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Current Views on Neurological Disorders in Patients with Post-Cochlear Syndrome (Literature Review)

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Abstract Neurological and psychiatric disorders of the central nervous system can occur in every severe infectious disease; currently, during the pandemic of coronavirus infection, this is one of the leading debilitating viral afflictions. Worldwide, more than 200 million people have been infected with COVID-19. Most recover after a month, but many experience prolonged onset of symptoms.

Keywords: Neurological and psychiatric disorders, COVID-19, postviral syndrome

Introduction. Since the outbreak of the new coronavirus infection COVID-19, caused by SARS-CoV-2, researchers' attention has been focused on the symptoms of respiratory system damage. This was largely due to previous experience with the 2009-2010 outbreak of influenza AH1N1, where lung problems were a major risk factor and cause of death. At the same time, other target organs for the virus were discussed in the literature: lungs, kidneys, heart, liver, pancreas, etc. Already in the first reports there was evidence of central nervous system involvement even at an early stage of the disease. Neurological manifestations associated with COVID-19 have been described as meningoencephalitis, acute necrotizing encephalopathy, demyelination, "classic" cerebrovascular diseases, primarily strokes, Guillain-Barré syndrome and its variants, such as Miller-Fisher syndrome. The main mechanisms discussed are direct damage to the nervous system by viral infection, virus-induced hyperinflammatory and hypercoagulable states and post-infection immune processes, to a lesser extent the results of hypoxic changes in brain tissue (not all patients had low blood saturation indices).

In June-July 2020, it became clear that some people - including those with mild symptoms of COVID-19 in the acute period of the disease - may suffer various debilitating symptoms for many months after initial infection. Almost 70% of people have one or more organs affected 3-6 months after the first symptoms of SARS-CoV-2 infection.

In the work of J.F. Ludvigsson showed that post-onset symptoms can occur in both adults and children, although they continued to be attributed to "risk factors" - obesity, arterial hypertension, diabetes mellitus.

It is clear from the publications that although "common" symptoms such as dyspnoea, headache and myalgia were mentioned, the authors regarded the clinical manifestations in postvaccination syndrome mainly as the result of organ and system dysfunction in the acute phase of the disease. Thus, A. Dennis, M. Wamil, S. Kapuretal observed 201 individuals (mean age 44 years (standard deviation 11.0), 70% female, 87% white, 31% healthcare workers) from April to

September 2020 after infection with SARS-CoV-2 (mean 140 (105-160) days after the first symptoms of infection). They described the most frequent symptoms, linking them to organs and systems: fatigue (98%), muscle pain (88%), breathlessness (87%) and headaches (83%), often cardiorespiratory (92%) and gastrointestinal (73%) symptoms. The authors reported evidence of heart (32%), lung (33%), kidney (12%), liver (10%), pancreas (17%) and spleen (6%) involvement. Single (66%) and multiorgan (25%) disorders were observed, which were associated with previous hospitalisation in the acute period of COVID-19 ($p<0.05$).Однако совершенно очевидно, что постковидный синдром носит системный характер: симптомы, связанные с какой-либо системой органов, практически всегда сосуществуют с симптомами нарушения функции другой (а чаще – нескольких) органной системы (например, проблемы сердца и кишечные проблемы, нарушения зрения). Цитируемые авторы указывали, что у 42% пациентов было 10 или более симптомов.

Thus, according to BDavido, S.SeangR.Tubiana, & deTruchis, after a short period of recovery, patients presented with a relapse-like clinic with persistent symptoms: myalgia, severe fatigue, fever, shortness of breath, chest tightness, tachycardia, headaches, anxiety. They were predominantly young women (sex ratio 4:1) around 40 years of age. The authors noted "biological abnormalities" (no lymphocytopenia or elevated C-reactive protein (CRP) - evidence of viral inflammation) and, in rare cases, no sign of infection on chest CT, which the authors seemed to regard as important evidence of COVID-19 infection.

Post-infection syndrome is probably not a unique phenomenon and coincides in its clinical manifestations with myalgic encephalomyelitis (chronic fatigue syndrome), post-infection conditions after chikungunya outbreak, Ebola fever. It is likely that other known post-infectious complications may also have a common nature, e.g. chronic borreliosis (Lyme disease), particularly neuroborreliosis, which manifests as frequent headaches, asthenic syndrome with emotional lability, anger, spitefulness, aggressiveness, dizziness and unsteadiness of gait, forgetfulness, slow thinking, reduced attention span, memory disturbances, inability to attend to routine tasks, dependence on loved ones, emaciation of vocabulary, loss of interest in traditional hobbies, narrowing of social networks. There are 6 groups of symptoms in post-Lyme syndrome: "Cognitive and fatigue", "Eye and balance disorders", "Signs of infection", "Mood related problems", "Musculoskeletal pain" and "Neurological". The effects of infection caused by the Epstein-Barr virus look similar and, as with other infections, the course of the disease has a wave-like pattern Myalgic encephalomyelitis (chronic fatigue syndrome) is often caused by infection and immune system activation, developing a definite and rather long time after the infection, which has not allowed a definitive causal relationship to be described for a long time and appears as a dysregulated pathology of the autonomic nervous system and immune process disorders. The authors link the clinical picture of myalgic encephalomyelitis to brainstem damage. There are also clinical guidelines for post-Lyme syndrome.

It should be noted that such diseases as post-Lyme syndrome, chronic fatigue syndrome are not always perceived by doctors unambiguously, and many doctors believe that such diseases do not exist or they are a product of morbid imagination of patients and unscrupulous doctors (in the literature this phenomenon was named "post-Lyme wars"). The situation is aggravated by the lack of precise diagnostic criteria for these diseases (conditions). At the same time, let us recall the existence not only of primary syphilis, but also of secondary and tertiary syphilis: Borrelia are spirochaetes and are in many ways similar to treponema pale. In other words, post-infectious conditions have been well known to medicine for centuries and have never before been as controversial. On 25 February 2021, the World Health Organisation (WHO) recognised the existence of postinfections and published a statement by Professor Martin McKee on COVID-19[2]. Analysis of the "disease pattern"

shows that a significant number of symptoms are related to some kind of pathology in the nervous system. Four signs (enlarged lymph nodes, aneurysmal and other vein changes, skin rashes and hair loss - other extracerebral manifestations of systemic vasculitis can be discussed here) are unequivocally unrelated to nervous regulation. However, the remaining 8 signs (diarrhoea, urinary disorders, sexual dysfunction, weight loss, cardialgia, heart rhythm disorders, myalgia, and arthalgia) could also be of neurogenic origin. Just these functions are regulated by the sympathetic, parasympathetic and metasympathetic parts of the nervous system.

It should be noted that damage to the central nervous system is confirmed by neuroimaging techniques. Neuroimaging data provides a good opportunity to study the relationship between COVID-19 and the central nervous system. However, studies that have investigated the effects of COVID-19 on brain structures are relatively few and the data are often contradictory.

Patients who underwent COVID-19 had lower mean values of diffusion coefficient and axial diffusion coefficient in the right upper fronto-occipital bundle.

In the 18F-FDG-PET studies, patients with COVID-19 showed widespread hypometabolism in cerebral areas including frontal cortex, insular and subcortical areas, observed 6 months after the diagnosis of COVID-19 .

Frontal hypometabolism was associated with first-time cognitive impairment. Patients with COVID-19 with long COVID showed hypometabolism in various brain regions including the frontal and temporal lobes, the trunk and the cerebellum. Metabolic scores in the frontal and temporal lobes clearly separated patients with long COVID from healthy controls and correlated with duration of pain syndrome, high BP and insomnia . These findings are confirmed in other studies, with frontal and temporal lobe abnormalities being detected in patients with both acute COVID-19 and after formal recovery.

The question arises: what is the mechanism of damage to the nervous system? SARS-CoV-2 is known to have a low affinity to nerve tissue: its penetration into nerve endings in the nasal mucosa has been discussed, sometimes explaining anosmia and avulsion, migration along the "olfactory tract" or via the vagus or trigeminal tract, but definitive and conclusive evidence is lacking. SARS-CoV-2 protein was detected on histochemical examination in the endothelium of cerebral vessels, but not in neurons or microglia cells. The authors note that the presence of SARS-CoV-2 in the CNS leads to a local CNS response mediated by HLA-DR+ microglia as effectors of the myeloid-induced inflammatory response. The authors correctly write that since they were able to detect SARS-CoV-2 RNA in brain regions such as the cerebellum, which is not directly linked by any "pathways" to the olfactory mucosa, there may be other mechanisms of virus entry into the CNS, possibly in addition or in combination with axonal transport. For example, migration of leukocytes carrying SARS-CoV-2 across the blood-brain barrier cannot be excluded (this is almost impossible to imagine: erythrocyte diapedesis is active cell passage directly through endothelial cells, leukocytes (neutrophils - microphages) have no such property) or virus penetration into the endothelium of CNS vessels. As a confirmation of the authors' considerations, immunoreactivity to the SARS-CoV-2 protein was detected in cerebral endothelial cells and leptomeningeal membranes. Endothelial cells are a major element of the blood-brain barrier, which protects the nervous tissue itself against viruses, among other things. It is of course possible to imagine the permeability of this barrier being impaired in the infection described, since not only viruses but also fibrinogen and erythrocytes end up in the extravasal space. However, virus entry into the tissue does not lead to its entry into the cell as this intimate process requires specific binding sites on the cell membrane with the virus, in this case receptors for ACE-2.

Two considerations by the authors of the cited work, which partly overlap with the assumptions outlined in this paper, are interesting:

1) the detection of traces of SARS-CoV-2 in the brainstem, which includes the main respiratory and cardiovascular control centre, suggests that neural tissue damage may exacerbate or cause CNS-mediated respiratory or cardiac dysfunction;

2) SARS-CoV-2 in the endothelium of brain tissue could lead to vascular damage and a wider spread of the virus to other brain regions, which would cause the disease to become more severe or to become chronic (a questionable assumption on the grounds previously expressed).

The histological changes in the brain tissue described above in the form of microglial nodules and neuronal phagocytosis (neuronophagy) in the brainstem, cortex and limbic structures, lymphocytic infiltration of the tissue, may explain the persistent vegetative abnormalities and anxiety (panic attacks). The inflammatory responses characteristic of COVID-19 infection may play a leading role in the damage to brain structures. It is inflammation that plays a key role in the acute period of the disease in the development of complications by triggering intravascular coagulation of the blood, having a direct negative effect on many functions, including that of the brain tissue.

Infiltration of the virus into the endothelial cells of the cerebral vasculature activates neutrophils, macrophages, intravascular clotting and leads to microthrombosis and impaired vascular permeability. Tumour necrosis factor (TNF-α), cytokines can pass through the blood-brain barrier due to its increased permeability. Cytokines activate microglia cells. Macro- and especially micro-hypoxic ischaemic damage and infarcts in brain tissue mediate pathological 'synaptic pruning' by microglia (cells of macrophage nature) - a reduction in the number of synaptic connections. Microglia secrete specific inflammatory mediators, including quinolinic acid, which leads to increased glutamate levels and upregulation of NMDA receptors, which can cause mnemonic disturbances as well as causing hallucinations and nightmares and disturbing sleep. Among the complications of COVID-19 infection is acute transverse myelitis (TMA), an extremely rare neurological disease (1.34-4.6 cases per million per year). A clinical review of 43 cases of patients with COVID-19-associated OPM and 3 cases of serious adverse events of OPM after administration of the ChAdOx1 nCoV-19 vaccine (AZD1222, published between March 2020 and January 2021 (21 countries) were performed. The clinical presentation is typical: acute onset of paralysis, with sensory impairment and impaired pelvic function due to spinal cord lesions. The patients included 23 males (53%) and 20 females (47%) aged between 21 and 73 years (mean age 49 years), with two peaks at 29 and 58 years, excluding 3 paediatric cases. The clinical manifestations were quadriplegia (58%) and paraplegia (42%). MRI findings (40 patients) revealed local lesions ≤3 spinal cord segments (12 cases, 30%) at cervical (5 cases) and thoracic spinal cord levels (7 cases); 28 cases (70%) had longitudinally extensive lesions involving ≥4 spinal cord segments (cervicothoracic in 18 cases and thoracolumbar-sacral in 10 patients). Acute disseminated encephalomyelitis (ODM) developed in 8 patients, mostly women (67%) aged 27 to 64 years. Three patients also had blindness due to optomyelitis, and another 2 had acute motor axonal neuropathy. The majority of cases (68%) had a latency period of 10 days to 6 weeks, which may indicate postinfectious neurological complications mediated by the host response to the virus. In 32% of cases, a short duration (15 h to 5 days) indicated a possible direct neurotropic effect of SARS-CoV-2, although again indirect effects could not be excluded. The 3 cases of UTI among 11,636 participants in the AZD1222 vaccine trial gives an extremely high incidence (0.02%), given that the global incidence of UTI associated with COVID-19 is 0.5 cases per 1 million (note that not all cases are described), and the overall incidence of this pathology is at most 0.00046%. The pathogenesis remains unknown, but the authors suggest that SARS-CoV-2 antigens - possibly also present in the AZD1222 COVID-19 vaccine or its chimpanzee adenovirus adjuvant - may induce immune mechanisms leading to the development of myelitis.

Acute necrotising encephalopathy is another severe form of immune damage to the brain in COVID-19 infection. This pathology is not directly related to COVID-19 infection and occurs in a variety of diseases, including influenza A/H1N1.

While the reasoning and findings are quite convincing in the acute phase of the disease, no such information is available for the post-coVID syndrome. Moreover, there is no evidence of viral infection either. Consequently, recognizing brain tissue damage, one has to look for other, non-infectious causes of brain damage. Such a cause is likely to be immune-induced chronic inflammation involving the microvasculature, which may be called immunothrombosis, thrombovasculitis, or endotheliopathy. A key role in the development of the process is played by various antibodies that form immune complexes or have a direct damaging effect on nervous tissue structures. Antiphospholipid antibodies and antibodies to myelin-oligodendrocyte glycoprotein are among the well-known ones.

Numerous other conditions - various skin vasculitis, visible (including aneurysmal) venous lesions, the appearance of dystrophic nail changes (transverse striation, Bo lines), Kawasaki-like syndrome with vasa vasorum damage, etc. are additional factors that allow to talk about immunothrombosis.

Neuronal lesions in COVID-19 patients are due to the fact that the infection itself can damage nerve fibres, vascular endothelium with the development of both local and systemic lesions. As for central brain functions, they may be impaired due to viral, dysmetabolic, cytotoxic, vascular effects, which are accompanied by cerebral oedema and as a consequence lead to neuronal degeneration. Almost all COVID-19 patients suffer from asthenia, anxiety disorders and depression. Particularly worrying is the development of cognitive impairment of varying severity. The question of the reversibility of cognitive impairment and the factors contributing to its severity remain poorly understood. The problems of cognitive rehabilitation and possibilities of non-medical correction of patients who have had coronavirus infection, as well as their differences from post-stroke cognitive disorders, remain poorly studied.

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