DOI: https://doi.org/10.17816/rmmar111888
Research Article

Microstructural changes in the brain in persons with mild COVID-19

Larisa V. Lukina, Natalia I. Ananieva, Natalya Yu. Safonova, Yan A. Ershov

V.M. Bekhterev National Medical Research Center of psychiatry and neurology, Saint Petersburg, Russia

BACKGROUND: The purpose of this was to investigate, using voxel-based MR morphometry, changes in the volume of brain structures in persons who had undergone a new coronavirus disease.

MATERIALS AND METHODS: 34 patients with mild COVID-19 between 4 months and one year were examined. All study participants were scanned at two-time points: before COVID-19 infection and re-imaging after infection. The comparison group consisted of 30 healthy volunteers who did not have COVID-19 and were comparable in terms of sex, age, timing, and MRI protocol.

RESULTS: In the main and control groups a significant increase in the volume of individual segments of the large hemisphere cortex, subcortical gray matter, and white matter of the brain was detected. Signs of the atrophic process were registered in the cerebellar cortex and left frontal lobe. In the main group, there was an increase of cortical volume practically in all cerebral lobes with some emphasis on the posterior parts of the right hemisphere. When analyzing changes in subcortical gray matter in the main group, there was a reliable ($p \leqslant 0.05$) increase in its total volume due to left caudate nucleus, pale ball, right amygdala body, and ventral diencephalon. Increased volume of white matter in the brain in COVID-19 patients was detected in the left isthmus and rostral part of the right cingulate gyrus, left paracentral lobe, and right precuneus.

CONCLUSION: the cerebellum is affected quite early by SARS-CoV-2, as we recorded atrophic changes in its cortex at 4–12 months. In COVID-19, the microstructural integrity, predominantly of gray matter and other brain segments, is impaired. Increased volume of these structures indicates the duration of the inflammatory process. An increase in the volume of these structures may indicate the duration of the inflammatory process.

Keywords: brain; cerebellum; COVID-19; MRI; SARS-CoV-2; segmentation; voxel-based morphometry.

To cite this article:
Lukina LV, Ananieva NI, Safonova NYu, Ershov YA. Microstructural changes in the brain in persons with mild COVID-19. *Russian Military Medical Academy Reports*. 2022;41(4):355–363. DOI: https://doi.org/10.17816/rmmar111888

Received: 12.10.2022 **Accepted**: 14.10.2022 **Published**: 17.11.2022

УДК 616-002.2
DOI: https://doi.org/10.17816/rmmar111888
Научная статья

Микроструктурные изменения головного мозга у лиц, перенесших легкую форму COVID-19

Л.В. Лукина, Н.И. Ананьева, Н.Ю. Сафонова, Я.А. Ершов

Национальный медицинский исследовательский центр психиатрии и неврологии им. В.М. Бехтерева, Санкт-Петербург, Россия

Актуальность. В статье приведены данные лонгитюдного исследования головного мозга лиц, перенесших легкую форму COVID-19.

Цель — изучение с помощью метода магнитно-резонансной воксель-базированной морфометрии изменения объемов структур головного мозга у лиц, перенесших новую коронавирусную инфекцию COVID-19.

Материалы и методы. Обследовано 34 пациента, перенесших легкую форму COVID-19 в сроки от 4 мес до года. Все участники исследования были обследованы до заболевания COVID-19 с повторной визуализацией после перенесенной инфекции. Группу сравнения составили 30 здоровых добровольцев, не болевших COVID-19 и сопоставимых по полу, возрасту, сроку проведения и протоколу магнитно-резонансной томографии.

Результаты. В основной и контрольной группах было выявлено достоверное увеличение объема отдельных сегментов коры больших полушарий, подкоркового серого вещества, а также белого вещества мозга. В коре мозжечка и левой лобной доли были зафиксированы признаки атрофического процесса. В основной группе зафиксировано увеличение объема коры практически во всех долях головного мозга с некоторым акцентом на задние отделы правого полушария. При анализе изменений субкортикального серого вещества в основной группе было зафиксировано достоверное ($p \leqslant 0,05$) увеличение его общего объема за счет левого хвостатого ядра, бледного шара, правого миндалевидного тела и вентрального диэнцефалона. Увеличение объема белого вещества головного мозга у переболевших COVID-19 было выявлено в перешейке левой и ростральной части правой поясной извилины, парацентральной дольке слева, а также в правом предклинье.

Заключение. Мозжечок достаточно рано поражается SARS-CoV-2, так как в сроки 4–12 мес мы зафиксировали атрофические изменения в его коре. При COVID-19 нарушается микроструктурная целостность преимущественно серого вещества и других сегментов головного мозга. Увеличение объема этих структур может указывать на продолжительность воспалительного процесса.

Ключевые слова: воксель-базированная морфометрия; головной мозг; COVID-19; мозжечок; МРТ; SARS-CoV-2; сегментация.

Как цитировать:
Лукина Л.В., Ананьева Н.И., Сафонова Н.Ю., Ершов Я.А. Микроструктурные изменения головного мозга у лиц, перенесших легкую форму COVID-19 // Известия Российской Военно-медицинской академии. 2022. Т. 41. № 4. С. 355–363. DOI: https://doi.org/10.17816/rmmar111888

Рукопись получена: 12.10.2022 **Рукопись одобрена**: 14.10.2022 **Опубликована**: 17.11.2022

BACKGROUND

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, the views of doctors on a coronavirus infection, which was new for everyone, have changed significantly. Initially, it appears that SARS-CoV-2, which belongs to the group of respiratory viruses, primarily affects the respiratory system and has only an indirect effect on other body systems, including the brain. However, SARS-CoV-2 is now established to have neuroinvasive and neurotropic potentials.

One of the mechanisms explaining the neurotropic nature of coronaviruses is the ability of several brain structures to express the integral transmembrane protein angiotensin-converting enzyme (ACE) 2. This functional cellular protein functions as a receptor for the SARS-CoV-2 receptor-binding domain and ensures its penetration into the central nervous system. The cerebellum is one of the brain structures demonstrating high levels of ACE2 expression and representing a potential target for SARS-CoV-2 [1].

Systemic dysfunction and direct viral brain injury cause various neuropathological disorders associated with COVID-19 [2]. A study revealed that the increase in neurological symptoms in patients with COVID-19 can be facilitated by transconnectome diffusion of pathological changes through the structural network of the brain [3]. However, despite research in this field, which brain structures are most susceptible to this virus and which functional connections are affected remain not completely clear.

Owing to the time factor, most neuroimaging studies of COVID-19 represent evaluations of structural magnetic resonance imaging (MRI) of the brain and often present only a description of individual clinical cases because large-scale data are still being accumulated. In addition, most were brain studies in patients with severe COVID-19. Moreover, whether brain changes are possible in milder COVID-19 and which specific structures are affected, and at what time interval remain unclear.

Cerebellar lesions in COVID-19 are more often described in the literature as acute conditions that are well visualized on MRI with acute necrotizing encephalopathy, acute cerebellitis, posterior reversible encephalopathy syndrome, ischemia, or hemorrhage in the cerebellum. However, certain studies have tried to identify microstructural changes in the cerebellum. Thus, Guedj et al. used positron emission tomography with fluorodeoxyglucose (F-FDG PET) and revealed hypometabolism in the structures of the olfactory analyzer and cerebellum of patients with a history of COVID-19, regarding the resulting changes as a substrate for the long-term consequences of infection. Hafiz et al. reported a decrease in functional connectivity in several layers of the vermiform lobules of the cerebellum in COVID-19 convalescents when performing functional MRI (fMRI) at rest, compared with control individuals without COVID-19 [4, 5]. The authors suggested the involvement of these parts of the cerebellar vermis in the cognition and processing of emotions, and their lesions can cause chronic fatigue in patients who have recovered from COVID-19.

Many studies that performed pathoanatomical studies of the brain of patients who died from COVID-19 have confirmed that the cerebellum is one of the main targets of SARS-CoV-2. In one of these studies, microglia were activated in the brainstem and cerebellum, and infiltration with cytotoxic T-lymphocytes was revealed, which indicates an ongoing neuroinflammation in these structures [6]. Another postmortem study established the presence of microhemorrhages in the cerebellum, whereas the distribution and morphology of microcerebral hemorrhages differed clearly from those associated with hypertension, severe systemic diseases, and cerebral amyloid angiopathy [7]. The authors suggested that microhemorrhages may be due to SARS-CoV-2-induced endotheliitis and more general vasculopathic changes and may correlate with an increased risk of vascular encephalopathy. In support of this opinion, several studies have indicated the detection of viral particles in endothelial cells of cerebral vessels. In the postmortem examination of the brain of a patient who died from a cerebellar hemorrhage, Al-Dalahmah et al. revealed unique findings and evident neuronophagia and microglial nodules in the inferior olivary bodies and to a lesser extent in the dentate nuclei in the presence of mild perivascular lymphocytic infiltrates [8]. They suggested that the changes result from synergism between hypoxia and systemic inflammation, leading to cytokine induction of microglial activation, causing neuronophagia. Previously, phagocytosis of neurons was described only in epidemic parotiditis and enterovirus infection.

Unlike previous studies, Vidal et al., who examined the chronology of brain damage after infection of transgenic mice with SARS-CoV-2, noted that the maximum spread of the virus throughout the brain was registered 6–7 days after vaccination; however, the cerebellum remained intact [9].

For obvious reasons, no data are presented on morphological changes in the brain in the long-term period following recovery from COVID-19. The question of the timing of persistent neuroinflammation and hypoxia following recovery from this infection remains unresolved, and one of the methods that help decide indirectly on this process is a quantitative assessment of the volume of brain structures using neuroimaging techniques.

According to these data, still, no single point of view has been agreed on the specificity of damage to individual brain structures in COVID-19 and the pathogenesis of this lesion. The mechanisms of virus penetration into the nervous system, chronology of the spread of infection,

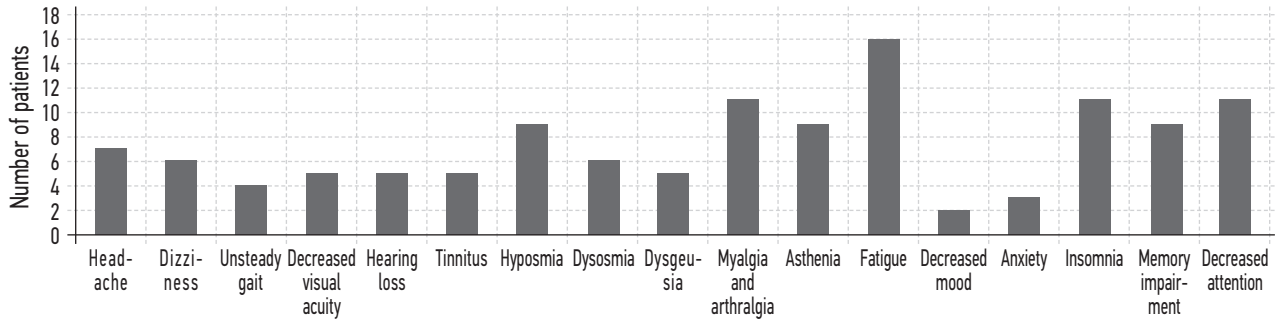

Fig. 1. Complaints of patients who had a history of COVID-19

selectivity of damage to individual brain structures and their influence on the clinical presentation of the acute period, and formation of long-term consequences of this new infection must be substantiated.

The study aimed to analyze, using magnetic resonance (MR) voxel-based morphometry (VBM), changes in the volumes of brain structures and assess the specificity of their damage in people with a history of mild COVID-19.

MATERIALS AND METHODS

To assess changes in the overall volume of the brain and its structures, a longitudinal research model was used with mathematical processing of MRI findings of the brain using MR VBM. The participants were scanned twice, that is, before diagnosis of COVID-19 and 4–12 months after diagnosis. The control group included healthy volunteers without a history of COVID-19.

The initial model used for comparison was the database of morphometric indicators "Gender characteristics of normal age-related aging of the central nervous system"*. The inclusion criteria were as follows: availability of high-quality neuroimaging data obtained before the pandemic, absence of structural changes in the brain of any origin in the primary scanned images, and absence of factors that could potentially cause structural changes in the brain substance in the period between scans.

After the screening, the main study group included 34 patients (13 men, 21 women) aged 20–71 years, who had mild COVID-19 within 4 months to 1 year and received outpatient treatment. In the assessment, 21 patients had complaints that arose during the acute period of COVID-19 and persisted until the study period. The nature of the complaints of the main study group is presented in Fig. 1.

The most frequent complaints in the main group were frequent fatigue, decreased attention, insomnia, myalgia, and arthralgia. Other common included hyposmia, asthenia, and memory impairment. The neurological examination revealed no abnormalities in the neurological status. In addition, the patients did not have chronic diseases in the acute stage.

The control group included 30 healthy volunteers from the same database, without a history of COVID-19, who had no health complaints, or diseases in the acute stage, and were comparable in sex, age, and rescanning time with the main group.

The first and second brain scans were performed on an Atlas Exelart Vantage XGV MRI scanner (Toshiba, Japan) with a magnetic field induction of 1.5 Tesla. A standard 8-channel coil for the head was used. All study participants underwent initial and repeated scanning of the brain using a similar neuroimaging protocol, which included T1 in-phase (IP), T2-IP, T2 fluid-attenuated inversion recovery-IP, and three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE)-IP. In the next stage, 3D-MPRAGE-IP was performed according to the following protocol: repetition time = 12, echo time = 5, field of view = 25.6, MTX = 256, ST = 2.0, and FA = 20. The resulting 3D-MP-RAGE sequence files in the DICOM format were converted to NIFTI FSL format. The files were converted using the MRI Convert software package. Post-processing of data to determine the total brain volume and its segmented parts was performed using the MR VBM in the Free Surfer in Linux Ubuntu 16.04.1 LTS.

General statistical analysis of the results of MR VBM was performed using the Microsoft Excel software package. Before the comparative analysis, the samples were tested for normality using the Kolmogorov–Smirnov test. To assess the significance of differences, Student's t-test was used. Differences $p \leqslant 0.05$ were considered significant.

RESULTS

Our cross-sectional study of the brain in individuals with a history of COVID-19, with post-processing of MRI data using MR VBM, revealed significant changes in both the overall volume of the brain and its structures.

* Certificate of state registration of the database No. 2021621983 Russian Federation. N.I. Ananyeva, L.V. Lukina, E.V. Andreev, and P.M. Tikhonov, Gender Aspects of Normal Age-Related Aging of the Central Nervous System, No. 2021621830, decl. 09/02/2021, publ. 09/17/2021; applicant V.M. Bekhterev National Research Medical Center for Psychiatry and Neurology of the Ministry of Health of Russia, EDN JCJJLQ.

Using the MR VBM method, in the period from 4 months to 1 year after COVID-19 diagnosis, the volumes of the gray matter in certain brain structures decreased significantly (Fig. 2).

In patients who recovered from COVID-19, a loss of the gray matter was recorded in the cortex of the right ($p \leqslant 0.01$) and, to a lesser extent, left ($p \leqslant 0.05$) hemispheres of the cerebellum. In addition to the cerebellum, microstructural volume reductions were noted in the left frontal lobe, namely, in the orbital part of the inferior frontal gyrus ($p \leqslant 0.05$) and the frontal pole ($p \leqslant 0.05$). In the control group, the second scan revealed a decrease in the volume of the cortex of the left cerebellar hemisphere ($p \leqslant 0.05$); however, an increase in its volume was recorded in the orbital part of the inferior frontal gyrus.

When analyzing microstructural changes in other brain areas in the main and control groups, a significant change in individual segments was revealed; however, unlike changes in the cerebellum and left frontal lobe, these changes included an increase in the volume of both gray and white matter.

When detailing changes in brain structures separately for the gray and white matter, differences were also found in the morphology of its segments (Fig. 3).

The volume of the cortical gray matter was also increased in nearly all lobes of the brain, with some emphasis on the posterior parts of the right hemisphere, in patients who recovered from COVID-19. In the control group, the considered segments remained intact.

When analyzing changes in the subcortical gray matter in patients who recovered from COVID-19, a significant ($p \leqslant 0.05$) increase in its total volume was recorded owing to a microstructural increase in the left caudate nucleus, globus pallidus, right amygdala, and ventral diencephalon, which included hypothalamic and red nuclei. In the control group, only an increase in the volume of the left ventral diencephalon was detected.

Lesions to the white matter of the brain in COVID-19 survivors were associated with an increase in the volume of the isthmus of the left and rostral parts of the right cingulate gyrus, paracentral lobule on the left, and right precuneus. The described segments in the control group did not differ significantly in the first and second scans.

DISCUSSION

This longitudinal MRI study of patients before and after COVID-19 diagnosis showed the presence of microstructural changes in the brain, indicating that following clinical recovery, the pathophysiological component of the infectious process persists.

Lu et al. noted brain changes in patients who recovered from COVID-19, 3 months after clinical and laboratory recovery, even in the absence of neurological symptoms [10]. The present study showed that microstructural changes in both total volumes and individual segments of the brain are longer and can persist for 4–12 months after recovery from COVID-19. These long-term changes may result from various pathogenetic mechanisms such

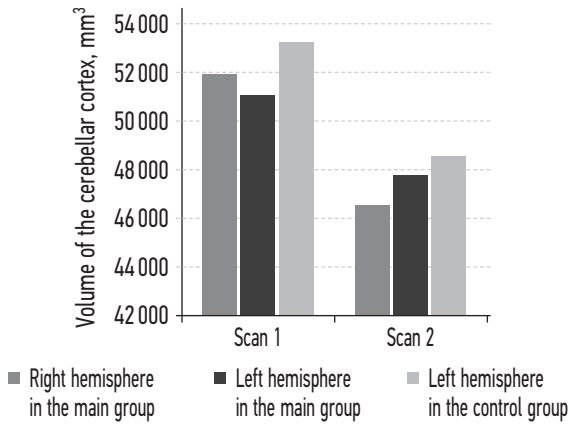

Fig. 2. Reduction of the cerebellar cortex volume

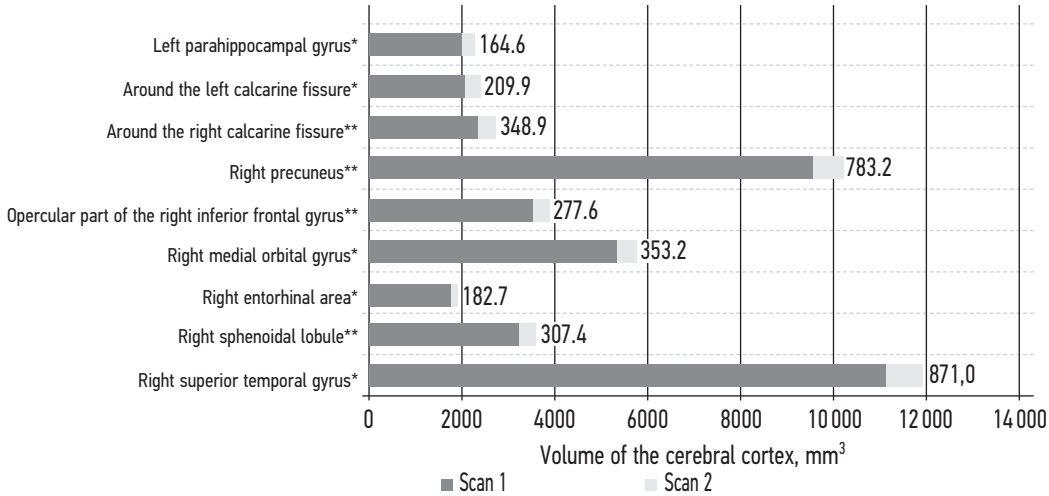

Fig. 3. Distribution of changes in the cortical gray matter in the main group. Significance of differences in changes in the brain volume: * $p \leqslant 0.05$; ** $p \leqslant 0.01$

as direct viral infection, cerebrovascular changes, systemic inflammation, and persisting somatic dysfunction.

The distribution of microstructural changes in brain segments demonstrated major damage to the gray matter of the hemispheres, with some emphasis on the posterior sections and predominantly right-sided lateralization. Such a distribution of changes in volumes suggests a greater vulnerability of the cortex than the white matter in the presence of COVID-19. Other authors also reported the predominance of changes in the right parts of the brain, which may depend on the different functional activity of the cerebral hemispheres and requires clarification using functional neuroimaging methods.

Historically, the cerebellum has been considered a structure solely responsible for the coordination and control of fine movements. Such conclusions were made at the beginning of the XIX century and were based on the monitoring of experimental animals with damaged cerebellum. However, in the last 25 years, in connection with the development of both structural and functional neuroimaging methods, a paradigm shift has occurred toward the concept of the cerebellum's multiple functionality [11]. Many studies have provided evidence of the role of the cerebellum not only in motor control but also in the implementation of non-motor functions, namely, attention, speech, working memory, pain, emotions, cognitive control, and social cognition, and the formation of addictions [12, 13]. Data confirm the involvement of the cerebellum in nociception [14], which confirms the multitasking of this brain structure.

According to the classical motor concept, the cerebellum is connected to the contralateral hemisphere of the brain through two polysynaptic circuits, namely, an input channel that synapses with the pontine nuclei and then enters the cerebellum, and an output channel that projects to the deep cerebellar nuclei, then to the thalamus, and finally to the motor areas of the cerebral cortex. However, the accumulated neuropsychological and neuroimaging data reveal an extensive functional network connecting the cerebellum with virtually the entire neocortex. Cerebellum connections originate not only from the motor areas but also from the prefrontal, parietal, superior temporal, and parahippocampal areas, and the conductors from the dentate nuclei return to the associative areas of the cortex, forming closed loops [15]. These loops represent a functional unit of cerebrocerebellar interactions and allow the cerebellum to participate in the control of both movement and cognition [16]. Based on the hypothesis of the cerebellum's multiple functions, various pathological processes affecting the cerebellum may be clinically expressed not only by motor disorders but also by neuropsychiatric disorders.

At the start of the COVID-19 pandemic, data on neurotropism and neuroinvasion of the new virus were insufficient; moreover, the possibility of SARS-CoV-2 influencing the cerebellum was not considered. However, the pathanatomical data accumulated over the past 2 years indicate the specificity of damage to individual brain structures, particularly the cerebellum. Thus, Siddiqui et al. described the enhanced penetration of SARS-CoV-2 into the parietal cortex and cerebellum, suggesting that these brain areas may be specific targets for the virus [17]. In 2020, German scientists published in Lancet Neurology data on a postmortem study of the brain tissue of patients who died from acute COVID-19; accordingly, they detected heart attacks only in 14% of cases, whereas the majority of patients had astrogliosis. Moreover, the activation of microglia and infiltration with cytotoxic T-lymphocytes were recorded in the brainstem and cerebellum [6]. Perivascular lymphocytic inflammation of CD8-positive T-cells mixed with CD8-positive macrophages detected in the brainstem and cerebellum causes microvascular damage to these structures [18]. Cerebellar injury is also caused by hypoxia [19]. The data presented indicate some specificity of cerebellar lesions in COVID-19, which is also probably due to the high expression of ACE2 in this brain region. The above changes result in the atrophy of the cortex, which can manifest as neurological disorders.

This study using MR VBM enabled us to establish that from 4 to 12 months after recovery from COVID-19, neuron loss occurs in the cortex of both hemispheres of the cerebellum, as evidenced by a significant decrease in its volume. Atrophic changes in the cortex also affected the orbital part of the left inferior frontal gyrus and frontal pole. The loss of cortical volume in these structures is most probably associated with neuronal death caused by direct or indirect neurotropism of SARS-CoV-2. The frontal lobes are connected to the contralateral hemisphere of the cerebellum via the frontopontocerebellar pathway, which supports the hypothesis of Parsons et al. about the transconnectome spread of the pathological process through the functional networks of the brain in patients with COVID-19 [3]. Damage to the frontopontocerebellar pathway in patients with a history of COVID-19 can lead to ataxia, astasia-abasia, adiadochokinesis, intentional tremors in clinical presentation, changes in emotional response, and cognitive and speech disorders. These data can help neurologists in monitoring patients in the long term after recovery from COVID-19.

In the course of this study, we registered differences in the volumes of seven common brain segments, nine segments of the gray matter, and four segments of the white matter. These brain areas, in varying degrees, belonged to the hippocampal complex, cortical centers of vision, and olfactory complex. In contrast to the cerebellum and left frontal lobe, these structures showed an increase in volume on rescanning, suggesting an ongoing neuroinflammatory process that persists 4–12 months after recovery from COVID-19.

DOI: https://doi.org/10.17816/rmmar111888

CONCLUSIONS

Since the onset of the pandemic, the opinion of the medical community about COVID-19 as a purely respiratory disease has completely changed. To date, a characteristic aspect of COVID-19 is the multisystemic lesion with high individual specificity of the clinical presentation. Moreover, there is no doubt about the neuroinvasiveness of this virus and the possibility of mediated damage to the central nervous system through systemic mechanisms.

The influence of SARS-CoV-2 on the central nervous system was extremely diverse and prolonged over time. Our study and analysis of the current literature show that the cerebellum may be one of the targets of SARS-CoV-2 with early damage since atrophic changes in its cortex are evident already within 4–12 months. These data should be taken into account when drawing up individual plans for the follow-up of patients who had a history of COVID-19.

Our data indicate that SARS-CoV-2 disrupts the microstructural integrity of not only the cerebellum but also other segments of the brain. An increase in the volume of these structures indicates the duration of the inflammatory process.

To clarify the nature of the cerebellar lesion and its functional integrity, we plan to analyze functional neuroimaging data and compare the results of radiation diagnostic methods with neurological and pathopsychological data. In addition, three scans are required to assess the dynamics of microstructural changes.

ADDITIONAL INFORMATION

Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Ethical considerations. The study was approved by the local ethics committee of St. Petersburg V.M. Bekhterev National Research Medical Center for Psychiatry and Neurology of the Ministry of Health of Russia.

Author contributions. All authors made significant contributions to the study and preparation of the article, and read and approved the final version before its publication.

REFERENCES

1. Siddiqui R, Mungroo MR, Khan NA. SARS-CoV-2 invasion of the central nervous: a brief review. *Hosp Pract* (*1995*). 2021;49(3):157–163. DOI: 10.1080/21548331.2021.1887677

2. Lou JJ, Movassaghi M, Gordy D, et al. Neuropathology of COVID-19 (neuro-COVID): clinicopathological update. *Free Neuropathol.* 2021;2:2. DOI: 10.17879/freeneuropathology-2021-2993

3. Parsons N, Outsikas A, Parish A, et al. Modelling the Anatomic Distribution of Neurologic Events in Patients with COVID-19: A Systematic Review of MRI Findings. *AJNR Am J Neuroradiol.* 2021;42(7):1190–1195. DOI: 10.3174/ajnr.A7113

4. Guedj E, Million M, Dudouet P, et al. ^{18}F-FDG brain PET hypometabolism in post-SARS-CoV-2 infection: substrate for persistent/delayed disorders? *Eur J Nucl Med Mol Imaging.* 2021;48(2):592–595. DOI: 10.1007/s00259-020-04973-x

5. Hafiz R, Gandhi TK, Mishra S, et al. Assessing functional connectivity differences and work-related fatigue in surviving COVID-negative patients. *bioRxiv*. 2022;2022.02.01.478677. Preprint. DOI: 10.1101/2022.02.01.478677

6. Matschke J, Lütgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol.* 2020;19(11):919–929. DOI: 10.1016/S1474-4422(20)30308-2

7. Kirschenbaum D, Imbach LL, Rushing EJ, et al. Intracerebral endotheliitis and microbleeds are neuropathological features of COVID-19. *Neuropathol Appl Neurobiol.* 2021;47(3):454–459. DOI: 10.1111/nan.12677

8. Al-Dalahmah O, Thakur KT, Nordvig AS, et al. Neuronophagia and microglial nodules in a SARS-CoV-2 patient with cerebellar hemorrhage. *Acta Neuropathol Commun.* 2020;8(1):147. DOI: 10.1186/s40478-020-01024-2

9. Vidal E, López-Figueroa C, Rodon J, et al. Chronological brain lesions after SARS-CoV-2 infection in hACE2-transgenic mice. *Vet Pathol.* 2022;59(4):613–626. DOI: 10.1177/03009858211066841

10. Lu Y, Li X, Geng D, et al. Cerebral Micro-Structural Changes in COVID-19 Patients — An MRI-based 3-month Follow-up Study. *EClinicalMedicine.* 2020;25:100484. DOI: 10.1016/j.eclinm.2020.100484

11. Diedrichsen J, King M, Hernandez-Castillo C, et al. Universal Transform or Multiple Functionality? Understanding the Contribution of the Human Cerebellum across Task Domains. *Neuron.* 2019;102(5):918–928. DOI: 10.1016/j.neuron.2019.04.021

12. Strick PL, Dum RP, Fiez JA. Cerebellum and nonmotor function. *Annu Rev Neurosci.* 2009;32:413–434. DOI: 10.1146/annurev.neuro.31.060407.125606

13. Clark SV, Semmel ES, Aleksonis HA, et al. Cerebellar-Subcortical-Cortical Systems as Modulators of Cognitive Functions. *Neuropsychol Rev.* 2021;31(3):422–446. DOI: 10.1007/s11065-020-09465-1

14. Saab CY, Willis WD. The cerebellum: organization, functions and its role in nociception. *Brain Res Brain Res Rev.* 2003;42(1):85–95. DOI: 10.1016/s0165-0173(03)00151-6

15. Salmi J, Pallesen KJ, Neuvonen T, et al. Cognitive and motor loops of the human cerebro-cerebellar system. *J CognNeurosci.* 2010;22(11):2663–2676. DOI: 10.1162/jocn.2009.21382

16. Strick PL, Dum RP, Fiez JA. Cerebellum and nonmotor function. *Annu Rev Neurosci.* 2009;32:413–434. DOI: 10.1146/annurev.neuro.31.060407.125606

17. Siddiqui R, Mungroo MR, Khan NA. SARS-CoV-2 invasion of the central nervous: a brief review. *HospPract.* 1995;2021(49):157–163. DOI: 10.1080/21548331.2021.1887677

18. Colombo D, Falasca L, Marchioni L, et al. Neuropathology and inflammatory cell characterization in 10 autoptic COVID-19 brains. *Cells.* 2021;10(9):2262. DOI: 10.3390/cells10092262

19. Malik P, Patel K, Akrmah M, et al. COVID-19: a disease with a potpourri of histopathologic findings — a literature review and comparison to the closely related SARS and MERS. *SN Compr Clin Med.* 2021;3(12):2407–2434. DOI: 10.1007/s42399-021-01029-5

СПИСОК ЛИТЕРАТУРЫ

1. Siddiqui R., Mungroo M.R., Khan N.A. SARS-CoV-2 invasion of the central nervous: a brief review // Hosp. Pract (1995). 2021. Vol. 49, No. 3. P. 157–163. DOI: 10.1080/21548331.2021.1887677
2. Lou J.J., Movassaghi M., Gordy D., et al. Neuropathology of COVID-19 (neuro-COVID): clinicopathological update // Free Neuropathol. 2021. Vol. 2. Art. 2. DOI: 10.17879/freeneuropathology-2021-2993
3. Parsons N., Outsikas A., Parish A., et al. Modelling the Anatomic Distribution of Neurologic Events in Patients with COVID-19: A Systematic Review of MRI Findings // AJNR Am. J. Neuroradiol. 2021. Vol. 42, No. 7. P. 1190–1195. DOI: 10.3174/ajnr.A7113
4. Guedj E., Million M., Dudouet P., et al. ^{18}F-FDG brain PET hypometabolism in post-SARS-CoV-2 infection: substrate for persistent/delayed disorders? // Eur. J. Nucl. Med. Mol. Imaging. 2021. Vol. 48, No. 2. P. 592–595. DOI: 10.1007/s00259-020-04973-x
5. Hafiz R., Gandhi T.K., Mishra S., et al. Assessing functional connectivity differences and work-related fatigue in surviving COVID-negative patients. Preprint // bioRxiv. 2022. Art. 2022.02.01.478677. Preprint. DOI: 10.1101/2022.02.01.478677
6. Matschke J., Lütgehetmann M., Hagel C., et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series // Lancet Neurol. 2020. Vol. 19, No. 11. P. 919–929. DOI: 10.1016/S1474-4422(20)30308-2
7. Kirschenbaum D., Imbach L.L., Rushing E.J., et al. Intracerebral endotheliitis and microbleeds are neuropathological features of COVID-19 // Neuropathol. Appl. Neurobiol. 2021. Vol. 47, No. 3. P. 454–459. DOI: 10.1111/nan.12677
8. Al-Dalahmah O., Thakur K.T., Nordvig A.S., et al. Neuronophagia and microglial nodules in a SARS-CoV-2 patient with cerebellar hemorrhage // Acta Neuropathol. Commun. 2020. Vol. 8, No. 1. P. 147. DOI: 10.1186/s40478-020-01024-2
9. Vidal E., López-Figueroa C., Rodon J., et al. Chronological brain lesions after SARS-CoV-2 infection in hACE2-transgenic mice // Vet. Pathol. 2022. Vol. 59, No. 4. P. 613–626. DOI: 10.1177/03009858211066841
10. Lu Y., Li X., Geng D., et al. Cerebral Micro-Structural Changes in COVID-19 Patients — An MRI-based 3-month Follow-up Study // EClinicalMedicine. 2020. Vol. 25. Art. 100484. DOI: 10.1016/j.eclinm.2020.100484
11. Diedrichsen J., King M., Hernandez-Castillo C., et al. Universal Transform or Multiple Functionality? Understanding the Contribution of the Human Cerebellum across Task Domains // Neuron. 2019. Vol. 102, No. 5. P. 918–928. DOI: 10.1016/j.neuron.2019.04.021
12. Strick P.L., Dum R.P., Fiez J.A. Cerebellum and nonmotor function // Annu. Rev. Neurosci. 2009. Vol. 32. P. 413–434. DOI: 10.1146/annurev.neuro.31.060407.125606
13. Clark S.V., Semmel E.S., Aleksonis H.A., et al. Cerebellar-Subcortical-Cortical Systems as Modulators of Cognitive Functions // Neuropsychol. Rev. 2021. Vol. 31, No. 3. P. 422–446. DOI: 10.1007/s11065-020-09465-1
14. Saab C.Y., Willis W.D. The cerebellum: organization, functions and its role in nociception // Brain Res. Brain Res. Rev. 2003. Vol. 42, No. 1. P. 85–95. DOI: 10.1016/s0165-0173(03)00151-6
15. Salmi J., Pallesen K.J., Neuvonen T., et al. Cognitive and motor loops of the human cerebro-cerebellar system // J. Cogn. Neurosci. 2010. Vol. 22, No. 11. P. 2663–2676. DOI: 10.1162/jocn.2009.21382
16. Strick P.L., Dum R.P., Fiez J.A. Cerebellum and nonmotor function // Annu. Rev. Neurosci. 2009. Vol. 32. P. 413–434. DOI: 10.1146/annurev.neuro.31.060407.125606
17. Siddiqui R., Mungroo M.R., Khan N.A. SARS-CoV-2 invasion of the central nervous: a brief review // Hosp. Pract. 1995. Vol. 2021, No. 49. P. 57–163. DOI: 10.1080/21548331.2021.1887677
18. Colombo D., Falasca L., Marchioni L., et al. Neuropathology and inflammatory cell characterization in 10 autoptic COVID-19 brains // Cells. 2021. Vol. 10, No. 9.P. 2262. DOI: 10.3390/cells10092262
19. Malik P., Patel K., Akrmah M., et al. COVID-19: a disease with a potpourri of histopathologic findings — a literature review and comparison to the closely related SARS and MERS // SN Compr. Clin. Med. 2021. Vol. 3, No. 12. P. 2407–2434. DOI: 10.1007/s42399-021-01029-5

AUTHORS' INFO

***Larisa V Lukina,** M.D., Ph.D. (Medicine),
Senior Researcher;
address: 3, Bekhterev str., Saint Petersburg, 192019, Russia;
ORCID: https://orcid.org/0000-0001-8500-7268;
Scopus Author ID: 16520904200; eLibrary SPIN: 4693-5577;
Author ID: 220209; ResearcherId: AAK-5570-2021;
e-mail: larisalu@yandex.ru

Natalia I Ananieva, M.D., D.Sc. (Medicine), Professor;
ORCID: https://orcid.org/0000-0002-7087-0437;
Scopus Author ID: 25623015500; eLibrary SPIN: 2924-5761;
Author ID: 518253; ResearcherId: O-8903-2014;
e-mail: ananieva_n@mail.ru

ОБ АВТОРАХ

***Лариса Викторовна Лукина,** канд. мед. наук,
старший научный сотрудник;
адрес: Россия, 192019, г. Санкт-Петербург, ул. Бехтерева, д. 3;
ORCID: https://orcid.org/0000-0001-8500-7268;
Scopus Author ID: 16520904200; eLibrary SPIN: 4693-5577;
Author ID: 220209; ResearcherId: AAK-5570-2021;
e-mail: larisalu@yandex.ru

Наталия Исаевна Ананьева, докт. мед. наук, профессор;
ORCID: https://orcid.org/0000-0002-7087-0437;
Scopus Author ID: 25623015500; eLibrary SPIN: 2924-5761;
Author ID: 518253; ResearcherId: O-8903-2014;
e-mail: ananieva_n@mail.ru

* Corresponding author / Автор, ответственный за переписку

AUTHORS' INFO

Natalia Yu. Safonova, M.D., Ph.D. (Medicine),
Senior Researcher;
ORCID: https://orcid.org/0000-0001-5847-4936;
Scopus Author ID: 57208056100; eLibrary SPIN: 9233-4754;
Author ID: 702314; ResearcherId: AAJ-6703-2020;
e-mail: astarta@yandex.ru

Yan A. Ershov, assistant-researcher;
ORCID: https://orcid.org/0000-0002-2258-2131;
eLibrary SPIN: 7404-8401; ResearcherId: CAA-2212-2022;
e-mail: boarboar123@gmail.com

ОБ АВТОРАХ

Наталья Юрьевна Сафонова, канд. мед. наук,
старший научный сотрудник;
ORCID: https://orcid.org/0000-0001-5847-4936;
Scopus Author ID: 57208056100; eLibrary SPIN: 9233-4754;
Author ID: 702314; ResearcherId: AAJ-6703-2020;
e-mail: astarta@yandex.ru

Ян Александрович Ершов, лаборант-исследователь;
ORCID: https://orcid.org/0000-0002-2258-2131;
eLibrary SPIN: 7404-8401; ResearcherId: CAA-2212-2022;
e-mail: boarboar123@gmail.com