Multiple Sclerosis and COVID-19: An Overview on Risk, Severity, and Association With Disease Modifying Therapies

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ABSTRACT: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, emerged in December 2019, sparking a global health crisis. While initially recognized as a respiratory illness, it has become evident that Coronavirus disease 2019 (COVID-19) also affects the central nervous system. This comprehensive review focuses on the neurological manifestations of COVID-19 and its impact on patients with preexisting neurological disorders, particularly those with multiple sclerosis (MS) receiving disease-modifying therapies. Advancements in management, including vaccinations, antiviral therapy, and targeted prophylaxis, have led to a decline in the incidence and severity of COVID-19. Nevertheless, significant complications persist, particularly in patients with advanced MS, who are highly vulnerable to infectious agents like SARS-CoV-2. This review explores the evolving understanding of MS and its association with SARS-CoV-2, encompassing neuroinvasiveness, pathogenesis, disease severity, and outcomes. Research findings reveal substantial neurological implications for some MS patients with COVID-19, with a potential risk of disease relapse and severity. A notable proportion of MS patients experiencing COVID-19 may manifest new symptoms, experience exacerbation of existing symptoms, or encounter both simultaneously, underscoring the diverse neurological effects of the virus. While vaccination and therapeutics have mitigated the overall impact, specific subgroups, especially those on anti-CD20 therapy and with existing disability, remain at higher risk, necessitating ongoing vigilance and tailored care.

KEYWORDS: COVID-19, SARS-CoV-2, multiple sclerosis, disease-modifying therapies

Introduction and Background

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the brain and spinal cord.[1] It predominantly affects young individuals, commonly with diagnoses occurring between ages 20 and 40.[2] There is a higher incidence rate among Caucasians, followed by Blacks, Hispanics, and Asians to a lesser degree. Additionally, females are more predisposed to the disease than males. In the United States, the prevalence of MS is approaching 1 million.[3]

The initial case of COVID-19 was reported in December 2019, precipitating a swift global dissemination of the SARS-CoV-2 virus, resulting in widespread fatalities.[4] In the spring of 2020, the outbreak was declared a global pandemic. The disease was primarily categorized as a respiratory illness, leading to mild cases with upper/lower respiratory tract infections, and severe cases resulting in acute respiratory failure.[5] However, as knowledge about the disease mechanism evolved, it became evident that COVID-19 also affected other organ systems, including the cardiovascular, renal, central, and peripheral nervous systems, with neurologic complications being common.

During the early stage of the pandemic (from January 16, 2020, to February 19, 2020), a retrospective, observational case series reported that approximately 36.4% of the 214 hospitalized patients with COVID-19 presented with neurologic manifestations.[6] Demyelinating lesions in the brain, spinal cord, and optic nerve have been observed in case reports of SARS-CoV-2 patients, hinting at potential involvement in neuroimmune disorders like multiple sclerosis (MS).[7] Patients with chronic autoimmune neurological disorders such as multiple sclerosis are considered at high risk for serious complications.[8,9]

This review offers vital insights into the impact of COVID-19 on multiple sclerosis (MS), providing clinicians and researchers with an understanding of disease severity, outcomes, and management strategies. It illuminates the complex interplay between the immune system, viral invasion, and neurologic complications, to help guide clinical decision-making and enhancing patient care in this vulnerable population. By focusing on the risk of MS patients contracting COVID-19, the effects of disease-modifying therapies, and the clinical course, this paper contributes an overview of new and valuable information in the field.

Pathophysiology

The entry of SARS-CoV-2 into the host cell and subsequent disease development is highly complex. Upon viral attachment to the host cell, a cascade of events follows, including viral replication and systemic distribution.[10] The immune response of the host, coordinated through the complex interaction of innate and adaptive immune mechanisms, plays a pivotal role in eliminating the virus.

Patients with autoimmune disorders and those with compromised immune states are particularly vulnerable to adverse outcomes stemming from SARS-CoV-2 infection.[11] This susceptibility arises from the alteration of their immune defense mechanisms, rendering them more prone to infections and less responsive to medications. Consequently, these individuals exhibit an exaggerated inflammatory response that hampers their ability to effectively clear the virus and mount an adequate antibody response.

Pathophysiology of MS

Multiple sclerosis (MS) is an immune-mediated disease characterized by inflammation, demyelination, axonal loss, and delayed neurodegeneration.[1,12] The inflammatory response disrupts the blood-brain barrier, leading to the infiltration of immune cells, primarily triggered by T cells, and to a lesser degree, B cells.[12] Although the exact etiology remains inconclusive,[13] both genetic and environmental factors are thought to contribute to the diverse clinical presentation and rates of disease progression in MS patients.[14]

Autoimmunity is hypothesized to be triggered by an antigen, possibly a virus or bacteria. The Epstein-Barr virus is widely believed to be involved, and CD4+ T cells are activated in response to the antigen by antigen-presenting cells and B cells. Focal inflammation results in MS plaques, marked by edema, demyelination, and axonal injury. Environmental factors, such as geographic patterns and vitamin D deficiency, may also play a role in predisposing individuals to MS.[15] Clinically, the inflammatory response leads to disease relapse.

Pathophysiology of COVID-19

SARS-CoV-2 also triggers an inflammatory response. It is a positive-stranded RNA virus belonging to the coronaviridae family, genus beta coronavirus.[10] The virus is composed of 4 structural proteins: Spike (S), membrane (M), envelope (E), and nucleocapsid (N). The spike proteins (S1, S2) play a key role in invading host cells, utilizing the angiotensin-converting enzyme 2 (ACE2) receptor for entry.[10]

SARS-CoV-2 invasion into the CNS. SARS-CoV-2 attaches to angiotensin-converting enzyme 2 (ACE2) receptors located on the epithelial surface, which are present not only in the respiratory system but also in various organs, including the central nervous system.[16,17] ACE2 expression has been detected in pluripotent stem cell-derived neurons, predominantly located in neuronal cell bodies and to a lesser extent in dendrites and axons.[17] SARS-CoV-2 is thought to invade the CNS via the olfactory epithelium, which is supported by the detection of ACE2 and SARS-CoV-2 RNAs in the nasal cavity of COVID-19 patients.[18] In a cross-sectional study conducted in Milan, Italy, 33.9% reported either having a taste or olfactory disorder with 18.6% experiencing both.[18] SARS-CoV-2 invasion into the nasal epithelium through trans-synaptic spread as well as penetration of the blood-brain barrier may explain the prevalence of taste and olfactory disorders in COVID-19 patients.[18]

Chen et al demonstrated high levels of ACE2 expression in specific brain regions, such as the thalamus, choroid plexus, tuberomammillary bodies, raphe nuclei, and substantia nigra. ACE2 is highly expressed in neurons located in the posterior cingulate cortex and middle temporal gyrus, as well as in non-neuron cells like oligodendrocytes, astrocytes, and endothelial cells to a lesser extent. Low levels were found in the hippocampus and were undetectable in the prefrontal cortex.[19] Other proposed mechanisms of entry into the CNS include direct spread from the respiratory tract to the brainstem via mechanoreceptors and chemoreceptors.[17] However, more studies are needed to validate this.

Cytokine storm. Following viral entry and replication within the host cell, COVID-19 drives a widespread inflammatory response, releasing inflammatory cytokines such as interleukins, CXCL-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, tumor necrosis factor, and interferons.[10,20] Interleukins 1 and 6 are key players in driving the innate immune response's inflammation process.[20] This excessive inflammatory response and immune cell activation are referred to as a cytokine storm. Cytokines regulate the immune response and mediate the inflammatory process. Over-amplification of the immune reaction and excessive pro-inflammatory cytokine release, together, result in tissue damage and organ dysfunction.[21]

Viral Influence on MS

In general, MS patients are more susceptible to infections and tend to utilize more infection-related healthcare resources compared to the general population.[22] An acute infection can lead to worsened symptoms, causing a pseudo-flare of prior symptoms. The increased vulnerability to infections is attributed to factors such as the use of disease-modifying therapies (DMTs), disease-related disability, and underlying comorbidities that weaken the immune system. Hospitalization rates among MS patients are elevated, particularly in individuals with profound disabilities, older males, and those with lower socioeconomic status.[23]

The link between infectious etiologies, such as Epstein-Barr virus (EBV), and the development of MS has been explored with several mechanisms proposed including inflammation, molecular mimicry with activation of B/T cells and glial cells.[24]

A large cohort study of US military personnel was followed for 20 years and found a 32-fold increased risk of MS among those infected with EBV, indicating a significant association.[25] The high prevalence of EBV seropositivity in the general population suggests that additional risk factors and genetic factors may influence the pathogenic effects of this agent in the development of MS. Furthermore, an MS-associated virus like EBV might interact with SARS-CoV-2 and potentially impact MS progression through various mechanisms, including EBV or viral reactivation.[26,27]

Regarding COVID-19-induced MS, it has been proposed that the infection caused by coronaviruses may trigger the clinical manifestation of MS due to the virus's ability to invade the nervous system, leading to inflammation and demyelination.[28,29] SARS-CoV-2 has been detected in the cerebrospinal fluid of patients presenting with demyelination, supporting its potential to affect the central nervous system.[30]

Recent case reports have suggested that SARS-CoV-2 might be responsible for initiating the demyelination process in individuals who previously had no symptoms associated with nervous system disorders.[31-33] Additionally, some cases have reported MS-onset following non-mRNA COVID-19 vaccination.[34-37] MRI studies in these cases revealed a mix of old and new lesions, as well as classical demyelinating syndromes, suggesting that there may have been clinically latent diseases before vaccination.[37] These findings imply that the viral infection-induced inflammatory response might accelerate early mechanisms leading to the development of neurodegenerative processes, thereby triggering a first clinical event in individuals with pre-clinical MS.[29,37]

In contrast to the smaller, case-based investigations, a large-scale population-based study by Zarifkar et al[38] did not identify an increased frequency of new-onset MS between COVID-19-positive and COVID-19-negative individuals. Specifically, of their COVID-19-positive population, 14 out of 43 375 individuals developed MS 12 months after their positive test. Additionally, it is noteworthy that the study examined a range of neuroimmune disorders and found no alterations in the frequencies of multiple sclerosis, myasthenia gravis, or Guillain-Barré syndrome following occurrences of COVID-19, influenza, or bacterial pneumonia.

Clinical Course, Risk Factors, Management, and DMTs

The COVID-19 Infections in MS (COViMS) registry was established at the beginning of the pandemic to collect data on COVID-19 cases in individuals with MS.[40] Analysis of the COViMS registry data has revealed several factors associated with a severe clinical course of COVID-19 in MS patients. These factors include disability, older age, cardiovascular comorbidities, recent corticosteroid treatment, and Black race.[23,39,40] Other studies have corroborated similar trends.[16]

MS patients generally exhibit similar COVID-19 symptoms compared to the general population, and there is no evidence to suggest an increased risk of contracting SARS-CoV-2 in this group.[21] However, individuals with increased disability from MS are at a higher risk of severe COVID-19 infection.[16] MS patients with severe cases of COVID-19 tend to experience increased hospitalization rates, admissions to the intensive care unit (ICU), and a higher need for ventilatory assistance.[16]

The COViMS registry has also provided insights into how SARS-CoV-2 affects individuals with other demyelinating disorders, such as neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody disease (MOGAD).[39] The COViMS registry revealed that among 82 patients who died, 74 had MS compared to 8 with NMOSD. Among those with MS who died, 85% were hospitalized, 61% were admitted to the ICU, and 51% required ventilator support. For those patients using disease-modifying therapy, more deaths were reported for patients using the anti-CD20 therapy.[39] Interestingly, both MS and NMOSD patients using anti-CD20 therapy showed a higher number of reported deaths.[39]

Mortality rates of MS patients with COVID-19 were found to be 3.3% and 3.2% in separate studies using the COViMS registry and the New York COVID-19 Neuroimmunology Consortium (NYCNIC) registry, respectively.[23,41] Additionally, advanced age was found to be independently associated with COVID-19 disease severity in MS patients, with a 77% increased risk of mortality and a 30% increased risk of severe clinical outcomes with every 10-year increase in age.

Furthermore, race and gender were also identified as predictors of clinical disease course and severity. Male sex was associated with a 3-fold increased risk of mortality and a higher likelihood of hospitalization. Black patients with MS and COVID-19 did not have an increased risk of death, but they had a higher risk of hospitalization and over a 2-fold increased risk of ICU admission.[23]

Long-Haul

Regarding recovery and long-haul COVID-19-related symptoms in MS patients, individuals with prior significant disabilities appear to be most affected.[16] In a prospective and longitudinal cohort study, data from the United Kingdom Multiple Sclerosis Register showed that 29.7% of MS patients experienced prolonged symptoms lasting more than 1 month, and 12.4% experienced symptoms lasting more than 3 months.[42] Either new or worsened fatigue was the most common persistent symptom following the acute phase.[42] Other commonly reported symptoms were lower respiratory tract symptoms such as chest discomfort, cough or dyspnea, gastrointestinal symptoms, and ageusia/anosmia.[42] Prolonged symptoms were more prevalent among women and those who likely suffered from anxiety and or depression.[42]

Clinical management

In terms of clinical management, beyond providing necessary supportive care, it is imperative to address the mental well-being of patients, promote increased physical activity, and ensure proper nutrition. The early implementation of social distancing measures and lockdowns during the COVID-19 pandemic has led to heightened susceptibility to depression and anxiety among individuals with MS.[43]

Vitamin D deficiency has been identified as a potential predisposing factor for the development of MS.[43] It plays a role in the modulation of the immune system by regulating cytokine release and the functioning of lymphocytes. Notably, insufficient levels of vitamin D have been linked to unfavorable outcomes in MS, with associations detected during relapses as well. Studies have indicated a positive therapeutic effect of vitamin D supplementation in the context of COVID-19.[43] This supplementation has demonstrated a capacity to mitigate the severity of COVID-19, yielding lower rates of ICU admissions and improved survival rates.[43] Given these findings, a strong recommendation for vitamin D supplementation is warranted among individuals with MS. Particular attention is merited for those affected by COVID-19, emphasizing adequate supplementation as required.

Regarding prophylactic measures, the initial promise of tixagevimab-cilgavimab necessitated investigation.[44] A comprehensive meta-analysis involving 6 studies, focusing on organ transplant recipients and those in states of immunocompromise, unveiled the dual efficacy of tixagevimab-cilgavimab. This therapy exhibited a marked reduction in the risk of SARS-CoV-2 infection, accompanied by noteworthy reductions in both hospitalization rates and disease severity.[45] Additionally, tixagevimab-cilgavimab was shown to enhance antibody production in individuals undergoing therapies, leading to B cell depletion.[46] However, recent data underscores its inefficacy against newer COVID-19 variants. As a result, the U.S. Food and Drug Administration has withdrawn support for the use of tixagevimab-cilgavimab, effective as of January 26, 2023.[44]

Effects of disease-modifying therapy (DMT) and COVID-19

Approximately 70% of MS patients are on some form of disease-modifying therapy either with an immunomodulator or immunosuppressant.[43] In general, MS patients on disease-modifying therapies do not appear to be at an increased risk of contracting COVID-19. Some DMTs such as glatiramer acetate and interferons are believed to have some protection against SARS-COV2.[46,47] Both medications are believed to be effective in lowering the risk of COVID-19 by modulating the immune response from Th1 to Th2, resulting in an anti-inflammatory response.[43] Teriflunomide is also thought to have a protective effect by suppressing viral replication through its inhibitory effects on dihydroorotate dehydrogenase and pyrimidine synthesis.[43] The majority of reported cases of patients using Teriflunomide exhibit mild symptoms. Studies conducted on DMTs with dimethyl fumarate, natalizumab, and fingolimod, show low rates of disease severity or complications.[43] However, this does not hold for those on medications targeting CD20, such as Ocrelizumab and Rituximab.[16] A recent study demonstrated that patients with MS treated with anti-CD20 medications had an increased risk of COVID-19 infection compared to other DMTs such as interferons and glatiramer acetate.[47]

B-cells play a crucial role in humoral immunity and antigen presentation, stimulating T cells to produce cytokines and antibodies. Medications that target B cells, such as Ocrelizumab and Rituximab, were associated with increased rates of hospital admissions, including ICU admissions and mechanical ventilator use, compared to other DMTs.[16] Interestingly, in terms of disease severity and outcomes, patients on Rituximab had poorer outcomes compared to those on Ocrelizumab.[16]

Post-administration of COVID-19 vaccines, individuals diagnosed with multiple sclerosis (MS) undergoing treatment with ocrelizumab may exhibit a deficiency in antibody-mediated immunity. However, they demonstrate a sustained level of T-cell immunity analogous to that observed in the general population.[48] Notably, T-cell immunity has been established as a crucial defense mechanism against COVID-19 infection. It has been suggested that Rituximab has a stronger impact on the immune system compared to Ocrelizumab, and this difference appears to be based on dosage.[49] There are case reports of MS patients on Ocrelizumab without serious complications.[50,51] Simpson-Yap et al[52] demonstrated in an international clinician-reported study that Rituximab had the highest association with disease severity compared to other DMTs, including Ocrelizumab. This is likely due to its stronger affinity to the CD20 binding site. Anti-CD20 DMTs, as a group, were associated with higher risks of hospitalization and ICU admission, with the risk being higher with Rituximab.

A Swedish MS registry study also found similar findings. Among the 164 confirmed COVID-19 cases reviewed, 56.2% were on Rituximab, 13% on Natalizumab, 9.3% on Dimethyl fumarate, and 3.4% on Interferon beta and Fingolimod.[53] Rituximab had higher rates of hospitalization, whereas Natalizumab showed a statistically significant reduction in the odds of hospitalization compared to Rituximab. Glatiramer, Fingolimod, and Cladribine, when pooled together, were associated with a 76% reduction in the odds of hospitalization. Fingolimod and Alemtuzumab were not associated with hospitalization. Each additional year of Rituximab therapy increased the odds of hospitalization. Ocrelizumab constituted only 1.7% of the cases, but when anti-CD20 therapies were combined, they were associated with a 3-fold increased odds of hospitalization.

On the other hand, Longinetti et al reported an increased risk of hospitalization for MS patients on Rituximab in another Swedish registry, but the risk of poor COVID-19 outcomes was small and insignificant after adjusting for confounders like socioeconomic status, comorbidities, and MS severity. The risk of hospitalization also diminished when adjusted with the use of Dimethyl fumarate or Fingolimod as reference.[54] These findings might be due to a lack of power and the lower medication dosage used in Sweden.

Regarding other DMTs such as Alemtuzumab and Cladribine, a study by Dalla Costa et al utilized data from the European registry "Remote Assessment of Disease and Relapse in Central Nervous System Disorders" (RADAR-CNS) and found that MS patients had a higher likelihood of contracting COVID-19 using these medications compared to injectables. In general, both Cladribine and Alemtuzumab are associated with mild infections.[43,55]

Several studies have highlighted an elevated susceptibility to COVID-19 infection among multiple sclerosis (MS) patients undergoing disease-modifying therapy. However, a noteworthy study by Cross et al, utilizing the phase 3 ALITHIOS database, revealed a contrasting trend. They observed a diminished risk of COVID-19 infection among patients diagnosed with relapsing multiple sclerosis (RMS) and undergoing treatment with Ofatumumab, a B-cell-depleting therapy.[56] Furthermore, individuals administered Ofatumumab who contracted COVID-19 typically manifested mild symptoms and demonstrated a favorable recovery trajectory.[56]

Given that DMTs reduce the chances of developing new symptoms, it is recommended to withhold DMTs for 4 weeks in MS patients with severe COVID-19 infection. However, caution is advised for those on Sphingosine-1-phosphate (S1P) therapy and Natalizumab.[16,57]

Vaccines

Vaccines are designed to elicit an immune response, but they also carry a risk of immunological adverse events.[58] Previous studies on various vaccines, such as influenza, Hepatitis A or B, HPV, MMR, and DTaP, have shown a rare risk of demyelination after vaccination.[59,60] COVID-19 vaccines were first authorized for emergency use in December 2020 and are based on mRNA coding for the spike protein (BNT-162b2, mRNA-1273), recombinant protein (Novavax), or a viral vector (J&J).[61] The most common side effects reported with COVID-19 vaccines include flu-like symptoms and injection site reactions.[62] However, there have been cases of symptoms affecting the central nervous system.[63]

Patients with multiple sclerosis represent a unique population due to the relapsing-remitting course of their disease and the likelihood of being on a DMT. A systematic review of case reports and case series found 32 occurrences of CNS demyelination following vaccination against SARS-CoV-2, with the majority of cases occurring after the initial vaccine dose.[64] The

demyelinating syndromes were more commonly seen with the mRNA vaccine, and the most common presentations were an MS-like pattern or transverse myelitis.[64] These MS-like events encompassed both new-onset and relapse of symptoms. Importantly, over half of the cases had a documented history of immune-mediated disease, and 11 of these diseases affected the CNS. One study identified risk factors associated with vaccine-induced MS, including the use of an mRNA vaccine, low serum vitamin D, positive EBNA1-IgG, and a family history of MS.[65] A meta-analysis of approximately 15 000 patients with MS who were vaccinated against SARS-CoV-2 found a low prevalence of relapse at 1.9%, signifying a low risk of adverse events among patients with MS.[66] Despite the possibility of disease relapse after vaccination, patients with MS demonstrated a high willingness to be vaccinated, as the benefits of vaccination outweigh the potential risks of complications from infection.[67]

The effectiveness of the vaccine in patients with MS while on immunomodulatory medication is also a topic of concern. A systematic review found that the ability of the vaccine to induce a humoral response in patients with MS was significantly decreased when they were taking a sphingosine-1 phosphate modulator or CD-20 monoclonal antibodies compared to other therapies.[68] Sphingosine-1 phosphate modulators, such as fingolimod, reduce the number of circulating lymphocytes by interfering with trafficking out of the lymph nodes, while CD-20 monoclonal antibodies, such as rituximab, deplete CD-20 positive B cells, blunting the immune system's ability to produce immunoglobulins.[43] In this study, mRNA vaccines were more effective in producing an immune response in patients with MS. The timing of anti-CD20 treatment to vaccination is crucial, as those who received anti-CD20 therapy within 6 months of their vaccination showed a decreased immunological response.[69] A third dose of the COVID-19 vaccine is safe and beneficial, especially for patients with MS on anti-CD20 therapy, providing more benefit compared to those on fingolimod, a sphingosine-1 phosphate modulator.[70,71] A case series supported these findings, demonstrating that MS patients on anti-CD20 therapy had a higher incidence of COVID-19 after only 2 vaccine doses compared to those on fingolimod.[71] Therefore, those on anti-CD20 therapy should be considered for revaccination.

Conclusion

COVID-19 has had a significant impact on the field of medicine and has also affected the management of certain neurological disorders, including multiple sclerosis (MS). In the early phases of the pandemic, there was a lack of understanding regarding how COVID-19 would affect MS patients. Given the comorbidities and immunosuppressed state of many MS patients, there was concern about an increased risk of hospitalization, disease severity, and mortality.

However, with the development of vaccines, prophylactic therapies, antivirals, and the implementation of social distancing measures, there has been a notable reduction in hospitalization rates, disease severity, and mortality associated with COVID-19. Despite this progress, certain special populations, such as those on therapy with anti-CD20, older age, and those with existing MS severity or disability, remain at higher risk.

Ongoing research and data collection are essential, especially with the presence of new mutations of SARS-CoV-2. Despite the uncertainties, the data presented throughout various studies during the pandemic indicate that continued care for MS patients can be safely provided without feared complications. Continued surveillance of individuals with MS and their encounters with the SARS-CoV-2 virus remains crucial, as it could offer valuable insights for customizing treatments against future viruses and enhancing our understanding of how viruses affect MS patients. This knowledge has the potential to illuminate disease mechanisms, thereby opening avenues for innovative therapeutic strategies to address this condition.

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REFERENCES

1. Ward M, Goldman MD. Epidemiology and pathophysiology of multiple sclerosis. *Continuum (Minneap Minn)*. 2022;28:988-1005.
2. Małecka I, Przybek-Skrzypecka J, Kurowska K, Mirowska-Guzel D, Członkowska A. Clinical and laboratory parameters by age for patients diagnosed with multiple sclerosis between 2000 and 2015. *Neurol Neurochir Pol*. 2021;55:387-393.
3. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: a population-based estimate using health claims data. *Neurology*. 2019;92:e1029-e1040.
4. Li J, Lai S, Gao GF, Shi W. The emergence, genomic diversity and global spread of SARS-COV-2. *Nature*. 2021;600:408-418.
5. Hu W, Chen X, He B, et al. Clinical characteristics of 16 patients with COVID-19 infection outside of Wuhan, China: a retrospective, single-center study. *Ann Transl Med*. 2020;8:642.
6. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77:683-690.
7. MacDougall M, El-Hajj Sleiman J, Beauchemin P, Rangachari M. SARS-CoV-2 and multiple sclerosis: potential for disease exacerbation. *Front Immunol*. 2022;13:871276.
8. Al-Ramadan A, Rabab'h O, Shah J, Gharaibeh A. Acute and post-acute neurological complications of COVID-19. *Neurol Int*. 2021;13:102-119.
9. Mainali S, Darsie ME. Neurologic and neuroscientific evidence in aged COVID-19 patients. *Front Aging Neurosci*. 2021;13:648662.
10. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. *Clin Immunol*. 2020;215:108427.
11. DeWolf S, Laracy JC, Perales MA, Kamboj M, Van Den Brink MRM, Vardhana S. SARS-CoV-2 in immunocompromised individuals. *Immunity*. 2022;55:1779-1798.
12. Dobson R, Giovannoni G. Multiple sclerosis – a review. *Eur J Neurol*. 2019; 26:27-40.
13. UpToDate. Pathogenesis and epidemiology of multiple sclerosis. 2023. Accessed August 14, 2023. https://www.uptodate.com/contents/pathogenesis-and-epidemiology-of-multiple-sclerosis?search=multiple%20sclerosis&topicRef=1689&source=see_link
14. Rousseau BA, Bhaduri-McIntosh S. Inflammation and Epstein–Barr virus at the crossroads of multiple sclerosis and post-acute sequelae of COVID-19 infection. *Viruses*. 2023;15:949.
15. Tafti D, Ehsan M, Xixis KL. Multiple sclerosis. *StatPearls*. StatPearls Publishing; 2023. Accessed August 14, 2023. http://www.ncbi.nlm.nih.gov/books/NBK499849/
16. Chaudhry F, Jageka C, Levy PD, Cerghet M, Lisak RP. Review of the COVID-19 risk in multiple sclerosis. *J Cell Immunol*. 2021;3:68-77.
17. Xu J, Lazartigues E. Expression of ACE2 in human neurons supports the neuroinvasive potential of COVID-19 virus. *Cell Mol Neurobiol*. 2022;42:305-309.
18. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infections: a cross-sectional study. *Clin Infect Dis*. 2020;71:889-890.
19. Chen R, Wang K, Yu J, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains. *Front Neurol*. 2021; 11:573095.
20. Parasher A. COVID-19: current understanding of its pathophysiology, clinical presentation and treatment. *Postgrad Med J*. 2021;97:312-320.
21. Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. *BMJ*. 2020;371:m3862.
22. Brownlee W, Bourdette D, Broadley S, Killestein J, Ciccarelli O. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. *Neurology*. 2020;94:949-952.
23. Salter A, Fox RJ, Newsome SD, et al. Outcomes and risk factors associated with SARS-CoV-2 infection in a North American registry of patients with multiple sclerosis. *JAMA Neurol*. 2021;78:699-708.
24. Meier UC, Cipian RC, Karimi A, Ramasamy R, Middeldorp JM. Cumulative roles for Epstein-Barr virus, human endogenous retroviruses, and human herpes virus-6 in driving an inflammatory cascade underlying MS pathogenesis. *Front Immunol*. 2021;12:757302.
25. Bjornevik K, Cortese M, Healy BC, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science*. 2022;375:296-301.
26. Waubant E, Lucas R, Mowry E, et al. Environmental and genetic risk factors for MS: an integrated review. *Ann Clin Transl Neurol*. 2019;6:1905-1922.
27. Bellucci G, Rinaldi V, Buscarinu MC, et al. Multiple sclerosis and SARS-CoV-2: has the interplay started? *Front Immunol*. 2021;12:755333.
28. Schirinzi T, Landi D, Liguori C. COVID-19: dealing with a potential risk factor for chronic neurological disorders. *J Neurol*. 2021;268:1171-1178.
29. Dziedzic A, Saluk-Bijak J, Miller E, Niemcewicz M, Bijak M. The impact of SARS-CoV-2 infection on the development of neurodegeneration in multiple sclerosis. *Int J Mol Sci*. 2021;22:1804.
30. Domingues RB, Mendes-Correa MC, De Moura Leite FBV, et al. First case of SARS-COV-2 sequencing in cerebrospinal fluid of a patient with suspected demyelinating disease. *J Neurol*. 2020;267:3154-3156.
31. Fragoso YD, Pacheco FAS, Silveira GL, Oliveira RA, Carvalho VM, Martimbianco ALC. COVID-19 in a temporal relation to the onset of multiple sclerosis. *Mult Scler Relat Disord*. 2021;50:102863.
32. Zanin L, Saraceno G, Panciani PP, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neurochir (Wien)*. 2020;162:1491-1494.
33. Palao M, Fernández-Díaz E, Gracia-Gil J, Romero-Sánchez CM, Díaz-Maroto I, Segura T. Multiple sclerosis following SARS-CoV-2 infection. *Mult Scler Relat Disord*. 2020;45:102377.
34. Khayat-Khoei M, Bhattacharyya S, Katz J, et al. COVID-19 mRNA vaccination leading to CNS inflammation: a case series. *J Neurol*. 2022;269: 1093-1106.
35. Havla J, Schultz Y, Zimmermann H, Hohlfeld R, Danek A, Kümpfel T. First manifestation of multiple sclerosis after immunization with the Pfizer-BioNTech COVID-19 vaccine. *J Neurol*. 2022;269:55-58.
36. Fujimori J, Miyazawa K, Nakashima I. Initial clinical manifestation of multiple sclerosis after immunization with the Pfizer-BioNTech COVID-19 vaccine. *J Neuroimmunol*. 2021;361:577755.
37. Toljan K, Amin M, Kunchok A, Ontaneda D. New diagnosis of multiple sclerosis in the setting of mRNA COVID-19 vaccine exposure. *J Neuroimmunol*. 2022;362:577785.
38. Zarifkar P, Peinkhofer C, Benros ME, Kondziella D. Frequency of neurological diseases after COVID-19, influenza A/B and bacterial pneumonia. *Front Neurol*. 2022;13:904796.
39. Newsome SD, Cross AH, Fox RJ, et al. Covid-19 in patients with neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein antibody disease in North America: from the COViMS registry. *Neurol Neuroimmunol Neuroinflamm*. 2021;8:e1057.

40. Home. COViMS Registry. 2022. Accessed July 11, 2023. https://www.covims.org

41. Klineova S, Harel A, Straus Farber R, et al. Outcomes of COVID-19 infection in multiple sclerosis and related conditions: one-year pandemic experience of the multicenter New York COVID-19 Neuroimmunology Consortium (NYCNIC). Mult Scler Relat Disord. 2021;55:103153.

42. Garjani A, Middleton RM, Nicholas R, Evangelou N. Recovery from COVID-19 in multiple sclerosis: a prospective and longitudinal cohort study of the United Kingdom multiple sclerosis register. *Neurol Neuroimmunol Neuroinflamm*. 2022;9:e1118.

43. Muñoz-Jurado A, Escribano BM, Agüera E, Caballero-Villarraso J, Galván A, Túnez I. SARS-CoV-2 infection in multiple sclerosis patients: interaction with treatments, adjuvant therapies, and vaccines against COVID-19. *J Neurol*. 2022;269:4581-4603.

44. Immune Deficiency Foundation. Update - Evusheld no longer authorized in the U.S. Immune Deficiency Foundation. Published January 26, 2023. Accessed February 24, 2023. https://primaryimmune.org/news/update-astrazenecas-evusheld-authorized-covid-19-preventative-immunocompromised

45. Soeroto AY, Yanto TA, Kurniawan A, Hariyanto TI. Efficacy and safety of tixagevimab-cilgavimab as pre-exposure prophylaxis for COVID-19: a systematic review and meta-analysis. *Rev Med Virol*. 2023;33:e2420.

46. Conte WL, Golzarri-Arroyo L. Tixagevimab and Cilgavimab (Evusheld) boosts antibody levels to SARS-CoV-2 in patients with multiple sclerosis on b-cell depleters. *Mult Scler Relat Disord*. 2022;63:103905.

47. Reder AT, Centonze D, Naylor ML, et al. Covid-19 in patients with multiple sclerosis: associations with disease-modifying therapies. *CNS Drugs*. 2021;35:317-330.

48. Habek M, Željko C, Savić Mlakar A, et al. Humoral and cellular immunity in convalescent and vaccinated COVID-19 people with multiple sclerosis: effects of disease modifying therapies. *Mult Scler Relat Disord*. 2022;59:103682.

49. Smith TE, Madhavan M, Gratch D, et al. Risk of COVID-19 infection and severe disease in MS patients on different disease-modifying therapies. *Mult Scler Relat Disord*. 2022;60:103735.

50. Novi G, Mikulska M, Briano F, et al. COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role? *Mult Scler Relat Disord*. 2020;42:102120.

51. Hughes R, Whitley L, Fitovski K, et al. COVID-19 in ocrelizumab-treated people with multiple sclerosis. *Mult Scler Relat Disord*. 2021;49:102725.

52. Simpson-Yap S, Pirmani A, Kalincik T, et al. Updated results of the COVID-19 in MS global data sharing initiative: anti-CD20 and other risk factors associated with COVID-19 severity. *Neurol Neuroimmunol Neuroinflamm*. 2022;9:e200021.

53. Spelman T, Forsberg L, McKay K, Glaser A, Hillert J. Increased rate of hospitalisation for COVID-19 among rituximab-treated multiple sclerosis patients: a study of the Swedish multiple sclerosis registry. *Mult Scler*. 2022;28:1051-1059.

54. Longinetti E, Bower H, McKay KA, et al. COVID-19 clinical outcomes and DMT of MS patients and population-based controls. *Ann Clin Transl Neurol*. 2022;9:1449-1458.

55. Jack D, Damian D, Nolting A, Galazka A. COVID-19 in patients with multiple sclerosis treated with cladribine tablets: an update. *Mult Scler Relat Disord*. 2021;51:102929.

56. Cross AH, Delgado S, Habek M, et al. COVID-19 outcomes and vaccination in people with relapsing multiple sclerosis treated with ofatumumab. *Neurol Ther*. 2022;11:741-758.

57. Hollen C, Bernard J. Multiple sclerosis management during the COVID-19 pandemic. *Curr Neurol Neurosci Rep*. 2022;22:537-543.

58. Nakayama T. Causal relationship between immunological responses and adverse reactions following vaccination. *Vaccine*. 2019;37:366-371.

59. Karussis D, Petrou P. The spectrum of post-vaccination inflammatory CNS demyelinating syndromes. *Autoimmun Rev*. 2014;13:215-224.

60. Agmon-Levin N, Kivity S, Szyper-Kravitz M, Shoenfeld Y. Transverse myelitis and vaccines: a multi-analysis. *Lupus*. 2009;18:1198-1204.

61. CDC. COVID-19 vaccination. Centers for Disease Control and Prevention. Published February 11, 2020. Accessed August 14, 2023. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/overview-COVID-19-vaccines.html

62. Briggs FBS, Mateen FJ, Schmidt H, et al. Covid-19 vaccination reactogenicity in persons with multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2022;9:e1104.

63. Allahyari F, Molaee H, Hosseini Nejad J. Covid-19 vaccines and neurological complications: a systematic review. *Z Naturforsch C J Biosci*. 2022;78:1-8.

64. Ismail II, Salama S. A systematic review of cases of CNS demyelination following COVID-19 vaccination. *J Neuroimmunol*. 2022;362:577765.

65. Alluqmani M. New-onset multiple sclerosis post-COVID-19 vaccination and correlation with possible predictors in a case-control study. *Cureus*. 2023;15:e36323.

66. Stefanou MI, Palaiodimou L, Theodorou A, et al. Safety of COVID-19 vaccines in multiple sclerosis: a systematic review and meta-analysis. *Mult Scler*. 2023;29:585-594.

67. Yazdani A, Mirmosayyeb O, Ghaffary EM, Hashemi MS, Ghajarzadeh M. COVID-19 vaccines and patients with multiple sclerosis: willingness, unwillingness, and hesitancy: a systematic review and meta-analysis. *Neurol Sci*. 2022;43:4085-4094.

68. Gombolay GY, Dutt M, Tyor W. Immune responses to SARS-CoV-2 vaccination in multiple sclerosis: a systematic review/meta-analysis. *Ann Clin Transl Neurol*. 2022;9:1321-1331.

69. Wu X, Wang L, Shen L, Tang K. Response of COVID-19 vaccination in multiple sclerosis patients following disease-modifying therapies: a meta-analysis. *eBioMedicine*. 2022;81:104102.

70. König M, Torgauten HM, Tran TT, et al. Immunogenicity and safety of a third SARS-CoV-2 vaccine dose in patients with multiple sclerosis and weak immune response after COVID-19 vaccination. *JAMA Neurol*. 2022;79:307-309.

71. Januel E, De Seze J, Vermersch P, et al. Post-vaccine COVID-19 in patients with multiple sclerosis or neuromyelitis optica. *Mult Scler*. 2022;28:1155-1159.