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Демиелинизирующее заболевание у пациентки с церебральным венозным тромбозом на фоне манифестной новой коронавирусной инфекции

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АННОТАЦИЯ

В настоящее время при выявлении неврологических расстройств на фоне новой коронавирусной инфекции у клиницистов возникают вопросы: неврологические проявления обусловлены новой коронавирусной инфекцией, либо имеет место сочетание нескольких видов патологии центральной нервной системы с COVID-19. Представлено клиническое наблюдение пациентки 57 лет с демиелинизирующим заболеванием головного мозга и церебральным венозным тромбозом на фоне клинически перенесённой COVID-19. Проведена дифференциальная диагностика с рассеянным склерозом, острым рассеянным энцефаломиелитом, оптикомиелитом, церебральной аутосомно-доминантной артериопатией с подкорковыми инфарктами и лейкоэнцефалопатией, саркоидозом, антифосфолипидным синдромом, митохондриальной энцефалопатией с лактатацидозом и инсультоподобными эпизодами (MELAS) и тромбозом вен больших полушарий. Освещены вероятные патогенетические варианты развития демиелинизации и возможная связь с церебральным венозным тромбозом и COVID-19.

Ключевые слова: *демиелинизирующие заболевания ЦНС, церебральный венозный тромбоз, COVID-19, молекулярно-генетическое исследование*.

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Demyelinating disease in a patient with cerebral venous thrombosis and covid-19 clinical manifestations

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ABSTRACT

Actually, verifying neurological disorders associated with COVID-19 make clinicians ask several questions: the manifestation of neurological pathology is due to COVID-19, or there is a combination of several CNS pathologies with COVID-19. We report a clinical case of a 57-year-old female patient with demyelinating disease of the central nervous system, cerebral venous thrombosis associated with clinically transferred COVID-19. Differential diagnosis was performed with multiple sclerosis, acute multiple encephalomyelitis, opticomyelitis, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, sarcoidosis, antiphospholipid syndrome, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) and thrombosis veins of the large hemispheres. Probable pathogenetic variants of demyelination development and possible connection with cerebral venous thrombosis and COVID-19 are highlighted.

Keywords: *demyelinating diseases of the central nervous system, cerebral venous thrombosis, COVID-19, molecular genetic analysis*.

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A new coronavirus infection and respiratory symptoms, contribute to numerous neurological disorders [1]. In a study by Mao et al. (2020), 78 of 214 patients diagnosed with COVID-19 had various neurological disorders. Some were from the central nervous system, such as ischemic stroke, cerebral hemorrhage, acute hemorrhagic encephalitis, necrotizing encephalopathy, encephalitis, meningitis, meningoencephalitis, ventriculitis, myelitis, demyelinating and neurodegenerative brain diseases. Others were from the peripheral nervous system, including Guillain–Barre syndrome, Miller–Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, and cranial mononeuropathies.

The SARS-CoV-2 virus promotes increased production of pro-inflammatory cytokines, including interleukins (IL) IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor α, and interferon γ. These cytokines can penetrate the blood-brain barrier, affecting macrophages, microglia, and astrocytes and inducing a pro-inflammatory condition [2]. IL-6 exacerbates clinical manifestations, neuroinflammation, and demyelination, mainly by stimulating the formation of pathogenic T-helper cells. Another possible explanation may be the production of antibodies against myelin caused by the SARS-CoV-2 virus [3].

Recently, cases of cerebral venous thrombosis associated with COVID-19 have been increasingly mentioned in the literature [4]. Thus, a meta-analysis by Baldini et al. (2021) showed that in patients hospitalized with infection caused by SARS-CoV-2, the incidence of cerebral venous thrombosis among cerebrovascular complications was 4.2%.

The development of cerebral venous thrombosis is based on the triad of Virchow (1856; damage of the vascular wall integrity, blood flow velocity, rheological properties of blood, and an imbalance between prothrombotic and fibrinolytic processes). Infection with SARS-CoV-2 contributes to the development of endothelial dysfunction, a hyperinflammatory response, and hypercoagulation by complement activation, a cytokine storm, platelet dysfunction, and hypoxia, causing a slowdown in blood flow. Therefore, a new coronavirus infection triggers a cascade of pathophysiological reactions, affecting all components of Virchow's triad [5].

Haacke et al. (2021) believe that local disorder of venous blood flow leads to the remodeling of medullary veins with the subsequent destruction of the endothelium and the release of monocytes and cytokines, which, in turn, provokes an autoimmune demyelinating process, tissue death, and atrophy. Abnormal blood flow causes endothelial cell hyperplasia with progression to occlusive vascular inflammation and is a precursor to vascular cell infiltration and demyelination.

The relationship between the cerebral venous system and demyelinating diseases of the brain was mentioned back in 1863 when an autopsy revealed a perivenular location of demyelinating plaques in the juxtacortical, periventricular, and infratentorial brain areas in a patient with multilocular (multiple) sclerosis (MS), which later (more than after 100 years) was confirmed using high-field magnetic resonance imaging (MRI) [6].

In MS, early pathomorphological studies of the brain showed a venocentric pattern of local inflammatory demyelination [7]. Kapadia et al. (2020) hypothesized that one of the main pathogenetic mechanisms of MS is autoimmune vasculopathy. Pathomorphological studies of the brain of MS patients have shown that inflammatory lymphocytic infiltration often occurs in the walls of veins and venules proximal to active segments of lesions. Limited inflammatory changes in the venous wall can be considered a form of local venous vasculitis or cerebral venulitis [8]. As the inflammatory process develops, the cellular infiltrate spreads into the perivascular space and causes demyelination [9].

Subacute or chronic inflammatory lesions of the cerebral veins can cause vasculitis, focal intimal hyperplasia, and thickening of collagen fibers, which increases vascular wall permeability and induces hemorrhage. In addition, impaired venous blood flow leads to increased venous pressure, chronic cerebral edema, decreased perfusion pressure, and damage to the blood-brain barrier, followed by ischemic infarction and hemorrhage [10].

Zamboni et al. (2009) proposed the "chronic cerebrospinal venous insufficiency" hypothesis to indicate the relationship between MS and venous disorders. According to this hypothesis, the development of MS is promoted by impaired venous outflow due to numerous intraluminal stenosing malformations (abnormal formation of valves, septum, interseptum, and segmental hypoplasia/agenesia), especially in the internal jugular veins and

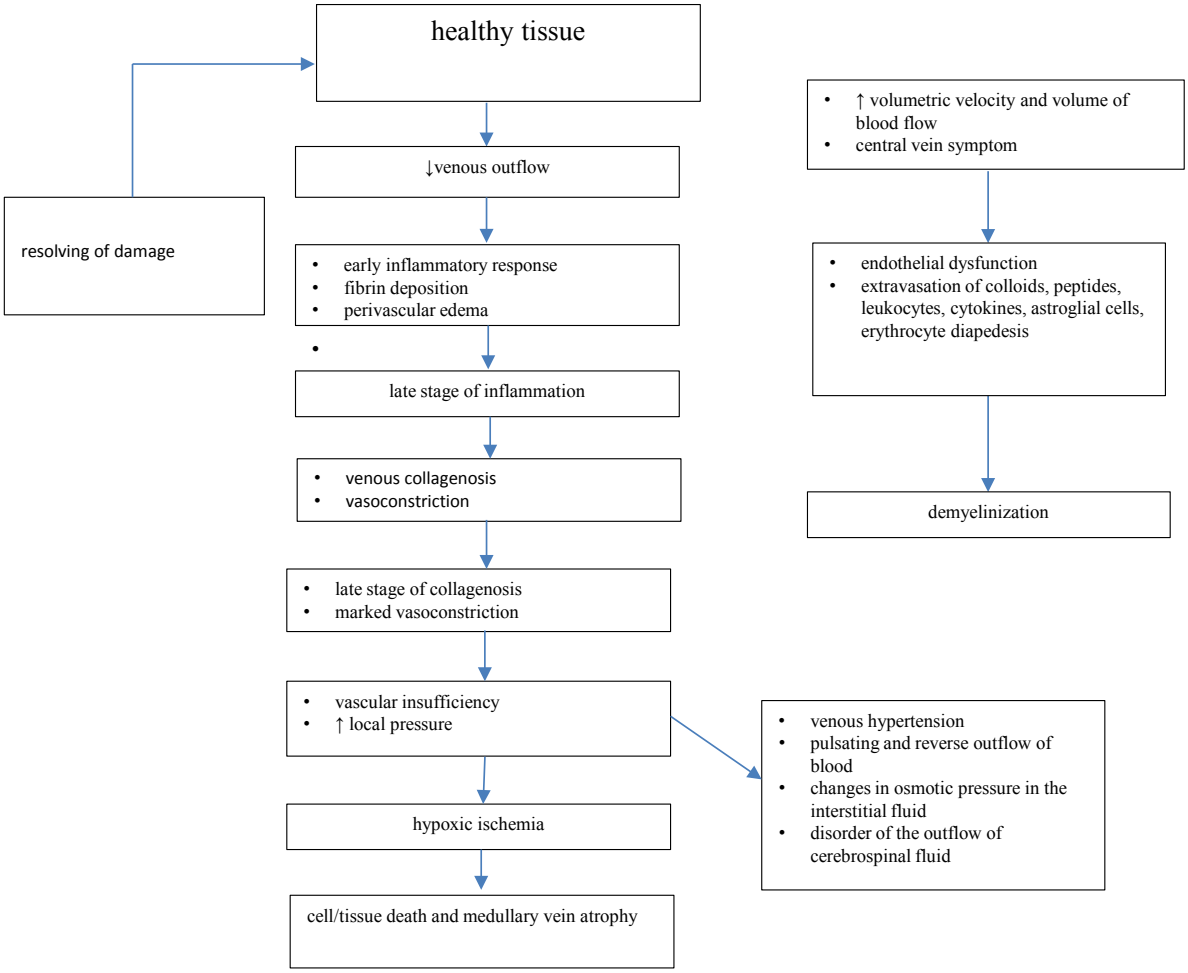


Fig. 1. Mechanisms of cerebral venous thrombosis development and demyelination

azygos vein. The difficulty of venous outflow at the extracranial level was explained by obstruction of both internal jugular veins [11–15], which increased pressure in the intracranial veins [16, 17]. However, to date, this concept remains debatable [18].

Broman et al. (1964) diagnosed demyelination in MS using trypan blue to stain plaques and revealed that each plaque had central veins and pathologically altered vein components, namely lymphocytes, intramural fibrinoid deposition, a thickening of collagen fibers, and perivenous iron deposition. At the same time, vein staining correlated with the degree of demyelination.

This was also confirmed in the work of Fog et al. (1964), who demonstrated that MS lesions not only develop around small veins but, more interestingly, the course and size of the veins determine the shape, distribution, and size of the plaques. Shunting of blood from poorly perfused lesions causes acute symptomatic deterioration of MS, whereas blood flow restoration, in turn, can lead to rapid clinical improvement. This hemodynamic mechanism can explain the emergence and disappearance of MS foci over time and the persistence of foci in a chronic dysfunctional course [19]. Kamel et al. (2021) believe that SARS-CoV-2 can induce the development of MS similar to the Epstein-Barr virus.

Vein damage is accompanied by fibrin deposition, which is a sign of the processing activity and can progress to the development of occlusive venous thrombosis and subsequent hemorrhage [20]. Ginsberg et al. (1976) revealed that fibrin formation is a predictor of the development of clinical manifestations in allergic encephalomyelitis. Research by Keith et al. (2017) also indicated a significant role of venous insufficiency and vasogenic edema in the progression of white matter lesions noted in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Figure 1 describes the mechanisms of cerebral venous thrombosis development and demyelination.

Clinical case presentation.

Female patient I., age 57 years, was admitted to the neurological department of the clinic of the Mechnikov North-Western State Medical University on August 30, 2021, with complaints of daily headaches with an intensity of 6 to 10 points on a visual analog scale (VAS) of a diffuse nature, which increases in the supine position, after physical activity, and is refractory to conventional painkillers.

Her history shows that the patient had noted periodic headaches since adolescence (from 14 to 15 years). At the same time, the headache was aching or burning, localized in the right temporal region, began at night or in the morning, with periodic spread to the frontal region to the left temple, with an intensity of 5 to 8 points according to the VAS, was accompanied by photophobia, phonophobia, nausea, and dizziness which were stopped by intake of a serotonin 5-HT1 receptor agonist (sumatriptan succinate tablet).

In October 2020, after contact with a patient with a new coronavirus infection, the patient had complaints of a febrile temperature that persisted for a week, asthenia, and an increase in the incidence and severity of headache (up to 10 VAS points) that was not relieved by the intake of analgesics, nonsteroidal anti-inflammatory drugs, and sumatriptan. Complaints of decreased memory and concentration also gradually appeared. Her PCR test[1] for SARS-CoV-2 was negative. The analysis for antibodies [immunoglobulin class G (IgG)] to the antigens of the SARS-CoV-2 virus from December 2020 showed an increase in antibody titer.

In November 2020, the patient sought medical help from a neurologist at a primary healthcare facility. An MRI of the brain was recommended.

MRI of the brain with intravenous contrast as of March 23, 2021. Subcortically and paraventricularly in the white matter of the brain in the temporal, frontal, and parietal lobes (4 to 8 mm), in the left frontal lobe (16×14 mm), in the right temporal lobe (up to 20×13 mm), in the region of the basal ganglia (up to 3 mm), multiple foci of gliosis were visualized with blurred contours, prone to fusion, characterized by a hyperintense signal on T2-weighted images (WI), isointense on T1-WI, without perifocal edema and mass effect. The foci showed no limitation and magnetic resonance (MR) diffusion and did not accumulate a contrast agent (Fig. 2).

Conclusion. MR presentation showed multiple focal changes in the brain of a dystrophic and dyscirculatory nature, without signs of limited MR diffusion and accumulation of a contrast agent; moderate external hydrocephalus *ex vacuo*. Given the relatively young age of the patient and pronounced changes in the white matter of the brain, in addition to the early morphological manifestations of dyscirculatory encephalopathy, the presence of a genetically determined arteriolopathy of the CADASIL type (lesion of the temporal lobes, an early clinical sign of migraine, memory loss) must be ruled out. The demyelinating process at the inactivity stage was the least probable (no foci in the corpus callosum).

The patient denied smoking and consumption of narcotic agents and alcohol; had chronic gastritis, not in exacerbation. Hereditary history was aggravated maternally (the mother had leukemia, a migraine, and an acute cerebrovascular accident at 76).

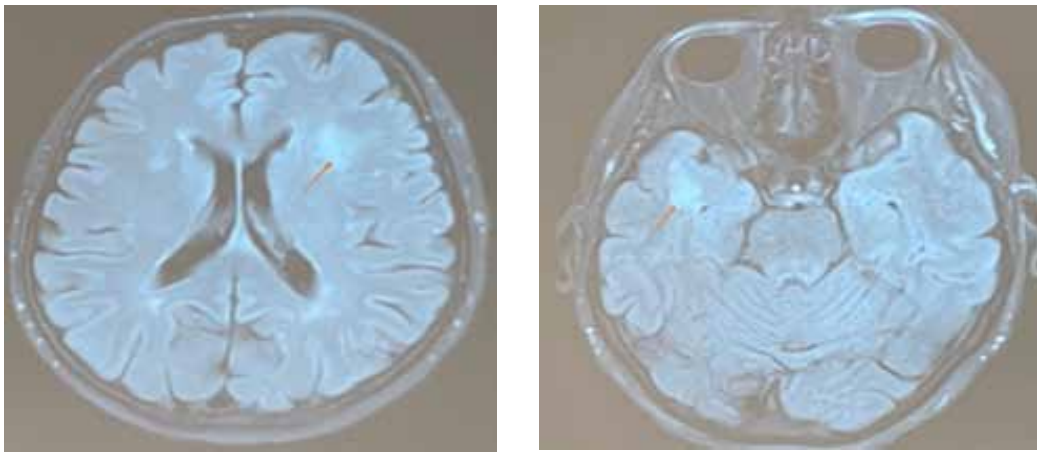
Upon admission to the clinic, attention was drawn to the neurological status, tongue deviation to the left, and positive reflexes of oral automatism. Deep hand reflexes were flexion- and extensor-elbow D = S, of average vivacity. Carporadial reflex was D > S, of average vivacity; leg reflexes were S > D at the knees. Achilles' reflexes were D = S, of low vivacity. There were (+) Babinsky pathological reflexes on the right and (±) Chaddock pathological reflexes on both sides. Finger-nose and heel-shin tests showed slight ataxia on both sides. In Romberg's position, the patient staggered without clear lateralization.

Laboratory and instrumental studies were performed at the outpatient stage.

Results of gene diagnostics (for the presence of genetically determined arteriopathy according to the CADASIL type) dated 08/05/2021. No pathogenic variants were found in exons 2–6 and 11 of the NOTCH3 gene. Mutations in exons 2–6 of the NOTCH3 gene were not detected.

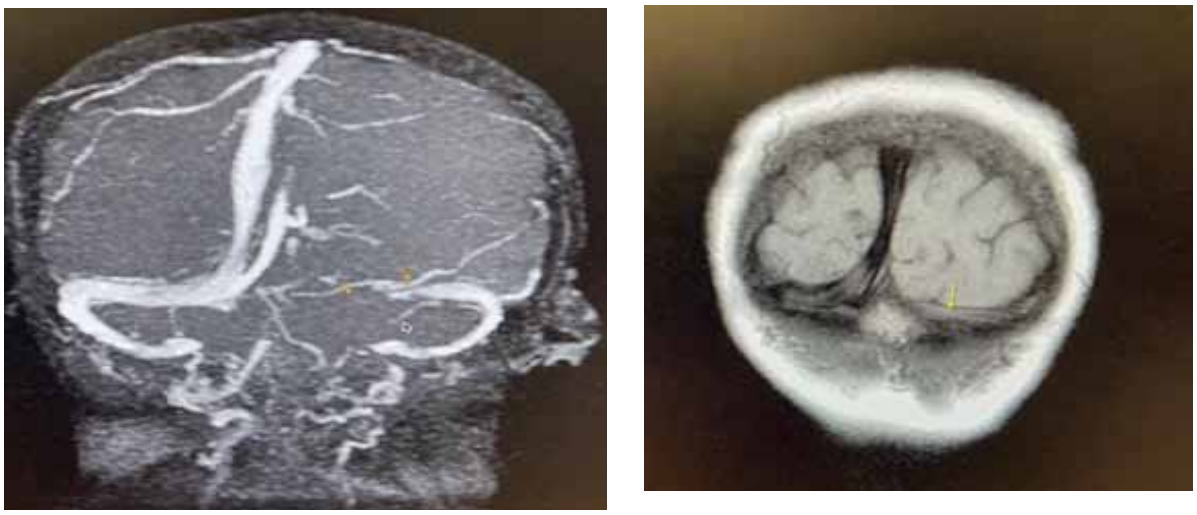
Laboratory studies of the present hospitalization. In a clinical blood test, attention was drawn to an increase in the erythrocyte sedimentation rate up to 29 mm/h (reference values 2–15 mm/h). The serum lactate level was 1.1 mmol/l (reference values 0.5–2.2 mmol/l). Serodiagnostics of autoimmune and inflammatory diseases revealed angiotensin-converting

[1]PCR — polymerase chain reaction.



A B

Fig. 2. Foci of hyperintense magnetic resonance signal on T2-weighted image and FLAIR impulse sequence in the right temporal lobe (B); in the white matter of the frontal lobes.



A B

Fig. 3. Magnetic resonance venographic presentation: the absence of a signal from the blood flow in a significant part of the left transverse sinus (A), which does not rule out thrombosis or the slowing of blood flow (B), considering the Cor N1 weighted image.

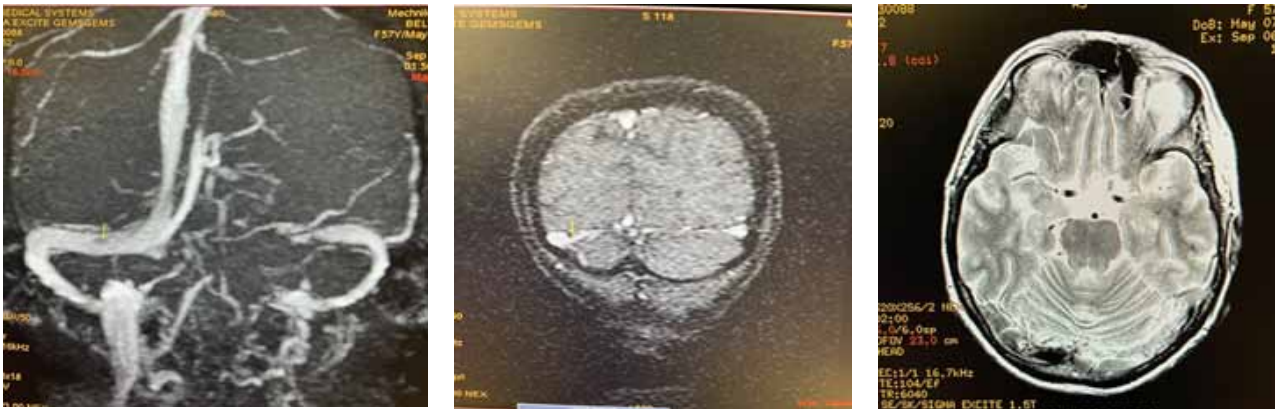
enzyme activity, and diagnostics of sarcoidosis showed 46.50 U (reference values 20–70 U); antibodies to β_2-glycoprotein class I IgG, A, M were 6.17 RU/ml (reference values <20 RU/ml). General clinical analysis of cerebrospinal fluid showed a slight increase in protein content to 0.392 g/l. Blood immunochemical analysis of revealed D-dimer of 0.096 ng/ml (reference values 0–0.44 ng/ml).

MR-venosinusography was performed on the patient to determine the state of the cerebral veins and sinuses.

MR-venosinusography of the brain dated 09/07/2021 (Figs. 3, 4).

Genetic analysis of risk factors for thrombosis. The study of the –455 G>A polymorphism in the FGB gene encoding fibrinogen-A/A was associated with an increased risk of venous thrombosis, ischemic stroke, and pregnancy pathology (miscarriage, fetoplacental insufficiency).

Diagnostics of cerebrospinal fluid and biomarkers of diseases of the central nervous system in the cerebrospinal fluid. Oligoclonal IgG in the cerebrospinal fluid and the blood was determined as a pathological type of IgG synthesis, namely oligoclonal in the cerebrospinal fluid (OSV+) and polyclonal in blood serum (reference values are polyclonal IgG in cerebrospinal



A B C

Fig. 4. Magnetic resonance venographic signs with a suspected single thrombus in the right transverse sinus (A). However, considering the raw data (B) and the native T2-weighted image, these changes are arachnoidal granulations growing into the sinus (C).

fluid and blood serum); free λ-chains of immunoglobulins in fluid higher than 0.35 μg/ml (reference values 0–0.1 μg/ml), free κ-chains of immunoglobulins in fluid higher than 0.89 μg/ml (reference values 0–0.5 μg/ml).

Instrumental research.

Electroencephalography from 09/01/2021. Moderate diffuse changes in bioelectrical activity from the surface of the cerebral cortex. Signs of irrigation of stem structures at the meso- and diencephalic levels. Indirect signs of liquor-dynamic disorders. No specific epileptiform activity was revealed.

Consultation with an ophthalmologist on 09/02/2021. There are no data for the stagnation of the optic nerve head. Retinal angiopathy. Presbyopia.

Based on the clinical, laboratory, and instrumental findings and the results of radiodiagnosis methods, cerebral venous thrombosis with a thrombus in the left transverse sinus (according to MR-venography) with cephalgic syndrome, demyelinating disease of the central nervous system with bilateral pyramidal insufficiency, mild static-locomotor disorders, and decompensation were diagnosed.

The neurometabolic (Cytoflavin), analgesic (Gabapentin, Ketorolac), anticoagulant [sodium enoxaparin (Clexane) → warfarin], and venotonic (L-lysine aescinat) therapy was performed in the clinic.

During therapy, improvement was noted in the form of a decrease in the severity and frequency of cephalgia and a decrease in static-locomotor disorders.

When hyperintensity of the white matter of the brain was detected during neuroimaging, differential diagnostics with several diseases were performed (Table 1).

The originality of the presented case consists of the combination of a demyelinating process in the brain (late onset of MS?) and the occurrence of cerebral venous thrombosis associated with a new coronavirus infection, which requires follow-up. Complex pathogenetic pathways of development caused by impaired venous blood flow (Houck et al., 2019) and leading to brain demyelination through endothelial dysfunction, extravasation of colloids, peptides, cytokines, leukocytes with erythrocyte diapedesis, and their possible induction under the influence of SARS-CoV-2 necessitate further study to confirm the concept of the role of the venous system in the processes of demyelination of the brain white matter in a case with of a history of COVID-19.

ДОПОЛНИТЕЛЬНО

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Table 1. Differential diagnostics.

Identified changes	Signs confirming the diagnosis	Signs excluding the diagnosis
1	2	3
MS	Presence of T2-hyperintense lesions (subcortically, paraventricularly) according to MRI of the brain, dissemination in space. Oligoclonal IgG increased levels of κ- and λ-chains of immunoglobulins in the cerebrospinal fluid.	Typical clinical presentation of MS and dissemination over time. No new T2-hyperintense or contrast-enhancing lesions compared with previous MR studies. There is no simultaneously contrast-enhancing focus and accumulating focus of hyperintensity according to T2-WI and age discrepancy.
Acute disseminated encephalomyelitis	History data: presumably COVID-19 in October 2020, with cerebral and intoxication syndromes. Presence of T2 hyperintensity foci in the white matter of the brain, periventricular, in the basal ganglia. Absence of dissemination of the pathological process in time, according to neuroimaging data.	Отсутствие обратной динамики клинических проявлений в течение года. Скудная неврологогическая сиптоматика. Клиническая МР-картина: 1) преимущественно «острые симптомные» очаги в белом веществе; 2) множественные большие, часто сливные очаги с положительным масс-эффектом; 3) располагаются супра- и/или инфратенториально
Optocomyelitis	Hyperintense foci on T2-WI on brain imaging. Oligoclonal IgG increased the content of κ- and λ-chains of immunoglobulins in the cerebrospinal fluid.	Major criteria: 1) optic neuritis with damage to one or both eyes; 2) transverse myelitis with an MRI-confirmed spinal cord lesion that extends over more than three vertebral segments on T2-WI and is hypointense on T1-WI. Minor criteria: 1) lesions in the caudal medulla oblongata, hypothalamus and/or brainstem, “linear” lesions located periventricularly or in the corpus callosum but not ovoid and not extending into the parenchyma of the cerebral hemispheres; 2) positive blood serum or cerebrospinal fluid test for NMO-IgG/antibodies to aquaporin 4.
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	Relatively young age of the patient. Migraine-like headache. Complaints about decreased concentration. Family history (mother had similar headaches). The presence of T2-hyperintense foci in the white matter of the brain, in the temporal and frontal lobes, and the region of the basal ganglia.	Negative results of gene diagnostics (no mutations were detected in exons 2–6 and 11 of the NOTCH3 gene). *NB!* However, over 200 mutations in the NOTCH3 gene are known to be associated with the development of CADASIL; the CADASIL syndrome associated with mutations in the HTRA1 gene and inherited in an autosomal recessive manner should not be disregarded.
Sarcoidosis	MRI presentation shows multiple T2-hyperintense lesions in the white matter of the brain.	In sarcoidosis, the nervous system lesion is usually associated with lesions of the lungs and intrathoracic lymph nodes and the clinical presentation is rarely predominant. Serodiagnostics dated 09/03/2021 showed angiotensin-converting enzyme activity within the reference values.

1	2	3
Antiphospholipid syndrome	Female gender. Migraine-like headache. Cerebral thrombosis	There are no typical manifestations, such as thrombocytopenia, livedo reticularis, nephropathy, cardiac valvulopathy, or chronic leg ulcers. Data for the pregnancy pathology. An increase in the level of antibodies to β_2-glycoprotein, according to the data of an immunological blood test.
MELAS (mitochondrial encephalopathy with stroke-like episodes and lactic acidosis)	Migraine-like headache with nausea and vomiting. Cognitive disorders. Cortical, subcortical foci.	Strokes with “posterior” localization, damage to symmetrical areas of the brain with an interval of 1–3 months. Epileptic seizures. Episodes of impaired consciousness. Myoclonus. Poor exercise tolerance (feeling worse, myalgia), myopathic syndrome (myopathic face), cardiomyopathy. Sensorineural hearing loss. Endocrinopathy. An increase in the level of lactic acid in the blood serum and cerebrospinal fluid.

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Contribution of the authors. *Ye.G. Klocheva* — conducting research, preparing the manuscript, approval and sending for publication; *F.Z. Olimova* — conducting research, preparing the manuscript, approval and sending for publication; *V.V. Goldobin* — conducting research, preparing the manuscript, approval and sending for publication; *Ju.D. Bogatenkova* — conducting research, approval and sending for publication.

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