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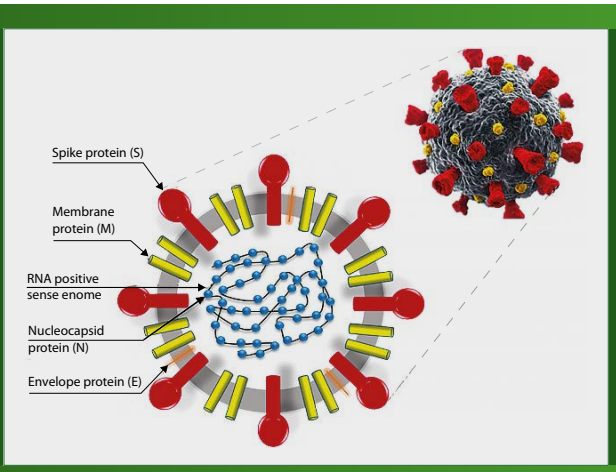

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Neurologia i Neurochirurgia Polska also known under the name of *Polish Journal of Neurology and Neurosurgery (PJNNS)* is a premier research and educational platform of the Polish Neurological Society and Polish Society of Neurosurgeons. It has a long and accomplished history dating back to earlier days of the XX Century. The journal publishes the results of basic and clinical research contributing to the understanding, diagnosis, and treatment of neurological and neurosurgical disorders.

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Table of Contents

EDITORIAL NOTE

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Journal's Leading Topics & Thank You to Our Reviewers

Zbigniew K. Wszolek[1], Jarosław Sławek[2]

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[2]Co-Editor-in-Chief, Department of Neurology and Psychiatry, Medical University of Gdansk, Gdansk, Poland

Since 2021, Neurologia i Neurochirurgia Polska (the Polish Journal of Neurology and Neurosurgery, PJNNS) has published twice a year an issue that contains a compilation of articles on various aspects of a particular neurological subspecialty topic, a Leading Topic (LT). Each LT consists of manuscripts including invited reviews, reviews, and original research articles. Each LT is accompanied by an editorial written by the LT editor appointed by the PJNNS editors-in-chief. So far, PJNNS has published four LTs (Tab. 1).

In this very first issue of 2023, we are pleased to present the fifth LT, this time on neurological complications related to COVID-19. This LT has been edited by Prof. Alina Kułakowska from the Medical University of Bialystok in Bialystok, Poland, the President Elect of the Polish Neurological Society. This is also the first issue in which LT articles have made up the entire issue. As the Journal's editors, we are very proud of the success of LT. LT articles are frequently downloaded and extensively cited. We plan to continue this feature in forthcoming issues of PJNNS.

We would also like to thank our reviewers for providing assistance to PJNNS by reviewing the submitted manuscripts. They are partly responsible for the ever-improving bibliometrics of the Journal. We are particularly grateful to those reviewers who have provided us with multiple reviews. Table 2 lists those who provided reviews for PJNNS in 2022. The names of reviewers who provided three or more reviews are highlighted in green.

Table 1. Leading Topic issues

Issue (number/year)	Leading Topic Editor
3/2022	Alicja Kalinowska-Łyszczarz, M.D., Ph.D., Poznan University of Medical Sciences, Poznan, Poland [1]
1/2022	Natalia Szejko, M.D., Ph.D., Medical University of Warsaw, Warsaw, Poland [2]
6/2021	Joanna Siuda, M.D., Ph.D., Medical University of Silesia, Katowice, Poland [3]
2/2021	Jarosław Sławek, M.D., Ph.D., Medical University of Gdansk, Gdansk, Poland, and Wolfgang H. Jost, M.D., Ph.D., Parkinson-Klinik Ortenau, Wolfach, Germany [4]

Table 2. Alphabetical list of PJNNS reviewers in 2022. Names of reviewers who provided three or more reviews appear in green

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3. Wojciech Ambrosius, Poland
4. Mohamed Arnaout, Egypt
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Table 2. cont. Alphabetical list of PJNNS reviewers in 2022. Names of reviewers who provided three or more reviews appear in green

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23. Jarosław Dulski, United States
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102. Cesare Zoia, Italy

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INVITED EDITORIAL

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LEADING TOPIC

Leading Topic Editor: Alina Kułakowska, MD, PhD, Department of Neurology, Medical University of Bialystok, Bialystok, Poland

SARS-CoV-2 and the nervous system

Alina Kułakowska

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As guest editor of the current issue of Leading Topic published in the Polish Journal of Neurology and Neurosurgery, I am pleased to present a series of articles regarding the influence of SARS-CoV-2 infection on the nervous system, the occurrence of post-COVID-19 neurological symptoms, and the response to vaccination against COVID-19 in patients suffering from neurological disorders.

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), the pathogen causing COVID-19 disease (coronavirus disease 2019), has caused a pandemic that has resulted in unprecedented global health, social and economic consequences. Worldwide, more than 670 million people were taken ill, of whom 6,823,598 have died. In Poland, the first case of COVID-19 was recorded on 4 March, 2020, 6,378,299 people have fallen ill, and over 118,000 have lost their lives for this reason (data correct as of 29 January, 2023) [1].

SARS-CoV-2 is a single-stranded sense RNA virus belonging to the family Coronaviridae. There are four major structural proteins in the viral particle: the spike (S protein — responsible for binding to the host cell receptor), membrane (M), envelope (E), and nucleocapsid (N) protein. From the beginning of the pandemic, SARS-CoV-2 has evolved numerous times, and mutations to the viral genome have significantly affected its pathogenic potential. Mutations of the virus connected with the highest threat to the population have been named by the World Health Organisation: 'Variants of Concern' (VOCs). Omicron, the current SARS-CoV-2 mutation, has been the most mutated VOC so far [2].

Although SARS-CoV-2 is not a classic neurotropic virus, neurological symptoms in COVID-19 patients have been reported since the outbreak of the pandemic. The maintenance of homeostasis within the central nervous system (CNS) is secured by a number of protective mechanisms, among which the blood-brain-barrier (BBB) plays a key role. Passage through the BBB is rigorously restricted through physical (intercellular and adherence junctions) and metabolic barriers [3]. BBB disruption is one of the key pathological processes involved in various diseases of the CNS [4, 5]. Proinflammatory cytokines and disease-specific proteins (e.g. SARS-CoV-2 derived S protein) can cause BBB disturbances, leading to its increased permeability. Suprewicz et al. [6] have described interactions of the SARS-CoV-2 and its S protein with brain structures and the endothelium that form the BBB. Although SARS-CoV-2 cannot easily cross the BBB, it can enter the CNS through various direct (e.g. using immune cells as a carriage — 'Trojan horse' phenomenon) and indirect (e.g. increased permeability of the BBB caused by chronic hypoxia and cytokine storm) mechanisms.

In the acute period of COVID-19, the most frequently noted problems of the nervous system are: encephalopathy, coma and strokes, as well as headaches and olfactory disorders (Tab. 1). On the other hand, meningoencephalitis and encephalitis have been rarely diagnosed [7–9]. Predisposing factors for the onset of neurological disorders include older age, male sex, Caucasian race, and a history of neurological disease. The co-occurrence of encephalopathy, coma or stroke during SARS-CoV-2 infection significantly increases the risk

Table 1. The most common neurological and psychiatric disorders in patients with COVID-19 [7, 35]

In the acute period of COVID-19	At 6 months after COVID-19
Encephalopathy	Anxiety disorders
Stroke	Mood disorders
Coma	Insomnia
Headache	Cognitive deficit ('brain fog')
Olfactory and gustatory disorders	Psychotic disorders

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of death [7]. The pathomechanism of encephalopathy in the course of COVID-19 is not yet fully understood. However, strokes are usually caused by thromboembolic disorders observed in SARS-CoV-2 infection [10]. Polish neurologists concerned with the treatment of stroke have diligently conducted epidemiological research into stroke in the course of COVID-19 [11–15], and have actively participated in international studies [16].

Headaches and disorders of smell and taste are also frequently reported by patients with COVID-19 [7]. Headaches are symptomatic, and their causative factors may include fever and chronic hypoxia in the course of the underlying disease, or drugs used in its treatment. Straburzynski et al. [17] have attempted to explain the aetiopathogenesis of headaches due to COVID-19 in relation to the innate immune response to viral infection. Some factors in innate immunity have been shown to facilitate headache (e.g. interferons, interleukin (IL) –1-β, IL-6, and tumour necrosis factor). The virus may also cause headache by the activation of pattern recognition receptors (e.g. Toll-like receptor 7). In turn, olfactory disorders in most patients occur in the acute period of COVID-19 and are transient, resolving after a few weeks, or even days. It is assumed that in such cases the cause of anosmia/hyposmia is the depletion of sustentacular cells caused by the SARS-CoV-2 infection and their subsequent restoration by days 10–14 post-infection. However, in some patients, the sense of smell is permanently damaged [18]. This is quite difficult to explain because olfactory sensory neurons do not express a receptor protein for SARS-CoV-2, and are not infected or destroyed by this virus.

However, it has been shown by Zazhytska et al. that the virus can alter cellular morphology and the transcriptome of cells it cannot infect, e.g. olfactory sensory neurons [19]. SARS-CoV-2-mediated nuclear reorganisation is non-cell autonomous. Downregulation of olfactory pathways may explain COVID-19-induced anosmia. These findings help us to understand how it is possible that SARS-CoV-2, which directly infects only about 1% of the patient's body cells, can cause severe damage to so many different organs. The results obtained by Zazhytska et al. [19] provide a potential explanation for neurological disorders caused by a virus with no tropism to neurons.

Analysis of the results of magnetic resonance imaging collected by the UK Biobank showed that patients who had COVID-19, compared to those who did not suffer from the infection, have changes suggesting damage in areas functionally related to the primary olfactory cortex, reduction in the thickness of grey matter in the orbitofrontal cortex and parahippocampal gyrus, and greater generalised brain atrophy. People who have recovered from SARS-CoV-2 infection have also shown impairment of executive functions [20]. These results raise some concerns about the future risk of developing neurodegenerative diseases in patients who have had this infection.

However, as indicated in the article published in this issue [21], based on the analysis of publications that appeared up until the end of November, 2022, post-COVID-19 parkinsonism is very rare, and the described cases of parkinsonism, being temporally related to COVID-19, seem to have a very diverse aetiology. An analysis of the literature [22] indicates that the most common hyperkinetic movement disorders associated with a history of SARS-CoV-2 infection include myoclonus and ataxia, whereas chorea, tremor and dystonia are extremely rare. Interestingly, hyperkinetic disorders found after COVID-19 seem to have an autoimmune basis and respond well to treatment with glucocorticoids and immunoglobulins [23].

Clinical observations indicate that many COVID-19 patients, after the acute period of the disease when the virus RNA is no longer detected in their body, continue to report chronic signs/symptoms resulting from the dysfunction of various organs and systems [24, 25]. The phenomenon of persistence of signs/symptoms four weeks after the onset of SARS-CoV-2 infection has been referred to as 'post-COVID syndrome'. A similar persistence of symptoms after infection was also observed during epidemics caused by other coronaviruses, such as SARS (severe acute respiratory syndrome coronavirus) in 2003 and MERS (Middle East respiratory syndrome) in 2012. Generally, there are two periods of post-COVID syndrome: the interval between the 4^{th} and 12^{th} weeks from the onset of the disease (subacute post-COVID syndrome) and the period beyond 12 weeks from the onset of the first symptoms of COVID-19 (chronic post-COVID syndrome) [26].

Reports on the health consequences of COVID-19 indicate that post-COVID syndrome is relatively common. A follow-up of 488 patients in the USA 60 days after the onset of COVID-19 showed that 32.6% had persistent symptoms, including 18.9% who developed new symptoms or experienced exacerbation of their existing symptoms. The most commonly reported symptoms were shortness of breath when climbing stairs (22.9%), cough (15.4%), and persistent loss of smell and/or taste (13.1%) [27]. A post-acute COVID-19 Italian study [2] showed the persistence of symptoms after approximately 60 days from the onset of COVID-19 in 87.4% of 143 patients. Fatigue (53.1%), dyspnoea (43.4%), arthralgia (27.3%) and chest pain (21.7%) were most frequent, with 55% of the patients reporting at least three symptoms. Quality of life, as assessed in the EuroQol scale [28], was reduced in 44.1% of the respondents. Similarly, a French study which included 150 patients after COVID-19 showed the persistence of symptoms in approximately two thirds of them after approximately 60 days from the onset of the disease [29]. Other studies, including those conducted in the UK (assessment of 110 patients 8–12 weeks after admission to hospital) [30] and in Spain (277 patients 10–14 weeks after disease onset) [31] yielded similar results. Fatigue, shortness of breath, post-traumatic stress disorder, depression, anxiety, trouble concentrating and sleep disturbances were reported in at least 30% of subjects.

Table 2. The risk trajectories of neurological and psychiatric disorders at 2 years after COVID-19 [38]

Risk returned to baseline	Risk still increased
Anxiety disorders	Cognitive deficit ('brain fog')
Mood disorders	Dementia
	Psychotic disorders
	Epilepsy or seizures

In Wuhan, China, a prospective study was conducted (The Post-acute COVID-19 Chinese Study) to assess the long-term consequences of COVID-19 [32]. A total of 1,733 patients were examined six months after the onset of the disease. The follow-up involved an interview (the subjects also completed appropriate questionnaires), physical examination, a 6-minute walk test (6MWT) [33], laboratory blood tests, and in some cases specialist examinations evaluating the function of the respiratory system, computed tomography and ultrasound imaging. Most patients (76%) reported at least one complaint. As in other studies, muscle fatigue/weakness (63%), sleep disorders (26%), anxiety/depression (23%), disorders of smell (11%) and appetite (7%), headache and muscle pain (2%) were most commonly reported. It has been shown that female sex predisposes to fatigue and anxiety/depression [32].

In the course of post-COVID syndrome, symptoms from various organs may occur, but it is the nervous system that is most frequently affected [34]. In order to assess the neurological and psychiatric consequences of COVID-19, a retrospective study was conducted in the USA using electronic medical records. Data from 236,379 patients was analysed. It was shown that within six months of contracting COVID-19, 33.62% of them had a neurological or psychiatric diagnosis, and in 12.8% this diagnosis was made for the first time (Tab. 1). A more severe course of COVID-19 increased the risk of developing a disease of the nervous system — a neurological or psychiatric issue was found in 46.42% of patients who required hospitalisation in an intensive care unit due to COVID-19 [35].

Most observations indicate that a more severe course of SARS-CoV-2 infection (defined, for instance, as the need for hospitalisation in an ICU or the need for passive and/or active ventilation) predisposes to post-COVID syndrome [30, 32, 36]. This fact is also confirmed by the observation of Polish patients suffering from multiple sclerosis (MS) treated with disease-modifying drugs who have survived SARS-CoV-2 infections [37].

Taquet et al., continuing their previous retrospective study [35] over a longer 2-year period, analysed the persistence of various nervous system ailments in a group of 1,284,437 patients who had recovered from COVID-19. It was shown that the increased incidence of mood and anxiety disorders was transient. However, the increased risk of psychotic disorder, cognitive deficit, dementia, epilepsy or seizures persisted throughout (Tab. 2). The differing trajectories may suggest a different pathogenesis for these outcomes. The neurological and psychiatric outcomes were similar during the Delta and Omicron variant waves [38].

In turn, Chatys-Bogacka et al., retrospectively using a neuropsychological questionnaire specially designed for this purpose, searched for demographic factors influencing the incidence and course of post-COVID symptoms over time. They found that in patients who did not require hospitalisation due to COVID-19, the occurrence and duration of COVID-19-associated brain fog depended on sex. Women reported more frequent problems with writing, reading, counting and communicating thoughts. However, there were no sex-related differences in experiencing problems with multitasking, remembering information from the past, determining the current date or field orientation [39]. Similarly, retrospectively assessing post-COVID fatigue in patients requiring prior hospitalisation due to COVID-19, Mazurkiewicz et al. found this symptom in the majority of patients, and noted that the presence of fatigue was predicted by female sex [40].

Since the beginning of the COVID-19 pandemic, much attention has been paid to patients suffering from autoimmune diseases, and neurologists have been particularly concerned about patients treated with immunosuppressive drugs [41–43].

In this issue, we also present two articles concerning the impact of SARS-CoV-2 infection on the course of multiple sclerosis [44] and other autoimmune diseases of the nervous system [45]. The introduction of vaccination against SARS-CoV-2 was another challenge in this group of patients. On the one hand, the necessity for vaccinations was beyond doubt [46]; on the other hand, there were concerns about the effectiveness of preventive vaccinations in patients treated with immunosuppressive therapies. Observations of potential side effects of the vaccines used, which ultimately turned out to be safe and well tolerated [47, 48], aroused great interest as well. This edition also includes two articles discussing the immune response to SARS-CoV-2 infection and COVID-19 vaccination [49, 50].

I hope that readers of the Polish Journal of Neurology and Neurosurgery will find this Leading Topic not only interesting but also useful in clinical practice. However, it must be remembered that the story of the COVID-19 pandemic is not yet at an end, and there are still many unknowns about the effects of SARS-CoV-2 on the nervous system.

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INVITED EDITORIAL

This Invited Editorial accompanies a Short communication, see page 131

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LEADING TOPIC

Leading Topic Editor: Alina Kułakowska, MD, PhD, Department of Neurology, Medical University of Bialystok, Bialystok, Poland

Electrophysiological and neuroimaging tools to evaluate neurological symptoms, manifestations, and complications in patients with long COVID-19

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According to the latest literature, the SARS-CoV-2 virus is not confined to the respiratory tract, and can affect both the central (CNS) and the peripheral (PNS) nervous systems, leading to neurological symptoms, manifestations and complications after acute infection [1]. Systemic hematogenous or retrograde neuronal spreads are the main mechanisms contributing to short- and long-term neurological impairments after SARS-CoV-2 infection [2–4].

The main neurological symptoms include taste and olfactory dysfunction, myalgia, headache, altered mental status, confusion, delirium, and dizziness, which may present separately. Moreover, neurological manifestations and complications such as stroke, cerebral venous thrombosis, seizures, meningoencephalitis, Guillain–Barré syndrome, Miller Fisher syndrome, acute myelitis, and posterior reversible encephalopathy syndrome (PRES) have also been observed [5].

Clinical and structured assessments are critical to identify neurological impairments after COVID-19; however, several non-invasive neuroimaging techniques can be used to confirm findings on neurological examination, facilitate diagnosis, understand prognosis, and assist in long-term rehabilitation. Non-invasive brain imaging techniques can be classified into structure-based [e.g. computer tomography and magnetic resonance imaging (MRI)], metabolic-based (functional magnetic resonance imaging — fMRI, near-infrared spectroscopy — NIRS, etc.), and electrophysiological-based (mainly electro- and magneto-encephalography).

Structural and metabolic techniques are classically considered as having a very good spatial 'resolution' but a rather poor temporal one, while electrophysiological techniques are seen as having an excellent temporal resolution but a poor spatial one [6].

Among the neuroimaging techniques with high temporal resolution, electroencephalography (EEG) is mainly used in the evaluation of patients after COVID-19. EEG abnormalities are common in patients with COVID-19 and can be correlated with disease severity and pre-existing neurological conditions [7]. EEG studies focus on both cortical excitability (i.e. a qualitative study), and brain electrical activity patterns and their interference in cognitive behaviour (i.e. a quantitative study). Qualitative EEG studies have found frontal sharp waves in nearly all patients with COVID-19 who presented epileptiform discharges [8], bifrontal monomorphic diphasic periodic delta slow waves [9], diffuse background slowing, focal slowing, and frontal intermittent rhythmic delta activity (FIRDA) [10]. In addition, Gogia et al. [11] found that 50% of deceased patients had generalised diffuse severe slowing, indicating a global process. EEG abnormalities have been frequently observed in the frontal region and may serve as potential biomarkers of COVID-19 encephalopathy [7].

Concerning quantitative EEG studies, Cecchetti et al. [12] showed that patients with COVID-19 were characterised by a lower individual alpha frequency (power spectrum) compared to healthy subjects, and patients who showed stronger connectivity in the delta band at baseline concomitantly had better cognitive performance. Some authors have reported brainstem damage after COVID-19, mainly in the reticular activation system and cortical cholinergic projections, which have been previously related to changes in the tonic alpha rhythm in a healthy brain [13–16]. In addition, delta oscillations, especially in the anterior regions of the brain, have been associated with better performance on attention shifting and working memory tasks [17]. Based on nonlinear EEG features, Appelt et al. [18] observed a reduction in brain activity at rest

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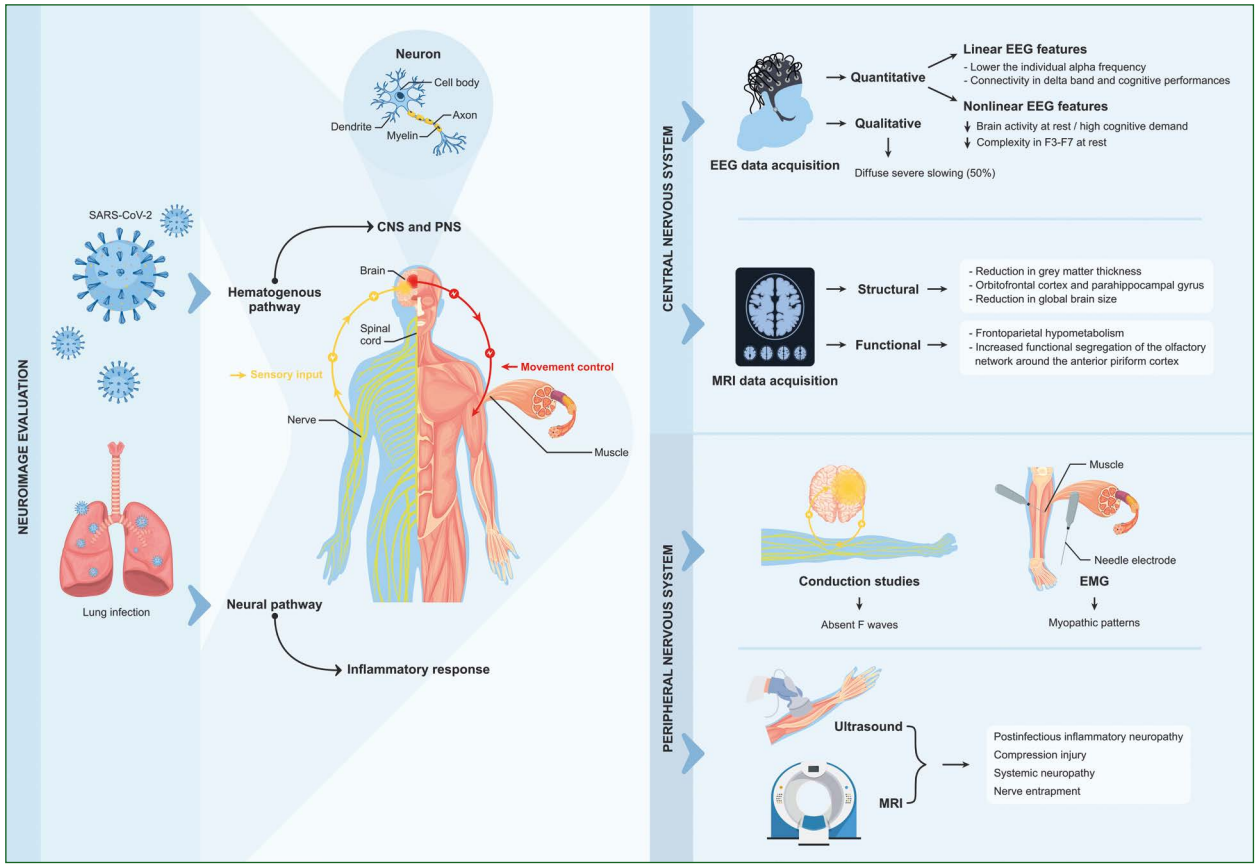

Figure 1. Mechanisms of CNS and PNS infection by SARS-CoV-2, and main neuroimaging tools used for evaluation

in the F2–F4 areas and during high cognitive demands in the F3–F7 areas. In the COVID-19 group at 6–12 months after acute infection, a reduction in signal complexity was found in F3–F7 areas at rest. During the same period, cognitive function worsened, and correlations between nonlinear EEG features and cognitive tests were also observed [18].

Structural and functional brain images have also been used in several studies to understand the impact of SARS-CoV-2 infection on the brain. At the structural level, images can be evaluated through visual or quantitative inspection (volumetry), and previous findings have revealed a lower cortical volume in the orbitofrontal, frontal, and cingulate regions of patients with COVID-19 compared to controls. In addition, cerebrospinal fluid analysis has shown that regional grey matter volume and thickness decrease were negatively associated with neuroinflammation [19]. Multimodal brain imaging data, obtained as part of the UK Biobank imaging study, showed three main changes in SARS-CoV-2 cases: (1) a greater reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus; (2) greater changes in markers of tissue damage in regions functionally connected to the primary olfactory cortex; and (3) a greater reduction in global brain size [20]. At the functional level, studies have shown frontoparietal hypometabolism based on 18F-fluoro-2-deoxy-D-glucose, positron emission tomography (^{18}FDG PET) analysis [21]. Esposito et al. [22] showed that an increased functional segregation of the olfactory network around the anterior piriform cortex node, besides calibrating the clinically observable olfactory impairment, might eventually trigger a counteracting reaction to a more widespread neurological involvement.

These findings support the idea that the PNS should be systematically evaluated after COVID-19, using electrophysiological and structural techniques. Patients with COVID-19 more frequently present absent F waves, which has been attributed to motor neuron hypoexcitability [23], and many authors have reported myopathic patterns on electromyography (EMG), suggesting a direct action of COVID-19 on muscular fibres [24, 25]. In addition, peripheral nerve injury can occur secondarily to post-infectious inflammatory neuropathy, prone positioning-related stretch and/or compression injury, systemic neuropathy, or nerve entrapment from haematoma. Considering these cases, structural imaging, such as high-spatial-resolution MRI of peripheral nerves and high-spatial-resolution ultrasound, can be an excellent diagnostic tool [26].

A summary of the mechanisms of CNS and PNS infection by SARS-CoV-2, as well as the main neuroimaging tools used for evaluation, are described in Figure 1. It must be underlined that clinical and neurological assessments are essential at any stage of COVID-19, and that neuroimaging is a complementary set of techniques with the aim of understanding

the clinical evolution and prognosis of patients, in addition to providing readouts that may serve as potential biomarkers for neurodegenerative diseases occurring after COVID-19.

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Immune response to COVID-19 vaccines in patients with multiple sclerosis treated with disease-modifying therapies

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Scientific reports indicate that multiple sclerosis (MS) does not constitute a factor increasing the probability of contracting COVID-19, and neither does it increase the risk of the disease's severe course or death compared to the general population [1, 2]. There is also no convincing evidence that vaccination increases the risk of the development of MS or a relapse. It is believed that it is safe to vaccinate people with MS, and it would be wrong not to vaccinate solely because of having been diagnosed with MS [3, 4]. Vaccination, along with following the principles of prevention, is the best strategy in the era of COVID-19. An increasing number of studies have shown that when determining the indications for vaccination, as well as when determining the optimal moment to implement, the type of applied treatment modifying the course of the disease (DMT) should be taken into consideration. It has been shown that in people with MS (pwMS), some DMTs, especially the anti-CD20 monoclonal antibodies and sphingosine-1--phosphate receptor modulator (S1PRM), may have an impact on both post-infection and post-vaccination immune response to COVID-19 [5–9].

In this issue of *Neurologia i Neurochirurgia Polska,* the topic of immune response after vaccination and following COVID-19 infection in pwMS is addressed by Kulikowska et al. [10].

The authors of that study analysed the presence of antibodies against the spike (S) and nucleocapsid protein (N) of the SARS-CoV-2 virus in patients with relapsing-remitting multiple sclerosis treated with DMT. The analysis included both after infection and vaccinated individuals. The study included a population of Polish MS patients treated mainly with dimethyl fumarate (DMF), interferon beta (IFN-β), and glatiramer acetate (GA). A minor part of the study group consisted of patients taking fingolimod (FG) and cladribine (CLAD), while there were no patients treated with anti-CD20 monoclonal antibodies (ocrelizumab, OXR, rituximab, RTX, ofatumumab, and OFA). The main conclusion from the study was that pwMS treated with dimethyl fumarate, beta interferon, and glatiramer acetate can successfully produce antibodies against SARS--CoV-2, both after infection and after vaccination.

These results are consistent with the reports of other authors who state that these DMTs do not interfere with developing humoral immunity against SARS-CoV2 after vaccination or being infected with COVID-19 in people with MS [6–8].

However, most authors emphasise the impact of anti--CD20 and S1PRM on developing post-vaccination immunity [6–9].

On the basis of a prospective, multicentre cohort study with pwMS, in which SARS-CoV-2 vaccination with mRNA vaccines (BNT162b2, Pfizer/BioNTech or mRNA-1273, Moderna) has been carried out, Sormani et al. showed that treatment with anti-CD20 and fingolimod led to a reduced post-vaccination humoral response [11]. In the course of multivariate analysis, antibody concentration levels achieved by patients treated with ocrelizumab (a 201-fold decrease), fingolimod (26-fold decrease), and rituximab (20-fold decrease) were significantly lower compared to untreated subjects [11].

The aim of this study was to assess humoral response after mRNA vaccination in pwMS treated with high-efficiency DMTs [12]. Protective humoral response at the level of 100% was observed in untreated pwMS patients, 100% in patients treated with cladribine, 22.7% with ocrelizumab, and 3.8% with fingolimod. SARS-CoV-2 IgG antibody titres were high in untreated pwMS and those treated with cladribine. Only 22.7% of patients treated with ocrelizumab developed a humoral IgG response regardless of normal absolute lymphocyte count. The majority of patients treated with fingolimod had very low lymphocyte counts and did not develop SARS--COV-2 antibodies [12].

In a different study, Cohen et al. assessed the percentage of patients with reactive IgG anti-SARS-CoV-2 antibodies

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depending on the type of DMT used [13]. In pwSM who received an mRNA vaccine, Cohen et al. found that post-vaccination IgG rates were 40% for anti-CD20, 41% for sphingosine-1-phosphate receptor modulators (S1PRM), and 100% for all other DMTs. The authors concluded that anti-CD20 and S1PRM therapies reduce IgG response to SARS-CoV-2 vaccination. In terms of other DMTs, the IgG response is maintained [13].

48 studies involving 6,860 MS patients have been included in a recently published meta-analysis [14]. PwMS with anti-CD20 and S1PRM treatments had an attenuated serological response after full vaccination compared to those without DMTs. Additionally, pwMS vaccinated within the six months since their last anti-CD20 therapy were at significantly higher risk of blunted response compared to those receiving anti-CD20 therapy more than six months prior to vaccination. The authors found no significant associations between other treatments (including IFN-β, GA, DMF, TERI, NTZ, CLAD, and ALE) and humoral response to SARS-CoV-2 vaccines in pwMS. As for T-cell response, no significant difference was found between pwMS on anti-CD20 and those without DMTs after vaccination, while S1PRM was marginally associated with impaired cellular response [14].

Recently published research results concerning a new drug, ofatumumab, which is also a monoclonal anti-CD20 antibody, have provided interesting data.

Data presented at the 2022 AAN Annual Meeting from the ALITHIOS and KYRIOS trials suggests that ofatumumab is safe with up to four years of treatment, and does not prevent the cellular and humoral immune response to mRNA vaccines [15].

Further data from the ongoing KYRIOS open-label, prospective study showed that pwMS on ofatumamab are able to produce an immune response to the COVID-19 mRNA vaccine [16, 17]. All participants in KYRIOS who were vaccinated during treatment developed an immune response as soon as the first week after their initial vaccination, and the response in those who received a booster shot during treatment was similar to those who received a booster before treatment [16–18].

Even though treatment with small doses of ofatumumab results in B-cell depletion and is associated with an impaired humoral response to SARS-CoV-2 vaccination, the T-cell response is maintained.

The research results presented above show that the majority of DMTs used in pwMS allow complete post-vaccination immunity to be obtained through the use of mRNA vaccines. Serological monitoring after SARS-CoV-2 vaccination may be indicated in patients treated with anti-CD20 (ocrelizumab) and S1PRM antibodies. In these cases, it seems beneficial to use a booster dose and determine the optimal interval between the last anti-CD20 therapy and vaccination [19].

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REVIEW ARTICLE

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LEADING TOPIC

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Blood-brain barrier function in response to SARS-CoV-2 and its spike protein

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ABSTRACT

The typical manifestation of coronavirus 2 (CoV-2) infection is a severe acute respiratory syndrome (SARS) accompanied by pneumonia (COVID-19). However, SARS-CoV-2 can also affect the brain, causing chronic neurological symptoms, variously known as long, post, post-acute, or persistent COVID-19 condition, and affecting up to 40% of patients. The symptoms (fatigue, dizziness, headache, sleep disorders, malaise, disturbances of memory and mood) usually are mild and resolve spontaneously. However, some patients develop acute and fatal complications, including stroke or encephalopathy. Damage to the brain vessels mediated by the coronavirus spike protein (S-protein) and overactive immune responses have been identified as leading causes of this condition. However, the molecular mechanism by which the virus affects the brain still needs to be fully delineated. In this review article, we focus on interactions between host molecules and S-protein as the mechanism allowing the transit of SARS-CoV-2 through the blood-brain barrier to reach the brain structures. In addition, we discuss the impact of S-protein mutations and the involvement of other cellular factors conditioning the pathophysiology of SARS-CoV-2 infection. Finally, we review current and future COVID-19 treatment options.

Key words: SARS-CoV-2, spike protein, blood-brain barrier, encephalopathy, stroke, cytokine storm, neuroinflammation

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Introduction

SARS-CoV-2 mainly causes inflammatory lung damage associated with thrombosis and increased pulmonary vascular permeability leading to haemorrhage and oedema [1]. In addition, the cytokine storm during the inflammatory cascade and the direct action of the SARS-CoV-2-derived spike protein affect other organs, including the central nervous system [2–4]. Compelling reports indicate that COVID-19 patients develop neurological symptoms during acute infection. They can also develop a chronic condition, long-COVID or PACS (Post-Acute COVID Syndrome), characterised by fatigue and neuropsychiatric symptoms [5–8]. More than 40% of COVID-19 patients exhibit neurological, potentially lethal, symptoms during SARS-CoV-2, increasing the need to understand the underlying molecular mechanisms and to develop effective countermeasures [9–11].

Neuroinflammation, which typically accompanies central nervous system (CNS) damage, can be mediated directly by the viral invasion of CNS cells or indirectly by mediators that govern the development of systemic inflammation [3, 12]. Briefly, direct action of the SARS-CoV-2 spike protein

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(S1-protein), which circulates in the blood after being cleaved by the proteases during the viral invasion, and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) released by host immunocompetent cells in response to it, impede the blood--brain barrier (BBB) integrity, resulting in viral entry through the endothelium followed by infection of astrocytes [2, 3–15]. Symptoms can range from mild headache, nausea, impaired consciousness or reduced cognition to severe, potentially lethal conditions including encephalopathy, delirium, and acute disseminated encephalomyelitis [9–11]. Multicentre analyses have revealed that stroke (60%+) and encephalopathy (up to 42%) account for most neurological complications associated with SARS-CoV-2 infection. Encephalitis and Guillain-Barré syndrome are considerably less frequent, with incidence rates of 13% and 9%, respectively [11, 16]. Younger patients are more susceptible to ischaemic stroke associated with recurrent vascular occlusion and greater morbidity for COVID-19 patients than influenza patients. Among all neurological symptoms of SARS-CoV-2, patients with stroke and inflammatory syndromes had the worst prognosis [17, 18]. In the majority of cases, neuroimaging reveals ischaemia with large vessel occlusion, perfusion abnormalities, and haemorrhage in locations not typically associated with hypertension. In addition, post mortem analyses of COVID-19 patients have identified a link between microvascular disease and microhaemorrhages [22, 23].

In conclusion, all of these neurological complications may result directly or indirectly from an impairment of the blood-brain barrier (BBB) caused by SARS-CoV-2 infection.

Role of blood-brain barrier in maintaining central nervous system homeostasis

The blood-brain barrier is a specialised system of brain microvascular endothelial cells that guards the brain from circulating toxins, nourishes brain tissues, and filters harmful compounds from the brain to the bloodstream [19]. The proper functioning of the central nervous system is ensured by close interaction between the brain endothelium and other neurovascular/glial components such as astrocytes, pericytes, neurons, and basement membranes [20, 21]. Passage through the BBB is strictly regulated by physical (intercellular tight and adherens junctions) and metabolic (enzymes, transporters etc.) barriers [22, 23]. Notably, there is a functional difference between the brain endothelial cells' abluminal and luminal membrane surfaces due to the differential expression of specific transporters, secretory bodies, and the release of enzymes locally [24]. Due to its restricted permeability, the BBB is a major obstacle for delivering therapeutic agents into the CNS [25]. Leakage or disruption of the BBB plays a crucial role in the pathogenesis of numerous brain diseases such as Alzheimer's Disease, multiple sclerosis, ischaemia, Parkinson's Disease, and PACS/neuro-COVID-19 [26–30].

Interaction of SARS-CoV-2 with host cells

The crown-like (corona) appearance of the virion is attributable to the spike (S) protein, which is assembled in homotrimer form and inserted in multiple copies into the host membrane. In SARS-CoV-2, the S-protein is cleaved by furin into the S1 and S2 subunits during their biosynthesis within the infected cells. In many other coronaviruses, the S-protein is only cleaved when they reach the target cells. Thus, the S-protein on the mature virion consists of non-covalently linked S1 and S2 subunits. The former subunit binds the cell receptor — angiotensin-converting enzyme 2 (ACE2), while the S2 subunit anchors the S-protein to the membrane. ACE2 engagement by the S1-protein triggers conformational changes in both subunits (S1 and S2) that lead to the formation of a fusion pore by bringing the viral and cellular membranes together [31]. As shown in Figure 1, for SARS-CoV-2, this process exposes the S2 site, followed by its subsequent cleavage by a transmembrane protease, serine 2 (TMPRSS2), resulting in bringing the virus closer to the cell surface and ultimately fusion of the S2 subunit to the membrane. Importantly, the S1 subunit is released from the ACE2 receptor to the bloodstream, where it has been detected in unvaccinated and infected patients, leading to inflammation triggered by direct and indirect action of the S-protein throughout the body [15].

Other cell attachment factors/co-receptors for SARS-CoV-2

ACE2 is the primary receptor responsible for the entry and expansion of the SARS-CoV-2 virus in human cells. Nevertheless, several reports have indicated that ACE2 alone cannot ensure SARS-CoV-2's entry into cells, and additional co-receptors or attachment factors have been proposed for this process [32, 33]. Blood-brain barrier endothelial cells express several of these factors, linking SARS-CoV-2 with neurological symptoms. Due to the substantial genetic relatedness between SARS-CoV-2 and other coronaviruses, particularly SARS-CoV-1, specific targets by which the virus interacts with human cells have been described (Fig. 2) [34].

Extracellular vimentin

A link between extracellular vimentin and SARS-CoV-2 infection has been established by several studies [33, 35–38]. Vimentin (Vim) is a type III intermediate filament-forming protein and an essential cytoskeleton element. In addition, Vim exists in the extracellular environment and on the surface of various cells regardless of its expression due to its secretion by immune cells triggered by inflammation [44] and by endothelial cells in tumours [39]. Recent studies have shown that Vim directly interacts with S-protein, and that blocking Vim on the cell surface significantly reduces the entry

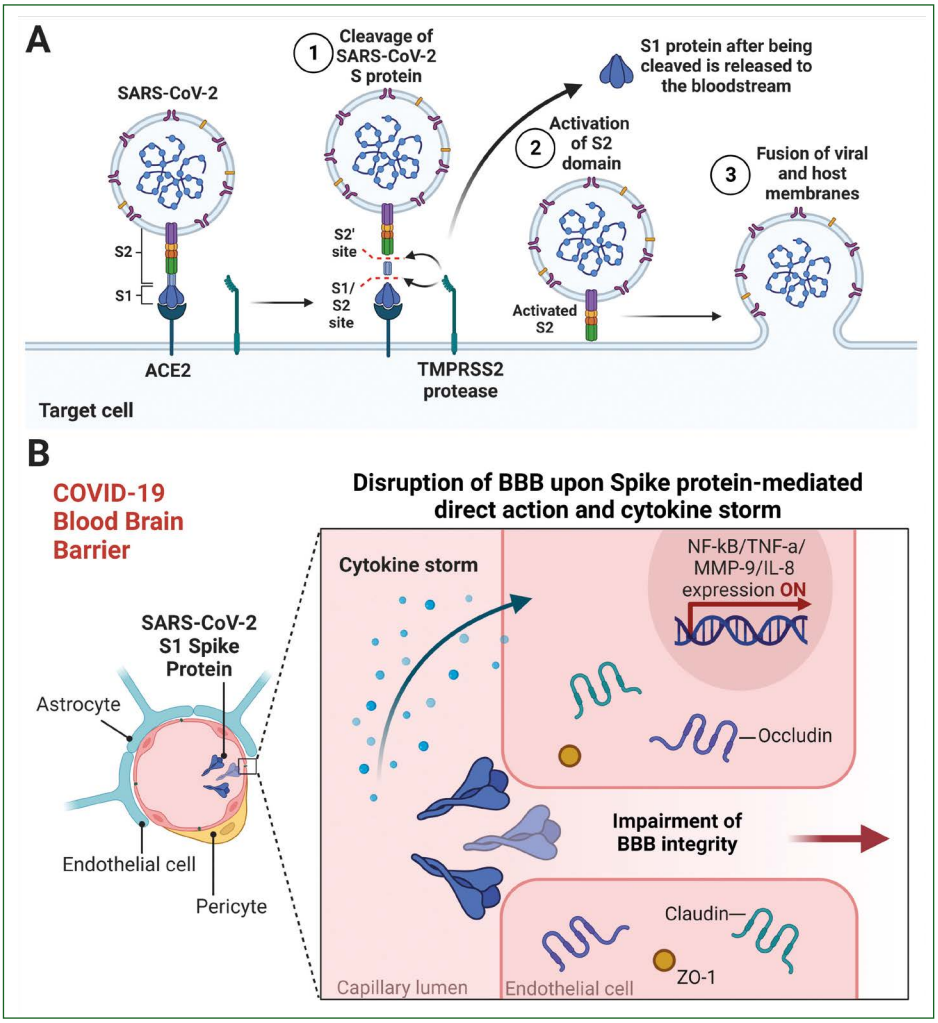

Figure 1. ACE2- and TMPRSS2-mediated SARS-CoV-2 cell entry indicates a possible explanation for presence of S1 protein in free form in circulation **(A)**. Scheme shows SARS-CoV-2 Spike S1 protein-driven disruption of blood-brain barrier. Direct action of S-protein and cytokine storm causes tight junctional complex rupture and enhances autocrine downstream proinflammatory signalling in endothelial cells **(B)**. Illustration created in Biorender

of SARS-CoV-2 into host cells [33]. Specifically, antibodies targeting the vimentin C-terminal domain block entry of the pseudovirus containing S-protein by up to 80% in cells expressing extracellular vimentin and ACE2 [33] *in vitro*, and anti-vimentin antibodies show potential therapeutic value *in vivo* [40]. Similarly, an inhibitory effect on viral uptake has been recorded for other vimentin-blocking compounds [36]. Moreover, limiting the concentration of vimentin in the blood suppresses SARS-CoV-2 replication and, in turn, virus-triggered inflammation [33, 38].

Neuropilin-1

Neuropilin-1 (NRP1) is another putative attachment protein or co-receptor for SARS-CoV-2 since its selective inhibitors or anti-NRP1 antibodies reduce the virus entry to host cells [41]. NRP1 physiologically has the ability to bind all of the furin-cleaved proteins and acts as an inhibitor for neuronal demyelination and a suppressor of inflammatory signalling that preserves BBB integrity [41].

Heparan sulfate

Heparan sulfate (HS), a polysaccharide attached to various cell surfaces or extracellular matrix proteins, is another compound associated with SARS-CoV-2 uptake by host cells. HS participates in several biological processes, including cell adhesion, signalling, and angiogenesis [42]. Interestingly, the S-protein interacts with cellular HS through a domain adjacent to its receptor-binding domain (RBD) [43]. Furthermore, HS inhibitors, such as heparin derivatives and mitoxantrone, may directly block the interaction between HS and S1 protein, inhibiting the uptake of both pseudotyped and authentic SARS--CoV-2 [44]. Similar effects have been observed for sunitinib and BNTX, drugs that indirectly inhibit HS-mediated viral entry by rearrangement of the actin network [49].

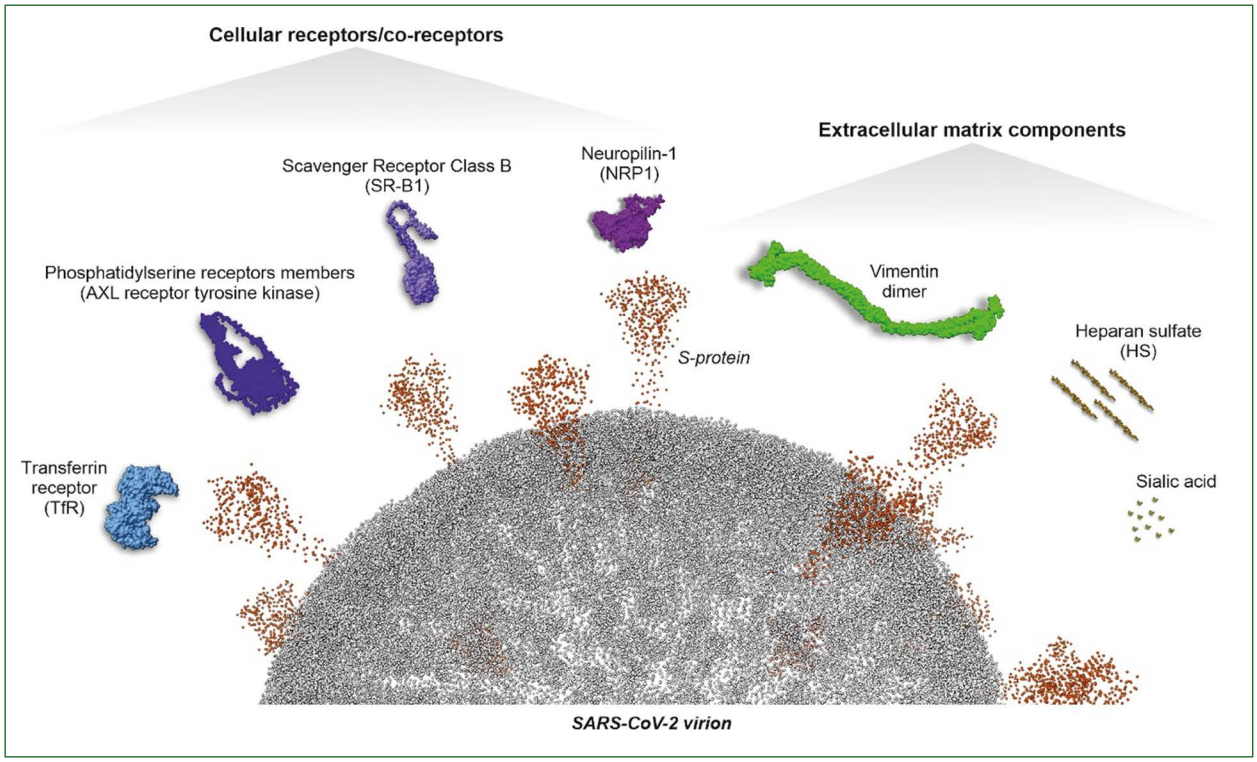

Figure 2. Host molecules interacting with S-protein of SARS-CoV-2. Visualisation performed using ChimeraX v.1.4 software [98] with proportional dimensions, based on 3D model of SARS-CoV-2 virion [99] and 3D models of proteins predicted using AlphaFold v2.2.2 tool [100] as well as heparan sulfate (octamer) and sialic acid molecules

Sialic acid

Sialic acids on the surface of BBB-forming endothelial cells play a vital role in the transport kinetics between the blood and the brain, hence appearing to be naturally associated with the invasion of CNS by SARS-CoV-2. Indeed, the direct binding of S-protein to sialic acid has been observed with electron microscopy and *in silico* studies [45]. However, due to conflicting conclusions, the role of sialic acid in the process of SARS-CoV-2 penetration is not clearly defined [46, 47]. For instance, ACE2 glycosylation inhibition studies with neuraminidase indicate that sialic acids on the ACE2 receptor prevent ACE2/spike protein interaction [46]. On the other hand, it has been reported that gangliosides could serve as ligands for the receptor-binding domain of the SARS-CoV-2 spike protein, thus improving viral uptake [47].

Scavenger receptor class B, type I

Scavenger Receptor Class B, Type I (SR-B1) on immune cells is involved in processes of the innate immune response. On the BBB, SR-B1 acts as a major high-density lipoprotein (HDL) receptor that modulates reverse sterol transport. Since the S1-subunit attaches to cholesterol and possibly HDL components, improving viral uptake *in vitro*, SR-B1 may be implicated in this process. For example, the SARS-CoV-2 infection of the cells overexpressing SR-B1 has been shown to be enhanced, while the viral uptake in SR-B1 knockout cells is reduced [48]. Similarly, in a study with cholesterol-poor synthetic biological HDL targeting SR-B1, 80% inhibition of SARS-CoV-2 pseudovirus uptake was observed [49].

Phosphatidylserine receptors

Phosphatidylserine (PS) receptors (PSR) namely TIM (TIM-1 and TIM-4), and TAM (AXL) have been reported as factors that enhance SARS-CoV-2's attachment to cells, promote uptake of virions, and boost ACE2-dependent infection of SARS-CoV-2. Wang et al. indicated that AXL interacts directly with the N-terminal domain of the SARS-CoV-2 S-protein [50]. But contradicting that, Bohan et al. stated that AXL does not bind to S-protein but rather to PS, which is abundant on the surface of the SARS-CoV-2 virion [51]. Furthermore, bemcentinib, an AXL inhibitor, significantly inhibited SARS-CoV-2 viral uptake into Vero 6 cells.

Transferrin receptor

Transferrin receptor (TfR) is highly expressed in brain capillary endothelial cells, but not the peripheral endothelium. TfR is responsible for the transport of iron into the brain parenchyma to maintain iron homeostasis, which is crucial for proper brain function, e.g. metabolism and neural conductivity. TfR is another protein involved in viral uptake by direct interaction with Spike S1 RBD. An anti-TfR antibody shows

a potent inhibitory effect on SARS-CoV-2 infection in mice [52]. *In vitro* studies have indicated that low doses of ferristatin II reduce the uptake of different variants of concern (VOCs) of SARS-CoV-2 [53].

Blood-brain barrier and SARS-CoV-2

Given the unique properties of the BBB, viruses such as SARS-CoV-2 are unable to enter the CNS easily. However, numerous case reports of patients with neurological complications indicate that nearly 60% of all COVID-19 patients have had disrupted BBB, resulting in increased permeability [54]. Post-mortem histopathological examinations indicate the presence of SARS-CoV-2 in different types of glial and endothelial cells within the brain [55]. Due to the large number of co-receptors/attachment factors other than ACE2 that may play a role in viral invasion, the mechanisms utilised by SARS-CoV-2 to enter the brain and cause neurological disorders still need to be fully understood.

So far, two major routes for virus entry into the CNS have been identified: retrograde neuronal transport, and hematogenous transmission including immune cells as vectors in a mechanism known as the 'Trojan horse'. The neuroinvasive route involves direct or indirect contact with the oral mucosa and eyes, and also implicates the olfactory, vagus, and trigeminal nerves as the primary cranial nerves involved in viral entry into the CNS [61]. Other mechanisms involve the indirect action of S-protein and the cascade of events associated with cytotoxicity and systemic inflammatory responses (the cytokine storm) that lead to the deterioration of the BBB. However, this review focuses on the hematogenous route, which involves the brain endothelium more profoundly.

Direct interaction of SARS-Cov-2 with BBB

Although initial *in vitro* studies have shown that SARS-CoV-2 is incapable of infection and replication in endothelial cells, numerous post mortem reports of patients who died from COVID-19 have demonstrated the presence of virus particles within the brain vasculature, pericytes, and neurons [55, 56]. These inconsistencies indicate that BBB infection is more complex and requires further examination. As mentioned previously, SARS-CoV-2 can infect endothelial cells by interacting with ACE2 on their surface [14]. However, the degree of infection is substantially less pronounced than in the primary target lung cells of SARS-CoV-2 — type II pneumocytes. On the other hand, overexpression of ACE2 in the endothelium of the cerebral circulation occurs in patients with hypertension and dementia and positively correlates with the severity of neurological symptoms [2, 57]. In addition, the S-protein may interact directly with the BBB, and S1, S1RBD, and S2 subunits exhibit pro-inflammatory effects, resulting in increased BBB permeability via damage to tight junctions (TJs) but not adherens junctions (AJs) [2, 58].

Trojan horse

One of the hallmarks of virus-induced neuropathogenesis is the breakdown of the BBB, which leads to uncontrolled infiltration of the virus-infected immune cells into the CNS via the 'Trojan horse' mechanism [59]. Using monocytes and macrophages as vectors, the viruses exploit the physiological process of CNS infiltration by immune response cells passing through the BBB. This process of permeation through endothelial cells, known as extravasation, consists of a series of consecutive steps, i.e. tethering, rolling, adhesion, and transmigration/diapedesis [60]. During this process, immune cells interact with adhesion molecules (ICAM, VCAM, E-Selectin) on the surface of the endothelium. Expression of these adhesion molecules is increased during SARS-CoV-2 infection, further contributing to the severity of neurological symptoms [58, 61]. Once the infected cells enter the CNS, the released virions can further infect glial cells, especially astrocytes and pericytes, whose impaired function further disrupts BBB homeostasis, leading to the loss of its function.

Adsorptive transcytosis

Direct passage of the virus across the BBB via interaction with receptors and co-receptors that facilitate infection, as well as the use of immune response cells as transporters, is not the only mechanism exploited by SARS-CoV-2 in order to penetrate endothelial barriers. Rhea et al. showed that iodine-labelled S-protein from SARS-CoV-2 can cross endothelial barriers through adsorptive transcytosis [3]. During this process, glycopeptides, i.e. spike protein with a positive charge circulating in the bloodstream, interact with endothelial cells' negatively charged surface [62]. Subsequently, the interaction causes invagination of the cell membrane and vesicle formation. Vesicles containing S-protein can now enter the intercellular space and may interact with the parenchyma side of the BBB.

Cytokine storm

In severe cases, COVID-19 is accompanied by a systemic inflammatory response, referred to as a cytokine storm, contributing to the disease's lethality. Patients with a poor prognosis frequently have elevated serum levels of cytokines and chemokines, mainly IL-1, IL-6, IL-8, IL-12, and TNF-α [63].

These pro-inflammatory mediators exhibit a positive feedback-like effect that stimulates neighbouring cells to produce even more cytokines, thereby promoting the infiltration of other immune response cells into the site of infection. In addition, S-protein can interact with Toll-like receptors 2 and 4 (TLR2, TLR4) and, in turn, activate signalling pathways involving PI3K, AKT, MAPK, and NF-κB [64, 65]. Subsequently, translocation of NF-κB into the cell nucleus results in increased production of pro-inflammatory cytokines, as well as adhesion factors such as ICAM, VCAM, and E-Selectin. As the aforementioned cytokines exert either direct or indirect effects that increase vascular permeability, the severity of inflammation

correlates closely with BBB damage. For example, IL-1β indirectly increases the expression of matrix metalloproteinase 9 (MMP-9), which breaks down TJS-proteins (ZO-1, occludin, and claudin-5) [66]. Similarly, IL-6, IL-8, IL-12, and TNF-α lead to BBB breakdown [67]. Moreover, S-protein stimulates the production of VEGF, one of the most potent inducers of vascular permeability [68, 69]. The increased vascular permeability significantly contributes to virus entry into the CNS and glial cell infection, resulting in neurological disorders.

TJ disruption through cytoskeleton and glycocalyx involvement

Tight junctions, i.e. close cell-cell connections formed by complexes of proteins, i.e. cytoplasmic scaffolding: ZO-1, -2, -3, and transmembrane proteins: occludins, and claudins, play a critical role in maintaining BBB homeostasis by restricting paracellular permeability [19]. These junctional complexes require the involvement of actin cytoskeleton rearrangement in processes associated with the formation and maturation of cell-cell contacts. Recently, RhoA activation has been associated with SARS-CoV-2-mediated barrier breakdown, indicating that the signalling mechanism involves cytoskeletal components. RhoA is a key regulator of endothelial cytoskeleton and TJ complex dynamics; its activation has been shown to disrupt vascular integrity. SARS-CoV-2 S1 protein triggered activation of RhoA in a 3D microfluidic model of the BBB. The use of C3 transferase, a RhoA inhibitor, mitigated the negative effect of S1 on BBB permeability and TJ degradation [4].

Another study has implicated the interaction between hyaluronic acid (HA) and CD44 in the endothelial barrier breakdown during COVID-19 [70]. This work analysed circulating glycosaminoglycans levels and their degradative enzymes' activities among SARS-CoV-2-infected patients [70], and found that the glycocalyx was severely damaged, which corresponded with disease outcome. Moreover, the circulating HA fragments and hyaluronidase level strongly correlated with organ failure assessment scores and hyperinflammation. In conclusion, the authors suggested that HA fragments are released into blood circulation due to COVID-19-mediated dysregulation of HA biosynthesis and degradation, which leads to direct endothelial barrier disruption in a ROCK- and CD44--dependent manner, indicating a role for HA in the vascular pathology of COVID-19.

Coagulopathy

Since the beginning of the COVID-19 pandemic, numerous reports have indicated an increased incidence of thrombotic events in patients with SARS-CoV-2. The syndrome of life-threatening clotting complications has been named COVID-19--associated coagulopathy (CAC) [71]. Cohort studies have shown that the incidence of ischaemic stroke as a complication of thromboembolic events oscillated around 2% [72, 73]. In most cases, elevated levels of fibrinogen, D-dimers, C-reactive protein, and P-selectin are recorded in the plasma of patients with CAC [74].

Endothelial cells have an antithrombotic system that determines platelet aggregation (NO, prostacyclin) and coagulation (TPFI, EPCR, thrombomodulin). In addition, the heparan sulfate in the glycocalyx layer exhibits anticoagulant activity [75]. During SARS-CoV-2 infection, there is a state of hyperactivation of the immune response, which results in activation of the complement system, increased release of neutrophil extracellular traps, and overproduction of cytokines, chemokines, and reactive oxygen species [76].

This cascade of events results in an imbalance between fibrinolysis and coagulation. Furthermore, due to damage to the glycocalyx and a reduction in the production of thrombomodulin, nitric oxide, and prostacyclins, the anti-thrombogenic fibrinolytic activity of the endothelium decreases. Additionally, an increase in free fibrin, tissue factors, and P-selectin is noted, which is associated with an increase in the prothrombogenic activity of the endothelium. Thrombin, fibrinogen, and plasminogen levels increase in CAC and directly or indirectly damage the endothelial barrier. Thrombin increases BBB permeability by indirectly damaging TJ-forming proteins through phosphorylation of MMPs and TJs and upregulation of VEGF by Src kinase [77]. Fibrinogen at pathologically high levels destroys the junctions between actin filaments and TJ, which widens intercellular junctions, impairing endothelial integrity [78]. Ventricular administration of tissue plasminogen activator results in dose-dependent increased BBB permeability, suggesting plasminogen's direct involvement in endothelial injury [79].

ACE2, which is the master receptor for SARS-CoV-2, has a dual function, i.e. it regulates the renin-angiotensin-aldosterone system as well as the kallikrein-kinin system. Kinins are peptides with the ability to increase vascular permeability. An occupied ACE2 receptor during SARS-CoV-2 infection can cause dysregulation of kinin degradation, resulting in what has been called a 'kinin storm', leading to increased vascular permeability, inflammation, and ultimately organ damage, including to the brain [80].

Lung hypoxia increases BBB permeability

COVID-19 is a predominantly pulmonary disease that causes infection of the alveoli, impairing their function, and patients with SARS-CoV-2 are chronically hypoxic due to pathological changes in the lungs. Many studies have described so-called 'happy hypoxia' in SARS-CoV-2 infected patients, i.e. hypoxemia without signs of shortness of breath, which leads to chronic mild hypoxia (CMH) [81].

Hypoxia, encephalitis, and stroke are the leading long-term causes of neurocognitive symptoms in COVID-19 patients [88]. Multiple mechanisms of chronic hypoxia can result in BBB impairment. Hypoxia can induce cell death in endothelial and glial cells via the apoptosis pathway by activating hypoxia--inducible factor 1 (HIF-1) [89]. In addition, CMH has been shown to cause a temporary vascular leak in brain blood vessels, along with microglial activation and infiltration around

damaged vessels. CMH-induced increased endothelial permeability exerts a regional preference, with considerably higher prevalence within the brainstem and olfactory bulb compared to the cerebellum and cerebral cortex [82]. These regions have also been reported to have the most significant levels of angiogenic development, with a peak in VEGF production that may additionally influence hypoxic-induced BBB disruption. Furthermore, i*n vitro* coculture models of endothelial cells and astrocytes have shown that hypoxia causes a decrease in ZO-1 expression, which correlates with the rearrangement of activated filaments resulting in increased permeability to molecular tracers [83].

Mutations and their impact on severity of neurological complications

The high transmissibility and genetic diversity of SARS-CoV-2 have led to the emergence of mutated virus strains, some of which have been termed 'variants of concern' (VOCs) due to their increased infectiousness. VOC strains have critical point mutations within spike proteins that affect the virus's ability to survive in harsh conditions and evade the host's immune response. The most dangerous VOCs hold several common mutations.

For example, the D614G and P681R/H mutations in the S-protein increase the transmission and infectivity of the virus due to the increased affinity of the S1 subunit to the ACE receptor [84]. Remarkably, certain VOCs with a higher virulence can eliminate from circulation less pathogenic variants. Such displaced variants are then referred to as de-escalated variants if they meet at least one of the following criteria: (i) the variant is no longer circulating; (ii) although the strain has circulated for a long time in the population, it has no impact on the epidemiological situation; or (iii) the variant does not have specific, more virulent, properties based on scientific evidence.

SARS-CoV-2 is still evolving, and the emergence of more pathogenic mutants in the future is possible. For this reason, freshly discovered variants are closely monitored and listed as Variants of Interest (VOI) or Variants under Monitoring (VUM). A summary of the most common mutations, along with their impact on transmissibility and induction of the immune response, is set out in Table 1.

Recently, Taquet et al., in a massive two-year cohort study including almost 1.3 million patients, analysed risk trajectories of neurological and psychiatric outcomes after SARS-CoV-2 infection [85]. They compared the risk for adverse effects within CNS in cohorts (a minimum of 39,845 patients per group) of patients diagnosed with different VOCs of SARS-CoV-2, e.g. alpha (B.1.1.7), delta (B.1.617.2), and omicron (B.1.1.529) comparing them to control cohorts, before the emergence of those VOCs. Only minor changes were observed for the alpha variant in the six-month hazard risk of neurological and psychiatric events. In contrast, patients infected with the delta variant were at a significantly higher risk of anxiety, insomnia, cognitive disorders, seizures, and ischaemic stroke incidents, but at a lower risk of dementia. Mortality among patients diagnosed with the delta strain was also higher. The omicron variant caused an increased risk of dementia, as well as mood, nerve, and plexus disorders. However, the death rate was significantly lower than among patients before the emergence of omicron.

Unfortunately, despite extensive research into the pathogenicity and molecular mechanisms of SARS-CoV-2 infection, little is known about the direct impact of mutations in the S-protein on the integrity of the BBB. Most *in vitro* BBB studies are concerned with the effects of spike protein subunits derived from the Wild Wuhan strain of SARS-CoV-2.

SARS-CoV-2 treatment

Since the beginning of the COVID-19 pandemic, concerted efforts by researchers worldwide have led to the development of therapies, some using previously developed broad-spectrum drugs, and some that have been newly developed and are specifically placed to treat SARS-CoV-2. Implementing vaccination against COVID-19, using, among others, innovative mRNA vaccine technology, has been a great success, which significantly reduced severe adverse events (SAE), the frequency of hospitalisations, and consequently, mortality [86, 87].

Vaccination — current status

As of January 2023, nearly 5.6 billion people, 69.1% of the world's population, have received at least one dose of a COVID-19 vaccine. 13.19 billion doses have been administered globally, and 2.2 million are administered daily. Almost 26% of people in low-income countries have received at least one dose. In Poland, over 57.8 million doses have been administered so far, and 22.6 million people are considered fully vaccinated, with at least two doses administered [88]. There are several types of vaccines against SARS-CoV-2 [89]. mRNA-based vaccines use mRNAs developed in the laboratory that are encapsulated in liposome lipid envelopes that enable entry into human cells, where they stimulate ribosomes to produce viral S-protein or its fragment, which further triggers antibody production by plasmocytes conditioning a specific immune response. Other vaccines trigger an immune response using weakened, modified, or inactivated viruses. Viral vector vaccines contain a modified version of a vector virus that includes fragments of SARS-CoV-2 but cannot cause infection. In contrast, protein subunit vaccines contain the spike protein fragment but without vector virus. Additionally, protein subunit vaccines contain an adjuvant that modulates immune system responses in the future when the human body meets viral particles during infection again. Due to the high ability of SARS-CoV-2 to mutate, vaccine manufacturers regularly update their formulations to maintain a high level of effectiveness in preventing COVID-19, which requires repeated booster doses.

Table 1. Summary of key, emerging mutated variants of SARS-CoV-2 and its impact on immune response and severity of infection compared to Wild Wuhan strain of SARS-CoV-2. Its current status, according to World Health Organisation, is denoted as either VOC (Variant of Concern), VUM (Variant under Monitoring), VOM (Variant of Interest), or DEV (De-escalated Variants). Table created according to current (as of January 2023) reports of WHO (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports)

WHO label and lineage	WHO status	Spike mutations of interest	First detection date and place	Transmissibility	Impact on immunity	Severity
Alpha B.1.1.7	DEV	N501Y, D614G, P681H	September 2020, United Kingdom	↑	Comparable	↑
Beta B.1.351	DEV	K417N, E484K, N501Y, D614G, A701V	September 2020, South Africa	↑	↑	↑
Gamma P.1	DEV	K417T, E484K, N501Y, D614G, H655Y	December 2020, Brazil	↑	↑	↑
Delta B.1.617.2	DEV	L452R, T478K, D614G, P681R	December 2020, India	↑	↑	↑
Omicron BA.1	DEV	A67V, Δ69-70, T95I, G142D, Δ143-145, N211I, Δ212, ins215EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N6 79K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F	November 2021, South Africa and Botswana	↑	↑	↓
Omicron BA.2	VOC	142D, N211I, Δ212, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K	November 2021, South Africa	↑	↑	↓
Omicron BA.3	DEV	A67V, Δ69-70, Δ143-145, N211I, Δ212, G339D, S371F, S373P, S375F, D405N, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, D796Y, Q954H, N969K	November 2021, South Africa	No evidence	No evidence	No evidence
Omicron BA.4	VOC	As BA.2 + L452R, F486V, R493Q	January 2022, South Africa	No evidence	↑	No evidence
Omicron BA.5	VOC	As BA.2 + L452R, F486V, R493Q	February 2022, South Africa	No evidence	↑	Unclear
Omicron BA.2.75	VOI	W152R, F157L, I210V, G257S, D339H, G446S, N460K, Q493	May 2022, India	No evidence	↑	No evidence
Omicron XBB	VOI	As in BA.2.75 + N460K, F490S	Unclear	No evidence	↑	No evidence
Omicron BA.2.3.20	VUM	K444R, L452M, N460K	Unclear	No evidence	No evidence	No evidence
Omicron XBC	VUM	N440K, F486P	Unclear	No evidence	No evidence	No evidence

Antiviral drugs

Despite the high vaccination prevalence in all age groups, many people have yet to receive a full dose. In addition, among people with impaired immunity, such as the elderly or those undergoing hematological treatment, the response to vaccination has been insufficient. Therefore, it became necessary to look for antiviral therapies. Several drugs have been found useful and approved by global organisations that control the approval of medicines for COVID-19 treatment. Examples of such antiviral drugs used in treating SARS-CoV-2 are remdesivir, molnupiravir, nirmatrelvir, and ritonavir.

Remdesivir is approved for COVID-19 treatment in adults and pediatric patients who are at least 28 days of age and weigh at least 3 kilograms. Remdesivir is used both in clinical practice and at home by people diagnosed with mild to moderate SARS-CoV-2 at high risk for severe disease progression. Remdesivir is a nucleoside analogue that inhibits RNA-dependent RNA polymerase (RdRp) of different coronaviruses. Incorporation by RdRp results in highly limited RNA synthesis [90].

Molnupinavir, like remdesivir, is a nucleoside analogue with a broad antiviral spectrum. It also inhibits the replication of other coronaviruses, i.e. SARS-CoV-1, SARS-CoV-2, and MERS, as well as viruses from different families, RSB, HCV, and Ebola [91].

Nirmatrelvir and ritonavir are used in concurrent therapy because of their synergistic effect [92]. Nirmatrelvir is an oral protease inhibitor active against m^{PRO}, a viral protease involved in the replication process.

Ritonavir is a cytochrome p450 (CYP) 3A4 inhibitor that enhances the pharmacokinetics of protease inhibitors. Coadministration is required to increase nirmatrelvir concentration to the therapeutic range. Molnupinavir, nirmatrelvir, and ritonavir, unlike remdesivir, have yet to receive authorisation from the US Food and Drug Administration (FDA). However, the FDA granted Emergency Use Authorisation (EUA) status for these formulations in late 2021.

Monoclonal antibodies

SARS-CoV-2 targeting monoclonal antibodies (mAbs) are artificial antibodies that target specific epitopes within S-protein that act as neutralising agents limiting viral entry. Bebtelovimab and tixagevimab co-packaged with cilgavimab are SARS-COV-2-targeting mAbs authorised for use through a EUA [93, 94]. However, the COVID-19 Treatment Guidelines Panel recommends against using anti-SARS-CoV-2 mAbs to treat SARS-CoV-2 because the currently dominant Omicron variant is unlikely to be susceptible to mAbs, given its high variability within the S-protein sequence.

Immunomodulatory agents

Unlike previously mentioned compounds, immune modulators are therapeutic agents that do not target virus-infected cells but instead activate, suppress or boost immune responses. During SARS-CoV-2, immune modulators are especially useful during the cytokine storm due to their ability to suppress hyperinflammation. Several immunomodulatory drugs have been authorised to treat COVID-19, including anakinra, baricitinib, and tocilizumab.

Anakinra is an IL-1 receptor agonist used to treat hospitalised adults with SARS-CoV-2 requiring supplemental oxygen [95]. Baricitinib is a Janus kinase (JAK) inhibitor, preventing downstream activation of signalling pathways leading to the secretion of various interleukins, interferons, and growth factors [96]. Baricitinib treats COVID-19 in pediatric patients requiring oxygen supplementation, mechanical ventilation, or extracorporeal membrane oxygen (ECMO). Tocilizumab inhibits IL-6 action by competitive blockage of its receptor IL6-R, which inhibits downstream signal transduction that leads to infiltration of immune cells, e.g. B and T cells [97]. Tocilizumab has found use among pediatric patients requiring mechanical ventilation and ECMO, with concomitant administration of corticosteroids.

Conclusions

SARS-CoV-2 remains a substantial threat to global health and the global economy. Neurological and psychiatric disorders involve disruption of blood-brain barrier integrity, and their longitudinal effects are unknown. Despite the introduction of effective vaccines, continued research toward a deeper understanding of the intricate and complex processes involved in the pathophysiology of SARS-CoV-2 infections is still needed due to its high genetic variability and evolutionary dynamics. In particular, understanding the effects of S-protein from different VOCs on the integrity of the BBB is essential if we are to recognise the neurological consequences of COVID-19. Equally important is the education of medical professionals and patients about the aetiopathology, prevention, treatment, and mechanism of action of SARS-CoV-2.

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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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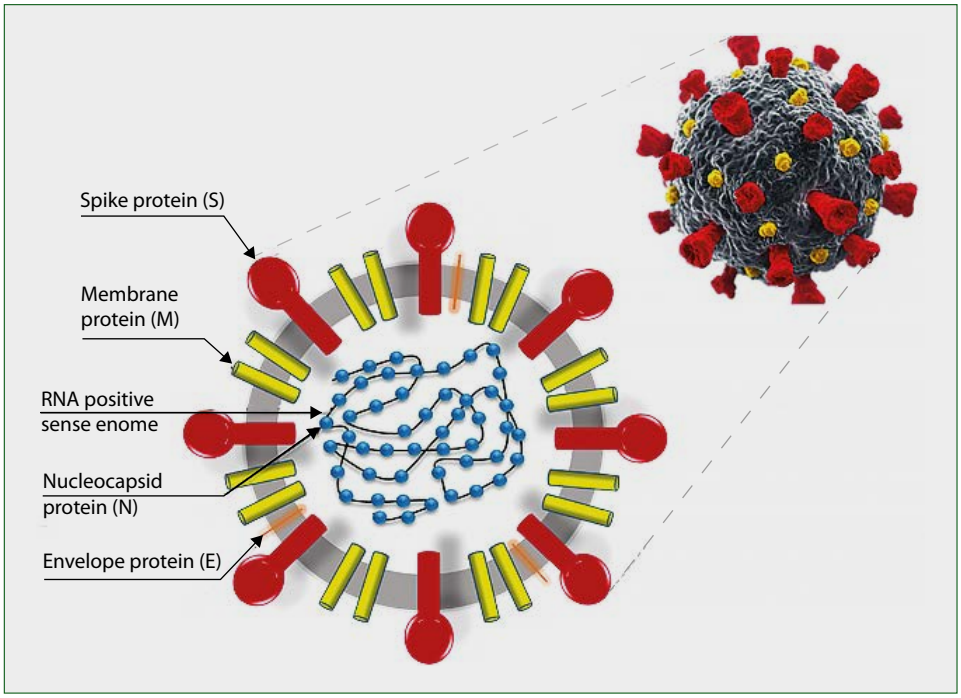

Figure 1. SARS-CoV-2 viral particle

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–Barre 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	Hospitaliaed 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/systematic 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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SARS-CoV-2 neurotropism and other possible causes of olfactory disorders in COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an acute infectious respiratory disease (AIRD) caused by infection with the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first cases were diagnosed and reported in Wuhan, central China, in November 2019. The disease initially occurred locally. However, the number of infected individuals increased dynamically and spread worldwide. The most common symptoms of the SARS-CoV-2 infection include malaise, fever, dry cough and dyspnoea. Over time, reports of new COVID-19 symptoms included taste and smell disorders. A potential cause of these disorders is related to neurotropism, i.e. the affinity of SARS-CoV-2 to the nervous system. Angiotensin-converting enzyme 2 receptor is essential in the pathogenesis of SARS-CoV-2 infection. The receptor is found in many tissues and organs, including the olfactory epithelium, neurons and neuroglial cells. Another potential cause is neuroinvasiveness, i.e. the ability of the virus to invade the central nervous system, and thereby damage its structures. As a result, olfactory disorders may occur. Other concepts, such as the inflammatory response of the body and the concept of stroke or damage to olfactory supporting cells, are also considered.

Key words: SARS-CoV-2, COVID-19, smell, taste, coronavirus, neurotropic

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Introduction

In November 2019, coronavirus disease 2019 (COVID-19) caused by infection with the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first diagnosed and reported in Wuhan, China. The epidemic initially occurred locally, with the first cases detected in individuals at a seafood market [1]. Over time, the number of patients increased rapidly and spread worldwide, reaching even Antarctica [2, 3]. Coronaviruses are RNA viruses that were originally associated with mild upper respiratory infections. However, in 2002, the first cases of severe acute respiratory syndrome (SARS) were reported in China. This syndrome causes severe respiratory failure due to an uncontrolled immune response leading to significant lung damage. The mortality rate for SARS is estimated to be 11% [4]. The first cases of Middle East Respiratory Syndrome (MERS), also caused by coronavirus infection, were reported in Saudi Arabia in 2012. The course of the disease can be asymptomatic or symptomatic. The symptoms may include a mild cold with flu-like symptoms or pneumonia. Furthermore, severe acute respiratory distress syndrome (SARS), multiple organ failure and death can also occur. Frequent gastrointestinal complaints and kidney failure are also common.

MERS has a high mortality rate of up to 35%. However, it is characterised by relatively low infectiousness [5]. In turn, the COVID-19-related mortality rate ranges from 2.3–7.2% due to the different courses of the disease resulting from age, race and comorbidities [6]. SARS-CoV-2, SARS-CoV-1 and MERS-CoV are coronaviruses of animal origin (zoonoses) [7].

COVID-19 is the first pandemic to have been caused by coronaviruses and the fifth documented pandemic overall, starting from the Spanish flu outbreak in 1918 [8]. From the outbreak of the COVID-19 pandemic until 29 October 2022,

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more than 626 million cases of infection and more than 6.5 million deaths had been confirmed worldwide [9]. Of note, the pandemic has had a devastating impact on the global economy and social life caused by many restrictions whose aim was to limit the spread of the virus [10], which occurs via airborne particles and droplets through direct contact with a sick person or contact with contaminated objects and other surfaces. Therefore, maintaining social distance and personal protective measures are of vital importance [6, 11]. The introduction of the COVID-19 vaccines was a significant breakthrough in the fight against the pandemic in November 2020. The vaccines reduce the risk of disease, hospitalisation and death, and carry a low risk of adverse reactions [12, 13].

Fever, dry cough, malaise and shortness of breath (dyspnoea) are the most common symptoms of SARS-CoV-2 infection [11]. However, smell and taste disorders became the symptoms increasingly reported by patients. Indeed sometimes such symptoms were the only symptoms reported. In our study, we focused on olfactory and taste disorders in COVID-19, paying particular attention to possible causes of their occurrence, including potential neurotropism, i.e. the affinity of SARS-Cov-2 to the nervous system.

Smell and taste disorders and other symptoms of COVID-19

During the first months of the COVID-19 pandemic, researchers paid special attention to the most common systemic symptoms, such as fever, dry cough, malaise, or shortness of breath. In their meta-analysis summarising 54 papers, Alimohamadi et al. found fever (81.2%), cough (58.5%), fatigue (38.5%), and dyspnoea (26.1%) to be the most prevalent symptoms. Of note, of these 54 reports, as many as 50 came from China [14]. In another meta-analysis, Grant et al. summarised the symptoms in 24,410 patients from nine countries based on 148 papers (127 of them from China). The most prevalent symptoms were fever (78%), cough (57%) and fatigue (31%). Smell disorders were very rare, being found in 317 (1.3%) patients [15]. Over time, the virus spread to other countries and continents. As a result, new reports began to appear, describing patients from many countries and races. New symptoms were often reported. Their severity and type were related to patients' age, the time elapsed since infection, and the occurrence of comorbidities. In their meta-analysis, Aziz et al. summarised reports from European, Asian and North and South American countries that included the symptoms of 11,074 patients with COVID-19. Of the 51 papers, only three came from China. Smell disorders were found in many patients (52%) [16]. The above differences may have been due to the fact that at the beginning of the pandemic, more attention was paid to the most prevalent severe systemic symptoms that could be health- and life-threatening. Smell and taste disorders in COVID-19 may not have been included since they may well have been considered less important. Early identification and diagnosis of systemic symptoms were significant for adequate treatment and isolation of patients. These differences may have been caused by mutations of the virus that could have led to different symptoms. They may also have been due to genetic and racial variability of patients, and hence a different immune response to infection and a diversity of symptoms. Over time, smell and taste disorders in COVID-19 were recognised as the early indicator of the disease.

Callejon-Leblic et al. analysed symptoms in 777 patients, and observed that smell and taste disorders correlated with a subsequent diagnosis of COVID-19 with an accuracy of 80%, sensitivity of 82%, and specificity of 78% [17]. Smell and taste disorders were also analysed as predictors of disease severity and subsequent hospitalisation. In their meta-analysis, Purja et al. noted a lower prevalence of smell and taste disorders in patients with severe disease and in those who required hospitalisation [18]. Next to smell and taste disorders, the occurrence of a wide range of other neurological disorders in COVID-19 was also significant. These symptoms could have resulted from damage to the central nervous system, such as encephalitis, headache, or encephalopathy, as well as to the peripheral nervous system, such as Guillain-Barré syndrome, or skeletal muscle symptoms (myalgia and myasthenia gravis). Delirium and psychosis were also reported [19, 20].

Anatomy and characteristics of olfactory epithelium

The olfactory epithelium is located in the upper nasal cavities, in the area known as the olfactory field or olfactory region. It occupies an area of about 4–6 cm^2. It is formed by the upper nasal concha with the adjacent upper part of the nasal cavity. Sometimes the olfactory field reaches the middle concha [21]. The approximate location of the olfactory epithelium is given in Figure 1.

The olfactory epithelium is composed of basal cells, olfactory sensory neurons (bipolar neurons) and sustentacular (or supporting) cells. It is covered with mucus produced by Bowman's glands on the lamina propria of the mucous membrane and by the secretion of goblet cells and supporting cells of the olfactory epithelium. The mucus contains odorant-binding proteins essential for binding odorants to bipolar

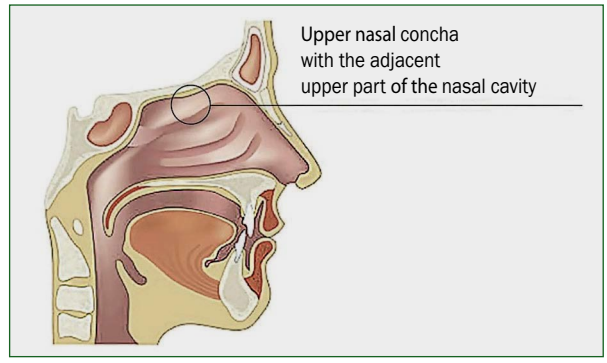

Figure 1. Approximate location of olfactory epithelium (olfactory field)

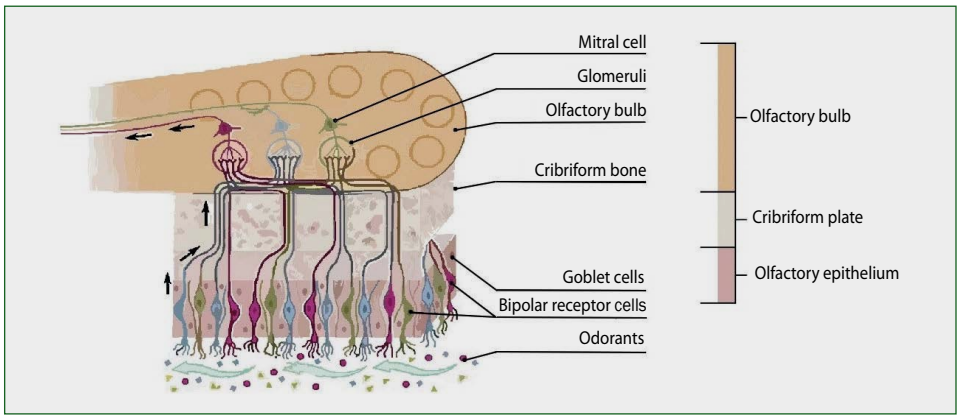

Figure 2. Structure of olfactory epithelium

cell receptors [22]. The structure of the olfactory epithelium is shown in Figure 2.

The olfactory epithelium, including bipolar cells, is characterised by high regenerative abilities after damage and constant cell replacement. However, these abilities decrease as a result of ageing, neurodegenerative diseases (e.g. Alzheimer's Disease, Parkinson's Disease), chronic and acute inflammation (e.g. chronic sinusitis, chronic rhinitis), and as a result of surgical treatment of the anterior cranial fossa [22, 23].

Does SARS-CoV-2 virus have neurotropic properties?

The neurotropism of the SARS-Cov-2 virus can be understood as its affinity and ability to penetrate, and replicate within, cells of the nervous system. Angiotensin-converting enzyme 2 (ACE2) is vital in this process. This is the main membrane receptor for SARS-Cov-2 to which the virus attaches via the spike protein. In addition, transmembrane serine protease 2 (TMPRSS2), which catalyses this process, is also crucial [24]. SARS-CoV-2 has a high affinity to the ACE2 receptor. It binds to this receptor 10–20 times more strongly than SARS-CoV. ACE2 is a commonly found receptor in the human body. It is located in the vascular endothelium, skeletal muscle, and nervous system cells. As a result, it can infect many organs and tissues [25]. In the brain, ACE2 is highly expressed in the choroid plexus, olfactory bulb and paraventricular nuclei of the thalamus [26, 27]. It is present in neuronal and non-neuronal cells of the central nervous system, such as endothelial cells and neuroglial cells (astrocytes and oligodendrocytes).

However, the highest expression of this receptor is found in excitable nerve cells of the medial temporal gyrus and posterior cingulate cortex. Note that very low expression of ACE2 is found in the hippocampus, which is the cortical olfactory centre [27]. When analysing neurotropism as a potential feature of the SARS-CoV-2 virus, three possible ways in which the virus could enter the CNS should be considered:

I. *Blood-borne route via the systemic circulation*. Crossing the blood-brain barrier (BBB) is crucial for the entry of SARS-CoV-2. One of the theories about the penetration of SARS-CoV-2 through the BBB is its ability to infect the endothelium of BBB vessels due to the presence of the ACE2 receptor in its cells [28]. Another potential cause is the ability of the virus to induce a cytokine storm, i.e. an excessive inflammatory and immune response which is typical of COVID-19. This results in increased permeability of the BBB by the increased inflammatory response of the vascular endothelium [29]. Another theory is related to the possibility of the virus entering the CNS through the mechanism known as the *Trojan horse*. It is possible that infected leukocytes, which express ACE2, can carry SARS-CoV-2 across the BBB to infect the CNS. This is facilitated by the increased production of leukocytes during infection and hypoxia often associated with COVID-19 [30]. The rich blood supply of the nasal mucosa and olfactory epithelium, as well as their vascular connection to the brain, may also be important in the blood-borne mechanism of viral access to the CNS [31].
II. *Peripheral nerve route.* Another possible route of infection is penetration of SARS-CoV-2 through the axons of the peripheral nerves. The following may be of vital importance: the trigeminal (V) and olfactory (I) nerves due to innervation of the nasal cavities, the vagus nerve (X) innervating the lower respiratory tract, and the glossopharyngeal (IX) and facial (VII) nerves innervating the upper respiratory tract. Of the above nerve pathways, no evidence of viral invasion via the glossopharyngeal or facial nerves has been reported yet [32].
III. *Lymphatic route.* The exact structure of the lymphatic system of the brain is not fully understood. It must be underlined that there is no classical lymphatic system in the CNS. However, it may be related to the pathogenesis of neuroinvasiveness of SARS-CoV-2. Bostanciklioglu proposed the thesis that the

olfactory and cervical lymphatic vessels could be part of the lymphatic drainage of the brain, which could provide a direct entry route for SARS-CoV-2 to the CNS [33].

Possible mechanisms of smell disorders in COVID-19

Local/systemic inflammation

An important aspect of a viral infection such as COVID-19 is related to increased inflammatory parameters in the serum of patients. This phenomenon can affect the occurrence of hyposmia. As early as 2013, Henkin et al. noted a clear relationship between the severity of systemic or local inflammation and the loss of smell. Levels of IL-6 were measured in samples of plasma, urine, saliva, and nasal mucus. The levels of IL-6 in nasal mucus were higher than those in any other biological fluid [34]. The above thesis may be confirmed by the occurrence of hyposmia in chronic systemic inflammatory rheumatic diseases, such as rheumatoid arthritis [35] or granulomatosis with polyangiitis [36]. In turn, Cazzolla et al. analysed serum IL-6 levels in patients with COVID-19 and found a correlation between increased serum IL-6 levels and the severity of olfactory impairment. In addition, it was noted that as hyposmia resolved, IL-6 levels decreased. Of note, there have also been frequent cases of a short duration of hyposmia in COVID-19, which may suggest the effect of local inflammation on olfactory receptor cells, rather than their permanent damage resulting from the SARS-CoV-2 infection [37].

Indirect damage to bipolar receptor cells and olfactory bulb neurons

As mentioned above, ACE2 receptor is a key enzyme in the aetiopathogenesis of the SARS-CoV-2 infection. It is found in the cells of many organs and tissues. However, ACE2 is not expressed in bipolar receptor cells or olfactory bulb neurons. The expression of ACE2 in non-neuronal cells of the olfactory epithelium, such as supporting cells and vascular pericytes, is also important. They are significant for the normal functioning of the olfactory epithelium through the delivery of nutrients and oxygen, and the removal of metabolic products [37, 38]. Therefore, olfactory impairment may be the result of indirect damage to neuronal and receptor cells due to a lack of nutrition resulting from the destruction of supporting cells by SARS-CoV-2. A potential cause of olfactory impairment in COVID-19 is also the effect of SARS-CoV-2 on olfactory epithelial cells at the molecular level. The viral infection causes a decrease in the activity of olfactory receptors and their signalling pathways. This is caused by reorganisation of the nuclear architecture of neuronal cells, which results in dispersion of the genes encoding olfactory receptors [40].

Concept of stroke/brain tissue damage

As stated previously, SARS-CoV-2 is neuroinvasive and can cause changes in the CNS. The causes of stroke in COVID-19 are usually complex and result from three factors known as Virchow's triad. They can occur due to venous stasis resulting from patient immobilisation during treatment, vascular endothelial injury resulting from the inflammatory response, and coagulopathy as a result of a generalised inflammatory response [41].

Nannoni et al. performed a meta-analysis that included 108,571 patients with COVID-19. Acute cerebrovascular disease was found in 1.4%. The most common manifestation was ischaemic stroke (87.4%), while intracerebral haemorrhage was much less prevalent (11.6%). The risk of stroke was significantly increased by cardiovascular disease, diabetes, and smoking [42]. However, when analysing the stroke/vascular aetiology of olfactory impairment in COVID-19, it is important to consider the relatively rapid recovery of the sense of smell in patients. Printza et al. reported that the great majority of patients (88%) had recovered their sense of smell by 61 days [43]. In another paper, McWilliams et al. summarised the severity of olfactory impairment during a 2-year follow-up. 38.2% of patients reported complete recovery, 54.3% partial, and 7.5% no recovery [44]. Based on the above, it can be concluded that the recovery of smell function in most patients was reported in a relatively short period of time. However, in some patients recovery was longer, or no recovery was reported. Neurological recovery in stroke patients is usually the highest during the first weeks of rehabilitation, reaching a plateau after three months. Six months after the occurrence of stroke, the effects of rehabilitation are usually lower [45]. Analysing the duration of symptoms, it is difficult to conclude whether olfactory impairment is related to the stroke/vascular concept of the CNS, since the recovery of smell function is characterised by relatively high variability in patients. Of note, stroke must involve the structures of the olfactory pathway to lead to olfactory impairment. Given the above-mentioned prevalence of stroke in COVID-19 (1.4% of cases), the concept of stroke would seem to be only a marginal cause of olfactory disorders in COVID-19.

Is COVID-19-related hearing loss also an example of SARS-CoV-2 neurotropism?

As the pandemic continued, there were reports of new disease symptoms, including hearing loss. Jaffari et al. and Dusan et al. reported the prevalence of hearing loss at 3.1% and 40.5% respectively, which is a large discrepancy. Therefore, it is impossible to assess the approximate prevalence of hearing loss in COVID-19 patients [46, 47]. Uranaka et al. evaluated the expression of ACE2, TMPRSS2 and Furin in mouse ear tissue. ACE2 was present in the nucleus of the epithelium of the middle ear and Eustachian tube, as well as in some nuclei of the hair cells in the organ of Corti, in the stria vascularis, and the spiral ganglion cells. The expression of TMPRSS2 and Furin was also reported in the cochlea [48]. The presence of the above substances in the human ear is possible, but further studies are warranted to confirm it.

Olfactory disorders in COVID-19 as a potential cause of neurodegeneration

Olfactory impairment is a common symptom in neurodegenerative diseases such as Parkinson's and Alzheimer's Diseases. Olfactory impairment is one of the initial symptoms of these conditions, and occurs long before cognitive impairment or motor dysfunction. Indeed it is considered one of the clinical markers of the early stages of the disease [49, 50]. Damage to brain tissue in the area of the limbic system and the olfactory bulb in the early stages of the disease can lead to long-term hearing impairment, which is characteristic of both Parkinson's and Alzheimer's and can occur in the course of COVID-19 [51, 52]. Given the previously mentioned similarities between neurodegenerative diseases and COVID-19, long-term olfactory loss with cognitive and emotional disturbances in the course of SARS-CoV-2 may be a symptom of dementia in the course of neurodegenerative processes [53]. To limit the extent of neurodegenerative processes in COVID-19, olfactory training is significant [54].

Conclusions

The COVID-19 pandemic that began in November 2019 has caused millions of deaths and paralysed the global economy and social life. The most common symptoms of SARS-CoV-2 infection were systemic symptoms such as fever, shortness of breath, malaise and cough. Over time, reports of new non-specific symptoms during COVID-19 were published. They included olfactory and taste disorders, which became characteristic features of the disease. Neurotropism, defined as the affinity to the nervous system and the ability of the virus to infect cells, was identified as a potential cause of these disorders. There have been several theories attempting to explain this phenomenon.

The crucial role is attributed to ACE2, which is the membrane receptor for the SARS-CoV-2 virus in many organs and tissues, including nervous tissue and the olfactory epithelium. It is also likely that the SARS-CoV-2 virus is characterised by neuroinvasiveness, i.e. the ability to invade the CNS, which can lead to olfactory disorders due to damage caused by the virus to CNS structures. Several potential pathomechanisms for these disorders are listed, i.e. inflammatory response, the concept of stroke, and damage to the supporting olfactory cells. This issue has not yet been fully understood, and requires further research.

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LEADING TOPIC

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COVID-19-related headache and innate immune response — a narrative review

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ABSTRACT

Headache is one of the most prevalent, although often underreported, symptoms of coronavirus disease 2019 (COVID-19). It is generally accepted that this symptom is a form of secondary headache due to systemic viral infection. There are several hypotheses that try to explain its aetiopathogenesis. One of the most compelling is related to innate immune response to viral infection. This rationale is supported by similarities to other viral infections and the temporal overlap between immunological reactions and headache. Moreover, several key factors in innate immunity have been shown to facilitate headache e.g. interferons, interleukin (IL) –1-β, IL-6, and tumour necrosis factor. There is also a possibility that the virus causes headache by the direct activation of afferents through pattern recognition receptors (i.e. Toll-like receptor 7). Moreover, some data on post-COVID-19 headache and after vaccination against SARS-CoV-2 infection suggests a similar cytokine-mediated pathomechanism in these clinical situations. Future research should look for evidence of causality between particular immune response factors and headache. Identifying key molecules responsible for headache during acute viral infection would be an important step towards managing one of the most prevalent secondary headache disorders.

Key words: SARS-CoV-2, pain, innate immune response, IL-1β, IL-6, TNF, IFN, TLR-7

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic precipitated great interest in the scientific community, prompting an unparalleled development of research data. In published studies, headache has often appeared as the most prevalent neurological complaint related to different aspects of the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been named as a symptom of COVID-19 [1] or its direct and indirect sequelae [2]. Moreover, headache has been identified as a prognostic factor [3], as well as an adverse reaction to therapeutic interventions and preventive strategies [4].

However, SARS-CoV-2 is a new headache factor only to a limited degree, and the complaint had been studied decades before the current pandemic. Consequently, the purpose of this review was to critically appraise the dataset published over the last two years in this area. Furthermore, we examine the most likely explanations for phenomena described in headache-related literature during the COVID-19 pandemic in the context of evidence accumulated in the past.

Considerations for review methods

Current guidelines describe headache as one of the cardinal COVID-19 symptoms [5]. However, initial reports

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Table 1. Prevalence of headache in acute viral respiratory tract infections

Aetiology	Study	Number of participants	Headache prevalence
Viral upper respiratory infection (miscellaneous pathogens)	Liu et al. 2013 [99]	4,755	25%
Influenza virus	Yang et al. 2015 [100]	49	69%
Rhinovirus	Zlateva et al. 2020 [101]	384	68%
Respiratory syncytial virus	Widmer et al. 2014 [102]	32	66%
Metapneumovirus		33	58%
Human coronaviruses	Zeng et al. 2018 [36]	258	1%
SARS-CoV-2	Lechien et al. 2020 [1]	1,420	70%
	Pullen et al. 2020 [11]	1,252	60%
	O'Keefe et al. 2021 [9]	337	66%
	García-Azorín et al. 2021 [10]	2,194	23%
	Straburzyński et al. 2021 [8]	130	72%

indicated its low prevalence in infected subjects (11.3%) [6]. It should be underlined that this data was obtained mostly from hospital-based retrospective case series, which are prone to bias resulting from selective data collection by healthcare providers and discriminatory reporting by patients. Consequently, even recently published meta-analyses based on these studies endorse the opinion that headache is not a prevalent acute COVID-19 symptom [7]. However, the above mentioned retrospective studies were followed by prospective research based on structured questionnaires. The latter placed headache among the most prevalent symptoms of COVID-19 (22–72%) [1, 8–11], although rarely an isolated one [12]. What is more, headache may be one of the most universal complaints in SARS-CoV-2 infection, occurring regardless of virus variant [13]. To conclude, the described underreporting has had a profound impact on evidence interpretation. Consequently, studies based on structured questionnaires specifically focused on headache are the ones with lowest bias risk for the purpose of this review.

The symptoms of COVID-19-related headache have been well characterised from the clinical point of view. However, little has been published on the subject of its pathogenesis. Consequently, only hypotheses have been proposed so far. In their comprehensive review, Caronna and Pozo-Rosich proposed several such concepts [14], e.g.:

- Direct damage to peripheral and central nervous system (CNS) mediated via virus affinity to angiotensin-converting enzyme 2 (ACE2) and its ability to cross the blood-brain barrier (BBB), especially when the latter is further damaged by inflammatory and coagulopathic processes.
- Hyperinflammation and cytokine storm with the prominent role of interleukin (IL)-6.
- Trigeminal system activation resulting from overlapping pathways of COVID-19 and primary headache disorders.

To assess data supporting these theories, our review concentrates on two major concepts: time and reference to non-COVID-19 headache scenarios. In the first, our rationale is that headache should occur simultaneously or be slightly preceded by a causal factor. As to the second concept, SARS-CoV-2 pathology shares many, mostly immune, mechanisms with disorders that have troubled humankind for millennia [5].

Headache in COVID-19 vs other viral respiratory tract infections

As mentioned above, SARS-CoV-2 causes headache in 22–72% of subjects, with the majority of prospective studies pointing to a 60–70% prevalence. These percentages are comparable to results from research on infections caused by common viruses, i.e. influenza, metapneumoviruses, respiratory syncytial viruses (RSV) and rhinoviruses (Tab. 1). However, most of these pathogens substantially differ in their biology e.g. the influenza virus can be both neurotropic and non-neurotropic [15]. It seems justified therefore to look for the source of infection-related headache in pathways that are common for all these pathogens, i.e. immune response.

SARS-CoV-2 tissue distribution

The upper respiratory tract, especially nasal ciliated cells, are the primary targets for SARS-CoV-2 in early COVID-19 stages [16]. The sinonasal mucosa is innervated by the first and second branch of the trigeminal nerve. Nerve endings of C and A-delta fibres are immersed in whatever biochemical or inflammatory processes take place in this area.

Viral sinonasal inflammation (acute rhinosinusitis) occurs in response to the replication of the virus in the nasal epithelium. Virus-derived molecules recognised by innate immune cells are referred to as pathogen-associated molecular patterns (PAMP). These structures are highly specific for given types of microorganisms (e.g. there are observations suggesting that the SARS-CoV-2 spike protein may act as a PAMP and cause neuroinflammation [17]). PAMP binding receptors are known as pattern recognition receptors (PRR). It is not

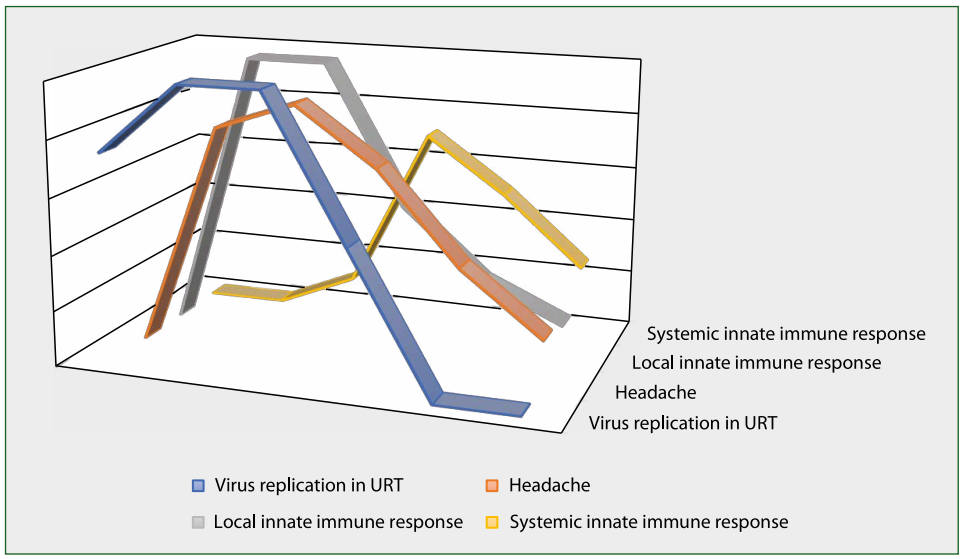

Figure 1. Schematic depiction of temporal changes in upper respiratory tract (URT) virus replication, innate immune response, and headache in mild/moderate COVID-19. Based on Schultze & Aschenbrenner 2021 [22] and O'Keefe et al. [9]

fully understood which PRRs are activated by SARS-CoV-2. However, experts suggest that the most probable targets are Toll-like receptors 3 (TLR3) and TLR7, retinoic acid-inducible gene 1 (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) [18]. These key sensors of viral infection are expressed intercellularly and respond to nucleic acids (RNA mostly), although in different ways. TLR3 and TLR7 recognise viral nucleic acid transported by the endosomal pathway (i.e. from outside the cell). RIG-1 and MDA-5 detect viruses that have entered the cell and started producing dsRNA during replication. The evidence for RIG-I and MDA5 expression in trigeminal afferents is lacking, and it seems likely that these neurons do not express TLR3 [19]. However, TLR7 is present on nasal mucosa nociceptors and, what is more, its stimulation in the nasal epithelium leads to brainstem activation [20].

It is worth noting that TLR3, TLR7, RIG-1 and MDA5 are expressed in nasal mucosa lymphoid tissue and nasal epithelial cells, leading to their activation and subsequent production of type I interferons and other pro-inflammatory cytokines [21–24]. Consequently, trigeminal afferents sustain exponential elevation of type I and III interferons (IFNs) followed by IL-1α, IL-1β, tumour necrosis factor (TNF), IL-6, C-X-C motif ligand (CXCL)-8, CXCL-10, CXCL-11, and C-C motif ligand (CCL)-5, followed by the next steps of immune response [25]. In a laboratory setting, this situation was simulated by experiments on an animal model. In that study, sinonasal stimulation with bradykinin caused the nociceptive activation of the trigeminal nucleus caudalis — a key region for headache [26]. This in turn may explain why patients with rhinosinusitis have headache and facial pain. In clinical settings, this was further supported by a study of COVID-19 patients that provided evidence for an association between acute inflammation of the sinonasal mucosa and headache/facial pain [8]. In other words, patients experiencing rhinosinusitis during COVID-19 had significantly higher odds of headache or facial pain. These correlations are multi-level and stretch beyond innate response and nasal cavity, e.g. a retrospective study found that patients experiencing headache and sinonasal symptoms have lower levels of anti-SARS-CoV2 IgG [27].

It has been confirmed that the coronavirus can penetrate different areas of the nervous system. Several mechanisms and routes to cross the BBB and spread within the CNS have been proposed, including virus affinity to ACE2 [14, 28, 29]. Some of these hypotheses assume that SARS-CoV-2 travels along the olfactory or trigeminal route [30], similarly to some neurotropic variants of the influenza virus [31]. Activation of the trigeminal ganglion, trigeminal nucleus caudalis and hypothalamus (among other regions) is considered paramount for some primary headache disorders (e.g. migraine). Consequently, this could explain headache pathomechanism occurring via a direct viral action in the trigeminal system [14, 30]. However, evidence published so far indicates moderate virus presence in the trigeminal ganglion or cranial nerve nuclei in the medulla oblongata [32, 33], and neither meningitis nor encephalitis are prevalent in COVID-19 [7, 34]. It should also be underlined that sole virus presence in CNS does not necessarily cause pain. For example, the human coronavirus is clearly neurotropic [35], and yet very seldom causes headache [36].

Molecules involved in innate immune response to SARS-CoV-2

Viral infections trigger innate and adaptive immune responses. These two reactions, although intertwined, have their own timelines, with innate being swifter and less specific. In other words, an innate reaction occurs at the same time as the

first infection symptoms, i.e. headache [8, 9, 11, 18] (Fig. 1). Studies analysing COVID-19-related headache have shed some light on its associations with innate immune response.

For example, in hospitalised patients, some infection symptoms (fever, myalgia,) have been associated with headache [37]. Fever occurs in response to, among others, endogenous pyrogens, such as IL-1, TNF or IL-6 [38]. These molecules are also part of the innate immune response in the upper respiratory tract mucosa in infections caused by the influenza virus, RSV or metapneumovirus [39, 40]. Moreover, IL-1, TNF or IL-6 contribute to calcitonin gene-related peptide (CGRP) release, although the latter phenomenon has been described only in animal cutaneous nociceptors [41].

IFNs are produced in response to SARS-CoV-2 most probably via the activation of toll-like receptors. When analysed in detail, innate immune response to SARS-CoV-2 infection is characterised by moderate levels of type I IFNs [42]. However, these molecules still play an important role in COVID-19. IFN-α (type I) and λ (type III) peak early in the disease course, especially in the nasal epithelium. A meta-analysis currently awaiting publication has shown that the application of type I IFN (β) is the cause of headache in multiple sclerosis patients [43]. IFN-α is also the cause of headache in many subjects treated with this molecule [44]. Moreover, earlier studies also pointed to possible migraine exacerbation by IFN-β therapy [45]. Type-I IFNs also activate mitogen-activated protein kinase – a pathway that is associated with pain processing in the trigeminovascular complex [46].

Type I IFNs initiate immune responses involving interleukin IL-1β, IL-6, TNF and some chemokines (CCL20, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL16) [18]. Consequently, these factors are more likely to participate in the origin of COVID-19-related headache than molecules that gain prominence later in COVID-19 course (CCL2, CCL3, CCL5, CXCL9, CXCL10, IL-1α, IL-17, IFN-β, IFN-γ, IL-10, IL-33) [18].

IL-6 plays an important role in the early phases of COVID-19 [18], and consequently, this particle should be considered as a possible trigger for headache in this infection. There is however contradictory evidence in this regard. On the one hand, IL-6 levels show positive linear correlation with headache intensity in COVID-19 [47]. On the other hand, headache is associated with lower, although still elevated, IL-6 levels [3]. Moreover, IL-6 is considered a key player in severe COVID-19 and cytokine storm [48] — a late complication occurring in a cohort with less prevalent headache. In reference to its nociceptive potential, it should be mentioned that patients with chronic and episodic tension-type headache (TTH) have elevated serum levels of IL-6 [49]. Moreover, this has been shown in animal migraine models to facilitate the excitability of dural afferents and allodynia [50]. It is therefore a molecule that may play an important role in triggering headache in systemic inflammation. Moreover, IL-6 receptor antagonist (tocilizumab) is a drug inducing clinical remission in giant-cell arteritis, a disease with headache as a prominent symptom [51].

TNF is an endogenous pyrogen and cytokine, playing an important role in early immune response to SARS-CoV-2 infection [18]. Moreover, it has been speculated for decades that it is a headache facilitator [52]. Four-hour TNF infusion has been associated with headache occurring in 65% of subjects [53]. Several studies have indicated that TNF may play a role in migraine pathogenesis [54]. It has also been shown to provoke the sensitisation of meningeal nociceptors [55]. Moreover, out of other cytokines analysed in one study, TNF has been most consistently associated with headache in aneurysmal subarachnoid haemorrhage [56].

As described above, time seems to be of great importance in the development of COVID-19-related headache. Since headache occurs early in the disease course, it is in this period that we should look for initiating factors. When analyses involve patients in later stages of the disease, then associations between inflammatory factors and headache are hard to find. For example, one highly comprehensive study found little association between a wide panel of cytokines and chemokines and headache [57]. The only factor associated with headache was, after adjustments, the level of IL-10. This cytokine is an important anti-inflammatory molecule targeted at the moderating effect of, among others, type I IFNs and TNF [58]. Higher levels of IL-10 may then support the hypothesis that IFNs and TNF play an important role in headache at early stages of the disease, and more IL-10 is secreted in later stages to alleviate this effect.

The above-described molecules form only a small fraction of innate immune response. Some elements have not been discussed due to little evidence allowing for their inclusion in this rationale (e.g. prostaglandins, galectins, innate immune cells including mast cells). However, other particles have been also implicated in early response to COVID-19 and associated headache. One study showed that headache in COVID-19 is associated with higher levels of NLR family pyrin domain containing 3 (NLRP3) inflammasome, and the high mobility group box 1 protein (HMGB1) [59]. The latter has been shown to be involved in trigeminal ganglion neuropathic pain [60]. Moreover, inflammasome is activated by SARS-CoV-2, which in turn leads to the activation of IL-1β and IL-18. IL-1β activates and sensitises the trigeminal ganglion [61, 62], while IL-18 may play some role in migraine [63].

In light of the described rationale, it might be surprising that COVID-19-related headache is associated with lower C-reactive protein levels [64, 65] (although these levels were still higher than in healthy subjects). However, it must be remembered that C-reactive protein is an unspecific inflammation marker rising moderately in the early phases of infection, and reaching higher levels when severe disease or complications develop. Therefore, it has probably a weaker association with processes causing headache.

Currently it is hardly possible to touch upon headache without mentioning CGRP. This molecule not only plays a pivotal role in primary headache disorders, but also participates

Table 2. Diagnostic criteria of acute headache attributed to systemic viral infection

A. Headache of any duration (but lasting < 3 months) fulfilling criterion C
B. Both of the following:
1. systemic viral infection has been diagnosed
2. no evidence of meningitic or encephalitic involvement
C. Evidence of causation demonstrated by at least two of the following:
1. headache has developed in temporal relation to onset of systemic viral infection
2. headache has significantly worsened in parallel with worsening of systemic viral infection
3. headache has significantly improved or resolved in parallel with improvement in, or resolution of, systemic viral infection
4. headache has one or both of following characteristics:
a. diffuse pain
b. moderate or severe intensity
D. Not better accounted for by another ICHD-3 diagnosis

in immune responses. TNF contributes to CGRP release in the trigeminal ganglion [66], while both TNF and IL-1β increase CGRP expression [67]. Moreover, nociceptive sensitisation caused by IL-6 is blocked by olcegepant, a CGRP antagonist [68]. It seems therefore justified to assume that COVID-19-related inflammation may lead to CGRP release at different levels of the trigeminal system [30]. However, in COVID-19 patients, serum levels of CGRP are lower than in healthy controls [69], while another study found no difference in CGRP levels between subjects with and without headache [59]. Finally, anti-CGRP treatments seem to have no effect on COVID-19 course [70].

Clinical features of COVID-19-related headache

Any headache should be classified according to the International Classification of Headache Disorders — 3 (ICHD-3). As regards COVID-19, it is currently diagnosed as "acute headache attributed to systemic viral infection" (Tab. 2). In some disorders, headache phenotype can contribute to identifying the pathological mechanism underlying this symptom (e.g. thunderclap headache in subarachnoid haemorrhage, postural headache in spontaneous intracranial hypotension [71]). In COVID-19 headache has however little specificity — the majority of patients appear to present symptoms similar to TTH 43–68% [8, 10, 72–75]. That is, pain is mostly bilateral, pressing and dull, and mild to moderate in intensity. This phenotype has been associated with lower C-reactive protein levels than headache with more migraine features (i.e. unilateral, pulsating, moderate to severe) [75]. Migraine phenotype is present in 25–50% of subjects [8, 73, 76], and is associated with a more severe COVID-19 course [14]. There is also some evidence that migraine-like headache in COVID-19 is associated with pre-existing migraine [74]. Accompanying autonomic symptoms (i.e. nausea or vomiting and hypersensitivity to light and sound) are not rare [64]. Non-nasal cranial autonomic symptoms (i.e. conjunctival injection and/or lacrimation, eyelid oedema, forehead and facial sweating, miosis and/or ptosis) occur rarely in the course of this infection. Naturally, nasal congestion and rhinorrhoea [8] are highly prevalent due to sinonasal inflammation. In conclusion, COVID-19-related headache may indicate a more effective and balanced immune response, especially when it resembles TTH.

Headache in COVID-19 has been associated with a better prognosis expressed as lower mortality and shorter disease duration [37, 65], although larger observations still await publication [77]. In COVID-19 α and λ IFNs peak early in a mild to moderate disease course. This might indicate that subjects able to develop this prompt immune response are apparently protected against severe COVID-19. This hypothesis is supported by experiments with rodents, where the administration of interferon I protected against cytokine storm [78]. However, it must be remembered that headache in COVID-19 is merely a symptom, and may herald serious complications e.g. cerebral venous sinus thrombosis [79] or encephalitis [80]. These conditions might be difficult to recognise during COVID-19 if headache is initially the only complaint. There is also some evidence that COVID-19 may lead to unusual changes in pre-existing migraine, e.g. there have been several case-reports of patients developing prolonged or unusual migraine aura during COVID-19 [81]. Consequently, caution is recommended, especially because many patients with COVID-19 complain of apparent 'red flags', e.g. mentioning "positional headache" or "worst headache ever" [10]. Moreover, comorbidities may have a strongly negative influence on prognosis [82].

Apart from a few case series, there is very little data on interventions effective in reducing COVID-19-related headache. In one study, paracetamol 1g iv or greater occipital nerve blocks were effective in reducing pain [47]. In another publication, indomethacin (50mg twice daily) was effective in a small case series of patients with acute (n = 21) and persistent COVID-19-related headache (n = 8) [83]. No data on preventive therapies is available, although several particles with potential simultaneously in viral infections and primary headache disorders have been proposed (e.g. low vitamin D3 levels are associated with more frequent headaches [74] and COVID-19 risk [75]).

Post-COVID-19 syndrome and headache

Headache is a common symptom of post-COVID-19 syndrome included in some diagnostic guidelines [84]. A study assessing data from 905 subjects with COVID-19-related headache showed that 31.1% of patients still had headache after one month, 16.8% after three months, and 16% after nine months [2]. These numbers were slightly lower in a recent meta-analysis: 47.1% during the acute phase, 10.6% at three

months and 8.4% after six months [85]. Nevertheless, both of these studies indicate that headache in post-COVID-19 syndrome has a poor prognosis. Approximately equal groups in post-COVID-19 headache have migraine and TTH phenotype-headache [2].

The pathomechanism of post-COVD-19 headache is unknown, although there is some evidence that patients with post-COVID may have increased IL-6 levels [86, 87]. Another study indicated elevated levels of IFN-α, TNF, G-CSF, IL-17A, IL-6, IL-1β, while IL-13 and CXCL-10 were decreased [88]. Although no clear association with pre-existing primary headache disorder has been confirmed, several scenarios are possible:

- persistent secondary headache due to COVID-19
- first manifestation of previous asymptomatic primary headache disorder
- exacerbation of previous low-grade primary headache disorder.

Post-vaccination headache

The COVID-19 pandemic has provided further data in the area of headache related to innate immune response, albeit not directly related to infection, but rather to vaccination. A recent meta-analysis including 83 studies of 1.57 million subjects revealed that headache occurs after the first and second COVID-19-vaccination dose in 22% and 29% of patients respectively [4]. Patterns similar to COVID-19 can be observed in cases of vaccine-related headache. Headache occurs early after vaccination [89–92] and is often accompanied by other systemic symptoms (i.e. myalgia and fever [91]). Similarly to COVID-19, headache after vaccination has more often a TTH phenotype, with migraine-like features present in one third of cases. Post-vaccination headache is not vaccine- or even pathogen-specific, i.e. it is present after vector and mRNA vaccinations. Moreover, immunisation against other types of viruses (e.g. influenza [93], human papillomavirus [94], Ebola [95]) is also commonly associated with headache. The risk of headache after COVID-19 vaccination is doubled by a pre-existing primary headache disorder (e.g. migraine) [91, 92].

The above observations may point to a common mechanism of vaccination- and COVID-19-related headache, with the only common denominator being immune response. One study showed that SARS-CoV-2 spike protein, a major antigen in vaccines, may act as a PAMP and cause neuroinflammation [17]. However, pain should be less prevalent after a second vaccine dose, if this mechanism is responsible for headache (when humoral immunity leads to faster spike protein elimination). Another study showed that after the first dose of SARS-CoV-2 mRNA vaccine (BNT162b2) a prompt release of IFN-γ, CXCL-10, IL-6, IL-8, IL-15, CCL-3, CCL-4 is observed, with some changes lasting for more than one week [96]. After the second dose IFN-γ, CXCL-10, IL-15 and IL-6 were elevated to levels several times higher than after the first dose. This pattern is mirrored by headache, which usually occurs within the first 24 hours, remits after a couple of days after the first vaccination [89–92], and is more prevalent after the second dose [4]. As a side issue, it should be mentioned that CCL-2 and IL-3 were not significantly increased throughout the study, TNF concentrations were only slightly higher, and type I and III IFNs were not analysed at all in this study [96].

It is important to remember that headache might be a primary complaint in patients presenting with vaccination complications. Probably the most widely cited source of post-vaccination headache is vector-vaccine-induced immune thrombotic thrombocytopenia (VITT), [4] although even less prevalent complications have been described (e.g. Tolosa-Hunt syndrome [97]). The major difference between headache in VITT and after vaccination is time. Post-vaccination headache occurs in the first 24 hours, while in VITT it occurs after several (7–10) days [98].

Conclusions and future research

Probably the most important question about COVID-19-related headache remains unanswered. It seems that the pandemic has run its primary course and will recur as a milder disease. Reduction in interest from the scientific community will follow. Meanwhile, the mechanism of headache in COVID-19 and the common pathways for other viral infections and primary headache disorders remain unknown.

Our rationale indicates that elements of innate immune response can trigger headache, peak early in COVID-19 alongside headache, and play an important role in protecting against severe disease course, allowing for a better prognosis in subjects with COVID-19-related headache. Consequently, it seems likely that interactions between innate immune response (especially in the sinonasal area) and trigeminal system play a crucial role in the aetiopathogenesis of headache secondary to COVID-19.

Moreover, if innate immune reaction to SARS-CoV-2 can trigger headache, then probably similar pathways are activated in other clinical situations (e.g. infections, immunisation, immunomodulatory treatment, autoimmune disorders). Future research should look for evidence of causality between particular immune response factors and headache. If found, such a correlation could have important clinical consequences for diagnosis and treatment strategies in a wide variety of disorders with prominent immune response.

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LEADING TOPIC

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Incidence and characteristics of post-COVID-19 parkinsonism and dyskinesia related to COVID-19 vaccines

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ABSTRACT

Background. Coronavirus disease 2019 (COVID-19) is an infectious disease mainly affecting the respiratory system; however, a significant prevalence of neurological symptoms has been noted.

Objectives. To investigate the incidence and characteristics of post-COVID-19 parkinsonism and to study dyskinesia related to COVID-19 vaccines.

Material and methods. The MEDLINE, PubMed, Scopus, and Web of Science databases were searched for all manuscripts relevant to post-COVID-19 parkinsonism and dyskinesia related to COVID-19 vaccines. Subsequently, we extracted and analysed data from the manuscripts in a structured manner.

Results. We found 24 patients with post-COVID-19 parkinsonism, with a mean onset age of 58 years after a mean of 30 days from the COVID-19 onset. Akinetic-rigid (n = 11) and mixed (n = 6) subtypes were the most common. Asymmetry was present in 13/15 patients. Brain MRI was unremarkable in 11/19, whereas dopaminergic system imaging was abnormal in 8/8 patients. Responsiveness to dopaminergic treatment was observed in 12/15 patients. Four patients improved after immunomodulatory therapy. Comorbidities were present in 9/24, encephalopathy symptoms in 11/24, and loss of smell in 9/13 patients. Most patients (n = 14) suffered serious COVID-19-related complications and three were treated with haloperidol. Parkinsonism improved (n = 5) or resolved (n = 4) during the follow-up.

Five patients, with a mean age of 52, developed dyskinesia at a mean of 25 hours after receiving the COVID-19 mRNA vaccines. One patient had a history of neuropsychiatric symptoms and developed functional dyskinesia of the tongue. Four patients had a previous history of Parkinson's Disease (PD) with a mean duration of 10 years and developed dyskinesia and dystonia, which resolved (n = 2) or improved (n = 2) during the follow-up.

Conclusions. Post-COVID-19 parkinsonism is a very rare complication, and it is likely that this is an umbrella syndrome that includes many different etiologies. Dyskinesia due to COVID-19 vaccines is exceedingly rare and probably has the same pathophysiological basis as in other conditions with exacerbation of PD symptoms.

Key words: SARS-CoV-2, Parkinson's Disease, levodopa, dopaminergic, vaccination, dystonia

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Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a novel strain of coronavirus that causes coronavirus disease 2019 (COVID-19), an infectious disease mainly affecting the respiratory system [1, 2]. The first case of COVID-19 was confirmed in Wuhan, China, on 8 December, 2019 [1]. The subsequent outbreak of pneumonia that spread across the globe led to the declaration of a pandemic by the World Health Organisation in March 2020.

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Apart from respiratory symptoms, many patients affected by COVID-19 have presented symptoms and signs suggestive of central (dizziness, headache, altered consciousness, stroke, ataxia, seizure) and peripheral (disorders of smell and taste, vision impairment, neuralgia) nervous system involvement [3, 4]. Furthermore, considering the 1918 flu pandemic with post-encephalitic parkinsonism and the particularly high prevalence of neurological symptoms in COVID-19, concerns have arisen regarding a future increase in the prevalence of parkinsonism and other neurodegenerative disorders [2, 5, 6].

By early December 2022, three years after the index case of COVID-19, more than 640 million cases had been confirmed, and almost 13 billion vaccines administered [24]. The literature on COVID-19, its short- and long-term complications, and the safety of COVID-19 vaccines, continues to grow [7]. As most papers reporting neurological complications in detail are case reports, we felt there was a strong need to review and analyse them collectively in order to draw more meaningful conclusions.

This paper adds to the growing body of knowledge on the capability of COVID-19 to cause parkinsonism by reviewing and summarising all of the published cases of post-COVID-19 parkinsonism. In addition, we investigated any possible relationship between COVID-19 vaccines and dyskinesia.

Material and methods

We searched the MEDLINE, PubMed, Scopus, and Web of Science databases for all manuscripts in English published up to the end of November, 2022 reporting parkinsonism due to COVID-19 or dyskinesia related to COVID-19 vaccination. We used the following search terms: 'parkinsonism' and 'SARS-CoV-2'; 'parkinsonism' and 'COVID', 'dyskinesia' and 'SARS-CoV-2'; 'dyskinesia' and 'COVID'; and 'dyskinesia' and 'vaccine'. Subsequently, we screened the titles and abstracts to check that they were pertinent to the review topic. In addition, we searched the reference lists of the relevant articles and websites to verify the comprehensiveness of the bibliography. Next, we extracted the data from the full-text manuscripts in a structured manner. In the patients with parkinsonism due to COVID-19, we collected data on sex, age, comorbidities, COVID-19 pneumonia severity according to the National Institutes of Health guidelines [8], loss of smell, symptoms of encephalopathy, other COVID-19 complications, the timespan between parkinsonism onset and first COVID-19 symptoms, the subtype of parkinsonism [9, 10], asymmetry of parkinsonism, brain magnetic resonance imaging (MRI) findings, dopaminergic system imaging, by 6-^{18}F-fluoro-L-dopa (^{18}F-FDOPA) positron emission tomography (PET) or ^{123}I-ioflupane (DaTscan) single-photon emission computerised tomography (SPECT), responsiveness to levodopa or other dopaminergic medications, application of immunomodulatory therapy and response to thereof, follow-up time, and outcomes. In the patients with dyskinesia related to COVID-19 vaccination, we retrieved data on sex, age, comorbidities, presentation of dyskinesia, number and type of vaccine, time of symptoms onset since vaccination, concomitant symptoms, brain MRI findings, management, follow-up time and outcomes.

Results

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram is presented in Figure 1.

Our search identified 468 records in MEDLINE, 1,846 in PubMed, 637 in Scopus and 255 in Web of Science. After removing duplicates (n = 2,359), this yielded 1,796 papers. Next, we screened the papers and removed 1,775 that were not relevant to the subject of this review. We did not identify any other relevant study via citation or website searching. Finally, we retrieved and reviewed the data from the remaining 21 manuscripts, including 18 papers reporting parkinsonism due to COVID-19 and three on dyskinesia following COVID-19 vaccination.

Parkinsonism related to COVID-19 [11–28]

A summary of the data retrieved on patients with parkinsonism due to COVID-19 is set out in Table 1. The material is heterogenous, and the presented information refers to the number of patients who underwent a specific procedure (e.g. neuroimaging).

A total of 24 patients (nine females, 13 males, and two sex not reported) developed parkinsonism related to COVID-19. The mean age of parkinsonism onset was 58 years (range 31–75) after a mean of 30 days (range 0–120) from the first COVID-19 symptoms. The most common parkinsonism subtype was akinetic-rigid (n = 11), followed by mixed (n = 6). Asymmetry was present in 13/15 patients with sufficient data. Brain MRI was unremarkable in 11/19 patients. Dopamine transporter single-photon emission computerised tomography (DaTscan-SPECT) (n = 7) and ^{1}-F-fluorodopa positron emission tomography (^{1}-F-FDOPA PET) (n = 1) were abnormal in 8/8 patients, and asymmetry was noted in 7/8 cases. Responsiveness to levodopa was observed in 11/15 patients (good in 10 and moderate in one), with a mean daily dose of 400mg (range 220-600). Additionally, one patient responded well to a small dose of pramipexole (0.375 mg/day). Lack of response to dopaminergic therapy was noted only in two patients on levodopa (daily doses of 300 mg and 450 mg), and in another one on a small dose of apomorphine (2 mg/day).

Twelve patients were treated with immunomodulatory therapy, including steroids (n = 9), intravenous immunoglobulins (n = 3), and convalescent plasma (n = 2). Most patients did not benefit from the immunomodulatory treatment (n = 7), although improvement was noted in four.

In the whole group, mean follow-up was 160 days (range 6–360), during which parkinsonism resolved in four and

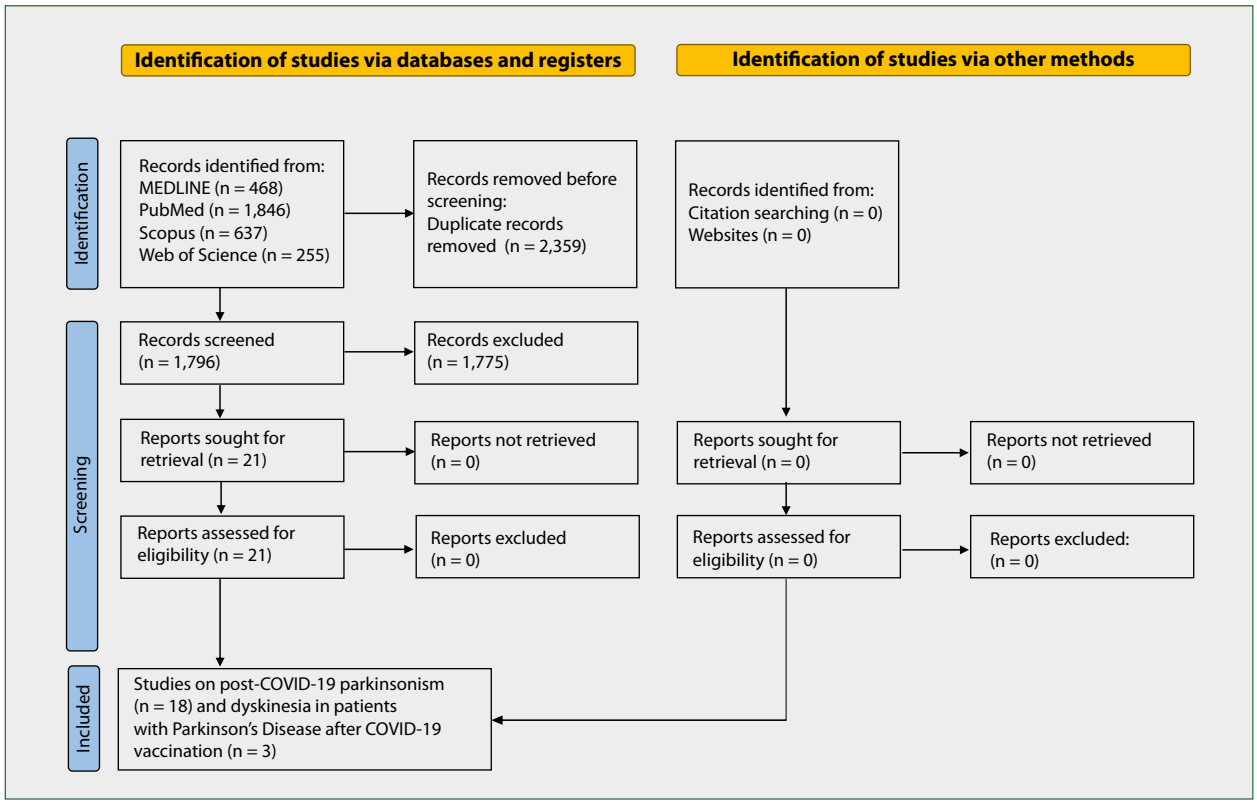

Figure 1. PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases, registers, and other sources From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

improved in five of the 15 patients with follow-up outcomes data.

Comorbidities were present in 9/24 patients, the most common being cardiovascular disease (n = 7), whereas 10 patients had an unremarkable history, and in five data was not reported. COVID-19 pneumonia severity was ascertained as mild in seven, moderate in five, severe in six, and critical in five patients. Encephalopathy symptoms were present in 11, not reported in three, and absent in 10 patients. Loss of smell was noted in nine patients, whereas four patients had normal smell, and in 11 patients ability to smell information was not provided.

Most patients (n = 14) suffered from complications in the acute phase of COVID-19, the most common being acute kidney injury (n = 5), mental problems (n = 4), and coagulation disorders (n = 3). However, individual patients developed other serious complications, including extrapontine osmotic demyelination syndrome, severe encephalitis with coma, and others. In addition, three patients were treated with haloperidol; however, only in one case was the time and dose provided (total 28mg over five days), and in another one approximate duration of treatment was noted (three months). In addition, one patient treated with haloperidol had DaTscan-SPECT performed, which showed asymmetrically reduced striatal activity.

Dyskinesia related to COVID-19 vaccination [29–31]

The data on dyskinesia due to COVID-19 vaccination is set out in Table 2. Five patients (three females, two males) with a mean age of 52 years (range 20–79) developed dyskinesia at a mean of 25 hours (range 6–72) after receiving the mRNA COVID-19 vaccine. Besides dyskinesia, other symptoms, including fatigue, fever, and insomnia, were observed in three of them.

The first patient was a female in her early 20s with a one-year history of depression, anxiety, and insomnia, who developed tongue dyskinesia three days after receiving her first COVID-19 mRNA vaccine. Her brain MRI was normal, and extensive diagnostic work-up was unrevealing. She was diagnosed with functional dyskinesia of the tongue, and during the 11-month follow-up, her involuntary movements became more tremor-like, combining irregular tongue tremor and jerks. The other four patients (two females and two males) had a previous history of Parkinson's Disease (PD) with a mean duration of 10 years (range 5–13); however, they did not develop troublesome dyskinesia and indeed only occasionally displayed slight dyskinesia. In addition, one patient was treated with subthalamic deep brain stimulation (DBS-STN), and another one with a levodopa/carbidopa intestinal gel

Table 1. Summary of data retrieved on patients with parkinsonism due to COVID-19

Number	Paper	Sex	Age (years)	Comorbidities	COVID-19 pneumonia severity	Loss of smell	Symptoms of encephalopathy	Other COVID-19 complications	Timespan between parkinsonism onset and first COVID-19 symptoms (days)
1	Ghosh et al. (2021)	F	65	Diabetes mellitus	Severe	N/R	Yes	Severe osmotic demyelination syndrome with hyperglycaemic hyper-osmolar state	11
2	Maramattom et al. (2021)	M	75	None	Mild	N/R	Yes	Severe COVID-19 encephalitis with coma	3
3	Rao et al. (2021)	M	72	None	Severe	Yes	No	Acute kidney injury, peripheral thrombophlebitis	14
4	Rao et al. (2021)	M	66	Diabetes mellitus, Cardiovascular disease, Seizures	Severe	N/R	No	Acute kidney injury	21
5	Rao et al. (2021)	M	74	None	Moderate	N/R	No	Acute kidney injury	21
6	Fearon et al. (2021)	M	46	N/R	Critical	N/R	N/R	Acute kidney injury, disseminated intravascular coagulation	N/R
7	Morassi et al. (2021)	F	70	Cardiovascular disease, Depression (trazodone, fluoxetine, benzodiazepines)	Severe	No	Yes	Delirium controlled with haloperidol; seizures	31
8	Morassi et al. (2021)	F	73	Cardiovascular disease, Depression with psychotic symptoms (olanzapine, amisulpride)	Mild	No	Yes	Aspiration pneumonia, infected bedsores	0
9	Ong et al. (2021)	M	31	None	Severe	N/R	Yes	Delirium controlled with haloperidol	15
10	Akilli et al. (2021)	M	72	Diabetes mellitus, Cardiovascular disease	Critical	N/R	Yes	Acute respiratory distress syndrome	2
11	Makhoul &Jankovic (2021)	F	64	N/R	Mild	Yes	No	N/R	5
12	Cohen at al. (2020)	M	45	Cardiovascular disease, Asthma	Moderate	Yes	No	None	18
13	Faber et al. (2020)	F	35	None	Mild	Yes	No	None	10
14	Mendez-Guerrero et al. (2020)	M	58	Cardiovascular disease	Critical	Yes	Yes	Acute respiratory distress syndrome	38
15	Tiraboschi et al. (2020)	F	40	Obesity	Critical	Yes	Yes	Delirium, generalised tonic-clonic seizures, stereotypical paroxysmal lower-limb and choreiform upper limb movements treated with haloperidol	57
16	Roy et al. (2021)	M	60	Cardiovascular disease, Diabetes mellitus	Critical	N/R	Yes	Septic shock, ventricular tachycardia, acute renal failure requiring haemodialysis, COVID-induced coagulopathy	8
17	Cavallieri et al. (2021)	M	67	None	Moderate	Yes	No	None	120
18	Cavallieri et al. (2021)	M	45	None	Mild	Yes	No	None	90
19	Ayele et al. (2021)	F	35	None	Moderate	Yes	Yes	Fluctuating mentation and abnormal behaviour, fever, and visual hallucination	10
20	Pilotto et al. (2020)	M	73	N/R	N/R	N/R	Yes	N/R	0
21	Rass et al.	N/R	N/R	N/R	Severe	N/R	N/R	N/R	N/R
22	Rass et al.	N/R	N/R	N/R	Moderate	N/R	N/R	N/R	N/R
23	Beckers et al. (2022)	F	50	None	Mild	No	No	None	N/R
24	Beckers et al. (2022)	F	50	None	Mild	No	No	None	N/R

F — female; M — male; N/R — not reported →

Table 1. cont. Summary of data retrieved on patients with parkinsonism due to COVID-19

Number	Subtype of parkinsonism	Asymmetry of parkinsonism	Brain MRI findings	Dopaminergic system imaging	Levodopa responsiveness (dose in mg/day)	Immunomodulatory herapy	Effect of immunomodulatory therapy on neurological deficits	Time of follow-up (days)	Follow-up outcome
1	Akinetic-rigid	No	Abnormal (osmotic demyelination syndrome with predominant basal ganglia)	N/R	Good response (500 mg)	Steroids before development of neurological symptoms	Deterioration	120	Significant improvement
2	Akinetic-rigid	N/R	N/R	N/R	No response (300 mg/day)	Steroids	None	210	Significant improvement
3	Gait difficulty	N/R	N/R	N/R	Good response (220 mg/day)	Steroids	None	120	Resolution of symptoms
4	Akinetic-rigid	Yes	Unremarkable	N/R	Good response	Steroids	None	30	Significant improvement
5	Mixed	N/R	Unremarkable	N/R	Good response	N/R	N/R	150	Significant improvement
6	Mixed	Yes	Bilateral lesions in basal ganglia	N/R	Unresponsive (450 mg/day)	N/R	N/R	360	Severe parkinsonism unresponsive to L-Dopa
7	Akinetic-rigid	Yes	*De novo* slight ventricular enlargement	Abnormal, left side more affected	Moderate response (400 mg/day)	Steroids, intravenous immunoglobulins	None	270	Gait difficulty, cognitive decline
8	Akinetic-rigid	N/R	Unremarkable	N/R	Good response (400 mg/day)	Steroids, intravenous immunoglobulins	None	30	Death
9	Akinetic-rigid	No	Abnormal (bilateral thalamic and pontine lesions)	N/R	N/R	Steroids	Improvement	6	Resolution of symptoms
10	Akinetic-rigid	No	Unremarkable	N/R	N/R	Convalescent plasma treatment	Improvement	60	Resolution of symptoms
11	Tremor-dominant	Yes	N/R	Abnormal, right side affected	N/R	N/R	N/R	N/R	N/R
12	Akinetic-rigid	Yes	Unremarkable	Abnormal, left more side affected	Good response (pramipexole, 0.375 mg)	Steroids	None	N/R	N/R
13	Akinetic-rigid	Yes	Unremarkable	Abnormal, left side affected	Good response (600 mg/day)	N/R	N/R	N/R	N/R
14	Mixed	Yes	Unremarkable	Abnormal, left side affected	No response (apomorphine, 2 mg)	N/R	N/R	53	Partial improvement
15	Mixed	Yes	Unremarkable	N/R	N/R	Intravenous immunoglobulins	Improvement, however simultaneous withdrawal of haloperidol	143	Resolution of symptoms
16	Akinetic-rigid	N/R	Basal ganglia and corona radiata stroke	N/R	Good response (300 mg/day)	Convalescent plasma treatment	N/R	120	Partial improvement
17	Tremor-dominant	Yes	Mild white matter hyperintensities	Abnormal bilaterally	N/R	N/R	N/R	N/R	N/R
18	Tremor-dominant	Yes	Unremarkable	Abnormal bilaterally	N/R	N/R	N/R	N/R	N/R
19	Mixed	Yes	Symmetrical non-enhancing, T1 isointense, T2 and FLAIR hyperintense lesions with no diffusion restriction in both pallidal regions	N/R	Good response (375 mg/day)	Steroids	Improvement	N/R	Significant improvement
20	N/R	N/R	T2 frontal hyperintensities	N/R	N/R	N/R	N/R	N/R	Severe neurological deficit
21	N/R	N/R	N/R	N/R	N/R	N/R	N/R	360	Persistence of parkinsonism
22	N/R	N/R	N/R	N/R	N/R	N/R	N/R	360	Persistence of parkinsonism
23	Akinetic-rigid	Yes	Unremarkable	Abnormal	Good response	No	Not applicable	N/R	N/R
24	Mixed	Yes	Unremarkable	Not performed	Good response	No	Not applicable	N/R	N/R

F — female; M — male; N/R — not reported

Table 2. Summary of data retrieved on patients with dyskinesia related to COVID-19 mRNA vaccine

Number	Paper	Sex	Age (years)	Comorbidities	Presentation	Number and type of vaccine	Time of symptoms onset since vaccination (hours)	Concomitant symptoms	Brain MRI	Management	Time of follow-up (days)	Follow-up outcome
1	Demartini et al. (2022)	F	20	One year history of depression, anxiety and insomnia	Functional involuntary movements of tongue (tremor-like dyskinesia)	First dose mRNA COVID-19 vaccine	72	Tiredness and fatigue	Normal	N/R	330	Deterioration
2	Erro et al. (2021)	F	61	Parkinson's Disease for 11 years and no dyskinesia	Severe generalised dyskinesia and/or confusion	First dose mRNA COVID-19 vaccine	6	None	N/R	Reduction of levodopa dose	21	Remained without dyskinesia with wearing off
3	Erro et al. (2021)	F	79	Parkinson's Disease for 5 years with occasional slight peak of dose dyskinesia	Severe dyskinesia	First dose mRNA COVID-19 vaccine	24	Fever, confusion, delusions	N/R	Paracetamol and reduction of levodopa dose	14	Mild confusion and dyskinesia more severe than before vaccination
4	Imbalzano et al. (2022)	M	46	Parkinson's Disease for 9 years, treated with subthalamic deep brain stimulation	Left foot dystonia	Third (booster) dose mRNA COVID-19 vaccine	12	Low back pain, insomnia	N/R	Increasing DBS-STN parameters and adding additional levodopa dose	5	Resolution of symptoms and restoration of previous therapeutic regimen
5	Imbalzano et al. (2022)	M	55	Parkinson's Disease for 13 years, treated with levodopa carbidopa intestinal gel (LCIG) infusion	Severe dyskinesia	Third (booster) dose mRNA COVID-19 vaccine	12	None	N/R	Reduction of LCIG dose with partial improvement	5	Almost complete resolution of dyskinesia and restoration of previous therapeutic regimen

F — female; M — male; N/R — not reported

infusion. Two developed symptoms after receiving their first COVID-19 vaccine, whereas the other two only presented involuntary movements after the third (booster) dose. Three of these patients developed severe post-vaccination dyskinesia that was managed by a reduction in the levodopa dose. One patient manifested left foot dystonia that was alleviated by increasing the levodopa dose and the DBS-STN parameters. During mean follow-up of 11 days (range 5–21) the symptoms spontaneously improved in all four patients; however, only two could return to their original treatment regimen.

Discussion

The age at onset in post-COVID parkinsonism was similar to that in sporadic PD [32]. Asymmetry of parkinsonism was present in the majority of patients. Although this is not limited to sporadic PD or secondary parkinsonism, it occurs more often in the former [32]. An akinetic-rigid subtype of parkinsonism was the most common in the present review, and has also been reported to be the most frequent phenotype of sporadic PD [32]. The prevalence of other subtypes is challenging to compare, as most previous papers on sporadic PD used different and inconsistent classification systems [10].

Responsiveness to levodopa, one of the supportive features of sporadic PD [33], was also present in most patients with post-COVID parkinsonism. Among the three non-responders to dopaminergic medications, one received a small dose of apomorphine (equal to 20 mg of levodopa), another underwent severe COVID-19 encephalitis with coma, and the third suffered from disseminated intravascular coagulation and had severe lesions in the basal ganglia (oedema with small haemorrhagic foci). The dopaminergic system imaging (DaTscan-SPECT) was performed only in the first case and showed bilaterally reduced asymmetric nigrostriatal uptake. It is tempting to believe that the first case had sporadic PD and was just undertreated; however, his symptoms significantly improved during the follow-up without any PD-specific treatment, which supports the secondary aetiology of parkinsonism in this patient [21]. Brain MRI was unremarkable, whereas dopamine system imaging was abnormal and asymmetric in most patients in whom the dopaminergic system was evaluated, which may suggest sporadic PD as opposed to secondary or atypical parkinsonism. In eight patients, various abnormalities were evidenced by MRI. Interestingly, four responded to levodopa, comprising one with extrapontine osmotic demyelination syndrome, one with ventricular enlargement, one with basal ganglia stroke, and one with bilateral pallidal lesions. Moreover, five of the 11 patients with signs of encephalopathy had levodopa-responsive parkinsonism. This reminds us that forms of parkinsonism other than sporadic PD may also, albeit usually with poorer outcomes, respond to levodopa [34]. As the follow-up in these patients was short, it will be very interesting to see if their response changes over the long term.

Parkinsonism partially improved or resolved in more than half of the affected patients. In some cases, the improvement was spontaneous, whereas it was attributed to the immunomodulatory treatment or dopaminergic therapy in others. However, as the group was small and diverse, we did not identify any factors associated with better or worse outcomes. Although immunomodulatory therapy was used in half of the patients with post-COVID parkinsonism, only four benefitted from the treatment. Due to the different clinical settings, administration time, and type of therapy used, it is challenging for us to compare the effects of the therapy. This difficulty in evaluating the role of immunomodulatory treatment in managing post-COVID-19 parkinsonism is illustrated by the case of a 40-year-old female who suffered from critical COVID-19 pneumonia, followed by agitation, confusion, generalised-clonic seizures, and choreiform limb movements [22]. She received intravenous immunoglobulin therapy and started haloperidol. Over the following days she improved, but parkinsonism was noted. After approximately two months, the treatment with intravenous immunoglobulins was repeated, and she simultaneously tapered down haloperidol. Subsequently, she recovered completely within a few weeks [22]. However, the curative treatment (i.e. either immunomodulation or the withdrawal of a potentially offending drug or a combination of the two), is impossible to ascertain. Parkinsonism may be related to neuroleptic treatment.

Many patients afflicted with COVID have received amantadine, which was initially introduced as an antiviral drug in 1966. In recent decades, it was mainly used in PD due to its potential to increase dopamine and block NMDA receptors. It was initially suggested that it might be beneficial in COVID [35, 36]; however, a recent study on a large group of 552 patients did not confirm this observation [37]. Although there was no sufficient information available in the literature to analyse the impact of amantadine use on post-COVID parkinsonism, a causal relationship would be interesting to explore.

The heterogeneity of clinical presentation and follow-up outcomes of post-COVID-19 parkinsonism is probably related to different pathophysiological mechanisms, or a combination thereof. Similar to other coronaviruses, SARS-CoV-2 seems to have a tropism for the central nervous system [2, 38, 39]. Previous studies have shown that it may enter the brain through infiltration of the olfactory mucosa and spread through the olfactory projections via axonal transport [38]. Angiotensin-converting enzyme-2 (ACE-2) is the main cell entry receptor for SARS-CoV-2 [2, 38, 39]. The receptor is expressed in glia and neurons, particularly in the brainstem, cerebral cortex, hypothalamus, substantia nigra, and basal ganglia [2, 37, 38]. High expression of the ACE2 receptor in the dopaminergic neurons may explain the predilection of SARS-CoV-2 to affect these brain regions [38]. The inflammatory reaction and hypoxic-ischaemic damage in the central nervous system, rather than direct viral load, have been postulated as pathogenic mechanisms [38]. Moreover, it has been suggested

that expression of DOPA decarboxylase (DDC), an enzyme playing a crucial role in dopamine and serotonin synthesis, is functionally linked with ACE-2 expression, and that the systemic failure observed in some COVID-19 patients may be due to the disruption of the dopamine synthetic pathway [40]. The ACE-2 receptor is also highly expressed in intestinal epithelial cells [38, 40]. The infiltration and inflammation of intestinal mucosa may alter microflora and disturb the gut-brain axis [39]. As alterations of intestinal microbiome and gut inflammation have been linked to PD, this may be another mechanism involved in the development of post-COVID-19 parkinsonism [39]. Intraneuronal deposition of alpha-synuclein is the pathological hallmark of PD. Laboratory tests have shown that SARS-CoV-2 nucleocapsid protein can boost alpha-synuclein aggregation [41]. However, the alpha-synuclein levels in cerebrospinal fluid and blood of patients with COVID-19 and neurological symptoms did not differ from those with COVID-19 and no neurological manifestations or from healthy controls [38]. The ACE-2 receptor is also expressed in the vascular endothelium of the brain [38].

Therefore, SARS-CoV-2 may infiltrate the endothelial cells causing vasculitis and blood-brain barrier disruption [2, 38]. This mechanism may explain the high incidence of ischaemic and haemorrhagic brain injury in patients with COVID-19 [38]. Besides vascular damage, infiltration of the endothelium may open yet another route for SARS-CoV-2 invasion, being responsible for the presence of SARS-CoV-2 in brain regions that do not receive projections from olfactory nerves [2, 38].

Finally, the 'unmasking' of underlying latent PD by COVID-19 cannot be excluded [28]. Exacerbation of motor symptoms in patients with sporadic PD, short-lived or permanent, has been reported in infections (ranging from severe systemic infections to mild urinary tract infections), surgery, trauma, and psychological stress [28, 42]. The last of these is frequently reported as a precipitatory factor by many patients with sporadic PD [28]. It has been postulated that alteration of dopamine pathways by proinflammatory mediators, changes in intestinal microflora, stress hormones, and triggering of striatal glia-mediated inflammation may be the involved mechanisms [28, 42]. Individual genetic architecture impacts upon the risk of developing PD [10, 43]. As many genetic variants cause or increase the chances of developing PD, carriers thereof may be more susceptible to develop parkinsonism after COVID-19.

Hence, as many patients with post-COVID-19 parkinsonism display features of sporadic PD (i.e. similar age at onset, asymmetry, and response to levodopa), we speculate that in some cases, most likely those with a pre-existing genetic or other susceptibility to developing PD, COVID-19 can overtax their compensatory mechanisms and unmask PD. We suggest performing a brain MRI study and DaTscan-SPECT in all cases of post-covid parkinsonism [44].

The only patient who developed dyskinesia due to the COVID-19 vaccine and who had no history of PD was diagnosed with a functional movement disorder (FMD) [29]. Previous studies showed that 75% of patients diagnosed with FMD are females; they commonly have a history of pre-existing neuropsychiatric symptoms (particularly anxiety and depression), and many of them report precipitatory factors in the form of medical procedures or stressful life events [45, 46]. Therefore, in this case, the functional aetiology of the symptoms was attributed to the patient's expectations, beliefs, individual psychological profile, and predispositions [29].

The other four patients who developed dyskinesia and dystonia following the COVID-19 vaccine were at the advanced stage of PD, in which dyskinesia, dystonia, and motor fluctuations are expected to occur [47]. The precise mechanism by which the COVID-19 mRNA vaccine could trigger dyskinesia in PD is unknown; however, stimulation of the immune system and the resultant systemic inflammatory response may be one possible explanation [30, 31]. Furthermore, besides the mechanisms mentioned above involved in worsening PD symptoms, inflammatory cytokines may also increase the permeability of the blood-brain barrier, and thus increase the delivery of dopaminergic medication to the brain, which would explain the frequent worsening of dyskinesia during infections in patients with PD [30, 31]. However, given that more than 5 billion people worldwide have received at least two doses of COVID-19 vaccines and that only five cases with associated dyskinesia have been reported, the relationship between the two is close to chance levels, and simple coincidence cannot be excluded.

Conclusions

Despite initial concerns about a surge of post-COVID-19 parkinsonism, so far it remains a very rare complication. Most likely, post-COVID-19 parkinsonism is an umbrella syndrome that includes many different aetiologies. However, as the time elapsed and thus the follow-up since the index case of COVID-19 is still short, more observation time is needed to ascertain the relationship between COVID-19 and parkinsonism. In 1918 after the flu pandemic, post-encephalitic parkinsonism developed several years after recovery. In addition, it seems that dyskinesia due to COVID-19 vaccines is exceedingly rare and probably has the same pathophysiological basis as dyskinesia in other conditions with exacerbation of PD symptoms.

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Hyperkinetic movement disorders following SARS-CoV-2 infection and vaccination — an update

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ABSTRACT

The aim of this review was to summarise current knowledge regarding hyperkinetic movement disorders related to SARS-CoV-2 infection and vaccination in terms of phenomenology, epidemiology, pathogenesis and treatment. After a thorough review of the PubMed and Google Scholar databases (2020–2022), we identified myoclonus and ataxia sometimes accompanied by opsoclonus (AMS) as the two most frequent COVID-19 sequelae, with chorea, tremor and dystonia being very rare. The pathogenesis seems to be variable, but in the majority of AMS cases it was autoimmunological, with good response and recovery after corticosteroids or intravenous immunoglobulins infusions. Vaccination may be complicated by hyperkinetic movement disorders (e.g. tremor, dystonia), but this is very rare. Patients with Deep Brain Simulation depletion should not be postponed due to lockdowns as this may result in fatal outcomes.

Key words: ataxia, myoclonus, opsoclonus, chorea, tremor, dystonia, COVID-19, SARS-CoV-2

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Introduction

Post-COVID conditions are being reported worldwide under a broad range of names, including long COVID, post-acute COVID-19, long-term effects of COVID, post-acute COVID syndrome, chronic COVID, long-haul COVID, late sequelae and others, as well as the research term 'post-acute sequelae of SARS-COV-2 infection' (PASC). They may be a result of the persistance of acute phase symptoms or newly developed or recurrent symptoms after recovery. According to the WHO (World Health Organisation), post COVID-19 syndrome refers to cases with a history of probable or confirmed SARS-CoV-2 infection, usually at least three months after onset, with symptoms that last for at least two months and cannot be explained by an alternative diagnosis [1]. The most frequent complications of SARS-CoV-2 infection that may fulfill the definitions of PASC or Long-COVID include: fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnoea (24%). Among the neurological complications, the most common are cognitive decline, sleep problems, myalgia, and anosmia/dysgeusia) [2].

Several possible pathogenetic mechanisms of neurological symptoms associated with COVID-19 (direct viral invasion, hypoxic injury, coagulopathy, inflammatory response and immune dysfunction, side effects of medications, psychological — resulting in functional symptoms after recovery from severe life-threatening condition) have been recently described [3]. Myoclonus and tremor — the predominant movement disturbances associated with COVID-19 — are non-specific symptoms that often occur in critically ill patients as a result of hypoxia or toxic-metabolic disturbances [4]. In patients severely affected by COVID-19, with multiorgan failure, requiring mechanical ventilation and treatment in the Intensive Care Unit (ICU), neurological symptoms are most likely related to hypoxia and a toxic-metabolic cause or causative medications.

On the other hand, in patients with an asymptomatic or mild infection, with no history of severe hypoxia or multiorgan failure, the cause of movement disorders accompanying

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COVID-19 is most likely to be autoimmune. As in other infectious diseases, SARS-CoV-2 can result in autoimmunological reactions, probably due to the mimicry mechanism. Hyperkinetic movement disorders besides autoimmune neuropathies (e.g. Guillain-Barre syndrome) may represent the group of such conditions. Fortunately, they are not as frequent as other PASCs. As they respond well to immune therapies, all acute/subacute movement disorders following a SARS-CoV-2 infection have to be considered as being of autoimmune origin and properly treated. They usually occur a few weeks after recovery, and if treated may resolve in under two months. In this way, they do not fulfill the diagnosis of PASC.

The most frequently reported hyperkinetic movement disorder related to COVID-19 is myoclonus, often occurring in syndromes including ataxia and opsoclonus. Only a few cases of chorea, tremor and dystonia have been reported [5]. A systematic review of hyperkinetic syndromes following SARS-CoV-2 infection was presented in this journal in 2021 [6]. For this latest analysis, we reviewed the PubMed and Google Scholar databases for the period 2020–2022, searching for papers using the key words: 'ataxia', 'myoclonus', 'opsoclonus', 'chorea', 'dystonia', 'tremor', 'SARS-CoV-2', 'COVID-19', and 'vaccination' to update the literature. Key results are set out in Tables 1–3.

Ataxia/myoclonus/opsoclonus syndrome

To date, there have been 50 publications of case reports and case series of patients with myoclonus or ataxia or opsoclonus (or a combination of these) related to COVID-19 [7–56]. A total of 105 patients had been described in the medical literature up to the end of 2022. Forty-three of these 105 cases had a severe SARS-CoV-2 infection and required hospitalization in the ICU [48–56]. As the movement disorder could be a possible complication (hypoxia, medications) they were not included into analysis. Sixty two out of 105 cases developed movement disorders despite mild or moderate severity of infection — as these were possibly of autoimmune origin, these reports were included into detailed analysis.

Sixty two patients — 55 men and seven women aged 32–88 years — developed myoclonus or opsoclonus or ataxia after SARS-CoV-2 infection. The most frequent was myoclonus (57/62 patients), followed by ataxia (46/62), and opsoclonus (17/62). In two patients, myoclonus presented as an independent symptom. Thirty one subjects had ataxia-myoclonus syndrome (AMS), 14/62 had opsoclonus-myoclonus-ataxia syndrome (OMAS), and 3/62 patients had opsoclonus-myoclonus syndrome (OMS). The myoclonus type affecting COVID-19 patients was a positive one, but also action-sensitive and stimulus-sensitive in some cases. Symptoms were generalised, in some patients affecting their voice and gait. Seventeen patients presented additional signs such as dysarthria, dysphagia, and/or nystagmus as a manifestation of cerebellar syndrome. Thirteen patients presented neuropsychiatric symptoms that accompanied movement disturbances: two mild somnolence, one sopor, four confusion, four cognitive impairment, one psychomotor agitation with frontal lobe syndrome, and one psychomotor retardation.

The delay between the onset of COVID-19 infection and the onset of neurological symptoms was 2–42 days (mean 13). In the majority of cases, 43/62 patients, SARS-CoV-2 infection was mild or asymptomatic, usually with fever, cough, myalgia, general weakness and not requiring oxygen therapy. Fifteen out of 62 had a moderate course of infection and required non-invasive oxygen therapy. In four subjects, there was no precise data as to the severity of the COVID-19.

The neuroimaging studies (computed tomography — CT, magnetic resonance imaging —MRI), neurophysiological (electroencephalography, electroneurography, electromyography) did not show abnormalities in all reported cases. General examination of cerebrospinal fluid (CSF) was normal in 46 patients, isolated protein elevation was observed in six patients, isolated lymphocytic pleocytosis in one, and lymphocytic pleocytosis with elevated protein in one. Lumbar puncture was not performed in eight cases.SARS-CoV-2 RT-PCR in the CSF was negative in all tested cases. In three reports, autoantibodies were identified: against glial fibrillary acidic protein (GFAP) [16], leucine-rich glioma-inactivated 1 (LGI-1) [29], and glutamic acid decarboxylase (anti-GAD) [22]. Another study described a patient with post-COVID-19 ataxia-myoclonus syndrome in whom autoantibodies directed against Purkinje cells of the cerebellum, striatal and hippocampal neurons were identified by nerve tissue immunostaining with serum and CSF [13]. Franke et al. analysed the cerebrospinal fluid for antineuronal and antiglial antibodies among the patients with neurological symptoms after SARS-CoV-2 infection: anti-neuronal antibodies were present (IgG anti cerebellum granule cells in three cases, anti nucleus and proximal dendrites of Purkinje cells in two cases, myelinated fibres in the cerebellum in one case, neurophil of the olfactory bulb in one case, blood vessels in the brain in three cases, neurophil in the hippocampus in one case, and glia limitans and astrocytes in two cases) [56]. These studies may indicate molecular mimicry between autoantigens and SARS-CoV-2 as possible pathogenesis in such cases. A possible autoimmune cause is also indicated by FDG-PET studies in five cases of COVID-19-associated ataxia with myoclonus and/or encephalopathy which showed cortical hypometabolism and cerebellar and/or putaminal hypermetabolism [8, 13]. Cerebellar hypermetabolism in FDG-PET correlated with autoantibody target (against Purkinje cells and striatum) and clinical symptoms in a case reported by Grimaldi [13]. A combination of cortical hypometabolism and cerebellar hypermetabolism is unclear, and has been rarely reported due to infectious encephalitis [57] or in paraneoplastic cerebellar degeneration [58]. However, it may be the consequence of increased energy uptake due to the inflammatory process associated with an immune reaction in the cerebellum and cortical neurons damage or receptors/ion channels blockade due to parainfectious mechanisms [8].

Table 1. Characteristics of patients with myoclonus/opsoclonus/ataxia associated with COVID-19

Article	Age/ /gender	COVID-19 severity of infectious stage	Neurological symptoms	Time between acute infection and onset of neurological symptoms	Treatment/outcome
Rabano-Suarez et al. 2020 [7]	63/M	Mild	• Myoclonus • Dysarthria • Dysphagia • Mild somnolence	9 days	Propofol, Valproic acid, Levetiracetam, Clonazepam, Methylprednisolone 1 g/day, 5 g total plasmapheresis 5 cycles, Significant improvement
	88/F	Mild	• Myoclonus	21 days	Methylprednisolone 250 mg/day for 3 days, Complete recovery
	76/M	Mild	• Myoclonus	11 days	Clonazepam, Levetiracetam (no effect), Methylprednisolone 250 mg/day for 3 days, Recovery after 3 weeks
Delorme et al. 2020 [8]	72/M	Moderate	• Myoclonus • Ataxia • Psyhomotor agitation • Frontal lobe syndrome	12 days	IVIG 2 g/kg, Significant improvement, Complete recovery after 6 weeks
Wright et al. 2020 [9]	79/M	Mild	• Opsoclonus • Ataxia • Cognitive impairment	13 days	No data/improvement of cognitive function and resolution of eye movement abnormality after 19 days, death after 27 days due to general physical decline
Dijkstra et al. 2020 [10]	44/M	Mild	• Myoclonus • Ataxia • Voice tremor • Transient ocular flutter (no evident opsoclonus) • Cognitive impairment	1 week	Methylprednisolone 1g daily for 5 days, IVIG 0,4 g/kg for 3 days/partial recovery after 15 days, full recovery within 2 months
Schellekens et at. 2020 [11]	48/M	Mild	• Myoclonus • Ataxia • Saccadic intrusions of eye movement (no opsoclonus)	13 days	Levetiracetam, Partial recovery within 2 months
Shah et al. 2020 [12]	Middle aged/M	No data	• Myoclonus • Opsoclonus • Ataxia • Ataxic dysarthria	3 weeks	Methylprednisolone 1 g/day, Sodium valproate 20 mg/kg/day, Clonazepam 2 mg/day, Levetiracetam 2 g/day, Recovery within 1 week
Grimaldi et al. 2020 [13]	72/M	Moderate	• Myoclonus • Ataxia • Ataxic dysarthria • Action tremor	17 days	IVIG 0.4 g/kg/day for 5 days, Methylprednisolone 1 g/day for 5 days/ Recovery within 2 weeks
Salari et al. 2021[14]	42/M	Mild	• Myoclonus • Ataxia • Dysarthria • Cognitive deficits	Unknown	Methylprednisolone 1 g/day, 5 g total, Complete recovery after 1 month
	52/M	Mild	• Myoclonus • Ataxia	7 days	Methylprednisolone 1 g/day, 5 g total, Significant improvement after 1 month
	38/M	No data	• Myoclonus • Ataxia	8 days	Clonazepam 2 mg/day, Levetiracetam 1,000 mg/day, Methylprednisolone 1 g/day, 5 g total, Significant improvement after 2 weeks
Chan et al. 2021 [15]	44/M	Mild	• Myoclonus • Ataxia • Voice tremor • Mild rigidity in upper extremities	12 days	Methylprednisolone 1 g/day, 5 g total, Clonazepam 0.75 mg 2 × 1, Levetiracetam 1,000 mg 2 × 1, Significant improvement after 18 days
Asan et al. 2021 [16]	44/M	Mild	• Myoclonus • Ataxia	14 days	Methylprednisolone 1 g/day, 5 g total, Significant improvement after few days, Total recovery after 3 months

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Table 1. cont. Characteristics of patients with myoclonus/opsoclonus/ataxia associated with COVID-19

Article	Age/ /gender	COVID-19 severity of infectious stage	Neurological symptoms	Time between acute infection and onset of neurological symptoms	Treatment/outcome
Saha et al. 2021 [17]	78/F	Mild	• Myoclonus • Opsoclonus • Ataxia	14 days	IVIG 0.4 g/kg for 5 days, Methylprednisolone 1 g/day, Levetiracetam 1 g/day, Significant improvement after 7 days
Ishaq et al. 2021 [18]	63/M	Moderate	• Myoclonus • Opsoclonus • Ataxia • Confusion	23 days	Methylprednisolone 1 g/day, 5 g total followed by IVIG 0.4 g/kg for 5 days, Complete recovery after 4 weeks
Ram et al. 2021 [19]	79/M	Mild	• Myoclonus • Ataxia	10 days	Intravenous dexamethasone, 6 mg/day, Levetiracetam 2,000 mg/day, Complete recovery after 2 months
Otmani et al. 2021 [20]	59/M	Asymptomatic	• Myoclonus • Nystagmus	Unknown	Levetiracetam, IVIG, Methylprednisolone 1 g/day, 5 g total, Complete recovery after 21 days
Werner et al. 2021 [21]	62/M	Mild	• Ataxia • Dysarthria	16 days	Methylprednisolone 500 mg/day, 2.5 g total, Acyclovir, Significant improvement after 6 days
Emekli et al. 2021 [22]	54/M	Mild	• Ataxia • Dysarthria • Tremor • Confusion • Convergence spasm in ophtalmological examination	21 days	Methylprednisolone 1 g/day, 10 g total followed by oral steroids, IVIG 0.4 g/kg for 5 days, propranolol, Significant improvement after 1 month
Przytuła et al. 2021 [23]	49/M	Mild/ asymptomatic	• Myoclonus • Ataxia • Voice tremor	11 days	Methyloprednisolone 1 g/day, 5 g total followed by oral Prednisone 60 mg/day for 2 weeks, Significant improvement after 3 weeks
	62/M	Mild	• Myoclonus • Opsoclonus • Ataxia	11 days	IVIG 0.4 g/kg for 5 days, Methylprednisolone 1 g/day, 5 g total followed by oral prednisone (1 mg/kg/day) for 2 weeks with gradual dose reduction, Significant improvement after 2 weeks
Shetty et al. 2021 [24]	41/M	Mild	• Myoclonus • Gait ataxia	10 days	Clonazepam, Levetiracetam, Methylprednisolone 1 g/day, 5 g total, Significant improvement after 6 weeks
Giannantoni et al. 2021 [25]	67/M	Moderate	• Myoclonus • Ataxia • Ocular saccadic movements • Voice tremor • Generalised tremor	11 days	Methylprednisolone 1 g/day, 5 g total followed by oral prednisone (1 mg/kg/day) for 2 weeks with gradual dose reduction, Clonazepam, Levetiracetam, Improvement after 14 days
Sundar et al. 2021 [26]	60/M	Mild	• Myoclonus • Ataxia	14 days	Intravenous and oral steroids, Levetiracetam, Clonazepam, Complete recovery after 2 weeks
	53/M	Mild	• Myoclonus • Ataxia	7 days	Clonazepam, Methylprednisolone, followed by oral steroids, Complete recovery after 10 days
	47/M	Moderate	• Myoclonus • Opsoclonus • Ataxia • Voice tremor • Postural tremor of upper limbs • Generalised seizures	10 days	Methylprednisolone for 5 days, followed by oral steroids for a week, Clonazepam, Partial recovery

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Table 1. cont. Characteristics of patients with myoclonus/opsoclonus/ataxia associated with COVID-19

Article	Age/ /gender	COVID-19 severity of infectious stage	Neurological symptoms	Time between acute infection and onset of neurological symptoms	Treatment/outcome
Emamikhah et al. 2021 [27]	51/M	Mild	• Myoclonus • Opsoclonus • Ataxia • Voice tremor	2 weeks	Clonazepam 0.5 mg 4 × 1, Levetiracetam 500 mg 2 × 1, IVIG 2 g/kg, total dose 150 g, Complete recovery after 4 weeks
	54/M	Moderate	• Myoclonus • Ataxia	4 days	Levetiracetam 2,000 mg/day, Sodium valproate 1,000 mg/day IVIG in total dose 100 g, Partial recovery after one week
	52/M	Moderate	• Myoclonus • Ataxia • Voice tremor	16 days	Sodium valproate 1,000 mg/day, Clonazepam 1 mg 4 × 1, Partial recovery after 2 months
	42/F	Mild	• Myoclonus • Ataxia • Voice tremor	10 days	Sodium valproate, Clonazepam/ no data
	44/M	Mild	• Myoclonus • Opsoclonus • Ataxia • Voice tremor	3 days	Sodium valproate, Clonazepam, IVIG, Complete recovery after 2 months
	52/M	Mild	• Myoclonus • Ataxia • Voice tremor	3 weeks	Clonazepam, IVIG in total dose of 100 g, Significant improvement after 4 weeks
	39/M	Moderate	• Generalized seizures • Myoclonus • Opsoclonus • Ataxia • Voice tremor	10 days	Levetiracetam, Sodium valproate, Clonazepam, IVIG, Dexamethasone/ no data
Foucard et al. 2021 [28]	83/M	No data	• Myoclonus • Opsoclonus • Ataxic dysarthria • Confusion	10 days	IVIG 0.4 g/kg for 5 days, Steroids 1 g/day for 5 days, Diazepam/ significant improvement after 1 week
	63/M	No data	• Myoclonus • Ataxia • Ataxic dysarthria	6 weeks	IVIG 0.4 g/kg for 5 days/significant improvement after 1 week
Smyth et al. 2021 [29]	50/M	Moderate	• Myoclonus • Opsoclonus • Confusion	7 days	Levetiracetam 1,500 mg/day, Clonazepam 1 mg/day, Methylprednisolone 1 g/day for 3 days followed by oral prednisolone, Improvement after 11 days, recurrence of symptoms, complete recovery after Methylprednisolone 1 g/day for 3 days followed by oral prednisolone
Guerra et al. 2021 [30]	50/M	Asymptomatic	• Myoclonus • Ataxia	10 days	Methylprednisolone 250 mg/d for 3 days followed by oral steroids, Complete recovery after 1 week
	80/M	Moderate	• Myoclonus • Ataxia • Dysarthria	8 days	Methylprednisolone 120 mg/d for 5 days, Mild improvement after 1 week
Urrea-Mendoza et al. 2021 [31]	32/M	Moderate	• Myoclonus • Opsoclonus • Ataxia	12 days	Clonazepam 3 mg/day, Valproic acid 3,000 mg/day, Oral methylprednisolone 40 mg/day, Significant improvement after 24 days

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Table 1. cont. Characteristics of patients with myoclonus/opsoclonus/ataxia associated with COVID-19

Article	Age/ /gender	COVID-19 severity of infectious stage	Neurological symptoms	Time between acute infection and onset of neurological symptoms	Treatment/outcome
Sanguinetti et al. 2021 [32]	57/M	Mild	• Myoclonus • Opsoclonus	10 days	Clonazepam, IVIG 0.4 g/kg for 5 days, Intravenous, Methylprednisolone 80 mg/day Significant improvement
Chacko et al. 2021 [33]	53/F	Moderate	• Myoclonus • Opsoclonus • Sopor	14 days	Methylprednisolone followed by oral steroids, Rituximab, Plasmapheresis, Levetiracetam, Clobazam, Complete recovery after 32 days
Fernandes et al. 2021 [34]	58/F	Mild	• Myoclonus • Opsoclonus • Ataxia	14 days	Clonazepam, Levetiracetam, IVIG, Corticosteroids, No data on outcome
Vinod et al. 2021 [35]	52/M	Mild	• Myoclonus • Ataxia • Bilateral nystagmus • Generalised seizure	10 days	Midazolam, Levetiracetam, Clonazepam, Methylprednisolone 1 g/day, 5 g total, IVIG for 5 days, Significant improvement after 18 days
Tanu et al. 2021 [36]	52/M	Mild	• Myoclonus • Ataxia • Dysarthria • Bilateral horizontal gaze evoked nystagmus	8 days	Antibiotics, Anticoagulants, Dexamethasone 8 mg/day i.v., Valproic acid 600 mg/day, Clonazepam 1 mg/day, Significant improvement after 1 week
Talaei et al. 2021 [37]	53/F	No data	• Myoclonus • Opsoclonus • Axial rigidity	14 days	Myoclonic storm requiring intubation and ventilation, Steroids, Plasmapheresis, Significant improvement after 1 week
Serrazina et al. 2022 [38]	75/M	Moderate	• Myoclonus • Ataxia • fragmentation of ocular movements	9 days	Valproic acid 1,000 mg/day, Clonazepam 2 mg/day, Methylprednisolone for 5 days, followed by IVIG and then oral steroids, Partial recovery
Vijayaraghavan et al. 2022 [39]	64/W	Moderate	• Generalised seizure • Myoclonus • Opsoclonus • Ataxia	18 days	Methyloprednisolone 1g/day, 5 g total, Worsening of symptoms after a few days, IVIG 0.4 g/kg daily for 5 days, Rituximab 1 g IV, Complete recovery after 2 weeks
Rodriguez-Quiroga et al. 2022 [40]	60/M	Mild	• Myoclonus • Ataxia • Ocular flutter	10 days	IVIG 0.4 g/kg daily for 5 days, Methylprednisolone 1 g/day for 3 days, Levetiracetam, Full recovery in 18 days
	67/M	Mild	• Myoclonus • Ataxia • Dysarthria	11 days	Methylprednisolone 1 g/day for 3 days, Full recovery in 13 days
	36/M	Mild	• Myoclonus • Ataxia	15 days	Methylprednisolone 1 g/day for 3 days, Levetiracetam, Full recovery in 4 weeks
	44/M	Mild	• Myoclonus • Ataxia • Opsoclonus	13 days	Methylprednisolone 1 g/day for 3 days, Full recovery in 10 days
	33/M	Mild	• Myoclonus • Ataxia • Ocular flutter	8 days	Levetiracetam, Clonazepam, Full recovery in 6 weeks

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Table 1. cont. Characteristics of patients with myoclonus/opsoclonus/ataxia associated with COVID-19

Article	Age/ /gender	COVID-19 severity of infectious stage	Neurological symptoms	Time between acute infection and onset of neurological symptoms	Treatment/outcome
Mohamed et al. 2022 [41]	60/M	Asymptomatic	• Myoclonus • Dysarthria • Down-gaze paralysis	Unknown	Dexamethasone 12 mg/day for 3 days, Clonazepam, Levetiracetam, Progressive recovery
Kato et al. 2022 [42]	55/F	Mild	• Myoclonus • Gait disturbances • Mild somnolence	10 days	Methylprednisolone, Complete recovery after 3 days
Godani et al. 2022 [43]	71/M	Mild	• Myoclonus • Opsoclonus • Ataxia	2 days after COVID-19 resolution	Clonazepam for 1 month with no effect, IVIG 0.4 g/kg daily for 5 days — significant improvement after 17 days
Grazzini et al. 2022 [44]	70/M	Mild	• Myoclonus • Ataxia • Voice tremor, dysarthria • Tremor • Cognitive impairment	15 days	Clonazepam, Valproic acid, IVIG 0.4 g/kg for 5 days, Complete recovery after 2 months
	63/M	Mild	• Myoclonus • Ataxia • Tremor	2 days	Diazepam, Levetiracetam, IVIG 0.4 g/kg for 5 days, Worsening of symptoms 5 days after IVIG treatment start, Significant improvement after 25 days
	56/M	Mild	• Dysmetria • Ataxia • Psychomotor retardation	15 days	Plasmapheresis, Rapid clinical improvement
Chattopadhyay et al. 2022 [45]	70/M	Mild	• Ataxia • Dysarthria • Tremor	35 days	Methylprednisolone 1 g/day for 5 days, Significant improvement after 10 days
Osawa et al. 2022 [46]	52/M	Moderate	• Myoclonus • Ataxia	16 days	Methylprednisolone 1 g/day for 3 days, Benzothiamine, Cyanocobalamin, Pyridoxine improvement after 3 days, Complete recovery after 3 months
Przytuła et al. 2022 [47]	45/M	Mild	• Myoclonus • Ataxia • Voice tremor • Four-limbs tremor	12 days	Methyloprednisolone 1 g/day for 5 days followed by oral prednisone 70 mg/day for 4 weeks with gradual dose reduction, Significant improvement after 4 weeks

Cerebellar hyperperfusion in brain single photon emission computed tomography (SPECT) has been observed in patients with OMS [59]. A patient with post COVID-19 AMS reported by Osawa et al. revealed hyperperfusion in the cerebellum and hypoperfusion in the cerebral cortex, with frontal lobe predominance [46].

Patients have been treated symptomatically with antiepileptic medications (valproic acid 11/60 patients, levetiracetam 24/62, clonazepam 27/62, diazepam 2/62, midazolam 1/62, and clobazam 1/62) and immunotherapy including steroids (methylprednisolone 40/62 patients, dexamethasone 4/62), intravenous immunoglobulins (IVIG) 25/62 patients, of which steroids combined with IVIG were administered in 15/25, immunomodulatory medications (rituximab in 1/62 patient), and plasmapheresis in 4/62 patients. In subjects treated only by symptomatic medications (benzodiazepines, antiepileptic drugs) only a partial improvement was observed in follow-up [11, 27]. In one patient, benzodiazepines and antiepileptics were used for two months without improvement, only after the use of steroids and IVIG symptoms partially subsided [38]. In the majority of cases, symptomatic treatment has been combined with immunotherapy, and in these cases a significant improvement was observed between three days after the steroids administration [42, 46] and three months after the onset of treatment. There have also been reports of two patients who did not improve with steroids, but were then administered second-line IVIG or IVIG with rituximab with recovery [18, 39]. Treatment with corticosteroids seems to be

Table 2. Characteristics of patients with chorea associated with COVID-19 and SARS-CoV-2 vaccination

Article	Age/ /gender	COVID-19 severity of infectious stage	Neurological symptoms	Time between acute infection and onset of neurological symptoms	Neuroimaging	Treatment/outcome
Ashrafi et al. 2022 [60]	67/F	Moderate – with post-COVID encephalitis after 2 weeks	• Chorea on face and four limbs, with right arm dominance	3 months	MRI: bilateral hyperintensity on basal ganglia	Tetrabenazine 2 × 12.5 mg, Rapid recovery after a few days
	62/F	No data	• Four-limbs chorea with right-side dominance	15 days	MRI: unremarkable	Tetrabenazine, Significant improvement
Barberà et al. 2022 [61]	69/F	No data	• Four-limbs chorea • Right-side hemiparesis • Mixed aphasia	21 days	CT: cerebral venous sinus thrombosis, capsuloganglionic and thalamic infarcts with haemorrhagic transformation of left thalamic infarct	Anticoagulants, death
Sawczyńska et al. 2022 [62]	77/F	Moderate	• Four-limbs and orofacial chorea with left-side dominance • Confusional state	At one time with infection, 2 weeks after COVID-19 vaccination	MRI: diffuse white matter hyperintensities, cortical and subcortical atrophy	Methylprednisolone 1 g/day for five days followed by IVIG 2 g/kg over course of five days Diazepam, Remdesivir, Complete recovery in a few days
Hassan et al. 2021 [63]	58/M	Moderate	• Four-limbs chorea	4 days	MRI: chronic white matter hyperintensities	Ceftriaxone, Acyclovir, Dexamethasone, Risperidone, Omeprazole, Improvement after a few days
Cotta Ramusino et al. 2021 [64]	62/M	Mild	• Four-limbs, head and trunk chorea • Confusional state	At one time with infection	MRI - hypointense signal in dorsolateral portion of both putamina (SWI)	Haloperidol 4.5 mg/day, Tetrabenazine 50 mg/day, Dexamethasone, Significant improvement after a few days
Ghosh et al. 2021 [65]	60/M	Moderate	• Right limbs chorea	2 days	MRI: left striatal hyperintensity, Laboratory tests: acute hyperglycaemia	Intravenous fluids, Insulin recovery
Byrnes et al. 2020 [66]	36/M	Moderate	• Four-limbs chorea	At one time with infection	MRI: multifocal lesions affecting bilateral medial putamen, left cerebellum, hippocampus, punctate restricted diffusion in right basal ganglia	Midazolam, Diazepam, Methylprednisolone 500 mg/d for 5 days followed by IVIG 2 g/kg for 5 days and oral Prednisone, Improvement after a few days
Salari et al. [67]	13/M	N/A	• Right-sided hemichorea	7 days after 1st dose of COVID-19 vaccination (BBIBP-CorV (Sinopharm)	MRI: multiple white matter lesions, one of them enhanced with gadolinium	Methylprednisolone 1 g/day for 3 days followed by oral Prednisolone (50 mg/d), Tetrabenazine (25 mg/d), moderate improvement after 2 weeks, Significant improvement after 1 month
	18/M	N/A	• Left-sided hemichorea	7 days after COVID-19 vaccination (BBIBP-CorV (Sinopharm)	MRI: unremarkable	Methylprednisolone 1 g/day for 3 days followed by oral Prednisolone (50 mg/d), Tetrabenazine (25 mg/d), moderate improvement after 2 weeks

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Table 2. cont. Characteristics of patients with chorea associated with COVID-19 and SARS-CoV-2 vaccination

Article	Age/ /gender	COVID-19 severity of infectious stage	Neurological symptoms	Time between acute infection and onset of neurological symptoms	Neuroimaging	Treatment/outcome
Matar et al. 2021 [68]	88/M	N/A	• Left-sided hemichorea • Mild right-sided parkinsonian syndrome	16 days after 1st dose COVID-19 vaccination (Astra Zeneca, AZD1222)	MRI: Chronic small vessel ischaemic changes	Methylprednisolone 1 g/day for 3 days, Significant improvement after 1 day
	84/M	N/A	• Left-sided hemichorea	40 days after 1st dose COVID-19 vaccination (Astra Zeneca, AZD1222)	MRI: Chronic small vessel ischaemic changes	Methylprednisolone 1 g/day for 3 days, Significant improvement after 3 days
Ryu et al. 2021 [69]	83/M	N/A	• Right-sided hemichorea	1 day after 2nd dose of COVID-19 vaccination, 21 days after 1st dose (Pfizer--BioNTech)	MRI: unremarkable Brain SPECT — perfusion pattern asymmetrically decreased in left thalamus	Haloperidol 0.75 mg 2 × 1, Significant improvement after 2 weeks
Batot et al. 2022 [70]	90/M	N/A	• Left hemichorea--hemiballismus • Dysarthria	Hours after 2nd dose of COVID-19 vaccination, 21 days after 1st dose (Pfizer--BioNTech)	MRI: unremarkable Brain FDG-PET — increased metabolism of right putamen (compared to left side)	Tetrabenazine, with a gradual increase (up to 75 mg daily) for 3 weeks, followed by Olanzapine (up to 7.5 mg daily) for 1 week, No effect Methylprednisolone 1 g/day for 5 days, Significant improvement
Shahali et al. 2022 [71]	72/M	N/A	• Right-sided hemichorea	9 days after 1st dose of COVID-19 vaccination (Astra Zeneca ChAdOx1 nCoV-19)	MRI: left thalamus acute ischaemic infarct	Nadroparin 90 U/kg/day, Sodium ozagrel 160 mg/day, Edaravone 60 mg/day, Methylprednisolone 1 g/kg, Haloperidol 0.75 mg/day, Warfarin 0.125 mg/kg/day, Improvement during 2 weeks

equally effective, but significantly cheaper and more readily available than IVIG therapy. Therefore, we suggest starting with steroids and only in a case of non-responsiveness or contraindications following this treatment with IVIG [47].

Chorea

A total of eight patients (four women and four men, aged 36–77 years, mean 61) with COVID-19 [60–66] and an additional seven patients as an adverse event after vaccination against SARS-CoV-2 [67–71] (six men and one woman aged 13–90) have been reported to develop chorea (Tab. 2). Five patients had moderate, one patient had mild, and in two cases the severity of the COVID-19 was not reported. The delay between infection and the appearance of chorea was between less than 24 hours and 90 days after SARS-CoV-2 identification, mean 16.5 days. In post-vaccination cases, symptoms occured between seven and 40 days, mean 17 days after the first dose of COVID-19 vaccine and in two cases on the first day after the second dose of vaccine. Four post-COVID-19 and six post-vaccination patients had unilateral chorea. Four subjects had generalised symptoms, two presented with impaired consciousness, and one with mixed aphasia and right-side hemiparesis — this patient was diagnosed with cerebral venous sinus thrombosis, capsuloganglionic and thalamic infarcts with haemorrhagic transformation of the left thalamic infarct.

In diagnostic tests among post-COVID-19 infection cases, head MRI was normal in three subjects, four had pathological lesions in basal ganglia — one had hypointense susceptibility weighted imaging (SWI) signal in the dorsolateral portion of both putamina, one had left striatal hyperintensity on T1-weighted imaging, one had multifocal lesions affecting the bilateral medial putamen, left cerebellum, hippocampus, punctate restricted diffusion in the right basal ganglia, and one had bilateral hyperintensity on basal ganglia. One subject had bilateral thalamic infarcts with haemorrhagic transformation of the left thalamic infarct (CT). Moreover,

Table 3. Characteristics of patients with tremor associated with COVID-19

Article	Age/ /gender	COVID-19 severity of infectious stage	Neurological symptoms	Time between acute infection and onset of neurological symptoms	Diagnostic tests	Treatment/ /outcome
Henry et al. 2020 [72]	77/M	Moderate	• Essential tremor worsening • Bilateral dysmetria	No data	• Head CT: normal	Azithromycin, Ceftriaxone, No data of outcome
Klein et al. 2020 [73]	46/M	Mild	• Four-limbs postural tremor • Wide based gait	8 days	• MRI: chronic ischaemic lesions	Propranolol, Mild improvement
Diezma-Martin et al. 2020 [74]	70/M	Mild	• Four-limbs tremor • Orthostatic tremor • Voice tremor • Wide based gait	17 days	• MRI, CSF, laboratory tests: normal	Clonazepam, Mild improvement
Passaretti et al. 2021 [75]	60/M	Asymptomatic	• Essential tremor worsening	21 days	• MRI, laboratory tests: normal	Propranolol, No improvement
Pistola et al. 2021 [76]	46/M	Mild	• Intentional tremor • Dysmetria • Gait disturbances	10 days	• Head MRI: mild leptomeningeal enhancement • Oligoclonal bands detected in CSF • EEG: normal	Oral steroids, Antibiotics, Heparin, Significant improvement after 1 month

hippocampus, cerebellum and pons lesions were noted. Head MRI of post-vaccination patients was unremarkable in six cases, with multifocal white matter lesions, of which one was enhanced with gadolinium in one patient. One patient has been diagnosed with acute left thalamic infarct due to vaccine-induced prothrombotic immune thrombocytopenia [71]. Brain SPECT (single-photon emission computed tomography) was performed in one post-vaccination subject and revealed left thalamic hypoperfusion compared to the right side. Brain FDG-PET (fluoro-deoxy-glucose positon emission tomography) performed in a patient reported by Batot et al. showed increased metabolism of the right putamen (compared to the left side). Three weeks later, after steroid treatment, a repeated brain FDG-PET showed resolution of the right putamen and increased metabolism [70]. Among all cases, lumbar puncture was performed in seven patients revealing lymphocytic pleocytosis with elevated protein in one case, isolated lymphocytic pleocytosis in one case, isolated protein elevation in two cases, and normal CSF in three cases. 1/3 CSF tested positive for SARS-CoV-2, while other microbiological analyses of CSF (bacterial and viral) were negative. Various causes of chorea have been considered in the differential diagnosis of the reported cases. The previously mentioned subject developed hyperkinetic motor symptoms as a complication of cerebral sinus thrombosis [61]. A previously healthy non-diabetic patient reported by Ghosh et al. developed hyperglycaemia, ketonuria and metabolic acidosis, and secondary right hemichorea with striatal lesions in head MRI [65]. Diabetic striatopathy secondary to COVID-19 infection has been diagnosed. A polysubstance abusing homeless patient reported by Byrnes et al. developed four-limbs chorea during SARS-CoV-2 infection. His urine test was positive for cocaine, opiates, and benzodiazepines. Head MRI showed multifocal lesions affecting the bilateral medial putamen, left cerebellum, hippocampus and one focal lesion restricted diffusion in the right basal ganglia. Improvement in the subject's choreiform movements was only observed after immunotherapy using methylprednisolone and IVIG [66]. Other causes of choreiform movements in reported cases, including endocrinological and autoimmune systemic diseases, paraneoplastic and prion disease, were excluded.

10/15 patients were treated with steroids (8/15 i.v. methylprednisolone, 2/15 dexamethasone) and 2/15 patients received a combination of steroids and IVIG. Immunotherapy alone was administered in 2/15 cases, resulting in significant improvement of symptoms after 3–14 days. Steroids or IVIG combined with symptomatic treatment (tetrabenazine 4/15, risperidone 1/15, haloperidol 2/15, diazepam 2/15, midazolam 1/15) resulted in significant improvement of symptoms within a few days to one month after treatment initiation. Causal treatment was conducted in a patient with diabetic striatopathy secondary to COVID-19 using intravenous fluids and insulin, obtaining recovery of neurological symptoms. A patient diagnosed with cerebral venous sinus thrombosis recieved anticoagulant treatment complicated by haemorrhagic transformation of the left thalamic infarct, resulting in patient death. Additional

antibiotics or antivirals were administered in 3/15 patients (remdesivir, acyclovir, ceftriaxone). Symptomatic treatment alone was used in 3/15 patients, using tetrabenasine in two cases and haloperidol in the third case, obtaining significant improvement in choreiform movements within 14 days.

Tremor

Tremor as a non-specific movement complication after COVID-19 has not been frequently reported. A total of five patients (five men, aged 46–77 years, mean 60) have been reported with tremor as the dominant sign due to a mild/moderate course of COVID-19 [72–76] (Tab. 3). Apart from these reports, tremor coexisted in 17 patients with ataxia-myoclonus syndrome (AMS), opsoclonus-myoclonus-ataxia syndrome (OMAS), and opsoclonus-myoclonus syndrome (OMS) — limb tremor four [13, 22, 44, 45], voice tremor in nine [10, 15, 23, 27], and limb tremor combined with voice tremor in four [25, 26, 44, 47] (Tab. 1). In another two cases, functional tremor was diagnosed [77, 78] and one case featured tremor as an adverse reaction to remdesivir prescribed to treat the SARS-CoV-2 infection [79]. In addition, tremor has been associated with critically ill patients with multiple organ failure due to COVID-19 requiring invasive ventilation and ICU treatment [80, 81].

In addition to the aforementioned case reports and case series specifically focused on tremor as the main symptom, several observational studies have been done to assess the incidence of neurological symptoms after SARS-CoV-2 infection. Pilotto et al. conducted an observational study on 165 patients hospitalised due to COVID-19; after a six-month follow-up, tremor as a motor complication had occurred in 15/165 (9%) patients [82]. In another observational study of 2,750 convalescents, neurological complications were noted in 71, of whom only one developed tremor [83].

Among patients with dominant tremor as a complication of COVID-19 (Tab. 3), one had asymptomatic, three mild, and one moderate COVID-19. The time elapsed between infection and the appearance of tremor was 8–21 days (mean 14) after SARS-CoV-2 onset. Two patients were diagnosed with essential tremor before the pandemic, and SARS-CoV-2 infection caused rapid tremor worsening [72, 75]. All five patients had intentional and postural limbs tremor, and symptoms were combined with orthostatic tremor in one subject, and dysmetria with gait disturbances in four patients.

Imaging with MRI/CT was normal in four cases; in one patient, mild leptomeningeal enhancement was noted in MRI. In this case, oligoclonal bands were detected in CSF. In the other patients, CSF was normal. Two patients were treated symptomatically with propranolol, one with clonazepam; two of these patients had mild improvement and there was no recovery in the third. One patient was treated with antibiotics only but outcome data was not provided. One patient was treated with steroids and antibiotics with a complete recovery after one month of rehabilitation [76]. This last case, and similarly to the AMS time when symptoms appeared in the rest of the reported patients, may suggest, at least in some cases, the autoimmunological origin and necessity of immunological treatment.

Dystonia

One patient, a 78-year-old man, developed dystonia after COVID-19 [56] and one 38-year-old male was reported to have developed cervical dystonia 24 hours after SARS-CoV-2 vaccination. The 78-year-old with severe COVID-19 required mechanical ventilation and ICU admission. He developed upper limb asymetrical (right > left) dystonia and delirium. General examination of CSF was normal and negative for SARS-CoV-2. He was positivily tested for the presence of IgG autoantibodies in CSF against neurophil olfactory bulb, cerebellum and hippocampus neurons [56]. In another two cases, functional dystonia was diagnosed — in a 46-year-old female one week after mild COVID-19 [84], and in a 22-year-old female 24 hours after SARS-CoV-2 vaccination [85]. Moreover, dystonia has been reported as a side effect after COVID-19 vaccination in a total of 113 cases (53 after Pfizer/BioNTech, 23 after Moderna, 30 after AstraZeneca, and seven after Janssen) [86].

An important consideration regarding patients with dystonia during the pandemic is the limited availability of treating neurologists — a deterioration in the quality of life was observed in 65% of the 71 dystonia patients surveyed (due to delays in botulinum toxin appointments, depressed mood, less physical activity, and less access to rehabilitation) [86]. In an observational survey of Parkinson's Disease (PD) and dystonia patients treated with deep brain stimulation (DBS), 36% of dystonia patients reported difficulties in the management of the DBS device, and 100% discontinued outpatient neurological visits due to the lockdown [87].

Limited physician availability and delayed follow-up visits in patients with generalised dystonia treated with DBS should not delay implantable pulse generator battery replacement, as the dystonic state resulting from battery depletion can be potentially life-threatening [88].

Conclusions

Hyperkinetic movement disorders, although they are infrequent sequelae of SARS-CoV-2 infection, must be followed up carefully, as many of them are potentially treatable. This seems to be true specifically for ataxia, myoclonus and opsoclonus symptoms, whereas in cases of chorea the pathophysiology is more variable (not only autoimmunological) requiring specific or symptomatic treatment.

In all cases of movement disorders suspected of a SARS-CoV-2 infection history, even those without PCR confirmation, first line treatment with corticosteroids should be offered followed by IVIG or plasmapheresis. Patients already treated with DBS should be closely monitored as any delay in the replacement of batteries can prove fatal.

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COVID-19 and autoimmune diseases of the nervous system — an update

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ABSTRACT

Introduction. Due to a similar pathomechanism, COVID-19 infection may significantly affect the course of autoimmune diseases (AIDs). In our review, we aimed to assess the severity of SARS-CoV-2 infection, response to treatment, and the impact of COVID-19 infection on the course of the underlying disease in patients with neuroimmune diseases.

State of the art. In the time of the COVID-19 pandemic, it was important to determine the influence of COVID-19 infection on the course of autoimmune diseases due to the weakened immune system and immunosuppressive therapies.

Clinical implications. Many reports have indicated that in patients with AIDs, the existence of the disease is not associated with a worse prognosis in the course of the viral infection. Patients in advanced stages of the disease, elderly patients, and those with comorbidities are at risk of more frequent hospitalisations and higher mortality in the course of COVID-19. Moreover, some drugs used in AIDs have been tested for their efficacy in SARS-CoV-2 infection. Episodes of newly diagnosed myasthenia gravis, Guillain-Barré syndrome, acute disseminated encephalomyelitis (ADEM), and neuromyelitis optica spectrum disorder (NMOSD) secondary to COVID-19 or vaccination have also been reported. Vaccination against this pathogen is highly recommended in most patients with AIDs.

Future directions. Despite many studies on the association between COVID-19 and neuroimmune diseases, more specific data is needed. The approach to patients with AIDs should be individual, since many issues remain unresolved despite the long-lasting pandemic.

Key words: COVID-19, SARS-CoV-2, AIDs, neuroimmune diseases

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Introduction

Coronavirus Disease 2019 (COVID-19) is a contagious disorder caused by the novel coronavirus which belongs to the Betacoronavirus genera [1]. The first case of unusual viral pneumonia caused by SARS-CoV-2 was described in Wuhan, China, in December 2019. Despite the restrictions, a growing number of infections that spread worldwide resulted in the declaration of a pandemic within three months [1]. To date (October 2022), 615 million laboratory-confirmed cases of the disease and 6.5 million deaths have been reported worldwide [2].

Autoimmune diseases (AIDs) are caused by impairment of the immune system, which results in the production of antibodies against one's own tissues. This leads to clinical damage or impairment of their function [3]. At the time of the COVID-19 pandemic, patients affected by AIDs may be exposed to a more severe course of infection due to the failure of the immune system. Moreover, the use of immunosuppressants may also increase susceptibility to COVID-19.

We reviewed the literature to describe the impact of the pandemic on the course of neuroimmune diseases. The aim of our study was to assess the severity of COVID-19, the response

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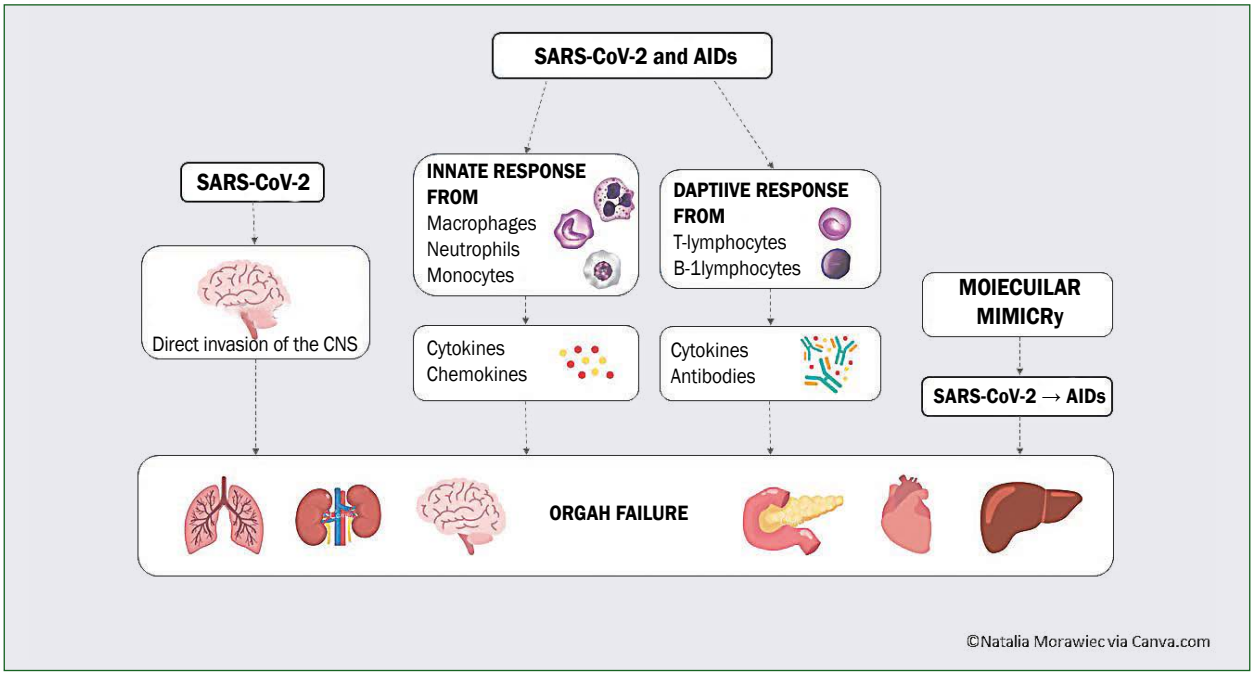

Figure 1. Similarities in pathophysiology of neuroimmune diseases and SARS-CoV-2. Both COVID-19 and AIDs activate immune system, which results in cytokine and antibody overproduction. Another mechanism of viral penetration is direct invasion of central nervous system by SARS-CoV-2. Due to molecular mimicry in cases with COVID-19, production of antibodies may lead to *de novo* occurrence of AIDs. AIDs — autoimmune diseases; CNS — central nervous system; IS – immune system

to treatment, and the impact of COVID-19 infection on the course of the underlying diseases in patients with autoimmune diseases of the nervous system.

Material and methods

This paper assesses and compares research on autoimmune diseases of the nervous system at the time of the COVID-19 pandemic. We reviewed the systematic literature, including our own papers on selected neuroimmune diseases and COVID-19. We searched PubMed, Scopus and Google Scholar using the phrases: 'COVID-19' and 'SARS-CoV-2' together with 'autoimmune', 'neuroimmune', 'multiple sclerosis', 'NMOSD', 'myasthenia gravis', 'Guillain-Barré syndrome' and 'ADEM'. As a result, relevant articles were selected. All the papers included in this review were published between 2020 and 2022.

Similarities in pathogenesis of SARS-CoV-2 infection and neuroimmune diseases

In AIDs and in SARS-CoV-2 infection, the inflammatory process affects various locations. Symptoms can occur in many organs and systems, such as the cardiovascular system, nervous system, lungs, kidneys, skin, or digestive tract [4]. Excessive production of cytokines and the activation of immune cells lead to the production of antibodies and organ failure in AIDs and SARS-CoV-2 infection. Overproduction of the proinflammatory molecules (IL-1, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, CXCL10, CCL2) results in cytokine storm [5]. Another similarity between AIDs and COVID-19 is that cells of the innate immune response (macrophages, monocytes, mast cells, neutrophils) are over-activated. Furthermore, dysregulation between the levels of B-cells and T-cells has been reported with reduced T-cell levels [4].

Furthermore, in some patients with COVID-19, the presence of autoantibodies characteristic of neuroimmune diseases has been found. Halpert and Shoenfeld reported infected cases with antibodies characteristic of Guillain-Barré syndrome (ANA, antinuclear antibodies), Miller-Fisher syndrome (aCL, anti-cardiolipin antibodies), neuromyelitis optica [anti-phosphatidylserine antibodies (IgM/IgG)], NMDA-receptor encephalitis [antiannexin V (IgM/IgG)], and myasthenia gravis (anti-GD1b antibodies) [6]. AIDs can also occur secondarily to COVID-19. Infection with the SARS-CoV-2 virus can lead to the activation of autoimmune processes due to molecular mimicry [7]. There is another hypothesis of direct viral invasion of the central nervous system. PCR-positive cerebrospinal fluid (present in several cases) seems to confirm this [8]. The above mechanisms are shown in Figure 1.

Course of neuroimmune disorders and impact on SARS-CoV-2 infection

In our review, we have selected the most common AIDs of the nervous system, which are presented below. Detailed information on the study groups, the course of the infection, treatment and clinical outcomes is given in Table 1.

Table 1. Autoimmune diseases of nervous system and COVID-19

Disease	Study [ref.]	Country	Details	COVID-19 (N)	COVID-19 symptoms	Treatment N (%)	Clinical outcomes
MS	Castillo Álvarez et al. [11]	Spain	N: 330 Female %: 75 Mean age: 47.91 Mean EDSS: 1.92	Positive PCR: 9 Serology: 3	Cough, fever, pharyngeal pain, myalgia, asthenia, headache, dyspnoea and anosmia	Interferon beta-1a: 2 (16.66%) Dimethyl fumarate: 2 (16.66%) Teriflunomide: 2 (16.66%) Fingolimod: 1 (8.33%) Cladribine: 1 (8.33%) Alemtuzumab: 1 (8.33%) No treatment: 3 (25%)	A more severe course of SARS-CoV-2 infection required hospitalisation in MS group compared to healthy controls. Risk of infection was twice as high as in general population. Mortality rate of COVID-19 in MS group was 11.1%
MS	Louapre et al. [12]	France	N: 347 Female %: 71.75 Mean age: 44.6 Mean EDSS: 2.0	Positive PCR: 146 Ground-glass opacity on CT scan: 62	Asthenia, fever, cough, anosmia, ageusia, headache, dyspnoea	Interferon beta: 20 (5.8%) Glatiramer: 33 (9.5%) Teriflunomide: 33 (9.5%) Dimethyl fumarate: 35 (10.1%) Natalizumab: 57 (16.4%) Fingolimod: 42 (12.1%) Ocrelizumab: 38 (11.0%) Rituximab: 17 (4.9%) Cladribine: 3 (0.9%) Alemtuzumab: 1 (0.3%) Other: 5 (1.4%) No treatment: 63 (18.2%)	Need for hospitalisation in older patients and subjects with higher EDSS. A more severe course of COVID-19 (severity score of 3 or more) correlated with lymphopenia. Mortality rate of COVID-19 in MS group was 3.5%
MS	Crescenzo et al. [16]	Italy	N: 1,034 Female %: 73.98 Mean age: 49 Mean EDSS: 4.0	Positive PCR: 11 Suspected: 18	Fever, dyspnoea	Dimethyl fumarate: 12/29 (41.4%) Fingolimod: 4/29 (13.8%) Natalizumab: 2/29 (6.9%) Ocrelizumab: 7/29 (24.1%) Teriflunomide: 2/29 (6.9%) Azathioprine: 1/29 (3.4%) No treatment: 1/29 (3.4%)	Need for hospitalisation in two male patients on FG and DMF. No deaths secondary to COVID-19 were reported in study group. No connection between DMT and a more severe course of infection. No connection between immunosuppression and a more severe course of infection
MS	Barzegar et al. [19]	Iran	N: 543 Female %: 81.22 Mean age: 35.28 Mean EDSS: 0.0	Positive PCR: 2 Ground-glass opacity on CT scan: 7	Fever, dyspnoea, sore throat, diarrhoea, cough, anosmia	Interferon beta: 296 (54.4%) Glatiramer acetate: 35 (6.5%) Fingolimod: 55 (10.1%) Dimethyl fumarate: 27 (5.1%) Teriflunomide: 20 (3.7%) Rituximab: 42 (7.7%) Natalizumab: 12 (2.2%) No treatment: 56 (10.3%)	A severe course of infection in fingolimod-treated patient and a critical course in one patient on rituximab

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Table 1. cont. Autoimmune diseases of nervous system and COVID-19

Disease	Study [ref.]	Country	Details	COVID-19 (N)	COVID-19 symptoms	Treatment N (%)	Clinical outcomes
MS	Vogel et al. [21]	USA	N: 1,019 Female %: 79.50% Mean age: 54.2 Mean EDSS: 2.76	Positive PCR: 7	Fever, dry cough, dysgeusia, anosmia	Glatiramer acetate: 83 (8.14%) Interferon beta-1: 44 (4.32%) Peginterferon beta-1a: 7 (< 1%) Fingolimod: 81 (7.95%) Siponimod: 8 (< 1%) Dimethyl fumarate: 87 (8.54%) Diroximel fumarate: 3 (< 1%) Teriflunomide: 45 (4.42%) Cladribine: 10 (< 1%) Natalizumab: 67 (6.58%) Rituximab: 38 (3.73%) Ocrelizumab: 238 (23.36%) Alemtuzumab: 7 (< 1%) Other: 10 (< 1%) No treatment: 270 (26.50%)	No need for hospitalisation and no deaths in study group. Thirty eight patients were exposed to COVID-19. Delay in drug administration in 98 (10%) patients and need to postpone medical visits in 64% due to COVID-19
MS and NMOSD	Alonso et al. [18]	Latin America (15 countries)	N: 16 Female %: 71.7 Mean age: 41 Mean EDSS: 4	Suspected: 27 Confirmed: 118	NI	**MS:** Interferon: 21 (16.2%) Glatiramer acetate: 2 (1.5%) Fingolimod: 30 (23.2%) Dimethyl fumarate: 13 (10%) Teriflunomide: 12 (9.3%) Cladribine: 4 (3.1%) Natalizumab: 8 (6.2%) Ocrelizumab: 10 (7.7%) Alemtuzumab: 5 (3.8%) Rituximab: 12 (9.3%) No treatment: 12 (9.3%) **NMOSD:** Azathioprine: 2 (12.5%) Mofetil mycophenolate: 2 (12.5%) Rituximab: 11 (68.7%)	**MS:** 15% of MS group required hospitalisation, particularly elderly patients. No deaths secondary to COVID-19 were reported in study population **NMOSD:** 56.25% of patients required hospitalisation. Mortality rate of COVID-19 was 31.2% in NMOSD group (all treated with rituximab)

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Table 1 cont. Autoimmune diseases of nervous system and COVID-19

Disease	Study [ref.]	Country	Details	COVID-19 (N)	COVID-19 symptoms	Treatment N (%)	Clinical outcomes
NMOSD	Sahraian et al. [25]	Iran	N: 130 Female %: 83.15 Mean age: 37.55	Positive PCR: 3 Ground-glass opacity on CT scan: 2	Fever, dyspnoea, myalgias, gastrointestinal complications, fatigue, vertigo, headache, odynophagia	Azathioprine: 22 (16.9%) Rituximab: 94 (72.3%) Mycophenolate mofetil: 2 (1.5%) Prednisolone: 1 (0.8%) Mitoxantrone: 1 (0.8%) Azathioprine & Prednisolone: 2 (1.5%) Rituximab & Mycophenolate mofetil: 1 (0.8%) Rituximab & Cyclophosphamide: 2 (1.5%)	Occurrence of COVID-19 was reported only in rituximab group. Three patients required hospitalisation. Infection rate in NMOSD patients was same as in general population. Gastrointestinal manifestations of infection were reported in 40% of subjects
NMOSD	Fan et al. [10]	China	N: 3,060 Female %: NI Mean age: NI Mean EDSS: NI	Confirmed: 2	NI	Methylprednisolone: 795 (25.98%) Azathioprine: 405 (13.24%) Mycophenolate mofetil: 832 (27.19%) Tacrolimus: 403 (13.17%) Rituximab: 381 (12.45%) Tocilizumab: 62 (2.03%) Cyclophosphamide: 39 (1.27%)	No increased risk of COVID-19 infection was found in study group (two confirmed cases). Successful recovery from viral pneumonia was reported in both patients
NMOSD	Yin et al. [23]	China	N: 535 Female %: 88.04 Mean age: 43.8 Mean EDSS: 1.5	Confirmed: 0	NI	Mycophenolate mofetil: 381 (71.2%) Azathioprine: 71 (13.27%) Other immunosuppressants: 34 (6.36%)	Treatment disruptions due to pandemic resulted in more relapses of NMOSD. No increased risk of COVID-19 infection was reported in study group (no confirmed cases).
MG	Tuncer et al. [32]	Turkey	N: 140 Female %: NI Mean age: NI	Positive PCR: 19	Fever, muscle pain, fatigue, anosmia	Prednisolone & IVIg: 1/19 (5.26%) Azathioprine: 1/19 (5.26%) Prednisolone & Azathioprine: 7/19 (36.84%) Prednisolone & Rituximab: 1/19 (5.26%) Prednisolone: 4/19 (21.05%) Prednisolone & Mycophenolate mofetil: 1/19 (5.26%) No treatment: 4/19 (21.05%)	A mild course of COVID-19 was observed in most MG patients. Two deaths secondary to SARS-CoV-2 infection were found in study group. Need for hospitalisation in six patients with MG
MG	Rodrigues et al. [34]	Brazil	N: 8 Female %: 87.5 Mean age: 47.13	Positive PCR: 8	Fever, shivering, odynophagia, headache, dyspnoea, dysphagia, dysphonia, post-prandial cough, bilateral ptosis, diplopia	Prednisone & Azathioprine & Pyridostigmine: 3 (37.5%) Pyridostigmine: 1 (12.5%) Prednisone & Methotrexate & Pyridostigmine: 1 (12.5%) Prednisone & Pyridostigmine & Rituximab: 1 (12.5%) No treatment: 2 (25%)	Exacerbation or myasthenic crisis in eight patients. Six patients required mechanical ventilation. In-hospital mortality was 25% and 37.5% in short-term follow-up

Table 1 cont. Autoimmune diseases of nervous system and COVID-19

Disease	Study [ref.]	Country	Details	COVID-19 (N)	COVID-19 symptoms	Treatment N (%)	Clinical outcomes
MG	Businaro et al. [31]	Italy	N: 162 Female %: 40.1 Mean age: 66	Positive PCR: 3 Suspected: 8	Ptosis, mild-to-moderate proximal and distal weakness in upper and lower limbs, diplopia, tongue weakness, neck weakness, dysphagia, facial muscle weakness	Prednisone < 10 mg/d: 31 (19.1%) Prednisone > 10 mg/d: 39 (24.1%) Azathioprine: 47 (29.0%) Other immunosuppressants: 7 (4.3%) No immunosuppressants: 63 (38.9%) Treatment with IVIg/PlEx: 26 (16.0%)	Mortality secondary to COVID-19 was found in two elderly patients. Exacerbation of MG during infection was reported in one patient
MG	Camelo-Filho et al. [35]	Brazil	N: 15 Female %: 60 Mean age: 45.22	Positive PCR: 15	Dyspnoea, fever, cough, myalgia	Prednisone: 4 (26.67%) Prednisone & Azathioprine & IVIg: 1 (6.67%) Prednisone & Methotrexate: 2 (13.33%) Prednisone & Cyclosporin: 1 (6.67%) Prednisone & Azathioprine: 4 (26.67%) No treatment: 1 (6.67%)	Exacerbation of MG or use of mechanical ventilation was reported in most patients from study group. 86.7% of patients needed hospitalisation in ICU. Death secondary to COVID-19 was reported in four patients
MG	Rzepiński et al. [33]	Poland	N: 30 Female %: 83.33 Mean age: 42.3	Positive PCR: 10	Fever, chills, myalgia, headache, cough, fatigue, ageusia, anosmia, dyspnoea	Plasma exchange: 4 (13.33 %) IVIg: 6 (20%) Cholinergic therapy: 29 (96.7%) Corticosteroids: 20 (66.7%) Non-steroidal immunosuppressants: 15 (50%)	11 patients needed hospitalisation. MG exacerbation due to COVID-19 in three patients. No deaths secondary to COVID-19 in study group
GBS	Filosto et al. [40]	Italy	N: 34 Female %: 26.67 Mean age: 59.2	PCR-positive/ seropositive: 30	Fever, cough, dyspnoea, dysgeusia, anosmia, gastrointestinal symptoms, paresis, facial diplegia with mild distal weakness, pharyngeal–cervical–brachial weakness, sensory impairment	Plasma exchange: 2/30 (6.67%) IVIg: 25/30 (83.33%) No treatment: 3/30 (10%)	More frequent admission to ICU among GBS COVID-19-positive patients. Need for mechanical ventilation in 25 patients. 90% of COVID-19-positive subjects and 100% of negative cases with classic form of GBS. A worse course of GBS was reported in COVID-19 group. No deaths secondary to COVID-19 were reported in study group
GBS	Rahimi et al. [44]	Multicentre	N: 31 Female %: 45.17 Mean age: 57.26	Positive PCR: 31	Paresthesia in feet and hands, symmetric weakness in lower limbs, facial palsy, acute proximal tetraparesis, gait difficulties, and root-type pain in all four limbs	NI	Need for hospitalisation in five patients with GBS. GBS secondary to COVID-19 was found mostly in elderly men
GBS	Gittermann et al. [41]	Multicentre	N: 30 Female %: 36.67 Mean age: 59.8	Positive PCR: 28 Seropositivity: 2	Fever, pneumonia, paresthesia, hyperesthesia and symmetrical weakness of limbs, areflexia, anosmia, ageusia, bilateral masseter weakness, paralysis of hypoglossal nerve, myalgia, diarrhoea, etc	IVIg: 27 (90%) Antiretroviral therapy: 8 (27%) Hydroxychloroquine: 12 (40%) Other (hydroxychloroquine, prednisone, and antiretroviral therapy but not immunoglobulins): NI	Older age and male sex positively correlated with occurrence of GBS. No deaths secondary to COVID-19 were reported in study group

Table 1 cont. Autoimmune diseases of nervous system and COVID-19

Disease	Study [ref.]	Country	Details	COVID-19 (N)	COVID-19 symptoms	Treatment N (%)	Clinical outcomes
GBS following vaccination	García-Grimshaw et al. [85]	Mexico	N: 7 Female %: Mean age: 51.71	NA	NA	IVIg: 7 (100%)	Incidence of GBS in studied population rated as 0.18/100,000. All cases of GBS occurred after first dose of BNT162b2 mRNA vaccine. No cases were reported after second dose
GBS following vaccination	Shapiro et al. [79]	Israel	N: 702 Female %: 48 Mean age: 53	NA	NA	Plasmapheresis: 1 (0.14%)	Forty eight patients had visited emergency department. Need for hospitalisation only in one patient (relapse of previous syndrome)
MFS following vaccination	Siddiqi et al. [86]	Pakistan	N: 1 (case report) Male Age: 53	NA	NA	IVIg Pregabalin	Case of MFS following first dose of Sinovac–Coronavac COVID-19 vaccine. Complete resolution of symptoms 10 weeks after discharge
ADEM	Zelada-Ríos et al. [48]	Multicentre	N: 20 Female %: 25 Mean age: 49.8	Positive PCR: 20 Seropositivity: 1	Pyramidal signs, brainstem signs, cerebellar signs, seizures, peripheral nerve compromise	Dexamethasone: 2 (10%) Methylprednisolone: 5 (25%) IVIg: 1 (5%) Methylprednisolone & IVIg: 5 (25%) IVIg & Tocilizumab: 1 (5%) Supportive: 1 (5%) NI: 5 (25%)	66.7% with a severe course of infection. One positive PCR for COVID-19 in CSF. Occurrence of encephalopathy in most cases. A fully favourable outcome was reported in 7/9 patients in follow-up, while a partially favourable outcome was found in 2/9 patients. Two deaths secondary to COVID-19 were reported in study group
ADEM	Manzano et al. [49]	Multicentre	N: 46 Female %: 37 Mean age: 49.5	Positive PCR: 34 Seropositivity: 6 Method not specified: 2 Suspected: 4	Seizures, encephalopathy, aphasia, focal motor and sensory deficits, cranial nerve deficits, cerebellar deficits, urinary retention, autonomic instability	Methylprednisolone i.v.: 24 (52%) Oral steroids: 10 (22%) IVIg: 2 (4%) IVIg & Methylprednisolone & PlEx: 11 (24%) Plasmapheresis: 2 (4%) Rituximab: 1 (2%) Ocrelizumab: 1 (2%) Cyclophosphamide: 1 (2%) Neurosurgical intervention: 2 (4%) Mannitol: 1 (2%) Supportive care: 9 (20%) No treatment: 5 (11%)	Need for ICU admission in 67% of cases. Haemorrhage on brain MRI in 42% of cases. Non-inflammatory CSF in 30% of patients. Nine deaths secondary to COVID-19 were reported in study group

ADEM — acute disseminated encephalomyelitis; AE — autoimmune encephalitis; AHLE — acute haemorrhagic leukoencephalitis; CT — computed tomography; DMF — dimethyl fumarate; DMT — disease-modifying therapy; FG — fingolimod; GBS — Guillain–Barré Syndrome; ICU — Intensive Care Unit; IVIg — intravenous immunoglobulin; LD — limited data; MFS — Miller–Fisher Syndrome; MG — myasthenia gravis; MS — multiple sclerosis; NA — not applicable; NMOSD — Neuromyelitis Optica Spectrum Disorder; NI — no information; N — number of patients; PlEx — plasma exchange

Multiple sclerosis

Multiple sclerosis (MS) is a chronic demyelinating disease that affects the central nervous system. It is usually diagnosed between 20 and 40 years of age. It is characterised by remissions and exacerbations, which gradually lead to disability [9]. Due to the autoimmune nature of the disease and the immunomodulatory therapies, it was important to determine the impact of COVID-19 on the course of MS. In most studies, the existence of MS has not been shown to significantly increase the risk of COVID-19 infection [10]. However, some reports have indicated that MS patients are more susceptible to it [11]. Older obese patients and subjects with higher disability scores were found to be more at risk of a worse course of SARS-CoV-2 [12]. However, in some cases, younger, less disabled patients could be more vulnerable because of their more frequent social interactions [13]. COVID-19 infection can also contribute to the exacerbation of the underlying disease. There have been some reports related to COVID-19-induced relapse and failure of the applied treatment due to the viral invasion [8, 9].

Most studies have found no significant correlation between disease-modifying therapy (DMT) and a more severe course of COVID-19 [4, 5, 7]. Alonso et al. showed that patients on rituximab were more at risk of death from SARS-CoV-2 [18]. Additionally, Barzegar et al. [19] demonstrated that one patient who was administered rituximab had a critical course of disease. Some data has suggested that anti-CD20 therapies could contribute to a higher probability of infection and a severe course of COVID-19 [20]. Another cross-sectional study showed that natalizumab was related to a higher risk of infection. Treatment in hospital settings has also been reported to be connected to higher susceptibility as opposed to home-based drug administration [21]. However, all these findings should be interpreted with caution because of the different conclusions made by the various authors.

Neuromyelitis Optica Spectrum Disorder

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an inflammatory demyelinating disease affecting the optic nerves and the spinal cord. It is characterised by the presence of IgG autoantibodies against aquaporin 4 (AQP4) [22]. Due to increased susceptibility to bacterial and viral infections following immunosuppressive therapies, it was crucial to determine the impact of SARS-CoV-2 on the course of the disease. Several studies found no increased risk of infection due to NMOSD [4, 14]. In their meta-analysis, Barzegar et al. [24] showed that the prevalence of COVID-19 in patients with NMOSD was 1.2%, while the mortality rates ranged from 0 to 31.3%. In terms of immunosuppressive treatment, no risk of drug administration has been reported during the pandemic. However, patients should follow the restrictions and observe social distancing [10].

Studies showed that the administration of rituximab and the presence of comorbidities could be risk factors for COVID-19 [24]. Studies also found that patients on rituximab were more likely to develop gastrointestinal manifestations of COVID-19 infection and a worse course of the disease that required hospitalisation (60%) [25]. Research showed an increased risk of relapse during the pandemic, not only due to COVID-19 infection, but also to the accompanying chronic stress [23].

There are some reports on NMOSD following COVID-19 infection or vaccination. Based on 11 reports, Mirmosayyeb et al. [26] showed that a first episode of NMOSD could occur after SARS-CoV-2 infection. Furthermore, some cases of NMOSD with the presence of MRI lesions and AQP4 IgG after COVID-19 vaccination have also been reported [14–16]. Despite the rising concerns, resolving this issue would require further investigation and long-term surveillance of such patients.

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction. It is characterised by the presence of IgG antibodies against the nicotinic acetylcholine receptor (nAChR) [30]. Patients with MG are more susceptible to SARS-CoV-2, particularly those with a higher Myasthenia Gravis Foundation of America (MGFA) clinical class [31]. Well-controlled MG and the absence of comorbidities has been shown to correlate positively with a milder course of COVID-19 infection [32]. Interestingly, according to a Polish study, COVID-19 infection does not necessarily worsen MG severity as assessed by the MGFA classification [33]. Exacerbation of the disease caused by COVID-19 occurred in 10–15% of patients with MG. Rodrigues et al. described eight patients with MG exacerbation and myasthenic crisis during the viral infection. The main risk factors for a worse prognosis and death included long-term corticosteroid use, older age, cancer, and rituximab use [34]. Patients with MG could be more vulnerable to a severe course of COVID-19. However, there is some evidence that immunosuppressive therapy may have a protective effect [35]. The type of treatment does not influence the occurrence of SARS-CoV-2. Patients should continue their therapy during the pandemic [31]. Studies have shown that azathioprine, mycophenolate mofetil, and cyclophosphamide do not significantly affect the outcomes. Large doses of corticosteroids and the administration of rituximab could be related to higher mortality rates [34]. However, corticosteroids may actually play a protective effect in moderate and severe COVID-19 [32].

SARS-CoV-2 infection may not only exacerbate the disease, but also contribute to the development of a new episode of MG. This unexpected neurological manifestation suggests that the virus could induce the production of antibodies. However, further studies are warranted in this regard [26, 27].

Guillain-Barré syndrome

Guillain-Barré Syndrome (GBS) belongs to the most common acquired demyelinating polyneuropathies. The exact cause of the disease is unknown. Nerve damage is associated with autoimmune processes [38]. The onset of GBS is usually preceded by an infection, mostly of the lower respiratory tract.

The pathogens that could be aetiological factors of GBS include *Campylobacter jejuni*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, the *Zika* virus, etc. Since 2020, new cases of GBS secondary to SARS-CoV-2 have been reported [39].

Filosto et al. [40] observed a significant increase in GBS during the pandemic. Moreover, COVID-19-associated GBS had a more severe course than non-COVID-19 GBS. The first manifestation of GBS usually occurs 5–21 days after infection. The highest incidence is among older men (aged 60+ years), yet the mean age before the pandemic was 40 years [41]. The red flags that may indicate the occurrence of GBS in the course of infection include anosmia, ageusia, cranial neuropathies and lymphocytopenia. Early diagnosis and the initiation of treatment are essential. The primary therapeutic methods are IVIg and plasma exchange [42]. In COVID-19-related and non-related GBS, the response to treatment is similar [40]. Li et al. [43] made a systematic review describing patients with Miller-Fisher syndrome, a variant of GBS, after SARS-CoV-2 infection. These unusual manifestations of the viral infection underline the importance of follow-up and neurological examination in COVID-19 patients [44].

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a demyelinating autoimmune disease with sudden episodes of inflammation in the brain and the spinal cord [45]. It can occur at any age, although most cases are seen in children [46]. ADEM is usually triggered by infection or vaccination. There is limited data on the COVID-19 course in patients with pre-existing ADEM. Hussein et al. [47] showed a case of Coxsackie-induced ADEM exacerbated by SARS-CoV-2 infection. Treatment with steroids and plasmapheresis resulted in a favourable outcome. Zelada-Ríos et al. [48] published a systematic synthesis of worldwide cases of ADEM secondary to COVID-19 (Tab. 1). They found that the prevalence of this condition was higher among adult men than in children. The mean time from the onset of infection to the development of ADEM was 23.2 days (4–60 days). Another meta-analysis showed the existence of acute haemorrhagic leukoencephalitis (AHLE) in the course of SARS-CoV-2 infection, with high rates of brain haemorrhage on MRI (30%) [49]. In most patients, steroid therapy, IVIg and plasmapheresis are effective methods of treatment [35,38]. Unfortunately, ADEM in the course of COVID-19 contributes to more frequent hospitalisation in intensive care units, higher mortality, and long-term neurological deficits [50].

Other autoimmune diseases

Cases of other neuroimmune disorders secondary to COVID-19 have also been reported. Autoimmune encephalitis is brain inflammation with the production of antibodies against self-antigens [51]. Anti-NMDAR, anti-MOG, anti-GAD, anti-GD1a and anti-CASPR2 are significant molecules that play a role in its origin [52]. There is limited data on AE and COVID-19. Payus et al. [8] demonstrated that most COVID-19-associated cases (77%) occurred during the acute phase of the infection. Thirty percent of patients presented with neurological symptoms before developing fever and respiratory symptoms. Apart from typical infectious symptoms, the most common presentations are as follows: psychomotor agitation, hallucinations, seizure, anxiety, thought disorganisation, persecutory delusions and insomnia [8]. Treatment with corticosteroids, IVIg, plasma exchange and antiseizure medications is effective in most cases. Limbic encephalitis (LE) may be another complication of SARS-CoV-2. This is a form of encephalitis limited to the medial temporal lobes and is caused by autoimmunity [53]. It is characterised by the production of auto-antibodies, such as anti-Hu, anti-Ma2 and anti-NMDAR [54]. It is mainly diagnosed as a paraneoplastic phenomenon. There are some reports of LE associated with SARS-CoV-2 [39–42]. The mean age of patients was 73.8 years (66–80 years), as reported by Pizzanelli et al. The most common symptoms included seizures, neuropsychiatric symptoms, confusion and amnesia. Typical lesions in medial temporal lobes were present on brain MRI. In all described cases, the disease resolved after treatment with corticosteroids, IVIg, or plasma exchange [58].

Effects of treatment of neuroimmune diseases on SARS-CoV-2 infection

The use of immunosuppressants and adhering to the principles of social distancing seem to be safe in most cases, and do not increase susceptibility to COVID-19 infection. Some drugs used in neuroimmune diseases have been tested for their effectiveness in COVID-19 [59].

Glucocorticoids, which are widely used in AIDs, reduce mortality from severe COVID-19. However, some data has indicated that high doses during AID treatment could worsen the prognosis and be associated with a higher risk of hospitalisation and death [60].

In our previous review, we included some immunomodulatory drugs (interferons, teriflunomide and leflunomide) used in MS that were tested in SARS-CoV-2 infection [59]. Rabie et al. [61] showed that the use of teriflunomide in patients with COVID-19 reduced the cytokine storm. Other studies showed that leflunomide, a dihydroorotate dehydrogenase (DHODH) inhibitor, was associated with faster hospital discharge or reduction in C-reactive protein (CRP) levels in COVID-19 cases [61, 62]. IMU-838 is another promising candidate from this group. It has shown antiviral properties in patients infected with SARS-CoV-2 [64]. Yousefi et al. [65] assessed fingolimod as one of the potential drugs that could stop the virus from invading the CNS. However, the above studies did not consider lymphopenia to be a significant indicator in patients. The National Institutes of Health suggests the use of IL-6 inhibitors (tocilizumab, sarilumab and siltuximab) during SARS-CoV-2 infection. IL-6 inhibitors are also in the research phase related to NMOSD. In COVID-19,

they may contribute to the reduction of the cytokine storm [66]. Another meta-analysis showed the efficacy of IVIg in the course of COVID-19 infection [67]. Plasmapheresis is a different method worthy of consideration. Both of them should be used within 14 days of the onset of infection, which may reduce mortality and shorten hospitalisation [68]. A reduction in proinflammatory cytokine levels and the immune response was also observed in patients with acute respiratory distress syndrome (ARDS) after plasmapheresis [69].

However, all these studies have their limitations due to the pandemic's dynamics and the insufficient number of results confirming treatment efficacy. Therefore, further studies are warranted.

COVID-19 vaccination in patients with neuroimmune disorders

There have been concerns raised about the efficacy and safety of vaccines against COVID-19 in patients with AIDs. In MS patients, vaccination did not increase the risk of relapse or vaccine ineffectiveness [70]. Nevertheless, DMTs can significantly affect the development of the humoral response. Kulikowska et al. [71] revealed that vaccination in MS patients treated with dimethyl fumarate, interferon beta and glatiramer acetate significantly induces the production of IgG and IgA against S protein ($p < 0.0001$). Patients treated with the above-mentioned drugs can efficiently produce antibodies against SARS-CoV 2. In the case of therapies with anti-CD20 antibodies, alemtuzumab and natalizumab, it is recommended to plan the vaccination date individually depending on the last drug administration [70]. In fingolimod-treated patients, attention should be paid to the presence of lymphopenia [72]. In NMOSD patients, vaccination is also safe and not associated with disease progression [73]. Patients treated with rituximab showed a poorer response, and could be at risk of infection despite vaccination [74]. In MG cases, vaccination theoretically may cause disease exacerbation, but patients with MGFA I and II should not avoid vaccination [73, 74]. Qualification for vaccination in other cases should be done on an individual basis, bearing in mind that the benefits outweigh the risks in most patients [77]. The occurrence of COVID-19 had a worse effect on MG than vaccine administration [76]. In patients with a previous episode of GBS not associated with COVID-19, vaccination is recommended. However, age and risk factors must be considered [78, 79]. We found no data about the safety or efficacy of SARS-CoV-2 vaccines in patients with a history of ADEM. Some reports have shown cases of MG, GBS, NMOSD and ADEM following vaccination against SARS-CoV-2 [77–81, 84–86]. Nevertheless, this should be interpreted with caution. Only single cases of such phenomena are usually reported. According to Kaulen et al. [81], severe neurological complications after COVID-19 vaccination are extremely rare (< 0.1%).

Conclusions

Overall, the pathogenesis and immune response in AIDs and COVID-19 share many common features. Both are heterogeneous conditions in which immune-mediated mechanisms can lead to multiple organ failure. The main concern for patients with AIDs is whether the infection is associated with a worse prognosis or an exacerbation of the underlying disease.

In most of the above studies, the presence of AIDs did not significantly affect the infection course. In patients with many comorbidities and advanced disease, the need for hospitalisation and the mortality rate may be higher. The approach to patients with AIDs should be individual because many issues remain unresolved despite the long-lasting pandemic. There is a lack of comprehensive research into specific topics.

However, we hope that our review contributes to a better understanding of the connections between neuroimmune diseases and COVID-19.

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LEADING TOPIC

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Navigating the landscape of COVID-19 for Multiple Sclerosis patients and clinicians

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ABSTRACT

The purpose of this literature review was to summarise relevant findings regarding the clinical management of multiple sclerosis (MS) in the COVID-19 pandemic, with the focus on patient risks, and the implications of disease-modifying treatment, both on COVID-19 severity and on the response to the SARS-CoV-2 vaccinations. Although MS per se does not seem to put patients at risk for more severe COVID-19, alongside the risk factors known to apply to the general population, progressive disease course, higher disability status, and B-cell depleting therapies may all negatively affect infection severity. The question of COVID-19 sequelae in patients with MS (pwMS) remains unresolved, challenging researchers to further explore this area. The safety profile of COVID-19 vaccinations in pwMS is similar to that of the general population. The efficacy of the vaccination might be affected by B-cell depletion, as well as by S1PR-modulating medications that attenuate humoral responses to the COVID-19 vaccination. Future research should focus on gathering evidence regarding the clinical course of MS following COVID-19 infection and vaccination in larger studies, as well as on establishing the safest and most efficient schedule of COVID-19 vaccination in pwMS on cell-depleting therapies.

Key words: multiple sclerosis, COVID-19, SARS-CoV-2, COVID-19 vaccination, disease-modifying therapy

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Introduction

Since patients with multiple sclerosis (MS) are a group considered to be vulnerable to hospitalisation and death from lower respiratory tract infections [1–4], one of the most pressing matters regarding the outbreak of the Coronavirus disease (COVID-19) pandemic, caused by the SARS-CoV-2 virus infection, was determining the influence of the underlying neurological condition on susceptibility to COVID-19.

Another issue was the impact of disease-modifying therapies (DMTs) on this susceptibility, and answering the question as to whether or not patients' treatment could be continued while they were infected with COVID-19. And when vaccinations were eventually approved, it became crucial to establish their safety in the MS population and their efficacy, especially in patients treated with immune therapies.

The neurological world adapted fairly quickly to the pandemic reality, releasing subsequent versions of recommendations with regards to DMT initiation in the pandemic, DMT continuation in the case of COVID-19 infection [5, 6], COVID-19 vaccinations [7–9], and even telemedicine [10] in the context of the MS population.

In this review, we have aimed to answer the key questions that MS patients and their clinicians may ask in the context of SARS-CoV-2 infection, thus facilitating a complex navigation through the landscape of the pandemic.

Are MS patients at risk of severe COVID-19, and how does the infection influence their subsequent MS course?

COVID-19 morbidity and mortality in the MS population

Although early reports on the outcomes of COVID-19 in patients with MS (pwMS) yielded mostly reassuring results [11–14, 16, 17, 21], a French study of 347 pwMS found that 21%

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of them had a more severe course of the infection, and 3.5% had a fatal outcome [15]. Comparing outcomes among hospitalised patients, fatality rates were higher in pwMS than in the general population for most age groups, suggesting that MS was associated with increased mortality. A systematic review of studies comprising 4,310 pwMS and COVID-19 revealed that 837 of them were hospitalised and 130 died, representing 20.7% and 3.0% of the sample, respectively [20]. Although the mortality rate in this review was not increased, the authors suggested that this result could be a function of demographic characteristics of pwMS, who tend to be on average younger and more female than the average population, and thus less susceptible to severe infection. Indeed, a study exploring COVID-19 general mortality risk factors in a cohort of 1,931 MS patients revealed that those at high risk comprised less than 1% of the sample [21].

In a retrospective study comparing patients with and without a concurrent MS diagnosis, the authors described lower rates of ICU admission, use of ventilation, and in-hospital mortality in pwMS [19]. After an age group-stratified analysis, the positive effect of comorbid MS on admissions to ICU and ventilation use, although attenuated, remained significant, but no difference between MS and non-MS patients was found in terms of in-hospital mortality.

In a pooled analysis of studies comprising 5,634 patients [22], crude death rates in pwMS and the general population did not differ substantially, but a 24% increased risk of death was found in pwMS after age-standardisation.

The ever growing data on COVID-19 in pwMS often throws up contradictory evidence, which can cause confusion. However, most authors agree that the course of COVID-19 in pwMS is mostly favourable i.e. asymptomatic or mild. Importantly, although multiple sclerosis patients are on average younger, and more frequently women, than the general population, it is worth acknowledging that discrepancies in analysed samples' demographics between different studies do affect the results. Preliminary studies included relatively small samples and from countries that had been differently affected by COVID-19, especially during the first wave, with diverse safety measures taken by the various governments affecting COVID-19 prevalence and causing inconsistent results. Moreover, there is a profound heterogeneity in the outcome measuring scales used for statistical analysis across the studies on COVID-19, as well as in the varying hospital admission criteria, COVID-19 diagnostic tools, and even COVID-19 definition, with some researchers considering both suspected and confirmed cases, while others have been taking into account only PCR-confirmed SARS-CoV-2 infections. All these factors contribute to a major difficulty in attempting outcome comparisons.

The number of possible variables and factors impacting the course of COVID-19 in pwMS made it crucial to evaluate specific risk factors accounting for morbidity and mortality in this population, shifting the focus to the adoption of a more personalised approach.

Risk factors for severe COVID-19 in MS patients

Rapidly conducted research around novel coronavirus disease enabled the prompt identification of risk factors associated with COVID-19 severity in the general population, as well as in pwMS [23]. The assessment of demographic and clinical characteristics conducted by Louapre et al. provided the first insights into MS-related factors associated with unfavourable disease course [15]. The authors identified older age, male sex, obesity, and disability (in the form of a higher EDSS score) as independent risk factors for increasing COVID-19 severity. Similar findings were reported by Sormani et al. [24], who found older age, male sex, higher EDSS, as well as methylprednisolone use within one month before infection, to be predictors of worse outcomes in both univariate and multivariate analyses. Other variables associated with the risk of severe SARS-CoV-2 infection identified in this study were: progressive MS course, longer disease duration, comorbidities, increased BMI, and treatment with an anti-CD20 drug.

The COViMS Registry associated older age, male sex, obesity, ambulatory disability, cardiovascular comorbidities, and recent corticosteroid treatment with higher risks of hospitalisation and mortality [25]. Black race and rituximab exposure were associated with an increased risk for hospitalisation, but not for death [25]. The association with hospitalisation persisted for ocrelizumab exposure, although only to a slight extent. An analysis of pooled updated cohorts of SARS-CoV2 cases in MS patients from Italy and France confirmed this finding, indicating that both anti-CD20 agents significantly increase the risk for severe disease course, although the influence of rituximab was of a greater magnitude [26]. Consistently, recently updated results of the MS Global Data Sharing Initiative, comprising 5,648 patients, have reinforced previous reports in what is the largest sample to date [27].

Unexpectedly, not being on DMT therapy has been associated with an increased risk of severe COVID-19 in pwMS, as most of the studies have proved that patients on DMTs have more favourable outcomes of SARS-CoV-2 infection [28, 29]. However, this finding was successfully explained by other factors putting pwMS without DMT at risk, since they are usually affected by progressive disease course and/or higher disability, precluding them from receiving most DMTs, or are older than the typical MS population [27].

Recovery from COVID-19 in MS patients

Current research provides quite consistent data regarding COVID-19 symptoms and infection course in MS patients, suggesting that most pwMS develop a relatively mild infection, with symptoms similar to those observed in the general population [30–32].

The link between viral infections and multiple sclerosis exacerbations has been researched extensively, meaning that a proper exploration of the risk of COVID-19-triggered worsening and relapses is of great importance. Neurological manifestations of SARS-CoV-2 infection have suggested a possible neurotropism of the novel infectious agent, which could potentially increase the risk of future neurodegeneration, especially in those considered vulnerable due to the underlying chronic neurological conditions [33–35].

Nevertheless, real-world data regarding a link between COVID-19 and MS course is limited, and the results are contradictory. In a sample of 404 patients, Garjani et al. [36] observed MS exacerbations in 57% of patients who contracted SARS-CoV-2. Among those patients, 20% reported developing new symptoms and 51% experienced worsening of preexisting ones. The authors also found that DMT treatment reduced the risk of developing new MS symptoms. In a relatively small sample of 111 patients, Conway et al. observed neurological deterioration in 36.9% of pwMS following a SARS-CoV-2 infection, with a correlation between COVID-19 severity and the frequency of neurological complications, mostly pseudo-relapses and worsening of preexisting symptoms [37]. Those results were in line with the general population studies, where infection severity and hospitalisation for COVID-19 were associated with a higher risk of neurological symptoms post-COVID-19 [38]. In contrast to previous findings, an Austrian matched-control study comprising 211 MS patients with COVID-19 and 211 MS controls revealed that neither relapse nor disability worsening risk was increased in the MS and COVID-19 group [39]. Similarly, in a relatively small retrospective study, pwMS who contracted SARS-CoV-2 presented a lower incidence of disease exacerbation and an unaltered relapse risk following the infection [40].

An important insight into relapse risk was presented in a study of Chinese pwMS, where a significant increase in relapse rate during the pandemic was observed, but only in those patients who experienced treatment discontinuation, dose reduction, or were not receiving any MS therapy [41].

Long COVID in patients with multiple sclerosis

'Long COVID' is defined as symptoms that continue or develop after acute COVID-19 and includes both ongoing symptomatic COVID-19 (4-12 weeks) and post-COVID-19 syndrome [42].

Post-COVID-19 syndrome develops during or after COVID-19, and lasts for more than 12 weeks. The symptoms include dyspnoea, cough, fatigue, cognitive impairment, sleep disturbances, headache, loss of smell and/or taste, gastrointestinal problems, joint/muscle pain, and psychiatric symptoms, and cannot be explained by an alternative diagnosis [42].

The prevalence of prolonged COVID-19 symptoms was assessed by Garjani et al. [43] in non-hospitalised pwMS. They concluded that 30% of the sample experienced residual COVID-19 symptoms for at least four weeks and in 12% of patients these persisted for at least 12 weeks. These results exceeded those seen in the general population. Moreover, among MS patients, preexisting severe disability and, as described for the general population, female sex and higher anxiety/depression levels, predisposed to COVID-19 sequelae.

Bsteh et al. [39] found that residual fatigue, dyspnoea, and hyposmia persisted for 3–6 months in a small proportion of patients before resolving, mostly within 12 months.

Another study reported that nearly 45% of pwMS with COVID-19 reported residual symptoms after the initial infection, of whom 20% had symptoms lasting more than 12 weeks. The most commonly reported were: fatigue and cognition complaints including concentration, attention, memory domains, and headache [44].

COVID-19 sequelae in pwMS have been under-researched with limited data, and guidelines for management tailored to this population are yet to emerge.

How do different disease-modifying therapies (DMTs) influence COVID-19 severity in MS patients?

Disease-modifying therapies are used for controlling disease activity in multiple sclerosis, mainly by reducing the rate of relapses and radiological activity [45]. Their mode of action is through altering the immune system either by immunomodulation or immunosuppression, and thus the emergence of a novel, dangerous infectious agent posed an important threat to DMT safety during the pandemic outbreak; however, thanks to their antiviral properties, some DMTs have been evaluated for their effectiveness in COVID-19 [46, 47].

Beta-interferons, type I interferons originally known for their antiviral effects, have been used in MS as a first-line, moderate-efficacy therapy, and have proved particularly useful for pregnant or breastfeeding pwMS [48]. From the beginning of the pandemic, beta-interferons were designated as a safe medication to continue and to start during the pandemic [49–53]. Emerging research provided evidence that beta-interferons did not increase the risk of severe SARS-CoV-2 infection, and most patients on this therapy were recovering safely from COVID-19 [54]. Some studies suggested that beta-interferons might even provide some level of protection, lowering the odds of developing infection when compared to other therapies [55]. Prosperini et al. [56] concluded that beta-interferons exerted a favourable effect on mortality, even after adjusting for age and progressive disease course in a multivariable meta-regression.

This hypothesis has recently been challenged by the results of a large study on a cohort of 5,568 patients with COVID-19 and MS, which showed there was no difference in hospitalisation rate, ICU admission percentage, or death risk between beta-interferons and pooled other DMTs [57], although the authors reveal that in comparison to those treated with other DMTs, patients treated with beta-interferons were slightly older and more frequently diagnosed with progressive MS, both of which predispose to a poor COVID-19 outcome.

Glatiramer acetate (GA), a molecule resembling myelin basic protein (MBP), is a first-line immunomodulatory medication that has been associated with a low risk for COVID-19 severity [50–53]. Current research concludes that this medication does not increase morbidity or mortality of COVID-19, as fatality rates in glatiramer acetate-treated pwMS remained among the lowest [15, 55]. GA was recently evaluated in comparison to a no-DMT group among pwMS suffering from COVID-19, which revealed that untreated patients were 5% more likely to be hospitalised and 1% more likely to die, although these results should be interpreted with caution because the outcomes in untreated patients were generally considered to be a function of confounding factors [27].

Teriflunomide is a selective dihydroorotate dehydrogenase inhibitor interfering with DNA synthesis, targeting especially lymphocytes and thus potentially causing slight lymphopenia [58–60]. However, teriflunomide has not been associated with significant immunosuppression and phase III clinical trials did not indicate an increased risk for infections [59]. This data, in combination with potential antiviral priorities owing to pyrimidine synthesis blockage, resulted in teriflunomide being categorised as a low-risk medication in the context of COVID-19 severity, with treatment continuation generally recommended in pwMS [50–53]. The outcomes of preliminary case reports as well as studies conducted on relatively small samples further reinforced this recommendation [15, 61, 62]. In a pooled cohort of 5,634 patients, teriflunomide was associated with lower lethality in both univariate and multivariate models [56].

Dimethyl fumarate is another first-line medication with immunomodulatory properties, modifying lymphocyte subsets proportions, as well as reducing pro-inflammatory cytokine production [63]. In some patients, dimethyl fumarate has been proven to cause lymphopenia with a small proportion of patients developing grade 3 lymphopenia (ALC 200–499/μL) [64]. While this fact may be of concern, the research data so far does not indicate an elevated risk of severe COVID-19 in dimethyl fumarate-treated pwMS [24, 55]. Conversely, the authors of the North American Registry of Patients With Multiple Sclerosis study found decreased odds of ICU admission and/or ventilation in patients on dimethyl fumarate [25]. Importantly, the latest reports from the Global Data Sharing Initiative found no association between this medication and increased severity of SARS-CoV-2 infection, and no increase in the probability of hospitalisation, ICU admission/artificial ventilation, or death compared to GA [27].

Sphingozine 1-phosphate receptor (S1PR) modulators act as DMTs in MS by preventing lymphocyte excretion. Decreasing the amount of peripheral, circulating immune cells, S1PR--modulators reduce the autoimmune reaction within the CNS [65, 66]. Through their mode of action, S1PR-modulators induce lymphopenia, which can render patients potentially prone to infections. However, common viral infections do not seem to severely affect S1PR-treated patients [67]. There are now four S1PR-modulators approved for treating MS — fingolimod, siponimod, ozanimod, and ponesimod [68]. With fingolimod being the first S1PR-modulator registered in MS, most of the available literature focuses on its influence on COVID-19 severity. Current research does not find an increased risk for severe COVID-19 in fingolimod-treated pwMS [69]. In a review of fingolimod-treated patients from Novartis database safety and clinical trials, the outcomes of COVID-19 were similar to those observed in the standard population [70]. This same study evaluated the risks for siponimod patients as well, concluding that even though pwMS treated with siponimod tend to be older and with a higher disability (as siponimod is registered for secondary progressive disease), they do not seem to be vulnerable to severe COVID-19. However, because of the spontaneous nature of case reporting, incomplete data accumulation, and the low number of siponimod-treated patients, caution should be exercised when interpreting these results.

Natalizumab is a second-line highly effective medication for MS. A monoclonal antibody, binding alpha-4-beta-1-integrin on immune cells, natalizumab reduces immunosurveillance of the CNS, blocking adhesion to the endothelium and limiting migration across the blood-brain barrier [71, 72]. Although patients receiving natalizumab are not considered high risk for common infections, reduced viral clearance from CNS with a combination of SARS-CoV-2 neurotrophic properties initially raised concerns of possible encephalitis [73]. Current research does not find evidence of natalizumab increasing severity rates in COVID-19 pwMS [24, 25, 27]. Consistent with these results, a recently published systematic review found that natalizumab was associated with a decreased risk of severe COVID-19 compared to no DMT [74].

Cladribine in tablets, a purine analogue, is a cell-depleting drug used in highly active relapsing-remitting MS (RRMS). Administered as two short treatment courses one year apart, cladribine induces lymphocyte apoptosis, causing the nadir shortly after the start of each cycle followed by gradual lymphocyte recovery, and is considered an immune reconstitution therapy (IRT) [75]. Although its beneficial effects on MS course persist over the long term, it causes transient lymphopenia, which theoretically could increase the risk of infections. Thus cladribine was marked as an intermediate/high-risk therapy during the COVID-19 pandemic [51–53]. Scant evidence exists regarding the safety of cladribine and COVID-19. One of the early studies assessing the prevalence of COVID-19 among DMT-treated pwMS concluded that IRT was associated with an increased risk of infection compared to beta-interferons and GA, although it is worth noting that no elevated risk for infection severity was detected and that the influence of cladribine was studied in a combination with another IRT, namely alemtuzumab [76]. Importantly, the Global Data Sharing Initiative found no association between increased risk for severe COVID-19 and cladribine exposure, although the number of patients on cladribine was relatively low [27]. In a group of cladribine-treated MS patients from

the Merck KGaA Global Patient Safety Database, 160 with confirmed and 101 with suspected COVID-19, the majority of the sample presented with a mild infection and only one patient (0.4%) had a fatal outcome, further indicating that cladribine-treated pwMS are not at a greater risk for severe SARS-CoV-2 infection [77]. A recently published systematic review of 5,138 MS patients with COVID-19 found a low hospitalisation rate (9.36%) and no fatal outcomes reported among 107 cladribine-treated pwMS, providing reassuring results [78]. To the best of our knowledge, no evidence exists of a greater risk for COVID-19 in cladribine-treated patients.

Alemtuzumab is an anti-CD52 monoclonal antibody that acts similarly to cladribine as immune reconstitution therapy providing long-term effects in RRMS through immune depletion and subsequent slow repopulation, although the reduction of lymphocyte counts can be prolonged and result in severe lymphopenia, causing susceptibility to infections [79]. Indeed, in phase III trials, alemtuzumab did significantly increase the risk of mild to moderate infections [80]. How this translates to the COVID-19 pandemic is of great importance, yet very little data is available on alemtuzumab use in relation to SARS-CoV-2 infection. As mentioned before, one study found an increased risk of contracting COVID-19 in patients on IRT compared to injectables [76]. Conversely, Biogen Safety Database results did not indicate a significant increase in the incidence of COVID-19 in patients on alemtuzumab, although the voluntary nature of pharmacovigilance data collection limits the significance of this finding [55]. While the first studies only included isolated cases of alemtuzumab patients, precluding the drawing of meaningful conclusions, reassuring results were obtained from the international sample of 2,340 patients, including 31 on alemtuzumab, where no increased risk for hospitalisation, ICU admission, and death was found in COVID-19 pwMS on this medication [81]. These results have been now replicated in the updated Global Data Sharing Initiative study, although the number of cases remains relatively low [27].

Anti-CD20 treatment is based on B-cell depletion and is considered a highly effective therapy for multiple sclerosis. Ocrelizumab is a humanised monoclonal antibody selectively depleting CD20+ B-cells used intravenously every six months for both RRMS and early primary progressive MS. Ofatumumab is a fully human anti-CD20 antibody that is administered subcutaneously on a monthly basis, and was most recently approved for the treatment of RRMS. Another anti-CD20 agent, rituximab, has not been approved for MS, but in some countries it has been used as an off-label medication for MS [82–84]. In an early Italian study, anti-CD20 was among the risk factors for severe COVID-19 in a multivariate model. The authors further evaluated the association between time since the last anti-CD20 infusion and total therapy duration, indicating there was a trend between anti-CD20 therapy duration and COVID-19 severity [24], while some researchers have suggested extending the interval of anti-CD20 dosing to reduce the risk of severe COVID-19 [85–87]. A pooled analysis by Sormani et al. confirmed that anti-CD20-treated patients have a higher risk of severe COVID-19. When separating the two most commonly used B-cell depleters, rituximab had a greater effect, although the influence of ocrelizumab remained significant [26]. Similar results were obtained from various studies and confirmed in a systematic review [22, 81, 88–91]. Although unfavourable results in anti-CD20-treated patients could be attributable to the fact that these patients typically have a higher degree of disability and a more progressive disease course, tested in multivariate models, ocrelizumab and rituximab persist as risk factors [26, 27]. Consistently, Global Data Sharing Initiative outcomes seem to confirm that rituximab and, to a lesser extent, ocrelizumab, independently increase COVID-19 severity [27]. The difference in the effect between those two anti-CD20 agents has been investigated, with some studies concluding that the discrepancy might exist due to a longer total treatment time and higher cumulative dose in rituximab-treated patients, since ocrelizumab has only recently become available, although the results are inconclusive [92–95].

Regarding ofatumumab and COVID-19 in MS patients, information is scarce. The largest available sample of pwMS and COVID-19 on ofatumumab was obtained from the ALTHIOS phase 3b extension study, where of 1,703 enrolled patients 245 reported COVID-19 [96]. Of those patients, 9.4% were hospitalised and 0.8% died, indicating that ofatumumab-treated pwMS mostly have a mild COVID-19 and lower risk for hospitalisation and death than the general MS population. Although these are promising outcomes, it should be emphasised that ALTHIOS is a study enrolling patients only up to 55 years old and without comorbid conditions, thereby excluding those most susceptible to severe infection. It should also be highlighted that a relatively short time of treatment with ofatumumab in reference to rituximab and ocrelizumab, and a lower cumulative dose, could result in a lower cumulative effect on immunity and prolonged cell depletion (Tab. 1).

COVID-19 vaccinations in MS patients — risks, benefits, and efficacy

Are patients with MS at risk of disease exacerbation following COVID-19 vaccination?

Since MS is an autoimmune disease, the question of the risks of disease deterioration after the COVID-19 vaccine emerges from the fact that similar immune reactions follow natural infection and vaccination, and that vaccination, by stimulating the immune system, could exacerbate the disease course in a similar way to what has been reported after infections in pwMS [97, 98]. Even though most studies do not find any significant association between vaccination and relapses in pwMS, with the one exception of the yellow fever vaccination, this area of research is of great interest and importance for both patients and their clinicians trying to apply a safe risk-benefit

Table 1. Safety of different disease-modifying therapies for Multiple Sclerosis with regards to COVID-19 severity and vaccine readiness

	Class/Drug	Mode of action	Efficacy	Class	In COVID-19
Very low infection risk, response to vaccine intact					
1.	Interferon beta	Immunomodulatory, pleiotropic immune effects	Moderate	Maintenance immunomodulatory	Safe to initiate and continue
2.	Glatiramer acetate	Immunomodulatory, pleiotropic immune effects	Moderate	Maintenance Immunomodulatory	Safe to initiate and continue
3.	Teriflunomide	Reduced *de novo* pyrimidine synthesis, antiproliferative	Moderate	Maintenance immunomodulatory	Safe to initiate and continue
Low infection risk, response to vaccine intact					
4.	Dimethyl fumarate	Pleiotropic, NRF2 activation, downregulation of NFk	Moderate	Maintenance immunomodulatory, potentially immunosuppressive when associated with lymphopenia	Safe to initiate and continue. However, caution should be exercised when managing patients with lymphopenia
5.	Natalizumab	Anti-VLA 4 selective adhesion molecule inhibitor	Very high	Maintenance immunosuppressive	Probably safe to initiate and continue. However, caution should be exercised in patients with active COVID-19 and recent infusion
Depending on the treatment phase: Low — to moderate infection risk, response to vaccine intact when lymphocyte count is > 500 /mm^3; Intermediate — to high infection risk, response to vaccine possibly blunted during depletion phase					
6.	Cladribine tablets	Immune depleting therapy	High/very high	IRT	Consider suspending
7.	Alemtuzumab	Immune depleting therapy	High/very high	IRT	Consider suspending
Low-to-moderate infection risk, response to vaccine blunted (humoral and cellular)					
8.	S1PR modulators (fingolimod, ozanimod, ponesimod, siponimod)	Selective S1P modulators prevent egress of lymphocytes from lymph nodes	High	Maintenance immunosuppressive	Probably safe to initiate and continue. Blunted response to COVID-19 vaccination
Intermediate/high infection risk, response to vaccine blunted (humoral)					
9.	Anti-CD20 (ocrelizumab, ofatumumab)	Anti-CD20, B-cell depleters	Very high	Maintenance immunosuppressive	Increased risk of severe COVID-19 for ocrelizumab and attenuated humoral response to COVID-19 vaccination in ocrelizumab-treated patients Consider planning vaccination according to treatment regimen — 4–6 months from last infusion and a minimum of 4–6 weeks before next infusion Data for ofatumumab is scarce

Modified from: https://practicalneurology.com/articles/2021-jan/ms-minute-the-covid-19-vaccine-vaccine-readiness-in-ms [Last accessed: 19.12.2022]

approach, especially during the pandemic [99, 100]. Most studies evaluating adverse events in pwMS after COVID-19 vaccination conclude that they are similar to those observed in the general population, mostly indicating pain at the injection site, fatigue, and flu-like symptoms [101–106]. A study of 1,661 pwMS vaccinated against COVID-19 showed that there was a slight increase in relapse rate at 90 days after the vaccination period, comparing the number of patients with at least one clinical relapse in this period to the number of patients with at least one clinical relapse in the previous 12 months [107]. Most relapses were mild, and the authors excluded relapses that occurred in patients with so-called 'unstable' disease, meaning patients with DMT change in each 90-day period; however, the study lacked an objective measure of disease activity such as MRI evidence. Studies with a shorter control time and smaller samples found no indication of an increased relapse rate in COVID-19-vaccinated patients [102, 107, 108]. Analysing a group of 2,346 German pwMS vaccinated against COVID-19, the authors found that the frequency of patient-reported relapses was 7.7% and that 14.8% of patients reported relapses within a year before the first vaccination. The authors also determined that: women compared to men, younger patients, those diagnosed with RRMS (as opposed to progressive forms), those not treated with DMTs, those with a lower disability level, and those who had their last relapse close to the date of their COVID-19 vaccination were all

prone to more often report relapses after vaccination [103]. Data on MS worsening after COVID-19 vaccination remains inconclusive, and more research is required.

How do different DMTs influence COVID-19 vaccination response?

Concern has been raised regarding DMTs immunomodulatory or immunosuppressive properties and vaccine efficacy. Previous studies evaluating the immune responses following infections in patients treated with DMTs found that although most DMTs did not seem to interfere with producing an effective response to infection, anti-CD20 therapies did decrease the odds of forming a humoral immune response [109–113]. These results now seem to be mirrored in the studies on the vaccine-induced immune response. Humoral response after COVID-19 vaccination has been extensively researched, and there exists strong evidence that anti-CD20 agents and S1PR-modulators impair humoral response to the COVID-19 vaccine in pwMS, causing lower seroconversion rates than in healthy controls and in other DMT-treated patients [114–121]. The level of seroconversion for anti-CD20- and S1PR-modulators-treated patients varies: 3.8% for ocrelizumab and 22.7% for fingolimod in a study by Achiron et al. [114], 52.6% for ocrelizumab and 63.6% for fingolimod in a study by Bsteh et al. [119], with one study [115] finding even 90.6%, 40.50%, and 61% seroconversion rates in fingolimod, ocrelizumab, and rituximab treated, respectively, in pwMS vaccinated with BNT162b2; and 100%, 61%, and 71% in those treated with fingolimod, ocrelizumab, and rituximab, respectively, and vaccinated with mRNA-1273.

While there is some uncertainty regarding other high-efficacy medications such as alemtuzumab and cladribine, with a few studies suggesting that patients treated with these therapies may produce lower titres of anti-S SARS-CoV-2 antibodies [118, 122], research articles, reviews and meta-analyses suggest that apart from anti-CD20 antibodies and S1PR-modulators the responses to COVID-19 vaccination do not differ from those in untreated pwMS.

This means that the majority of MS patients, including those treated with beta-interferons, glatiramer acetate, fumarates, teriflunomide, natalizumab, cladribine, and alemtuzumab, become seropositive after vaccination, similarly to healthy controls [123–131].

Some studies have evaluated factors associated with treatment protocols and antibody response, with Sormani et al. [115] finding a progressive trend between the time elapsed since the last infusion of rituximab and ocrelizumab and vaccination and antibody levels. Similar findings were reported by Pitzalis et al. [118], where the 6-month interval significantly increased antibody responses. Although Bsteh et al. [119] did not find an association between time from the last infusion and humoral response, their study concluded that B-cell depletion was a predictor of seronegativity. This has also been suggested in the study by Satyanarayan et al. [117], where a higher proportion of seroconverted patients were having circulating B cells (≥ 1 cell), although this kind of reconstitution was not always sufficient for the development of a humoral response. The same study also found shorter anti-CD20 therapy total time and prior COVID-19 increasing the odds of seroconversion. Similar results were obtained by Holryd et al. [116], who found a significant association between B-cell depletion and lower antibody titres and between time from the last anti-CD20 infusion and antibody titres. A study by Asplund Högelin et al. [132] found that B-cell levels are better predictors of seroconversion than time from the last infusion, and that seroconversion rates increase with decreasing rituximab concentration and higher B-cell counts.

Although humoral immunity is considered to be crucial to protection from breakthrough infections, cellular response contributes significantly to protection from severe COVID-19 [133, 134]. The T-cell response has also been studied in DMT-treated patients, with the latest research suggesting that cellular immunity after COVID-19 vaccination in pwMS on DMTs does not differ from that observed in healthy controls and untreated patients, apart from those treated S1PR-modulators, who seem to produce effective T-cell responses less often. Anti-CD20-treated patients have responses similar to, or even more robust than, untreated controls, which some authors suggest may be a compensation for weak antibody response [126–128, 135–139]. Because research on the effectiveness of maintained cellular response in anti-CD20-treated pwMS with negative seroconversion, as well as the influence of vaccination in fingolimod-treated patients on COVID-19, is still emerging, the data is as yet insufficient to draw meaningful conclusions. Even though there are now several types of COVID-19 vaccines available, most studies have evaluated the influence on immune responses and safety of mRNA vaccines in pwMS, and data regarding different types of vaccines is limited.

New SARS-CoV-2 variants and MS: early findings

The continuously changing properties of SARS-CoV-2 allow it to develop new variants, posing the triple threat of increased morbidity, mortality and vaccine inefficacy [140]. Thus, assessing the rate of breakthrough infections during new variant waves in vaccinated patients, as well as evaluating the safety and effectiveness of booster vaccines, is of great importance.

The reports on the third dose of the COVID-19 vaccine suggest that in pwMS the safety profile of the booster is similar to that of the first two doses [141–143]. Regarding the efficacy of the booster dose and anti-CD20 and S1PR-modulator treatment, currently there is no consensus, with some studies suggesting that the odds of developing humoral immunity after the booster in seronegative patients are low, although some patients seem to seroconvert after the booster [144–151]. In

seropositive patients on anti-CD20 and S1PR-modulators, the booster may upregulate antibody titres, providing better protection against COVID-19 [141, 143]. Preliminary findings from studies on breakthrough infections in patients on B-cell depleting therapies and fingolimod suggest that although there is an increase in risk for COVID-19, the infections are mostly mild to moderate, not requiring hospitalisation [146, 152]. The importance of vaccination for maintaining immunity against new variants was evaluated by Sormani et al. [153], showing that breakthrough infections in vaccinated patients during the Delta wave were mostly associated with low antibody titres after vaccination, and that the immunity that was waning over time was often insufficient during the Omicron wave, with a significant reduction of risk for Omicron infection in patients who received the booster dose.

Conclusions

Despite the rapid data accumulation and research development, and the fact that it has been three years since SARS-CoV-2's emergence, a good deal of uncertainty and controversy remains.

It seems that even if multiple sclerosis *per se* does not increase the risk of severe COVID-19, there are a lot of factors and patient characteristics, such as older age, male sex, progressive disease course, higher disability status, steroid and anti-CD20 treatment, that contribute to this risk and are worth acknowledging.

The implications of COVID-19 in pwMS are still unknown, with inconsistent evidence regarding relapses and disability worsening. COVID-19 vaccines seem safe in pwMS, but current research does not allow science to fully exclude the possibility of vaccination-induced disease exacerbation. Most pwMS develop immunity, although a proportion of patients treated with anti-CD20 and S1PR-modulators may have an impaired immune reaction to the vaccine and be at risk for breakthrough infection.

A personalised approach regarding risks and benefits in decision-making during the COVID-19 pandemic must remain important for clinicians taking care of multiple sclerosis patients.

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LEADING TOPIC

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Course of fatigue among patients previously hospitalised due to COVID-19

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ABSTRACT

Introduction. Discrepancies exist regarding the clinical course and prognostic factors for post-COVID fatigue. Therefore, our aim was to assess the timely course of fatigue and its possible predictors in patients previously hospitalised due to SARS-CoV-2 infection.

Material and methods. Patients and employees of the University Hospital in Krakow were assessed with the use of a validated neuropsychological questionnaire. Included were participants aged 18 or more, previously hospitalised due to COVID-19, who completed questionnaires only once > 3 months after the onset of infection. Individuals were retrospectively asked about the presence of eight symptoms of chronic fatigue syndrome at four timepoints: before COVID-19, within 0–4 weeks, 4–12 weeks, and > 12 weeks post-infection.

Results. We enrolled 204 patients [40.2% women, median age 58 (46–66) years] evaluated after a median of 187 (156–220) days from the first positive nasal swab test for SARS-CoV-2. The most common comorbidities were hypertension (44.61%), obesity (36.27%), smoking (28.43%), and hypercholesterolemia (21.08%); none of the patients required mechanical ventilation during hospitalisation. Before COVID-19, 43.62% of patients reported at least one symptom of chronic fatigue. Within 4, 4–12, and > 12 weeks after COVID-19, the prevalence of chronic fatigue was 76.96%, 75.49%, and 66.17%, respectively (all $p < 0.001$). The frequency of chronic fatigue symptoms decreased within > 12 weeks following the onset of infection but did not return to baseline values, except for self-reported lymph node enlargement. In a multivariable linear regression model, the number of fatigue symptoms was predicted by female sex [β 0.25 (0.12; 0.39), $p < 0.001$ and 0.26 (0.13; 0.39), $p < 0.001$ for weeks 0–12 and > 12, respectively], and age [for < 4 weeks, β –0.12 (–0.28; –0.01), $p = 0.029$].

Conclusions. Most patients previously hospitalised due to COVID-19 suffer from fatigue > 12 weeks after infection onset. The presence of fatigue is predicted by female sex and – only for the acute phase — age.

Key words: COVID-19, SARS-CoV-2, fatigue, long COVID, prognosis, middle aged, neurological manifestations

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Fatigue represents the most common post-acute sequelae of Coronavirus Disease 2019 (COVID-19) [1, 2]. Its prevalence in the acute phase of infection is estimated at more than 60% [3], even among patients who eventually do not develop long COVID syndrome [4]. As shown recently, irrespective of initial improvement, most individuals with a Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection will suffer from fatigue within three months following the onset of disease [5]. This non-specific group of symptoms is more often reported by patients with COVID-19 compared to other viral respiratory infections [6], and its presence significantly deteriorates the perceived quality of life and impairs both leisure activities and work performance [7–10]. It is also noteworthy that post-COVID symptoms, including fatigue, result in a significant burden of healthcare costs, as was recently revealed in a detailed analysis of nearly 30,000 people from the German Nationwide Inpatient Data [11].

Several factors have been shown to predict the presence of fatigue and other post-COVID symptoms [12]; however, discrepancies have been observed regarding the role of demographics, comorbidities and initial severity of infection [13].

For example, a longitudinal observation of 371 patients from India confirmed that predictors of long COVID, with fatigue being its most common self-reported symptom, included pre-existing medical conditions, vaccination status, a higher number of acute COVID-19 symptoms, and the severity of infection, but not sex [14]. In a cross-sectional study of two urban centres in Spain among 360 hospitalised patients assessed via telephone interviews two years after the acute phase of the SARS-CoV-2 infection, it was found that a number of comorbidities and dyspnoea were associated with post-COVID fatigue, but not sex [15]. On the other hand, in another Spanish cohort of mostly non hospitalised patients, post-COVID symptoms, including fatigue, were associated with older age and female sex within six months after the acute phase of infection [16]. A recent comprehensive review listed many possible risk factors for the development of fatigue during long COVID, such as female sex, older age, hospital admission, comorbidities, including chronic pulmonary diseases or migraine, and steroid administration among others [17]. However, other researchers have come to different conclusions, undermining the prognostic role of comorbidities [18] and the initial severity of COVID-19 [19].

When taking into account the course of post-COVID symptoms, including fatigue, this also varies according to the study [20]. For example, in a large online survey of 12,609 registered German stem cell donors who underwent COVID-19, there were no significant differences in the prevalence of post-COVID fatigue between three and 15 months after the initial infection [21]. On the other hand, a Norwegian group showed a tendency for fatigue to improve four months after the onset of COVID-19 [22], whereas Korean researchers observed an increasing fatigue rate between one and six months post-infection [23].

Therefore, we aimed to evaluate the timely course of fatigue and its possible predictors in a sample of patients previously hospitalised due to COVID-19.

Material and methods

Evaluation of post-COVID fatigue

Post-COVID fatigue was assessed with the use of a questionnaire called "The NeuroPsychological Complications of COVID-19" (NP-COVID), created for the purposes of the current study and further validated, as described previously [24]. In brief, patients were retrospectively asked about the presence of the following symptoms: 1) persistent fatigue, not caused by effort, and persisting after rest, 2) sore throat, 3) self-reported lymph node enlargement, 4) myalgia, 5) arthralgia, 6) headache, 7) non-restorative sleep, and 8) prolonged post-exercise fatigue [24]. These symptoms were previously included in a definition of chronic fatigue syndrome (CFS) by the Centres for Disease Control and Prevention in 1994 [25] and, since then, they have been widely used even in newer definitions of the CFS [26]. Moreover, as shown recently, CFS and post-COVID condition share similarities related to fatigue, exhaustion initiating exercise, post-exertional malaise, muscle and joint pain [27, 28].

Questionnaires were completed by patients once only, and the presence of the above-mentioned chronic fatigue symptoms was assessed over four time periods, i.e. before COVID-19, and within 0–4, 4–12, and > 12 weeks since the onset of infection, in accordance with the National Institute for Health and Care Excellence (NICE) guidelines [29, 30].

Patient enrollment

We enrolled patients who fulfilled the following inclusion criteria that were also described previously [24]: age 18 or more years; more than three months since the onset of the SARS-CoV-2 infection; diagnosis of COVID-19 confirmed by detection of viral RNA by reverse transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal swab; and ability to read and write. Additionally, for the purpose of the current study, we included only patients who had previously required hospitalisation due to SARS-CoV-2 infection.

Patient data was collected from the following sources: post-COVID ambulatory in the University Hospital in Krakow, where participants were encouraged to complete the paper version of the NP-COVID questionnaire, and an online link posted on Facebook, or sent via group e-mail to employees of the University Hospital in Krakow, that encompassed the online version of the questionnaire. Therefore, between April and August 2021, a total of 660 anonymous NP-COVID questionnaires were received. We then excluded questionnaires provided by patients with incomplete data, allowing 204 subjects to be included in the final analysis.

Bioethics and patient consent

We conducted this study within the CRACoV-HHS project (CRAcow in CoVid pandemics — Home, Hospital and Staff) and in accordance with the Declaration of Helsinki. The CRACoV-HHS project received approval of the Jagiellonian University Bioethics Committee. No additional approval from the Bioethics Committee was required since NP-COVID questionnaires were filled out anonymously [24]. Participants who were recruited in the post-COVID ambulatory in the University Hospital in Krakow signed written informed consent before the paper version of the NP-COVID questionnaire was handed to them. In accordance with Polish law, no written consent needed to be obtained from patients who completed the online questionnaire anonymously; however, full information on the aim of the survey was provided.

Statistics

Data was presented as counts and percentages (n, [%]), mean and standard deviations (SD), and median and interquartile ranges (IQR). Continuous variables were checked for normality with the Shapiro-Wilk test. Where the distribution was non-normal, data was compared using the Mann-Whitney test, Kruskal-Wallis test and Friedman's ANOVA, as appropriate. Categorical independent variables were tested with the $\chi 2$ test and Fisher's exact test, while categorical dependent variables were analysed with the Cochran's Q test and the McNemar $\chi 2$ test. We applied Bonferroni correction for pairwise comparisons of the questionnaire with a significance level < 0.008. For other analyses, a p-value below 0.05 was considered statistically significant. Multivariable linear models of chronic fatigue symptoms included all variables that showed an association with the number of symptoms in the univariable model ($p < 0.10$) and did not substantially correlate with other independent variables ($r > 0.5$). All of the models were adjusted for age and sex. Independent predictors were obtained with the stepwise backward procedure, R was calculated, and models were checked with the F test. Data was analysed using STATISTICA 13.0 software (Statsoft Inc, Tulsa, OK, USA).

Results

The dataset confirming the results of this study may be obtained from the corresponding author upon reasonable request.

Patient characteristics

A total of 204 patients (40.2% women, median age 58 years) hospitalised due to COVID-19 were enrolled in our study. The median observation time was 187 (156–220) days from the first positive nasal swab test for SARS-CoV-2. At least one comorbidity was found in 84.31% (n = 172) of patients, and 34.41% (n = 70) had > 3 chronic diseases, the most common being hypertension, obesity, smoking, and hypercholesterolemia (Tab. 1). The prevalence of chronic

Table 1. Demographics and characteristics of patients on hospital admission

Demographics	All patients (n = 204)
Age (years)	58 (46–66)
Female sex, n (%)	82 (40.20)
Comorbidities	
Hypertension, n (%)	91 (44.61)
Hypercholesterolemia, n (%)	43 (21.08)
Obesity, n (%)	74 (36.27)
Smoking, n (%)	58 (28.43)
Diabetes mellitus, n (%)	33 (16.18)
Ischaemic heart disease, n (%)	21 (10.29)
Atrial fibrillation, n (%)	13 (6.34)
Chronic heart failure	8 (3.92)
Prior CNS disease, n (%)	
Stroke in past	10 (4.90)
Dementia	14 (6.86)
Depression	23 (11.27)
Anxiety disorders	10 (4.90)
Asthma/COPD, n (%)	21 (10.29)
Neoplasm, n (%)	
— active	4 (1.96)
— in past	12 (5.88)
Chronic kidney disease stage III, n (%)	8 (3.92)
Alcohol abuse, n (%)	5 (2.45)
Treatment	
Anticoagulant, n (%)	16 (7.84)
Beta-adrenolytic, n (%)	38 (18.63)
Antidepressant, n (%)	25 (12.25)
Neuroleptic, n (%)	6 (2.94)
Benzodiazepine, n (%)	4 (1.96)
First COVID-19 symptoms	
Anosmia n (%)	40 (19.61)
Cough, n (%)	172 (84.31)
Dyspnoea, n (%)	138 (67.65)
Fever, n (%)	174 (85.29)
Gastrointestinal, n (%)	68 (33.33)
Hospital admission	
Oxygen therapy, n (%)	
Not required	26 (12.75)
Nasal cannula	137 (67.16)
Simple face mask	40 (19.61)
Non-invasive ventilation	1 (0.49)
MEWS score, n (%)	
1	157 (76.97)
2	33 (16.18)
3	14 (6.86)
Laboratory parameters	
CRP (mg/dL) (first 24 hours)	69.3 (31.7–110.0)
IL-6 (pg/mL) (first 48 hours)	33.3 (13.1–56.2)
Procalcitonin (ng/mL) (first 24 hours)	0.09 (0.05–0.17)
WBC ($\times 10^3$) (first 24 hours)	5.61 (4.10–7.50)

Values are presented as numbers and percentages [n, (%)] and median (interquartile range).
COPD — chronic obstructive pulmonary disease; CRP — C-reactive protein; CNS — central nervous system; IL-6 — interleukin-6; MEWS — Modified Early Warning Score; WBC — white blood cell count

Table 2. Prevalence of chronic fatigue symptoms prior to COVID-19 and within different time intervals since onset of infection

	Prior to COVID-19	0–4 weeks (acute phase)		4–12 weeks (post-acute phase)		> 12 weeks (chronic phase)	
	n (%)	n (%)	p-value *vs.* baseline	n (%)	p-value *vs.* baseline	n (%)	p-value *vs.* baseline
1.1 Persistent fatigue, not caused by effort, persisting after rest	31 (15.20)	123 (60.29)	< 0.001	111 (54.41)	< 0.001	86 (42.16)	< 0.001
1.2 Sore throat	10 (4.90)	39 (19.12)	< 0.001	26 (12.75)	0.001	26 (12.75)	< 0.001
1.3 Self-reported lymph node enlargement	2 (0.98)	16 (7.84)	< 0.001	8 (3.92)	0.034	9 (4.41)	0.020
1.4 Myalgia	31 (15.20)	101 (49.51)	< 0.001	79 (38.73)	< 0.001	62 (30.39)	< 0.001
1.5 Arthralgia	12 (5.88)	31 (15.20)	< 0.001	29 (14.21)	< 0.001	31 (15.19)	< 0.001
1.6 Headache	28 (13.72)	79 (38.73)	< 0.001	61 (29.90)	< 0.001	45 (22.06)	0.004
1.7 Non-restorative sleep	41 (20.10)	97 (47.55)	< 0.001	89 (43.63)	< 0.001	74 (36.28)	< 0.001
1.8 Prolonged post-exercise fatigue	41 (20.10)	128 (62.75)	< 0.001	118 (57.84)	< 0.001	99 (48.52)	< 0.001

Data is presented as numbers (n) and percentages (%) and compared with Cochran Q test for dependent variable. Bonferroni correction was applied for multiple pairwise comparisons, and significance level was < 0.008

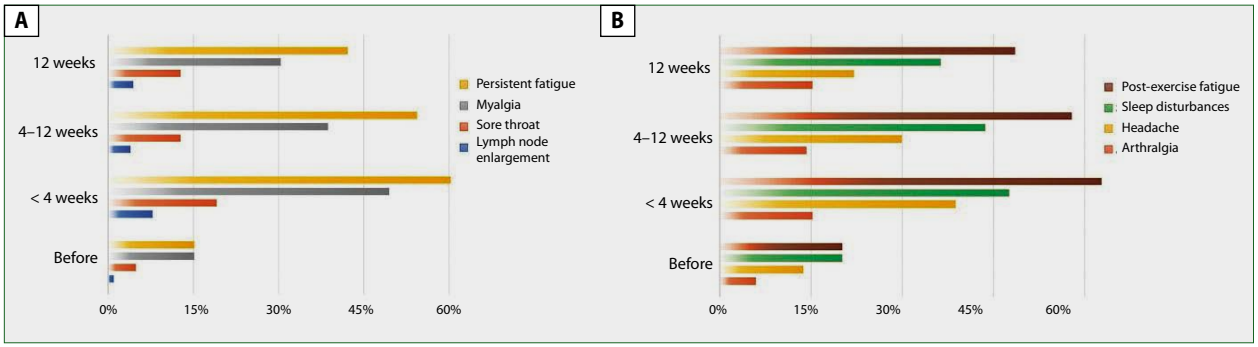

Figure 1. Pattern of chronic fatigue symptoms in acute (< 4 weeks), subacute (4–12 weeks), and chronic (> 12 weeks) phases of SARS-CoV-2 infection

heart failure, stroke, stage III chronic kidney disease, and active neoplasm was below 5%. Almost one in seven patients (14.71%, n = 30) had depression or anxiety disorders, and 16.17% (n = 33) were being treated with antidepressants, benzodiazepines, and neuroleptics.

The first symptoms of COVID-19 that were the most frequent were fever, cough and dyspnoea. On admission, laboratory tests showed a marked increase in C-reactive protein (CRP) and interleukin-6 (IL-6). During hospitalisation, 5.88% (n = 12) of patients were admitted to the Intensive Care Unit, 87.25% (n = 178) required oxygen therapy, mainly with a nasal cannula or simple oxygen mask, and none were mechanically ventilated (Tab. 1).

Chronic fatigue symptoms before and after COVID-19

Before COVID-19, 43.62% (n = 89) of patients reported at least one symptom of chronic fatigue (Tab. 2, Fig. 1). Within 4, 4–12, and > 12 weeks after COVID-19, the prevalence of chronic fatigue increased to 76.96% (n = 157), 75.49% (n = 154), and 66.17% (n = 135) of patients, respectively (all $p < 0.001$). The mean (± standard deviation) number of symptoms was 0.96 ± 1.41 prior to the SARS-CoV-2 infection, but increased to 3.01 ± 2.31, 2.55 ± 2.07 and 2.11 ± 2.04 for 4, 4–12, and > 12 weeks post-COVID, respectively ($p < 0.05$ with post-hoc Friedman ANOVA).

Table 3. Predictors of numerous symptoms of post-COVID-19 chronic fatigue in acute (< 4 weeks), subacute (4–12 weeks), and chronic (> 12 weeks) phases of infection, assessed retrospectively

< 4 weeks after onset of COVID-19	Univariable analysis		Multivariable analysis	
	β (95% CI)	p-value	β (95% CI)	p-value
Age (per year)	–0.12 (–0.25; 0.02)	0.097	–0.12 (–0.28; –0.01)	0.029
Female sex	0.23 (0.10; 0.37)	< 0.001	0.25 (0.12; 0.39)	< 0.001
Neoplasm in past	–0.11 (–0.26; 0.02)	0.091	–	–
Stroke in past	0.08 (–0.06; 0.21)	0.268	–	–
			R = 0.30, F = 6.56	
4–12 weeks after onset of COVID-19				
Age (per year)	–	0.745	–	–
Female sex	0.24 (0.07; 0.37)	< 0.001	0.25 (0.12; 0.39)	< 0.001
Antidepressants	0.12 (–0.01; 0.26)	0.077	–	–
MEWS score > 1	–0.11 (–0.25; 0.02)	0.092	–	–
			R = 0.24, F = 12.34	
> 12 weeks after onset of COVID-19				
Age (per year)	–	0.526	–	–
Female sex	0.26 (0.13; 0.40)	< 0.001	0.26 (0.13; 0.39)	< 0.001
Asthma/COPD	0.12 (–0.01; 0.26)	0.072	–	–
MEWS score > 1	–	0.275	–	–
			R = 0.26, F = 14.78	

In the first four weeks after infection, more than half of patients reported persistent fatigue not caused by effort, and post-exercise fatigue. The least frequent symptoms were lymph node enlargement, arthralgia, and sore throat (all < 20%). The frequency of symptoms decreased over the following weeks, but did not return to baseline values, except for self-reported lymph node enlargement. Furthermore, four out of 10 convalescents reported persistent fatigue not caused by effort, as well as post-exercise fatigue.

Determinants of chronic fatigue

Patients in the highest quartile of chronic fatigue symptoms were more frequently women compared to the first quartile (Suppl. Tab. 1). Interestingly, we did not observe an association between symptoms of chronic fatigue and numerous variables such as demographics, comorbidities, the first symptoms of COVID-19, severity score at admission, oxygen therapy, or pharmacological treatment, except for the higher prevalence of stroke in the past for analysis in the 4-week interval. In the multivariable linear regression model, the number of fatigue symptoms was predicted by female sex (all intervals) and age (< 4 weeks) (Tab. 3).

Discussion

Our study revealed that female sex was the only independent predictor of fatigue in a cohort of previously hospitalised patients, both in the acute phase of COVID-19 and also four and 12 weeks since the onset of infection. Our results accord with a recent Italian study of 247 patients that also confirmed the prognostic role of female sex in the persistence of neurological and psychiatric symptoms, including fatigue, seven weeks after the initial SARS-CoV-2 infection [31]. However, researchers also pointed to older age and the presence of comorbidities, especially depression, as additional risk factors for residual post-COVID symptoms, but that cohort comprised individuals approximately one decade younger than ours, with only less than half of them requiring hospitalisation due to COVID-19 [31]. Another recent study revealed that among 400 Brazilian patients previously hospitalised due to COVID-19, female sex, hypercholesterolemia, obesity and prone position in the acute phase of disease increased the risk of post-COVID syndrome, with fatigue prevalent in 42% and 27% of cases within three and six months after discharge, respectively [32]. These patients were at similar median age as in our study, but were more affected by comorbid conditions including hypertension and diabetes mellitus [32]. Another study of 504 previously hospitalised patients from Saudi Arabia followed-up three months after the onset of infection showed that the presence of post-COVID syndrome, with fatigue constituting its most common presentation, was associated with female sex, three or more comorbidities, steroid treatment, and symptoms of nasal congestion and depression during the acute phase of disease [33]. Female predominance among subjects with persistent post-COVID symptoms, with the most common being fatigue, sleep disturbances, and myalgia, was also confirmed in a cohort of 312 patients with cancer observed up to 14 months post-infection [34]. In a large cohort of more

than 12,000 adult patients from Sweden who were hospitalised due to COVID-19, it was found that post-COVID symptoms, with the prevalence of fatigue being 22%, were more common in women of middle age, and association with asthma and mental health disorders was less prominent compared to non-hospitalised individuals [35]. Interestingly, data from German health insurance organisations showed that CFS was more common in adults with COVID-19 than in the control group, whereas in children and adolescents there were no statistically significant differences between those infected with SARS-CoV-2 and unaffected individuals [36].

On the other hand, among more than 600 children and adolescents previously hospitalised due to COVID-19 in Argentina, risk factors for long COVID, with headache, cough, and fatigue comprising the most common symptoms, included older age apart from symptomatic infection and comorbidities, including diabetes [37]. In an Italian cohort of 428 patients, assessed 4–12 weeks after hospital discharge, it was found that female sex and severe SARS-CoV-2 infection were the main risk factors for post-COVID manifestations, among which chronic dyspnoea and fatigue were the most common [38]. Finally, a recent Czech study examining healthcare workers at least 12 weeks after the onset of SARS-CoV-2 infection, revealed that female sex and increasing age were the only significant predictors of post-COVID syndrome, with almost half of those patients reporting fatigue interfering with their daily life [39].

Therefore, it seems that female sex is the only consistent risk factor for residual post-COVID fatigue, both in younger [40] and older populations [41]. Notably, our cohort consisted mainly of patients in a relatively good clinical condition prior to the SARS-CoV-2 infection, as the prevalence of diseases known to increase COVID-associated mortality, such as stroke, dementia and neoplasm, was below 10% [3, 42–44].

Our study also showed that, despite a tendency to improve most patients still suffered from symptoms of fatigue within 12 weeks since the onset of the SARS-CoV-2 infection. Our results were similar to the conclusions coming from a longitudinal observation of nearly 2,000 Spanish patients, where fatigue only slightly improved between 8.4 and 13.2 months after hospital discharge, with more than half of individuals reporting this residual symptom [45]. Slow recovery from fatigue was also observed in a Danish post-COVID clinic where among 447 previously generally healthy individuals, of whom only 12% needed hospitalisation, as many as 33% and 62% of them reported moderate and severe fatigue, respectively, within six months of the onset of infection [46]. An observation of more than 9,000 Dutch patients, most of whom did not require hospitalisation, showed that three months after the SARS-CoV-2 infection, fatigue was significantly more often reported compared to the control group, with nearly half of the patients suffering from at least one residual post-COVID symptom. Interestingly, previous vaccination was not protective against fatigue, muscle and joint pain at three months [47].

On the other hand, in a group of 1,638 COVID-19 survivors, Egyptian researchers found that those fully vaccinated against SARS-CoV-2 exhibited significantly less severe post-COVID fatigue, and the presence of residual symptoms after SARS-CoV-2 infection was predicted only by its initial severity and a lack of previous vaccination [48]. A recent review of 33 studies revealed that the most common persistent post-COVID symptoms included not only chronic fatigue but also other elements of the CFS such as arthralgia, myalgia and intolerance to exertion [49]. Similarly, another systematic review of 24 articles showed that long COVID patients very commonly not only suffered from fatigue, but also reported myalgia and arthralgia [50]. Moreover, a prospective multicentre study in non-hospitalised subjects with COVID-19 showed that, despite improvement, patients still reported the persistence not only of fatigue but also of myalgia and headache within 12 weeks since the onset of infection [51]. Additionally, an international survey in a group of nearly 14,000 patients from 16 countries revealed that, apart from fatigue, insomnia and excessive daytime sleepiness, also perceived as important elements of the CFS, were the most commonly reported symptoms after hospitalisation due to COVID-19 [52]. A prospective Silesian registry of 200 COVID-19 patients, assessed c.100 days since the onset of infection, revealed that most individuals, both outpatients and hospitalised, suffered from insomnia [53]. Another review including 194 studies with around 735,000 participants showed that 45% of COVID-19 survivors experienced at least one post-COVID symptom, regardless of hospitalisation status, with the most common being fatigue [54]. However, a recent tele-assessment of COVID-19 survivors 1-6 months after their positive RT-PCR test showed that their score in a 30-second Chair Stand Test, used previously to assess fatigue effect [55], was significantly higher in outpatients compared to those requiring hospitalisation [56].

Thus, our study confirmed that a substantial proportion of patients still suffered from the symptoms of CFS within three months since the onset of SARS-CoV-2 infection.

Currently, many pathophysiological explanations for post-COVID fatigue are merely hypothesised. It has been postulated for example that SARS-CoV-2 infection may act as a trigger activating a complex network of neuropsychiatric symptoms, including fatigue, anxiety, depression, sleep and cognitive disturbances [57]. Fatigue, apart from anxiety and depression, could, in turn, significantly affect cognitive abilities even months after the initial infection [58, 59]. It has also been found that individuals with post-COVID symptoms assessed six months after hospital discharge expressed higher levels of interleukin-8 (IL-8), vascular endothelial growth factor (VEGF), and monocyte chemoattractant protein-1 (MCP-1) compared to people without post-COVID sequelae [60, 61]. Lately, changes in retinal microcirculation visualised using optical coherence tomography angiography have been shown to be a possible marker for chronic fatigue in patients after

COVID-19 [62], and high anti-SARS-CoV-2 immunoglobulin E levels have been found to correlate with a deterioration of physical function in patients after the acute phase of SARS-CoV-2 infection [63].

It has also been suggested that post-COVID fatigue syndrome might be due to damage to the sensory olfactory neurons leading to a reduction in cerebrospinal fluid flow through the cribriform plate and, consequently, reduced removal of brain waste [64]. Inflammation associated with COVID-19 [65–67] may also impair GABAergic transmission within the brain [68], as was shown during neurophysiological studies in a small cohort of 12 patients who recovered from the SARS-CoV-2 infection [69]. Disruption of transforming growth factor beta signalling, similar to that observed in myalgic encephalomyelitis/CFS, has also been proposed, and this is something which influences circadian rhythm [70]. Incomplete recovery of the immune system, together with initial lung or liver damage, and coagulation disturbances, have also been suggested in the pathophysiology of long COVID [71]. Interestingly, a recent review of 108 patients in the post-COVID ambulatory at the Mayo Clinic in the US showed that women more often exhibited the post-COVID phenotype with predominant fatigue, while dyspnoea was the leading clinical feature in men [72]. The authors were able to show that sex-related differences in the post-COVID phenotype could be attributed to various pathophysiology as the prevalence of fatigue was associated with an elevation of IL-6 levels that was more common than an increase in CRP or erythrocyte sedimentation rate [72].

This observation could at least partially explain the prognostic role of sex in post-COVID fatigue, as has been shown in previous studies, and confirmed in our research.

Our study has important limitations. Firstly, the study sample was rather small and consisted of individuals with a relatively good pre-COVID clinical status. However, we gathered detailed data regarding demographics, comorbidities, treatment, and laboratory tests. Secondly, the results were based on responses given retrospectively by patients a few months after the initial SARS-CoV-2 infection, which could have resulted in potential bias or underestimation of symptoms. Nevertheless, most patients reported residual fatigue, which aligned with findings from previous studies [73]. Thirdly, the NP-COVID questionnaire was created for the purposes of this study; however, it was validated as described before [24]. Fourthly, our study focused on patients with wild-type or Alpha variant SARS-CoV-2; therefore, the presented results might not be applicable to other variants, especially given that individuals infected with Omicron have been shown to be less likely to exhibit long-COVID [74]. Fifthly, we did not collect data on neuroimaging, both in the acute and chronic phase of the SARS-CoV-2 infection; however, its role in evaluating fatigue may become increasingly important, as has been recently shown for conditions other than COVID-19 [75].

In conclusion, most patients previously hospitalised due to COVID-19 suffer from fatigue symptoms within 12 weeks after the onset of the infection. The presence of fatigue is predicted by female sex and — though only for the acute phase — by age. Future studies on larger patient populations are needed to seek other potential risk factors for post-COVID fatigue and — hopefully — to deliver treatment options [76, 77].

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LEADING TOPIC

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Sex-related patient-reported brain fog symptoms in non-hospitalised COVID-19 patients

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ABSTRACT

Introduction. Previous studies on the prognostic role of sex in post-COVID-associated brain fog have yielded divergent results. Moreover, limited evidence exists regarding the evolution of brain fog symptoms over time, especially in ambulatory patients and separately for women and men. Therefore, the aim of the current study was to assess brain fog symptoms in non-hospitalised patients with COVID-19, according to their sex.

Material and methods. We created a neuropsychological questionnaire including eight questions on the presence of brain fog symptoms in the following four time periods: before COVID-19, and 0–4, 4–12, and > 12 weeks post-infection. The validity and reliability of the questionnaire were assessed. In this cross-sectional study, questionnaires were filled out anonymously and retrospectively once only by patients or through a survey link posted online. Included were patients ≥ 18 years, with > 3 months since the SARS-CoV-2 infection onset confirmed by RT-PCR from a nasopharyngeal swab.

Results. The study included 303 patients (79.53% women, 47.52% medical personnel). Median time between COVID-19 onset and questionnaire completion was 208 (IQR 161–248) days. Women, compared to men, reported a higher prevalence of problems with writing, reading, and counting (< 4 weeks, OR 3.05, 95% CI: 1.38–6.72; 4–12 weeks, OR 2.51, 95% CI: 1.02–6.14; > 12 weeks, OR 3.74, 95% CI: 1.12–12.56) and thoughts communication (< 4 weeks, OR 2.53, 95% CI: 1.41–4.54; 4–12 weeks, OR 3.74, 95% CI: 1.93–7.24; > 12 weeks, OR 2.00, 95% CI: 1.01–3.99). The difference between the two sexes in answering questions in an understandable/unambiguous manner was statistically significant between four and 12 weeks after infection (OR 2.63, 95% CI: 1.36–5.10), while a sex difference in recalling new information was found below 12 weeks (OR 2.54, 95% CI: 1.44–4.48 and OR 2.43, 95% CI: 1.37–4.31 for < 4 and 4–12 weeks, respectively). No sex differences in reporting problems with multitasking, remembering information from the past, determining the current date, or field orientation were noted.

Conclusions. Non-hospitalised women and men retrospectively report a different course of COVID-19-associated brain fog.

Key words: COVID-19, brain fog, sex, course of COVID-19, long COVID

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Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic spread worldwide, resulting in 6.7 million deaths as of 21 January, 2023 [1]. A substantial number of patients experienced persistent complications after the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection, affecting not only their respiratory system but also other organs [2–4]. Neurological manifestations have been observed not only throughout the acute phase of illness [5–9] but also during the post-infection period [10, 11]. Among these persistent symptoms, cognitive, memory and concentration disturbances have been reported by approximately one in four patients with a previous SARS-CoV-2 infection [12], and their presence interfered with daily activities and delayed the chance of complete recovery [13, 14]. In the literature, the term 'brain fog' was coined in order to gather these symptoms and was intended to convey the notion of cognitive impairment including difficulties with concentration and intellectual clarity, mental fatigue, and anxiety [10, 11, 15]. The prevalence of post-COVID sequelae appears to be six-fold higher than after other viral infections [16].

So far, most studies have concentrated on the prevalence of brain fog in individuals previously hospitalised due to COVID-19 [17–19], and its association with other factors such as age and comorbidities [20]. However, studies concerning the prognostic role of sex have yielded divergent results [21–23].

For example, a systematic review of 66 studies showed that female sex was a risk factor for neuropsychiatric sequelae of SARS-CoV-2 infection, apart from disease severity and duration of symptoms [24]. On the other hand, a recent meta-analysis of 51 studies revealed that the prevalence of persistent psychiatric and neurological symptoms after COVID-19 was only weakly correlated with other factors, including hospitalisation, severity of infection, and length of follow-up [25]. Another study evaluating 23 symptoms of COVID-19, including confusion, in 451 Norwegian non-hospitalised patients, showed that six months after infection the persistence of symptoms was associated with their number, and with the number of comorbidities, but not with sex [21]. There is also limited evidence as to how disturbances perceived as brain fog evolve over time, especially in ambulatory patients and separately for women and men.

Therefore, the aim of the current study was to assess the symptoms of brain fog in previously non-hospitalised patients with COVID-19, according to their sex.

Material and methods

Development of neuropsychological questionnaire

In a three-step approach, we prepared a short, precise questionnaire containing questions allowing the clear description of the most common neuropsychiatric problems after COVID-19 divided into three domains, including brain fog, chronic fatigue, and emotional disturbances. The impact of these symptoms on daily living and occupational activities was also investigated. In the current study, we have presented only the results related to the first part of the questionnaire involving patient-reported brain fog symptoms.

The creation of the Post-COVID Brain Fog (BF-COVID) questionnaire was described previously [26]. In brief, as a first step, we searched the PubMed database for the spectrum of post-COVID symptoms and possible tools to assess for their presence [26]. Then, we interviewed 12 neurologists who had experienced COVID-19 and asked them open-ended questions regarding their personal and professional experience of problems with concentration, memory, sleep and speech before and after their infection [26]. All interviews were recorded and lasted up to 15 minutes. The interviews were then analysed by two researchers (Żaneta Chatys-Bogacka and Iwona Mazurkiewicz) in order to bring out a specific profile and evaluation of the complaints. Based on this information, an anonymous BF-COVID questionnaire was created and included questions about the symptoms, their severity and impact on everyday life and work. In accordance with the guidelines of the National Institute for Health and Care Excellence (NICE) [10], the BF-COVID questionnaire applied retrospectively to the following time periods: before COVID-19, the acute phase of infection (i.e. 0–4 weeks since the onset of COVID-19), the post-acute phase (i.e. 4–12 weeks post-infection), and the chronic phase (i.e. more than 12 weeks post-infection). Patients were asked to complete the questionnaire retrospectively only once, and to respond if the symptoms occurred during the above-mentioned time periods. The BF-COVID questionnaire was administered in Polish, and was translated into English for the purposes of this paper. In addition, through the BF-COVID questionnaire, we collected basic epidemiological data, including age, sex, date of the confirmed COVID-19 diagnosis, date of the questionnaire completion, and date of hospitalisation due to SARS-CoV-2 infection.

Content and face validity

As a second step, the BF-COVID questionnaire was validated in a group of 70 people comprising neurologists, independent physicians, neuropsychologists, physiotherapists and speech therapists, who were asked to complete the drafted version. Based on their opinions and expert consensus, the design of the questionnaire was optimised. Eight items were corrected, i.e. questions regarding the presence of persistent fatigue, sore throat, sensation of lymph node enlargement, myalgia, arthralgia, headache, non-restorative sleep, and prolonged post-exercise fatigue were excluded from the brain fog evaluation questionnaire.

Thus, the final version of the questionnaire was created, consisting of eight detailed questions, assessed retrospectively by patients in four different time periods (Tab. 1).

Table 1. Elements of brain fog self-assessed by patients in Post-COVID Brain Fog questionnaire. Patients responded either 'yes' or 'no' to each question in four time periods assessed retrospectively

Did you experience problems with:	Before COVID-19	0–4 weeks since COVID-19 onset	4–12 weeks post-infection	More than 12 weeks post-infection
1. Writing, reading, and counting?	Yes/No	Yes/No	Yes/No	Yes/No
2. Answering questions in an understandable or unambiguous manner?	Yes/No	Yes/No	Yes/No	Yes/No
3. Thoughts communicating during a conversation in a way that others can understand?	Yes/No	Yes/No	Yes/No	Yes/No
4. Performing several independent tasks simultaneously?	Yes/No	Yes/No	Yes/No	Yes/No
5. Recalling new information?	Yes/No	Yes/No	Yes/No	Yes/No
6. Remembering information from past, for example, recognising people or remembering events?	Yes/No	Yes/No	Yes/No	Yes/No
7. Determining current date and naming days of week?	Yes/No	Yes/No	Yes/No	Yes/No
8. Finding right way in a familiar place?	Yes/No	Yes/No	Yes/No	Yes/No

As a third step, individuals attending the ambulatory for post-COVID patients in the University Hospital in Krakow were encouraged to complete the final paper version of the BF-COVID questionnaire. An invitation to complete the online version with a link was also sent to employees of the University Hospital in Krakow via mass e-mail correspondence. A link to the survey with an invitation to participate was also posted on Facebook [27].

Psychometric analysis

The validity and reliability of the BF-COVID questionnaire were assessed as described previously [26].

Study participants

Inclusion criteria for the study participation were as follows: age ≥ 18 years, > 3 months since the onset of COVID-19, confirmation of diagnosis by detection of viral RNA by reverse transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal swab, and the ability to write and read.

Data collection began on 22 April, 2021 and finished on 9 August, 2021. We received 660 BF-COVID questionnaires. After exclusion of individuals previously hospitalised due to COVID-19 and incomplete questionnaires, 303 ambulatory patients with a history of SARS-CoV-2 infection were included in the final analysis.

Statistics

Continuous variables were presented as medians (interquartile ranges) and compared by the Mann-Whitney U or Kruskal-Wallis test since all distributions were non-normal according to the Shapiro-Wilk test. For clarity, the number of multiple symptoms of brain fog was presented as mean ± standard deviation. Categorical variables were demonstrated as counts and percentages and analysed using the Chi-square test, Fisher's exact, or McNemar's test, as appropriate. These results were expressed as odds ratio (OR) and 95% confidence interval (CI). Bonferroni correction was applied for pairwise comparisons, and the p-value was set at < 0.008. For other comparisons, the significance level was set at $p < 0.05$. Data was analysed using STATISTICA v13.0 software (Statsoft Inc., Tulsa, OK, USA).

Ethics approval and consent to participate

This study was performed as part of the CRACoV-HHS project (CRAcow in CoVid pandemics — Home, Hospital and Staff) for which Jagiellonian University Bioethics Committee approval was received. Due to the fact that the BF-COVID survey was anonymous, after consulting a legal opinion it was established that data collection in this study did not require additional approval from the Bioethics Committee. The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants recruited in the ambulatory for post-COVID patients in the University Hospital in Krakow before they filled out a paper version of the BF-COVID questionnaire. According to Polish law, when online questionnaires are completed anonymously, no written consent to obtain is needed from these subjects, although the aim of such a survey must be provided. Therefore, data collection with the use of an online anonymous link in this study was performed according to the above-mentioned legal guidelines.

Availability of data and material

The dataset analysed during the current study is not publicly available due to privacy restrictions, but is available from the corresponding author upon reasonable request.

Results

Psychometric properties

The results of the psychometric analysis of the BF-COVID questionnaire can be found in our previous paper [26].

Patient characteristics

A total of 303 patients, females n = 241 (79.53%), medical personnel n = 144 (47.52%), were included in this

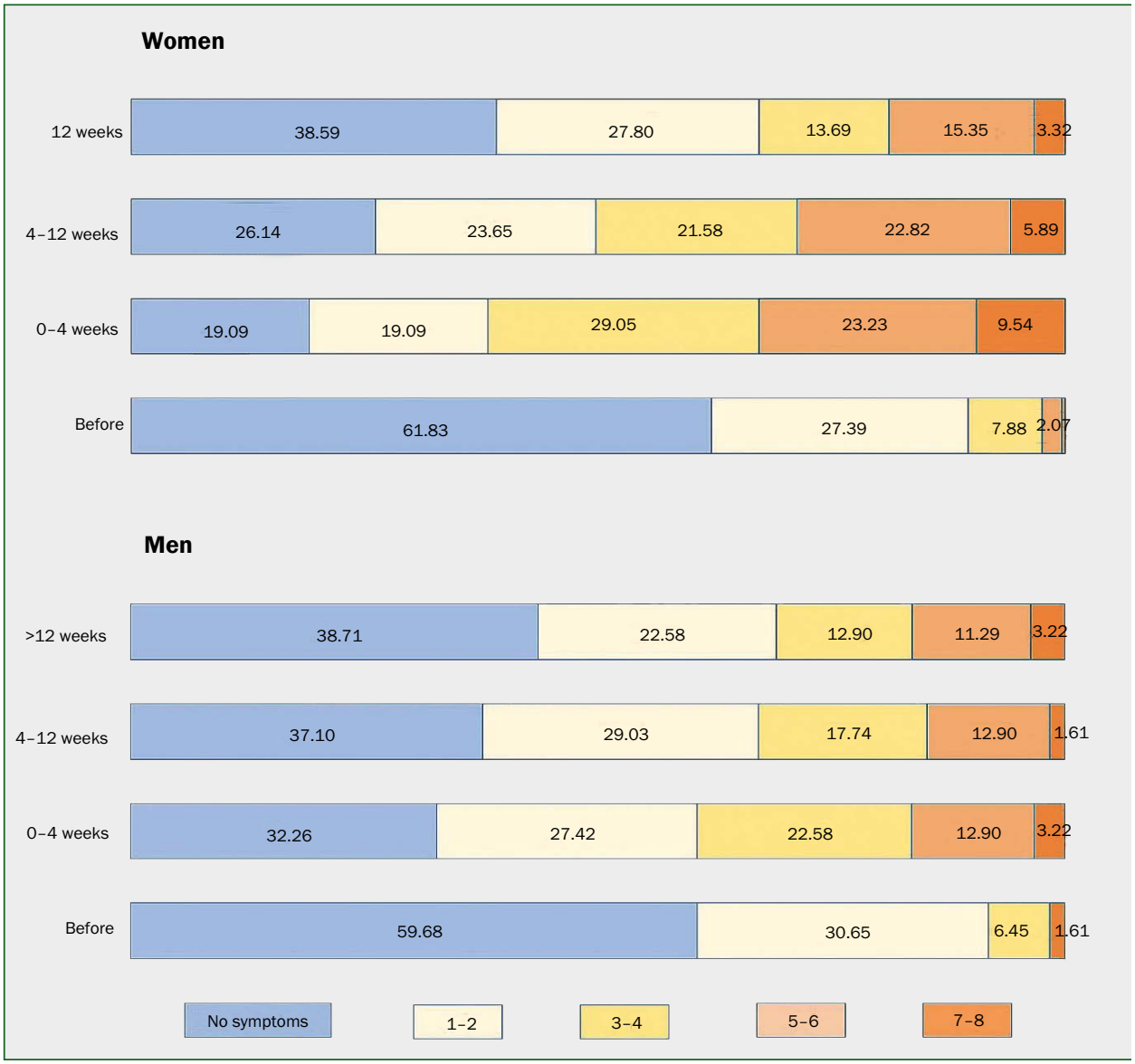

Figure 1. Prevalence of multiple brain fog symptoms in four time periods reported retrospectively by women and men. Data is presented as a percentage of positive responses to Questions 1–8

cross-sectional study. Median time between COVID-19 onset and completion of the BF-COVID questionnaire was 208 days (interquartile range 161–248). There were no differences in age between females and males [39 (30–49) *vs.* 35 (31–40) years, p = 0.149].

Complex symptomatology of brain fog

The mean number of brain fog symptoms was 0.79 ± 1.32, 3.01 ± 2.35, 2.57 ± 2.31 and 1.91 ± 2.17 for the pre-COVID, < 4 weeks, 4–12 weeks, and > 12 weeks intervals, respectively (p < 0.001).

Regarding the pre-COVID-19 period, 38.61% of patients responded positively to at least one questionnaire question, including 28.05%, 7.59%, 1.65% and 0.66% for multiple positive responses to 1–2, 3–4, 5–6, and 7–8 questions respectively. When retrospective analysis of the four weeks since a positive PCR test was made, 78.22% of patients declared at least one positive response, with a growing prevalence of multiple positive responses (20.79%, 27.72%, 21.12%, 8.25% for 1–2, 3–4, 5–6 and 7–8 symptoms, respectively). When reporting symptoms after 12 weeks, 61.39% of patients declared at least one symptom, and the prevalence of multiple positive responses remained high at 26.73%, 13.53%, 14.52%, and 3.30%, respectively.

Women, compared to men, had a higher prevalence of any, and of multiple, reported brain fog symptoms within four and 12 weeks since the onset of COVID-19 (3.20 ± 2.39 *vs.* 2.28 ± 2.03, p = 0.007 and 2.76 ± 2.35 *vs.* 1.85 ± 2.00, p = 0.008, respectively). There was no difference in the number of self-declared brain fog symptoms between the groups before COVID-19 (p = 0.728) and after more than 12 weeks post-infection (p = 0.259) (Fig. 1).

Burden of elements of brain fog in four time periods reported retrospectively by patients

Women

The prevalence of all symptoms increased during the first four weeks of infection (Questions 1–8, Suppl. Fig. 1, Tab. 2). After more than 12 weeks since the COVID-19 onset, self-reported problems with writing, reading and counting, answering questions in an understandable/unambiguous manner, communication of thoughts, multitasking and memory (Questions 1–6) partially, but not completely, diminished. A normalisation was observed for determining the current date and field orientation (Questions 7–8, Suppl. Fig. 1, Tab. 2).

Men

Within the first four weeks of infection, an increase in problems with writing, reading and counting, answering questions in an understandable/unambiguous manner, thoughts communication, multitasking, and fresh memory impairment was reported (Questions 1–5, Suppl. Fig. 1, Tab. 2). There was an increase in the number of patients with a self-declared long-term memory impairment, problems determining the date, and field orientation (Questions 6–8), which was statistically insignificant.

Regarding symptoms resolution, the frequency of perceived writing, reading and counting problems normalised within 4–12 weeks; multitasking problems did so in more than 12 weeks. The remaining symptoms (i.e. precise response, communication of thoughts, and partial impairment of fresh memory, covered in Questions 2, 3 and 5) decreased after more than 12 weeks since the COVID-19 onset (Suppl. Fig.1, Tab. 2).

Differences in brain fog symptoms between women and men

Women, compared to men, reported a higher prevalence of problems with writing, reading, and counting [Question 1; for < 4 weeks, odds ratio (OR) 3.05, 95% confidence interval (CI): 1.38–6.72; for 4–12 weeks, OR 2.51, 95% CI: 1.02–6.14; for >12 weeks, OR 3.74, 95% CI: 1.12–12.56) and communication of thoughts (Question 3; for < 4 weeks, OR; 2.53, 95% CI: 1.41–4.54; for 4–12 weeks, OR; 3.74, 95% CI: 1.93–7.24; for > 12 weeks OR 2.00, 95% CI: 1.01–3.99) (Fig. 2, Suppl. Fig. 1). A difference in the self-declared 'answering questions in an understandable/unambiguous manner' (Question 2) was statistically significant between 4–12 weeks post-infection (OR 2.63, 95% CI: 1.36–5.10), while impairment of recalling new information (Question 5) was observed below 12 weeks (OR 2.54, 95% CI: 1.44-4.48 and OR 2.43, 95% CI: 1.37–4.31 for < 4 weeks and 4–12 weeks, respectively) (Fig. 2). There was a trend towards persistence of both symptoms for 12 weeks (Question 2, p = 0.065 and Question 5, p = 0.073). We observed no sex differences in reporting problems with multitasking (Question 4), remembering information from the past (Question 6), determining the current date (Question 7), or field orientation (Question 8).

Table 2. Elements of brain fog in four time periods reported retrospectively by women and men after COVID-19

Problems with:	Prior to COVID-19			0–4 weeks			4–12 weeks			> 12 weeks		
	Women	Men	p-value	Women	Men	p-value	Women	Men	p-value	Women	Men	p-value
1. Writing, reading, and counting, n (%)	7 (2.92)	1 (1.61)	1.000	75 (31.12)	8 (12.90)	0.004	51 (21.16)	6 (9.68)	0.039	40 (16.95)	3 (5.17)	0.022
2. Answering the questions in an understandable or unambiguous manner, n (%)	14 (5.81)	3 (4.84)	1.000	104 (43.15)	21 (33.87)	0.186	99 (41.08)	13 (20.97)	0.003	69 (29.24)	10 (17.24)	0.065
3. Thoughts communicating during a conversation in a way that others can understand, n (%)	36 (14.94)	4 (6.45)	0.929	136 (56.43)	21 (33.87)	0.002	120 (49.79)	13 (20.97)	< 0.001	81 (34.32)	12 (20.69)	0.046
4. Performing several independent tasks simultaneously, n (%)	33 (13.69)	13 (20.97)	0.154	137 (56.85)	32 (51.61)	0.459	127 (52.70)	25 (40.32)	0.082	88 (37.29)	19 (32.76)	0.521
5. Recalling new information, n (%)	54 (22.41)	8 (12.90)	0.099	163 (67.63)	28 (45.16)	< 0.001	146 (60.58)	24 (38.71)	0.002	108 (45.76)	19 (32.76)	0.073
6. Remembering information from the past, for example, recognizing people or remembering events, n (%)	27 (10.79)	11 (17.74)	0.136	68 (28.22)	20 (32.26)	0.531	52 (21.58)	20 (32.26)	0.078	41 (17.37)	14 (24.14)	0.237
7. Determining the current date and naming the days of the week, n (%)	15 (6.22)	6 (9.68)	0.340	54 (22.41)	7 (11.29)	0.512	44 (18.26)	7 (11.29)	0.191	30 (12.71)	7 (12.07)	0.895
8. Finding the right way in a familiar place, n (%)	6 (2.49)	2 (3.23)	0.668	34 (14.11)	4 (6.45)	0.132	25 (10.37)	7 (11.29)	0.843	17 (7.20)	4 (6.90)	1.000

Data is presented as numbers and percentages of patients who responded 'yes' to each question in each of four time periods assessed retrospectively

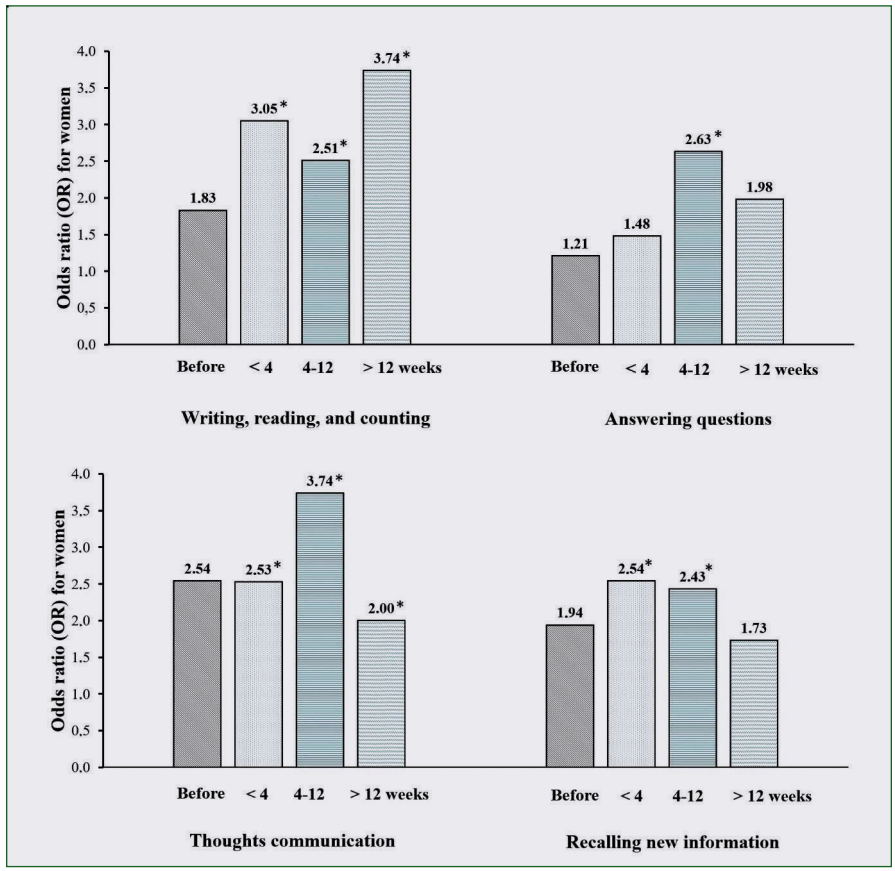

Figure 2. Sex-related risk of brain fog symptoms during four time periods assessed retrospectively by patients. OR — odds ratio

Discussion

To the best of our knowledge, this is one of the first studies to reveal that the retrospectively self-reported course of brain fog after COVID-19 in women compared to men differs in relation both to the quality and the quantity of symptoms. Women more often reported problems with writing, reading, counting and communication of thoughts. They also more often declared difficulties with answering questions in an understandable/unambiguous manner between four and 12 weeks after the onset of COVID-19, and in recalling new information up to 12 weeks after infection. To date, one retrospective study has investigated the quality of brain fog symptoms in 50 individuals from the UK, the majority of whom were not hospitalised due to COVID-19 [28]. In this group, mostly females (n = 42) contacted by e-mail 4–6 months after illness, it was shown that difficulties in memory, language, attention and executive function reported by patients lasted from weeks to months after the acute phase of the SARS-CoV-2 infection, and then gradually improved over months [28]. Due to the small sample size, the authors, however, were unable to search for sex differences.

In a large study comprising nearly 1,600 patients from five hospitals in Spain, and followed during two visits — at mean 8.5 and 13.2 months after hospital discharge — it was shown that the prevalence of brain fog, concentration and memory loss decreased between the first and the second follow-up visit, although between 2.4% and 6.3% of patients developed these symptoms only during the second visit [29]. No sex differences were noted between patients who reported new-onset cognitive symptoms during the first and the second follow-up visit; however, this studied group was older (mean age 61.5 years) than the patients participating in our research [29]. A previous study of 303 non-hospitalised patients from the USA who completed an online survey showed that the prevalence of brain fog at 30 and at more than 60 days after SARS-CoV-2 infection onset was similar, being 30.8% and 33.1% respectively [30]. The number of persistent COVID-19 symptoms did not change during the follow-up period; no significant sex differences were found, although women more often suffered from post-COVID sequelae, including brain fog, fatigue, and stress or anxiety [30]. A recent Iranian study on a large sample of nearly 2,700 hospitalised patients based on telephone interviews showed that female sex was a risk factor for reporting brain fog three months after SARS-CoV-2 infection, although only one question concerning the ability to concentrate compared to their pre-COVID ability was asked [31]. A large meta-analysis of 20 studies on more than 13,000 hospitalised patients showed that female sex increased the risk of any new or persistent mental health symptom 1.67-fold after COVID-19 [23].

A higher prevalence of neurological long COVID symptoms in women was also confirmed in a recent retrospective study of 213 subjects attending outpatient service [32]. In a mixed cohort of 217 hospitalised and non-hospitalised patients from Spain, it was shown that during follow-up visits two and six months after the onset of COVID-19, symptoms such as fatigue, emotional affectation, and cognitive deficits were more prominent in women than in men [33]. The exception here was depression, more often found in men two months, but not six months, after SARS-CoV-2 infection [33]. Another study of Italian patients with COVID-19, half of whom were hospitalised, revealed that female sex increased the risk of psychological distress more than 5-fold [34]. A large multicentre UK study of 1,077 patients showed that female sex, apart from middle age (between 40 and 59 years), a higher number of comorbidities (two or more), and a greater severity of the acute phase of illness, increased the risk of the lack of recovery six months after hospital discharge due to COVID-19 [35]. However, cognitive impairment remained independent from the recovery cluster [35]. Finally, a retrospective analysis of electronic records of more than 270,000 COVID-19 survivors showed that the risk of long COVID was slightly higher in females [36]. Recent studies have revealed that post-COVID sequelae are more common in middle-aged women [37] and in those aged 20 or older [38], suggesting the potential role of an interaction between age and sex.

Therefore, the results of our research are consistent with previous studies showing that female sex increases the risk of post-COVID brain fog symptoms. Our study additionally has revealed that self-declared neurocognitive symptoms of brain fog, affecting memory, language, and attention, are especially more common in women after the SARS-CoV-2 infection.

Our study, although of a retrospective design, is among the first to have shed more light on the course of brain fog symptoms during and after COVID-19. In a previous Brazilian study of 236 patients, of whom 86.3% were non-hospitalised, and who were at a similar median age as our group, the authors compared symptoms during the acute phase of COVID-19 and long COVID, i.e. 5-8 months after the infection [39]. They found that fatigue was present in 33.9% of patients in the acute phase and persisted in 21.2% of individuals [39]. Memory problems were reported by 39.8% of patients only during long COVID, and were then associated with sleep complaints and depressive mood [39].

In our study on the contrary, memory problems were most commonly reported retrospectively by patients during the first four weeks of disease. Sarabadani et al. [40] studied the change of COVID-19 symptoms over time in social media, based on nearly 23,000 Reddit posts, with the use of machine learning tools. The authors were able to show that symptoms perceived as brain fog, such as mental discomfort, distress, and confusion, were prominent after recovery from the acute phase of illness and remained longer, even for as long as 38 to 50 days, compared to other symptoms [40]. However, the number of COVID-19 symptoms was smaller after the acute phase of the disease [40]. On the other hand, in an Italian study of 465 patients, it was shown than any of the COVID-19 symptoms, including fatigue, had decreased at 9-month follow-up compared to the onset of infection [34]. Similar conclusions came from a study of Ecuadorian patients with mild COVID-19, in whom improvement in cognitive performance measured by Montreal Cognitive Assessment (MoCA) score was noted within 18 months after infection [41].

Thus, it seems that brain fog symptoms tend to decrease over the next few months after the onset of the SARS-CoV-2 infection.

With the increasing prevalence of post-COVID brain fog symptoms worldwide, the need for an easily obtained yet sensitive assessment tool still exists. The authors of previous studies used different ways to evaluate post-COVID symptoms, both prospectively and retrospectively. For example, one question regarding concentration ability was asked by telephone interview three months after hospital discharge [31], whereas other researchers used a list of 25 possible post-COVID symptoms that was shown to patients every three months during an online survey [30]. There have also been studies that have used more specific neuropsychological testing, such as MoCA [42], the 10-item Kessler Psychological Distress Scale questionnaire [34], or even a battery of standardised neurocognitive instruments [43]. Similarly to our study, researchers from Wuhan first interviewed 30 patients who recovered from COVID-19, and on the basis of these interviews, as well as medical expert opinion, developed a follow-up questionnaire regarding post-COVID symptoms [44].

Nevertheless, there is still no consensus regarding the type of tool preferred to assess post-COVID symptoms, although NICE guidelines underline that patients after the acute phase of infection should be specifically asked about possible symptoms such as fatigue, brain fog, concentration or memory loss, and sleep disturbances [10].

Currently, there are several hypotheses for the pathophysiology of neuropsychiatric symptoms after COVID-19, including brain fog. An Italian study of 67 patients after mild SARS-CoV-2 infection revealed that COVID-19 survivors compared to healthy controls more often experienced cognitive difficulties that were confirmed during neuropsychological testing showing impairments in attention and executive functions [45]. The presence of these deficits was associated with reduced primary motor cortex excitability and several other parameters in transcranial magnetic stimulation studies, suggesting alterations of cholinergic and GABA-ergic neurotransmission [45]. It also seems that metabolic dysfunction, with insulin resistance and obesity, together with chronic inflammation, may predispose to the post-acute sequelae of COVID-19 [46]. Persistent neuropsychiatric symptoms may develop due to neuroinflammation [47], leading to a dysfunction of microglia and mitochondria [48] and the aggregation of tau protein and subsequent neurodegeneration [49].

The higher incidence and longer duration of self-declared cognitive symptoms in women could be explained by their

stronger immune responses and chronic inflammatory cascade induced by the SARS-CoV-2 viral fragments hidden in the brain or other reservoirs [50]. The complex interplay between genetic and hormonal factors could also contribute to the sex differences in the course of COVID-19-associated brain fog [51]. Oestrogen can exert a pro-inflammatory activity, and genes of immune regulation are encoded on X chromosomes [52]. Previous studies also showed that in many neurological and psychiatric illnesses, sex-associated differences in response to stress stimuli might affect brain health, and thus cognitive symptoms and their recovery [53]. This has also been shown in depression and anxiety disorders, and their influence on the higher prevalence of brain fog symptoms in women could have been amplified during the COVID-19 pandemic [54]. Additionally, anxiety, depression, and stress may share similar proinflammatory pathophysiological pathways that in the case of COVID-19 were found to be altered by a patients's biological sex [55].

Therefore, the results of our study could be perceived as hypothesis-generating.

Our study has important limitations. Firstly, the research had a cross-sectional design and was based on symptoms reported retrospectively by patients a few months after COVID-19 onset, with questionnaires filled out only once. Moreover, as the questionnaires were filled out anonymously, it was not possible to confirm the validity of responses. Secondly, in the literature there are different definitions regarding what is perceived to be brain fog, although we used the meaning proposed by NICE and the Centers for Disease Control and Prevention [10, 15]. Thirdly, there was an uneven distribution of sex in our sample, with nearly 80% of our patients being female. However, when performing a post hoc power calculation, this is satisfactory. Fourthly, there was a potential bias in response to the online survey between sexes because females tend to participate more often in such surveys, a phenomenon observed in previous studies [56]. Fifthly, there was no data regarding education, ethnicity and comorbidities, even though an influence of the latter on the prognosis in long COVID-19 has been previously documented [57]. There was also no information on the presence of neurological and psychiatric conditions that could have influenced the act of filling out the questionnaire, as well as no data on the results of additional diagnostic tests [58]. Finally, some patients were vaccinated against COVID-19 before filling out the questionnaire, although this applied only to 19% of cases.

In conclusion, our present study suggests that brain fog symptoms in non-hospitalised patients with the SARS-CoV-2 infection differ between women and men. Our study is also among the first to present details on the timeline of brain fog symptoms during and after COVID-19. Future studies will deliver new data on this topic, and — hopefully — also treatment options in women and men [59].

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LEADING TOPIC

Leading Topic Editor: Alina Kułakowska, MD, PhD, Department of Neurology, Medical University of Bialystok, Bialystok, Poland

Antibodies against SARS-CoV-2 S and N proteins in relapsing-remitting multiple sclerosis patients treated with disease-modifying therapies

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ABSTRACT

Clinical rationale for the study. The course of COVID-19 in people with multiple sclerosis (PwMS) has been described, while the serological status after SARS-CoV-2 infection or vaccination, especially in patients treated with disease-modifying therapies (DMT), is still under investigation. This is a significant clinical problem, as certain DMTs may predispose to a severe course of viral infections.

Aim of the study. We analyzed the presence of antibodies against spike (S) and nucleocapsid (N) proteins of SARS-CoV-2 in relapsing-remitting PwMS treated with DMT, especially dimethyl fumarate, interferon beta, and glatiramer acetate, in a single multiple sclerosis (MS) centre in north-eastern Poland (the Department of Neurology, Medical University of Bialystok).

Material and methods. The presence of antibodies against S and N proteins in PwMS was assessed twice: on visit one (between May and June 2020) (n = 186) and on visit two (between May and June 2021) (n = 88). Samples were taken from 68 individuals on both visits. Demographic and clinical data was collected: duration of MS, Expanded Disability Status Scale Score (EDSS), type of DMT, history of COVID-19 (positive PCR or antigen test in the past), vaccination status, and the type of vaccine.

Results. It was shown that on visit one: 3.7% (n = 7) PwMS were positive for IgA against S protein (IgA-S), 3.2% (n = 6) for IgG against S (IgG-S) protein, and none of those examined was positive for IgG against N protein (IgG-N). On visit two, the most common detected antibodies were IgG-S (71.3%; n = 62), then IgA-S (65.1%; n = 55), and the least common was IgG-N (18.2%; n = 16). On visit two: 20.45% of PwMS had a history of a positive SARS-CoV-2 PCR or antigen test during the last year. By the time of visit two, 42.05% (n = 37) of patients who participated in visit two had been full-course vaccinated against COVID-19. It was demonstrated that vaccination against SARS-CoV-2 significantly induces the production of IgG-S and IgA-S ($p < 0.0001$), while no difference between vaccinated and unvaccinated patients was shown in the detection of IgG-N. There was no correlation between COVID-19 infection and antibodies against proteins S and N in the study group. Moreover, the presented study did not show any relationship between the ability to produce antibodies against the S protein with any of the used DMTs.

Conclusions and clinical implications. According to our study, PwMS treated with dimethyl fumarate, interferon beta, or glatiramer acetate can efficiently produce antibodies against SARS-CoV-2 both after infection and after vaccination.

Key words: COVID-19, SARS-CoV-2, multiple sclerosis, disease-modifying therapies, antibodies, vaccines, serology

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Introduction

The coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was announced by the World Health Organisation on 11 March, 2020 [1]. In COVID-19 diagnostics, molecular (real-time polymerase chain reaction; RT-PCR) and serological tests to detect specific antibodies against the virus are used [2].

Since the introduction of vaccines against COVID-19, the assessment of antibodies against SARS-CoV-2 is a highly important element of a post-vaccine immune response evaluation. SARS-CoV-2 belongs to the beta-coronavirus group, and is one of the five pathogenic human coronaviruses. The virus is made up of the following proteins: spike protein (S), membrane protein (M), envelope protein (E), and nucleocapsid protein (N). The virus uses angiotensin-converting enzyme (ACE) receptors, which are present in many human organs, to penetrate the host cells.

The element of the S protein: S1 subunit – the receptor-binding domain (RBD) binds to the ACE receptor, which leads to cell infection [3]. The antibodies against the S protein have neutralising properties. Antibodies against N protein do not have neutralising properties, but indicate a past infection [4, 5]. The SARS-CoV-2 virus attacks the mucous membranes. Therefore, the production of IgA starts early and persists for about two months after infection. IgG antibodies are detectable c.14 days after the infection and are present for at least a few months [4, 6]. The sensitivity of IgG detection after at least 14 days from the onset of COVID-19 is 100% for the Enzyme-Linked Immunosorbent Assay (ELISA), Chemiluminescent Immunoassay (CLIA), and Lateral Flow Immunoassay (LFIA) methods [7]. Current reports indicate that the cumulative assessment of anti-S antibodies and anti-N protein antibodies, assessed in two classes of immunoglobulins (IgG and IgA), constitute both a sensitive and specific serological diagnostic approach to SARS-CoV-2 infection [8].

Multiple sclerosis (MS), as a chronic autoimmune disease of the central nervous system, may, under certain circumstances, predispose to a more severe course of COVID-19 [9]. In MS pathogenesis, activation of circulating T and B lymphocytes and excessive production of pro-inflammatory cytokines (e.g. IL-17, IL-6) plays an important role [10]. In treating MS, immunomodulatory and immunosuppressive medications (disease-modifying therapies or DMTs) are used [11]. Certain DMTs may predispose to the development of viral infections and worsen the prognosis [9, 12]. On the other hand, studies evaluating the course of COVID-19 in people with MS (PwMS), including those treated with DMTs, have indicated a relatively mild course of infection in most cases [13, 14].

Clinical rationale for study

To the best of our knowledge, no analysis of antibodies against the SARS-CoV-2 protein (S and N) has been carried out in north-eastern Poland or indeed north-eastern Europe. Moreover, the current literature does not provide data on the presence of antibodies as well against N and S proteins in other MS populations.

Here we assess the presence of anti-S antibodies in class IgG (IgG-S), IgA (IgA-S), and anti-N protein antibodies in class IgG (IgG-N) in PwMS treated with different DMTs in a single MS centre in north-eastern Poland i.e. the Department of Neurology, Medical University of Bialystok (MUB).

Material and methods

Study group

PwMS who had the relapsing-remitting course of disease (RR PwMS) diagnosed according to the McDonald's 2010 and 2017 criteria, and who were being treated with DMTs at the Department of Neurology, MUB, were included in this study. Blood samples were collected during two routine visits to the MS centre. The first visit (visit 1) was between May and June 2020, and the second one (visit 2) one year later, between May and June 2021. 186 patients participated in visit 1, 88 patients participated in visit 2, and 68 individuals took part in both visits. On each visit, the following survey data was collected: duration of MS, Expanded Disability Status Scale score (EDSS), type of used DMT, COVID-19 history (positive PCR or antigen test in the past), vaccination against SARS-CoV-2 status, and the type of used vaccine against COVID-19. During both visits, each study participant was examined by a neurologist. All individuals signed informed consent to participate in this study. The study was approved (approval No. APK.002.230.2020) by the Bioethics Committee at the Medical University of Bialystok, Poland. The clinical characteristics of the study group are set out in Table 1.

Laboratory tests

Assessment of antibodies against the SARS-CoV-2 virus was conducted: IgG-S, IgA-S, IgG-N. Serum levels of the IgG-S and IgA-S antibodies were assessed with the ELISA using the anti-SARS-CoV-2 IgA and IgG kits (Euroimmun, Medizinische Labordiagnostika AG, Germany) adhering to the manufacturer's instructions. The results were assessed semi-quantitatively by calculating the value of the ratio of the extinction of the person sample to the extinction of the calibrator. Results were interpreted according to the manufacturer's recommendation: ratio values < 0.8 were considered negative, ≥ 0.8 to < 1.1 as borderline, and ≥ 1.1 as positive.

Serum levels of the IgG antibodies against the N protein of the SARS-CoV-2 were measured by Chemiluminescent Microparticle Immunoassay (CMIA) on the automatic Alinity system (Abbott, Chicago, IL, USA). The obtained chemiluminescent reaction was assessed as relative light units (RLU). The level of serum antibodies was directly proportional to the RLU detected by the system optics. The S/C (serum/cut-off)

Table 1. Study group characteristics

Group visit 1					
DMT	DMF	INF	GA	Other*	All
n	(n = 79)	(n = 49)	(n = 37)	(n = 21)	(n = 186)
Sex					
Female	67.09% (n = 53)	63.27% (n = 31)	62.16% (n = 23)	80.95% (n = 17)	66.67% (n = 124)
Male	32.91% (n = 26)	36.73% (n = 18)	37.83% (n = 14)	19.05% (n = 4)	33.33% (n = 62)
Age					
Mean	38	46	45	44	42
SD	10.5	12.2	12.4	13.7	12.1
MS duration					
Mean	8.6	9.0	9.1	10.0	9.0
SD	5.79	5.41	6.39	5.72	5.78
EDSS					
Mean	1.6	1.8	2.5	2.5	1.9
SD	1.18	1.01	1.17	1.62	1.25
Group visit 2					
DMT	DMF	INF	GA	Other**	All
n	(n = 29)	(n = 34)	(n = 18)	(n = 7)	(n = 88)
Sex					
Female	58.62% (n = 17)	67.65% (n = 23)	44.44% (n = 8)	71.42% (n = 5)	60.23% (n = 53)
Male	41.38% (n = 12)	32.35% (n = 11)	55.56% (n = 10)	28.57% (n = 2)	39.77% (n = 35)
Age					
Mean	37	42	45	48	41
SD	10.1	12.1	11.6	8.5	11.5
MS duration					
Mean	6.5	7.6	10.4	9.1	8.0
SD	6.03	5.00	9.31	6.82	6.59
EDSS					
Mean	1.5	1.8	2.3	2.6	1.8
SD	1.26	1.10	1.23	1.88	1.28
History of COVID-19					
Yes	13.79% (n = 4)	17.65% (n = 6)	33.33% (n = 6)	28.57% (n = 2)	20.45% (n = 18)
No	86.21% (n = 25)	79.41% (n = 27)	66.67% (n = 12)	71.43% (n = 5)	78.41% (n = 69)
Questionable	0% (n = 0)	2.94% (n = 1)	0% (n = 0)	0% (n = 0)	1.14% (n = 1)
Vaccine against COVID-19 (full vaccine course)					
None	58.62% (n = 17)	58.82% (n = 20)	61.11% (n = 11)	42.86% (n = 3)	57.95% (n = 51)
Pfizer (2 doses)	31.03% (n = 9)	29.41% (n = 10)	33.33% (n = 6)	28.57% (n = 2)	30.68% (n = 27)
Astra Zeneca (2 doses)	3.45% (n = 1)	2.94% (n = 1)	0% (n = 0)	28.57% (n = 2)	4.55% (n = 4)
Moderna (2 doses)	3.45% (n = 1)	8.82% (n = 3)	5.56% (n = 1)	0% (n = 0)	5.68% (n = 5)
Johnson & Johnson (1 dose)	3.45 (n = 1)	0%(n = 0)	0% (n = 0)	0% (n = 0)	1.14% (n = 1)
Group visit 1 + 2					
DMT	DMF	INF	GA	Other***	All
n	(n = 23)	(n = 26)	(n = 15)	(n = 4)	(n = 68)
Sex					
Female	17.39% (n = 14)	65.38% (n = 17)	46.67% (n = 7)	75.00% (n = 3)	60.29% (n = 41)
Male	39.13% (n = 9)	34.62% (n = 9)	56.33% (n = 8)	25.00% (n = 1)	39.71% (n = 27)

→

Table 1. cont. Study group characteristics

	Group visit 1				
Age					
Mean	37	43	46	52	42
SD	9.7	12.6	10.4	8.2	11.5
MS duration					
Mean	6.7	8.7	10.2	4.2	8.1
SD	5.24	4.69	7.49	2.63	5.65
EDSS					
Mean	1.3	1.8	2.6	1.2	1.8
SD	1.27	0.92	1.18	0.96	1.18
History of COVID-19					
Yes	4.35% (n = 1)	19.23% (n = 5)	33.33% (n = 5)	50.00% (n = 2)	19.12% (n = 13)
No	95.65% (n = 22)	76.92% (n = 20)	66.67% (n = 10)	50.00% (n = 2)	79.41% (n = 54)
Questionable	0.00% (n = 0)	3.85% (n = 1)	0.00% (n = 0)	0.00% (n = 0)	4.47% (n = 1)
Vaccine (full vaccine course)					
None	52.17% (n = 12)	46.15% (n = 12)	53.33% (n = 8)	25.00% (n = 1)	48.53% (n = 33)
Pfizer (2 doses)	34.78% (n = 8)	38.46% (n = 10)	40.00% (n = 6)	25.00% (n = 1)	36.76% (n = 25)
Astra Zeneca (2 doses)	4.35% (n = 1)	3.85% (n = 1)	0.00% (n = 0)	50.00% (n = 2)	5.88% (n = 4)
Moderna (2 doses)	4.35% (n = 1)	11.54% (n = 3)	6.67% (n = 1)	0.00% (n = 0)	7.35% (n = 5)
Johnson&Johnson (1 dose)	4.35% (n = 1)	0.00% (n = 0)	0.00% (n = 0)	0.00% (n = 0)	1.47% (n = 1)

Group visit 1 — patients participated in first visit; group visit 2 — patients participated in second visit; group visit 1 + 2 — patients participated in both first and second visits; DMT — disease-modifying therapy; DMF — dimethyl fumarate; INF — interferon; GA — glatiramer acetate; MS — multiple sclerosis, EDSS — Expanded Disability Status Scale; SD — standard deviation; yes — positive antigen/PCR test in past; no — no positive antigen/PCR test in past
*other: teriflunomide (n = 11); fingolimod (n = 5); cladribine (n = 3); natalizumab (n = 2) **other: teriflunomide (n = 5); fingolimod (n = 1); cladribine (n = 1) ***other: teriflunomide (n = 4)

index was determined based on the above relationship. A titre ≥ 1.4 was considered a positive result.

Statistical analysis

The statistical analysis was based on a description of groups of patients by DMT and demographic variables (sex, age, MS duration, EDSS). This was followed by estimating the Odds Ratio for positive Ig bioassays based on logistic regression models (logit link function). The Wald test evaluated the presence of antibodies, vaccination status, vaccine type, multiple sclerosis disease duration, EDSS, DMTs, and COVID status. Tukey's multiple comparison test was conducted to account for all paired comparisons. Graphical representations supported these statistical models, mainly forest plots comparing the least mean square estimations of the odds ratio and the 95% confidence interval. The whole analysis was realised with R software (V4.1.0, R Core Team 2021).

Results

Visit 1

On visit 1, 186 PwMS were enrolled in the study, of whom 66.67% (n = 124) were women. The mean age of the PwMS was 42 years (± 12.1). The mean disease duration was 9 years (± 5.78). The most commonly used DMT was dimethyl fumarate (42.47%; n = 79), followed by interferon-beta (26.34%; n = 49), and then glatiramer acetate (19.89%; n = 37). Detailed data on the characteristics of the study group during visit 1 are set out in Table 1.

During visit 1, 6.98% (n = 13) of the PwMS had positive antibodies to the S protein: 3.22% (n = 6) IgG-S and 3.76% (n = 7) IgA-S. No IgG-N was detected in any of the tested samples. At the time of visit 1, no patient had a history of positive antigen or PCR test for SARS-CoV-2. In addition, on visit 1, vaccinations against COVID-19 were not yet available. Detailed data on the analysis of anti-SARS-CoV-2 antibodies are set out in Table 2.

Visit 2

On visit 2, 88 PwMS participated, of whom 60.22% were women (n = 53). The mean age of PwMS was 41 years (± 11.5), and the mean disease duration was 8.0 years (± 6.59). The most commonly used DMT was interferon-beta (38.63%; n = 34), followed by dimethyl fumarate (32.95%; n = 29), and then glatiramer acetate (20.45%; n = 18). Patients attending visit 2 did not significantly differ in sex, age, disease duration, or EDSS from those on visit 1. At visit 2, 20.45% (n = 18) of the PwMS had a history of a positive SARS-CoV-2 antigen or PCR result [hereinafter referred to as COVID-19 (+)]. One person obtained questionable results. The mean time from COVID-19 onset to antibodies determination was 151 days (SD ± 66.75). On visit 2, 42.04% (n = 37) of the PwMS had already

Table 2. Analysis of anti-SARS-CoV-2 antibodies

Antibody type	IgA-S	IgG-N	IgG-S
Group visit 1			
Percentage of positive results	3.8% (n = 7)	0.0% (n = 0)	3.2% (n = 6)
Sex			
Female	4.8% (n = 6)	0.0% (n = 0)	3.2% (n = 4)
Male	1.6% (n = 1)	0.0% (n = 0)	3.2% (n = 2)
DMT			
DMF	1.3% (n = 1)	0.0% (n = 0)	2.5% (n = 2)
INF	4.1% (n = 2)	0.0% (n = 0)	4.1% (n = 2)
GA	5.4% (n = 2)	0.0% (n = 0)	2.7% (n = 1)
Other*	9.5% (n = 2)	0.0% (n = 0)	4.8% (n = 1)
History of COVID-19/Vaccine status			
COVID (+)		0.00% (n = 0)	
Vaccine (+)		0.00% (n = 0)	
Group visit 2			
Percentage of positive results	64.7% (n = 55)	18.4% (n = 16)	71.3% (n = 62)
Sex			
Female	69.2% (n = 36)	15.1% (n = 8)	73.6% (n = 39)
Male	57.6% (n = 19)	23.5% (n = 8)	67.6% (n = 23)
DMT			
DMF	62.1% (n = 18)	6.9% (n = 2)	72.4% (n = 21)
INF	63.6% (n = 21)	27.3% (n = 9)	64.7% (n = 22)
GA	68.8% (n = 11)	16.7% (n = 3)	82.4% (n = 14)
Other**	71.4% (n = 5)	28.6% (n = 2)	71.4% (n = 5)
History of COVID-19/Vaccine status			
COVID-19 (–)	61.2% (n = 41)	14.5% (n = 10)	66.7% (n = 46)
COVID-19 (+)	77.8% (n = 14)	33.3% (n = 6)	88.9% (n = 16)
Vaccine (–)	42.9% (n = 21)	18.0% (n = 9)	54.0% (n = 27)
Vaccine (+)	94.4% (n = 34)	18.9% (n = 7)	94.6% (n = 35)
Group visit 1 + 2			
Percentage of positive results	72.1% (n = 49)	17.6% (n = 12)	76.5% (n = 52)
Sex			
Female	78.0% (n = 32)	14.6% (n = 6)	78.0% (n = 32)
Male	63.0% (n = 17)	22.2% (n = 6)	74.1% (n = 20)
DMT			
DMF	69.6% (n = 16)	4.3% (n = 1)	78.3% (n = 18)
INF	73.1% (n = 19)	30.8% (n = 8)	76.9% (n = 20)
GA	66.7% (n = 10)	13.3% (n = 2)	73.3% (n = 11)
Other***	100.0% (n = 4)	25.0% (n = 1)	75.0% (n = 3)
History COVID-19/Vaccine status on visit 2			
COVID-19 (–)	64.81% (n = 35)	22.22% (n = 12)	70.37% (n = 38)
COVID-19 (+)	92.31% (n = 12)	38.46% (n = 5)	92.31% (n = 12)
Vaccine (–)	46.88% (n = 15)	18.75% (n = 6)	53.13% (n = 17)
Vaccine (+)	91.43% (n = 32)	17.14% (n = 6)	94.29% (n = 33)

Group visit 1 — patients participated in first visit; group visit 2 — patients participated in second visit; group visit 1 + 2 — patients participated in both first and second visits; IgG-S — IgG antibodies against S protein; IgA-S — antibodies against S protein; IgG-N — IgG antibodies against N protein; Ig — immunoglobulin; DMT — disease-modifying therapy; DMF — dimethyl fumarate; INF — interferon; GA — glatiramer acetate; history of COVID-19 — positive antigen or PCR test in past; COVID-19 (–) — no positive antigen/PCR test in past; COVID-19 (+) — positive history of COVID-19; vaccine (–) — patients who were not vaccinated against COVID-19; vaccine (+) — patients who were full-course vaccinated against COVID-19
*other: teriflunomide (n = 11); fingolimod (n = 5); cladribine (n = 3); natalizumab (n = 2)
**other: teriflunomide (n = 5); fingolimod (n = 1); cladribine (n = 1)
***other: teriflunomide (n = 4)

Table 3. Analysis of anti-SARS-CoV-2 antibodies in subgroups of patients on visit 2

Subgroup	IgA-S	IgG-N	IgG-S
COVID-19 (–) and vaccine (–) n = 46	41.5% (n = 17)	19.0% (n = 8)	50.0% (n = 21)
COVID-19 (–) and vaccine (+) n = 51	92.3% (n = 24)	7.4% (n = 2)	92.6% (n = 25)
COVID-19 (+) and vaccine (–) n = 11	50.0% (n = 4)	12.5% (n = 1)	75.0% (n = 6)
COVID-19 (+) and vaccine (+) n = 25	100.0% (n = 10)	50.0% (n = 5)	100.0% (n = 10)

IgG-S — IgG antibodies against S protein; IgA-S — antibodies against S protein; IgG-N — IgG antibodies against N protein; COVID-19 (–) — no positive antigen/PCR test in past; COVID-19 (+) — positive antigen /PCR test in past; vaccine (–) — patients who were not vaccinated against COVID-19 with any dose; vaccine (+) — patients who were full-course vaccinated against COVID-19

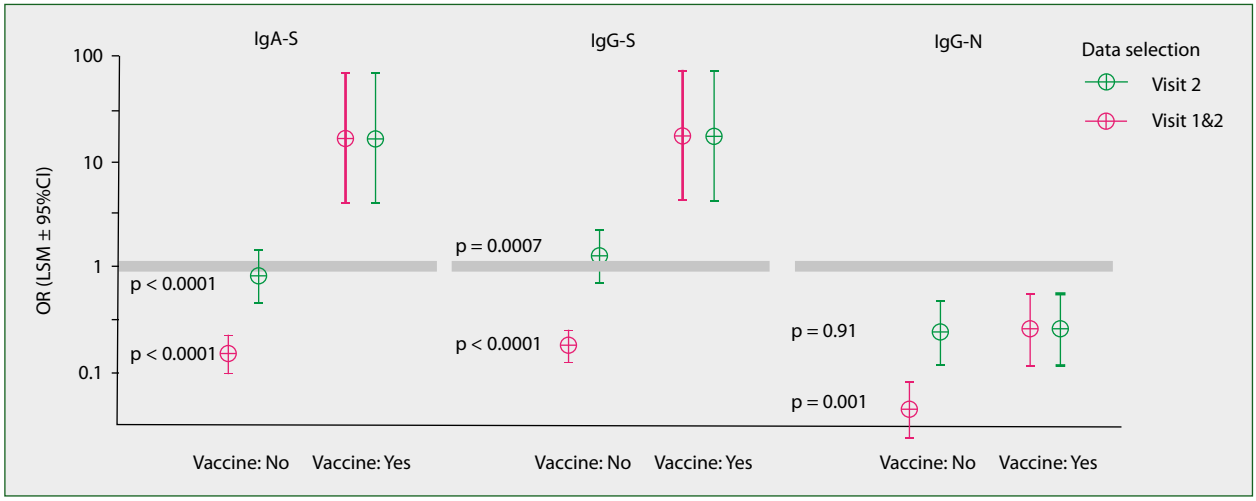

Figure 1. Odds Ratio of positive anti-SARS-COV-2 antibodies test by vaccine status at visit 2 and at visit 1 and 2

been vaccinated with the full anti-SARS-CoV-2 vaccine course. The PwMS were mostly vaccinated with the Pfizer-BioNTech (COMIRNATY) vaccine (72.97%; n = 27). The mean time from the first dose (after Pfizer, AstraZeneca, Moderna and Johnson & Johnson vaccines) was 56.59 days (SD ± 39.79) and from the second dose (after Pfizer, AstraZeneca, and Moderna vaccines) was 28 days (SD ± 27.84). Detailed data on the characteristics of the study group during visit 2 is set out in Table 1. On visit 2, IgG-S were the most common in PwMS (71.3%, n = 62). IgA-S were present in 64.7% (n = 55), and PwMS and IgG-N in 18.4% (n = 16). The distribution of antibodies did not differ between males and females and between patients treated with individual DMTs. Detailed data on the analysis of anti-SARS-CoV-2 antibodies is set out in Table 2.

On visit 2, PwMS were divided into four subgroups: 1) COVID-19 (–) and not vaccinated with any dose of vaccine; 2) COVID-19 (–) and vaccinated with the full course of vaccination; 3) COVID-19 (+) and not vaccinated with any dose of vaccine; and 4) COVID-19 (+) and vaccinated with a full course of vaccination. Detailed data on the presence of antibodies in subgroups on visit 2 is set out in Table 3.

The vaccine increased the chance of detection of IgG-S and IgA-S, while no stat istical difference was indicated for the detection of IgG-N (IgA-S, $p < 0.0001$; IgG-S, $p < 0.0001$; IgG-N $p = 0.91$) (Fig. 1). Moreover, no effect of the individual vaccine type on the presence of antibodies was demonstrated. In addition, no variation in vaccine effect in relation to the used DMT was detected (IgA-S, $p = 0.28$; IgG-S, $p = 0.26$; IgG-N, $p = 0.99$).

In the logistic regression model, no statistical difference between the results of any immunoglobulin tests could be identified between the COVID-19 (+) and COVID-19 (–) groups. There was no DMT effect on antibody production against SARS-CoV-2. There was no association between EDSS and antibody results (IgA-S, $p = 0.80$; IgG-S, $p = 0.50$; IgG-N, $p = 0.41$). The history of COVID-19 was not associated with any of the used DMTs. No effect of the MS duration on the synthesis of antibodies against SARS-CoV-2 was demonstrated.

Both visits

Sixty-eight patients participated in both visits, of whom 60.29% (n = 41) were women. The mean age of the patients was 42 years (± 11.5). The mean disease duration was 8.1 years

Table 4. Analysis of anti-SARS-CoV-2 antibodies in subgroups (patients attended both visits 1 and 2)

Level	IgA-S	IgG-N	IgG-S
COVID-19 (–) and vaccine (–) n = 31	42.9% (n = 12)	17.9% (n = 5)	50.0% (n = 14)
COVID-19 (–) and vaccine (+) n = 49	92.0% (n = 23)	7.7% (n = 2)	92.3% (n = 24)
COVID-19 (+) and vaccine (–) n = 7	75.0% (n = 3)	25.0% (n = 1)	75.0% (n = 3)
COVID-19 (+) and vaccine (+) n = 22	100.0% (n = 9)	44.4% (n = 4)	100.0% (n = 9)

IgG-S — IgG antibodies against S protein; IgA-S — antibodies against S protein; IgG-N — IgG antibodies against N protein; COVID-19 (–) — no positive antigen/PCR test in past; COVID-19 (+) — positive history of COVID-19; vaccine (–) — patients who were not vaccinated against COVID-19 with any dose of vaccine; vaccine (+) — patients who were vaccinated with full course against COVID-19

(± 6.59). In this group of patients, the most common DMT was INF (38.23%; n = 26), then DMF (33.82%; n = 23), and then GA (22.06%; n = 15). Detailed data on the characteristics of the study group that participated in both visits 1 and 2 is set out in Table 1.

On visits 1 and 2, 2.9% (n = 2) and 76.47% (n = 52) PwMS were IgG-S positive, respectively. On visit 1, 2.9% (n = 2) PwMS were IgA-S positive, compared to 72.06% (n = 49) on visit 2. On visit 1, none of the PwMS detected IgG-N; on visit 2, these antibodies were present in 17.65% (n = 12). Detailed data on the analysis of anti-SARS-CoV-2 antibodies is set out in Table 2.

The PwMS who participated in both visits were divided into four subgroups: 1) COVID (–) and not vaccinated with any dose of vaccine; 2) COVID (–) and vaccinated with a full course of vaccine; 3) COVID (+) and not vaccinated with any dose of vaccine; and 4) COVID (+) and vaccinated with a full course of vaccine. In the COVID (+) and vaccinated PwMS (n = 9), 100% were positive for both IgG-S and IgA-S. When analysing the entire group of vaccinated PwMS (n = 35), regardless of the earlier SARS-CoV-2 infection history, the presence of IgG-S was demonstrated in 94.3% (n = 33), and IgA-S in 94.1% (n = 32). Detailed data on the analysis of anti-SARS-CoV-2 antibodies in subgroups is set out in Table 4.

Discussion

This study presents the serological status of PwMS treated with DMTs in a single MS centre in north-eastern Poland. Antibodies were assessed for two SARS-COV-2 proteins (S and N) in two immune classes (IgA and IgG). The study group included PwMS vaccinated with a full course against COVID-19 and unvaccinated, with and without a history of SARS-CoV-2 infection. The age of the study group, the percentage of each sex, and the average duration of the disease corresponded with the entire population of PwMS in Poland [11]. Although it is known that PwMS are at higher risk of death from some infections including respiratory failure, recent reports have shown that PwMS do not suffer from COVID-19 more severely than the general population, and there is no significantly higher mortality in this group of patients [13, 15, 16].

However, the serological response to SARS-CoV-2 infection and vaccination is still being investigated [17]. Serological tests determine who has been exposed to the virus and are an essential tool for assessing vaccine immunity. In our study, PwMS were examined for the ability to produce antibodies against SARS-CoV-2, both after infection and vaccination. For this reason, our study determined antibodies against the N and S proteins. Available vaccines against SARS-CoV-2 induce the production of antibodies against the spike (S) protein only [18]. After infection, antibodies to various coronavirus proteins may be synthesised, e.g. against S and N protein [19]. The clinically most important difference between these antibodies is that only antibodies to the S protein have neutralising properties, which means they have protective properties against subsequent infection [5].

During visit 1, approximately 3–4 months after the beginning of the pandemic, only a few patients had antibodies against the S protein; no antibodies against the N protein were detected in any of the participants. This proves the low prevalence of SARS-CoV-2 infection among PwMS at that time. This was probably due to the extensive restrictions in Poland and the self-isolation of PwMS in the first months of the pandemic. No epidemiological studies conducted in Poland in 2020 have been published. Therefore, the data from visit 1 cannot be compared. The OBSER-CO seroepidemiological study conducted in Poland in May–June 2021 calculated the prevalence of SARS-CoV-2 in the 20–59 year-old age group (Podlaskie Voivodeship, Poland) to be 46.8-52.5% [20]. Our research shows that PwMS had lower exposure to the SARS-CoV-2 virus compared to the general population of a similar age. Similar conclusions were observed by Morales et al. in Spain, who assessed the incidence of COVID-19 in the local MS population as being lower than that in the Spanish general population [21].

This is probably, as mentioned earlier, due to the high fear of COVID-19 and the self-isolation of PwMS, especially among those treated with DMT. Neurologists treated PwMS from the first months of the pandemic, appealed for epidemiological

vigilance, and called for an improved sanitary regime due to the suspected more severe course of the disease. The data from visit 2 clearly showed the dynamics of the pandemic development, including the introduction of vaccination against COVID-19. The most common antibodies detected during visit 2 were IgG-S (71.6%), then IgA-S (65.1%), and the least common among PwMS were IgG-N (18.2%). In one study of 546 (74.2% taking DMT) PwMS, 11.7% (n = 64) of them had antibodies to SARS-CoV-2 [22]. Unfortunately, this study did not mention either the class of antibodies or the protein against which these antibodies were directed.

In another multicentre study by Sormani et al., conducted on 423 PwMS in Italy, Turkey, and Brazil, who were taking DMTs, the prevalence of IgG antibodies against SARS-CoV-2 was 76.8% [23]. Another study (n = 28) in PwMS with confirmed COVID-19 reported IgG seroprevalence in 83.3% (n = 20) of patients [23].

The results of the abovementioned studies seem to be in line with our observations. In our cohort, the mean time from COVID-19 positive antigen/PCR result to antibodies determination was 151 days (SD ± 66.75), and the mean time from the first dose of vaccine was 56.59 days (SD ± 39.79) and from the second dose was 28 days (SD ± 27.84). Recent data from a general Norwegian population shows that neutralising antibodies produced after the disease are maintained in 95% 10–12 months after COVID-19 onset [24]. Antibodies to S protein, produced after vaccination, are also detected one year after immunisation [25]. Therefore, in the study group, the time from vaccination and infection to sample collection was selected so that humoral immunity had time to develop and not disappear. Our work presents an analysis of antibodies in the IgG and IgA class and against individual SARS-CoV-2 proteins (S and N). It should be noted that no commercial IgA-N tests were available at the time of our study.

It is worth emphasising that most patients in the study group were treated with DMF, GA, or INF, and that DMT is most used in Poland. It has been demonstrated that PwMS treated with DMTs (particularly DMF, GA, INF) are immunocompetent in producing antibodies to SARS-CoV-2. It has also been demonstrated that vaccination against SARS-CoV-2 significantly induces the production of antibodies to the S protein ($p < 0.0001$), which has neutralising properties. Recent studies and meta analyses have confirmed the efficacy of COVID-19 vaccines among PwMS treated with DMF, INF, and GA [26]. The presented study showed that more vaccinated PwMS with no history of COVID-19 (92.6%; n = 25) produce neutralising antibodies than do those who suffered from COVID-19 but were not vaccinated (75.0%; n = 6). This indicates that vaccination is more effective than infection in generating immunity against SARS-CoV-2.

Moreover, in the group of PwMS who were infected with COVID-19 and vaccinated, the presence of neutralising antibodies was 100%. On visit 2, among both unvaccinated patients and those who had no history of COVID-19, neutralising antibodies were found in 50% (n = 21), which shows that there is a group of PwMS who have contracted SARS-CoV-2 asymptomatically, producing immune antibodies. The presented study did not show any relationship between the ability to produce antibodies against the S protein concerning any of the tested DMTs.

This study has some limitations. Notably, the proportion of PwMS treated with individual DMTs was uneven. Most patients were treated with DMF, INF, or GA. The results of the study refer only to these medications. It should be noted that the study did not include PwMS treated with ocrelizumab or another anti-CD-20 DMT. A study conducted on 473 PwMS has shown that anti-CD-20 treatment generates a lower antibody response after COVID-19 and after vaccination ($p > 0.001$) [27]. Other studies and reviews conducted so far confirm these conclusions [28, 29]. Soromani et al., in a study conducted on 780 PwMS, indicated that patients treated with fingolimod did not produce neutralising antibodies effectively after vaccination, possibly related to the leukopenia present with fingolimod treatment [26, 30]. Although our study group included patients treated with fingolimod, cladribine, and natalizumab, these groups of patients were too small for a reliable statistical analysis. In the presented study, it was impossible to demonstrate the vaccine's effect on the production of antibodies, as a majority of the participants were vaccinated with the Pfizer vaccine.

As expected, the analysis of responses against the N protein was inconsistent. Statistical analyses showed that IgG-N is not associated with infection of COVID-19. A study carried out among 683 healthcare workers at one hospital in Tokyo showed that IgG-N antibodies are the most reliable test for assessing past SARS-CoV-2 infections, including asymptomatic infections [31]. Our research does not confirm that conclusion, but the different study groups are worth noting. It seems that assessment of past infection on the basis of the N protein test is ineffective in the group of PwMS treated with DMT. The relationship between IgG-N and time from COVID-19 was also analysed, which confirmed statistical insignificance. So far, no other studies have been published analysing the anti-N protein response in PwMS. Investigating this problem in a larger group of patients with multiple sclerosis should be considered in the future. To sum up, it is worth emphasising that analyses were carried out on a population not-examined (so far) in terms of humoral response to SARS-CoV-2. Multiple sclerosis patients are a diverse population that, in addition to genetic factors, are also influenced by environmental factors. The research we present is novel because analysis of antibodies against the SARS-CoV-2 protein has not previously been carried out in north-eastern Poland. Moreover, the current literature does not provide data on the presence of antibodies against N and S proteins in other multiple sclerosis populations.

Clinical implications/future research

We have here demonstrated that vaccination against SARS-CoV-2 significantly induces the production of antibodies against the S protein, while no difference between vaccinated and unvaccinated patients was shown in the detection of the N protein. The PwMS population requires further research in terms of serology after SARS-CoV-2 infection. Moreover, the present study did not show any relationship between the ability to produce antibodies against the S protein concerning any of the used DMTs (particularly DMF, GA, and INF). Our research showed that PwMS treated with a DMT used in the study group, especially DMF, GA and INF, are immunocompetent in producing antibodies against the SARS-CoV-2 virus, and that the prevalence of SARS-CoV-2 is lower than in the general population.

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SHORT COMMUNICATION

This Short communication is accompanied by Invited Editorial, see page 8

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LEADING TOPIC

Leading Topic Editor: Alina Kułakowska, MD, PhD, Department of Neurology, Medical University of Bialystok, Bialystok, Poland

High prevalence of electroencephalographic frontal intermittent rhythmic delta activity in patients with moderately severe COVID-19

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ABSTRACT

Introduction. The aim of our study was to analyse EEG findings in patients with COVID-19 not requiring respiratory support.

Material and methods. We reviewed EEGs performed in patients with COVID-19 between April 2020 and May 2021 at the University Hospital in Kraków, Poland. Demographic and clinical data, including comorbid conditions, discharge disposition, survival, neuroimaging findings, laboratory results, and treatment was collected.

Results. The study included 44 EEGs performed in 35 patients (51.4% females), aged 65.5 ± 13.9 years. Almost all patients had at least one comorbidity, and one-third had one or more preexisting neurological conditions. Three quarters of EEGs were abnormal. The most frequent EEG finding was background slowing (16 patients; 45.7%). Frontal findings included frontally predominant rhythmic delta (FIRDA) in 10 (28.6%) patients and focal slowing in the left frontal lobe. Patients with abnormal EEG significantly more often required oxygen supplementation ($p = 0.003$) and were less likely to recover ($p = 0.048$).

Conclusions and clinical implications. Patients with COVID-19 infection may frequently manifest with an abnormal EEG. FIRDA seems to be a frequent EEG pattern in less severe cases of COVID-19 infection. Future studies are needed to establish whether COVID-19 infection increases the risk for FIRDA, and to investigate its pathogenesis.

Key words: FIRDA, COVID-19, EEG abnormalities, prevalence, prognosis

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Introduction

Neurological symptoms and signs have been reported in the majority of patients with COVID-19 [1]. While clinical seizures affect only a small proportion of patients, electroencephalographic (EEG) abnormalities have been reported in 88–96% of cases, with generalised background slowing being the most frequent finding [2–4]. No clear and specific EEG pattern, however, has reliably been found in this population. EEG abnormalities in frontal lobes have been recently proposed as a biomarker of COVID-19-related encephalopathy [2, 6–8]. The majority of studies on EEG abnormalities in COVID-19 have focused on critically ill patients. Less is known about EEG findings in patients with a less severe course of infection.

The main goal of our study was to analyse the EEG findings in hospitalised patients with COVID-19 not requiring respiratory support, with a special focus on frontal lobe-related abnormalities.

Material and methods

We retrospectively reviewed consecutive EEGs of patients with COVID-19 hospitalised from April 2020 to May 2021 in the Department of Neurology of the University Hospital in Krakow.

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Patients were included if they were ≥ 18 years old and had a positive SARS-CoV-2 nasopharyngeal RT-PCR swab. The following patient data was recorded: age, sex, medical history, neuroimaging findings, laboratory results, treatment, and outcome (i.e. recovered, discharged with disability, or deceased). All patients underwent 21-channel EEG (video-EEG) recordings using 19 silver/silver chloride electrodes affixed to the scalp according to the international 10–20 system with additional ground and reference electrodes (DigiTrack, Elmiko). A single channel ECG was recorded simultaneously. EEGs were performed for a short duration (routine for approximately 20–30 min). EEG recordings were performed with an Elmiko DigiTrack device. Additional precautions for EEG technicians included an N95 respirator, gloves, gown, and eye protection (goggles or face shield). EEGs were reviewed using bipolar and monopolar montages by two neurophysiologists (MB, DW-K) according to the American Clinical Neurophysiology Society (ACNS) terminology. During readings, high pass and low pass filters were usually at 1 Hz (range 0.05–5 Hz) and 70 Hz (range 5–100 Hz), respectively [9]. The following EEG features were assessed: dominant background activity, focal/generalised slowing, generalised/lateralised rhythmic delta activity, periodic discharges, and epileptiform discharges/electrographic seizures/non-convulsive status epilepticus (NCSE). Frontal intermittent rhythmic delta activity (FIRDA) was defined as predominantly frontal rhythmic delta activity (1–4 Hz) [10].

Respiratory status, presence of metabolic abnormalities, medication, and level of consciousness during EEG were also noted. No patient required mechanical ventilation.

We additionally reviewed all reports from EEG studies performed in our centre between June 2016 and December 2020 for the presence of FIRDA.

Our study protocol was approved by the local bioethics committee. Informed consent was waived due to the retrospective nature of this study.

Discrete variable was expressed as a mean ± standard deviation (SD) and qualitative data was characterised with percentages. The significance of the differences between groups were analysed using the $\chi 2$ test or Fisher exact test (qualitative data) or with Student t-test. Analysis of potential independent predictors of poor outcome (death or disability at discharge as a dependent variable) was performed by logistic regression modelling. The initial model involved all the variables that differed between patients with poor or good outcomes at the level of $p < 0.2$ in univariate analysis. Subsequent models were built using the backward selection method.

Results

Patients

This study included 35 patients with the mean age of 65.5 ± 13.9 years. Neurological manifestations comorbid with COVID-19 were the reason for admission in the great majority of patients (31/35; 88.6%) and included: altered mental status (18 patients), seizures (eight patients), stroke (3), headache (1), subarachnoid haemorrhage (1), and posterior reversible encephalopathy syndrome (1). Almost all patients (32/35; 91.4%) had at leastone comorbidity. One-third of patients (12, 34.3%) had preexisting neurological conditions, including a prior history of epilepsy (5, 14.3%), ischaemic stroke (4), surgical treatment of brain metastasis (1), or brain tumour (2). All patients underwent at least one neuroimaging procedure. Various abnormalities in those studies were found in 21 patients (60%). One-third of the cohort underwent lumbar puncture which revealed abnormalities of cerebrospinal fluid in all but one patient. Most patients (27/35; 81.8%) required oxygen supplementation and had metabolic abnormalities other than decreased oxygen (26/35; 74.3%). Two thirds of patients (24/35; 68.6%) received neuroactive medication during EEG. Decreased awareness during EEG was seen in 37.1% (13/35) of patients. Twenty patients (57.1%) recovered, 10 patients (28.6%) were discharged with disability, and five patients died (14.3%).

EEG findings

Forty four EEG recordings were obtained. Indications for EEG studies were as follows: altered mental status (33), seizures (8), and follow-up (3). Three quarters of recordings were abnormal, and three quarters of patients had at least one abnormal EEG. The most frequent EEG finding was background slowing (16 patients; 45.7%). Frontal findings included FIRDA in 10 (28.6%) patients, and focal slowing in the left frontal lobe in one patient. Epileptiform discharges were noted in five patients. EEG findings and clinical characteristics of patients during EEG recording are set out in Table 1.

We compared patients with abnormal and normal first EEG recording in terms of their demographic and clinical variables (Table 1). Patients with abnormal EEG significantly more often required oxygen supplementation ($p = 0.003$) and were less likely to recover ($p = 0.048$). In the second univariate analysis, patients with and without FIRDA were compared. Subjects with FIRDA more frequently underwent MRI ($p = 0.05$). There was also a trend towards more frequent use of oxygen supplementation in patients with FIRDA ($p = 0.054$).

Multivariate analysis revealed the need for oxygen supplementation as the only independent predictor of a poor outcome ($p = 0.008$).

Between June 2016 and December 2019, a total of 6,431 EEG recordings were carried out in our centre. The presence of FIRDA was reported in 112 (1.7%) studies, comprising 108 inpatients (3.2%) and four outpatients (0.1%).

Discussion

Here, we report EEG findings in patients with a moderately severe COVID-19 infection. The most frequent EEG findings were diffuse background slowing, focal slowing, and frontal intermittent rhythmic delta activity, found in one third of patients.

Table 1. Comparison of clinical characteristics between patients with abnormal and normal first EEG and between patients with and without frontal intermittent rhythmic delta activity (FIRDA)

Variable	Patients with abnormal first EEG (N = 26) n, (%)	Patients with normal first EEG (N = 9) n, (%)	p-value*	Patients with FIRDA (N = 1) n, (%)	Patients without FIRDA (N = 25) n, (%)	p-value*
Age, years [mean ± SD]	67.1 (12.2)	60.7 (18.0)	0.23**	67.3 (10.6)	64.8 (15.2)	0.63**
Women	13 (50.0)	5 (55.5)	1.0	5 (50.0)	13 (52.0)	1.0
Neurological symptoms upon admission	23 (88.5)	8 (88.9)	1.0	9 (90.0)	22 (88.0)	1.0
Comorbidities	25 (96.1)	7 (77.8)	0.16	10 (100.0)	22 (88.0)	0.54
History of epilepsy	5 (19.3)	0	0.30	1 (10.0)	4 (16.0)	1.0
CT	23 (88.5)	9 (100)	0.55	8 (80.0)	24 (96.0)	0.19
MRI	16 (61.5)	6 (66.7)	1.0	9 (90.0)	13 (52.0)	0.05
CT angiography	10 (38.5)	5 (55.5)	0.45	3 (30.0)	12 (48.0)	0.46
Abnormal neuroimaging	17 (65.4)	4 (44.4)	0.43	6 (60.0)	15 (60.0)	1.0
Lumbar puncture	9 (34.6)	3 (33.3)	1.0	4 (40.0)	8 (32.0)	0.71
Abnormal CSF	9 (34.6)	2 (22.2)	0.69	4 (40.0)	7 (28.0)	0.69
EEG on neuroactive drugs	20 (76.9)	4 (44.4)	0.10	7 (70.0)	17 (68.0)	1.0
Epileptiform discharges	5 (19.2)	–	0.11	0	5 (20.0)	0.29
Other EEG abnormalities	24 (92.3)	–	0.003	–	14 (56.0)	0.45
EEG slowing	16 (61.5)	–	0.19	6 (60%)	10 (40.0)	1.0
FIRDA	10 (38.5)	–	0.048	–	–	1.0
Focal EEG abnormalities	8 (30.8)	–	0.23	2 (20%)	6 (24.0)	0.054
Decreased awareness during EEG	12 (46.2)	1 (11.1)	0.30	4 (40.0)	11 (44.0)	1.0
Oxygen supplementation	20 (76.9)	2 (22.2)	1.0	9 (90.0)	13 (52.0)	0.49
Metabolic abnormalities other than decreased oxygen saturation	21 (80.8)	5 (55.5)	0.69	8 (80.0)	18 (72.0)	1.0
Outcome	12 (46.2)	8 (88.9)		7 (70.0)	13 (52.0)	0.29
Recovery	9 (34.6)	1 (11.1)		3 (30.0)	7 (28.0)	1.0
Disability	5 (19.2)	0		0	5 (20.0)	1.0
Death	8 (30.8)	3 (33.3)		3 (30.0)	8 (32.0)	
Seizures during hospitalisation	8 (30.8)	4 (44.4)		3 (30.0)	9 (36.0)	
Final diagnosis: COVID only						

CSF — cerebrospinal fluid; CT — computed tomography; EEG — electroencephalography; FIRDA — frontal intermittent rhythmic delta activity; MRI — magnetic resonance imaging
*Fisher exact test; ** Student's t-test

Previous systematic reviews of COVID-19 patients [2–4] have reported that EEG findings were nonspecific, with the majority of cases having generalised background slowing. Likewise, the most common EEG abnormality in our cohort was diffuse background slowing, found in half of the patients. Unlike most studies [2–4, 11] a quarter of our patients had normal EEG. However, most previously studied patients were specified as being critically ill, intubated, or having multiorgan failure [4–6, 13]. The lower percentage of background slowing and the high proportion of subjects with normal EEGs were probably related to the less severe course of COVID-19 infection in our patients.

The high frequency of background slowing (45.7%) and generalised rhythmic delta activity (28.4%) in our cohort suggest the presence of a nonspecific diffuse encephalopathy in COVID-19 patients not requiring ICU treatment.

Patients with normal and abnormal EEG did not differ in terms of any demographic and clinical characteristics, except for the need for oxygen supplementation. The frequency of any EEG abnormalities was higher in patients requiring oxygen supplementation ($p = 0.003$). This might suggest that preexisting lower values of oxygen saturation leading to oxygen therapy may contribute to EEG abnormalities. Patients with a normal first EEG were more likely to recover ($p = 0.048$). Electroencephalographic abnormalities were previously found to be associated with a worse outcome in COVID-19 patients [5].

We could not confirm this finding in our cohort, for at least three reasons. The sample could be too small to establish a significant impact of EEG abnormalities. The population studied consisted of less severely affected patients, in whom factors other than EEG abnormalities could play a more important role. And finally, the need for oxygen supplementation was closely related to the presence of EEG abnormalities, and the predictive role of the former supplanted the value of the latter variable.

The most interesting finding in our study was the high prevalence of FIRDA, which was recorded in almost one third of patients. On the contrary, FIRDA was seen in only 1.7% out of 6,431 EEG studies (3.2% of inpatient studies) performed in our hospital between June 2016 and December 2019. The latter frequency was similar to previously published studies on the prevalence of FIRDA [10, 14].

To the best of our knowledge, the prevalence of FIRDA in patients with COVID-19 has never been specifically studied. Previous systematic reviews of COVID-19 patients [2–4] did not reveal consistent EEG findings specific to a COVID-19 infection. In several studies [6, 15–18], frequent frontal abnormalities were found and suggested as a potential EEG biomarker of COVID-19 encephalopathy related to the concept of entry of the SARS-CoV-2 virus to the brain through the olfactory nerves and subsequent spread to the orbitofrontal regions. Galanopoulos et al. found frontal sharp waves in nearly all patients with epileptiform discharges. In a small study from Italy, frontal prevalence of slow waves was noted in more than half of cases [15]. Vellieux et al. reported non-reactive bifrontal monomorphic diphasic periodic delta slow waves in two patients with COVID-19 [17].

FIRDA is a nonspecific EEG pattern and has been reported in a wide variety of cerebral lesions and different metabolic disturbances [10, 14]. The neurophysiological mechanisms underlying the high frequency of FIRDA in our cohort are unclear. This may reflect subclinical encephalopathy related to cerebral involvement with frontal predominance in COVID-19, or mild hypoxic encephalopathy, as most patients required oxygen supplementation. One third of patients had a preexisting neurological condition, which may also cause FIRDA abnormalities.

The majority of studies published so far have focused on EEG changes during an acute phase of COVID-19 infection. Cognitive decline after COVID-19 along with EEG signal alterations have also been reported [19]. Further studies are needed to explain this correlation.

This study has several limitations. Firstly, the sample was small. EEG studies have been significantly underused due to exposure concerns and limited resources. Secondly, this was a retrospective study, and all data was extracted from electronic medical records. Thirdly, we utilised only routine EEG without continuous monitoring, and a substantial percentage of electrographic seizures could have been missed. However, unlike many other studies [6, 11] we used a full set of electrodes in all cases.

Conclusion

Patients with a COVID-19 infection may frequently manifest with an abnormal EEG, mainly with background slowing. FIRDA seems to be a frequent EEG pattern in less severe cases of COVID-19 infection.

Clinical implications/future directions

Background slowing and FIRDA may reflect subclinical COVID-19 related encephalopathy or mild hypoxic encephalopathy. The neurophysiological mechanisms underlying the high frequency of FIRDA in less severe cases of COVID-19 are unclear. Future studies are needed to establish whether COVID-19 infection increases the risk for FIRDA, and to investigate the pathogenesis of this EEG pattern.

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LEADING TOPIC

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International study: Global impact of COVID-19 on stroke care — the Polish contribution

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To the Editors

The most severe consequences of the COVID-19 pandemic were reported during its first wave in 2019. Although airway inflammation is part of the main clinical picture of COVID-19, the consequences of a SARS-Cov2 infection can also include coagulation disorders, cardiomyopathy and endotheliopathy, which lead to stroke in 1.5% of patients. With the global reach of the pandemic came collaboration between scientists and clinicians from around the world. This transfer of knowledge between various medical centres contributed to greatly improved understanding of the mechanisms of transmission and the different manifestations of infection.

To assess the global impact of the pandemic on stroke hospitalisations and outcomes, Prof. Nogueira inspired the international community of neurologists and neurointerventionalists from six continents, 70 countries and almost 500 hospital stroke centres to participate in large, cross-sectional, observational, retrospective studies. Thirteen Polish centres participated in this important project. This article presents a summary of the results from five analyses, focusing on ischaemic stroke, reperfusion therapy, subarachnoid haemorrhage, and cerebral venous thrombosis, before and during the pandemic, and includes the contribution of Polish centres.

To date, over 500 million cases of COVID-19 have been confirmed worldwide. Although respiratory infection is the main clinical feature of COVID-19, the consequences of

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a SARS-CoV-2 infection can also include coagulation disorders, cardiomyopathy and endotheliopathy, which are associated with stroke in up to 1.5% of patients. The sudden outbreak of the pandemic immediately favoured collaboration between Polish clinicians who have published several articles in this matter [1–7]. The transfer of knowledge between medical centres across the world was also important. This contributed to improved recognition and understanding of the mechanisms of transmission and the course of COVID-19 in patients with stroke and other neurological diseases.

As an example of international collaboration between stroke centres, Prof. Raul G. Nogueira, Director of the University of Pittsburgh Medical Centre (UPMC)'s Stroke Institute, initiated several studies on the course of cerebrovascular disease and the organisation of care provided to patients during the COVID-19 pandemic in relation to analogous parameters before the pandemic [8–12]. UPMC is an important stroke centre for patient care, teaching, clinical and basic research in several areas of neurology, including stroke, and Prof. Nogueira has played a global leadership role in many landmark stroke thrombectomy trials.

To assess the global impact of the pandemic on stroke hospitalisations and outcomes, Prof. Nogueira inspired the international community of neurologists and neurointerventionalists from six continents, 70 countries and almost 500 hospital stroke centres to participate in large cross-sectional, observational, retrospective studies [8–15]. As highlighted in an editorial by Prof. Bart M. Demaerschalk entitled: 'Where in the World Have All the Strokes Gone?' [16], Nogueira and his collaborators comprehensively described the global changes that took place in stroke care management at the height of the COVID-19 pandemic, and provided potential systemic explanations for these changes associated with COVID-19 or societal behaviour.

We had the opportunity to listen to a lecture by Prof. Nogueira during a conference organised by the Cerebrovascular Diseases Section of the Polish Neurological Society in 2021. An invitation to collaborate in the global COVID-19 stroke studies was received by Prof. Anna Członkowska, who was then Chair of the Cerebrovascular Diseases Section. This invitation was extended to the heads of neurology/stroke departments involved in the SITS and RESQ registers, and led to the participation of 13 Polish (not only academic) stroke centres (**listed below) in the global COVID-19 stroke studies.

Here, we present a summary of the results from five analyses, focusing on ischaemic stroke, reperfusion therapy, subarachnoid haemorrhage (SAH), and cerebral venous thrombosis (CVT) before and during the pandemic. The contribution of Polish centres is described — the names of the Polish clinicians involved can be found in the original papers.

The first paper entitled: 'Global impact of COVID-19 on stroke care and IV thrombolysis' compared the impact of the COVID-19 pandemic on intravenous thrombolysis (IVT), IVT transfers and stroke hospitalisations over four months during the height of the outbreak (from 1 March to 30 June 2020) with two four-month pre-pandemic periods [8]. In total, 325 stroke centres from 70 countries, including 11 from Poland, participated in this study. Data was collected from 91,373 stroke patients hospitalised before and 80,894 stroke patients hospitalised during the pandemic. Data from 1,815 stroke patients hospitalised before and 1,749 hospitalised during the pandemic were submitted by Polish investigators.

Overall, stroke admissions declined by 11.5% [95% confidence interval (CI) −11.7 to −11.3, $p < 0.0001$] during the pandemic months compared to immediately before. Furthermore, in the four months preceding the pandemic, there were 13,334 IVT procedures compared to 11,570 therapies during the pandemic, which represents a 13.2% (95% CI −13.8 to −12.7, $p < 0.0001$) decline. In addition, the number of inter-facility IVT transfers decreased from 1,337 to 1,178, which represents an 11.9% decrease (95% CI −13.7 to −10.3, $p = 0.001$). The decline in patient volumes was greater in primary stroke centres and centres with higher COVID-19 volumes. Some recovery in stroke hospitalisation volumes was noted (9.5%, 95% CI 9.2 to 9.8, $p < 0.0001$) over the two later pandemic months (May, June) compared to the earlier two months (March, April). Overall, 1.48% of COVID-19 patients suffered from a stroke diagnosis and 3.3% of all stroke admissions were associated with SARS-CoV-2 infection.

After the first wave of the pandemic, a later study entitled: 'Global impact of the COVID-19 pandemic on stroke volumes and cerebrovascular events: One-year follow-up' compared the period from 1 March 2020 to 28 February 2021 to the year before (i.e. 1 March 2019 to 29 February 2020) [9]. Volume data was obtained for COVID-19 admissions and for four stroke metrics: ischaemic stroke and intracranial haemorrhage (ICH) admissions, IVT and mechanical thrombectomy procedures from 275 stroke centres in 56 countries. Nine Polish centres provided data for ischaemic stroke admissions (4,511 patients in the year before the pandemic, and 4,638 patients in the one-year pandemic period), ICH admissions (601 and 666 patients, respectively), IVT (1,142 and 1,066 patients, respectively) and mechanical thrombectomy procedures (527 and 601 patients, respectively).

Overall, there were 148,895 stroke admissions in the one-year period immediately before the pandemic and 138,453 admissions during the one-year pandemic period, which represents a 7% decline (95% CI 7.1 to 6.9; $p < 0.0001$). ICH volumes decreased by 4.8% (5.1 to 4.6; $p < 0.0001$) and IVT volumes by 6.1% (6.4 to 5.8; $p < 0.0001$). There were no significant changes in mechanical thrombectomy volumes (0.7%; 0.6 to 0.9; $p = 0.49$). These results suggest that during the first year of the pandemic, stroke care was maintained for more severe diseases.

Other interesting international findings on outcomes were described in the publication: 'Safety and outcome of revascularisation treatment in patients with acute ischaemic stroke and COVID-19: The Global COVID-19 Stroke Registry' [10] that was initiated by Dr. Patrik Michel and Dr. Joao Pedro Marto of the Lausanne University Hospital in collaboration with Professors Raoul Nogueira and Thanh Nguyen. This study examined

the association of acutely revascularised COVID-19 with ICH complications and clinical outcomes between March 2020 and June 2021. Of 15,128 included patients with acute ischaemic stroke from 105 centres, including nine Polish centres, 853 (5.6%) were diagnosed with COVID-19. In total, 38.7% of patients received IVT only and 61.3% had thrombectomy. Revascularised patients with COVID-19 had higher rates of symptomatic ICH (SICH); [adjusted odds ratio (OR) 1.53; 95% CI 1.16–2.01], symptomatic SAH (SSAH; OR 1.80; 95% CI 1.20–2.69), SICH and/or SSAH combined (OR 1.56; 95% CI 1.23–1.99), 24-hour (OR 2.47; 95% CI 1.58 to 3.86) and 3-month mortality (OR 1.88; 95% CI 1.52 to 2.33). COVID-19 patients also had an unfavourable shift in the distribution of the modified Rankin score at three months (OR 1.42; 95% CI 1.26–1.60).

The manuscript 'Global impact of the COVID-19 pandemic on subarachnoid haemorrhage (SAH) hospitalisations, aneurysm treatment and in-hospital mortality: 1-year follow-up' assessed differences in the incidence and severity of aneurysmal SAH (aSAH) presentation and ruptured aneurysm treatment modalities in the first year of the pandemic compared to the preceding year [11]. The analysis included 16,247 aSAH admissions, 8,300 ruptured aneurysm coilings and 4,240 ruptured aneurysm clipping procedures. Polish authors from nine centres included data from patients hospitalised before and during the pandemic for aSAH (163 and 169, respectively); endovascular coiling (101 and 115, respectively), surgical clipping (46 and 40, respectively), and non-traumatic SAH (221 and 217, respectively).

Overall, there was a decline in aSAH admissions (−6.4%; 95% CI −7.0% to −5.8%; p = 0.0001) in the first year of the pandemic compared to the year before. There was a trend towards a decline in mild and moderate SAH at presentation by Hunt Hess Grade, but there were no difference concerning higher SAH severity of presentation on admission. The rates of ruptured aneurysm clipping remained the same (30.7% *vs.* 31.2%; p = 0.58), whereas there was an increase in ruptured aneurysm coiling (53.97% *vs.* 56.5%; p = 0.009). No differences in in-hospital aSAH mortality rates were recorded (19.1% *vs.* 20.1%; p = 0.12) pre- and during the pandemic.

Finally, CVT and mortality were studied in the publication: 'Global impact of the COVID-19 pandemic on volume of cerebral venous thrombosis and mortality' [12]. Across the study period from January 2019 to May 2021, there were 3,210 CVT hospitalisations in 171 centres. Nine Polish centres contributed data on 82 patients.

No differences in CVT volumes or CVT mortality rates were noted between 2019 and 2020. During the pandemic, COVID-19 diagnoses were present in 7.6% of all CVT hospitalisations, while CVT was present in 0.04% of COVID-19 hospitalisations. In the first pandemic year of 2020, CVT mortality was higher in patients who were COVID-positive than in those who were COVID-negative [8/53 (15.0%) *vs.* 41/910 (4.5%); p = 0.004]. In the first five months of 2021, there was a rise in CVT volumes in relation to 2019 (27.5%; 95% CI 24.2–32.0; p < 0.0001) and 2020 (41.4%; 95% CI, 37.0–46.0; p < 0.0001). There was also a rise in CVT mortality in the first five months of 2020 and 2021 in relation to the first five months of 2019 (2019 *vs.* 2020: 2.26% *vs.* 4.74%, p = 0.05; 2019 *vs.* 2021: 2.26% *vs.* 4.99%, p = 0.03). The increase in mortality during the first five months of 2021 may be partially attributable to 26 cases of vaccine-induced immune thrombotic thrombocytopenia, which resulted in six deaths [17].

The joint effort of this global coalition of stroke researchers and clinicians during very difficult times has contributed to advances in the knowledge and expertise related to the diagnosis and therapy applied to patients with cerebrovascular disease during the COVID-19 pandemic.

Acknowledgments: *On behalf of all Polish neurologists who participated, we would like to thank Prof. Nogueira and his team for the opportunity to collaborate on such an important project. We would also like to thank all our Polish colleagues who participated and we encourage active cooperation in further international scientific projects. More detailed subanalyses comparing Poland to other countries or regions are possible. If any researchers would like to submit a proposal to the coordinating centre — the data and statistical assistance will be provided. Anna Członkowska, Anetta Lasek-Bal*

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4. Neurological Ward with Stroke Unit, District Hospital in Skarzysko-Kamienna
5. Department of Neurology, T. Marciniak's Hospital in Wroclaw
6. Department of Neurology and Cerebrovascular Disorders Poznan
7. University of Medical Sciences; 107th Military Hospital with Polyclinic, Walcz
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9. Department of Neurology, Medical University of Lublin
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LEADING TOPIC

Leading Topic Editor: Alina Kułakowska, MD, PhD, Department of Neurology, Medical University of Bialystok, Bialystok, Poland

Incidence of dystonia related to COVID-19 infection

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Key words: percutaneous balloon compression, trigeminal neuralgia, delayed disappearance, symptom duration

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To the Editors

In December 2019 cases of infection caused by the new coronavirus SARS-CoV-2 were reported for the first time in the Chinese city of Wuhan. The virus spread at an immense speed, first in China, then worldwide. By March 2020 there was a global pandemic, which was confirmed by the World Health Organisation (WHO). According to the data of the WHO, there had been 663,640,386 confirmed cases of COVID-19, including 6,713,093 deaths, reported to the WHO up until January 2023. In the description of clinical manifestations, the respiratory system was the initial concern. However, the symptoms of headache and fatigue soon shifted the focus towards neurological involvement [1]. Neurological symptoms such as loss of smell and taste, CNS-related cerebrovascular events, strokes, epilepsy, and encephalopathies were reported, as were pathologies affecting the peripheral nervous system such as muscular pain [2]. Furthermore, cognitive impairment and autoimmune-associated pathologies such as Guillain-Barré syndrome and vasculitis has also been described [3]. In 2020, Paniz-Mondolfi et al. detected the virus in neural and endothelial cells in the frontal brain of a patient who had died from SARS-CoV2 infection [4]. For the route into the brain, different pathways are conceivable. These include the retrograde route via the olfactory nerve or a disrupted blood-brain barrier through leukocyte migrates [5]. The pathophysiological correlation can possibly be explained by the binding of the viral spike protein to angiotensin converting enzyme 2 (ACE2), which is expressed in many tissues, as well as in the brain [6]. In addition to that, autoimmune processes possibly triggered by T-cell involvement or the virus itself are being considered [7].

We performed a literature search in the PubMed database focused on the period from the outbreak of the infection in December 2019 until January 2023. We only considered articles in English. The filters applied included books and documents, clinical trials, meta-analyses, randomised controlled trials, reviews, systematic reviews, and case reports. We did not consider articles with a paediatric background. We also disregarded an association with pregnancy, vaccination, or therapeutic procedures in the context of infection.

We also looked to see if there were any cases reported to our dystonia outpatient clinic that were suspected to be related to COVID-19 infection, or if there was evidence of increased prevalence.

We began the literature search by using the keywords 'COVID-19', 'SARS-CoV-2' and 'neurological symptoms'. The term 'symptoms' was synonymous with 'complications' and 'manifestations'. This keyword search yielded 1,423 hits. We reviewed the individual titles. In case of unclear relevance, we additionally evaluated the respective abstracts, and full texts if available. Eventually we found 261 publications that had been published since the outbreak of the infection until the beginning of January 2023 and that dealt with the relationship between SARS-CoV-2 and neurological symptoms. The vast majority of these were reviews and systematic reviews. A wide range of neurological symptoms were described in this literature, but dystonia was not among them. A narrowed search using the keywords 'SARS-CoV-2 and dystonia' yielded four hits. Of these, two articles were not relevant to the topic and a third addressed the issue of worsening movement disorders that already existed before infection. In their review, Brandão et al. addressed the issue of movement disorders that occurred in the setting of SARS-CoV-2 infection. Based on

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their literature search of 200 articles, they found 44 articles in which movement disorders were mentioned. From these, they extracted 93 patient cases in which a movement disorder had newly occurred during a SARS-CoV-2 infection. Dystonia was documented in just one case [8]. This case was based on the analyses of Franke et al. Using blood and cerebrospinal fluid samples, they had investigated possible autoimmune processes associated with SARS-CoV-2 infection. Their studies were based on data from 11 critically ill patients receiving intensive care. For one patient they described upper extremity dystonia. This was a 78-year-old male with a PCR-confirmed SARS-CoV-2 infection. Delirium was coexistent [9]. No further search results were found.

Since the epidemic of encephalitis lethargica 100 years ago, medicine has been aware of the possibility of extrapyramidal motor disorders due to infection [10]. The association of dystonia and encephalitis in general has been described and discussed several times already [11, 12]. Since the neurological symptoms of SARS-CoV-2 infection include encephalitis, we expanded our literature search to include the keywords 'encephalitis' and 'SARS-CoV-2'. This yielded 245 hits. 10 of these articles focused specifically on the above-mentioned topic. Based on the abstracts and the available full texts, we found no evidence for a description of dystonia occurring under SARS-CoV-2-associated encephalitis.

In our view, another aspect arose from the frequently described association of autoimmune-triggered diseases and dystonia [13]. COVID-19 is also seen as a possible trigger of autoimmune processes in the context of infection [14, 15]. For these keywords, the literature search yielded 760 hits, 93 of which were related to the above-mentioned context. They dealt with possible autoimmune processes related to all organ systems. Dystonia among autoimmune-triggered diseases caused by COVID-19 was found in the literature.

We have not had more enrollments in our dystonia outpatient clinic than in previous years, nor have we seen any cases where a correlation might be suspected.

Infection with COVID-19 may be associated with a variety of concomitant neurological symptoms in addition with respiratory system involvement. Our literature search revealed evidence of one case in which dystonia had occurred secondary to infection. This was a 78-year-old male patient with a severe course requiring intensive care. His dystonia was described for the upper extremities with right-sided emphasis. Delirium was coexistent [9]. Whether the rare mention of new-onset dystonia in our literature search (n = 1) equates to a low incidence of dystonia among SARS-CoV-2 infection cannot be adequately assessed based on the current data. The conclusion that dystonia is a rather rare symptom might be obvious but cannot be considered conclusive. In the case of dystonia, the cause could lie in the distant past. It might be necessary to reexamine the question of how frequently it actually occurs in the course of the disease.

Further analyses and studies are needed to determine whether dystonia, although extremely rare, is one of the neurological symptoms of COVID-19 infection, or whether the result of our literature search is a mere chance finding with no relevance. Therefore, physicians should be sensitive to the early course of the infection and also to its long-term course

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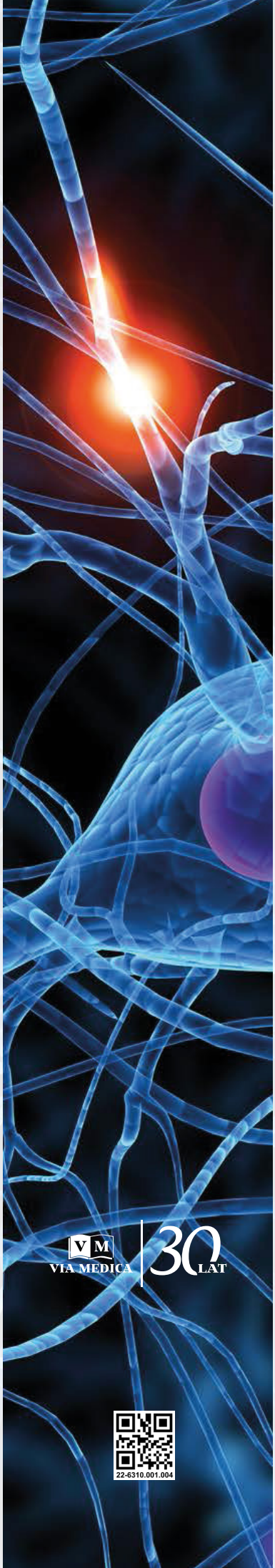

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