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# Neurological Involvement in Coronavirus Disease 2019 (COVID-19)

**Buechner Susanne MD* and Tesolin Lucia MD**

*Department of Neurology/Stroke Unit, General Hospital of Bolzano, Bolzano/Bozen, Italy.*

***Correspondence:**
Dr. Susanne Buechner, Department of Neurology/Stroke Unit, General Hospital of Bolzano, Italy, Tel: +39-0471-908589; Fax: +39-0471-908591.

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## ABSTRACT

*Coronavirus disease 2019 (COVID-19) is a global pandemic, caused by a virus known as SARS-CoV-2. Many different neurological symptoms and complications have been reported in COVID-19 patients, such as headache, anosmia and Guillain-Barré syndrome, as well as encephalitis, stroke and seizures. We have summarized all these neurological manifestations in a short overview. Our understanding of neurological involvement in COVID-19 is still limited, therefore careful assessment should be performed, and neurologists need to be involved.*

## Keywords

COVID-19, SARS-CoV-2, Neurological symptoms, NEURO-COVID.

## Abbreviations

ACE: Angiotensin-converting Enzyme; CNS: Central Nervous System; COVID-19: Coronavirus Disease 2019; GBS: Guillain-Barré Syndrome; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; PCR: Polymerase Chain Reaction; SARS-Coronavirus / SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; WHO: World Health Organization.

## Commentary

In December 2019 a novel virus emerged in Wuhan, China, which was named severe acute respiratory syndrome coronavirus 2 (SARS-Coronavirus-2: SARS-CoV-2) [1]. The World Health Organization (WHO) labeled the related disease as coronavirus disease 2019 (COVID-19), characterized mainly by a respiratory illness ranging from mild to very severe clinical presentations [2]. COVID-19 rapidly spread to multiple countries; on 11 March 2020, COVID-19 has been declared a world pandemic by WHO [3].

In a few weeks, our world has become a very different place for everybody, including those involved in patient care. Many new challenges had to be handled, especially for those involved in the care of COVID-19 patients. However, the sudden emergency had an important impact to all health care activities, including those of neurologists. For example, patients with acute stroke have risked suboptimal outcome due to difficulties in managing effective treatment of the acute presentation, or post-stroke care such as rehabilitation. Another challenge for neurologists has been the problem of providing an adequate ongoing care for patients affected with chronic neurological diseases such as Parkinson's disease or neuromuscular disorders, as people had been asked by the authorities to stay indoors. Finally, doubts regarding the use of immunosuppressive and immunomodulatory treatments in the setting of COVID-19 have appeared. On the one hand, there has been the fear of a higher risk for SARS-CoV-2 infection, on the other hand, the fear of exacerbation of the underlying neurological disease when stopping the immunotherapy. In order to respond to all these challenges, respecting the patient's health and the medical staff's safety, guidelines regarding the management of some neurological disorders during COVID-19 pandemic have been developed [4-6].

At a certain point, some patients diagnosed with COVID-19 have not just shown typical respiratory symptoms, but also neurological manifestations, such as headache or myalgia [2]. Finally, a case of COVID-19 with encephalitis was reported in Beijing, China [7]. Reports regarding neurological manifestations of the SARS-CoV-2 pandemic have started to be published. In our department of Neurology, the term "NEUROCOVID" has started to be used.

But what kind of neurological manifestations in COVID-19 have been reported in literature so far? We have found the description of the following symptoms and complications:

## Neurological symptoms

As mentioned before, neurological symptoms have been observed early in patients with COVID-19 in China. Retrospective observational studies regarding the clinical characteristics of coronavirus disease 2019 included often un-specific neurological symptoms such as headache, dizziness, myalgia or fatigue [2,8-10]. A retrospective case series of 214 hospitalized COVID-19 patients from Wuhan described exclusively neurological manifestations [11]. Overall, 36.4% had neurological complications including headache, dizziness, impaired consciousness, but also acute cerebrovascular disease or taste or smell impairment.

## Cerebrovascular disease

One single, retrospective observation study analyzed acute cerebrovascular disease after COVID-19 in 221 affected patients [12]. Overall, 13 patients had cerebrovascular disorders, in detail, 11 patients suffered from acute ischemic stroke, 1 patient from cerebral hemorrhage and another patient from cerebral venous sinus thrombosis. Italian neurologists working in COVID-19 hotspot areas observed a dramatic increase in the number of vascular events, one of the reasons why they opened so-called neuro-Covid-19 units [13]. Both, ischemic and hemorrhagic cerebrovascular diseases have been observed in COVID-19 patients: some authors reported large-vessel strokes, especially in young male patients, sometimes early in the course of the SARS-CoV-2 infection [14,15]; other authors described patients suffering from subarachnoid hemorrhage after aneurysm rupture or from ischemic stroke with massive hemorrhagic conversion [16].

## Smell and Taste disorders

The above mentioned olfactory and gustatory dysfunctions in COVID-19 patients have become a frequent subject of study, also because anosmia and ageusia can represent the first or even only symptom of COVID-19 [17]. Most studies consisted of questionnaires, frequently given to hundred of patients [18-21]. The detected occurrence of taste and/or olfactory disorders were extremely variable, but some studies reported very high percentages (85.6%) [19]. In order to demonstrate that an altered taste and/or smell might be useful for the identification of otherwise asymptomatic carries, special surveys were given to apparently healthy populations during the COVID-19 pandemic [22-23].

## Guillain Barré Syndrome

The involvement of the peripheral nervous system has been confirmed also by the publication of several case reports talking about Guillain-Barré syndrome (GBS) or GBS variants associated with SARS-CoV-2 infection [24-28], even if the authors themselves were not always sure if the association was causal or a coincidence [24].

## Myelitis

There was also a 66-year-old male who developed GBS-like symptoms after SARS-CoV-2 infection. However, due to a sensory level T10 and urinary and bowel incontinence, a post-infectious acute myelitis was diagnosed [29].

## Meningitis/Encephalitis/Encephalopathy

The involvement of the central nervous system (CNS) in patients with COVID-19 infection is of great interest, and after the first case of COVID-19 encephalitis [7], several case reports about meningitis/encephalitis/meningoencephalitis associated with SARS-CoV-2 have been published [30-32]. Even an acute hemorrhagic necrotizing encephalopathy in a female in her late fifties was reported [33]. However, some authors labeled the CNS manifestations in the acute setting of COVID-19 infection just as an "encephalopathy", also because cerebrospinal fluid (CSF) examination with the search for SARS-CoV-2 was negative or had not been performed at all [34,35]. Finally, some authors made only descriptions of CNS symptoms in COVID-19 patients, such as seizures and altered consciousness, without reporting a conclusive diagnosis [36,37].

This brief overview of current literature shows that COVID-19 seems to be associated with a lot of different neurological symptoms and complications. However, the pathogenesis of nervous system manifestations associated with SARS-CoV-2 is still unclear. Also, the above-mentioned publications did not always demonstrate a sure correlation. For example, the data could not evidence a causal relationship between SARS-CoV-2 and stroke [15,16]. Only in two encephalitic patients, PCR for SARS-CoV-2 in CSF was found to be positive [7,30]. In most cases, the search for the new coronavirus in CSF was negative or has not been done [31,32,34]. Sometimes CSF examination was missing completely [29], as well as brain magnetic resonance imaging [29,31,32,35]. The results regarding the olfactory and taste disorders in COVID-19 are based only on questionnaires. Also, the diagnosis of GBS were not always confirmed by CSF examination or electromyography testing [27]. Even the results of the retrospective observational study on neurological manifestations of 214 hospitalized patients were mainly based on subjective descriptions and not on imaging, neurophysiology or CSF data [11].

For sure, these considerations are not a critic of the authors of these studies or case reports, because during a health emergency there is no time to perform a careful assessment of all clinical features, especially if patients are suffering mainly from a new respiratory disease and presenting with severe, life-threatening health problems. In addition, the assumption that the reported neurological manifestations might be provoked by the SARS-CoV-2 infection is based on the genomic similarities of SARS-CoV-2 with other coronaviruses (SARS-CoV and MERS-CoV). These coronaviruses have demonstrated to be neurothropic and neuroinvasive, exploiting the angiotensin-converting enzyme (ACE) 2 receptor to gain entry inside the cells, including glial cells and neurons [38,39]. Due to this neuroinvasion, some authors believe also in a contributing factor of SARS-CoV-2 to respiratory failure of patients with COVID-19 [40]. Furthermore, even if the pathophysiological mechanism of SARS-CoV-2 has not been

demonstrated yet, the altered sense of smell or taste commonly reported in COVID-19 patients [17-19] might be explained by the spread of the virus through the nasal mucosa via the olfactory nerve across the cribriform plate to the brain during the infection phase [41]. Finally, COVID-19 infections provoke changes in the coagulation system and a significant inflammatory response [42,43]. A storm of cytokines and a state of hypercoagulability might increase the risk of ischemic stroke.

In conclusion, the understanding of the neurological involvement in COVID-19 is still limited and clinical features such as headache or fatigue and impaired consciousness might be considered as non-specific symptoms, may be just effects of the systemic illness and respiratory distress. However, in our own experience we observed prolonged duration of delirium of COVID-19 patients without previous hypoxia after mechanical ventilation removal. As delirium is a clinical expression of acute brain dysfunction [44], we cannot deny a neurological involvement in SARS-CoV-2 infection. For sure, in the near future, additional reports regarding neurological manifestations of COVID-19 will be published. If possible, however, data should be complemented by imaging, neurophysiology or CSF examination. For that reason, we believe that neurologists should be involved in the care of COVID-19 patients.

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