. Acute infection may cause damage to mitochondria, impaired CNS function, higher level of ANS autoantibodies, PVN dysfunction and cytokine storm (the "hit"), which lead to complications after convalescence in the form of ME/CFS ("run"). This includes chronic inflammation, cytokine release syndrome and abnormal function of T-cells and natural killer cells. Damage to the central nervous system results in neuronal degeneration, demyelination, and subsequent functional impairment (see *Fig.2*).

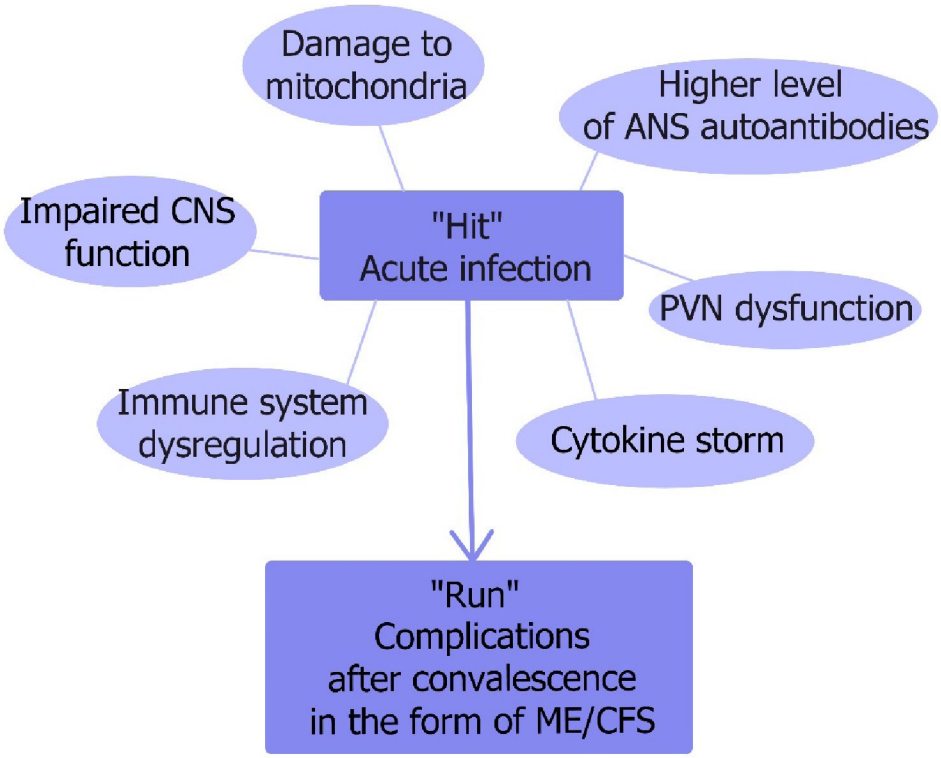

Fig. 2 – The "hit and run" hypothesis

According to mitochondrial function studies in ME/CFS, *abnormalities in mitochondrial enzyme levels* could be involved in the pathology of orthostatic intolerance and post-exertional malaise. For example, the anti-oxidant coenzyme Q10 levels have been found to be lower in ME/CFS than in healthy controls in some studies. However, the mechanisms behind mitochondrial abnormalities after acute infections are still unclear.

Lastly, stressful life events associated with the illness and the pandemic are also a major factor in developing ME/CFS.

A case study

A 13-year-old girl presented with a number of pronounced symptoms including temperature changes, ankle pains, headaches of 18 months duration. Analyses have shown

slight deviations from the norm, and the treatment has been mostly ineffective. A more detailed report on subjective and objective data is presented below.

Subjective data:

The temperature ranging from 32°C to over 42°C in the axillary region in the daytime with a difference of 4-5 °C in the left and right armpits; the temperature rising and falling in a 5 minute period of time;

Severe fatigue after exertion;

Headaches irradiating from the middle of the head to the temporal region, sometimes unilateral; dizziness, nausea and bitterness in the mouth, noise intolerance;

Ankle pain, irradiating to the knees in worsened state; very cold feet, goosebumps, numbness in the legs appearing frequently after sitting on a chair;

Objective data:

Complete blood count: absolute lymphopenia (1 thousand/μL on average, the norm being 1.5-4.8 thousand/μL (age 12-14 years)); occasional leukopenia (3.8 thousand/μL, the norm being 4.5 - 13.0 thousand/μL); mild anemia (Hb count measured 107-119 g/L, the norm being 115-150 g/L);

Urinalysis: normal;

Blood biochemistry: ASO ranging from 986 during the onset of the disease to 400-700 during the course of the disease (the norm being up to 200); LDH measured not higher than 130 on average (the age norm being not less than 150); CRP - less than 1 (the norm being up to 5);

ENMG of the lower extremities showed severe lesion of the tibial motor nerves of an axonal nature (not confirmed by neurological symptoms);

ECG: orthostatic tachycardia.

The *treatment* measures taken and their effectiveness are as follows: two courses of antibiotic therapy (Cefuroxime and Clarithromycin), two courses of Phenybut and an Adaptol course have had no effect; a Neuromidin course caused a side effect: a very strong pain syndrome along the entire length of the legs at the slightest movement; after two weeks of Wobenzym course, the temperature has fallen to 32-34°C and has lasted for a month without rising; Grandaxin course – no effect. Non-pharmacological treatment has been used as well: acupuncture caused a temporary decrease in the frequency of headaches, a course of hyperbaric oxygen therapy has produced no effect, exercise therapy has been ineffective and has triggered a drop in temperature below 32°C, heart rate elevating up to 170 bpm. on minimal physical exertion. Ultimately, the course of treatment has been mostly ineffective.

The symptoms observed in the course of study, including thermoregulation disorders, the temperature varying in different parts of the body and changing in short periods of time; pronounced post-exertional malaise; headaches and dizziness, noise intolerance; ankle pains, cold feet and numbness in the legs from sitting, are highly suggestive of ME/CFS. Many of the symptoms also point to the supposed mechanism behind the patient's condition – the hypothalamic paraventricular nucleus (PVN) dysfunction. PVN is responsible for thermoregulation and serves as a stress-integrator within the brain, therefore, its altered function could manifest in the temperature rises and

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sudden falls and hyper-sensitivity to normal otherwise stressors, such as exertion and street noise.

Treatment options. There is currently no validated treatment for post COVID-19 condition. Since the symptoms and mechanisms of the post-COVID syndrome resemble those of post-infectious ME/CFS, some treatment methods used in ME/CFS could be useful in the post-COVID syndrome. Based on the symptoms, cognitive behavioral therapy, energy management and medicine (including painkillers and sleeping draughts) may be administered. Immunosuppressive options in patients with an increased level of autoantibodies against the autonomic nervous system may be effective. Graded exercise therapy is an option, although recent studies as well as the case discussed above have shown that it may accentuate post-exertional malaise in some patients. Social, cultural, and financial support, a balanced diet and consistent sleep schedule are also of great importance.

Conclusions: as a result of the analysis several conclusions have been made:

First, COVID-19 infection could act as an infectious trigger for ME/CFS, which manifests itself in the form of the post-COVID syndrome.

Second, as there is no specific treatment for ME/CFS, the treatment for the post-COVID syndrome is mainly symptomatic and not very effective.

Third, there is an urgent need for the existence of the post-COVID syndrome itself to be recognized in Belarus for proper management of the patients and improvement of their quality of life.

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