

Neurological manifestations of COVID-19.

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Abstract.

Objective of the article is to provide more comprehensive data of the prevalence of neurological comorbid disorders and preexisting neurological disorders in patients with COVID-19.

Method. We systematically searched the literature through Pubmed, based on the search of combination of keywords: Covid 19, coronavirus, neurological disorders, stroke, complications, neurorehabilitation.

Results. The increased biomedical interest in the problem of COVID-19 is due to its high contagiousness, variable symptomatology, severe course and multiple organ failure in a pandemic, the critical importance of the state of the nervous system. The manifestations can be considered as direct effects of the virus on the nervous system, para-infectious or post-infectious immune-mediated disease, and neurological complications of the systemic effects of COVID-19.

Conclusion. The article deals with brief aspects of some factors contributing to the development of neurological disorders in COVID-19 patients. The study results of coronavirus infection of foreign researchers are summarized.

Key words: Covid-19, nervous system, neurological diseases, rehabilitation.

Background:

In the greater part of cases, COVID-19 is a respiratory virus that causes fever, aches, fatigue, sore throat, cough and, in more severe cases, shortness of breath and respiratory distress. Yet we now understand that COVID-19 can also infect cells outside of the respiratory tract and cause a wide range of symptoms from gastrointestinal disease (diarrhoea and nausea) to cardiovascular disease. It is becoming increasingly clear that coronavirus can trigger a huge range of neurological problems. These manifestations can be considered as direct effects of the virus on the nervous system, para-infectious or post-infectious immune-mediated disease, and neurological complications of the systemic effects of COVID-19 [1,2]. The brain has traditionally been the target organ in a variety of infectious diseases and critical illnesses, either as a direct insult or as a secondary result of infection. Apart from the central nervous system (CNS), the peripheral nervous system (PNS) is particularly vulnerable during immune-mediated diseases associated with infections, and prolonged immobilization during critical hospitalization can also severely impact nerves and muscles [3,4].

More severe neurological symptoms were usually observed in patients with more severe airway damage, but, again, it is difficult to determine if this reflects a direct neurological lesion or the presence of common concomitant diseases such as hypertension, diabetes or obesity. In addition to this, isolated cases of more serious neurological conditions associated with COVID-19 begin to appear, including potential cases of encephalitis or encephalopathy, acute disseminated necrotizing encephalomyelitis, and Guillain-Barré syndrome. Caution is

recommended so that clinicians can differentiate between the cases where neurological disease is directly associated with COVID-19 from those that present as non-etiological comorbidities.

Methods and materials:

We systematically searched the literature through Pubmed, based on the search of combination of keywords: Covid 19, coronavirus, neurological disorders, stroke, complications, neurorehabilitation. References of retrieved articles were also screened. Case reports, case series, editorials, reviews, case-control and cohort studies were evaluated, and relevant information was abstracted. Duplicate publications were excluded from further evaluation. Reference lists of all articles that met the criteria and references of relevant review articles were examined to identify studies that may have been missed by the database search.

Results:

The central and peripheral nervous system involvement may be related to hypoxia and endothelial damage, uncontrollable immune reaction and inflammation, electrolyte imbalance, hypercoagulable state and disseminated intravascular coagulation, septic shock and/or multiple organ failure[5]. Some neurological diseases are associated with weakness of the muscles responsible for swallowing (bulbar paresis), weakness of the respiratory muscles, or weakness of the heart muscle (as in motor neuron disease or some myopathies). These factors increase the risk of a more severe course of coronavirus infection. Neurological manifestations associated with Covid-19 is described in the Table 1

Table 1.
Neurological manifestations associated with Covid-19

Dizziness
Headache
Stupor
Delirium
Seizures
Coma
Hyposmia
Myalgias
Aches above the eyes

The most common symptoms at onset of illness are fever, cough, and myalgia or fatigue; less common symptoms are sputum production, headache, haemoptysis, and diarrhea [6]. A neuronal dissemination model of coronavirus invasion, in which the virus infects a peripheral neuron and relies on the machinery of active transport, synaptic terminals and retrograde transport to the neuronal cell body in remote areas of the brain, has been postulated [7, 8], (Figure 1). Once the virus was established in the brain, there was evidence of dissemination along the neurotransmitter pathways, such as the serotonergic dorsal raphe system or hematogenously through the Virchow–Robin spaces. Prior studies have shown that both SARS-CoV and MERS directly induced neuronal death in the respiratory center in the medulla through an upregulation of IL-1, IL-6 and TNF alpha cytokine response, possibly through either an inflammatory response or autophagy. However, these observations were conducted with SARS, and further studies will be needed to determine whether they are also applicable to the novel SARS-CoV-2 virus.

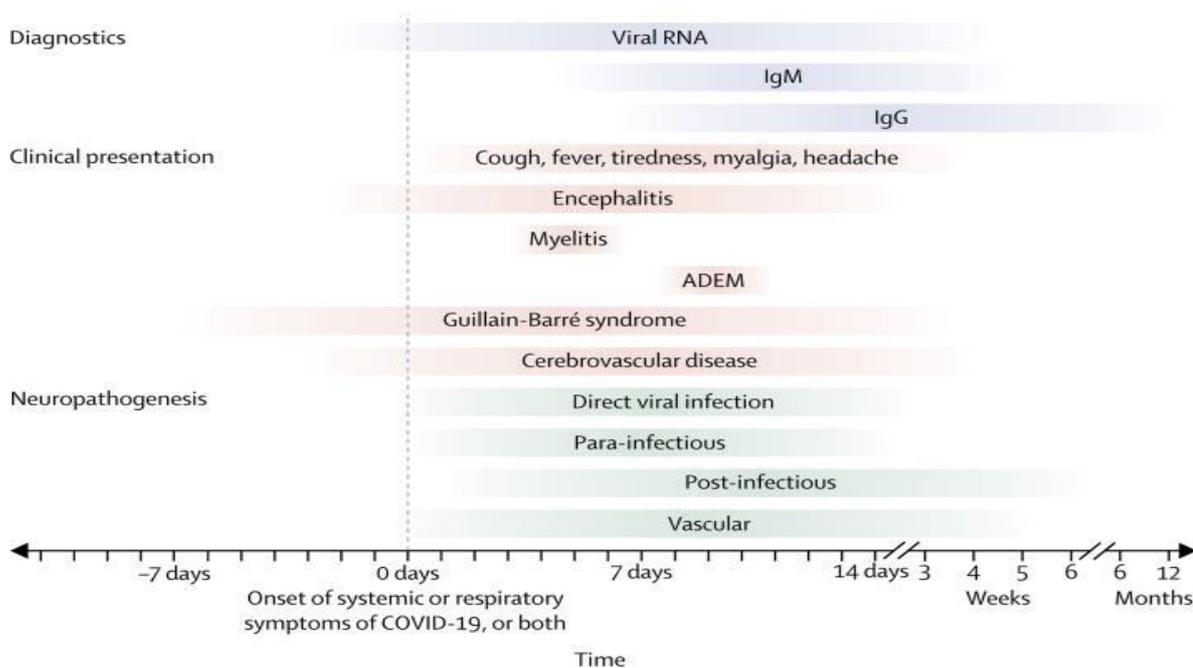


Fig 1. Timeline of clinical events and diagnostic investigations.

Stroke, as the cornerstone of neurological emergency and a major cause of mortality and disability, should not be neglected at the expense of extreme community and health-care COVID-19-measures [9]. A stroke is an acute cerebrovascular accident (CVA), which is characterized by a sudden (within minutes, less often - hours) occurrence of focal neurological symptoms (motor, speech, sensory, coordinating, visual and other disorders) and / or cerebral disorders (changes in consciousness, headache, vomiting, etc.) that persist for more than 24 hours or lead to the death of the patient in a short period of time due to the cause of cerebrovascular origin.

Two clinical and pathogenetic forms of stroke are distinguished:

1) **Ischemic stroke (cerebral infarction)** due to acute focal cerebral ischemia, leading to infarction (zone of ischemic necrosis) of the brain;

2) **Hemorrhagic stroke (non-traumatic intracerebral hemorrhage)** due to rupture of the intracerebral vessel and the penetration of blood into the brain parenchyma or rupture of an arterial aneurysm with subarachnoid hemorrhage.

CVA also includes **transient cerebrovascular accidents**, which are characterized by the sudden onset of focal neurological symptoms that develop in a patient with cardiovascular disease (arterial hypertension, atherosclerosis, atrial fibrillation, vasculitis, etc.), lasts a few minutes, less often than hours, but not more than 24 hours and end with a full restoration of impaired functions.

The apparent association of COVID-19 and stroke, however, is likely due to the fact that both conditions share similar risk factors. There is ample evidence that the severity of COVID-19 infection in humans is directly related to the presence of cardiovascular co-morbidities, such as hypertension, diabetes mellitus and elderly status predisposing to large vessel disease

The term "risk factors" refers to the characteristics of the lifestyle and living conditions, as well as the human body, which are not causes of diseases, but increase the likelihood of their occurrence (Table 2).

Table 2

Risk factors (RF) for cerebrovascular disease associated with Covid 19.

modifiable RFs
arterial hypertension ,

heart disease,
atrial fibrillation,
lipid metabolism disorders,
diabetes mellitus,
pathology of the main arteries of the head,
hemostatic disorders
non-modifiable RFs
gender,
age,
ethnicity,
heredity
lifestyle-related RFs
tobacco smoking
overweight,
low physical activity,
poor diet (in particular, insufficient consumption of fruits and vegetables, alcohol abuse),
prolonged psycho-emotional stress or acute stress.

Encephalitis is the inflammation of the brain parenchyma, usually caused by an infection or the body's immune defences. Although it is strictly speaking a pathological diagnosis, for practical purposes, clinical evidence of brain inflammation is accepted, such as a CSF pleiocytosis, imaging changes, or focal abnormalities on EEG. Detection of virus in the CSF per se does not provide a diagnosis of encephalitis if there is no evidence of brain inflammation [10].

Encephalopathy is a pathobiological process in the brain that usually develops over hours to days and can manifest as changed personality, behaviour, cognition, or consciousness (including clinical presentations of delirium or coma) [11]. The largest study to date, [12] from Wuhan, China, retrospectively described 214 patients with COVID-19, of whom 53 (25%) had CNS symptoms, including dizziness (36 [17%] patients), headache (28 [13%]), and impaired consciousness (16 [7%]). 27 (51%) of the patients with CNS symptoms had severe respiratory disease, but there was little further detail. In a French series of 58 intensive care patients with COVID-19, 49 (84%) had neurological complications, including 40 (69%) with encephalopathy and 39 (67%) with corticospinal tract signs [13]. MRI in 13 patients showed leptomenigeal enhancement for eight and acute ischaemic change for two; CSF examination for seven patients showed no pleiocytosis. 15 (33%) of 45 patients who had been discharged had a dysexecutive syndrome. Additionally, some case reports have appeared, including a woman with encephalopathy with imaging changes consistent with acute necrotising encephalopathy [14] and a fatal case in which viral particles were found in endothelial cells and neural tissue, although there was no indication of whether this was associated with inflammation [15].



Fig 2. Acute stroke with Covid 19.

Most patients with peripheral neuropathies without additional disease, with the exception of a few specific categories, do not have the additional risks associated with COVID-19. Guillain-Barré syndrome is an acute polyradiculopathy characterised by rapidly progressive, symmetrical limb weakness, areflexia on examination, sensory symptoms, and, in some patients, facial weakness, although several variants exist [16]. In an observational study of 214 patients with a confirmed diagnosis of COVID-19, 8.9 % presented with peripheral nervous system (PNS) symptoms including hypogeusia, hyposmia, hypoplasia and neuralgia. The most common complaints were hypogeusia and hyposmia [17]. Loss of smell (anosmia) and taste (ageusia) have emerged as common symptoms of COVID-19, either with other features or in isolation, suggesting that they might be useful diagnostic markers [18]. A study of 259 patients, [19] including 68 who were positive for SARS-CoV-2, found that abnormal smell and taste were both strongly associated with COVID-19. In a European study, olfactory dysfunction was reported for 357 (86%) of 417 COVID-19 patients; 342 (82%) reported gustatory disorders [20]. These symptoms were reported more frequently for COVID-19 patients than for a historical cohort of influenza patients [21]. Subclinical deficits in smell, taste, or both have also been detected [22,23].

Discussion.

Our narrative review summarized the so far documented neurological complications of COVID-19 that involve the central and the peripheral nervous system. The neurological manifestations include dizziness, headache, myalgias, hypogeusia and hyposmia, but also highlights less common but more serious disorders including polyneuropathy, myositis, cerebrovascular diseases and rarely encephalitis. In patients with neuropathy, cerebrovascular disease, or acute disseminated encephalomyelitis, in whom the damage is probably caused by the host's response to viral infection, establishing causality is even more challenging, especially if patients present after the virus has been cleared from the nasopharynx. Clinical case definitions for COVID-19 that are based on the history and typical findings for chest imaging and blood investigations will be useful [24, 25].

Brain infarction is, as a rule, the result of the interaction of many diverse etiopathogenic factors that can be divided into local and systemic: 1) local: morphological changes in the brachiocephalic or intracerebral arteries, atherosclerotic lesions of the vessels of the aortic arch and cerebral arteries, heart damage as a source of thromboembolic cerebral infarction, fibromuscular dysplasia of the walls of the brachiocephalic and cerebral arteries, arteritis, changes in the cervical spine, anomalies in the structure of the vessels of the neck and brain, etc. 2) systemic factors: disorders of central and cerebral hemodynamics, coagulopathy, polycythemia, certain forms of leukemia, hypovolemia, etc. In every second case, the cause of intracerebral nontraumatic hemorrhage is arterial hypertension, cerebral amyloid angiopathy accounts for about 10-12%, about 10% are due to the use of anticoagulants, 8% are caused by tumors, and all other causes account for about 20%. Intracerebral hemorrhages can develop either as a result of rupture of a vessel, or by diapedesis, usually against the background of previous arterial hypertension. Risk assessment, non-pharmacological therapy and preventive counseling should be carried out in all patients with neurological disorders, regardless of the type and severity of the disease according to the above principles. These actions are particularly important for patients with hypertension and clinical manifestations of atherosclerosis of any localization.

Conclusion:

Thus, the increased biomedical interest in the problem of COVID-19 is due to its high contagiousness, variable symptomatology, severe course and multiple organ failure in a pandemic, the critical importance of the state of the nervous system. The exact

pathophysiological mechanisms underlying the development of cerebrovascular disorders in patients with COVID-19 remains to be studied. To predict the outcome of COVID-19, further focused research is needed to evaluate the functional status of the central nervous system and develop a personalized approach to therapy.

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