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Impact of SARS-CoV-2 on the nervous system

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ABSTRACT

Introduction. The ongoing COVID-19 pandemic is the largest global public health struggle. The spread of the novel coronavirus had resulted in almost 7 million deaths worldwide by January 2023.

State of the art. The most common symptoms during the acute phase of COVID-19 are respiratory. However, many individuals present various neurological deficits at different stages of the infection. Furthermore, there are post-infectious complications that can be present within weeks after the initial symptoms. Both the central and peripheral nervous systems (CNS and PNS, respectively) can be affected. Many potential mechanisms and hypotheses regarding the neuropathology behind COVID-19 have been proposed.

Clinical implications. The distribution of neurological symptoms during COVID-19 infection among studies differs greatly, which is mostly due to differing inclusion criteria. One of the most significant is incidence involving CNS circulation. In this review, we present basic information regarding the novel coronavirus, the possible routes along which the pathogen can reach the nervous system, neuropathology mechanisms, and neurological symptoms following COVID-19.

Future directions. It seems that many factors, resulting both from the properties of the virus and from systemic responses to infection, play a role in developing neurological symptoms. The long-term effect of the virus on the nervous system is still unknown.

Key words: COVID-19, SARS-CoV-2, nervous system, stroke, long-COVID

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Introduction

In March 2020, the World Health Organisation (WHO) declared coronavirus disease 2019 (COVID-19) to be a pandemic. The first cases had been reported from Wuhan, China, three months earlier. Since then, the global spread of the novel coronavirus has resulted in almost 7 million deaths worldwide [1]. Despite the introduction of vaccination, for many reasons the number of cases is still high, and the ongoing pandemic is today's biggest global public health struggle.

Coronaviruses (CoVs) belong to the subfamily Coronavirinae (family Coronaviridae), which is divided into four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. The first two exclusively infect mammals, manifesting with respiratory tract symptoms in humans and gastrointestinal symptoms in animals [2]. The latter two genera

primarily infect birds, with rare exceptions for mammals. Therefore, the range of hosts for CoVs is very wide, and it is common for interspecies spillover to occur for new CoVs [3].

Numerous studies based on wild animals have revealed the greatest variety of coronaviruses in bats and avian species. This indicates that they are natural reservoirs of the viruses [2]. Furthermore, phylogenetic studies of these species suggest the possible coevolution of the virus with their hosts. However, many coronaviruses found in bats and other mammals are the results of recent cross-species transmission [4]. Studies based on analysis of the RNA-dependent RNA polymerase genomic region indicated that the most recent common ancestor for the four coronavirus genera occurred around 10,100 years ago [2]. However, more recent estimations suggest that the history of coronaviruses goes back much further as standard nucleotide models may underestimate the timeline of evolution by millions of years [5].

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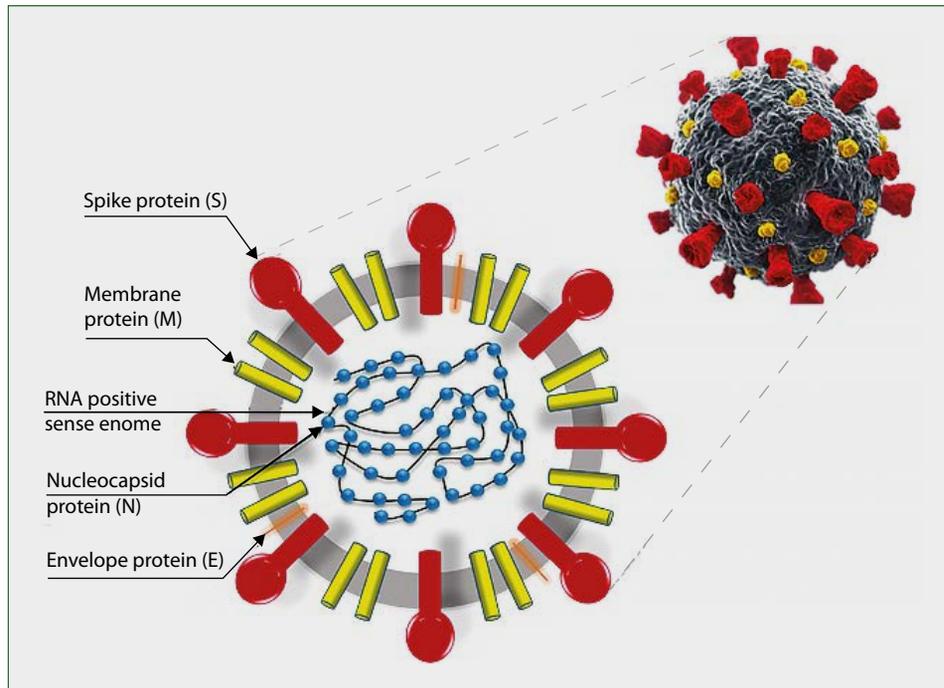


Figure 1. SARS-CoV-2 viral particle

SARS-CoV-2 is a relatively large, enveloped, single-stranded sense RNA virus. Coronaviruses are spherical with club-shaped spikes on the surface. There are four major structural proteins in the coronaviral genome: the spike (S), membrane (M), envelope (E), and nucleocapsid (N) protein [6]. The S protein is responsible for binding to the host cell surface receptors and viral entry. It is composed of two sub-units: S1, which contains a receptor-binding domain that binds to the host receptor angiotensin-converting enzyme 2 (ACE-2), and S2, which mediates viral cell-membrane fusion [7]. The S protein has a key role in the invasiveness of the virus and has made it the most common target for vaccine development [8]. The M protein defines the shape of the envelope, while E and N proteins are involved in viral assembly and budding (Fig. 1).

Recent coronavirus outbreaks

In recent decades, two major coronavirus outbreaks have occurred. The first was caused by severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), and the second by Middle East respiratory syndrome coronavirus (MERS-CoV). Both had much higher fatality rates (c.10% and 35–40%, respectively) compared to the novel SARS-CoV-2 coronavirus (c.2–3%) [9, 10]. The cellular target of SARS-CoV-1 and SARS-CoV-2 is identical: ACE-2. The genetic sequence of SARS-CoV-2 is about 80% similar to that of SARS-CoV-1 and 55% to that of MERS-CoV [11, 12].

A question naturally arises as to why SARS-CoV-2 is so much more infectious compared to SARS-CoV-1. There are a few differences that might partly explain this. Even though

both target the same receptor, small structural differences enable SARS-CoV-2 to make a stronger bond with it. Moreover, the novel coronavirus has much higher reproduction numbers and a greater affinity for the upper respiratory tract [13].

A very interesting aspect reflecting the spread of both viruses is the peak virus load. It appears that the highest load for SARS-CoV-2 occurs at the time of symptom onset or in the first few days, giving it the highest infectiousness potential. In comparison, the peak virus load for SARS-CoV-1 is found in the second week of the infection. Therefore, early case detection was much more effective for the previous coronavirus and contributed to limiting its infectiousness [14]. Basic data regarding recent coronavirus outbreaks is presented in Table 1.

Current variant of concern

Every mutation to the viral genome can significantly affect the pathogenic potential of the virus. RNA viruses evolve and mutate faster than DNA viruses [17]. From the beginning of the COVID-19 pandemic, SARS-CoV-2 evolved numerous times. Some of the variants have been marked as variants of concern (VOCs) by the WHO. This means that their threat to populations is considered to be high based on viral transmissibility, the level of protection that is provided by vaccination, the virulence, and the impact on global health [18].

The fifth VOC is the Omicron variant, which is currently circulating. What makes this a subject of concern is its increased transmission efficiency. Omicron is the most mutated VOC so far [19]. In an extremely short time, the new variant replaced the previous Delta VOC. Furthermore, Omicron

Table 1. Recent coronavirus outbreaks [12, 15, 16]

Pandemic	Pathogen	Year	Original Location	Hosts	Reservoir/ /intermediary host	Territories	Cases	Fatal cases	Viral replication efficiency comparison
Severe acute respiratory syndrome (SARS)	SARS-CoV	2002–2003	Foshan, China	Bats	Civet cats	29 countries	> 8,000	774	↑
Middle East respiratory syndrome (MERS)	MERS-CoV	2012	Jeddah, Saudi Arabia	Bats	Camels	27 countries	~ 2,500	858	↑↑
COVID-19	SARS-CoV-2	2019-ongoing	Wuhan, China	Bats	Pangolins	228 countries and territories	~ 650,000,000	> 6.5M	↑↑↑

has shown partial resistance to immunity induced by early COVID-19 vaccines, as well as an increased risk of reinfection due to multiple mutations [20]. However, it seems that Omicron is less pathogenic compared to previous VOCs [21].

Respiratory tract infection

During the pandemic, it became clear that people of all ages are at risk of being infected with SARS-CoV-2 [22, 23]. However, the clinical manifestation varies due to the susceptibility of the host, ranging from mild symptoms to severe respiratory failure. Most of those who are prone to severe infection and require hospitalisation are individuals over 60 years old with comorbid diseases [24]. In children and young adults, many infections are asymptomatic. In the majority of cases, the human-to-human transmission of SARS-CoV-2 takes place through respiratory droplets (and much less commonly through fomites or aerosols). Both symptomatic and asymptomatic hosts take part in virus transmission. Therefore, there are many difficulties limiting the spread of the pandemic.

First of all, the virus binds to epithelial cells of the respiratory tract, replicates, and migrates down to alveolar epithelial cells in the lungs. The first targeted host receptor is the ACE-2 receptor. The rapid replication and interferences with ACE-2 peptidase activity can lead to a strong immune response [25]. The high virus load from the beginning of the infection is one of the factors raising the risk of a severe clinical course of COVID-19, especially in elderly patients [26]. In some patients, excessive immune reaction called the ‘cytokine storm’ is triggered by SARS-CoV-2 and manifests as acute overproduction and uncontrolled release of pro-inflammatory markers. This leads to the most severe clinical courses of COVID-19, such as acute respiratory distress syndrome (ARDS).

The most common symptoms during the acute phase of COVID-19 are fever, cough, dyspnoea, malaise, fatigue, sputum/secretion, smell, and taste abnormalities. Some less common symptoms are dermatological manifestations, myalgia, sore throat, rhinitis, chest pain, and diarrhoea. The prevalence of neurological symptoms during the acute phase varies

among studies. However, in most analyses, it is estimated at about 20% [27]. Critical disease requiring hospitalisation with respiratory failure, shock, or multiorgan dysfunction is reported in about 5% of patients [28]. The overall case fatality rate has been estimated to be 2% throughout the pandemic [29]. During the first two years of the pandemic, COVID-19 was the third leading cause of death in the United States [30]. Not all infected individuals develop clinical symptoms. The number of asymptomatic carriers is very hard to establish because in most countries the strategy was to test people presenting with symptoms. However, it is estimated that asymptomatic carriers account for one in three infected individuals [31].

Routes leading SARS-CoV-2 to nervous system

There are numerous complications involving the nervous system after COVID-19 [32]. They have been reported at every stage of infection, from the acute phase two weeks after recovery from respiratory symptoms. In different mechanisms, both the central and peripheral nervous systems (CNS and PNS, respectively) can be affected. Since the beginning of the pandemic, there has been much discussion about whether the virus has neuroinvasive properties, whether it triggers a misdirected immune/autoimmune response toward the nervous system, or whether the neurological manifestation is the result of mainly cardio-respiratory distress. Over time, much clinical evidence of neurological symptoms has been reported all over the world.

The range of neurological manifestations is very wide. Apart from clinical evidence, SARS-CoV-2 RNA has been detected in cerebrospinal fluid (CSF) in a meningitis case and in the olfactory bulb post-mortem in several cases, and hypometabolism of the limbic cortex was detected in individuals with persistent hyposmia after infection [33–35]. A study based on the MRI images from Biobank in the UK examined individuals before and after SARS-CoV-2 infection. The results showed changes in a significant proportion of patients involving mainly limbic parts of the brain. It is not yet known

whether the deterioration is reversible, permanent, or may lead to further neurodegeneration, as observational times are not currently sufficient [36].

Initially, most reported neurological symptoms were said to be caused by a systemic reaction to COVID-19 (inflammation, hypoxia, etc.). However, the ACE-2 receptor, the primary target for SARS-CoV-2, is not only expressed in airway epithelia but also in kidney cells, the small intestine, lung parenchyma, vascular endothelium, and the CNS (e.g. the cerebral cortex, striatum, brainstem, choroid plexus, paraventricular nuclei of the thalamus, middle temporal gyrus, and posterior cingulate gyrus) [37]. Nevertheless, a low level of ACE-2 expression in the brain has raised concern that the virus itself could be responsible for the neurological symptoms. Several studies have attempted to explain that there are more proteins that can be used by the virus to infect cells (e.g. neuropilin 1, BASIGIN, cathepsin L, and furin) with a broader expression in the human brain [38].

There is much uncertainty about how the virus causes various neurological symptoms and what the mode of entry is. Several possible mechanisms have been proposed. The first is neuroinvasion via the olfactory tract. Alterations of smell and taste are common in COVID-19. These symptoms are explained by an olfactory cleft oedema, olfactory epithelium, and olfactory bulb injury in the course of the infection [39]. However, the possibility of coronavirus migration by retrograde axonal transport to the olfactory bulb and eventual spread to the hippocampus and other brain structures have been previously described in animal models [40]. Permanent anosmia has also been described in individuals who recovered from herpes simplex encephalitis, often with other neurological dysfunctions (e.g. cognitive deficits) [41]. The possibility of the virus entering through the trigeminal nerve and the vagus nerve has also been considered [42].

The other possible route of infection is via hematogenous access. Post-mortem studies show the presence of capillary injury to the lungs with the presence of SARS-CoV-2, opening the door to pulmonary microcirculation [43]. Zeng et al. [44] analysed samples of almost 100 patients hospitalised due to COVID-19, and 41% of blood samples were positive for SARS-CoV-2 RNA. Notably, even in the setting of a pathogenic factor in the bloodstream, the brain is rarely affected due to the presence of protection by natural barriers, such as the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCB). However, more and more evidence suggests that SARS-CoV-2 may contribute to dysfunction and loss of integrity of these protective structures' mechanisms.

The cytokine storm and peripheral hyperinflammatory state may indirectly contribute to impaired BBB permeability [45]. Among others, IL-1, TNF- α , IL-6, and IL-12 can disintegrate the BBB [46, 47]. Another factor contributing to BBB disruption is hypoxia, which is common in patients with COVID-19 [48]. Therefore, it is possible that several factors play a role in the end result of SARS-CoV-2 crossing the natural brain barriers.

One analysis examined the cerebrospinal fluid of 127 individuals with COVID-19 and neurological involvement from 17 European university centres, and the results most frequently showed BCB dysfunction. The authors pointed out that persistent dysfunction accompanied by high cytokine levels may contribute to acute and distant neurological complications [49]. Certain viruses can infiltrate the cerebrospinal fluid through the choroid plexus (e.g. Zika virus) [50]. One study tested whether there would be any tropism of the virus towards human organoid pluripotent stem cells of the choroid plexus. The result of the experiment was positive, but the significance of these findings is unclear in terms of the neuroinvasive properties reflected in clinical symptoms [51].

Disruption of the BBB in the course of COVID-19 has been demonstrated in several studies. Therefore, another hypothesis of SARS-CoV-2 entering the CNS arises: the migration of leukocytes carrying the virus through weakened brain barriers. This pathway is called the 'Trojan horse' and was first proposed for other viruses such as human immunodeficiency virus 1 and tick-borne encephalitis virus [52]. Leukocytes entering the CNS produce pro-inflammatory cytokines and chemokines, and chemokine production by astrocytes can follow in terms of inflammation. Such a sequence of events may create a vicious circle of neuroinflammation. Additionally, hypothetically, this route enables direct infection of vascular endothelial cells in the brain spreading directly to glial cells [53]. However, the possibility of SARS-CoV-2 using the 'Trojan horse' strategy has not been fully investigated.

Neuropathology mechanisms

The CNS and PNS can be targeted by SARS-CoV-2 through several mechanisms. Evidence indicates that the end effect of neuronal deficit may be caused by indirect influence of the virus and, to a lesser extent, direct influence. The cascade of systemic reactions, like the overproduction of cytokines, as a hallmark of the cytokine storm may have neurotoxic effects and contribute to BBB permeability [54]. Furthermore, hyperactivation of the immune system can lead to thrombosis in the venous and arterial circulation.

Several mechanisms leading to thrombogenesis and a number of dysfunctions of the coagulation system of SARS-CoV-2 have been proposed, such as platelet activation, thrombocytopenia, leukocyte activation, overproduction of inflammatory pro-aggregating cytokines, endothelial dysfunction, and complement system activation [55]. Therefore, complications that have been frequently observed in the course of SARS-CoV-2 infection include cardiac injury, especially in individuals with pre-existing cardiovascular diseases, and acute ischaemic stroke [56]. It is worth mentioning again that endothelial cells express ACE-2, the main target receptor for SARS-CoV-2.

It is common for patients with COVID-19 pneumonia to develop hypoxemia. Furthermore, many authors present examples of 'silent hypoxia' (also known as 'mysterious hypoxia' or 'asymptomatic hypoxia'), which presents as hypoxia without appropriate signs of respiratory discomfort [57]. Prolonged hypoxia can lead to many neurological complications. Most common are oligodendroglial cell injury, induced demyelination, white matter microhaemorrhages, and BBB disruption. In the course of acute hypoxemia, hypoxic ischaemic encephalopathy may occur [58]. The typical MRI changes for hypoxia, excluding ischaemic infarcts, were found in patients from many hospitals after severe COVID-19 [59].

The direct impact of SARS-CoV-2 on the nervous system is a subject of constant discussion. However, beyond hypothetical considerations, in tissue-based neuropathological analyses, SARS-CoV-2 has been detected in the brain by reverse transcriptase polymerase chain reaction, immunohistochemistry, and electron microscopy [60]. The significance of these findings is unclear. Questions remain about how much it contributes to some acute neurological symptoms, and whether the virus has neurodegenerative potential in long-term observation.

In other post-mortem brain tissue analyses of patients who died from COVID-19, the activation of microglia and infiltration of cytotoxic T lymphocytes was present with the greatest intensity in the brainstem and cerebellum [61]. Microglia are the immune cells of the brain. They maintain homeostasis in the CNS, and become activated in response to injury, inflammation, or immunological stimuli [62]. Dysregulation of these cells may result in their hyperactivation, escaping neuronal control and leading to persistent inflammation and neurotoxicity [63]. Interestingly, human microglia express ACE-2. Therefore, some authors suggest that microglial activation by SARS-CoV-2 infection may be an important mechanism leading to neurological complications in the course of COVID-19 [64].

Environmental factors play an important role in the pathogenesis of autoimmune disorders. Some are considered to be a trigger in susceptible individuals (such as genetically and immunologically predisposed individuals). Among other microorganisms, certain viruses are connected to several autoimmune neurological disorders. A wide range of pathogens has been described in multiple cases with a temporal relationship to Guillain-Barré syndrome (GBS), such as *Cytomegalovirus*, Epstein-Barr virus, influenza, human immunodeficiency virus, and Zika virus [65, 66].

There are now numerous reports of GBS following COVID-19. Based on studies in animal models, the main mechanism behind GBS is molecular mimicry. An interesting analysis examined selected human proteins associated with immune-mediated neuropathies, which demonstrated that SARS-CoV-2 shares two relevant hexapeptides with human heat shock proteins (60 and 90) [67].

Most relevant neurological symptoms

The distribution of neurological symptoms during COVID-19 infection among studies differs greatly, which is mostly due to different inclusion criteria. Furthermore, there are post-infectious complications that can be present within weeks after initial symptoms. Table 2 presents neurological symptoms frequency of selected large-number analyses of individuals hospitalised due to COVID-19.

Cerebrovascular incidence

In the course of SARS-CoV-2 infection, several cerebrovascular complications have been reported. The incidence involving CNS circulation is estimated to be about 1–2% [75, 76]. The most commonly reported is acute ischaemic stroke, with a high prevalence of the cryptogenic subtype. With a much lower frequency, haemorrhagic stroke and cerebral venous sinus thrombosis have also been observed as a COVID-19 complication [77].

In a large meta-analysis of individuals with ischaemic stroke in the course of COVID-19, patients were younger and less likely to have hypertension compared to the stroke cohort without SARS-CoV-2 infection [78]. In-hospital mortality was higher for individuals with COVID-19, even with similar stroke intervention to that of non-infected patients with acute ischaemia [79]. The combination of the mechanisms described above is blamed for cerebrovascular complications in patients with COVID-19, including dysfunctions of the coagulation in the course of the cytokine storm, activated endothelium, and contribution toward a more permeable BBB.

An important step towards better understanding of the process leading to cerebral circulation dysfunction during COVID-19 is the work of Lee et al. [80]. They examined brain samples from patients who died in the course of SARS-CoV-2 infection and had post-mortem microvascular abnormalities in MRI. Based on the findings, they concluded that immune complexes with complement activation also play a major role in microvascular injury.

Olfactory dysfunction

Loss of smell is one of the most common symptoms accompanying COVID-19 (with a prevalence of up to 84% in some studies) [39]. It appears that alterations in smell perception can be the only symptom of SARS-CoV-2 infection, or can precede other symptoms. Persistent hyposmia affects some survivors, and the rate has been estimated at 7% by Boscolo-Rizzo et al. [81] in one year of observation of 100 patients after mild COVID-19. There is evidence from PET examinations of cortical hypometabolism in COVID-19 survivors with isolated persistent hyposmia.

Table 2. Neurological symptoms during acute/post-acute stage of infection in large analyses of patients hospitalised due to COVID-19

Reference	Country	Study group characteristics	Study group No.	Patients with neurological symptoms No.	Neurological symptoms (% in all patients with neurological symptoms)
Frontera et al. [68]	New York, USA	Hospitalised individuals	4,491	606	Toxic/metabolic encephalopathy (6.8) Ischaemic stroke/TIA (1.4) Intracerebral/Intraventricular haemorrhage (0.4) Seizure (1.6) Hypoxic/ischaemic brain injury (1.4) Movement disorders (0.9) Neuropathy (0.8) Myopathy (0.5) Guillain-Barre syndrome ((0.1)
Karadaş et al. [69]	Turkey	Hospitalised individuals; conscious/able to communicate	239	239	Headache (26.7) Muscle pain (15.1) Sleep disorder (12.6) Smell impairment (7.5) Cerebrovascular disorders (3.8) Trigeminal neuralgia (3.3) Guillain-Barre syndrome (0.4) Restless leg syndrome (1.7)
European Academy of Neurology Neuro-COVID Registry [70]	13 countries	Self-report symptoms; Clinically captured neurological symptoms (in-hospital)	3,083	3,743	Self-reported: Headache (38) Anosmia or ageusia (28) Clinically verified: Acute encephalopathy (49) Coma (17) Stroke (6)
Rifino et al. [71]	Italy	Hospitalised individuals	1,760	137	Ischaemic stroke (27) Haemorrhagic stroke (8) Transient ischaemic attacks (2.9) Cerebral venous thrombosis (0.7) Peripheral neuropathies (22.6) Altered mental status (35.8)
Studat-Neto et al. [72]	Brazil	Hospitalised individuals	1,208	89	Encephalopathy (44.4) Stroke (16.7) Seizures (9) Neuromuscular disorders (5.6) Other acute brain lesions (3.4) Mild nonspecific symptoms (11.2)
Mao et al. [73]	China	Hospitalised individuals (over half with severe infection due to respiratory status)	214	78	Acute cerebrovascular disease (6.5) Impaired consciousness (17.2) Skeletal muscle injury (24.1)
Wnuk et al. [74]	Poland	Hospitalised individuals	200	169	Fatigue (74) Decreased mood (53.8) Myalgia (51.5) Muscle weakness (50.3) Headache (43.8)

Guillain–Barre syndrome

It is hard to determine the accurate number of GBS cases during the COVID-19 pandemic, because most reports come from single case-report studies or case series. There are over 100 reports on GBS following COVID-19 [82]. The time relation in presented cases suggests a post-infectious mechanism. Predominantly, patients present sensorimotor demyelinating GBS, and facial palsy is common [83]. However, it is possible that some are coincidental as the relation is usually uncertain. In a one-year observational study during the pandemic from 14 hospitals in Northern Italy, the incidence of GBS increased by 59%, and half of the cases were positive for SARS-CoV-2 [84]. However, Keddie et al. found no clues suggesting SARS-CoV-2 was causative of the inflammatory polyneuropathy when analysing GBS cases in the UK before and during the COVID-19 pandemic. Furthermore, the number of GBS incidences has actually fallen during the pandemic. The reason for this is unclear, but it may have been caused by national lockdowns reducing the transmission of pathogens inducing GBS (e.g. *Campylobacter jejuni*) [85].

Non-specific symptoms

Numerous neurological symptoms accompanying many respiratory/systemic inflammatory diseases are also present in the course of COVID-19. Headache is commonly reported and is estimated to be present in up to 15% of individuals, with more prevalence in non-hospitalised patients [86][87]. Post-infectious fatigue is detected in numerous viral infections (e.g. SARS coronavirus, West Nile virus, Epstein–Barr virus, enteroviruses, Dengue virus, human herpesvirus-6) and occurs in about 40% of individuals infected with SARS-CoV-2 [88]. An equally high percentage of individuals (up to 44%) present myalgia. The ACE-2 receptor is present in skeletal muscles, which is relevant when taking into consideration the mechanism of action of SARS-CoV-2. Furthermore, interleukin-6 (which is elevated in the cytokine storm) can cause myalgia by inducing prostaglandin E2 production [89].

Other observed sequelae of COVID-19 infection are encephalopathy and encephalitis. These life-threatening conditions are triggered by intense hypoxic and metabolic changes. In most cases, individuals who had encephalopathy/encephalitis in the course of the infection were either severely or critically ill (predominantly on mechanical ventilation) [90].

Symptoms present beyond acute infection

A typical COVID-19 infection lasts up to four weeks. However, there are increasing reports that a large percentage of patients suffer from post-infectious symptoms which do not resolve for weeks, or even months. The terminology denoting lasting symptoms varies among studies, but common terms include ‘long COVID’, ‘post-acute sequelae of

COVID-19’, ‘long haulers’, ‘ongoing symptomatic COVID-19’, ‘post-COVID-19 syndrome’, ‘post-acute COVID-19’, ‘persistent COVID-19 symptoms’, and ‘long-term COVID-19 effects’. Most authors divide persistent symptoms into those which last between four and 12 weeks after the initial infection from those lasting over 12 weeks. The most common symptom in most studies is fatigue, which is present in more than half of affected individuals (58%) [91]. Other common symptoms of long COVID are headache, sleep disorders, malaise, memory issues, attention disorders, hair loss, dyspnoea, ageusia, anosmia, cough, memory loss, chest discomfort, anxiety, depression, and digestive disorders [91, 92].

A term that has repeatedly come up is ‘brain fog’ or ‘COVID fog’ (first used among patients and social platforms and later in clinical practice). This condition refers to cognitive impairment among patients who have survived COVID-19. The impairment can affect executive functioning, processing speed, category fluency, memory encoding, and recall [93]. The explanation for these cognitive dysfunctions lasting months after the acute phase of infection is not clear. However, some known pathologies may play a role, such as the activation of microglia (dysfunctional) and broad cytokine activation. Interestingly, among many elevated cytokines, CCL11 can be elevated in the plasma of patients with long COVID and has also been linked to cognitive impairment observed in normal ageing [94]. In a large 6-month observational study of patients after SARS-CoV-2 infection, besides persisting neurological symptoms, many individuals had psychiatric sequelae from COVID-19 (e.g. an increased risk of psychotic disorders was detected) [95].

Conclusions

There are still multiple questions regarding COVID-19. We know much about the virus itself based on previous coronavirus studies and recent findings. However, the scale of the spread of SARS-CoV-2, its constant mutation, and multiple complications after initial infection make it a major and current threat to global health. The mechanism that leads to neurological complications requires much research and observation on many levels. The long-term effect of the virus on the nervous system is still unknown.

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