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Neurological symptoms observed in patients with COVID-19

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Abstract

Infection with the novel coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) has triggered the largest pandemic of the early 21st century. The disease primarily affects the respiratory system and may present as a common respiratory viral infection, but more severe cases can progress to acute pneumonia or acute respiratory distress syndrome, with heart and kidney failure, digestive symptoms, liver failure, and sometimes death. In SARS-CoV-2 infection, respiratory symptoms are frequently accompanied by neurological manifestations ranging from headaches, dizziness, anosmia, and asthenia to severe complications such as ataxia, seizures, and strokes. A study was conducted on a cohort of 5649 patients clinically and paraclinically diagnosed with coronavirus disease 2019 (COVID-19), admitted to the Victor Babeş Clinical Hospital for Infectious Diseases and Pneumophthisiology, Craiova, Romania, between 2020 and 2022, to identify the most common signs of neurological involvement. The most common signs of neurological involvement in COVID-19 were asthenia, headache, and myalgia. The most severe complications in COVID-19 were strokes.

Keywords: COVID-19, SARS-CoV-2, neurological manifestations, central nervous system.

Introduction

Coronaviruses are pathogens [ribonucleic acid (RNA) viruses] that primarily affect the respiratory system. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), identified in 2019 in China, triggered a disease named by *World Health Organization* (WHO) experts as coronavirus disease 2019 (COVID-19). In February 2020, due to the spread of the disease worldwide and the large number of infected people, the *WHO* declared the disease a pandemic (the disease affected over 771 820 937 individuals in 232 countries and regions and caused approximately 6 978 175 deaths in the first four years following the identification of the virus and the disease) [1, 2].

The onset of the global COVID-19 pandemic has had a profound impact on the world, on the economies of all countries, and on healthcare systems worldwide [3, 4]. Consequently, various movement restrictions were implemented globally, leading in some countries to nationwide lockdowns, social isolation, high morbidity and mortality rates, and the interruption of certain healthcare services for patients with chronic conditions, pregnant women, or children [5, 6].

It is currently known that the SARS-CoV-2 enters the human body *via* the respiratory system, most often causing mild symptoms such as fever or low-grade fever, cough, chest pain, fatigue, shortness of breath, etc. More severe cases of the disease can progress to acute pneumonia or acute respiratory distress syndrome (ARDS), with heart and kidney failure, digestive symptoms, liver failure, and sometimes, the patient's death [7, 8].

In SARS-CoV-2 infection, respiratory symptoms are frequently accompanied by neurological manifestations; these range from milder symptoms such as headache, dizziness, anosmia, and fatigue to severe complications such as ataxia, seizures, and strokes [9, 10]. It appears that neurological symptoms are a direct consequence of the virus entering the central nervous system (CNS) *via* the hematogenous or ophthalmic route. In the CNS, the virus infects neurons and glial cells, primarily causing neurodegenerative lesions. Neurological manifestations usually appear immediately after infection or during the recovery period [11, 12].

Studies in laboratory animals (mice) have shown that coronaviruses localize predominantly in the brainstem, which would explain, at least in part, the cardiorespiratory disorders, including ARDS [13–15].

Aim

In this study, we aimed to assess neurological symptoms

in patients infected with SARS-CoV-2 who developed COVID-19 and were admitted to the Victor Babeş Clinical Hospital for Infectious Diseases and Pneumophthisiology, Craiova, Romania, between 2020 and 2022.

Patients, Materials and Methods

We analyzed a cohort of 5649 patients clinically and laboratory-confirmed with COVID-19 who were admitted to the Victor Babeş Clinical Hospital for Infectious Diseases and Pneumophthisiology, Craiova, between 2020 and 2022. Within the cohort, patients ranged in age from three to 104 years. Patients presented with mild, moderate, and severe forms of the disease or were asymptomatic but had been in contact with COVID-19 patients and tested positive for COVID-19 *via* real-time reverse transcription polymerase chain reaction (RT–PCR). Patients with mild forms of the disease or asymptomatic patients were hospitalized as a measure to prevent the spread of the SARS-CoV-2 virus, in accordance with Decision No. 3 of February 28, 2020, of the Romanian National Committee for Special Emergency Situations "regarding the management of cases of infection with the novel coronavirus".

In our study, we analyzed the medical data and documents contained in the patients' clinical observation charts. Data collection and processing were performed using the MATLAB development environment, and the data were then transferred to the Excel analysis system to obtain the most accurate data and graphs possible.

The research was approved by the University and Scientific Ethics and Deontology Committee of University of Medicine and Pharmacy of Craiova (Approval No. 129/26.02.2025).

Statistical analysis was performed on data obtained from the medical records of 5649 patients with clinically and paraclinically confirmed COVID-19, hospitalized in the Victor Babeş Clinical Hospital for Infectious Diseases and Pneumophthisiology, Craiova. Data extraction and preprocessing were carried out using MATLAB, after which the dataset was transferred to Microsoft Excel for descriptive statistical analysis and graphical representation. Continuous variables were summarized descriptively, while categorical variables were expressed as absolute numbers and percentages.

The study population was analyzed according to year of hospitalization, sex, age group, and the presence of neurological manifestations. The frequency of the main neurological symptoms and complications, including asthenia, headache, myalgia, dizziness, anosmia, and stroke, was calculated for the entire cohort. Comparative descriptive analyses were further performed according to age categories and sex.

The relationships between neurological manifestations and selected clinical parameters or comorbidities were assessed using Pearson's χ^2 (*chi*-squared) test. This test was applied to evaluate associations between categorical variables, including sex, febrile or subfebrile status, digestive symptoms, cardiovascular disease (CVD), diabetes mellitus, hepatic disease, and renal disease. For each comparison, the χ^2 value and the corresponding *p*-value were determined.

Statistical significance was set at $p<0.05$. All reported *p*-values were two-sided. The results were presented as frequencies, percentages, and graphical distributions.

Results

At the Victor Babeş Clinical Hospital for Infectious Diseases and Pneumophthisiology, Craiova, 5649 patients were admitted over the three years of the COVID-19 pandemic, as follows: in 2020, 1404 patients were admitted (of whom 688 were women and 716 were men); in 2021, 3670 patients were admitted (of whom 1838 were women and 1832 were men), and in 2022, 575 patients were admitted (of whom 287 were women and 288 were men). In total, 2813 women and 2836 men were hospitalized. The ratio of women to men hospitalized with COVID-19 was approximately 1:1. These data also show that the highest number of patients diagnosed with COVID-19 occurred in 2021 (Figure 1), a trend consistent with the progression of the COVID-19 pandemic in Romania. It can be said that in the first year of the pandemic, 24.85% of the patients in the analyzed cohort were hospitalized; in the second year, 64.97% were hospitalized; and in the third year of the pandemic, 10.18% were hospitalized. The decrease in the number of patients infected with COVID-19 and hospitalized in the third year of the pandemic was the result of preventive measures, including COVID-19 vaccinations.

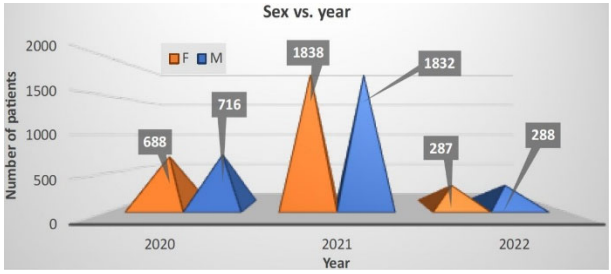

Figure 1 – ***Distribution of hospitalized COVID-19 patients by gender over three years of the pandemic. COVID-19: Coronavirus disease 2019; F: Female; M: Male.***

An analysis of the cohort of hospitalized patients by age revealed that the COVID-19 pandemic affected all age groups, ranging from three years old to over 100 years old. It should be noted that there was a positive correlation between patient age and the number of patients. Thus, while there were 203 hospitalized patients under the age of 20 (children and adolescents) (3.59% of the total cohort), the number of patients aged between 51 and 80 with COVID-19 admitted to the Infectious Diseases Clinic was 3480 (*i.e.*, 61.65%) (Figure 2).

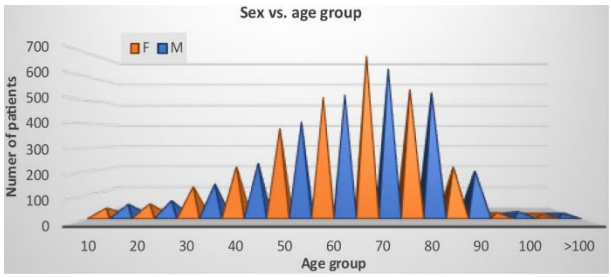

Figure 2 – ***Distribution of the cohort of hospitalized patients by age and gender. F: Female; M: Male.***

Regarding the distribution of patients hospitalized with COVID-19 at the Victor Babeş Clinical Hospital for Infectious Diseases and Pneumophthisiology, Craiova, an almost equal representation of both sexes was observed across all age groups (Figure 2).

The most common symptom indicating neurological involvement in our study was asthenia. It was noted in the medical records' of 2461 patients (43.56% of the entire cohort) (Figure 3), manifesting as persistent fatigue, low energy levels, or depression. Other patients described asthenia as a lack of energy, physical weakness, apathy, sleep and mood disturbances, difficulty concentrating, and irritability, sometimes associated with headaches and muscle pain. One possible cause of asthenia is tissue hypoxia resulting from pulmonary impairment.

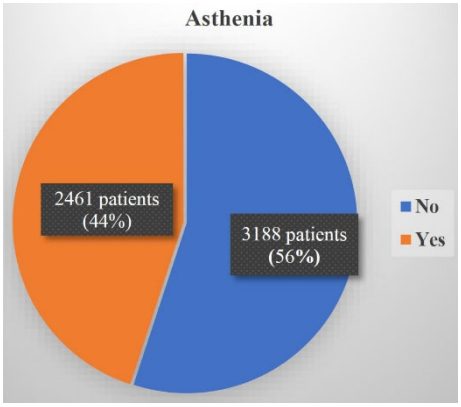

Figure 3 – ***Distribution of patients who presented with asthenia.***

Our study found that asthenia was more common in patients over 60 years of age and became the dominant symptom in those over 90 years of age. While only 579 patients under the age of 50 presented with asthenia, among those over 60, asthenia was observed in 1877 patients (Figure 4). Asthenia was frequently associated with CVDs (the χ^2 statistic is 25.1647; the p-value is <0.00001; the result is significant at $p<0.05$), with digestive symptoms, and with fever (the χ^2 statistic is 4.5908; the p-value is 0.032145; the result is significant at $p<0.05$), but it was not associated with low-grade fever.

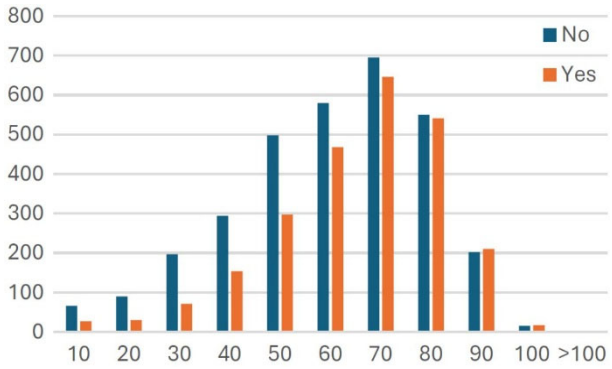

Figure 4 – ***Distribution of patients with asthenia by age.***

Headache was identified in 1251 patients (approximately 22% of the entire cohort) (Figure 5). It was described as a headache of varying intensity and duration (ranging from a few hours to several days), with considerable variation from one patient to another. The morphological basis of this symptom was most likely changes in the meningo-cerebral vessels. In some patients, headaches are associated with digestive symptoms (loss of appetite, nausea, or vomiting).

In our study, headache was predominant in women and in older patients (the χ^2 statistic is 39.4814; the p-value is <0.00001; the result is significant at $p<0.05$), was frequently associated with subfebrile (the χ^2 statistic is 7.1607; the p-value is 0.007452; the result is significant at $p<0.05$) and febrile (the χ^2 statistic is 66.7051; the p-value is <0.00001; the result is significant at $p<0.05$) and with CVDs (the χ^2 statistic is 5.3875; the p-value is 0.020281; the result is significant at $p<0.05$).

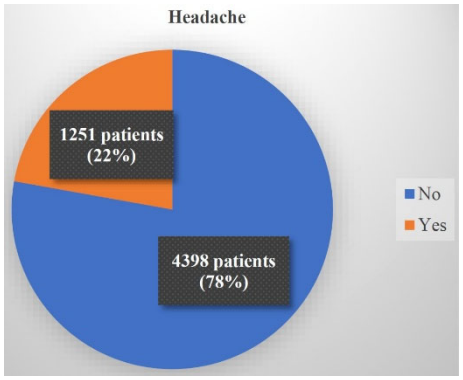

Figure 5 – ***Graph of COVID-19 patients affected by headache.***

Myalgia was described by patients as generalized muscle pain and, less frequently, as muscle pain localized to a specific area of the body, of mild or moderate intensity, in the absence of prior physical exertion. Myalgia was often accompanied by muscle fatigue or a feeling of heaviness when walking. In our study, myalgia was reported in 930 patients, representing approximately 17% of the entire patient cohort (Figure 6). It was reported more frequently by elderly patients (Figure 7) and those with CVDs (the χ^2 statistic is 5.4488; the p-value is 0.019581; the result is significant at $p<0.05$); liver disease (the χ^2 statistic is 4.5466; the p-value is 0.032984; the result is significant at $p<0.05$) or by patients with low-grade fever (the χ^2 statistic is 4.7063; the p-value is 0.030053; the result is significant at $p<0.05$) and fever (the χ^2 statistic is 48.4969; the p-value is <0.00001; the result is significant at $p<0.05$).

Dizziness was reported in only 735 patients (Figure 8) as a balance disorder, particularly upon sudden changes in body position, unsteadiness while walking associated with digestive disorders (nausea, vomiting), or visual disturbances. It occurred more frequently after the age of 50 and in association with fever (the χ^2 statistic is 7.2824; the p-value is 0.006963; the result is significant at $p<0.05$).

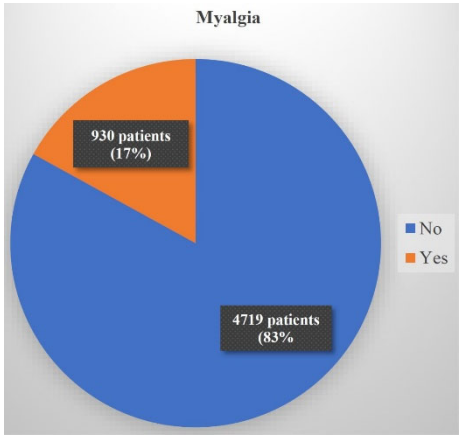

Figure 6 – ***Patients who presented myalgia.***

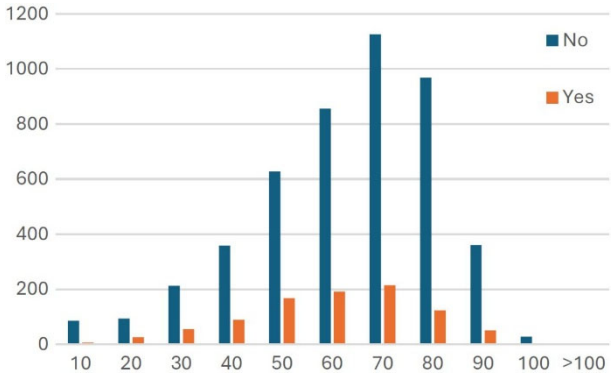

Figure 7 – ***Age of patients who presented myalgia. It can be observed that most patients with myalgia were over 50 years of age.***

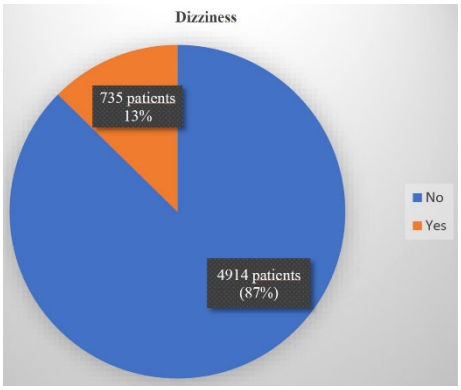

Figure 8 – ***Graphical representation of patients who presented dizziness.***

Anosmia, which manifests as a partial or complete loss of the sense of smell, can be temporary (caused by viral infections, sinus problems, or nasal congestion) or permanent (due to head trauma or neurodegenerative diseases). In our study, we recorded a total of 536 patients (approximately 9.4%) with anosmia (Figure 9). The symptom occurred across all age groups (except for children under five years of age), more frequently in females (the χ^2 statistic is 16.7641; the p-value is 0.000042; the result is significant at $p<0.05$). Anosmia was associated with diabetes (the χ^2 statistic is 4.3949; the p-value is 0.036048; the result is significant at $p<0.05$), with CVDs (the χ^2 statistic is 25.5406; the p-value is <0.00001; the result is significant at $p<0.05$), as well as with liver diseases (the χ^2 statistic is 10.7993; the p-value is 0.001015; the result is significant at $p<0.05$) and with febrile conditions (the χ^2 statistic is 4.3683; the p-value is 0.036614; the result is significant at $p<0.05$). In some patients, anosmia was accompanied by ageusia (diminished sense of taste).

One of the most serious forms of brain damage associated with COVID-19 has been stroke. In our study, over the three years of the pandemic, 186 patients were diagnosed with stroke, representing approximately 3.46% of the entire analyzed cohort (Figure 10). Stroke predominantly affected individuals over 60 years of age and those with diabetes (the χ^2 statistic is 25.7911; the p-value is <0.00001; the result is significant at $p<0.05$), CVDs (the χ^2 statistic is 109.6637; the p-value is <0.00001; the result is significant at $p<0.05$) and kidney disease (the χ^2 statistic is 14.1754; the p-value is 0.000167; the result is significant at $p<0.05$).

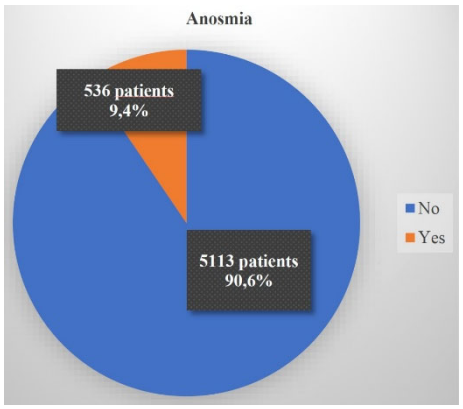

Figure 9 – ***Graph showing patients who experienced anosmia.***

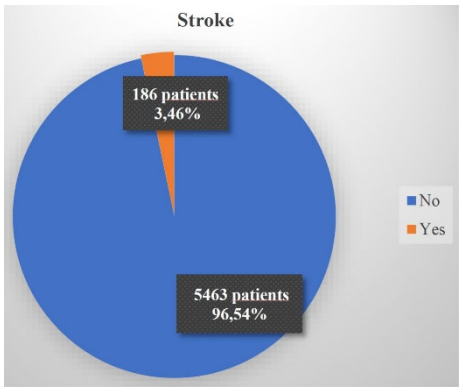

Figure 10 – ***Graph of patients who experienced at least one stroke episode during hospitalization.***

Discussions

COVID-19, caused by the SARS-CoV-2 coronavirus and initially characterized as a respiratory disease, has since emerged as a multisystemic disease with significant neurological implications [16–18].

It should be noted that CNS involvement has been observed in both experimental and clinical studies, as well as in infections with other coronaviruses [19, 20]. These studies [13, 21] have indicated a possible direct route of viral entry into the CNS *via* the olfactory nerve [22, 23].

Currently, two hypotheses for SARS-CoV-2 entry into the CNS are accepted: first, through systemic vascular dissemination, and second, through dissemination *via* the olfactory nerve [13, 21]. Once in the CNS, the virus invades nerve tissue *via* angiotensin-converting enzyme 2 (ACE2) receptors and infects both neurons and astrocytes [24, 25], causing a wide range of lesions, from degenerative changes to strokes [26, 27], with varied clinical manifestations, ranging from asthenia and headache to seizures.

Several studies have shown that COVID-19 patients, both adults and children, exhibited, in addition to respiratory symptoms, numerous neurological signs and symptoms right from the onset of the acute phase of the disease, and in some patients, these neurological signs persisted long-term as post-COVID symptoms [13, 28]. Recent studies have demonstrated a concerning association between COVID-19 infection and cognitive decline, with prevalence rates ranging from 17.5% to 68.5% [29–31]. It is known that SARS-

CoV-2 can cross the blood-brain barrier (BBB) and cause damage to the CNS. Preliminary studies have shown that COVID-19 is associated with multiple neurological symptoms (hypoesthesia, hyposmia, acute polyneuropathy, headaches, encephalopathy, encephalitis, acute cerebrovascular diseases, etc.) [32, 33].

The severity of the initial COVID-19 infection is an important factor in assessing cognitive decline, with hospitalized patients exhibiting a greater degree of cognitive decline compared to those with milder cases. Some authors found that cognitive decline was present in 75% of patients admitted to intensive care, compared to only 40% of those treated on an outpatient basis [34]. CNS involvement is complex and present in all cases, even in mild forms of COVID-19 infection. In our study, the most common symptom indicating neurological involvement was asthenia. According to some studies, most patients present with asthenia, both during the acute phase of COVID-19 and after recovery. Asthenia, defined as severe generalized weakness, frequently occurs in various infectious diseases and especially in viral infections. Typically, asthenia is often associated with irritability, emotional lability and anxiety, sweating, palpitations, and gastrointestinal disturbances [35].

Another sign of CNS involvement in COVID-19 investigated in our study was headache. In our cohort, 22% of patients presented with headaches. Researchers from Wuhan, China, in an observational study, found that 36.4% of patients with COVID-19 exhibited neurological manifestations, with dizziness (16.8%) being the most frequent symptom, closely followed by headache (13.1%) [36, 37]. Headaches may vary in intensity and duration from one patient to another, depending on the underlying pathophysiological mechanism. It may represent a nonspecific symptom or may be triggered by a severe neurological complication (persistent or recurrent headache) [38–41].

Another interesting symptom observed in the patients in our cohort was myalgia. Myalgia frequently occurs in viral infections or during intense muscular exertion. The intensity of these symptoms was reported differently by patients infected with SARS-CoV-2, depending on the severity of the viral infection. A meta-analysis conducted in Wuhan, China, at the start of the pandemic found that approximately 35.8% of patients with COVID-19 experienced myalgia. These were accompanied by fever (88.5%), cough (68.6%), sputum production (28.2%), and shortness of breath (21.9%); less common were dizziness, diarrhea, nausea, and vomiting [42].

Another meta-analysis conducted on a cohort of 8697 patients showed that myalgia was present in 21.9% of patients with COVID-19. Some studies have shown that muscle pain was one of the independent predictors of lack of symptom improvement in patients with COVID-19.

An example of direct and rapid damage to nerve tissue in COVID-19 infection is the presence of anosmia; in our study, anosmia was detected in 9.4% of hospitalized patients. In a study conducted by Lechien *et al.* on olfactory and gustatory function in patients with COVID-19, the authors found these symptoms in over 50% of the patients included in the study [35, 43].

Although anosmia has been frequently reported (51%) in patients with COVID-19, in association with cough and fever [42], the exact mechanism by which SARS-CoV-2 invades the olfactory nerve and bulb remains unknown. Furthermore, the cellular and molecular mechanisms responsible for the onset of neurological signs and symptoms are not fully understood.

Most studies indicate that the most common pathophysiological mechanism is triggered by the release of cytokines by T-cells and/or other immune effector cells. Cytokine release is a systemic inflammatory response that causes severe neurotoxicity. In patients with severe COVID-19, higher plasma concentrations of proinflammatory cytokines, such as interleukin (IL)-6, IL-1β, and interferon-gamma (IFN-γ), have been found. It is known that the presence of these cytokines leads to direct tissue damage and an additional inflammatory cascade [35, 44]. Excess cytokines accumulated intracerebrally have neurotoxic effects and directly affect the integrity of the BBB, leading to cerebral edema, which is responsible for multiple neurological signs.

Several studies have demonstrated a concerning association between COVID-19 infection and cognitive decline, with prevalence rates ranging from 17.5% to 68.5% [29, 45]. It appears that damage to nervous tissue, particularly associated with cognitive decline, occurs in severe forms of COVID-19 infection and in older adults [46].

The virus's entry into the CNS will trigger a state of low-grade chronic inflammation in the brain (neuroinflammation), which will be a critical contributor to post-COVID-19 cognitive decline [47, 48].

Conclusions

Neurological manifestations in patients with COVID-19 were diverse, ranging from mild symptoms such as headache and anosmia to severe conditions such as stroke. They most often occurred in older adults or those with comorbidities. A patient presented with one or more neurological manifestations depending on the overall severity of the disease.

Conflict of interests

The authors declare that they have no conflict of interests.

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