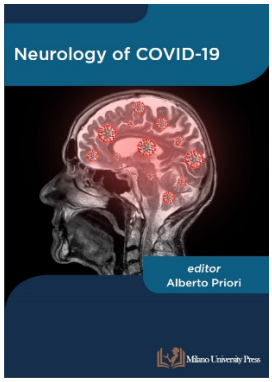

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Chapter 4. **Neurological manifestations: an overview**

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Chapter 4. Neurological manifestations: an overview

Chiara Manfredi, Emma Scelzo, Vincenzo Silani, Carlo Ferrarese, Alberto Priori

Introduction

Coronaviruses are enveloped, positive stranded RNA viruses which represent important human and animal pathogens, predominantly causing respiratory and gastrointestinal tract infections[1]. However, neurological symptoms have been reported in COVID-19 patients from all over the world (Table 4.1)[2-4].

Mao et al.[5], in the first retrospective study on neurological manifestations, estimated that more than one-third (36.4%) of patients with COVID-19 develop neuropsychiatric symptoms, out of which the most common were central nervous system (CNS) manifestations followed by peripheral nervous system (PNS) involvement[5].

Table 4.1: Summary of the neurological manifestations of COVID-19

Non-specific	CNS manifestations	PNS manifestations
Headache	Encephalitis	Smell and taste disturbances
Dizziness	Encephalopathy	GBS
Myalgia	Ischemic stroke/TIA	MFS
Lightheadness	Hemorragic stroke	Cranial neuropathy
Syncope	Subaracnoid Hemorrage	Optic neuritis
	Cerebral venous thrombosis	Posterior ischemic optic neuropathy
	Seizures	Myositis
	Myelitis	Rhabdomyolysis
	ADEM	
	CNS vasculitis	
	Movement disorders	

CNS: Central Nervous System; PNS: Peripheral Nervous System; TIA: Transient Ischemic Aattack; ADEM: Acute Disseminated Encephalomyelitis; GBS: Guillain-Barré Syndrome; MFS: Miller-Fisher Syndrome.

Neurological complications appear to be even more common in hospitalized patients. It has been reported that over 80% of COVID-19 patients who require hospitalization may develop neurological symptoms at some point during

their disease course[6]. Moreover, it seems that patients with a severe course of COVID-19 are more likely to develop neurological complications[5].

Rates of symptoms vary by geographical location and patient characteristics. Overall, the most common neurological manifestations reported in Asia, Europe and the US were smell and taste disturbances, myalgia, headache, encephalopathy, and dizziness. Cerebrovascular events, movement disorders, motor and sensory deficits, ataxia, and seizures are not common[2,5,6-8].

The EAN survey and the Global Consortium Study of Neurological Dysfunction in COVID-19

In April 2020, the European Academy of Neurology (EAN) core COVID-19 Task Force conducted a survey on neurological symptoms observed in patients with SARS-CoV-2 infection to assess their incidence and characteristics. They distributed a 17-question online survey to EAN members and other physicians worldwide, collecting data from a total of 2,343 responders (82% neurologists), mostly from Europe. According to the survey, the most frequent neurological symptoms were headache (61.9%), myalgia (50.4%), smell and taste disturbances (particularly anosmia, 49.2%, and ageusia, 39.8%), impaired consciousness (29.3%), and psychomotor agitation (26.7%). Other reported neurological symptoms were encephalopathy and acute cerebrovascular disorders (21%).

The results of the survey, in agreement with the data available in the literature, showed that neurological symptoms occurred predominantly in hospitalized patients and appeared at various times during the infection course. As expected, the most severe neurological features were reported by physicians in the Intensive Care Units (ICUs). Moreover, despite some observed differences, which could be attributable to the setting and the degree of involvement of the responders during the outbreak, there was no great difference in neurological manifestations between countries or continents[9].

From March to October 2020, the Global Consortium Study of Neurologic Dysfunction in COVID-19 (GCS-NeuroCOVID) and the EAN Neuro-COVID Registry (ENERGY) performed a multicohort study including COVID-19 patients from 13 countries and 4 continents. The study aimed to determine neurological phenotypes, incidence, and outcomes among hospitalized patients. This study showed that approximately 80% of the patients had neurological manifestations (both self-reported symptoms and/or neurological signs or syndrome). In particular, the most common self-reported symptoms included headache (37%) and smell or taste disturbances (26%), while the most prevalent neurological signs and/or syndromes were acute encephalopathy (49%), coma (17%), and stroke (6%). Moreover, the presence of any neurological sign was associated with higher in-hospital mortality, even after adjusting for age, sex, race, and ethnicity[10].

Neurological manifestations of COVID-19

Non-specific symptoms

SARS-CoV-2 can potentially present with several non-specific neurological symptoms. In the case series of Mao et al., the most common neurological symptoms were dizziness (16.8%), headache (13.1%), myalgia (10.7%), and altered mental status (14.8%)[5].

These data appear also to be in line with the results of the EAN survey. Interestingly, Favas et al. found that, in health care workers, the incidence of non-specific symptoms was higher compared with the general population[4].

Smell and taste disturbances

Smell and taste disturbances have been reported as common early symptoms in patients with COVID-19, and were rarely the only manifestation. Interestingly, they can be a sign of a milder form of infection and can occur both during and after presentation of general symptoms[11]. Early data suggested that smell and taste disturbances are due to the direct effects of the virus on the olfactory system and gustatory receptors[12], since the SARS-CoV-2 could enter the brain through the olfactory epithelium and the neural-mucosal interface[13]. Magnetic resonance imaging (MRI) signal abnormalities in one or both olfactory bulbs have been described in patients with COVID-19, sometimes resolved on follow-up imaging[14,15]. In an autoptic study, pathologic findings demonstrated severe and widespread tissue damage involving the olfactory nerve, the gyrus rectus, and the brainstem, along with numerous particles referable to virions of SARS-CoV-2[16]. According to a systematic review of 212 studies conducted by Favas et al., the most common smell disturbance was anosmia; other symptoms reported were hyposmia, phantosmia and parosmia. Among taste disturbances, the most commonly reported were dysgeusia and ageusia. Overall, the incidence of smell disturbances ranged from 4.9% to 85.6%, while incidence of taste disturbances varied from 0.3% to 88.8%[2]. Nevertheless, further data on long-term prognosis are needed. In one series, 72.6% of affected patients recovered their olfactory function within the first week after resolution of the disease[11], while in a survey of non-hospitalized patients with olfactory or gustatory dysfunction from Northern Italy, resolution rates after nearly a month from symptom onset were 87% and 82%, respectively[17].

CNS manifestations

Cerebrovascular diseases (CVD) were reported in 0.5-5.9% of COVID-19 patients and, of these, the most common type was acute ischemic stroke (0.4-4.9%) followed by hemorrhagic stroke (0.2-0.9%) and cerebral venous thrombosis[4].

These rates of cerebrovascular events associated with COVID-19 are mostly based on observational cohort studies on hospitalized COVID-19 patients from different epicenters around the world, mainly in China, Europe, and the US[5,18-21]. These reports reflect a wide variety of populations in terms of disease severity, comorbidities, and follow-up, all of which are likely to contribute to the rate of cerebrovascular events. Overall, the mean age of patients with COVID-19 and stroke appears to be similar to those without COVID-19. But the relative risk of CVD may vary according to the severity of the disease. In particular, early case series suggest that patients with a more severe illness could have a higher risk of developing an acute CVD[22]. These data are also supported by evidence that the incidence of acute CVD was higher in ICU patients (0.8-9.8%)[4].

Several cases of meningoencephalitis (both viral and apparently autoimmune) were reported in COVID-19 patients[4]. Moriguchi et al. described the first case of viral encephalitis with COVID-19, confirmed by cerebrospinal fluid (CSF) analysis[23]. Other cases of meningoencephalitis have been reported in patients in whom CSF was either negative for SARS-CoV-2 or not tested. Isolated meningoencephalitis without any respiratory involvement has also been reported[24,25].

Incidence of disturbances of consciousness and delirium ranged from 3.3% to 19.6% in retrospective studies[4]. Early studies indicate that 20-30% of COVID-19 patients will present with/or develop delirium or mental status changes during their hospitalization, with rates of 60-70% in cases of severe illness at all ages[26]. Encephalopathy is more common in critically ill patients with COVID-19. In a cohort study of 2,088 patients with COVID-19 admitted to an ICU, 55% presented delirium[27] .

A few retrospective studies have reported seizures, with an incidence ranging from 0.5% to 1.4%[4].

Posterior reversible encephalopathy syndrome (PRES) has also been reported and may be due to hypertension and renal failure in some patients[28-30]. In one case series, neuroradiological findings consistent with PRES were seen in over 1%[31].

A few case reports have described patients with clinical and neuroimaging findings consistent with acute disseminated encephalomyelitis (ADEM)[4]. Some patients had myelitis with or without brain involvement. An additional case report describes a case of acute necrotizing encephalopathy in a patient with COVID-19[32].

Three cases of generalized myoclonus were reported from Spain, with normal CSF and imaging findings. In all these patients, myoclonus could not be explained by hypoxia, metabolic cause, or drug effect, and the EEG showed mild diffuse slowing without any epileptic activity. Patients were treated symptomatically with antiepileptic drugs (AEDs) and/or propofol sedation and appeared to recover gradually with immunotherapy[33].

PNS manifestations

All variants of Guillain-Barré syndrome (GBS) such as AIDP, AMAN, AMSAN have been reported in COVID-19 patients[4]. Cases of Miller Fisher syndrome (MFS) were also described, one of these being associated with serum GD1b-IgG antibodies[34]. Both para- and post-infectious patterns are described. GBS was a presenting feature in one case report by Zhao et al.[35]. However, while Toscano et al. reported a series of five patients with GBS, with an interval between COVID-19 onset and symptoms of GBS ranging from 5 to 10 days[36], a cohort study from the UK failed to show any specific association between GBS and COVID-19 infection[37]. Therefore, it is still not certain if there is a potential causal association of COVID-19 with the risk of GBS.

Several peripheral nerve and plexus syndromes have been reported in patients with COVID-19 including cranial neuropathies (facial nerve palsy, ocular motor neuropathies, Tapia syndrome), peripheral motor neuropathy, and neuralgic amyotrophy[38-40].

Since myalgia and fatigue are common symptoms in COVID-19, some speculate that COVID-19 may be associated with a viral myositis, although there is still no conclusive evidence for this[41]. Different studies have reported the incidence of rhabdomyolysis to be 0.2-2.6%[4].

Long-term effects

The issue of the long-term effects of the SARS-CoV-2 infection is much more complex. These have been described in various ways, including "Long COVID" and "post-COVID syndrome". In particular, there is some evidence to suggest that both patients recovering from a severe illness and patients with milder symptoms who never required hospitalization may report prolonged neurological symptoms that persist for weeks to months after the acute infection[42-44].

In a survey of 180 non-hospitalized COVID-19 patients, over 50% reported having at least one persistent symptom (most frequently fatigue and anosmia) approximately 4 months after the onset of symptoms[45]. Moreover, preliminary data related to extrapyramidal disorders[46] and cognitive disturbances[47] are still coming in, but the whole picture of the consequences of the pandemic will only be clarified after longitudinal studies are completed.

Take-home message

- Over one-third of patients with COVID-19 develop neuropsychiatric symptoms.
- Central nervous system manifestations are more common than peripheral nervous system symptoms.
- The most common neurological manifestations are smell and taste disturbances, myalgia, headache, encephalopathy, and dizziness.
- Patients may report long-lasting neurological symptoms that persist for weeks to months after the acute infection.

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