The Nervous System Disorders in COVID-19: From Theory to Practice

Tatyana Zakharycheva¹, Tatyana Makhovskaya², Alexandra Shirokova³, and Irina Shikina⁴

¹ Far Eastern State Medical University, Khabarovsk, Russia
dolika@inbox.ru

² Central State Medical Academy of the Administrative Office of the President of the Russian Federation, Moscow, Russia
makhovskayat@mail.ru

³ Diagnostic Centre “Viveya” of the Ministry of Health of the Khabarovsk Territory, Khabarovsk, Russia
a.s.shirokova@mail.ru

⁴ Central Research Institute for Organization and Informatization of Medical Care, Ministry of Health of Russia, Moscow, Russia
shikina_irina@mail.ru

Abstract. The article presents a state-of-the-art literature review and personal view on spectrum and pathogenesis of the nervous system lesions in the case of coronavirus infection COVID-19 known to date - from theory, medical and social significance to the main clinical options for lesions of the nervous system in the novel coronavirus infection COVID-19. Basic information is also presented on factors modifying the course and outcome of infectious lesions in the nervous system, mechanisms of their development and possible outcomes scenarios in case of novel coronavirus infection COVID-19. Today’s level of knowledge for nervous system damages due to COVID-19 are considered to be life-threatening, and their consequences can have a huge negative impact on the quality of life, especially in those with pre-morbidities.

Keywords: Coronavirus · COVID-19 · Nervous system disorders

1 Introduction

The medical and social significance of infectious lesions of the nervous system is due to a wide range of pathogens, adverse course and outcome of diseases, absence of antiviral therapy and resistance of bacteria to antibacterial agents [1, 2]. The interaction between micro- and macroorganisms due to genetic variability, change of pathogens, and population ageing is also relevant. In present conditions beta-coronavirus SARS-CoV-2, causing “Coronavirus Disease 2019” (COVID-19) has become an extremely dangerous pathogen [3, 4]. Coronavirus infection has been known since the twentieth century as an acute viral disease with weak, predominant lesions of the upper respiratory tract and a
good outcome. At the same time, there are reports of finding coronaviruses in the brain of patients with multiple sclerosis [5, 6]. We provide our own view on the spectrum and pathogenesis of nervous system lesions in COVID-19 to our colleagues.

Microorganisms exist in a variety of conditions, living in habitats and biological objects. Therefore, viruses can be treated both as agents of infectious diseases and as factors contributing to the adaptive restructuring of the human body under changing conditions of the external and internal environment. In the latter case, viral diseases and nervous system lesions should be considered as adaptation diseases due to immune defect in humans [7, 8].

It is known that the infection process is determined by several factors such as the properties of a particular pathogen, infection method, the characteristics of the host body, etc. [9–11].

2 Materials and Methods

The article presents a state-of-the-art literature review and personal opinion on infectious lesions of the nervous system problem, known to date, specifically connected with the new novel coronavirus infection COVID-19. Analytical research has been carried out to provide basic information on factors modifying the course and outcome of infectious lesions of the nervous system, mechanisms of their development and possible scenarios of outcomes in the novel coronavirus infection. The researchers independently searched for literature published during the period 1980–2020. Prospective and retrospective observational studies of high methodological quality, analytical journals and original scientific articles were used for the analysis.

3 Results

Many authors have shown that antigens of the main HLA histocompatibility complex determine the intensity of cellular immune reactions [9, 12, 13]. They can be used as genetic markers encoding predisposition to COVID-19 disease and for predicting its course and outcome.

An important role in the pathogenesis of nervous system lesions at COVID-19 may belong to hematoencephalic barrier dysfunction (HBD) due to its pre-morbid characteristics and also due to the “cytokine storm”. The pathological process is aggravated by hypoxia, electrolyte imbalance, vitamins and mineral deficiency, intoxications, microtraumas, and microbial invasiveness factors [14].

Viruses can infect the lymphatic system, suppress the immune response and invade the host body [15].

The immune response to different infections may vary significantly. Data on the duration and intensity of immunity concerning SARS-CoV-2 are only accumulating. It should be assumed that in pre-morbid healthy individuals, specific post-infection immunity should be long and strong. In latent (inapparent) and erased forms of infection, as well as in weakened patients’ immunity may not be sustained, and re-infection may occur [16, 17]. Cross-immunity to other members of the coronavirus family has not been found [18].
There are two types of central nervous system infectious lesions. Neuroinfections or primary lesions are mainly caused by viruses that are traumatic to nerve cells and irreversibly damage them. Such diseases are characterized by heavy current and residual symptoms. Secondary (post-infection or para-infection) lesions are relatively benign, immune-mediated with vessel involvement, demyelination, more often reversible neuronal lesions [19, 20].

It is known that the leading role in the pathogenesis of COVID-19 is played by type 2 angiotensin-converting enzyme (ACE2), for which beta-coronavirus SARS-CoV-2 has high affinity. The binding of S1-protein coronavirus and ACE2 is the key stage of virus entry into the cell [21–23]. The high expression of AFP2 in the brain determines the tropism of the virus to neurons and glia. This determines the potential neurotropism of SARS-CoV-2 and ability of coronaviruses to cause neuronal death [24, 25]. According to Chinese researchers, 36.4% of patients with COVID-19 had neurological disorders. Their spectrum included anosmia and ageusia, viral meningitis, encephalitis, stroke, acute hemorrhagic necrotizing encephalopathy; post-infection acute disseminated encephalomyelitis, post-infection stem encephalitis, transverse myelitis, Guillain-Barre syndrome, myositis [26].

In connection with the data presented above, we can assume several possible types of nervous system damage at COVID-19.

Firstly, the development of diseases resulting from direct exposure of SARS-CoV-2 beta-coronavirus to the nervous system are following: meningitis, encephalitis, myelitis, encephalomyelitis, including subacute sclerosing panencephalitis as a result of the persistence of viral infection in patients with congenital or acquired immune system defects. The disease outcome in this scenario will be unfavorable.

Secondly, secondary meningitis in patients with purulent-septic complications occurring both with a relevant clinical presentation of purulent meningitis and with focal symptoms due to cerebrovascular complications.

Thirdly, secondary post- and para infection of the central nervous system lesions (acute disseminated acute encephalomyelitis, acute hemorrhagic leukoencephalitis).

Fourthly, acute inflammatory demyelinating (axonal) polyneuropathy (Guillain-Barre syndrome).

The uncontrolled release of endogenous inflammatory mediators, insufficient mechanisms limiting the damaging effect of cytokines, as well as metabolic and microcirculatory disorders in tissues are considered to be the main reasons for the development of organ system disorders in severe forms of COVID-19. The most frequent and severe complications of COVID-19 are acute respiratory distress syndrome and secondary bacterial infections that require intensive therapy with a ventilator. Patients might develop infectious toxic shock, acute damage to the kidneys and heart, and liver dysfunction [18]. Therefore, patients with severe forms of COVID-19 have a high probability of developing critical illness polyneuropathy (CIP) [13, 14]. We observed this type of polyneuropathy in a patient with severe flu A (H1N1) [27, 28].

Long-term clinical observations in the foci of tick-borne encephalitis indicate a particular severity of the disease in elderly and senile people. In this age group, the proportion of focal lesions of the nervous system was 42.3%. Disorders of vital functions were observed in 80.1% of cases. Lethality reached 21.2%. Adverse outcomes were
promoted by changes in nervous, cardiovascular, respiratory, immune and other systems caused by ageing [9]. Therefore, patients with COVID-19 of old age, suffering from immunosuppressive diseases, diabetes mellitus, chronic cardiovascular, pulmonary and neurological pathology require special attention [29, 30]. Infections, including respiratory diseases, can serve as triggers for acute vascular disorders. Chronic obstructive pulmonary disease (COPD) is an independent risk factor for cardiovascular disease, and cough associated with increased chest pressure can cause a thromboembolic stroke or dissection of carotid arteries [31, 32].

Hypoxia (acute and chronic) due to respiratory disorders also harms the central nervous system and may cause the development of acute hypoxic encephalopathy or dysfunction of the limbic-reticular complex and the appearance of vegetative disorders, neurosis-like disorders and focal neurological symptoms [33].

The infectious process development is characterized by phases. With COVID-19 there are at least three or four phases: 1) incubation; 2) clinical-symptomatic; 3) convalescence period; 4) distant. The latter period may manifest as asthenic and vegetative syndromes, as well as disorders of motor, cognitive and mental functions. Neurological consequences of COVID-19, in turn, according to existing classifications [1, 33, 34], can be subdivided into residual and progressive.

It is generally recognized that all the highest forms of human behavior are associated with the vital functions of nerve cells that synthesize catecholamines: neurotransmitters noradrenaline, serotonin, dopamine. In patients with neuroinfections at the peak of the infection process, as well as in the period of early and late convalescence period, asthenia, anxiety-depressive and vegetative disorders, sleep disorders are detected. Their severity correlates with clinical forms and disease severity [9, 35–37], which is explained by damage to brain cell structures [38–41]. Study of brains’ neurotransmitter systems allows not only to understand the pathogenesis of symptomatology in nervous system lesions including infectious ones but also to make pharmacological interventions of such disorders [42, 43].

The medical and social rehabilitation of COVID-19 rehabilitation centers is one of the important state tasks. Rehabilitation measures imply medication use - general tonic, vasoactive, nootropic, neurotrophic, adaptogenic, vitamin, antidepressants and anticonvulsants [44–47]. In the group of elderly and senile patients with cognitive disorders progressing, during the disease the use of dopamine agonists becomes relevant. The first-choice medicine is non-ergoline dopamine receptor agonist (piribedil) due to more favorable side effects profile [48–51].

A special group that requires close medical supervision are patients suffering from autoimmune inflammatory diseases of the nervous system such as multiple sclerosis, Guillain-Barre syndrome, myasthenia gravis and others. They have a high risk of exacerbation during or after COVID-19 [52].

4 Conclusion

The nervous system lesions due to COVID-19 are life-threatening, and their consequences can have a huge negative impact on a person’s life especially pre-morbidly burdened.
At COVID-19 several variants of nervous system lesions are possible: direct effect of SARS-CoV-2 beta-coronavirus on nerve cells with the persistence of the pathogen in the body; intermediate - with the development of secondary purulent meningitis and cerebrovascular complications; autoimmune demyelination of the central and/or peripheral nervous system; development of stroke, acute hypoxic encephalopathy or decompensation of chronic circulatory failure. COVID-19 is highly likely to exacerbate pre-existing conditions in patients suffering from autoimmune diseases of the nervous system.

Special COVID-19 severity and the prospect of its frequent adverse outcomes calls for the expediency of in-depth study of clinical manifestations of the disease, improvement of methods of prevention and early diagnosis of neurological complications as well as their rational pathogenetic treatment.

References

1. Gusev, E.I., Konovalov, A.N., Skvortsova, V.I.: Neurology: national guidelines. GEOTAR-Media 1, 880 (2018)
2. Sandakov, Y.P., Kochubey, A.V.: The activities concerning improvement of dispensary observation. Probl. sotsial’noi gigieny zdravoohranenii i istorii meditsiny 26(6), 428–431 (2018). https://doi.org/10.32687/0869-866x-2018-26-6-428-431
3. Antipova, T.: Coronavirus pandemic as black swan event. In International Conference on Integrated Science, vol. 136, pp. 356–366 (2020). https://doi.org/10.1007/978-3-030-49264-9_32
4. Mirskikh, I., Mingaleva, Z., Kuranov, V., Matseeva, S.: Digitization of medicine in russia: mainstream development and potential. In: International Conference on Integrated Science, pp. 337–345. Springer, Cham (2020). https://doi.org/10.1007/978-3-030-49264-9_32
5. Lobzin, Y.V., Pilipenko, V.V., Gromyko, Y.N.: Meningitis and encephalitis. Monograph. Foliant, St. Petersburg, pp. 2–54 (2006)
6. Lobzin Y.V., Kazantsev A.P.: Guide to Infectious Diseases, p. 736. Phoenix (1997)
7. Umansky, K.G.: Viral neuroinfections (problem of adaptive pathology). Review of the literature. Zhurnal nevropatologii i psikhiatrii imeni SS Korsakova 80(8), 1235 (1980)
8. Umansky, K.G.: Ubiquitous nature of viruses and presumption of innocence. Arkh. Patol. 42(10), 76–81 (1980)
9. Zakharycheva, T.A.: Tick-borne encephalitis in the Khabarovsk Territory: yesterday, today, tomorrow, p. 248 (2014)
10. Shirokova, A.S., Zakharycheva, T.A., Fleishman, M.Y., Obukhova, G.G.: Clinical and immunological features of adolescents - convalescents of enteroviral meningitis. Bull. Neurol. Psychiatry Neurosurg. 29–34 (2018)
11. Zaretskaya, Y.M.: Clinical immunogenetics, pp. 65–66 (1983)
12. Iyerusalimskiy, A.P.: Tick-borne encephalitis. A guide for doctors, p. 360 (2001)
13. Tsinserling, V.A., Chukhlovina, M.L.: Infectious lesions of the nervous system: issues of epidemiology, pathogenesis and diagnostics: a guide for doctors of multidisciplinary hospitals. ELBI-SPb. p. 448 (2005)
14. Somova, L.M.: Pathology of neuroinfections caused by viruses of the tick-borne encephalitis complex: monograph-atlas. LLC SYNERIA, p. 360 (2018)
15. Shikina, I.B.: The maintenance of security of the elderly and gerontic patients in the hospital conditions. Probl. sotsial’noi gigieny zdravoohranenii i istorii meditsiny 6, 44 (2007)
16. Armashevskaya, O.V., Ivanova, M.A., Chuchalina, L.Y.: Age features of pathology of women in the peri - and postmenopausal period. Adv. Gerontol. 30, 363–367 (2017)
17. Zhmerenetskiy, K.V., Sazonova, E.N., Voronina, N.V., et al.: COVID-19: only scientific facts. Far Eastern Med. J. 5–22 (2020)
18. Levin, O.S.: Polyneuropathies: clinical guidelines. Med. Inf. Agency 480 (2016)
19. Umansky, K.G.: Where do the controversial issues of neuroviral diseases lead? S-info 72 (1993)
20. Jia, H.P., Look, D.C., Shi, L., et al.: ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. J. Virol. 23, 14614–14621 (2005). https://doi.org/10.1128/JVI.79.23.14614-14621.2005
21. Tang, X., Wu, C., Li, X., et al.: On the origin and continuing evolution of SARS-CoV-2. Natl. Sci. Rev. (2020). https://doi.org/10.1093/natrev/nfaa096
22. Tortorici M.A., Veesler, D.: Structural insights into coronavirus entry. Adv. Virus Res. 93–116 (2019). https://doi.org/10.1016/bs.aivir.2019.08.002
23. Baig, A.M., Khaleeq, A., Ali, U., Syeda, H.: Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem. Neurosci. 11(7), 995–998 (2020). https://doi.org/10.1021/acschemneuro.0c00122
24. Netland, J., Meyerholz, D.K., Moore, S., Cassell, M., Perlman, S.: Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J. Virol. 82(15), 7264–7275 (2008). https://doi.org/10.1128/JVI.00737-08
25. Mao, L., Wang, M., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Hu, Y., Li, Y.: Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study (2020). https://doi.org/10.1101/2020.02.22.20026500
26. Lemann-Horn, F., Ludolph, A.: Treatment of nervous system diseases. MEDpress-Inform. 528 (2005)
27. Zakharycheva, T.A., Menshikov, A.B., Frolova, M.A., et al.: Damage to the nervous system in influenza A (H1N1). Far Eastern J. Infect. Pathol. 43–48 (2012)
28. Suslina, T.S., Gulevskaya, M.Y., Maximova, V.A., Morgunov: Cerebral circulation disorders: diagnosis, treatment, prevention. MEDpress-inform. 536 (2016)
29. Buzin, V.N., Mikhailova, Y.V., Chukhriyenko, I.Y., Buzina, T.S., Shikina, I.B., Mikhailov, A.Y.: Russian healthcare through the eyes of the population: dynamics of satisfaction over the past 14 years (2006–2019): review of sociological studies. Prev. Med. 23(3), 42–47 (2019). https://doi.org/10.17116/profmed20202303142
30. Chudnovsky, V.M., Makhovskaya, T.G., Mayor, A.Y., Yusupov, V.I., Nevozhai, V.I., Kiselyov, A.Y., Shikina, I.B.: The role of blood foaming in the mechanism of endovasal laser ablation. Phlebology 261–269 (2018). https://doi.org/10.17116/flebo201812041261
31. Tsiskaridze, A., Lindgren, A., Qureshi, A.: Iatrogenic stroke: a manual for practitioners. GEOTAR-Media, p. 432 (2019). [Russian]
32. Amelina, O.A., et.al.: Clinical neurology with the basics of medical and social expertise: a guide for doctors. SPb: Medline-Media, p. 594 (2006)
33. Shtock, V.N., Levin, O.S.: Handbook for the formulation of the clinical diagnosis of diseases of the nervous system. Med. Inf. Agency 520 (2019)
34. Sumlivaya, O.N., Vorobieva, N.N., Karakulova, Y.V.: Postinfectious syndrome in convalescents of ixodic tick-borne borreliosis. J. Infectol. 27–32 (2014)
35. Sumlivaya, O.N., Vorobieva, N.N., Karakulova, Y.V.: Postinfectious asthenia in convalescents after tick-borne encephalitis and methods of its relief. Perm Med. J. 41–48 (2017). https://doi.org/10.17816/pmj34541-48
36. Shirokova, A.S.: Cognitive functions in adolescents who have undergone enteroviral meningitis. Scientific and practical conference of neurologists. In: XX All-Russian Conference “Neuroimmunology. Multiple sclerosis”, p. 103 (2015)
37. Alekseeva, L.A., Skripchenko, N.V., Bessonova, T.V., et al.: Markers of damage to glial neurons in cerebrospinal fluid in children with meningitis. Clin. Lab. Diagnost. 204–210 (2017)
38. Skripchenko, N.V., Shirokova, A.S.: Neuron-specific enolase and S100 protein are biomarkers of brain damage. State of the issue and clinical application. Neurosurg. Neurol. Children 4(50), 16–25 (2016)
39. Sumlivaya, O.N.: The relationship between changes in serotonin and cytokines in patients with tick-borne encephalitis. Perm Med. J. 32, 68–73 (2015)
40. Lins, H., Wallesch, C.W., Wunderlich, M.T.: Sequential analyses of neurobiochemical markers of cerebral damage in cerebrospinal fluid and serum in Cnervous system infection. Acta Neurol. Scand. 112, 303–308 (2005)
41. Sumlivaya, O.N., Vorobieva, N.N., Karakulova, Y.V.: Participation of the serotoninergetic system in the formation of cerebrasthenic syndrome in tick-borne encephalitis and its correction. Pract. Med. 7(83), 68–71 (2014)
42. Shirokova, A.S., Skripchenko, N.V., Zakhar'cheva, T.A., Fleishman, M.Y.: Pharmacocorrection of asthenovegetative disorders in children and adolescents - convalescents of enteroviral meningitis. Bull. Neurol. Psychiatry Neurosurg. 9(104), 48–51 (2018)
43. Blinova, U., Rozhkova, D., Rozhkova, N.: Management accounting of innovation costs. Vestnik Univ. (1), 43–48 (2018). [Russian]. https://doi.org/10.26425/1816-4277-2018-1-43-48
44. Rozhkova, N., Blinova, U., Rozhkova, D.: The concept of management accounting based on the information technologies application. Inf. Technol. Sci. (2018). https://doi.org/10.1007/978-3-319-74980-8_8
45. Moroz, E.V., Zakhar'cheva, T.A., Antonyuk, M.V.: Clinical experience of using piribedil in chronic cerebrovascular disease with cognitive impairment. Neurol. Neuropsychiatry Psychosomat. 11(4), 100–103 (2019). https://doi.org/10.14412/2074-2711-2019-4-100-103
46. Parfenov, V.A.: Vascular cognitive impairment and chronic cerebral ischemia (discirculatory encephalopathy). Neurol. Neuropsychiatry Psychosomat. 11(3), 61–67 (2019). https://doi.org/10.14412/2074-2711-2019-3S-61-67
47. Nagaraja, D., Jayashree, S.: Randomized study of the dopamine receptor agonist piribedil in the treatment of mild cognitive impairment. Am. J. Psychiatry 158(9), 1517–1519 (2001). https://doi.org/10.1176/appi.ajp.158.9.1517
48. Perez-Lloret, S., Rascol, O.: Piribedil for the treatment of motor and non-motor symptoms of Parkinson disease. CNS Drugs 30(8), 703–717 (2016). https://doi.org/10.1007/s40263-016-0360-5
49. Moskalev, A.V.: Autoimmune diseases: diagnosis and treatment: a guide for doctors. GEOTAR-Media 224 (2017)
50. Murav'yeva, A., Mikhail'eva, Y., Shikina, I.: Organizational arrangements for medical assistance to patients with a new coronavirus infection Covid-19 in Stavropol Krai. Current problems of healthcare and medical statistics, p. 4 (2020). https://doi.org/10.24411/2312-2935-2020-00120