УДК: 616.89-02-022
DOI 10.21886/2219-8075-2021-12-1-33-37

COVID-19 associated delirium: pathogenetic mechanisms of induction and clinical features

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The present review describes pathogenetic mechanisms and clinical features of COVID-19 associated delirium. Potential factors leading to the named condition and pathophysiological chains were described elaborately, including older adults' manifestation analysis based on the latest clinical studies. A systematic literature review was conducted in the following databases: PubMed, Scopus, e-library, Google Scholar and others.

Keywords: delirium, COVID-19, comorbidity, older adults.

For citation: Tsoy L.V. COVID-19 associated delirium: pathogenetic mechanisms of induction and clinical features. *Medical Herald of the South of Russia.* 2021;12(1):33-37. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-33-37.

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COVID-19-ассоциированный делирий: механизмы развития и особенности течения

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Настоящий литературный обзор рассматривает механизмы развития COVID-19-ассоциированного делирия и особенности его клинических проявлений. Подробно описаны предрасполагающие к развитию данного состояния факторы и патофизиологические звенья, детали манифестации заболевания с симптомов делирия у пожилых лиц на основе анализа последних исследований. Системный поиск литературы производился по базам данных PubMed, Scopus, e-library, Google Scholar и др.

Ключевые слова: делирий, COVID-19, коморбидность, пожилой возраст.

Для цитирования: Цой Л.В. COVID-19-ассоциированный делирий: механизмы развития и особенности течения *Медицинский вестник Юга России.* 2021;12(1):33-37. DOI 10.21886/2219-8075-2021-12-1-33-37.

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Introduction

First, the spread of coronavirus was reported in Hankow, the People's Republic of China, in December 2019 [1, 2]. The World Health Organization announced a pandemic of the novel coronavirus on March 11, 2020[1]. COVID-19 induces the development of severe acute respiratory syndrome (SARS) and is responsible for a high rate of morbidity and lethality worldwide [3]. Pandemic has turned global with the number of registered cases of more than 80 million and lethal cases – 1.8 million[2].

COVID-19 manifestations are diverse, varying from flu-like to gastrointestinal symptoms. Lately, more and more specialists have reported neuropsychiatric symptoms [4]. The studies show that in 20–30% of cases, patients with coronavirus infection develop delirium or changes in psychological status during hospitalization. In severe cases, such changes are registered in 60–70%

[1] Archived: WHO Timeline – COVID-19 https://www.who.int/news/item/27-04-2020-who-timeline-covid-19
[2] Johns Hopkins Coronavirus Resource Center https://coronavirus.jhu.edu/map.html

of patients regardless of the patient's age [5]. French scientists that analyzed the condition of patients from two intensive care units at the Hospital of the University of Strasburg reported that in 84% of patients with COVID-19-associated acute respiratory distress syndrome, neurological disturbances developed, in particular, delirium [6].

Delirium is an indicator of vital functions in serious senior patients. In senior patients, typical fibril response is often not established. Frequently, the disease manifestations do not include dyspnea even when hypoxia develops. In 40% of cases, infection with coronavirus cannot be verified by visual diagnostic methods, thus increasing the risk of underestimation of the patient's condition as a potential case of COVID-19 infection. For this reason, delirium should be considered as a part of screening criteria [7].

Since the present article contains the analysis of foreign studies, including American, the definition of the condition by DSM-5 should be provided. Delirium is a disturbance in attention and awareness that develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, tends to fluctuate in severity during a day, and is characterized by behavior impairments caused by somatic changes [8].

Mechanisms and potential factors of the development of COVID-19 delirium

Potential mechanisms of the development of COVID-19-associated delirium include hypoxemia, oxidative stress caused by respiratory distress syndrome, hypoperfusion, and uremia caused by polyorganic failure associated with respiratory distress syndrome [9, 10]. Another study also showed a multifactorial nature of delirium development including a direct effect on the central nervous system (CNS) by the virus and involvement of cerebral vessels in the pathological process. Indirect causes included hypoxia, high fever, dehydration, inflammatory reaction manifested as cytokine storm, and metabolic disorders [7]. Apart from the specified reasons, researchers believe that the indication of high doses of sedative myorelaxant drugs that simplify the patient's transfer to artificial pulmonary ventilation (APV), long-term APV, and social isolation play their roles in the development of delirium [11].

CNS damage caused by the novel coronavirus is explained by the fact that the virus is tropic to the cells that express the receptors to the angiotensin-converting enzyme-2 that are found in neural and glial cells, as well as the mucosal layer of the upper section of the esophagus, enterocytes, vascular endothelium, ciliated epithelium of the upper respiratory tract, and type 2 pneumocytes. The damage of these cells leads to the manifestation of respiratory syndromes [12, 13, 14]. The brain is sensitive to circulating components of the renin-angiotensin converting system (RAS). However, they do not exert a negative effect due to the impermeability of the hematoencephalic barrier (HEB). In case of infection with coronavirus, an inflammatory response develops in the organism, which increases the permeability of the HEB and leads to the massive infiltration of the brain with the components of the RAS. In turn, the components of the RAS induce neuroinflammatory cascade, which leads to vast neurodegeneration with further development of cognitive dysfunctions [15, 16].

The data obtained experimentally during the study of coronaviruses that existed before SARS-Cov2 demonstrated significant neurologic impairments in the structure of clinical manifestations, which is caused by the damage of the CNS, in particular, the hippocampus with the virus. The accumulation of the virus induces the inflammatory process in the brain with uncontrolled activation of astrocytes, which leads to astrogliosis and neutrophil infiltration that permeates the HEB due to its increased permeability caused by the inflammation. This leads to the damage of neurons of the brain, including the hippocampus, which leads to clinical manifestations of dementia and cognitive impairments. The inflammatory process in the CNS can be prolonged and lead to remote disturbances in its functioning. This can explain somatic-vegetative and psychic changes after COVID-19-associated delirium [17].

Some experimental data obtained from experiments that involved animals and people infected with *Coronaviridae* family viruses suggest the involvement of the brain stem and vasomotor center of the medulla in the pathological process [13, 18].

Clinical peculiarities of COVID-19-associated delirium

The study performed by Erica B. Baller *et al.* included 19 patients with COVID-19-associated delirium. The researchers observed patients with impaired consciousness, expressed agitation, and disturbed attention as the main manifestations of the disease in the case when there are no other respiratory symptoms and other signs of infection [4].

A group of American scientists from the Harvard School of Medicine described 4 clinical cases registered in the Massachusetts General Hospital. All the described patients were older than 65 years old and had

light cognitive impairments and moderate dementia in the anamnesis. It must be mentioned that all the patients did not have the main symptoms of COVID-19 (increased temperature, cough, dyspnea). The primary symptoms were the changes in the psychological status, which led to hospitalization. Only in 2 out of 4 patients, typical signs of coronavirus effect were revealed with visualizing methods of the examination (positive ground-glass opacities in the lower sections of the lungs). In one half of the observed patients, high temperatures were not registered. In the other half, the temperature was subfebrile. In all 4 cases, a significant level of C-reactive protein was observed, which could indicate an uncontrolled immune response that provoked delirium. Multifocal myoclonus was described in 3 patients. The authors believe that the development of myoclonus was expected because this symptom is a general manifestation of encephalopathy and signals global brain dysfunction. Still, they highlight that myoclonus in patients with COVID-19-associated delirium is more evident than delirium that is usually described in patients with other pathologies. Myoclonus was observed at admission in 2 patients that further developed increased muscular tonus with rigidity. This can be associated with the viral damage of the basal ganglia that are more sensitive to neurotropic viruses. Besides, it was reported that at a certain time during hospitalization, all patients stopped digesting food. In 3 of them, progressing anarthria was registered that started with a decrease in the language output and resulted in mutism, in some cases. The dynamic of the loss of speech was quick (several hours to several days) [9].

Italian scientists described the cases of delirium as a manifestation of coronavirus infection observed in the specialized department for patients with dementia at the Geriatric Institute named after Golgi in patients older than 65 years old. They established the dependence of the lethal outcomes on the character of the disease onset. At the initial stage of the development of the disease, 78.6% of lethal cases had the signs of delirium and not typical respiratory symptoms of COVID-19. In the majority of cases, lethality was associated with high comorbidity. Besides, the scientists highlight that the severity of dementia in patients included in the study did not correlate with the rate of lethality from COVID-19. In 52.2% of patients included in the study, a hypoactive variant of delirium was observed with decreased psychomotor functions. In 47.6% of patients, agitation and aggressive behavior were registered, which could be characterized as hyperactive delirium. In some cases, there was a shift from hyperactive to hypoactive delirium. Psychotic symptoms were described in 19% of patients with the developed delirium. American and Italian researchers agreed that delirium could be considered as the first symptom of coronavirus infection in senior people before the development of hypoxia, fever, and inflammatory response [19].

On the contrary, another British study showed the prevalence of the hyperactive variant of COVID-19-associated delirium (53% vs 37%) registered as hypoactive delirium [20].

More often, delirium symptoms appeared at the stage of SARS according to the data obtained by American scientists Jonathan P. Rogers *et al*. (consciousness impairment — 65% of patients hospitalized admitted to the intensive care unit, agitation — 69%, distorted consciousness — 21%) [21].

Andrea Ticinesi in his study revealed a correlation in the development of delirium between the age of patients and a high rate of lethality if delirium developed during the period of hospitalization [22].

There are data on a significant worsening of a physical condition manifested as post-resuscitation weakness, cognitive impairments, depression, and post-traumatic stress disorder after the resolution of delirium condition [17, 20].

Conclusion

COVID-19-associated delirium is the result of a combination of pathological factors in one patient, including senior age and comorbidity not only by somatic but also by psychic diseases, in particular, dementia and cognitive impairments.

Along with the typical manifestation of delirium according to DSM-5 classification (impairments of consciousness and attention), patients had myoclonus, muscular rigidity, and loss of speech output to mutism, which can take delirium as a global dysfunction o the brain.

At this stage, it is impossible to affirm that COVID-19-associated delirium is the primary manifestation of the disease in senior patients with high comorbidity. However, it is necessary to include diagnostic criteria of delirium in senior patients as potential manifestations of coronavirus infection for the monitoring of the development and prevention of complications.

Financing. *The study did not have sponsorship.*

Финансирование. Исследование не имело спонсорской поддержки.

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

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Получено / Received: 26.12.2020
Принято к печати / Accepted: 13.01.2021