THE SPECIFICS OF ENCEPHALITIS AFTER COVID-19

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Encephalitis is a group of acute infectious diseases affecting the substance of the brain. They often lead to disability or death, and, therefore, require urgent medical attention. The article discusses the etiology, pathogenesis, and clinical picture of encephalitis, with special attention to the course of this disease after the COVID-19 pandemic. We note the growing number of encephalitis cases, especially of autoimmune variety and those caused by herpes. The possible reason behind this trend is the disruption of operation of the immune system brought by COVID-19, which manifests as a cytokine storm, neuroinflammation, and autoimmune reactions. There are cases of COVID-19-dependent encephalitis described. The pathways taken by SARS-CoV-2 to penetrate into the cells of the central nervous system have not yet been fully studied, although there are hypotheses that this happens both trans-synaptically through mechanoreceptors and chemoreceptors of the respiratory system into the medulla oblongata, and through receptors of the angiotensin converting enzyme 2.

Keywords: encephalitis, COVID-19, neuroinfection, autoimmune encephalitis

Author contribution: Bobrov MP — literature analysis, data collection, manuscript authoring; Voitenkov VB — literature analysis, study planning, data interpretation, manuscript authoring; Ekusheva EV — study planning, collection and analysis of literature; Kiparisova ES — collection and analysis of literature.

Compliance with ethical standards: the submitted article has not been previously published, all borrowings are correct.

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Received: 03.11.2023 **Accepted:** 20.12.2023 **Published online:** 29.12.2023

DOI: 10.47183/mes.2023.059

ОСОБЕННОСТИ ТЕЧЕНИЯ ЭНЦЕФАЛИТОВ ПОСЛЕ ПЕРЕНЕСЕННОЙ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ COVID-19

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Энцефалиты представляют собой группу острых инфекционных заболеваний, поражающих вещество головного мозга. Они часто приводят к инвалидности или летальному исходу и в связи с этим требуют неотложной медицинской помощи. В статье рассмотрены этиология, патогенез и клиническая картина энцефалитов. Особое внимание уделено течению энцефалитов после пандемии COVID-19. Отмечен рост числа энцефалитов, особенно среди аутоиммунных энцефалитов, энцефалитов, вызванных герпес-вирусами. Вероятно, эта тенденция связана с тем, что взаимодействие вируса COVID-19 с организмом приводит к нарушению работы иммунной системы, что проявляется развитием цитокинового шторма, нейровоспалением и развитием аутоиммунной реакции. Описаны случаи развития COVID-19-зависимого энцефалита. Механизмы проникновения вируса COVID-19 в клетки центральной нервной системы еще не до конца изучены, хотя и существуют гипотезы, что это происходит как транссинаптическим путем через механорецепторы и хеморецепторы респираторной системы в продолговатый мозг, так и через рецепторы ангиотензинпревращающего фермента 2.

Ключевые слова: энцефалит, COVID-19, нейроинфекция, аутоиммунный энцефалит

Вклад авторов: М. П. Бобров — анализ литературы, сбор данных, подготовка рукописи; В. Б. Войтенков — анализ литературы, планирование исследования, интерпретация данных, подготовка рукописи; Е. В. Екушева — планирование исследования, сбор и анализ литературы; Е. С. Кипарисова — сбор и анализ литературы.

Соблюдение этических стандартов: представленная статья ранее опубликована не была, все заимствования корректны.

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Статья получена: 03.11.2023 **Статья принята к печати:** 20.12.2023 **Опубликована онлайн:** 29.12.2023

DOI: 10.47183/mes.2023.059

Encephalitis is an acute inflammation of the brain tissue [1]. The urgency of discussion of this subject is substantiated by the severe course of the disease, need for emergency medical care, sometimes without delays, and the possible disability or lethal outcomes [2]. Understanding the etiology, links of pathogenesis, and knowing the clinical picture of encephalitis, a clinician can correctly diagnose the condition and initiate the necessary therapy.

Among neuroinfections, the share of encephalitis varies from 3.8 to 65%; this wide a range can probably be explained by the epidemiological situation in a given region and availability of advanced laboratory and diagnostic equipment therein [3–5]. Encephalitis is a polyethological disease, but its most common pathogens are viruses [5, 6]: they make up to 90% of all cases [4]. The prevailing varieties thereof are the tick-borne encephalitis (TBE) virus, enteroviruses (various strains of Coxsackieviruses and ECHO viruses), and herpes virus [7].

Autoimmune encephalitides (AIE) form a group of their own. They are characterized by an autoimmune inflammatory process in the brain and production of antibodies to extracellular or intracellular structures of the central nervous system [8]. The most common AIE is anti NMDAR encephalitis [9]. The known

reasons triggering autoimmune process in the context of this diseases are neoplasms and herpetic encephalitis [10].

The clinical picture of encephalitis includes a general infectious syndrome (weakness, fever, myalgia, arthralgia), a cerebral syndrome (nausea, vomiting, dizziness), and focal symptoms [11]. Depending on the cause, the prevailing conditions may be flaccid paralysis of upper limbs and neck (associated with tick-borne encephalitis) [12], oculomotor disorders (Von Economo encephalitis) [13], or mental disorders (autoimmune encephalitis) [14].

The purpose of this literature review is to analyze the course of encephalitis against the background of the new coronavirus infection, and to compare the respective data with those describing the pre-pandemic period.

Main part

The state of the person's immune system plays an important role in the pathogenesis of various forms of encephalitis. Over the past 3 years, the world has seen the COVID-19 pandemic brought by SARS-CoV-2.

In addition to the damage to respiratory system, COVID-19 caused extrapulmonary complications under the influence of several factors: a long-lasting inflammation; persistence of the virus or parts thereof in organs with possible reactivation of inflammation; production of antibodies that cross-respond with body tissues; development of coagulopathies [15]. The growth of neurological complications, including encephalitis, is natural. One of the pathways of damage to the central nervous system (CNS) may be through the link between SARS-CoV-2 and receptors of angiotensin-converting enzyme 2 (ACE 2), which are common in neurons and glial cells of the CNS [16]. Another considered pathway involves transsynaptic penetration into medulla oblongata through mechanoreceptors and chemoreceptors found in the lungs [17].

The analysis of data from 23 sources, which covered about 130,000 COVID-19 patients, showed that the proportion of patients with encephalitis is about 0.215%, while mortality is 13.4% [18]. Among all patients with neurological symptoms, the share of encephalitis ranges from 13 to 40% [19]. Neuroimaging scans of 127 patients revealed the following: 86 patients had nonspecific COVID-19-associated encephalitis; 13 — acute demyelinating encephalomyelitis; 4 — acute necrotic encephalopathy; 9 — limbic encephalitis; 5 — Bickerstaff brainstem encephalitis; 13 — encephalitis with focal or diffuse leptomeningeal disorders; 26 — concomitant encephalopathy and encephalitis with other clinical and morphological findings [19].

The symptoms registered in patients with encephalitis during the acute phase of COVID-19 were seizures (29.5%), confusion (23.2%), headache (20.5%), disorientation (15.2%), and a change in mental status [20]. In over half of the cases considered, laboratory examination revealed changes visible on MRI scans, EEG records, and in composition of the cerebrospinal fluid [20, 21].

COVID-19-associated encephalitis can develop a few weeks after the acute phase of the disease. A clinical case report [22] describes acute hemorrhagic leukoencephalitis in a 46-year-old patient who, after hospitalization with confirmed COVID-19, was discharged for quarantined treatment at home. Five weeks later, he was urgently taken to the hospital with complaints of headache and impaired consciousness. His neurological status included depression of consciousness (up to 11 points on the Glasgow Coma Scale), upper left limb plegia and lower left limb paresis (up to 3 points), while the tendon reflexes were preserved. Computed tomography revealed multifocal non-hemorrhagic lesions in both hemispheres of the brain, MRI — lesion of white matter in the bilateral frontal, parietal lobes, left thalamus, left cerebral peduncle and medulla oblongata. Lymphocytic pleocytosis with increased protein content was observed in the cerebrospinal fluid. The patient was prescribed intravenous administration of 1 g of methylprednisolone per day for 5 days. After 5 days, against the background of deterioration of the patient's condition, new MRI scans were made, and they showed greater number of lesions, now hemorrhagic, and edema with trunk wedging. The treatment plan was extended with reinforced decongestive therapy and a trepanation, but the patient died on the same day. A meta-analysis of the reported cases of acute hemorrhagic leukoencephalitis showed that their amount has grown compared to the pre-pandemic period, and the number of the associated deaths was up to 32% [23].

Herpes encephalitis (HE) is one of the most common varieties of the disease [24]. Typically, infection with a herpes virus occurs at an early age. It penetrates into the cell, release proteins, viral DNA, and begins production of new viral units [25]. Immune system triggers cellular immunity, which involves activation of CD8+ T cells, differentiation of CD4 cells into T helpers, production of humoral immunity elements (IFN-γ, IL-2, TNF-α), and activation of B lymphocytes. As a result, virus replication slows down and it becomes latent, persisting in sensory and sympathetic ganglia. A possible pathway to development of HE is retrograde transport of virus particles along the fibers of the olfactory or trigeminal nerves [26]. With COVID-19 in the background, CD 8- and CD 4- cells are depleted, gamma interferon production slows down, which probably leads to increased replication of the herpes virus and subsequent development of HE [25, 26].

Another consequence of the immune system's reaction to SARS-CoV-2 is cytokine storm. Some researchers believe that cytokine storm is a factor in the development of AIE in patients who had COVID-19 [27, 28]. A meta-analysis revealed that the most common type of the disease is limbic encephalitis (37%), followed by anti NMDAR encephalitis (26%). There were cases of encephalitis registered in vaccinated patients, with 38.5% of them having AstraZeneca vaccine, 33.8% — Pfizer vaccine, and 16.9% — Moderna vaccine [29, 30]. The mechanism of development of this condition after vaccination remains unclear. Russian vaccines, designed with the negative experience factored in, were not found to be associated with encephalitis, therefore, in our opinion, they can be the best recommendation for prevention of COVID-19 [31].

Influenza can develop complications in the form of influenza-associated encephalitis [5]. It was reasonable to expect that in the epidemic season of 2022–2023, in a population whose immunity has been weakened and modified by repeated infection with SARS-CoV-2, there will be more cases of damage to the nervous system done by the influenza virus. A group of researchers examined a Romanian cohort of children aged 1–6 years (n = 301), comparing the frequency of such cases with that registered during the previous epidemic seasons. They found that the 2022–2023 flu season was characterized by a large number of coinfections (viral, bacterial, fungal, and parasitic), which were more severe, with longer hospital stays and more complications ($p < 0.05$); moreover, the patients received oxygen therapy for significantly longer periods of time ($p < 0.05$), and none of them was vaccinated against influenza [32]. The researchers concluded that a history of COVID-19 aggravates flu, at least in minors, especially among young children who are more prone to developing serious complications. The second

conclusion of this study is a recommendation to encourage the widest possible flu vaccination.

The data obtained are of great interest from a fundamental point of view: it is well known that during the COVID-19 pandemic, the incidence of influenza significantly decreased throughout the world [33]. Moreover, the curve of incidence of all other airborne infections dropped [34, 35], and there were similar trends registered for infections transmitted otherwise (in particular, HIV and hepatitis B) [36]. SARS-CoV-2 was assumed to actively suppress circulation of other infectious agents during the pandemic, but currently, we are witnessing a return of other nosological forms, and, as we tried to highlight in this work, there are noticeable changes in their patterns and character of damage to the CNS.

There is no doubt that any encephalitis should be treated immediately. The common approach is to identify its etiology, cause, and begin etiotropic treatment [11, 37–40], adding pathogenetic and symptomatic therapy. It is also necessary to account for the possibility of a more severe course of the disease in people with a history of COVID-19.

CONCLUSION

Encephalitis is a catastrophic condition that can lead to death. Timely diagnosis and adequate therapy improves the prognosis for patients. In recent years, there has been an increase in the number of encephalitis cases, including its autoimmune varieties, and the amount of lethal outcomes therefrom has also grown. It is not always possible to identify clinical and diagnostic signs of encephalitis, and the clinical picture may be blurred or interpreted as a manifestation of another nosology. The COVID-19 pandemic and the specifics of its course, including effects on the immune system, cytokine storm, and subsequent development of long COVID, are the likely factors conditioning the growing frequency of encephalitis. The mechanisms of SARS-CoV-2 penetration into cells and the ways the virus interacts with the nervous system remain partially unknown, but it is certain that encephalitis concomitant with COVID-19 worsens the patient's prognosis. Further investigation of this issue and the development of treatment protocols will contribute to prevention of complications and lethal outcomes.

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