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CNS autoimmune disorders and COVID-19

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CNS autoimmune disorders and COVID-19

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Editorial: CNS autoimmune disorders and COVID-19

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Editorial on the Research Topic
CNS autoimmune disorders and COVID-19

Acute autoimmune disorders involving the central nervous system (CNS) are a group of diseases that occur when the immune system attacks and damages brain and spinal cord cells and tissues. neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein antibody disease (MOGAD) and multiple sclerosis (MS) are some examples of CNS autoimmune disorders (1). COVID-19 is a highly contagious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and belongs to the Coronaviridae family.

Since late 2019, COVID-19 has been spreading globally and has affected all people around the world (2). COVID-19 may increase the risk of developing neurological symptoms, such as headaches, confusion, ageusia, and anosmia (3), as well as some neurological disorders, like encephalopathy, stroke, seizures, hypoxic/ischemic brain injury, and a number of CNS autoimmune diseases (4). On the other hand, COVID-19 infection can deteriorate the pre-existing neurological diseases in affected individuals (5, 6).

With respect to CNS autoimmune disorders, several reports have been published on individuals developing different forms of autoimmune encephalitis following COVID-19 infection (7). These include patients with anti-*N*-Methyl-D-Aspartate Receptor encephalitis, anti-Myelin oligodendrocyte glycoprotein (MOG) antibody encephalitis, acute disseminated encephalomyelitis (ADEM), as well as other variants of autoimmune encephalitis (7, 8). Moreover, COVID-19 has been shown to cause demyelinating diseases of CNS in a number of reports (8).

Additionally, acute inflammatory demyelinating polyneuropathy (AIDP) is one of the commonly reported autoimmune diseases after COVID-19 infection (9). Guillain-Barré syndrome (GBS) is probably the most frequent subtype of AIDP reported among these patients and presents with muscle weakness, paralysis, and impairments in coordination and balance which could have devastating outcomes if not treated urgently (8). Other forms of polyneuropathy have also been reported among affected individuals (8).

Lastly, COVID-19 has been shown to exacerbate preexisting neurological conditions (5, 6). The immune response to the virus may further worsen the symptoms of conditions such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, epilepsy, and stroke probably in the setting of increased inflammation (6, 7). Specifically, with regards to multiple sclerosis, this is explained by alterations in the T cell counts during the disease course as well as fluctuations in body temperature that can worsen some neurological symptoms in these patients (6).

Another relevant area that has been investigated is the susceptibility of individuals suffering from neurological diseases or taking immunosuppressive/immunomodulatory medications to COVID-19 and their disease outcome. Patients taking anti-CD20 medications, which deplete B-cells, may be more prone to contract COVID-19 although it may not necessarily increase rates of hospitalization (9).

COVID-19 can affect the central nervous system through a variety of routes (10). In some individuals, SARS-CoV-2 may trigger an overactive immune response of Th1, Th2, NK cell, DC, and elevated levels of pro-inflammatory cytokines of IL-1β, IL-2, IL-6, IL-8, IL-12, IL-17 that results in the development of autoantibodies against the CNS. These autoantibodies can attack the protective myelin coating of the nerves, resulting in inflammation and damage. In addition, the olfactory bulb is another route that SARS-CoV-2 can pass, cross the blood-brain barrier (BBB), and infect the CNS (10). Even though there is increasing evidence linking COVID-19 and the autoimmune diseases of the CNS, more research is required to better understand the mechanisms that underlay this relationship and to determine whether or not COVID-19 contributes to the development of autoimmune diseases of the CNS.

The development of vaccines against COVID-19 has been the most important tool to fight the COVID-19 pandemic and decrease the disease severity, hospitalization rates, and mortality (11). However, there are some reports on neurological complications of these vaccines (12). The majority of these complications are mild and transient, such as headaches, while a small number of people may develop more serious side effects (13). These include cerebral sinus venous thrombosis, Bell's palsy, transverse myelitis, and GBS (14). Of note, the evidence on these complications comes mostly from case reports which do not provide strong evidence regarding this association (14).

In this issue, eleven interesting studies have presented that focus on CNS autoimmune diseases and COVID-19 infection, as outlined below.

Lotan et al. investigated the risk of CNS demyelinating diseases following COVID-19 infection through a systematic review. They showed that the risk of developing these diseases or experiencing relapses in the setting of COVID-19 infection remains relatively low with a favorable outcome. Elizalde-Díaz et al. further explained the relationship between inflammatory and humoral immune markers activated through COVID-19 infection and their effect on neural cells and subsequent neurological complications seen among some patients.

Czarnowska et al. reported on the safety of the COVID-19 vaccine among patients with MS on disease-modifying therapies and found overall favorable outcomes with low risk. On the other hand, three case studies reported on autoimmune complications of COVID-19 vaccines, including a case of multiple autoimmune syndromes in Poli et al. study, a case of immune thrombotic thrombocytopenia with cerebral venous thrombosis and hemorrhage in Chen et al. study, a case of acute disseminated encephalomyelitis by Bastide et al., and a patient with NMO reported by Ghelmez et al.. Moreover, Rinaldi et al. reported six patients with CNS inflammatory demyelinating events (two acute transverse myelitis, three multiple sclerosis, and one NMOSD) following COVID-19 infection.

The humoral response to COVID-19 vaccines and immunogenicity among patients with pre-existing CNS autoimmune disorders was assessed by three studies. Dominelli et al. showed that disease-modifying therapies, specifically depleting/sequestering-out treatments, lower the humoral response to COVID-19 vaccines, while cellular responses are still achieved. Similarly, van Dam et al. looked at the humoral response to the vaccine among patients with MS who had contracted COVID-19 before, and found increased humoral responses in patients without anti-CD20 therapies, but decreased responses among those treated with ocrelizumab. Lastly, Sedaghat et al. studied a group of patients with multiple sclerosis who had remained seronegative following two doses of inactivated COVID-19 vaccines and suggested adenoviral vector or mRNA-based vaccines may be a better choice as the third dose in these cases.

In conclusion, the current evidence demonstrates how the COVID-19 pandemic has led to the development of CNS autoimmune diseases such as MS, NMOSD, autoimmune encephalitis, and AIDP. These complications, however, remain relatively infrequent despite the large number of people affected by COVID-19. On the other hand, patients with pre-existing neurological disorders are affected, both with deterioration/relapse of their symptoms and with the increased risk of developing a more severe infection in the setting of immunosuppressive/immunomodulatory therapies. Of note, the current evidence on this topic is still limited and warrants further studies on larger populations with prospective designs. Lastly, the COVID-19 vaccine has shown to be safe and very effective in decreasing disease contraction, severity, and mortality, although it rarely can lead to CNS autoimmune disorders. The vaccination strategies among patients on disease-modifying therapies is another challenging topic that requires further investigation.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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Multiple Autoimmune Syndromes Including Acute Disseminated Encephalomyelitis, Myasthenia Gravis, and Thyroiditis Following Messenger Ribonucleic Acid-Based COVID-19 Vaccination: A Case Report

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The global pandemic has resulted from the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19). To control the spread of the pandemic, SARS-CoV-2 vaccines have been developed. Messenger ribonucleic acid (mRNA)-based COVID-19 vaccines have been the most widely used. We present the case of a 65-year-old patient, who was diagnosed with acute disseminated encephalomyelitis, ocular myasthenia gravis, and autoimmune thyroiditis, following his third mRNA COVID-19 vaccination. On admission, the patient showed mild left-sided hemiparesis, contralateral dissociated sensory loss, dizziness, and right-sided deafness. Brain MRI revealed multiple acute inflammatory contrast-enhancing periventricular and brainstem lesions with involvement of vestibulo-cerebellar tract and cochlear nuclei. Despite steroid pulse and intravenous immunoglobulin therapy, clinical symptoms and MRI lesions worsened, and additional signs of ocular myasthenia gravis and elevated but asymptomatic thyroid antibodies developed. After repeated plasma exchange, all clinical symptoms resolved. This is, to the best of our knowledge, the first case report of multiple autoimmune syndromes triggered by COVID-19 vaccination. The rare occurrence of such treatable autoimmune complications should not question the importance of vaccination programs during the COVID-19 pandemic.

Keywords: multiple autoimmune syndrome, ADEM, thyroiditis, myasthenia gravis, mRNA-based COVID-19 vaccines

INTRODUCTION

Besides specific vaccine complications (such as vaccine-induced thrombotic thrombocytopenia after vector-based COVID-19 vaccines), the association between new-onset autoimmune disease and vaccination could not be established yet, most likely due to low incidence. However, cases of vaccine-triggered autoimmune phenomena have been reported, and different mechanisms have been suggested (molecular mimicry, production of autoantibodies, and vaccine adjuvants) (1). Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease

that affects multiple areas of the central nervous system and typically presents with multifocal neurologic symptoms. It is commonly considered a monophasic disease with a rare recurrent or multiphasic variant (2). Up to three-quarters of ADEM events are associated with viral infections (3). Prior immunizations may also trigger ADEM events (4). A causal relationship between inactivated and mRNA SARS-CoV-2 vaccination has been reported (5–8). Myasthenia gravis due to acetylcholine receptor (AChR) autoantibodies, which prevent transmission of the excitatory cascade at the neuromuscular junction during muscle contraction, maybe rarely, also induced by mRNA COVID-19 vaccination (9). Likewise, cases of autoimmune thyroiditis have been described following exposure to inactivated and mRNA-based SARS-CoV-2 vaccines (10).

We report a patient, who developed all of these three autoimmune disorders shortly after being vaccinated for SARS-CoV-2.

CASE DESCRIPTION

A 65-year-old male patient was referred for the subacute onset of paresis of the left arm, followed by loss of pain and temperature sensation on the right side of the body, as well as right-sided deafness with vertigo, 3 days after receiving the third dose of the mRNA-based Pfizer-BioNTech COVID-19 vaccine, without any acute allergic reactions.

His medical history was relevant for multiphasic ADEM, with two previous clinical episodes, 10 and 11 years prior to this admission. In the first event, the patient manifested mild right-sided sensorimotor hemiparesis and Th11/Th12 paraplegia with urinary incontinence in the second event. At that time, cerebral and spinal cord magnetic resonance imaging (MRI) showed multiple T2-weighted hyperintense lesions involving supratentorial areas and, respectively, the spinal cord, all with T1 contrast enhancement. Cerebrospinal fluid (CSF) showed lymphocytic pleocytosis (50 and 7 cells/mm^3, respectively), while protein and glucose levels were within reference ranges. Oligoclonal banding was not present in both events. Confirming the diagnosis of ADEM, stereotactic brain biopsy showed typical perivenous inflammatory demyelination. The patient fully recovered under intravenous high-dose corticosteroids both times. A Follow-up MRI of the brain solely showed minor periventricular white matter sequelae; spinal cord lesions were completely resolved.

The patient's family history was positive for Graves' disease by a daughter; further (auto)immune disorders or neurological diseases were denied.

On the current admission, the patient was alert and oriented and presented mild left-sided hemiparesis (MRC 4/5) with contralateral dissociated sensory loss, and right-sided vestibulocochlear nerve deficit. Brain MRI revealed acute inflammatory gadolinium-enhancing lesions on the right cerebellar peduncle, as well as pons and medulla oblongata. CSF analysis showed lymphocytic pleocytosis (54 cells/mm^3), while protein and glucose levels were normal. Oligoclonal bands were searched in serum and CSF by isoelectric focusing, with negative results (type 1 pattern). Screening for bacterial, viral, and fungal neuro infections was negative. Tests were also negative for antibodies targeting antigens associated with demyelinating disorders of the central nervous system (myelin oligodendrocyte protein and aquaporin-4), as well as onconeural-, and anti-ganglioside antibodies. The CSF cytological analysis excluded circulating malignant cells. Biochemical serum markers for sarcoidosis (angiotensin-converting enzyme and soluble interleukin-2 receptor) were unremarkable, and CD4/CD8 ratio in CSF and bronchoalveolar lavage were not elevated. Interleukin-10 in CSF was normal, and chemokine CXC ligand 13 slightly increased. Complete blood count and markers of systemic autoimmunity (including antinuclear, extractable nuclear antigen, anti-neutrophil cytoplasmic, and antiphospholipid antibodies, as well as complement C3 and C4) were normal/negative.

The patient was treated with high-dose intravenous methylprednisolone (1 g daily) for five days. Due to non-response, intravenous immunoglobulin therapy with a total dose of 2 g/kg, fractionated in 5 days, was started. Rapid clinical deterioration with the development of severe left-sided hemiparesis (MRC 2/5), hemiataxia, and major difficulties to walk was accompanied by new periventricular and progressive infratentorial and upper cervical spinal cord contrast-enhancing lesions on follow-up MRI (**Figure 1**).

Furthermore, the patient developed fluctuating binocular horizontal diplopia and ptosis of the right eye, with worsened toward the end of the day. Diagnostic pyridostigmine (60 mg orally) did not improve ocular symptoms within a 1-h observation period. Immunologic testing showed elevated anti-AChR antibody titers (2.1 nmol/L, normal range is <0.4). Autoantibodies against muscle-specific kinase and titin were negative. No thymoma was detected on chest computed tomography (CT). The patient was newly diagnosed with ocular myasthenia gravis and started on oral pyridostigmine 90 mg twice a day.

On further laboratory investigations, positive anti-thyroglobulin antibodies (21.4 IU/ml, normal range is <4.5), anti-thyroid peroxidase antibodies (197.9 KU/L, normal range is <60), and anti-thyroid stimulating hormone (TSH) receptor autoantibodies (2.09 IU/L, normal range is 1.75) were detected. Thyroid function (TSH, triiodothyronine, and thyroxine), however, was normal, with no past medical history of thyroid disease. Thyroid ultrasonography was normal. Subacute thyroiditis was first diagnosed based on the patient's laboratory findings.

Considering the clinical worsening and the development of multiple autoimmune disorders despite treatment with corticosteroids and intravenous immunoglobulins, plasmapheresis was indicated. Seven plasma exchanges were conducted within 13 days. The hemiparesis improved, and the patient regained walking ability. Follow-up MRI brain and spinal cord scans after the third plasma exchange already revealed reduced lesion size and contrast enhancement. Ocular myasthenic symptoms resolved completely. Anti-thyroid and anti-AChR autoantibodies were no longer detectable. The patient was referred to rehabilitation, where clinical status

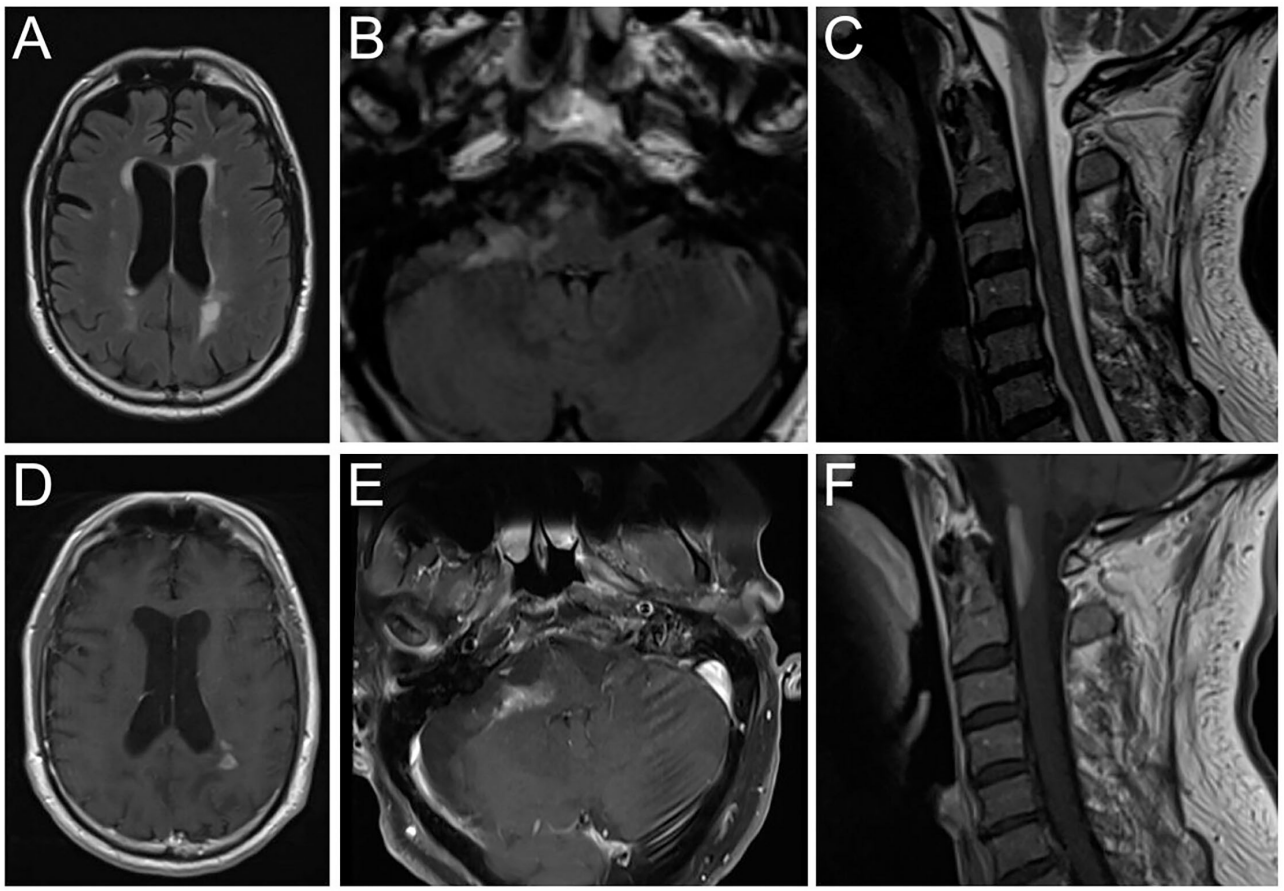

FIGURE 1 | Brain magnetic resonance imaging showing FLAIR hyperintense lesions **(A–C)** and T1 contrast-enhancement **(D–F)** in the periventricular white matter **(A,D)**, right cerebellar peduncle **(B,E)** and medulla oblongata/upper cervical spinal cord **(C,F)**. FLAIR, Fluid attenuated inversion recovery.

further improved until 1 month after plasma exchange (three months after onset).

DISCUSSION

Our patient met the diagnostic criteria for ADEM set by the International Pediatric MS Study Group (2), and alternative diagnoses, such as infectious or another autoimmune encephalitis, were excluded. ADEM, following vaccination, is a well-known entity and has been reported after mRNA SARS-CoV-2 vaccination (Moderna and BioNTech/Pfizer), even among older adults such as our patient (5–7), but also after inactivated vaccine (Sinovac) (8). Previously reported cases of vaccination-triggered ADEM had an excellent response to systemic corticosteroids and/or intravenous immunoglobulins. Our patient, however, deteriorated under first-line therapy and required plasmapheresis. Steroid resistance is commonly observed in cases like ours with fulminant and/or multiphasic ADEM (11, 12). Moreover, our patient simultaneously developed two other autoimmune disorders, i.e., ocular myasthenia gravis and subacute thyroiditis. In contrast to ADEM, these were first-in-life episodes. Both have been separately described following both mRNA (BioNTech/Pfizer) (9, 10) and inactivated (Sinovac) (13) SARS-CoV-2 vaccination. A literature search, however, did not identify any case with a multiple autoimmune syndromes similar to ours. The missed opportunity of testing neutralizing antibodies against SARS-CoV-2 in serum and/or CSF before immunoglobulin therapy and plasmapheresis may be considered a limitation of our case study. The presence of these in either compartment, however, would not have proven the causal link with autoimmune reaction.

The rare occurrence and favorable outcomes of vaccination-triggered ADEM, myasthenia gravis, and subacute thyroiditis, as well as the fact that severe (multiple) autoimmune syndromes may also occur after COVID-19 infection (14–17), do not detract from the public health imperative to vaccinate against COVID-19. However, clinicians should be aware that those autoimmune diseases can potentially occur alone or simultaneously, following both mRNA-based and inactivated SARS-CoV-2 vaccines, and may affect patients of any age. Extended half-life monoclonal neutralizing antibodies against SARS-CoV-2 may be considered to protect patients with insufficient immunity, in whom further vaccines are not advised (18).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KP conducted the literature search and drafted the first version of the manuscript. SP and UZ made critical revisions. All authors approved the submitted version of the manuscript.

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Analysis of Side Effects Following Vaccination Against COVID-19 Among Individuals With Multiple Sclerosis Treated With DMTs in Poland

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Background and Objectives: Since vaccination against COVID-19 is available for over a year and the population of immunized individuals with autoimmune disorders is higher than several months before, an evaluation of safety and registered adverse events can be made. We conducted a large study of side effects following the COVID-19 vaccine among patients with multiple (MS) sclerosis treated with disease-modifying therapies (DMTs) and analyzed factors predisposing for particular adverse events.

Methods: We gathered data of individuals with MS treated with DMTs from 19 Polish MS Centers, who reported at least one adverse event following COVID-19 vaccination. The information was obtained by neurologists using a questionnaire. The same questionnaire was used at all MS Centers. To assess the relevance of reported adverse events, we used Fisher's exact test, *t*-test, and *U*-Menn-Whutney test.

Results: A total of 1,668 patients with MS and reports of adverse events after COVID-19 vaccination were finally included in the study. Besides one case marked as "red flag", all adverse events were classified as mild. Pain at the injection site was the most common adverse event, with a greater frequency after the first dose. Pain at the injection site was significantly more frequent after the first dose among individuals with a lower disability (EDSS $\leq$2). The reported adverse events following immunization did not differ over sex. According to age, pain at the injection site was more common among individuals between 30 and 40 years old, only after the first vaccination dose. None of the DMTs predisposed for particular side effects.

Conclusions: According to our findings, vaccination against COVID-19 among patients with MS treated with DMTs is safe. Our study can contribute to reducing hesitancy toward vaccination among patients with MS.

Keywords: multiple sclerosis, vaccination, SARS-CoV-2, COVID-19, side effects

INTRODUCTION

The long-term impact of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection on individuals with autoimmune disorders is unknown. Among patients with multiple sclerosis (MS), the course of the infection can be severe in those with a higher level of disability, comorbid diseases, older, and on high effective therapies (1).

In general, vaccination is recommended for individuals with MS. Systemic infection can worsen the course of MS, so prevention is advisable. Most vaccines are considered safe for patients under disease-modifying therapies (DMTs). However, live vaccines are contraindicated under immunosuppressive treatment in most cases (2).

The first vaccines against coronavirus disease 2019 (COVID-19) were approved by the end of 2020. Their high effectiveness was reported in early studies. The mortality and hospitalization rate of SARS-CoV-2 infection is significantly lower in vaccinated persons (3, 4). Throughout the COVID-19 pandemic, diverse variants of SARS-CoV-2 have emerged. The latest variant (Omicron) seems to be more infectious than the original virus (5). The effectiveness of vaccination varies across virus variants and is still under investigation. However, a beneficial role of vaccination is suggested against old and novel variants. The proposed mechanism behind this is the immunological T cell memory induced by vaccination to cross-recognize different variants (6). Therefore, vaccination against COVID-19 is highly recommended, especially for those with autoimmune and other comorbid diseases (7).

Numerous adverse events were reported after the COVID-19 vaccination. However, the overwhelming majority of side effects are mild and self-limiting. In rare cases, serious post-vaccine incidents were observed, including neurological side effects (8).

Here we report adverse events after COVID-19 vaccination among individuals with multiple sclerosis treated with different disease-modifying therapies in Poland and identify any predisposing factors for the occurrence of side effects.

MATERIALS AND METHODS

The Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society published an announcement about the study at www.ptneuro.pl, and every MS Center in Poland was invited to participate. Finally, participants were recruited from 19 Polish MS Centers. The data was obtained by neurologists using a questionnaire. The same questionnaire was used at all MS Centers (available in Supplementary Materials). Patients were recruited to the study during standard or unplanned visits at a particular MS Center or over the telephone.

We included individuals who had any adverse event after COVID-19 vaccination and confirmed diagnosis of MS according to 2010 and 2017 McDonald criteria. Disability was assessed by the Expanded Disability Status Scale (EDSS). All patients were treated with one of the DMTs available in Poland (interferon, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, alemtuzumab, cladribine, natalizumab, or ocrelizumab).

We collected patient demographics, data regarding specific features of multiple sclerosis, information about vaccination against SARS-CoV-2, presence of adverse events after vaccination), and information regarding relapses following

immunization or worsening of MS symptomatology. Incidence classified as relapse must have had a clear monophasic course, objective findings typical of multiple sclerosis verified by a neurologist, lasted over 24 h, and were not related to fever or infection. Gathered data included side effects after the first or second dose of different vaccines. The analysis did not include side effects after the third dose, as the observation time would be insufficient and the number of patients too little.

Categorical variables were characterized by frequency and percentage. Continuous variables were reported by their median, mean value, and interquartile range. For statistical comparisons, the $\chi 2$ test of homogeneity of odds was calculated. To assess the relevance of reported adverse events, we used Fisher's exact test, *t*-test, and *U*-Mann-Whitney test.

All calculations were performed using STATA 15 software (StataCorp 2017) (7).

The study was approved (approval No. 62/2021) by the Bioethics Committee at Collegium Medicum, Jan Kochanowski University in Kielce, Poland.

RESULTS

A total of 1,668 individuals with MS and reports of adverse events after COVID-19 vaccination were included in the study. Among participating MS Centers 3,264 patients were vaccinated with at least one dose. Therefore, the percentage of individuals reporting any adverse events was 51% and the percentage of patients denying any side effects was 49%. Thirty-seven patients with missing data were excluded. Demographic and clinical data regarding features of multiple sclerosis are presented in **Table 1**. The average observation time was 7 months (range: 1–12 months).

The distribution of vaccines against SARS-CoV-2 administered among the cohort was as follows: 1,215 (72.84%) patients immunized with the BioNTech-Pfizer vaccine, 223 (13.37%) with the Oxford-Astra Zeneca vaccine, 155 (9.29%) with the Moderna vaccine, and 75 (4.5%) with the Johnson & Johnson vaccine. More than three-quarters (77.34%) of individuals were administered vaccines using genetically engineered mRNA to induce an immune

TABLE 1 | Demographics and clinical characteristics of patients with MS who presented with side effects following vaccination against SARS-CoV-2.

	N	(%)	Mean	Median	IQR	SD
Study population	1,668	100				
Sex						
Female	1,209	72.48				
Male	459	27.52				
Whole study population age			41.88	42	16	11.07
Female age			42.03	42	16	11.21
Male age			41.49	41	16	10.68
Disease course						
RRMS	1,585	95.02				
SPMS	42	2.52				
PPMS	41	2.46				
EDSS			2.36	2	2.5	1.48
≤2	917	54.98				
3–4	658	39.44				
≥5	93	5.58				
Disease duration			9.44	8	9	6.34
DMTs						
Interferon beta	377	22.6				
Glatiramer acetate	134	8.03				
Dimethyl fumarate	665	39.87				
Teriflunomide	168	10.07				
Fingolimod	74	4.44				
Natalizumab	105	6.29				
Ocrelizumab	77	4.62				
Cladribine	14	0.84				
Alemtuzumab	10	0.6				
Mitoxantrone	6	0.36				
Others	38	2.28				

AMS, multiple sclerosis; SD, standard deviation; IQR, interquartile range; RRMS, relapsing-remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; EDSS, the expanded disability status scale; DMTs, disease-modifying therapies.

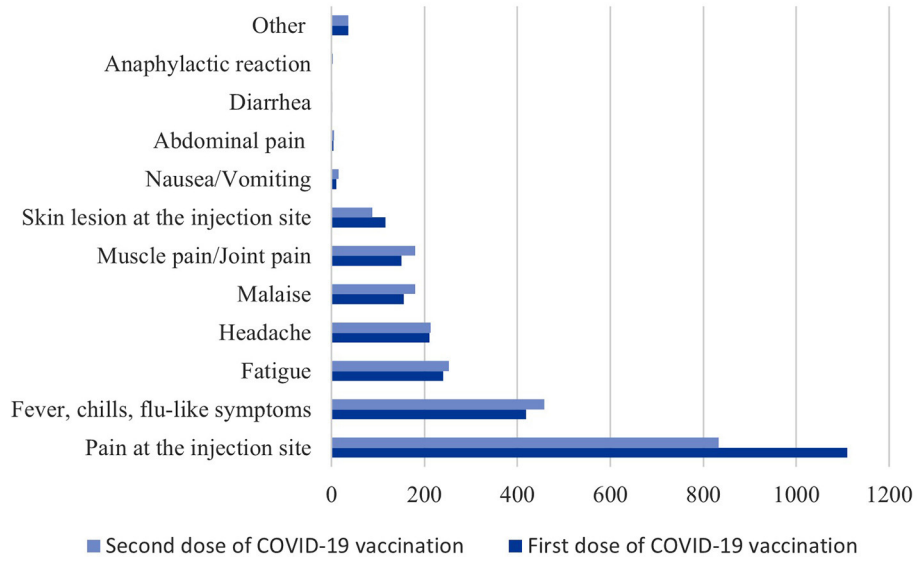

FIGURE 1 | The distribution of adverse events reported in individuals with MS treated with DMTs in Poland.

response (BioNTech Pfizer vaccine; Moderna vaccine). The first vaccination dose was given to all patients and the second to 1,573 (94.3%) people.

The reported adverse events were almost exclusively mild. The distribution of particular side effects among the cohort is presented in **Figure 1**. The most common, with a greater frequency after the first dose, was pain at the injection site. Fever/chills/flu-like symptoms, fatigue, headache, malaise, and muscle/joint pain were more often present after the second dose. In the majority of cases, the reported symptoms were self-limiting. The adverse events resolved within 7 days in 98.3% of patients after the first dose and 97.6% after the second dose. The proportion of most common adverse events following particular vaccines is shown in **Table 2**. All differences were statistically significant.

The mRNA vaccines significantly predisposed for developing pain at the injection site in comparison to vaccines using non-replicating viral vectors (Oxford-Astra Zeneca vaccine; Johnson & Johnson vaccine) ($p = 0.001$). However, being administered with vector vaccines increased propensity for fever, headache, fatigue, skin lesion at the injection site, and muscle/joint pain following immunization ($p = 0.000$, $p = 0.000$, $p = 0.001$, $p = 0.004$; $p = 0.000$, respectively).

Generally, the observed side effects were not multisymptomatic. After the first dose, 844 (50.6%) individuals had one adverse event and 655 (41.64%) after the second dose. The number of reported adverse events by individual patients is shown in **Figure 2**.

Only one adverse event was classified as "Red-Flag". It was a pro-thrombotic incidence in a 42 years old female patient 2 weeks after the first dose of the Oxford-Astra Zeneca vaccine. The patient complained of chest pain, the laboratory finding showed elevated D-dimers level, but pulmonary embolism was excluded. Currently, the patients fells well and further diagnostics did not confirm any thromboembolism. Three patients had anaphylactic reactions immediately after immunization (one individual after both doses). There were no fatal outcomes following vaccination.

None of the DMTs significantly predisposed for particular adverse events or longer duration of side effects. However, the sample size for cladribine, alemtuzumab, and mitoxantrone was insufficient for statistical analysis.

The reported adverse events following immunization did not differ between sex. According to age, pain at the injection site was more common among individuals between 30 and 40 years old, only after the first vaccination dose ($p = 0.001$). The proportion of most common adverse events divided by age is shown in **Figures 3A,B**. The mean duration of the disease was similar for all side effects, there were none relevant differences.

Pain at the injection site was significantly more frequent after the first dose among individuals with a lower disability (EDSS $\leq$ 2) ($p = 0.027$). However, a headache was the dominant adverse event after the first dose in individuals with moderate disability (EDSS 3–4) ($p = 0.005$). The proportion of patients with the most common adverse events divided by EDSS is shown in **Figures 4A,B**.

Among individuals with RRMS, 4.42% of patients (70 people) had relapses up to 3 months before vaccination. After immunization (up to 3 months), 67 patients (4.02%) had

TABLE 2 | The proportion of most common side effects after particular vaccines administered among the cohort.

	Pain at the injection site (%)	Skin lesion at the injection site (%)	Fever, chills, flu-like symptoms (%)	Fatigue (%)	Headache (%)	Muscle pain/Joint pain (%)	Malaise (%)
First dose							
BioNTech, Pfizer vaccine	68.89	4.86	20.08	12.59	10.04	7.16	7.08
Oxford, Astra Zeneca Vaccine	60.99	11.21	43.05	22.42	22.42	17.04	20.18
Moderna vaccine	64.52	15.48	27.74	16.13	16.77	10.97	10.97
Johnson & Johnson vaccine	49.33	10.67	48	17.33	17.33	12	10.67
Pearson chi2	0.001	0.000	0.000	0.001	0.000	0.000	0.000
Fisher's exact *p*-value	0.001	0.000	0.000	0.002	0.000	0.000	0.000
Second dose							
BioNTech, Pfizer vaccine	54.98	4.53	26.42	14.73	10.29	9.3	9.71
Oxford, Astra Zeneca Vaccine	36.77	8.97	26.01	16.14	24.66	12.56	10.76
Moderna vaccine	52.26	8.39	50.32	24.52	20	24.52	24.52
Pearson chi2	0.000	0.002	0.000	0.000	0.000	0.000	0.000
Fisher's exact *p*-value	0.000	0.002	0.000	0.000	0.000	0.000	0.000

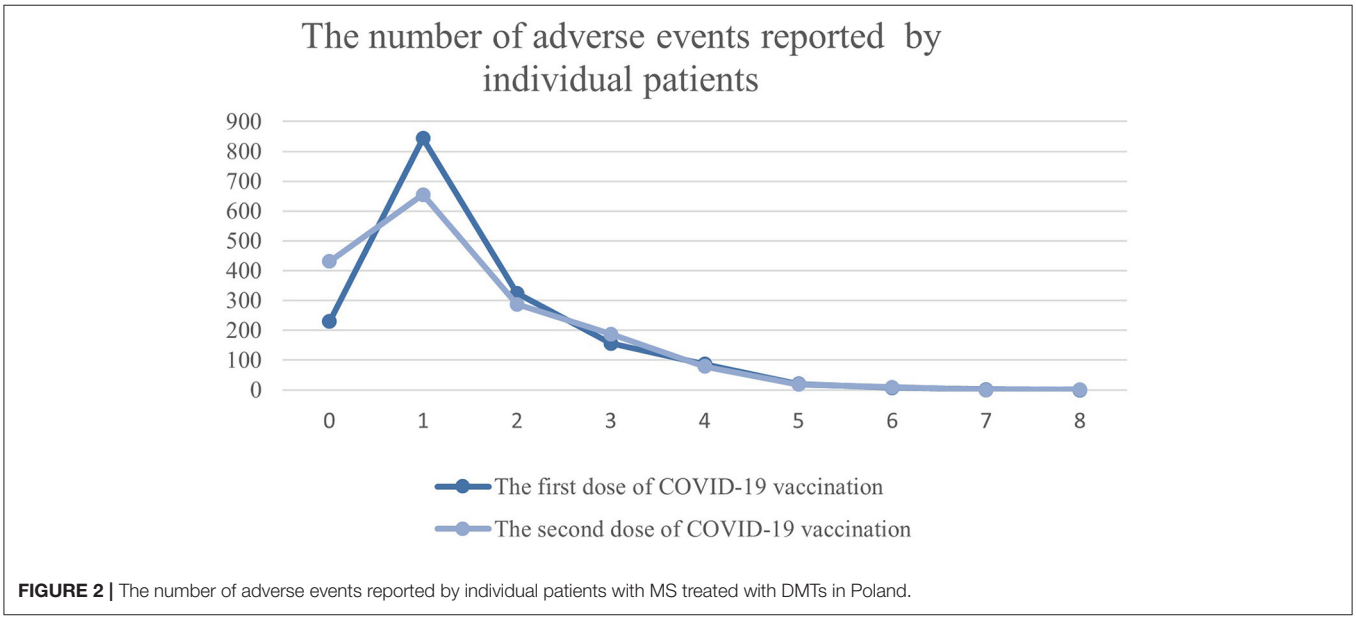

FIGURE 2 | The number of adverse events reported by individual patients with MS treated with DMTs in Poland.

relapsed, but only 22.39% of them within the first 21 days. In 29 cases (1.74%), the worsening occurred after the first dose and in 38 (2.28%) after the second dose. Magnetic resonance imaging (MRI) was not routinely performed.

DISCUSSION

The real-world data regarding vaccination against SARS-CoV-2 among individuals with autoimmune disorders is limited. This study analyzes the range of adverse events following the COVID-19 vaccine reported in patients with multiple sclerosis treated with DMTs.

In our observation, almost all reported adverse events were mild and self-limiting. The most common were pain at the injection site, fever/chills/flu-like symptoms, and fatigue. A similar range and frequency of adverse events were found in clinical trials evaluating COVID-19 vaccinations in general population (9). Pain at the injection site after the first dose

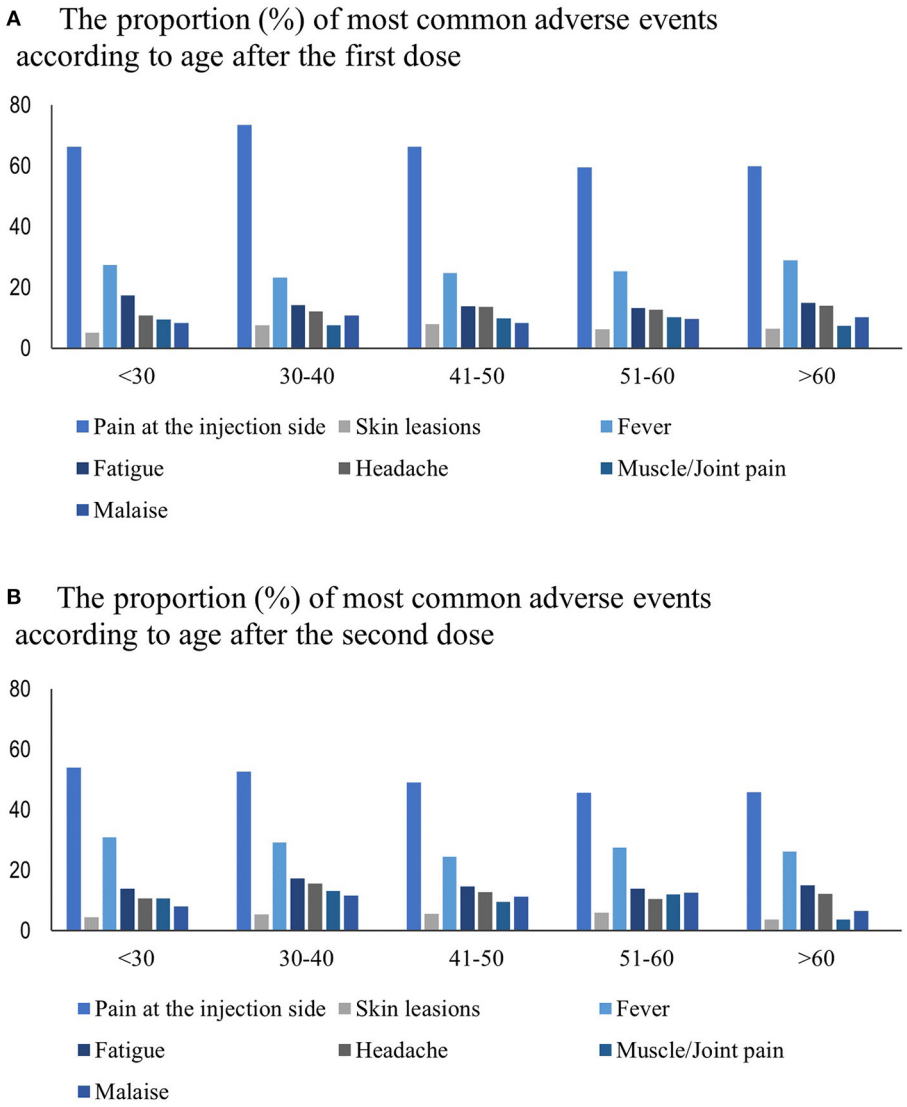

FIGURE 3 | (A) The proportion (%) of most common adverse events according to age after the first dose. **(B)** The proportion (%) of most common adverse events according to age after the second dose.

of vaccination was more common for individuals with lower disability and patients under 40 years old. The same observations were made on a smaller cohort of people with SM by Achiron et al. (10). In several other studies, based on the general population, also younger patients reported any adverse events more often (11, 12). Therefore, the shift toward younger patients may not be related to the coexistence of autoimmune diseases.

Three patients had developed anaphylactic reactions immediately after immunization. Only one patient had a pro-thrombotic "Red-Flag" (chest pain, elevated D-dimers level) without a final diagnosis of any embolism.

Interestingly, in clinical trials of COVID-19 vaccines, the percentage of adverse events in the placebo group was quite high (approximately one-third). The most frequent were headaches and fatigue (13). It is important to acknowledge the fact, as the mentioned symptoms were also common among patients with MS and, in some cases, might be related to other factors (e.g., anxiety related to the safety of the vaccine).

The occurrence of relapses following vaccination was very low in our cohort and not higher in comparison to the 3 month period before immunization. There are case reports in the literature showing a temporal relation between the COVID-19 vaccine and relapse (14). However, the greater frequency of relapses following vaccination against SARS-CoV-2 has not been observed in our study or other studies conducted on a larger number of patients, including the third dose (10, 14, 15).

None of the DMTs among the cohort were predisposed to a particular adverse event. There was no difference between monoclonal antibodies, sphingosine-1-phosphate receptor modulators, and other therapies in terms of type or the duration

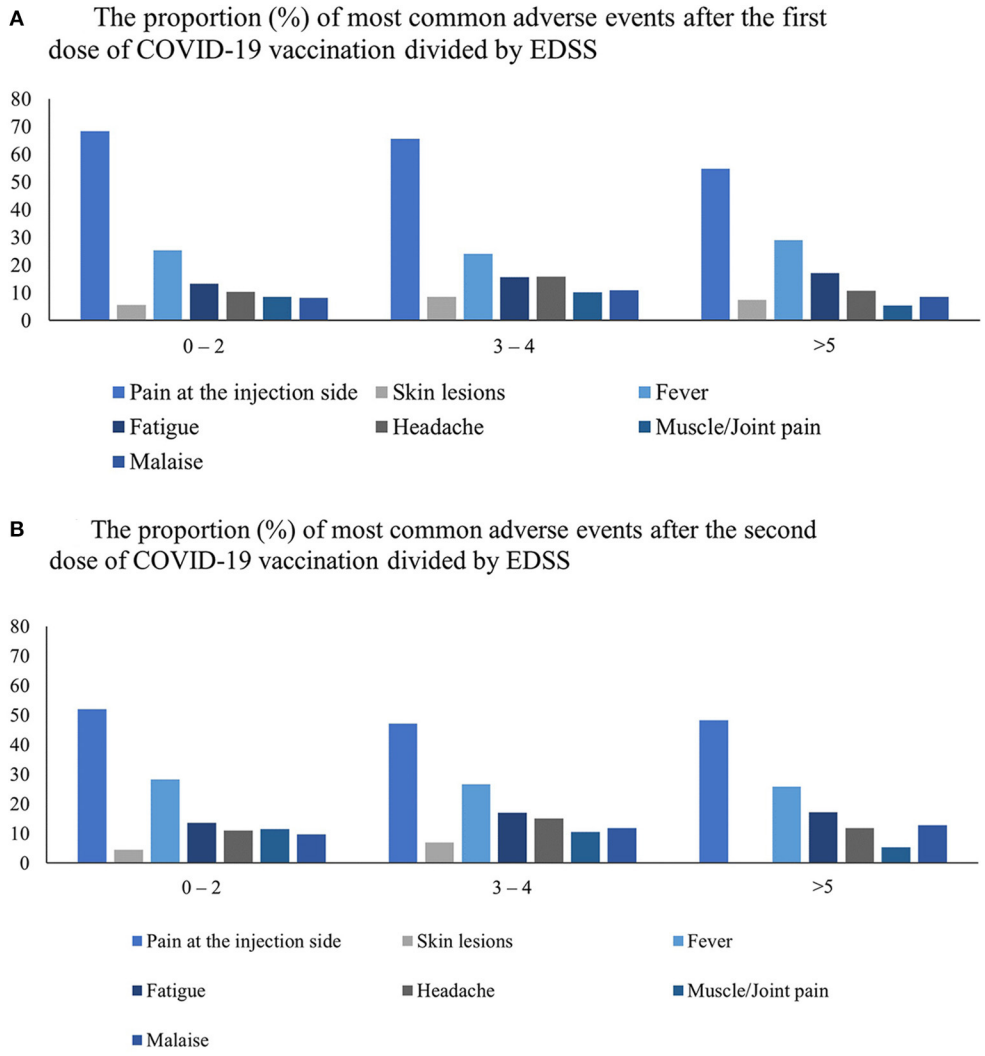

FIGURE 4 | The proportion (%) of most common side effects after COVID-19 vaccination among the cohort was divided by three categories of disability assessed by EDSS after the first **(A)** and the second dose **(B)**.

of reported side effects. Patients with MS were vaccinated in Poland, keeping a time interval between the administration of certain DMTs according to guidelines, consistent with international consensus (16). The vast majority of our cohort was administered vaccines based on mRNA. Therefore, based on our findings, we can conclude that mRNA vaccines are safe, even on high-efficacy therapies. Among individuals immunized with the use of non-replicating viral vectors, the reported adverse events were also mild, but as the number of patients was much smaller in comparison to patients administered with mRNA vaccines, a larger observation is required to draw conclusions.

The results of our study provide an argument for pro immunization among hesitating individuals. As we know from several studies, there are multiple issues holding patients back from getting vaccinated (17, 18). Most are related to the novelty of the vaccination and concerns about its safety. Also, their effectiveness is constantly undermined by false information on the Internet and social media (19). This creates a big challenge for health workers worldwide. Most clinical trials are based on the general population. Therefore, our study proving vaccination safety among individuals with MS can be a convincing tool for these particular patients.

There are several limitations to our study. Although the study included a large representation of patients with MS treated with DMTs in Poland, the total number of individuals treated with DMTs is much higher. We did not include non-treated with DMTs patients and those with a high level of disability (EDSS >8). Furthermore, the representation of different types of MS is unequal in the cohort as mostly patients with RRMS are included. Finally, the reports of adverse events were in most cases retrospective and based, besides relapses, on

subjective assessment of the patient, so it might be imprecise in some individuals.

CONCLUSIONS

The reason for COVID-19 vaccination hesitancy is multifactorial. However, there are genuine fears of potential adverse events, especially among individuals with autoimmune diseases. Our study demonstrates the safety of vaccination against SARS-CoV-2 among patients with MS treated with DMTs. Almost all reported symptoms were mild and self-limiting, some were more frequent in younger patients and with lower EDSS.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The name of the repository and accession number can be found below: GitHub, https://github.com/Aczarnowska/MS-adverse-events-COVID19.

ETHICS STATEMENT

The study was approved (approval No. 62/2021) by the Bioethics Committee at Collegium Medicum, Jan Kochanowski University in Kielce, Poland. Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional Requirements.

AUTHOR CONTRIBUTIONS

ACz, JT, KK-T, AS, MA-S, HB-P, WB, and AK: conceptualization. ACz, OZ, MW, MM, KN, AJ-W, KR, BL, MP, IR-Ż, AP, MŚ-M, MSi, ACi, AW, AJ, MSta, KK, KD, AK-Ł, WG, AW-H, EK, JC-Ł, JU, AP-D, MC, AM, JKu, JKo, MB, MSto, KK-B, NN, PW, AP-P, MN, BZ-P, EJ, JZa, MM-J, JZw, BZ, and AP: patient enrollment and data collection. ACz and OZ: formal analysis. ACz, OZ, WB, and AK: methodology. AK: project administration. OZ: software. WB and AK: supervision. ACz: writing—original draft. WB and AK: writing—review & editing. All authors have read and agreed to the published version of the manuscript.

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Atypical acute disseminated encephalomyelitis with systemic inflammation after a first dose of AztraZaneca COVID-19 vaccine. A case report

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Background: Only a few cases of acute disseminated encephalomyelitis (ADEM) following coronavirus disease 19 (COVID-19) vaccination have been described since the beginning of the vaccination campaign.

Results: Here we report the first case of central nervous system (CNS) demyelination with systemic inflammatory findings on whole body 19-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) following the ChAdOx1 nCoV-19 vaccine.

Conclusions: Clinicians should stay aware of potential new adverse events after immunization.

KEYWORDS

acute disseminated encephalomyelitis (ADEM), COVID-19, vaccination, systemic inflammation, fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT)

Introduction

Since the beginning of the pandemic, vaccines were produced in record time. Real-world studies indicated an excellent safety profile. Despite these studies, the scientific community must stay aware of rare but severe complications and report them. This allows more accuracy of the real-world safety profile of the vaccine. We can take appropriate measures, as we did with the AztraZaneca vaccine (ChAdOx1 nCoV-19) and its thromboembolic complications (1). The ChAdOx1 nCoV-19 is a vaccine based on a recombinant adenoviral vector encoding the spike protein of SARS-CoV-2 (2). Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory disorder of the central nervous system (CNS) that occurs after an antigenic challenge. The post-vaccine etiology represents 5% of all ADEM cases and the annual incidence of ADEM ranges from 1 to 10 per million (3). Here we report the first case of central nervous system (CNS) demyelination with systemic inflammatory findings on whole

body 19-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) following the ChAdOx1 nCoV-19 vaccine.

Case report

A previously healthy 49-year-old female received her first dose of ChAdOx1 nCoV-19 vaccine. She experienced mild flu-like symptoms during the following 48 h. One week later, the patient presented another episode of flu-like symptoms with fever, fatigue, neck pain, followed over the next few days by rapidly progressive sensitive symptoms including paresthesia in both legs, up to the chest, Lhermitte's phenomenon and sphincter dysfunction. In April, the patient came to the neurological consultation at another hospital. During the examination a hypoesthesia with a thoracic (Th) 8 level was noticed with a sensory ataxia. A full spine magnetic resonance imaging (MRI) was normal but somatosensory evoked potentials (SSEPs) showed abnormal conduction above the sensory decussation in the lower brainstem. Four weeks later, the patient came to our neurological outpatient clinic. Her symptoms had worsened with sensory symptoms now involving her hands, worsening sensory ataxia and of sphincter dysfunction. Her neurological examination showed normal strength, hypoesthesia to all modalities with a Th 8 level, absent plantar response, impaired tandem walking and the presence of a Romberg sign.

An MRI of the brain was obtained and revealed large, ill-defined T2 fluid attenuated inversion recovery (FLAIR) hyperintensities of periventricular and deep white matter, along with smaller lesions infratentorially (Figure 1, part1). Subcortical U fibers were spared, and so were the cortex and deep gray matter. Lesions showed mildly increased diffusivity and were mostly non-enhancing. They exerted no mass effect. No meningeal enhancement was noted. MRI of the spinal cord revealed the appearance of numerous contiguous short-segment cervical and thoracic lesions, showing variably increased T2 signal intensity and contrast enhancement (Figure 1, part 2). The

Abbreviations: ADEM, acute disseminated encephalomyelitis; Coronavirus disease 19, COVID-19; CNS, central nervous system; FDG-PET/CT, whole body 19-fluorodeoxyglucose positron emission tomography with computed tomography; Th, thoracic; MRI, magnetic resonance imaging; SSEPs, somatosensory evoked potentials; FLAIR, fluid attenuated inversion recovery; ADC, apparent diffusion coefficient PMR-GCA, polymyalgia rheumatic associated with a giant cell arteritis.

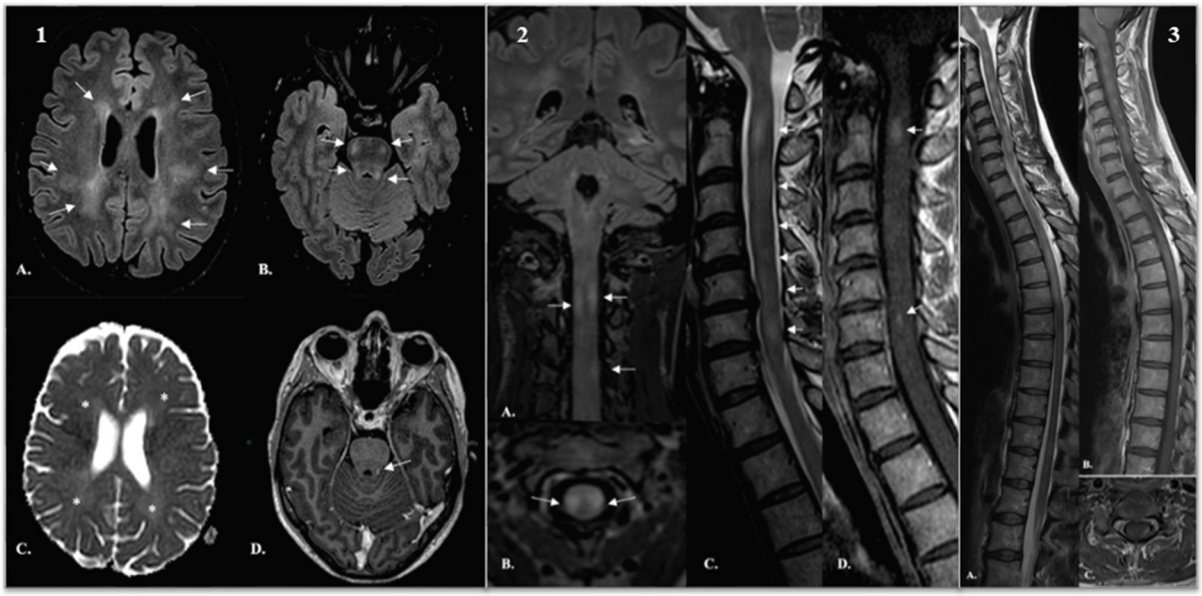

FIGURE 1
Part 1: (A,B) Axial T2 FLAIR-weighted images demonstrated extensive, asymmetric involvement of periventricular and deep white matter [arrows in (A)]. Smaller lesions were observed in the ponto-mesencephalic tegmentum, superior and middle cerebellar peduncles [arrows in (B)]. (C) Lesions were mildly hyperintense on ADC cartography, revealing increased diffusivity (*). (D) A small focus of contrast enhancement was demonstrated in the left superior cerebellar peduncle (arrow). Part 2: (A–C) Reformatted coronal (A) and axial (B) T2 FLAIR-weighted images and sagittal T2-weighted images and sagittal T2 weighted image (C) reveal multiple short-segment hyperintensities (arrows). Lesions are asymmetric and excentrically located and involve both white and gray matter. Signal intensity is variable, from midly to markedly increased. (D) Sagittal post-gadolinium T1-weighted image shows scattered foci of enhancement (arrows). Part 3: (A–C) Sagittal T2 (A) and post-contrast sagittal (B) and axial (C) T1-weighted images demonstrate progression of disease. We found lesions on the entire spinal cord. FLAIR, fluid attenuated inversion recovery; ADC, apparent diffusion coefficient.

TABLE 1 Clinical evolution and complementary assessments done during patient follow-up.

Temporality	Neurological examination	Laboratory investigations	Cerebrospinal fluid investigations	MRIs	Others	Treatment
April 2021	Hypoesthesia with a Th8 level Lhermitte phenomenon Sensitive ataxia Sphincter dysfunction.	Thyroid, hepatic, hematologic and renal functions normal.	None.	Normal spinal MRI.	SSEPs: asymetric conduction of the somesthetic influx with a subcortical but supralemniscal level.	
May and June 2021	As above but with decreased pallesthesia and absent plantar response.	serum protein electrophoresis, vitamins, angiotensin converted enzyme, erythrocyte sedimentation speed, microbiological studies (including Tuberculosis – QuantiFERON blood test, HAV, HBV, EBV, CMV, HIV, HSV, Syphilis, Borrelia, Toxoplasma, JC virus, SARS-CoV-2), screening for antibodies targeting antigens associated with demyelinating disorders of the CNS (MOG, AQP4) and other auto-immune disorders (ANA, ANCA) remained negative.	8 WBC, protein level at 101 mg/dl, normal IgG/Albumin Index, OCBs identical in CSF and serum. Negative infectious panel.	Extensive, asymmetric involvement of periventricular and deep white matter. Smaller lesions were observed in the ponto-mesencephalic tegmentum, superior and middle cerebellar peduncles. Lesions were mildly hyperintense on ADC cartography, revealing increased diffusivity. A small focus of contrast enhancement was demonstrated in the left superior cerebellar peduncle.	Normal nerve conductive studies.	IV MP 1 gr/day, for 5 days.
July 2021	Paraparesis 2/5 in the right leg and 3/5 in the left leg. Apallesthesia up to iliac crests. Sensory level at Th5 level. Need walking aids	Negative MOG and AQP4 antibodies. Negative ANA and ANCA.		Numerous contiguous short-segment cervical and thoracic lesions, showing variably increased T2 signal intensity and contrast enhancement.		5 sessions of Therapeutic Plasma Exchange.
August 2021	Weakness worsened after an improvement.	Normal thyroid hormone level and autoantibodies. Negative ANA and ANCA Negative MOG antibody.	2 WBC, protein level at 95mg/dl, normal IgG/Albumin Index, OCBs identical in CSF and serum. Negative infectious panel.	Increase in the number and size of spinal cord lesions and the appearance of new foci of contrast enhancement. Brain findings were unchanged.	FDG PET-CT: increased glucose uptake in the thyroid, the pulmonary nodules, the thoracic aorta walls, the lumbar spinous processes and the whole spinal cord. Normal thyroid echography.	Rituximab 1 gr IV in 2 times at 15 days and another course of IV MP.
November 2021	Paraparesis 3+/5 in the right leg and 4+/5 in the left leg. Sensory level at Th12. Few steps without help.			Brain and spinal MRIs stable or regression of the most enhanced lesions.	FDG PET-CT: thyroid and pulmonary uptake disappeared or decreased, new uptake in scapular and pelvic belts, ischiatic, and great trochanters.	

Th, thoracic; SSEPs, somatosensory evoked potentials; WBC, white blood cells, OCBs, oligoclonal bands; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; IV, intravenous; MP, methylprednisolone; FDG PET-CT,fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT).

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spinal cord was moderately swollen. Nerve conductive studies were normal. A lumbar puncture showed a mild pleocytosis with 8 white blood cells, elevated protein levels (101 mg/dL), normal IgG/albumin index and identical oligoclonal bands in the cerebrospinal fluid (CSF) and serum (type 4 pattern). Based on the clinical history and the radiological aspects an inflammatory origin was retained. Our differential diagnosis workup was mainly focused on an infectious or an auto-immune causes. An infectious panel was negative. An exhaustive blood investigation was done with the intention to exclude auto-immune systemic diseases, no relevant findings were found. A screening for antibodies targeting antigens associated with demyelinating disorders of the CNS (MOG antibody disease and NMO spectrum) remained negative (Table 1).

Based on the exclusion of CNS infection or other autoimmune disorders, the diagnosis of atypical ADEM was made. The patient was treated with an intravenous course of methylprednisolone (1 g/day for 5 days). Her condition stabilized and she was transferred to a rehabilitation center.

Three weeks after discharge, she was readmitted because of a clinical deterioration. Neurological evaluation showed a new paraparesis, evaluated at 2/5 in the right leg and 3/5 in the left leg, complete loss of pallesthesia up to the iliac crests, a sensory Th 5 level, and a severe sensory ataxia requiring walking aids.

Six weeks afterwards, on July 14, an MRI showed an increase in the number and size of spinal cord lesions and the appearance of new foci of contrast enhancement (Figure 1, part 3). Brain findings were unchanged. She was treated with 5 sessions of plasma exchange. She improved and was discharged again to a rehabilitation center. Three weeks later, her weakness worsened. A new MRI showed there were new enhancing lesions in the brain stem and cervical spinal cord.

Because of the atypical course of the disease, the diagnosis of ADEM was reconsidered. Whole body fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) was obtained with the aim of excluding systemic inflammation, namely sarcoidosis despite negative biological markers. Results revealed increased glucose uptake not only in the spinal cord but also in the thyroid, the thoracic aorta walls and the lumbar spinous processes (Figure 2).

She did not have any complaints about osteo-articular or vascular systems. Further thyroid testing with echography, hormone levels and autoantibodies were normal. She received IV rituximab (1 g and another after 15 days) and another course of IV methylprednisolone (1 g/day for 5 days). Over the next 2 months, she progressively improved. At last follow-up, strength in her right and left lower limbs was evaluated at 3+/5 and 4+/5, respectively, the sensory level had dropped to the level of Th12 and she could take a few steps without aid. Another MRI showed stability or regression of most lesions.

On repeat whole body FDG-PET/CT (13 weeks after the first one), thyroid uptake had disappeared but other regions' abnormal uptake had decreased and new areas of increased uptake had appeared at the level of the scapular and pelvic girdles, ischiatic and great trochanters.

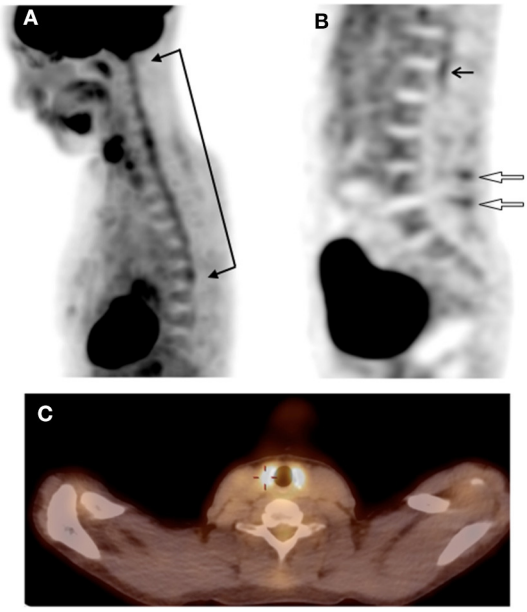

FIGURE 2
(A) sagittal view of FDG-PET/CT showing hypermetabolism of the spinal cord at the cervicothoracic level (between arrows). **(B)** sagittal view of FDG-PET/CT showing hypermetabolism of the spinal cord at the lumbosacral level (black arrow) and an interspinous hypermetabolism at two level of the lumbar spine (open arrows). **(C)** fused FDG-PET/CT image on the transverse plane showing a marked and diffuse hypermetabolism of the thyroid gland. FDG-PET/CT, whole body 19-fluorodeoxyglucose positron emission tomography with computed tomography.

Discussion

This case report raises two important points: the association between ChAdOx1 nCoV-19 and ADEM and the meaning of incidental findings in the FDG PET-CT.

A review of the SARS-CoV-2 vaccine and ADEM literature showed 13 reported cases of ADEM following the administration of a COVID-19 vaccine, which are summarized in Table 2 (4–14).

In comparison to prior cases except maybe one who had a pseudo relapse (14), our patient had a more protracted course, which evolved in two subsequent worsening phases until improvement 8 months later. These phases occurred each time after treatment cessation and there was no relapse after the symptomatic nadir which occurred in August (Table 1). Therefore, we conclude that these recurrences are part of the same monophasic course.

Also, the MRI evolution of the lesions is atypical for several reasons: the sub-acute evolution (longer than 3 months),

TABLE 2 Clinical and demographic characteristics of the 6 cases reporting with an ADEM post COVID vaccine.

Authors	Age/gender	Vaccine	Time of onset	Clinical picture	CSF/laboratory investigations	MRI	Treatment	Outcome/follow-up
Cao et al. (4)	24y/F	Sinovac, inactivated vaccine	1st dose, 14 d after	Memory decline, headache, low-grade fever, muscle stiffness, extremity weakness, and reduced appetite. GTCs after one week.	Negative anti-AQP4, anti-MOG antibodies, vasculitis, OCBs.	Brain lesions, no enhancement.	IVIG 20 g/d for 5 d.	No recurrences. Marked improvement. Complete resolution of MRI lesions. No seizures, 30d.
Ozgen Kenangil et al. (5)	46y/F	Sinovac, inactivated vaccine	2nd dose, 30d after	GTCs.	Negative OCBs.	Brain lesions, no enhancement.	IV MP 1 g/d for 7d.	No recurrences. Stable. No seizure recurrence.
Raknuzzaman et al. (6)	55y/M	mRNA-based vaccine	1st dose, 21d after	Headache, somnolence, delirium and GTCs.	Normal ESR.	Brain lesions.	IV MP 1 g/d for 5d followed by oral tapering steroids.	No recurrences. Improvement of MRI lesions and fully recovered, 30d.
Vogrig et al. (7)	56y/F	Pfizer-BioNTech COVID-19, mRNA-based vaccine	1st dose, 14d after	Malaise, chills, without fever, followed by unsteady gait, clumsiness of left arm.	Negative: anti-AQP4, anti-MOG antibodies, vasculitis, OCBs.	Brain lesions, no enhancement.	Prednisone 75mg q.d. with gradual tapering.	No recurrences. Partial improvement, 50d.
Kania et al. (8)	19y/F	Moderna, mRNA-based vaccine	1st dose, 14d after	Severe headache, fever, back and neck pain, nausea, vomiting, urinary retention.	Negative: anti-AQP4, anti-MOG antibodies, OCBs.	Brain and medullar lesions with enhancement.	IV MP and TPE (stopped because of allergic reaction)	No recurrences. Mild headache, 40d.
Rinaldi et al. (9)	45y/M	ChAdOx1 nCoV-19, viral vector	1st dose, 12d after	Numbness of all the upper limbs, trunk, and legs and progressive reduced visual acuity, dysarthria, dysphagia, clumsy right-hand movements and urge incontinence.	Negative: anti-AQP4, anti-MOG antibodies, ANA, ESR, OCBs.	Brain and medullar lesions with enhancement.	IV MP 1 g/d followed by oral prednisolone.	No recurrences. Complete recovery, 4months.
Permezel et al. (10)	63y/M	ChAdOx1 nCoV-19, viral vector	1st dose, 12d after	Vertigo, fatigue, declining cognition, disorientation and impaired attention.	Negative: anti-AQP4, anti-MOG, anti-neuronal, anti-NMDAR, anti-LGI-1 and anti-forantivoltage gated K+ channel antibodies. OCBs positive.	Brain and medullar lesions without enhancement.	IV MP 1 g/d 5d followed by TPE.	Death 20d after hospitalization.

(Continued)

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TABLE 2 (Continued)

Authors	Age/gender	Vaccine	Time of onset	Clinical picture	CSF/laboratory investigations	MRI	Treatment	Outcome/follow-up
Shimizu et al. (11)	88y/F	Pfizer-BioNTech COVID-19, mRNA-based vaccine	2nd dose, 29d after	Impaired consciousness and gaze-evoked nystagmus.	Negative: anti-onconeuronal, anti-ganglioside antinuclear, autoimmune vasculitis and MBP antibodies, OCBs.	Brain lesions without enhancement.	IV MP 1 g/d 3d.	Clinical and MRI improvement after 66d.
Al-Quliti et al. (12)	56y/F	ChAdOx1 nCoV-19, viral vector	1st dose, 10d after	Paraparesis and slurred speech.	/	Brain lesions	IV steroids.	Clinical improvement.
Nagaratnam et al. (13)	36y/F	ChAdOx1 nCoV-19, viral vector	1st dose, 14d after	Bilateral visual impairment and headache. Pseudo relapse 15d after the onset.	Negative: anti-AQP4, anti-MOG, ANCA, ANA. OCBs positive.	Brain lesions with enhancement and no spinal lesion.	Two courses of IV MP 1 g/d 3d with a prednisolone tapering plan.	Clinical resolution and MRI improvement at 42d.
Ancau et al. (14)	61y/M	ChAdOx1 nCoV-19, viral vector	1st dose, 2d after	Fever, headache, apathy and then unconsciousness and GS.	Negative: anti-AQP4, anti-MOG, ANA, ANCA, anti-neuronal and paraneoplasic antibodies, OCBs.	Brain lesions with hemorrhages.	IV MP 1 g/d 5d followed by TPE with concomitant oral MP.	MRI improvement at 5d and vegetative state after 98d.
Ancau et al. (14)	25y/F	ChAdOx1 nCoV-19, viral vector	1st dose, 9d after	Cephalalgia, thoracic back pain, paraplegic syndrome with Anesthesia below dermatome Th6, sphincter dysfunction.	Negative: anti-AQP4, anti-MOG, ANA, ANCA, anti-neuronal and paraneoplastic antibodies, OCBs.	Brain and spinal lesions with enhancement and hemorrhages.	IV MP 1 g/d 5d followed by TPE with concomitant oral MP	Clinical improvement of sensory symptoms at 42d.
Ancau et al. (14)	55y/F	ChAdOx1 nCoV-19, viral vector	1st dose, 9d after	Nausea, dizziness and meningism, worsened to severe spastic tetraparesis and coma.	Negative: anti-AQP4, anti-MOG, ANA, ANCA, anti-neuronal and paraneoplastic antibodies, OCBs.	Brain lesions with hemorrhages.	IV MP 1 g/d 5d.	Death
Our case report	49y/F	ChAdOx1 nCoV-19, viral vector	1st dose, 7d after	Neck pain, fatigue, fever, partial transverse myelitis and sphincter dysfunction Two recurrences.	Negative: AQP4, MOG antibodies, ANA, ANCA, ESR, OCBs.	Brain and medullar lesions with enhancement.	IV MP 1 g/d during 5d, TPE 5 sessions, Rituximab 2gr and IV MP 1 g/d during 5d.	Mild improvement, 9 months.

CSF, Cerebrospinal fluid; MRI, magnetic resonance imaging; FDG PET-CT, F-fluorodeoxyglucose positron emission tomography with computed tomography; Y, years; F,Female; M, Male; d, days, GTCs, Generalized Tonico-Clonic seizures; OCBs, OligoClonal Bands; ESR, Erythrocyte Sedimentation Rate; IV, Intravenous; IG, Immunoglobulins; MP, Methylprednisolone; TPE, Therapeutic Plasma Exchange; Th, Thoracic.

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the discordance between brain and spinal cord lesions in terms of how they evolved and their aspects, and the limited resolution on the last MRI after 7 months of follow-up. As some studies have described, some lesions could take up to 18 months to disappear (15) or persisted on follow-up imaging (16). We did have the information of the MRI evolution from only 3 previously reported cases as shown in Table 2: one with a complete resolution in 1 month (4) and the other two with a partial resolution at follow-up of 30 and 66d (6, 11). We retained the diagnosis of ADEM according to Sejvar et al. (17) but determined it atypical because of these particular findings.

It is the first reported case of post-ChAdOx1 nCoV-19 vaccination ADEM in which FDG-PET/CT was performed. The observed pulmonary nodules' hypercaption were very small (<5 mm) with a reduction of the glucose uptake at the FDG-PET/CT control. A basic control will be performed at one year with a CT.

The increased glucose uptake observed in the thyroid on the first FDG-PET/CT is difficult to interpret in our clinical setting. Mild FDG uptake by the thyroid is likely physiological and a normal variant but moderate-to-intense diffuse uptake is usually associated with elevated TSH, thyroiditis, hyperthyroidism or Graves' disease (18). One interesting study reported aortic and thyroid unexpected hypermetabolism without clinical relevance in a cohort of patients with anti-neutrophil cytoplasmic antibodies-associated vasculitis (19). In our case the complementary analysis and also the control FDG-PET/CT were normal, leading to the conclusion that the initial thyroid finding had no clinical relevance.

The increased uptake of the thoracic aorta and the lumbar spinous processes interspaces associated with the increased uptake of the scapular and pelvic girdles, ischiatic and great trochanters in the second FDG-PET/CT raised the question of polymyalgia rheumatic associated with a giant cell arteritis (PMR-GCA) diagnosis. Again, in our case we did not have any clinical correlation and our patient is substantially younger (40 years old) than the median age (70 years old) of diagnosis for this PMR-GCA entity (20). We did not find any description in the literature of the association of ADEM with vasculitis, in particular giant-cell arteritis. Large-vessel vasculitis is not classically associated with extensive myelitis. We only found a case report of NMO spectrum disorder which is a demyelinating auto-immune disease of the CNS, associated with Takayasu arteritis (21). The possibility of CNS and systemic vasculitis, triggered by the vaccination in our case, should be raised. Recent literature reports cases of vasculitis as cutaneous vasculitis (22), hypersensitivity angiitis, IgA vasculitis (23) and ANCA-associated vasculitis (24) following ChAdOx1 nCoV-19 vaccine and one case of eosinophilic granulomatosis with polyangiitis after the Moderna vaccine (25). We also found one reported case of CNS vasculitis following BNT162b2, Pfizer/BioN-Tech vaccine (26) but without FDG-PET/CT done. Vasculitis was described as a complication during COVID-19 because of direct endothelial damage (27) and ChAdOx1 nCoV-19 vaccine is associated with immune thrombosis and thrombocytopenia. To date, current data do not strongly support a causative link between vaccination and most of vasculitis (28). The hypothesis of two autoimmune disorders coexistence' rather than a large-vessel vasculitis with CNS involvement could also be raised and it is a situation already described in the literature (29, 30). In our case, the lack of clinical corresponding symptoms to the FDG-PET/CT findings does not allow to confirm a specific diagnosis. For all these reasons we will remain for now with the diagnosis of atypical ADEM with systemic inflammation without a clear diagnosis.

Conclusions

We report the first case of post-ChAdOx1 nCoV-19 vaccination atypical ADEM with incidental findings on the FDG-PET/CT consistent with a large-vessel vasculitis, in particular GCA given the hypermetabolism of scapular and pelvic girdles and typical of polymyalgia rheumatica. Their relevance remains debatable at this stage given the lack of corresponding symptoms. Clinicians should stay aware of potential new adverse events after immunization.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Comité d'Ethique de l'Hopital Erasme—CUB. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LB wrote the first draft of the manuscript. VL, SG, MC, and VO-I wrote sections of the manuscript. All authors

contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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COVID-19 and the risk of CNS demyelinating diseases: A systematic review

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Background: Viral infections are a proposed possible cause of inflammatory central nervous system (CNS) demyelinating diseases, including multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). During the past 2 years, CNS demyelinating events associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported, but causality is unclear.

Objective: To investigate the relationship between CNS demyelinating disease development and exacerbation with antecedent and/or concurrent SARS-CoV-2 infection.

Methods: A systematic literature review of all publications describing either a new diagnosis or relapse of CNS demyelinating diseases (MS, NMOSD, MOGAD) in association with SARS-CoV-2 infection was performed utilizing PRISMA guidelines. Descriptive statistics were used for data analysis, using a case analysis approach.

Results: Sixty-seven articles met the inclusion criteria for the study. Most of the reported cases of NMOSD ($n = 13$, 72.2% of reported cases) and MOGAD ($n = 27$, 96.5% of reported cases) were of new disease onset, presenting with typical clinical and radiographic features of these conditions, respectively. In contrast, reported MS cases varied amongst newly diagnosed cases ($n = 10$, 10.5% of reported cases), relapses ($n = 63$, 66.4%) and pseudo-relapses ($n = 22$, 23.2%). The median duration between COVID-19 infection and demyelinating event onset was 11.5 days (range 0–90 days) in NMOSD, 6 days (range−7 to +45 days) in MOGAD, and 13.5 days (range−21 to +180 days) in MS. Most cases received high-dose corticosteroids with a good clinical outcome.

Conclusion: Based upon available literature, the rate of CNS demyelinating events occurring in the setting of preceding or concurrent SARS-CoV-2 infection is relatively low considering the prevalence of SARS-CoV-2 infection. The clinical outcomes of new onset or relapsing MS, NMOSD, or MOGAD associated with antecedent or concurrent infection were mostly favorable. Larger prospective epidemiological studies are needed to better delineate the impact of COVID-19 on CNS demyelinating diseases.

KEYWORDS

COVID-19, multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), diagnosis, relapse, exacerbation

Introduction

Multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are immune-mediated inflammatory demyelinating diseases of the central nervous system (CNS). While the cause of these conditions is unknown, it is proposed that an interaction between genetic predisposition and behavioral, environmental, and personal factors contribute to disease development. Among the environmental factors involved, viral infections are considered a possible triggering factor.

Prior studies have shown a higher rate of multiple sclerosis (MS) exacerbation in temporal association with viral infections, especially upper respiratory tract infections caused by influenza A virus and Epstein Barr virus (EBV) (1). EBV has also been proposed as a causal agent in the onset of MS (2, 3). Likewise, preceding infections have been proposed as a possible trigger for the induction of pathogenic mechanisms leading to the development of NMOSD and MOGAD (4–10).

During the past 2 years, neurological complications associated with SARS-CoV-2 infection, the aetiologic agent of the coronavirus disease 2019 (COVID-19), have been reported. Some of these complications are thought to be caused by direct damage to the nervous system as a result of direct viral invasion (11). However, in most cases, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) CSF RNA test is negative, and an immune-mediated mechanism is postulated (12–15). In this latter category, reports of MS, NMOSD, and MOGAD cases presenting either as new diagnoses or disease relapses in temporal association with COVID-19 have been accumulating.

This systematic review aims to summarize the available data regarding the occurrence of new disease onset and disease exacerbation of MS, NMOSD, and MOGAD associated with SARS-CoV-2 infection.

Materials and methods

This systematic literature review was performed utilizing PRISMA guidelines. Electronic searches for published literature were conducted by a medical librarian using Ovid MEDLINE (1946 to present), Embase.com (1947 to present), and Web of Science (1900 to present). The searches were run in December 2021. A search update was run in May 2022.

The search strategy incorporated controlled vocabulary and free-text synonyms for the concepts of multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), relapse, new diagnosis, and COVID-19. The full database search strategies are documented in Appendix 1. No restrictions on language or any other search filters were applied. All identified studies were combined and de-duplicated in a single reference manager (EndNote). The citations were then uploaded into Covidence systematic review software.

The full reference list of all selected papers was screened for additional relevant sources. Publications meeting the purpose of the review that were not identified through the initial electronic search were added manually to the final review. The paper selection and data extraction process were carried out independently by two authors (IL and SN), with a third author available in case of disagreements.

To ensure maximal coverage of the currently available data pertinent for the topic of this review, we included all available case reports, case series, and cohort studies that met the pre-defined case selection criteria, presented either as manuscripts in peer-reviewed scientific journals or as posters or oral presentations in a scientific congress.

Descriptive statistics was used to present the data from reported cases, using a case analysis approach. Cases with missing data points were excluded from the analysis of the missing variable.

Case selection

We included patients of any age with confirmed COVID-19 and case description consistent with a new diagnosis or a relapse of MS, NMOSD, or MOGAD, in accordance with the 2017 revised McDonald criteria for MS (16), the 2015 international consensus diagnostic criteria for NMOSD (17), and the international recommendations on the diagnosis of MOGAD (18), respectively. Patients fulfilling a diagnosis of clinically isolated syndrome (CIS), considered as having a high likelihood of MS, were included as well. A relapse was defined as a clinical episode reflecting a focal or multifocal CNS demyelinating event lasting at least 24 h, in the absence of fever or active infection (16). When such an event was reported during an acute febrile state related to COVID-19, it was regarded as a pseudo-relapse, even when considered a relapse in the original publication.

COVID-19 cases were included if meeting one of the following criteria, as defined by the United States Centers for Disease Control and Prevention and the Infectious Diseases Society of America: (1) clinical symptoms consistent with COVID-19 without laboratory confirmation in the absence of an alternative explanation, (2) nasopharyngeal swab positive for COVID-19 PCR with or without symptoms, or (3) positive COVID-19 serologies with or without symptoms (19, 20).

No assumptions were made regarding the duration between COVID-19 and the onset of neurological manifestations. Missing data was noted as not available.

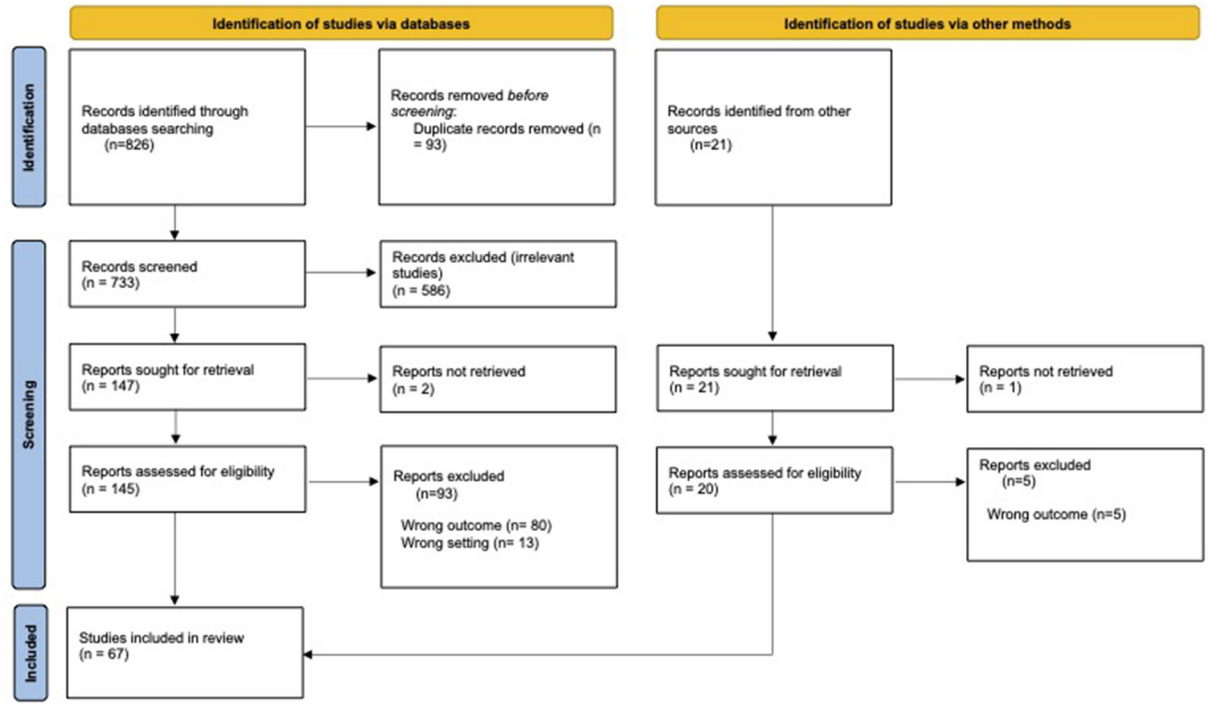

FIGURE 1
PRISMA flow chart of the article selection process.

Exclusion criteria

Cases describing clinical manifestations consistent with demyelinating events of the CNS (i.e., optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, etc.) not fulfilling the diagnostic criteria for MS, NMOSD, or MOGAD as described above, were excluded from this review. Papers reporting a suspected diagnosis of COVID-19 that do not fulfill the diagnostic criteria described above, and papers not available for full-text review were also excluded.

Results

Sixty-seven articles were included in the final review. Twelve articles describe post-COVID-19 NMOSD (21–32), 25 describe post-COVID-19 MOGAD (33–56), and 29 describe post-COVID-19 MS (57–85). One paper describes three patients with post-COVID-19 demyelinating events, of which one is NMOSD, one- MOGAD, and one- clinically isolated syndrome (CIS) (86). Another paper describes various CNS inflammatory diseases, of which three were MOGAD and one—NMOSD (87). A PRISMA flow chart illustrating the article selection process is presented in Figure 1.

Post-COVID-19 NMOSD

Cases of post-COVID-19 NMOSD are summarized in Table 1.

Collectively, 13 case reports and one case series describe the occurrence of 18 NMOSD-related clinical events in the context of COVID-19 (21–32, 86, 87). Eight patients were females, four were males, and in six cases the patients' sex was not reported. The mean age was 33.24 ± 18.5 years.

Ten case reports describe the onset of newly diagnosed NMOSD in people without previous neurological disease (22–26, 28–30, 32, 87). Two case reports describe people with previously undiagnosed neurological disease who then presented with a second clinical manifestation in temporal association to COVID-19, leading to an NMOSD diagnosis (27, 86). In one case, the aquaporin-4 antibodies (AQP4 Abs) were retrospectively found to be positive in a stored serum sample drawn 11 months before SARS-CoV-2 infection and more than a year before the clinical onset of NMOSD (31). Apostolos-Pereira et al. report a series of 34 NMOSD patients who developed COVID-19. Five of these patients (15%) developed neurological manifestations that were regarded as relapse or pseudo-relapse during or after SARS-CoV2 infection (21).

In 10 case reports, AQP4-IgG Abs were positive (22–27, 29, 31, 86, 87). In two case reports the AQP4 abs were negative

TABLE 1 COVID-19 and NMOSD: Cases of para- and post-infectious disease development, relapse or pseudo-relapse.

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	AQP4-IgG status	Time from diagnosis of COVID-19 to clinical onset	Method of COVID-19 diagnosis	CSF SARS-CoV-2 PCR	Treatment of acute attack	Outcome
Barone et al. (22)	1	New onset	M	35	NA	ON + acute myositis	Positive (titer not reported)	1 month	Clinical criteria + serology	NA	IVMP	Poor recovery of vision, full recovery of muscle symptoms
Batum et al. (23)	1	New onset	F	50	NA	LETM	Positive (titer not reported)	Concomitant	Clinical symptoms	NA	IVIG 0.4 g/kg for 5 days, then PLEX (10 courses every other day) + IVMP (750 mg every other day)	Some improvement in sensory function in the upper limbs, no motor improvement
Shaw et al. (29)	1	New onset	M	NA *Septuagenarian	NA	ON + TM	Positive (titer not reported)	9 days	SARS-CoV-2 PCR	NA	NA	Died due to sepsis and multiorgan failure
Chuang and Miskin (24)	1	New onset	NA	NA	NA	LETM + APS	Positive (titer not reported)	Neurological symptoms appeared shortly after COVID-19 diagnosis	Clinical symptoms + serology	NA	NA	NA
Corrêa et al. (25)	1	New onset	F	51	Caucasian	Encephalomyeloradiculitis	Positive (titer not reported)	2 weeks	SARS-CoV-2 PCR	Negative	IVMP 1 gr X5 days followed by PLEX	Remarkable improvement
Nasreldein et al. (28)	1	New onset	F	56	NA	BON+ diencephalic syndrome (lethargy and disorientation)	NA	2 weeks	SARS-CoV-2 PCR	NA	IVMP 1 gr/day (treatment duration not reported)	Deceased
Hooshmand et al. (27)	1	New diagnosis *Patient suffered from intractable emesis and visual loss 30 years prior	M	49	NA	ON	Positive (1:10 by FACS assay)	2 weeks	SARS-CoV-2 PCR	NA	NA	NA

(Continued)

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TABLE 1 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	AQP4-IgG status	Time from diagnosis of COVID-19 to clinical onset	Method of COVID-19 diagnosis	CSF SARS-CoV-2 PCR	Treatment of acute attack	Outcome
Shukla et al. (30)	1	New onset	F	13	Asian	BON, APS, brainstem syndrome, cerebral syndrome	Negative	NA	Clinical criteria + serology	NA	CS, IVIG, Rituximab	Improved
Khair et al. (86)	1	New onset *Patient had an undiagnosed ADEM-like demyelinating episode 6 month prior	F	14	NA	Left eye blurring of vision, neck pain, generalized fatigue, and right leg numbness	Positive (titer not reported)	Concomitant	SARS-CoV-2 PCR	NA	NA	NA
Ghosh et al. (26)	1	New onset	M	20	Asian-Indian	APS + LETM	Positive (titer not reported)	5 days	SARS-CoV-2 PCR	NA	IVMP 1 gr/d for 5 days; RTX	Some improvement of the motor power in all limbs and resolution of the sensory symptoms
Jentzer et al. (31)	1	New onset	F	71	Caucasian	LETM	Positive (titer not reported)	3 months	SARS-CoV-2 PCR	NA	NA	NA
Das et al. (32)	1	New onset	F	16		ON + LETM	Negative	4 months	Clinical symptoms + serology	NA	IVMP + oral prednisone taper + RTX	Improvement of vision; outcome of myelopathic symptoms not reported

(Continued)

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TABLE 1 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	AQP4-IgG status	Time from diagnosis of COVID-19 to clinical onset	Method of COVID-19 diagnosis	CSF SARS-CoV-2 PCR	Treatment of acute attack	Outcome
Aubart et al. (87)	1 *Also describes 3 MOGAD cases	New onset	F	14	NA	ON	Positive (titer not reported)	NA *Inclusion criteria required positive testing for SARS-CoV-2 infection performed <6 weeks before onset of neurological symptoms or seroconversion following the symptoms with a prior history of SARS-CoV-2 exposure.	SARS-CoV-2 PCR	NA	IVMP	Complete recovery
Apostolos-Pereira et al. (21)	34 NMOSD patients who developed COVID-19	Five patients (15%) presented neurologic manifestations (relapse or pseudo exacerbation) during or after SARS-CoV2 infection	NA	48, 25, 16, 22, 32	NA	2- ON, 1-visual acuity worsening in previous ON, 1-TM, 1- not reported	15 patients-positive; 7-negative; 7- not tested (all patients fulfilled the NMOSD diagnostic criteria). *The antibody status of the five patients who had relapse is not specified.	In one patient neurological symptoms appeared 7 days after the viral infection, in one- concomitantly with the febrile illness, in the other 3- not reported	18-SARS-CoV-2 PCR; 16-Clinical symptoms *The method of diagnosis of the five patients who had relapse is not specified.	NA	2- oral CS; 2-IVMP; 1- not reported	3- Good recovery; 1- Poor recovery; 1-Worsening of EDSS from 4.0 to 5.0

APS, area postrema syndrome; BON, bilateral optic neuritis; CS, corticosteroids; IVIG, intravenous immunoglobulins; IVMP, intravenous methylprednisolone; LETM, longitudinally extensive transverse myelitis; ON, optic neuritis; PLEX, plasma exchange; RTX, rituximab; TM, transverse myelitis.

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(30, 32) and each fulfilled the diagnostic criteria for seronegative NMOSD. In one report, AQ4 serostatus was not reported (28). In the case series by Apostolos-Pereira et al., 15 patients tested positive for the AQP4-IgG Abs, 7 tested negative, and in 7 the antibody testing was not available (all patients fulfilled the NMOSD diagnostic criteria). The AQP4 antibody status of the five patients who had a relapse was not specified (21).

Neurological symptoms appeared after a median of 11.5 days (range 0–90 days) from COVID-19 diagnosis. In all cases, COVID-19 symptoms preceded the occurrence of neurological symptoms.

Treatment consisted of corticosteroid (CS) monotherapy in seven cases (21, 22, 28, 87), CS + rituximab in two cases (26, 32), intravenous methylprednisolone (IVMP)+ intravenous immunoglobulin (IVIG)+plasma exchange (PLEX) in one case (23), CS +IVIG+ rituximab in one case (30), and CS + PLEX in one case (25). In the remaining six cases, the treatment regimen was not reported (21, 24, 27, 29, 86). A favorable outcome (i.e., improvement of neurological symptoms) was reported in eight patients (21, 25, 26, 30, 32, 87), while poor neurological outcome (i.e., worsening of neurological disability) was reported in four patients (21–23). Two patients deceased due to systemic complications (28, 29). The clinical outcome was not reported for the remaining four patients (24, 27, 31, 86).

Post-COVID-19 MOGAD

Post-COVID-19 MOGAD cases are summarized in Table 2.

A total of 28 cases of MOGAD occurring in temporal relation to COVID-19 have been described (33–47, 56, 86, 87). Seventeen were males, and 11 were females. The mean age was 28.1 ± 20.3 years (range 1–69 years; 10 patients <18 years old). The median time between COVID-19 and neurological symptoms was 6 days (range−7-+45 days). In one case, the neurological symptoms preceded the diagnosis of COVID-19 by 1 week (33). In four cases, neurological symptoms developed concomitantly with COVID-19 (37, 39, 42, 86), and in the remaining 23, COVID-19 diagnosis preceded the onset of neurological symptoms. In 27 (96.5%), a new diagnosis of MOGAD was made in people without prior neurological disease. In one case, a relapse occurred in a patient with known MOGAD (43). The MOG-IgG antibodies were positive in all cases. In one case, NMDAR antibodies and MOG-IgG antibodies were detected concomitantly (86). In another case, human herpes virus 6 (HHV6) PCR was also positive (46). Eighteen patients were treated with CS alone (intravenous methylprednisolone followed by oral prednisone taper, $n = 15$; IVMP alone, $n = 2$; details of steroid regimen were not described, $n = 1$) (42). One patient was treated with intravenous immunoglobulins (IVIG) alone (33). One patient received IVMP+ IVIG (45), three received IVMP + PLEX (40, 43, 46), and three received IVMP+ PLEX+ IVIG (48, 55, 56). One patient was not treated (87). The treatment regimen was not described for one patient (38). Clinical improvement was reported for 26 patients (93%).

Post COVID-19 MS

Table 3 illustrates MS cases occurring in the context of COVID-19.

Fifteen case reports and case series reported the occurrence of MS relapse/pseudo-relapse or the onset of a first demyelinating event consistent with MS or CIS in 19 patients (57, 63, 65–69, 76–79, 81, 82, 84, 86). Twelve observational case series and cohort studies documented the occurrence of relapses or pseudo-relapses among patients with a known diagnosis of MS and confirmed diagnosis of COVID-19 (58–61, 64, 71–75, 83, 85). Collectively, 54 relapses and 20 pseudo-relapses were reported in 804 patients (6.7 and 2.5%, respectively).

Three observational cohort studies of COVID-19 patients with various neurological manifestations reported MS cases (62, 70, 80). Overall, one case of multifocal demyelination consistent with MS and three MS relapses were reported among 481 patients (0.8%).

Considering all the reported cases, a total of 73 demyelinating events consistent with CIS/MS (10 new diagnoses and 63 relapses) and 22 events defined as pseudo-relapse were reported in 1,305 people (5.6 and 1.7%, respectively). Of these 73 events, 11 were in females, 10 in males, and sex was not reported in the remaining 64 cases. The mean age was 38.45 ± 15.93 years. Most relapses or first demyelinating events consistent with MS/CIS occurred after the onset of COVID-19. However, in two cases neurological symptoms preceded the diagnosis of COVID-19 by 6 and 21 days, respectively (57, 76). The median time from COVID-19 diagnosis to demyelinating event onset was 13.5 days (range−21-180 days).

Nine hundred eighty-six people with a known MS and COVID-19 diagnosis were reported. Of these, 624 (63.3%) were treated with various disease-modifying treatments (DMTs), 14 (1.5%) were not treated, and for 165 (16.7%), the information on DMTs was not reported. Twenty-one MS patients treated with DMTs (3.4%) had a relapse in temporal association with COVID-19. Five MS patients treated with DMTs (0.8%) had a pseudo relapse, and 144 (23.1%) did not have neurological worsening. The remaining 455 MS patients treated with DMTs (73%) were reported in larger cohorts in which some people were not treated. The information regarding relapses in these cohorts was not stratified between treated and untreated patients (61, 75).

Most MS/CIS cases received treatment with IVMP 1 gram for 3–5 days (57, 61, 65, 68, 76, 77, 79, 80, 82) and had a favorable outcome (57, 65, 68, 77–82). Treatment of pseudo-relapses was primarily focused on COVID-19 management, with return to baseline neurological status upon infection recovery (63, 69).

TABLE 2 COVID-19 and MOGAD: Cases of para- and post-infectious disease development or exacerbation.

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	CSF SARS-CoV-2 PCR	Time from diagnosis of COVID-19 to clinical onset	Treatment	Outcome
Zhou et al. (44)	1	New onset	M	26	Hispanic	BON +TM	SARS-CoV-2 PCR	Negative	A few days	IVMP 1 gr X 5d followed by oral prednisone taper	Rapid improvement in vision, outcome of myelopathic symptoms not reported
Ide et al. (35)	1	New onset	F	24	NA	ON+ TM (diagnosed as ADEM d/t additional brain lesions)	SARS-CoV-2 PCR	Negative	3 weeks	IVMP 1 gr X5 days followed by prednisolone taper	Visual symptoms Improved spontaneously; other symptoms improved after treatment
Khan et al. (36)	1	New onset	M	11	NA	BON	SARS-CoV-2 PCR	NA	4 days	IVMP + prednisone taper	Improved vision
Kogure et al. (37)	1	New onset	M	47	Asian	ON (clinically unilateral, but bilateral optic nerve enhancement on MRI)	SARS-CoV-2 PCR	Negative	Concomitant	IVMP 1 gr X 3 days + prednisone taper	Rapid improvement in pain and vision
Pinto et al. (40)	1	New onset	F	44	NA	CNS inflammatory vasculopathy	SARS-CoV-2 PCR	Negative (repeated twice)	7 days	IVMP 1 gr X5 days followed by oral prednisolone 60 mg/d, + PLEX	Rapid clinical improvement
Woodhall et al. (43)	1	Relapse	F	39	NA	ON	SARS-CoV-2 PCR	NA	6 days	IVMP 1 g/day for 5 days followed by five cycles of PLEX	Partial improvement

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TABLE 2 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	CSF SARS-CoV-2 PCR	Time from diagnosis of COVID-19 to clinical onset	Treatment	Outcome
Sawalha et al. (41)	1	New onset	M	44	Hispanic	BON	SARS-CoV-2 PCR	NA	One week	IVMP 1 g/day for 5 days followed by prednisone taper	Complete recovery in one eye, remarkable recovery but not complete in the other eye
Khair et al. (86)	1 *Also describes one case of NMOSD and one CIS	New onset *Concomitant NMDAR Abs	F	16	NA	Headache, blurred vision, leg numbness, and weakness.	SARS-CoV-2 PCR	NA	Concomitant	NA	NA
Lindan et al. (38)	1	New onset	M	4	NA	Seizures, facial palsy, and four limb dysfunction	SARS-CoV-2 serology	NA	NA	IVMP	Marked improvement
Peters et al. (39)	1	New onset	M	23	NA	Headaches and dysesthesia followed by seizures, inattention and cognitive slowing	SARS-CoV-2 PCR	Negative	Initial neurological symptoms developed concomitantly with positive COVID-testing; further symptoms developed over the next 4 weeks	IVMP 1 gr X5 days followed by oral steroid taper	Gradual clinical and radiological resolution

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TABLE 2 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	CSF SARS-CoV-2 PCR	Time from diagnosis of COVID-19 to clinical onset	Treatment	Outcome
Vraka et al. (42)	1 *Describes another case of encephalopathy with negative MOG-IgG	New onset	F	13 months	NA	ADEM	SARS-CoV-2 PCR	Negative	Concomitant	Steroids	Gradual improvement
Ahsan et al. (33)	1	New onset	F	7	NA	ADEM	SARS-CoV-2 serology	NA	Neurological symptoms preceded COVID-19 by a week	IVIG 2 g/kg over 3 days	Gradual improvement (almost returned to her baseline with mild dysarthria)
de Ruijter et al. (34)	1	New onset	M	15	Caucasian	BON	Clinical criteria	NA	A few weeks	IVMP 1 gr/d for 3 days	Improved (almost full recovery)
Durovic et al. (47)	1	New onset	M	22	NA	Encephalitis	SARS-CoV-2 PCR	Negative	3 days	IVMP 1 gr/d for 5 days	Complete clinical and radiological resolution
Jumah et al. (46)	1	New onset *Concomitant HHV6 infection	M	61	NA	LETM	SARS-CoV-2 PCR + serology	Negative	1 week	IVMP 1 gr/d for 5 days + prednisone taper + Gancyclovir, PLEX (7 sessions)	Marked improvement
Sinha et al. (45)	1	New onset	F	11	NA	BON	SARS-CoV-2 PCR	NA	3 days	IVMP 1 gr/d + IVIG 2gr/kg for 5 days + prednisone taper	Improved

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TABLE 2 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	CSF SARS-CoV-2 PCR	Time from diagnosis of COVID-19 to clinical onset	Treatment	Outcome
Yang et al. (55)	1	New onset	M	57	NA	LETM	SARS-CoV-2 PCR	NA	3 weeks	IVIG × 4 days, then five sessions of PLEX, then IVMP 1 gr/d for 5 days + steroid taper	NA
Assavapongpaiboon et al. (50)	1	New onset	F	35	Thai	BON	SARS-CoV-2 PCR	Negative	1 week	IVMP 1 gr/d for 5 days + steroid taper	Improved
Dias da Costa et al. (52)	1	New onset	M	31	NA	LETM	SARS-CoV-2 serology	Negative	21 days	IVMP 1 gr/d for 5 days + steroid taper	Almost complete resolution of motor and sensory symptoms, mild urinary symptoms
Doukas et al. (53)	1	New onset	M	40	NA	TM	SARS-CoV-2 serology	NA	12 days	IVMP 1 gr/d for 5 days + steroid taper	Gradual improvement
Jossy et al. (54)	1	New onset	M	38	NA	ON	SARS-CoV-2 serology	NA	6 weeks	IVMP 1 gr/d for 3 days + steroid taper	Complete resolution
Rojas-Correa et al. (49)	1	New onset	M	69	NA	BON	Clinical criteria	Negative	45 days	IVMP 1 gr/d for 5 days + steroid taper	Improved
Sardar et al. (48)	1	New onset	F	38	NA	BON *Diagnosed with concomitant idiopathic intracranial hypertension	Clinical criteria	NA	2 weeks	IVMP for 5 days, PLEX, IVIG for 5 days Acetazolamide	Significant improvement

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TABLE 2 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	CSF SARS-CoV-2 PCR	Time from diagnosis of COVID-19 to clinical onset	Treatment	Outcome
Žorić et al. (51)	1	New onset	M	63	NA	ON	SARS-CoV-2 serology	NA	4 weeks	IVMP 1 gr/d for 5 days + steroid taper	Improved
Aubart et al. (87)	3 *Also describes one case of NMOSD	New onset	2M, 1F	1.5, 4, 10	NA	ADEM	SARS-CoV-2 PCR or serology	NA	NA *Inclusion criteria required positive testing for SARS-CoV-2 infection performed <6 weeks before onset of neurological symptoms or seroconversion following the symptoms with a prior history of SARS-CoV-2 exposure.	2- IVMP, 1- not treated	Complete recovery
Cay-Martínez et al. (56)	1	New onset	F	7	NA	ADEM	SARS-CoV-2 serology	Negative	1 week	IVMP + PLEX + IVIG + oral prednisone taper	Resolution of facial and upper extremity weakness, mild improvement in leg weakness

ON, optic neuritis; BON, bilateral optic neuritis; TM, transverse myelitis; LETM, longitudinally extensive transverse myelitis; ADEM, acute demyelinating encephalomyelitis; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulins; PLEX, plasma exchange.

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TABLE 3 COVID-19 and MS: Cases of para- and post-infectious disease development, relapse or pseudo-relapse.

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	DMT before COVID-19 infection	Time from diagnosis of COVID-19 to clinical onset	CSF SARS-CoV-2 qPCR	Treatment	Outcome
Case reports												
Moore et al. (77)	1	New onset	M	28	NA	Brainstem syndrome (vertigo, oscillopsia, diplopia, facial numbness)	Clinical criteria	None	Neurological symptoms appeared 10 days after COVID-19 symptoms	Negative	IVMP 1 g/day for 3 days followed by prednisone taper	Improved
Pignolo et al. (79)	2	1 new onset, 1 relapse	M, F	21,52	NA	Hand paresthesia and facial nerve palsy; Right-sided weakness and clumsiness	Clinical criteria, serology	None (new onset) Cladribine (relapse)	MS onset a few days after COVID-19; MS relapse 2 months after COVID-19	Negative in one case (new onset), NA in the other	IVMP 1 g/day for 5 days	Relapse- fully resolved, new onset disease-partial recover
Fragoso et al. (66)	1	New onset	F	27	Caucasian	Left side dysesthesia	Clinical criteria	None	6 months	Negative	NA	NA
Wildemann et al. (81)	1	MS relapse and Takotsubo cardiomyopathy	F	39	NA	Brainstem syndrome (dizziness, diplopia, dysarthria, dysphagia)	SARS-CoV-2 PCR	DMF	10 days	Negative	IVMP 2 gr/day for 5 days + PLEX (seven courses)	Slow improvement
Yavari et al. (82)	1	New onset	F	24	NA	Diplopia, facial nerve palsy, fingertips paresthesia	SARS-CoV-2 PCR	None	1 month	NA	IVMP 1 gr/day for 4 days	Improved

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TABLE 3 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	DMT before COVID-19 infection	Time from diagnosis of COVID-19 to clinical onset	CSF SARS-CoV-2 qPCR	Treatment	Outcome
Palao et al. (78)	1	New onset	F	29	NA	ON	SARS-CoV-2 serology	None	2–3 weeks	Negative	IVMP 1 gr/day (treatment duration not reported) followed by oral prednisolone taper	Improved
Florae et al. (65)	1	Relapse *3 weeks post-partum	F	40	Caucasian	Right sided paresthesia and motor disability	SARS-CoV-2 PCR	None	No systemic symptoms, tested positive on swab PCR upon admission	NA	IVMP 1 gr/d for 3 days; hydroxychloroquine 4 g/day, lopinavir/ritonavir 4 tablets/day for 10 days, and azithromycin 1 g/day, for 3 days	Remission of neurological deficit after 2 weeks
Khair et al. (86)	1	CIS	M	8	NA	Double vision, worsening fine motor skills, and ataxic gait	Clinical criteria	None	1 month	NA	NA	NA
Kataria et al. (69)	3	Pseudo-relapse	2M, 1F	65, 52, 69	NA	Fatigue, general weakness	SARS-CoV-2 PCR	GA	Concomitant	NA	Only COVID-19 management	Improved to baseline status

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TABLE 3 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	DMT before COVID-19 infection	Time from diagnosis of COVID-19 to clinical onset	CSF SARS-CoV-2 qPCR	Treatment	Outcome
Barzegar et al. (57)	1	Relapse	F	42	NA	Muscle aches, gait difficulty, sensory disturbances, and weakness on the right side	SARS-CoV-2 PCR	Fingolimod	Neurological symptoms preceded COVID-19 symptoms by 6 days	NA	Initially IVMP 1 gr/d for 3 days; then azithromycin, ceftriaxone, hydroxychloroquine, oseltamivir, and piperacillin/tazobactam	Gradual improvement
Domingues et al. (63)	1	CIS	F	42	NA	Left side paresthesia	Clinical criteria	None	Concomitant	Positive	No steroids, COVID-19 management not detailed	Full recovery
Jaisankar et al. (67)	1	Pseudo-relapse	M	45	Caucasian	Dysphagia, altered mental status, general deterioration	SARS-CoV-2 PCR	None	COVID-19 diagnosed 2 weeks prior to neurological deterioration. *Also diagnosed with acute renal failure, anemia, PE and sepsis.	NA	IVMP (dose and duration not reported). Received fluids, packed red blood cells and transfusions, anticoagulants, ciprofloxacin	Ongoing disability

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TABLE 3 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	DMT before COVID-19 infection	Time from diagnosis of COVID-19 to clinical onset	CSF SARS-CoV-2 qPCR	Treatment	Outcome
Karsidag et al. (68)	2	Two patients with new-onset MS (* + 1 ADEM)	1F, 1M	42, 32	NA	Jaw and left facial pain and paresthesia; numbness in left jaw	Clinical criteria	None	2–3 weeks; 4 months	1 Negative, 1 Positive	1-IVMP 1 gr/d for 7 days; 1- IVMP 1 gr/d for 10 days	Improved
Möhn et al. (76)	1	Relapse	M	42	NA	Gait and limb ataxia	SARS-CoV-2 PCR	Teriflunomide	Neurological symptoms preceded COVID-19 by 3 weeks	NA	IVMP 1 gr/d for 4 days	Initial improvement, then worsened concomitantly to COVID symptoms
Finsterer (84)	1	Relapse	F	27	NA	TM	Clinical criteria	IFNβ-1a	2 weeks	NA	CS	Slow improvement
Observational case series and cohort studies of MS patients												
Khurana et al. (71)	5 RRMS patients	1 relapse	3F, 2M	Mean (SD) age 35.60 (13.94)	NA	NA	SARS-CoV-2 PCR	Treated with DMT, type not specified	NA	NA	NA	NA
Maghzi et al. (73)	3 RRMS, 1 SPMS, 1 RIS	No relapses	3M, 2F	Mean 53.6	NA	NA	SARS-CoV-2 PCR	Teriflunomide	NA	NA	NA	NA
Mantero et al. (74)	7 RRMS patients	No relapses. 1 pseudo-relapse	5F, 2M	Mean 35.9 ± 11.4	NA	Left hand paresthesia	Clinical criteria	DMF	Concomitant	NA	NA	NA

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TABLE 3 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	DMT before COVID-19 infection	Time from diagnosis of COVID-19 to clinical onset	CSF SARS-CoV-2 qPCR	Treatment	Outcome
Conway et al. (60)	72 RRMS, 21 SPMS, 8 PPMS, 2 CIS, eight related disorders	2/111 (1.8%) relapses, 19 (17.2%) pseudo-relapses and 27 (24.3%) with worsening of pre-existing MS symptoms. Five patients (4.5%) had new MRI lesions on T2 or T1Gd scans	85 females (77%)	Mean age 49 (SD 12.2) years	NA	NA	Clinical criteria	NA	NA		NA	NA
Chyzhyk et al. (59)	17 relapsing MS patients	No clinical or radiological signs of MS disease activity During 6 months of observation	4M, 13 F	Mean age 38 ± 7.6 years	NA	NA	Clinical criteria	Treated with DMT, type not specified	NA		NA	NA

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TABLE 3 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	DMT before COVID-19 infection	Time from diagnosis of COVID-19 to clinical onset	CSF SARS-CoV-2 qPCR	Treatment	Outcome
Czarnowska et al. (61)	426 individuals with MS	27 patients (6.34%) had a relapse at 3 months after the initial infection	142M, 284F	Mean 40.27 ± 10.12	NA	Symptoms during the relapse were as following: pyramidal track symptoms (16 people), cerebellar symptoms (eight people), sensory deficit (four people), brainstem symptoms (3 people), urinary incontinence (1 person)	SARS-CoV-2 PCR (n = 361), SARS-CoV-2 serology (n = 24) or combination of tests	Interferon beta (n = 77); GA (n = 43); DMF (n = 171); teriflunomide (n = 34); fingolimod (n = 16); natalizumab (n = 29); ocrelizumab (n = 29); cladribine (n = 7); alemtuzumab (n = 1); mitoxantrone (n = 1); ozanimod (n=12); other (n = 12); none (n = 4) *Type of DMT in patients who relapsed not specified	The mean time for relapse occurrence after the SARS-CoV-2 infection was 43 days		All treated with IVMP 3–5 gr	NA
Michelena et al. (75)	41 MS patients with confirmed COVID-19 diagnosis	25 patients (61%) reported neurological worsening, three patients (7.7%) met criteria for relapse	24 F, 17M	Mean 42.9 years (SD 11.3)	NA	Motor (n = 12) Sensory (n = 10) Visual (n = 7) Balance disorders (n = 3) Memory (n = 6) Fatigue (n = 13)	SARS-CoV-2 PCR	35 treated with DMTs (23-oral DMTs, 4-injectables, 8-monoclonal antibodies)	Concomitant (n = 16), within the 1st month (n = 5), beyond the 1st month (n = 4)	NA	CS (type, dose, and duration not reported)	NA

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TABLE 3 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	DMT before COVID-19 infection	Time from diagnosis of COVID-19 to clinical onset	CSF SARS-CoV-2 qPCR	Treatment	Outcome
Luetic et al. (72)	17 RRMS and 1 RIS patients	No MS relapses occurred during or after COVID-19 course.	13 F, 5M	Mean 41.2 ± 12.6	NA	NA	11-SARS-CoV-2 PCR; 8-Clinical criteria	Teriflunomide	NA	NA	NA	NA
Etemadifar et al. (64)	A retrospective cohort study comparing the risk of relapse in RRMS patients with (n = 56) and without COVID-19 (n = 69) *Within 6 months from COVID	4 patients in the MS-COVID-19 group (7.14%) had a relapse compared to 18 patients in the RRMS without COVID-19 group (26.09%). Incidence rate ratio: 0.275; p = 0.026	COVID-19 group: 40 F/15 M; non COVID-19 group: 62 F/ 7 M	COVID-19 group: 36.89 (±9.06); non-COVID-19 group: 36.19 (±8.97)	NA	2-limb paresthesia, 1-diplopia, 1-lower extremity weakness	SARS-CoV-2 PCR	Teriflunomide (n = 3); fingolimod (n = 9); DMF (n = 22); AZA (n = 5); Interferon ß 1b (n = 3; Interferon ß 1a (n = 6); GA(n = 3); RTX (n = 3); NTZ (n = 2) *Type of DMT in patients who relapsed not specified	Only reported that the 4 relapses in COVID-19 confirmed patients occurred after COVID-19 diagnosis	NA	NA	NA

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TABLE 3 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	DMT before COVID-19 infection	Time from diagnosis of COVID-19 to clinical onset	CSF SARS-CoV-2 qPCR	Treatment	Outcome
Etemadifar et al. (83)	A prospective-retrospective hybrid single center cohort study comparing the risk of relapse during 1 year pre- and post-COVID-19 period in 53 RRMS patients *Some patients may have been included in the previous study by the same first author	11 patients (20.75%) in the post-COVID-19 period and 16 patients (30.19%) in the pre-COVID-19 period experienced a relapse (p = 0.30)	45 F, 8M	Mean 38.42 (SD 8.77)	NA	NA	Clinical criteria or SARS-CoV-2 PCR *Number of patients in each group not specified	IFN beta (n = 4); DMF (n = 21); teriflunomide (n = 1); GA (n = 1); fingolimod (n = 12); RTX (n = 9); AZA (n = 2); none (n = 3)	NA	NA	NA	NA

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TABLE 3 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	DMT before COVID-19 infection	Time from diagnosis of COVID-19 to clinical onset	CSF SARS-CoV-2 qPCR	Treatment	Outcome
Barzegar et al. (58)	A retrospective observational study comparing the relapse rate among 41 MS patients with confirmed COVID-19 during a pre-defined at-risk period (from 2 weeks before to 5 weeks after COVID-19) and the previous 2 years	Five patients had a relapse during the defined at-risk period. Other two patients had neurological worsening that did not meet clinical relapse definition. Increased relapse rate during the at-risk period (RR: 2.566, 95% CI: 1.075–6.124, $P = 0.034$)	31 females, 10 males	Mean 35.10 ± 9.20,	NA	NA	SARS-CoV-2 PCR	NA	All relapses occurred after the onset of COVID-19 (Mean 3.2 weeks, range 1–5 weeks)		NA	NA
Paybast et al. (85)	202 MS patients followed for 1 year	25 patients developed COVID-19, of which 1 (4%) had a relapse	164F, 37M	38.09 ± 10.44	NA	TM	SARS-CoV-2 PCR	NA	NA	NA	PLEX	NA

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TABLE 3 (Continued)

References	Number of patients	Diagnosis	Gender	Age	Ethnicity	Clinical presentation	Method of COVID-19 diagnosis	DMT before COVID-19 infection	Time from diagnosis of COVID-19 to clinical onset	CSF SARS-CoV-2 qPCR	Treatment	Outcome
General observational studies												
Sandoval et al. (80)	13 pediatric patients with confirmed COVID-19 and new-onset neurological manifestations	1 patient with new-onset multifocal demyelination consistent with MS	M	14		ON, sixth nerve palsy, asymmetric paraparesis	SARS-CoV-2 PCR	None	No systemic symptoms, tested positive on swab PCR upon admission	NA	IVMP (dose and duration not reported)	Significant clinical improvement)
Khedr et al. (70)	439 patients with confirmed/probable COVID-19	2 MS relapse (among those with probable COVID-19, $n = 62$)	NA	NA	NA	NA	SARS-CoV-2 PCR	NA	NA	NA	NA	NA
Dhillon et al. (62)	Case series of 29 inpatients presented with COVID-19 and neurological disorders, 2 MS patients	1 MS relapse	M	56	White	Worsening of limb weakness and dysarthria	SARS-CoV-2 PCR	NA	NA	NA	NA	Ongoing disability

CIS, clinically isolated syndrome; DMT, disease modifying therapy; ON, optic neuritis; TM, transverse myelitis; IVMP, intravenous methylprednisolone; CS, corticosteroids; PLEX, plasma exchange.

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Discussion

This systematic review summarizes the currently available data on the occurrence of demyelinating CNS events in the context of COVID-19. As noted, the vast majority of NMOSD and MOGAD cases represent newly diagnosed cases presenting with the typical clinical, radiological, and laboratory findings associated with these two disorders. In contrast, the MS cases described vary between newly diagnosed cases, relapses, and pseudo-relapses. The patients' age of diagnosis in the three disease groups was relatively similar to the age of diagnosis reported in the literature for non-COVID-19 related cases. The clinical presentations and treatment approach were also similar to non-COVID-19 related cases (for further details, please see Tables 1–3).

Several mechanisms involved in the pathogenesis of demyelinating events in the context of SARS-CoV-2 infection have been proposed. These may be related to either direct viral neurotropism or induction of aberrant immune response. The neurotrophic features of the Coronavirus family have been previously reported for the Middle East respiratory syndrome coronavirus (MERS-COV) and SARS-COV-1, and similar evidence has been occasionally reported for SARS-CoV-2 (88–91). However, the fact that the SARS-CoV-2 PCR test in the CSF was negative in many of the reported cases (25, 35, 37, 39, 40, 42, 44, 66, 68, 77–79, 81) would argue against this mechanism of direct pathogenicity. Conversely, some evidence favors the theory of para-infectious or post-infectious immune-mediated etiology. In fact, SARS-CoV-2 infection leads to hyperactivation of pro-inflammatory T cells resulting in increased levels of inflammatory cytokines and chemokines (92) and decreased regulatory T cells to impair immune response (93). The resulting pro-inflammatory hyperimmune state may activate specific immune-mediated mechanisms resulting in CNS inflammation and damage. The favorable response to immunotherapy in the majority of the reported cases appears to support this theory.

The distinction between relapse and pseudo-relapse may not always be straightforward. According to the 2017 McDonald criteria, a relapse should be defined in the absence of fever or acute infection; hence, new or worsening neurological symptoms developed during a febrile illness or in the presence of acute infection in a patient with a known diagnosis of MS should not be defined as true relapse, but rather regarded as a pseudo-relapse. However, there may be situations where the diagnosis of true relapse should still be considered even in the context of acute infection. For example, a true relapse should be considered if the onset of new symptoms is associated with clinical signs that can be attributed to a specific anatomical localization that has not been previously described or correlated with the presence of a new symptomatic MRI lesion. Following this rationale, a few of the described clinical worsening in MS cases were felt to be better classified as pseudo-relapses (67, 69).

Prior studies propose that MS relapses in temporal association with viral infections occur between 1 and 2 weeks before infection to 3–5 weeks after (94–98). Andersen et al. and Correale et al. reported that the highest frequency of relapses and infection-related MS attacks occurred during the first 2 weeks after infection onset (94). In the series reported by Sibley et al., the median time between the onset of infection and occurrence of MS exacerbation was 8 days (95). Buljevac et al. reported a mean duration of 9.5 days between the onset of infection and clinical MS exacerbation. Both Buljevac et al. and Correale et al. also compared the relapse rate ratio during different time intervals and found that the highest rate ratio was observed from weeks 1 to 4, while the exacerbation rate ratio for weeks 3–5 was lower and not statistically significant compared to the non-at risk period (97, 98). Considering these data, MS relapses occurring more than 4–5 weeks from an infection are probably not related to the prior infectious insult. Therefore, MS cases that occurred >6 weeks from COVID-19 (64, 66, 68, 79, 83), although included in this review in order to provide a comprehensive review of available data, are thought to be more likely coincidental and not related to the preceding infectious insult. Likewise, the relation between SARS-CoV-2 infection and the NMOSD and MOGAD cases developing >6 weeks after the infection (31, 32, 49, 54) remains uncertain. The case of MOGAD occurring in temporal association to both HHV6 and COVID-19 infection (46) may also confound the association between COVID-19 and MOGAD.

The use of disease-modifying therapies (DMTs) may be associated with an increased risk of viral and bacterial infections. Early in the course of the COVID-19 pandemic, this notion led to significant concerns regarding COVID-19 outcomes for people with neuroimmunological diseases. While some reports described a less favorable COVID-19 course in people treated with B-cell depleting agents, the use of other DMTs does not seem to be associated with such an increased risk (99–101). Another aspect of interest is whether the efficacy of DMTs is maintained during the pandemic. However, the currently available data is not sufficient to answer this question. While relapses were reported in only 3.4% of MS patients treated with DMTs, information about DMTs use and relapses was available for a relatively small proportion of patients (169/624, 27.1%). The fact that the majority of NMOSD and MOGAD cases reported are of newly diagnoses rather than relapses of previously diagnosed disease, may suggest that the efficacy of immunotherapy during the pandemic is maintained. In the series reported by Apostolos-Pereira et al., 97% of NMOSD patients (33/34) continued their prescribed immunotherapy during the pandemic. The relatively low incidence of neurological exacerbation reported by the authors (5/34, 15%) may further support this theory (21). Still, prospective studies comparing the rate of relapse between COVID-19 patients treated with DMTs and untreated patients are required to answer this question.

The current literature pertaining to the occurrence of demyelinating events in temporal association with COVID-19 is primarily composed of case reports, case series, and relatively small cohort studies. Therefore, while the rate of such events appears low based upon this review, especially considering the high prevalence of SARS-CoV-2 infection, the available data does not permit the determination of whether the rate of CNS demyelinating events (either new onset or true relapse) differs among people with confirmed COVID-19 compared to those who do not contract the infection. Additional questions that remain unanswered at this point are whether there are differences in the severity of demyelinating attacks and the response to acute treatments between demyelinating events occurring in association with COVID-19 and those not associated with the infection.

In conclusion, the rate of CNS demyelinating events occurring in the context of SARS-CoV-2 infection is relatively low given the global prevalence of infection. The clinical outcomes of new-onset or relapsing MS, NMOSD, or MOGAD associated with antecedent or concurrent SARS-CoV-2 infection is mostly favorable. Larger prospective epidemiological studies are needed to better characterize the impact of COVID-19 on CNS demyelinating diseases.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

IL, SN, GM, and MiL contributed to the conception and design of the study. IL and MiL organized the database. IL and SN performed the data collection. IL wrote the first draft of the manuscript. MeL conducted the literature search. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.970383/full#supplementary-material

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Case report: Vaccine-induced immune thrombotic thrombocytopenia complicated by acute cerebral venous thrombosis and hemorrhage after AstraZeneca vaccines followed by Moderna COVID-19 vaccine booster and surgery

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Vaccine-induced thrombotic thrombocytopenia (VITT) is a well-known complication of adenoviral vector COVID-19 vaccines including ChAdOx1 nCoV-19 (AstraZeneca) and Ad26. COV2.S (Janssen, Johnson & Johnson). To date, only a few cases of mRNA COVID-19 vaccine such as mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech)-induced VITT have been reported. We report a case of VITT with acute cerebral venous thrombosis and hemorrhage after a booster of mRNA-1273 (Moderna) vaccine in a patient previously vaccinated with two doses of the AstraZeneca vaccine. A 42-year-old woman presented with sudden onset of weakness of the right upper limb with focal seizure. She had received two doses of AstraZeneca vaccines and a booster with Moderna vaccine 32 days before presentation. She had also undergone a laparoscopic myomectomy 12 days previously. Laboratory examinations revealed anemia (9.5 g/dl), thrombocytopenia (31 $\times$ $10^3/\mu l$), and markedly elevated d-dimer (>20.0 mg/L; reference value <0.5 mg/L). The initial brain computed tomography (CT) was normal, but a repeated scan 10 h later revealed hemorrhage at the left cerebrum. Before the results of the blood smear were received, on suspicion of thrombotic microangiopathy with thrombocytopenia and thrombosis, plasmapheresis and pulse steroid

therapy were initiated, followed by intravenous immunoglobulin (1 g/kg/day for two consecutive days) due to refractory thrombocytopenia. VITT was confirmed by positive anti-PF4 antibody and both heparin-induced and PF4-induced platelet activation testing. Clinicians should be aware that mRNA-1273 Moderna, an mRNA-based vaccine, may be associated with VITT with catastrophic complications. Additionally, prior exposure to the AstraZeneca vaccine and surgical procedure could also have precipitated or aggravated autoimmune heparin-induced thrombocytopenia/VITT-like presentation.

KEYWORDS

vaccine-induced thrombotic thrombocytopenia, cerebral hemorrhage, Moderna booster, autoimmune heparin-induced thrombocytopenia, cerebral venous thrombosis

Introduction

Coronavirus disease 2019 (COVID-19) has caused six million deaths globally since 2019, the majority with severe respiratory complications. Several vaccines against SARS-CoV-2 were developed and administered worldwide, including ChAdOx1 nCoV-19 (AstraZeneca), BNT162b2 (BioNTech/Pfizer), mRNA-1273 (Moderna), and Ad26.COV2.S (Janssen; Johnson & Johnson). Despite the high efficacy of these vaccines, the virus developed different variants, such as the omicron variant, making the vaccines less effective. To increase protection, a booster shot after two injections and combined multiple source-based vaccines were suggested. While these strategies were intended to improve immunity, they could also increase the risk of adverse effects.

Vaccine-induced immune thrombotic thrombocytopenia (VITT) was first reported by Greinacher et al. and proposed a pathophysiology resembling that of heparin-induced thrombocytopenia/thrombosis (1). The pathogenesis of these thrombotic events involves the generation of antibodies that bind to platelet factor 4 (PF4), resulting in platelet activation, aggregation, and thrombosis formation. Treatment strategies include anticoagulation, preferably with a non-heparin agent, correction of low fibrinogen with cryoprecipitate, consideration of intravenous immunoglobulin (IVIG), steroids, and plasmapheresis (2). In a prospective cohort study, patients with VITT who received AstraZeneca vaccines have a mortality rate of approximately 22%, which increased to 2.7 times among patients with cerebral venous thrombosis. The mortality associated with VITT was the highest among patients with a low platelet count and intracranial hemorrhage (3).

An association between adenoviral vector-based vaccines and VITT is well recognized. However, there is little to no information in the literature about VITT after receiving an mRNA vaccine such as the Moderna vaccine, or more precisely, VITT after a booster of the Moderna vaccine following previous exposure to the adenoviral AstraZeneca vaccine, which raises the possibility of a cumulative effect of induction of thrombogenic autoimmunity. Herein, we present such a case of VITT complicated by cerebral venous thrombosis and hemorrhage.

Case

A 42-year-old woman presented to the emergency room with sudden onset of weakness and numbness of the right upper limb. Her past medical history was unremarkable except for occasional headaches, which were related to her menstrual cycle and stress. She had been suffering from menorrhagia and dysmenorrhagia for a year, and a huge uterine myoma (9.3 × 10.2 × 7.7 cm over right posterior wall) was found. She only took iron supplements and had not used oral contraceptives before. She had received the first and second doses of the ChAdOx1 nCoV-19 (AstraZeneca) vaccine seven and 4 months before hospitalization, and she received a booster dose of the Moderna vaccine 32 days before the onset of symptoms. Of note, 12 days before the presentation, she had a laparoscopic myomectomy under general anesthesia. The medications used in anesthesia included fentanyl, lidocaine, propofol, rocuronium bromide, dexamethasone, glycopyrrolate, and desflurane inhalation. Her vital signs before, during, and after surgery were normal. She reported mild dizziness after surgery. Two days after surgery, she began to experience a mild headache, nausea, and lethargy. Frequent vaginal bleeding was also noted, but the amount of bleeding was small. The hemoglobin (15.3 g/dl; reference value 12–16 g/dl), platelet count (121 × 10^3/μl; reference value, 150–400 × 10^3/μl), coagulation parameters, and blood biochemistry tests were normal before the surgery. However, on the first postoperative day, she was found to be anemic (Hgb 8.2 g/dl) and thrombocytopenic (platelets 121 × 10^3/μl). The rapid decline of hemoglobin was thought to be due to blood loss (about 400 ml during surgery) and hemodilution (fluid replacement with colloid 500 ml and crystalloid 1,100 ml during surgery, and dextrose 5% in water 1,000 ml and 0.9% normal saline

1,000 ml after surgery). The platelet count further decreased to 31 × 10^3/μl 8 days later in the gynecology outpatient department visit. There was no heparin exposure, infection, or blood transfusion during that hospitalization.

On her current admission to the hospital, her body temperature was 36.8°C; blood pressure, 125/94 mmHg; heart rate, 96 beats per minute; respiratory rate, 22 times per minute. Physical and neurological examinations revealed mild pale conjunctiva, weakness of the right hand (Medical Research Council scale grade 3), and paresthesia of the right upper limb. The National Institutes of Health Stroke Scale score was 2. Laboratory studies showed anemia (9.5 g/dl), thrombocytopenia (31 × 10^3/μl), and elevated D-dimer (>20.0 mg/L; reference value <0.5 mg/L). Brain computed tomography (CT) without contrast enhancement revealed no remarkable findings. Antiplatelet treatment with aspirin 300 mg was orally administered on suspicion of acute ischemic stroke. Focal-onset aware seizure of the right upper and lower limbs was observed. The repeated brain CT still showed no abnormalities. Levetiracetam 1,500 mg was administered intravenously on suspicion of early poststroke seizure.

Ten hours after admission, she had progression of right-sided weakness and consciousness change. Brain CT revealed two lobar hemorrhages over the left frontal and parietal lobes with perifocal edema and mild midline shift (Figure 1A). She was intubated immediately. On suspicion of VITT or other autoimmune disorder-related thrombocytopenia such as catastrophic antiphospholipid syndrome, systemic lupus erythematosus (SLE) with central nervous system involvement, and thrombotic thrombocytopenic purpura, plasmapheresis was arranged, and methylprednisolone 1 g/day was administered intravenously. Unfortunately, her consciousness deteriorated rapidly, declined from E2M4VT to E1M1VT, and bilateral pupils were dilated to 8 mm without light reflexes. The follow-up brain CT revealed rapid expansion of hematoma with marked brain edema, midline shift, and uncal and tonsillar herniation. The lobar hemorrhage extended into the subdural and subarachnoid spaces (Figure 1B). Emergent decompressive craniectomy was performed after transfusion of two units of single-donor platelets. Plasmapheresis was undertaken immediately after the surgery. The intracranial cerebral pressure (ICP) increased to 120 mmHg on day 3 of admission, despite the use of mannitol, glycerol, 3% normal saline, and mechanical hyperventilation. The enzyme-linked immunosorbent assay for anti-PF4 polyanion antibody was positive (test value, 2.91 optical density; reference value, <0.4 optical density). ADAMTS-13 activity was normal, and markers of SLE or anti-phospholipid syndromes were all negative (Supplementary material). The blood smear was negative for schistocytes. The result of the platelet activation assay was consistent with VITT (Figure 2) thereby confirming the diagnosis of VITT.

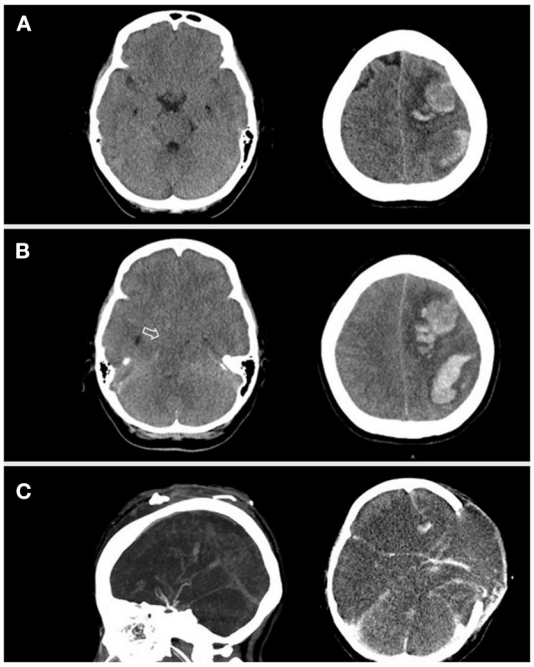

FIGURE 1
A series of brain CT over the disease course. **(A)** Brain CT revealed two lobar hemorrhages located in the left frontal and parietal lobes with perifocal edema. **(B)** Five hours later, the patient's brainstem reflex was lost, and brain CT showed progressive hemorrhage with diffuse cerebral edema and bilateral uncal herniation (arrow). **(C)** Contrast-enhanced brain CT obtained 5 days after craniectomy showed suboptimal vascular image quality due to prominent intracranial hypertension.

No improvement in thrombocytopenia was observed after 3 days of plasmapheresis (days 2, 4, and 5 of admission, Figure 3). We therefore switched to immunoglobulin (1 g/kg/day) administered intravenously for two consecutive days on days 5 and 6 of admission. However, platelet count remained low (16–34 × 10^3/μl), and plasmapheresis was restarted on day 9 of admission. The platelet count improved to 60 × 10^3/μl and 105 × 10^3/μl on days 10 and 11 of admission, respectively (Figure 3). Although the patient's peripheral arterial oxygen saturation was maintained at 99%—100% before, during, and after surgery, head CT on day 6 showed diffuse brain edema and loss of gray-white matter junction, involving the bilateral cerebrum, basal ganglia, brain stem, and cerebellum with obliteration of all ventricles (Figure 1C). The findings were indicative of diffuse hypoxic ischemic brain injury, which could be a result of decreased brain perfusion secondary to increased ICP. Autonomic dysfunction, arrhythmia, refractory shock, and central diabetes insidious with hypernatremia developed subsequently. Because of irreversible severe brain injury, her family decided on hospice care with withdrawal of ventilatory support on day 11 of admission, and the patient expired.

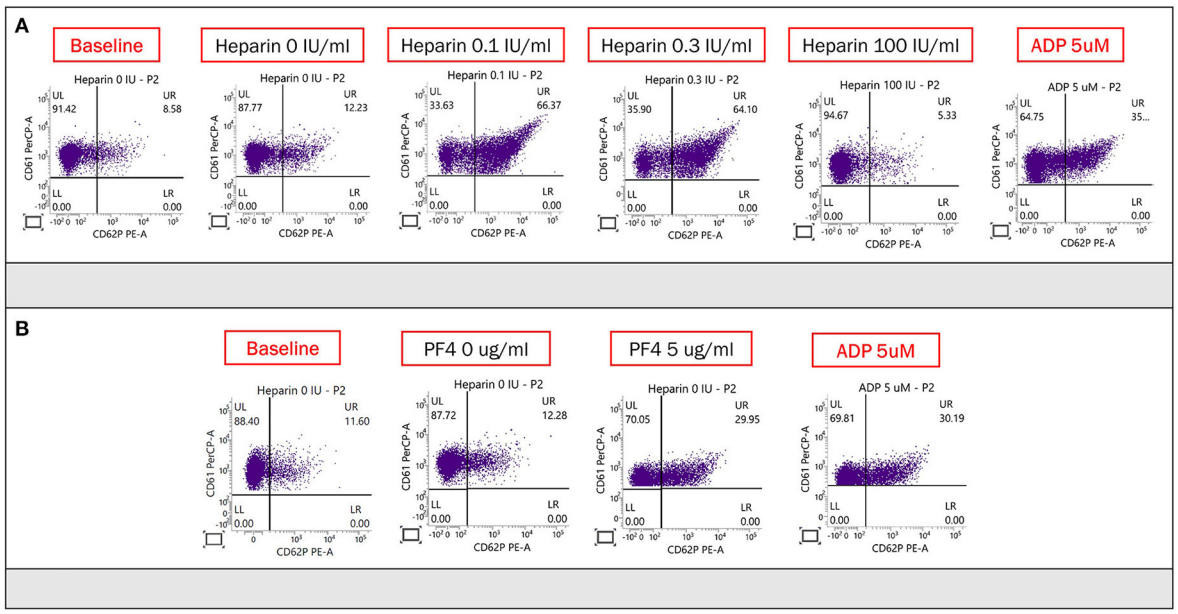

FIGURE 2
(A) Heparin-induced platelet activation assay was used to detect of HIT antibodies. CD61 (glycoprotein IIIa) and CD62p (p-selectin) served as markers of platelet identification and activation, respectively. Adenosine diphosphate was used to confirm normal platelet activation. The proportion of activated platelets was at least >11% in the presence of heparin (0.1 or 0.3 IU/ml) compared with baseline (no heparin), and the activation could be suppressed by a high dose of heparin (100 IU/ml). There was obvious platelet activation in the presence of the patient's plasma and low concentration (0.1 and 0.3 U/ml) of heparin, which was suppressed by the high concentration of heparin (100 U/ml). **(B)** PF4-induced flow cytometry-based platelet activation (PIFPA) revealed that the percentage of activated platelets increased from 12.28% baseline, no PF4 addition) to 29.95% with addition of 5 μg/ml PF4.

Discussion

We present a 42-year-old woman with VITT about a month following a Moderna COVID-19 vaccine booster, complicated by catastrophic cerebral venous thrombosis, intracranial hemorrhage, and uncal herniation, eventually leading to the patient's demise. To the best of our knowledge, there are no previous reports of VITT complicated with cerebral venous thrombosis and hemorrhage associated with the Moderna vaccine. Elevated anti-PF4 antibodies are not specific for VITT diagnosis, so we performed the heparin-induced platelet activation assay. This assay can be positive in both HIT and VITT (4). We therefore performed PF4-induced platelet activation by flow cytometry-based assay for confirmatory diagnosis of VITT. This can distinguish VITT from HIT because unlike HIT which requires the presence of heparin, platelet activation in VITT occurs in the presence of PF4 alone (5).

VITT is a rare, but severe complication of COVID-19 vaccines. Most cases were related to the AstraZeneca vaccine, and only few cases were reported to be related to the Moderna vaccine (6–8). According to the American Society of Hematology (2), the diagnosis of VITT must meet all five criteria including (1) COVID vaccination 4–42 days before symptom onset, (2) any venous or arterial thrombosis (often cerebral or abdominal location), (3) thrombocytopenia (platelet count $< 150 \times 10^9$/L), (4) positive anti-PF4 antibody, and (5) markedly elevated D-dimer (more than four times the upper limit of normal). Our patient met all these diagnostic criteria of VITT. A CT venography (CTV) was not performed initially, and the subsequent severe cerebral swelling precluded the assessment of venous filling defect by CTV (9). Because of the use of postoperative staples on the scalp and infusion pump from the second day after admission, the patient had no chance to receive brain magnetic resonance imaging. However, the preceding nausea, headache, followed by focal neurologic deficit with seizure imply the high probability of cerebral venous thrombosis (CVT) rather than arterial thrombosis, and the location of cerebral hemorrhage at juxtacortical white matter is suggestive of CVT with hemorrhagic transformation (10).

In this patient, the onset time of neurological symptoms was 32 days after the Moderna vaccination. Moderna vaccine-induced thrombocytopenic petechiae/purpura has been reported previously (8); however, our patient developed more life-threatening complications, including CVT and intracranial hemorrhage with rapid progression of brain edema and uncal herniation. The patient had undergone laparoscopic myomectomy 12 days before presentation and experienced mild headache, nausea, and lethargy after the surgery. In addition, mild thrombocytopenia was observed 1 day after

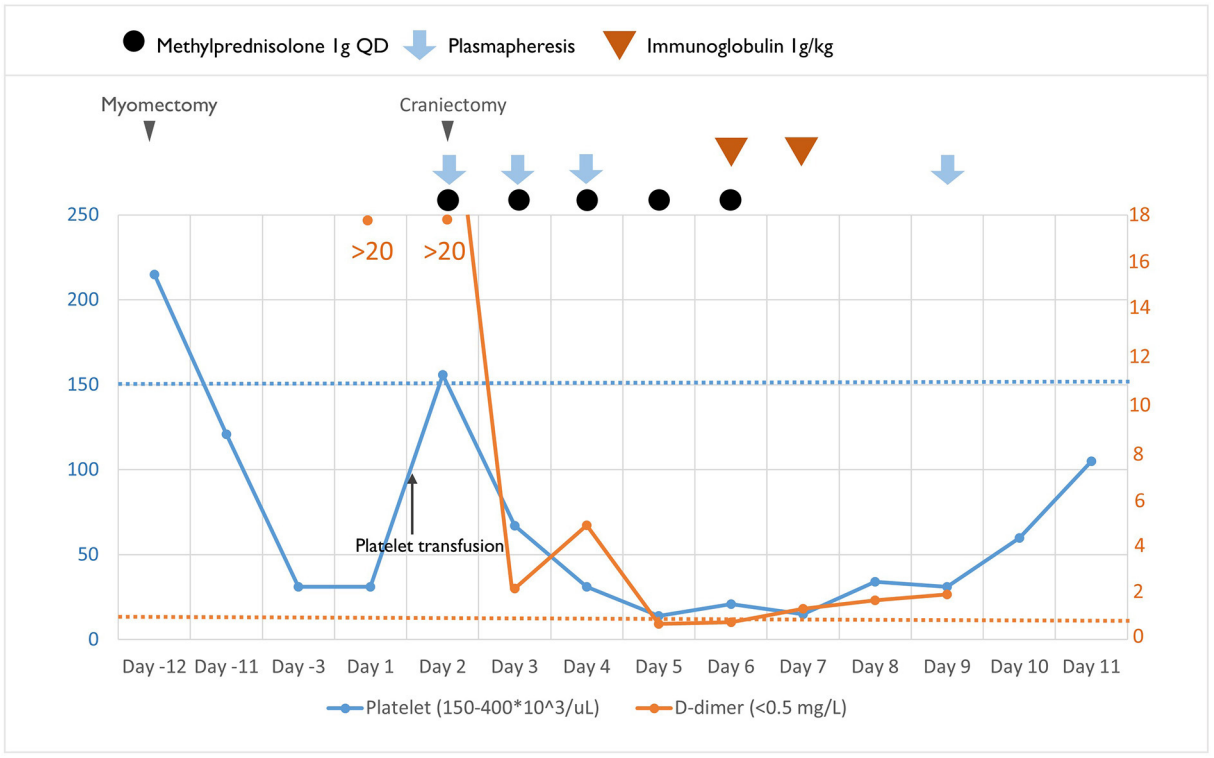

FIGURE 3
Clinical course, the laboratory studies and therapeutic agents used.

the surgery. Postoperative headaches are not uncommon in clinical practice, and postoperative thrombocytopenia can be caused by hemodilution and consumption. In our patient, spontaneous HIT, which is a subtype of HIT without preceding heparin exposure, could also explain a clinical and serologic picture similar to VITT. Spontaneous HIT has been largely reported after orthopedic surgery and some other exposures such as polyanionic medications or virus/bacterial infection (11). Occasionally, no preceding trigger is identified (12). From the available data in our patient, it was not possible to definitively determine if spontaneous HIT induced by laparoscopic myomectomy was the only cause of her clinical presentation with acute thrombosis or a precipitating factor for VITT development from prior exposure to the Moderna vaccine booster. It is also uncertain whether there may have been persistent low-level/subclinical HIT-like antibodies from more remote AstraZeneca vaccine exposure that may have added to the overall cumulative risk of thrombosis.

Once a diagnosis of VITT is established, treatment involves (1) IVIG 1 g/kg daily for 2 days, (2) non-heparin anticoagulant agents, (3) avoiding platelet transfusions, (4) corticosteroids that do not have sufficient data to prove their role, (5) avoiding aspirin, since it does not help with treatment or prophylaxis and may increase bleeding risk, and (6) plasmapheresis, which is an additional option when thrombosis progresses despite IVIG and non-heparin anticoagulants (13). Because VITT was not suspected initially in our patient, one dose of 300 mg aspirin was administered orally at the emergency room under the impression of acute ischemic stroke. For CVT, heparin is the standard treatment, but is best avoided in VITT cases. The safer anticoagulant for VITT is direct oral anticoagulant (DOAC). In our patient, the cerebral hemorrhage could have been a complication of aspirin or CVT. Unfortunately, the rapid expansion of the hematoma precluded the use of DOAC.

The initial uncertain diagnosis and a rapid and catastrophic course in our case led us to choose plasmapheresis and steroid pulse therapy first as broad coverage of VITT and other potential autoimmune diseases that were in the differential, such as catastrophic antiphospholipid syndrome, SLE with central nervous system involvement, and thrombotic thrombocytopenic purpura (14). Previous studies have suggested good efficacy of plasmapheresis for patients with VITT who have thrombocytopenia refractory to IVIG therapy (14, 15). In our patient, thrombocytopenia was not responsive to the initial three treatments of plasmapheresis. Partial improvement in thrombocytopenia was observed after 2 days of IVIG and another treatment of plasmapheresis. It appears that plasmapheresis overall was not effective in our patient, or possibly, the effect of plasmapheresis for thrombocytopenia was delayed.

Conclusion

While VITT is typically caused by adenovirus-based vaccines, our case highlights the possibility of the Moderna vaccine, a messenger RNA-based vaccine, as a potential precipitant of VITT in a patient with remote exposure to an adenoviral vaccine. The prior AstraZeneca vaccine exposure and the gynecologic surgical procedure before and after the Moderna vaccination respectively could have cumulatively precipitated or aggravated autoimmune HIT/VITT-like presentation. During the COVID-19 pandemic, awareness of this possibility could allow clinicians to consider VITT as a potential diagnosis in patients who present with thrombosis and low platelets and have received a COVID-19 vaccination, even if the time frame and vaccine type are not typical for VITT. Post-surgery headaches are common; however, since they are an early sign of increased intracranial pressure caused by CVT it is challenging for clinicians to identify the latter early based on this symptom alone. Generally, antiplatelet therapy should be started in patients with acute stroke as soon as possible after brain imaging has excluded hemorrhage. However, clinicians should look at laboratory data, evaluate the patient's past medical history, and consider other stroke mimics thoroughly before antiplatelets are given. In cases of VITT, aspirin is not recommended because of the increased bleeding risk. A high index of suspicion in such cases could facilitate early diagnosis, which could lead to timely and aggressive intervention, and in turn may help to prevent severe morbidity or mortality.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the patients for the publication of any potentially identifiable images or data included in this article.

Author contributions

Y-CC, C-CL, and Y-FS contributed to the conception and design of the study. C-HC, Y-QL, M-CT, B-KC, Y-PL, and T-HH contributed to the acquisition and analysis of data. Q-TC, YL, Y-CC, and Y-FS contributed to drafting the text or preparing the figures. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.989730/full#supplementary-material

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Double seropositive neuromyelitis optica associated with COVID-19: A case report

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Neuromyelitis optica spectrum disorders are characterized by severe demyelination and axonal damage with autoimmune mechanisms, predominantly targeting the optic nerves and the spinal cord. Patients often test positive for anti-AQP4 antibodies, while some have anti-MOG antibodies. Double seropositivity has been described, with a variable prevalence (0 to 26%) dependent on the testing method. The clinical significance of double seropositivity remains unclear. We present the case of a 65-year-old patient, admitted to our clinic with optical neuritis, followed up approximately 10 days later by cervical myelitis, who tested positive for both anti-AQP4 and anti-MOG antibodies. The clinical onset coincided with a mild form of SARS-CoV-2 infection. The neurological symptoms were initially relatively subdued, which delayed the diagnosis. The patient was not vaccinated against SARS-CoV-2. The clinical picture was compatible with an anti-AQP4 phenotype. The patient was started on corticosteroid therapy, under which the clinical response was good. Our case reinforces the idea that SARS-CoV-2 can precipitate autoimmune demyelinating diseases since SARS-CoV-2 infection has already been demonstrated as a risk factor for NMOSD relapses. To the best of our knowledge, this is the first reported case of double seropositive neuromyelitis optica associated with COVID-19. We expect that in the near future, as the true burden of COVID becomes clearer, we shall encounter other cases which can trace their apparent clinical onset to a SARS-CoV-2 infection. Careful attention should be paid to the apparent minor neurological symptoms of COVID-19.

KEYWORDS

neuromyelitis optica, anti-AQP4 antibodies, anti-MOG antibodies, COVID-19, NMOSD

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are rare autoimmune disorders characterized by severe demyelination and axonal damage, predominantly targeting the optic nerves (ONs) and the spinal cord (1). The AQP4-IgG serum antibodies play a direct role in the pathogenesis of NMOSD, targeting a water channel protein found in high concentrations in the astrocytic foot processes. A small percentage of ~12%

of patients who fulfill the clinical criteria for NMOSD are seronegative for AQP4-IgG (2). Approximately 40% of seronegative patients have anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies (3). Whether an anti-MOG disease is a distinctive clinical entity is still to be determined, but some common characteristics seem to be found more frequently in this group: a simultaneous manifestation of optic neuritis and myelitis at onset, simultaneous bilateral optic neuritis, myelitis more often affecting the lower portion of the spinal cord, and monophasic attack or fewer relapses than the AQP4-IgG seropositive patients (1, 4). SARS-CoV-2 is a new pathogen that has been shown to have significant interactions with the immune system, not only in the acute setting but also in the long term, exacerbating or initiating numerous autoimmune disorders (5).

Case presentation

We present the case of a 65-year-old Caucasian male, without any significant medical history, admitted to our clinic with bilateral lower limb motor deficit and distal paresthesia in all limbs, with an onset of ∼3 weeks prior. The patient also complained of sudden bilateral decreased visual acuity, more severe on the right side, which preceded the motor deficit by approximately 10 days and had a spontaneously favorable evolution and was partially remitted by the time of admission.

An ophthalmologist in another service evaluated the patient approximately 7 days from the onset of the visual symptoms, where he tested positive for SARS-CoV-2. At that moment, he had had mild respiratory symptoms (slight cough and rhinorrhea) for a∼2 days. The interval between the onset of the neurological and COVID-19 symptoms was ∼5 days.

The ophthalmological examination noted VOS Presbyopia 0.5 sc (0.7 c), VOD PHM, with a regular fundus examination in both eyes. At that time, sight in the left eye was already spontaneously improving, and the diagnosis was right retrobulbar optic neuritis. He was not started on any therapy and received a recommendation for a neurological evaluation and a brain MRI scan. The patient chose to isolate himself at home for 14 days, per the local recommendations at the time.

Approximately 3 days into the isolation period, he developed lower limb paresthesia, followed by paraparesis and ataxia, which progressively worsened until he could no longer walk.

Our initial clinical examination showed a slight loss of visual acuity in the right eye (he could read a newspaper), asymmetric paraparesis (3/5 MRC on the right, 4/5 MRC on the left), bilateral Babinski sign, distal paresthesia in all limbs, severe bilateral lower limb myoarthrokinetic and vibratory hypoesthesia, with important secondary ataxia, and a T10 sensory level on the left side; walking was impossible.

The full spine MRI revealed a non-enhancing, T2 and STIR hyperintense cervical demyelinating lesion extending from C4 to C7 levels (Figures 1A,B), cervical spondylotic changes, and

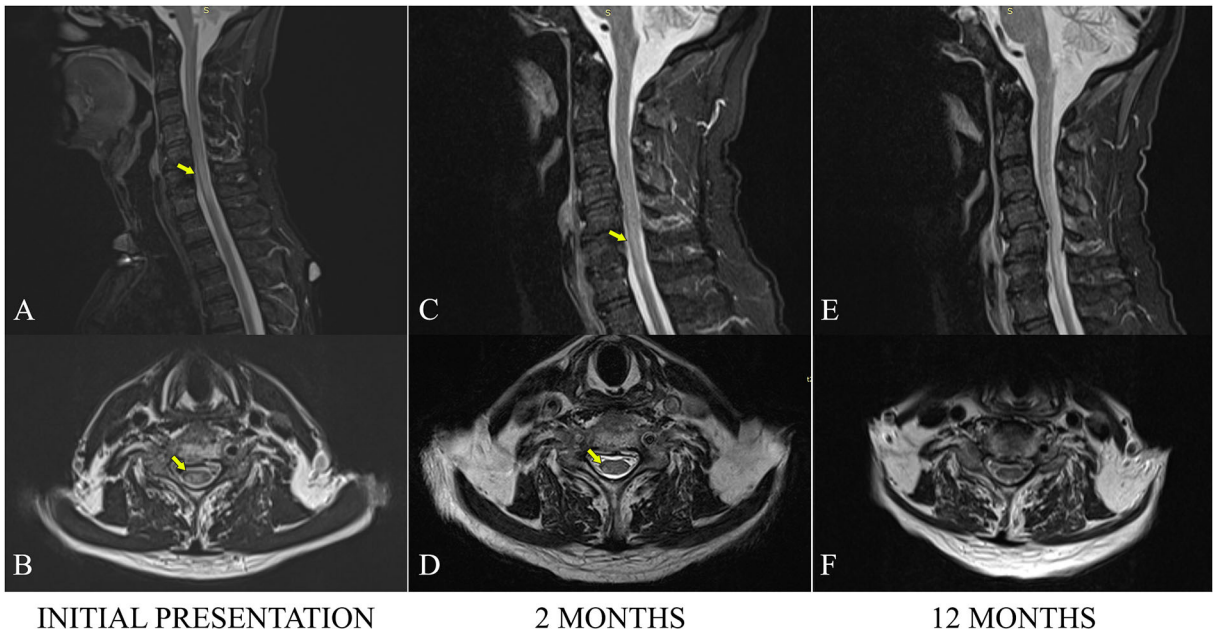

FIGURE 1
Sagittal MRI STIR sections of the cervical spine at admission **(A)**, 2 months **(C)**, and 12 months **(E)**. Axial MRI TSE sections at approximatively the same level (a plane passing through the upper C6 plateau) at admission **(B)**, 2 months **(D)**, and 12 months **(F)**. The hyperintense STIR cervical lesion is visible, extending from C4 to C7. Progressive fading of the increased signal is visible over time, especially on the axial images.

degenerative lumbar stenosis at L4–L5 levels. The cerebral MRI was unremarkable except for a slight STIR hyperintense signal affecting the right ON, extending posteriorly into the optic chiasm (Figure 2).

The patient was evaluated extensively for autoimmune disorders associated with myelitis, testing negative for ANA, c-ANCA, p-ANCA, anti-Ro, anti-La, and anti-neuronal antibodies. The infectious screening was negative except for the incidental presence of IgG against HCV. Testing for HIV, syphilis, and borreliosis was negative. The B12 serum level was normal. Serum anti-AQP4 antibodies and anti-MOG antibodies were both positive. The AQP4 was tested by indirect immunofluorescence with a titer of 1:1,000 ($N < 1{:}10$). The MOG testing was Western Blot.

The CSF had elevated protein levels (albumin 0.44 g‰, positive Pandy test) without pleocytosis (6 elements/μL) and no oligoclonal bands. The IgG index was normal (0.63).

Given the patient's history of optic neuritis, longitudinal extensive cervical myelitis, positive tests for anti-AQP4 and anti-MOG antibodies, and the exclusion of other possible causes that could have caused central nervous system demyelination, a diagnosis of neuromyelitis optica was reached.

The patient had been treated with iv Methylprednisolone 1,000 mg daily for 5 days with significant improvement of motor function (4-/5 MRC bilaterally) and partial remission of the paresthesia but with the persistence of the objective sensory deficits. The patient was able to walk using a Zimmer frame. He was discharged with oral prednisone at 1 mg/kg/day.

At the 2-month checkup, the patient had continued to improve, presenting with normal visual acuity, asymmetric paraparesis (4-/5 MRC on the right, 4+/5 MRC on the left), bilateral lower limb paresthesia up to the lower half of the thighs, and crural proprioceptive hypoesthesia, still requiring a frame for walking. The cervical MRI showed a slightly favorable evolution of the cervical lesion (Figures 1C,D). As a corticoid-sparing treatment, he was started on Azathioprine (AZA), gradually reaching a dose of 150 mg per day.

He was seen again at the 1-year mark, being stationary from a neurological point of view, with the persistence of the asymmetric paraparesis and sensory anomalies. The cervical MRI examination was discreetly improved, as the intramedullary pathological signal had continued to decrease in area and intensity (Figure 1F). AZA was continued in the same doses while prednisone tapering was initiated.

Discussion

As the last 2.5 years unfolded, SARS-CoV-2 has repeatedly been shown to initiate and decompensate many autoimmune diseases (6).

This seems to be a family effect for coronaviruses, but SARS-CoV-2 stands out among its peers (7). A recently published review underlines the potential of coronaviruses to spread and persist in the central nervous system (CNS) and their potential for neuropathogenesis. This persistence may be associated not only with the induction or exacerbation of long-term neuropathologies such as multiple sclerosis but may be able to

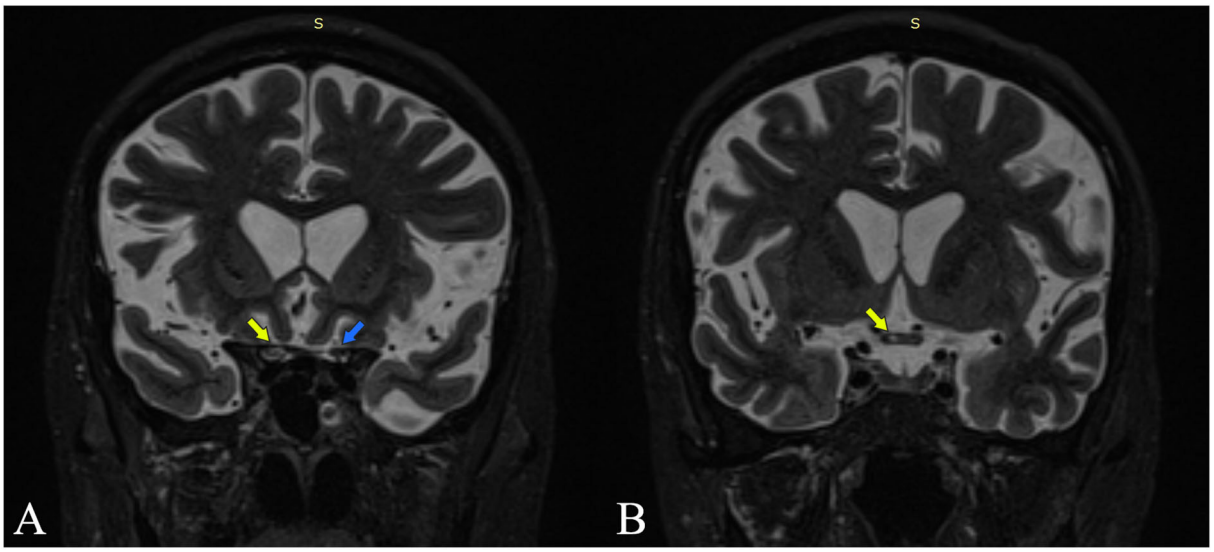

FIGURE 2
Coronal MRI STIR sections are at the intracranial optic nerves **(A)** and optic chiasm **(B)**. Yellow arrows point out increased STIR signal intensity at the level of the right optic nerve and the right side of the chiasm. The blue arrow points out the left optic nerve with normal signal intensity.

explain persistent neuropsychiatric symptoms associated with long COVID (8).

Although the exact mechanism of virus dissemination in the CNS has not been established, the two possible explanations are either hematogenous spread from the systemic circulation or trans-neuronal spread via the olfactory pathway. In addition, the CNS can be potentially compromised through an ischemic–hypoxic insult of the blood-brain barrier resulting from severe respiratory insufficiency or by immune-mediated mechanisms (9, 10). Anti-AQP4 antibodies have been shown to induce interleukin-6 (IL-6) production in astrocytes, and IL-6 signaling to endothelial cells induces blood-brain barrier dysfunction (11).

The link between SARS-CoV-2 and several neurologic autoimmune pathologies, including Guillain-Barré syndrome, multiple sclerosis, and vasculitis, has also been shown by multiple studies (12, 13).

Although SARS-CoV-2 is known as a risk factor for NMOSD relapses, a causal relationship is more difficult to prove (14). Still, accumulating data support a demyelinating aspect of SARS-CoV-2 infection (9). The ethiopathogenic process is not fully understood. Carlos A et al. hypothesized a possible loss of tolerance to self-antigens caused by a state of transient immunodeficiency of both acquired and innate components (15). According to Wu et al., a neuronal injury may be produced by immune-mediated pathways (16). The binding of the SARS-CoV-2 virus to the ACE2 receptors in the CNS triggers an intense local inflammatory response with impaired blood-brain barrier permeability (10).

Only a handful of cases of neuromyelitis optica with the onset in close temporal relation with a SARS-CoV-2 infection have been reported (17). Most of them tested positive for AQP4 antibodies. To our knowledge, ours is the first case having double seropositivity for AQP4 and MOG.

In NMOSD cohorts, the incidence of double seropositive patients is variable and method-dependent (18–20). In one study, Kezuka et al. found 26% of patients (6 out of 23) to be seropositive for both AQP4 and MOG antibodies (21). However, a study by Sato et al. on a group of 215 patients found no double seropositive cases (22). The discrepancy between the two results can be attributed to the method of detection: cell-based assay in Sato's study vs. ELISA in Kezuka's study. However, in a later study, Kezuka found two double-positive patients with a cell-based assay using full-length human MOG cDNA-expressing HEK cells (23). As mentioned above, in our case, AQP4 antibodies were tested by indirect immunofluorescence and MOG antibodies by Western Blot.

There are notable clinical differences between NMOSD with positive serology for AQP4 compared with MOG-positive cases. Cases with anti-AQP4 antibodies tend to involve the posterior part of the ON or the chiasma. The spinal cord involvement is usually cervicothoracic, while patients with anti-MOG antibodies tend to have anterior involvement of the ON, often bilateral and longitudinally more extensive, and a lower spinal cord involvement (often including the conus medularis) (24).

Regarding chiasmal involvement, a recent study has shown smaller differences than expected between the two groups, with a frequency of 20% in AQP4-positive patients and 16% in MOG-positive cases. In the MOG subgroup, the ON lesion was more often longitudinally extensive (25).

The differences seem to extend to treatment response, but the details are far from clear. Both situations require prompt immunosuppression, and both respond well to Rituximab. MOG-positive NMOSD seems to be more responsive to corticotherapy, with relapses being more frequent on steroid withdrawal (24).

The clinical picture of our patient, with posterior optical neuritis and cervical myelitis, was compatible with the anti-AQP4 phenotype. We believe the patient had suffered from optic neuritis with chiasmal involvement, with a clinical impact mainly on the right eye. This would explain the initially diminished visual acuity in both eyes and was supported by the MRI, which shows an extension of the inflammation in the optical chiasm (Figure 2).

Notably, the optic neuritis had a spontaneous favorable course, and the spinal lesions, while topographically extensive, were invalidating mainly due to the sensory ataxia. A CSF SARS-CoV-2 was not ordered, as it would not have been informative. The patient was admitted to our clinic 3 weeks after the onset, and previous studies have shown that even in cases where the virus can be detected in the CSF, this happens early in the course of the infection. The levels are low and quickly transient (26, 27).

Interestingly, our patient's onset of clinical neurological symptoms overlapped with COVID-19, the rarer of two situations. In the case series, 68% of transverse myelitis associated with SARS-CoV-2 infections had a latency of 10 days up to 6 weeks, suggesting the complications were mediated by the host's immune response to the infection. In the remaining 32%, the latencies varied from 15 h to 5 days, advocating a direct neurotropic effect of the virus (28).

As the spinal cord involvement ensued about 5 days after the debut of the respiratory symptoms of COVID-19 and progressively worsened during the next weeks, the autoimmune mechanism is a certainty. The situation is not so clear-cut regarding the optical neuritis, which had its onset approximately 5 days before SARS-CoV-2 manifested in the form of respiration. The incubation period for COVID-19 is considered to be 4–5 days in most cases, with a maximum of 14 days following exposure (29). The patient was unaware of any contact with known cases of SARS-CoV-2 infection, so we cannot place the exposure date. There have been rare reports of cases of optic neuritis in patients with concomitant SARS-CoV-2 infection and no known autoimmune pathology, but while an acute neurotropic effect of the virus cannot be excluded, the chiasmatic involvement with bilateral diminished visual acuity

and the fact that it was rapidly followed by myelitis, argue strongly in favor of an autoimmune mechanism in the context of NMOSD (30).

According to a recent study, more than a third of hospitalized COVID-19 infected patients developed neurological symptoms at some point, but unfortunately, most are not able to undergo extensive imagistic workup in the acute phase (31, 32). Taking into account that, even in our patient who had significantly impaired walking, the diagnosis was delayed for about 3 weeks and that some cases might have an even milder initial phase, we think that in the near future, as the true burden of COVID-19 becomes more clear, we might encounter other cases that can trace their apparent clinical onset to "minor" neurological symptoms following a SARS-CoV-2 infection. This aspect might become even more interesting as these patients get repeated infections with the same or different variants.

Conclusion

SARS-CoV-2 is known to significantly interfere with the immune processes of the body. Since NMOSD does not have a very high incidence, it took a while longer to become obvious that COVID-19 could be a triggering factor, but indeed this seems to be the case. The main serological and clinical forms appear to be of the AQP4 type.

Acute vision disturbances or distal sensory symptoms should be taken seriously in such patients, even if they are mild, with early diagnosis and treatment being the main way to reduce disability.

The significance of double seropositivity remains unclear, as we do not have sufficient evidence suggesting that both types of antibodies would be simultaneously pathological. Cell-based assays are the gold standard and should be used whenever possible. While serology can be used to orient some aspects of the treatment, double seropositive cases do not have this advantage. In such cases, we think the clinical orientation toward an AQP4 or MOG phenotype can be used instead.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Written informed consent was obtained from the participant for the publication of this case report.

Author contributions

AM and DA: writing. FA, AB, and AC: review and editing. ST: editing and supervision. All authors have read and approved the submitted version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Longitudinal SARS-CoV-2 humoral response in MS patients with and without SARS-CoV-2 infection prior to vaccination

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Introduction: During the COVID-19 pandemic, certain disease modifying therapies (DMTs) used in multiple sclerosis (MS), such as anti-CD20 therapies, have been associated with decreased humoral responses after SARS-CoV-2 vaccination. Hybrid immunity, referring to immunity after both vaccination and SARS-CoV-2 infection might increase humoral responses.

Methods: This was a substudy of two prospective cohort studies on SARS-CoV-2 antibodies after SARS-CoV-2 infection and vaccination. RBD-specific IgG titers of patients with MS and healthy controls who had experienced SARS-CoV-2 infection prior to the first vaccination were compared with those patients and healthy controls without prior infection. Humoral responses were measured at various time points after SARS-CoV-2 infection in convalescent patients and all patients prior to the first vaccination, 28 days after the first vaccination, and 28 days after the second vaccination.

Results: One hundred and two individuals [of which 34 patients with MS and DMTs (natalizumab or ocrelizumab), 30 patients without DMTs, and 38 healthy controls] were included. Fifty one of these individuals were convalescent. Median SARS-CoV-2 antibody titers were higher after the first vaccination in convalescent individuals compared with individuals without infection prior to vaccination. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody titers were comparable after the second vaccination in patients with MS with and without prior infection. However, in the convalescent ocrelizumab-treated patients, SARS-CoV-2 antibody titers did not increase after vaccinations.

Conclusion: In patients with MS without anti-CD20 therapies, SARS-CoV-2 infection before vaccination increases humoral responses after the first vaccination, similar to the healthy controls. In patients with MS treated with ocrelizumab (convalescent and non-convalescent), humoral responses remained low.

KEYWORDS

multiple sclerosis, SARS-CoV-2, COVID-19, disease modifying treatment, humoral response

Introduction

Since the start of the COVID-19 pandemic, humoral, and cellular immunity against SARS-CoV-2 antigen has been extensively studied after vaccinations. Within the population with multiple sclerosis (MS), anti-CD20 therapies (e.g., ocrelizumab and rituximab) were shown to severely impair humoral responses after SARS-CoV-2 vaccination (1). In patients with MS without disease modifying therapies (DMTs) or patients with MS on non-immunosuppressive DMTs, immunity after vaccination is largely comparable to healthy controls (2).

Despite vaccination, infection with SARS-CoV-2 can result in breakthrough COVID-19, even though vaccination is effective in preventing severe COVID-19. Hybrid immunity, resulting from SARS-CoV-2 infection and vaccination combined, has been shown to increase potency and breadth of SARS-CoV-2 antibodies in healthy individuals (3). The observation that SARS-CoV-2 breakthrough infections are more frequent among patients with MS and low SARS-CoV-2 antibody titers (4), gives rise to the question of whether hybrid immunity in MS leads to a better humoral immune response and clinical protection than vaccination only. In patients with MS, data are scarce regarding the effects of hybrid immunity on humoral responses and SARS-CoV-2 breakthrough infections.

The objective of this study was to evaluate the humoral immune response and SARS-CoV-2 breakthrough infections in patients with MS and healthy controls with and without SARS-CoV-2 infection prior to the first vaccination.

Materials and methods

From August to December 2020, before the availability of SARS-CoV-2 vaccinations, patients with MS from the Amsterdam MS Center, the Netherlands, were tested for SARS-CoV-2 antibodies (COMS-19 study, ClinicalTrials.gov Identifier: NCT04498286) (5). Patients with a positive SARS-CoV-2 antibody response or a positive PCR prior to vaccination were longitudinally followed in another prospective cohort study on vaccination against SARS-CoV-2 in patients with various immune-mediated inflammatory diseases (T2B!; Trial NL8900; Dutch Trial register) (6).

For this substudy, patients with MS treated with ocrelizumab, natalizumab, or no DMTs who have had a SARS-CoV-2 infection (defined by positive PCR and/or positive SARS-CoV-2 antibodies) prior to the first vaccination were included. Matched controls without prior SARS-CoV-2 infection from the T2B! study were included (1:1) matching for DMT, age, and sex. Furthermore, a group of healthy controls with and without SARS-CoV-2 infection prior to vaccination was included. All patients in the SARS-CoV-2 negative control groups were tested negative for SARS-CoV-2 antibodies at baseline (prior to the first vaccination).

Clinical data and data regarding SARS-CoV-2 (breakthrough) infections were retrieved from the medical files and electronic questionnaires, which were sent to patients every 2 months after the first vaccination. When a patient indicated a positive PCR or antigen test, that patient was contacted by a researcher at least 2 weeks after the positive test to verify and determine COVID-19 severity. Coronavirus disease (COVID-19) severity was based on the WHO classification.

In the COMS-19 study, serum samples were cross-sectionally collected by venipuncture in a large cohort of patients with MS and variable timing of sampling since SARS-CoV-2 infection and until the first vaccination. For follow-up in the T2B! study, serum samples were collected by venipuncture or by participants at home using a finger prick set. Samples were taken at predefined time points: at baseline (prior to the first vaccination) and day 28 after the first and second vaccination (when applicable). Serum was not available for all patients at all time points (see Table 1).

The serum was assessed using a quantitative anti-RBD IgG enzyme-linked immunosorbent assay (ELISA), as described previously (7). Anti-RBD IgG titers were expressed as arbitrary units (AU) per mL (AU/mL) and were compared with a serially diluted calibrator (arbitrarily assigned a value of 100 AU/mL) consisting of pooled convalescent plasma. Seroconversion after vaccination was defined as antibody titers >4 AU/mL.

Differences in proportions were analyzed using Fisher's exact test, and differences between continuous variables were analyzed using the Wilcoxon rank-sum test. Analyses were performed

TABLE 1 Baseline characteristics and data on humoral responses.

	Natalizumab (n: 18)		Ocrelizumab (n: 16)		No DMT (n: 30)		Healthy controls (n: 38)	
SARS-CoV-2 infection	**Yes,**	**No,**	**Yes,**	**No,**	**Yes,**	**No,**	**Yes,**	**No,**
prior to vaccination, n (%)	**9 (50)**	**9 (50)**	**8 (50)**	**8 (50)**	**15 (50)**	**15 (50)**	**19 (50)**	**19 (50)**
Age, mean (SD)	44 (12)	46 (8)	50 (10)	53 (3)	55 (9)	55 (3)	55 (3)	55 (4)
Female sex, *n* (%)	8 (89)	8 (89)	4 (50)	4 (50)	10 (67)	10 (67)	14 (74)	14 (74)
COVID-19 severity prior to vaccination, n (%)								
Asymptomatic	2 (33)	NA	3 (38)	NA	2 (13)	NA	3 (18)	NA
Mild	7 (78)	NA	4 (50)	NA	13 (87)	NA	14 (82)	NA
Moderate	0	NA	0	NA	0	NA	0	NA
Severe	0	NA	1 (13)	NA	0	NA	0	NA
Vaccination type primary immunization, n (%)								
AstraZeneca	1 (11)	1 (11)	1 (13)	0	4 (27)	0	0	0
Janssen	0	0	1 (13)	0	0	0	0	0
Moderna	2 (22)	2 (22)	3 (38)	7 (89)	3 (20)	8 (53)	13 (69)	13 (69)
Pfizer/BioNtech	6 (67)	6 (67)	3 (38)	1 (13)	8 (53)	7 (47)	6 (32)	6 (32)
Anti-RBD titer >4 AU/mL prior to first vaccination, n (%)								
Seroconversion	5 (63)	0	4 (67)	0	6 (75)	0	11 (61)	0
No seroconversion	3 (38)	9 (100)	2 (33)	7 (100)	2 (25)	15 (100)	7 (39)	18 (100)
Serology missing	0	0	2	1	7	0	1	1
Anti-RBD titer prior to first vaccination, median (IQR)								
Titer	7.5 (2.3–16.9)	NA	8.4 (0.7–31.8)	NA	6.2 (3.4–9.7)	NA	4.42 (1.2–13.0)	NA
Anti-RBD titer >4 AU/mL 28 days after 1st vaccination, n (%)								
Seroconversion	6 (100)	6 (67)	3 (50)	1 (14)	14 (93)	14 (93)	17 (100)	18 (100)
No seroconversion	0	3 (33)	3 (50)	6 (86)	1 (7)	1 (7)	0	0
Serology missing	3	0	2	1	0	0	2	1
Anti-RBD titer 28 days after 1st vaccination, median (IQR)								
Titer	180.0 (54.4–271.0)	12.9 (3.0–36.9)	11.7 (1.0–38.5)	0.5 (0.1–1.6)	163.0 (21.6–545.0)	23.3 (10.9–48.9)	300.0 (218.0–558.0)	22.9 (12.2–34.1)
Anti-RBD titer >4 AU/mL 28 days after 2nd vaccination, n (%)								
Seroconversion	9 (100)	9 (100)	2 (33)	3 (38)	14 (100)	14 (100)	15 (100)	19 (100)
No seroconversion	0	0	4 (67)	5 (63)	0	0	0	0
Serology missing	0	0	2	0	1	1	4	0
Anti-RBD titer 28 days after 2nd vaccination, median (IQR)								
Titer	205.0 (158.0–341.0)	135 (72.9–662)	0.6 (0.1–12.7)	1.0 (0.1–12.3)	188.0 (83.0–329.0)	157.0 (69.8–250.0)	356.0 (237.0–662.0)	228.0 (88.9–289.0)
Breakthrough infection in 180 days after second vaccination, n (%)								
SARS-CoV-2 infection	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	1 (7)	0 (0)	1 (5)

Baseline characteristics and humoral data in patients categories with SARS-CoV-2 infection prior to the primary vaccination and matched controls without prior SARS-CoV-2 infection. In two healthy controls, severity of COVID-19 is missing. Seroconversion after vaccination was defined as antibody titers >4 AU/mL. The median time in days between last ocrelizumab infusion and first vaccination was 116 (IQR 25–157) in convalescent patients and 136 (IQR 20–152) in non-convalescent ocrelizumab-treated patients.

in R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

One hundred and two participants were included in this substudy, of which 34 patients with MS and DMTs (natalizumab or ocrelizumab), 30 patients without DMTs, and 38 healthy controls. Baseline characteristics and humoral responses of participants with ($n = 51$) and without prior SARS-CoV-2 infection ($n = 51$) are described in the Table 1. Longitudinal results of SARS-CoV-2 anti-RBD antibody titers are presented in the Figure 1.

The exact time of SARS-CoV-2 infection prior to vaccination was available in 47% (24/51) of participants as PCR testing was not widely available in the Netherlands in early 2020. The median time from positive PCR to first vaccination in

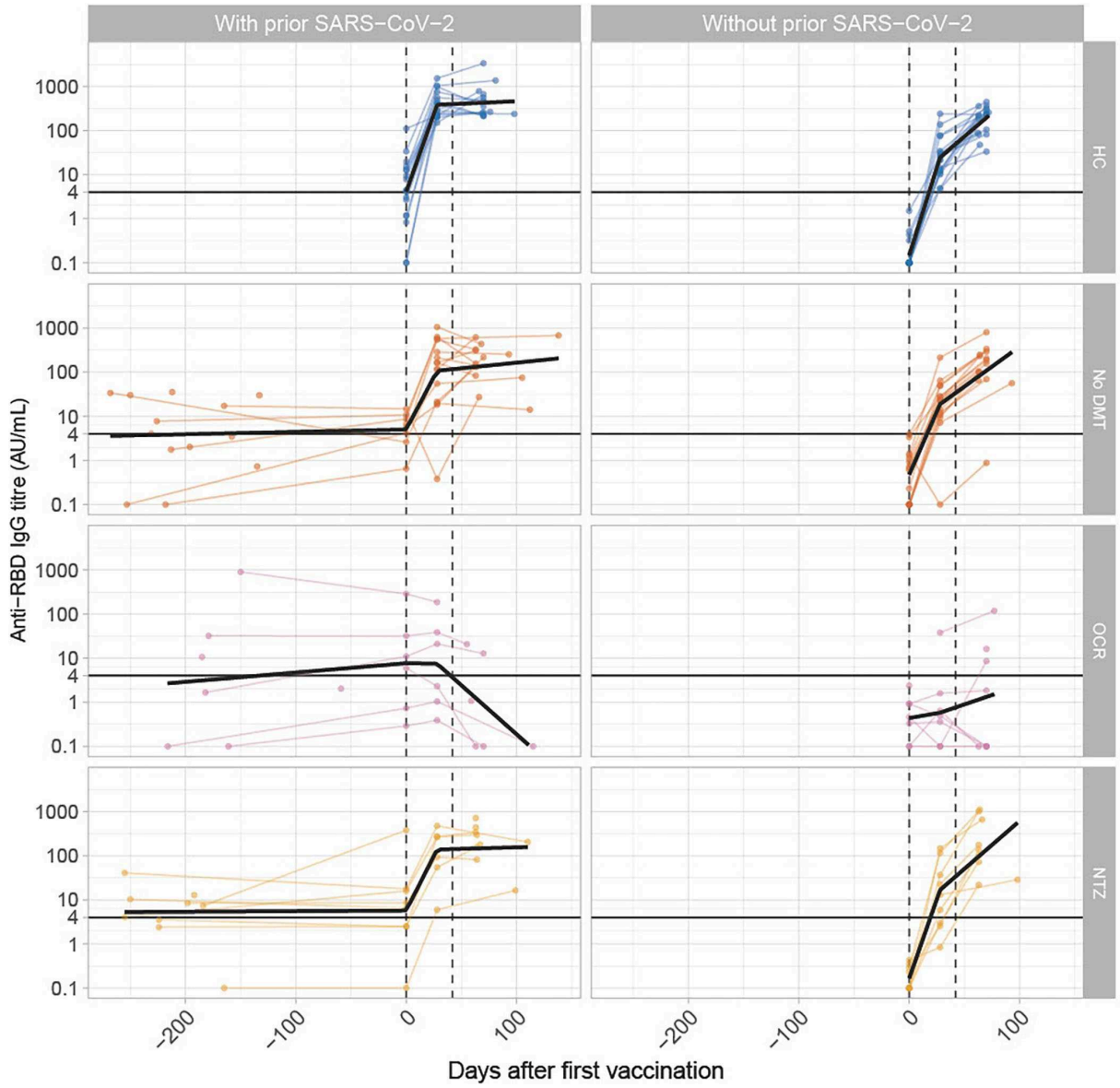

FIGURE 1
Longitudinal SARS-CoV-2 antibody titers in patients with and without prior SARS-CoV-2 infection. The figure shows anti-RBD titers over time in patients with MS in various treatment groups. The x-axis shows time in days before and after the first vaccination. The y-axis is a logarithmic scale of anti-RBD-IgG titers in AU/mL. The Dots indicate antibody titers for individual participants. The black line indicates the regression line per group to demonstrate a trend. The horizontal black line indicates the cut-off for seroconversion (>4 AU/mL). The dotted lines, respectively, indicate the median timing of the first and second vaccination, either with mRNA vaccines (Moderna/Pfizer) or ChAdOx1 nCoV-19 (AZD1222) vaccine from Oxford-AstraZeneca. The median time between the first and second vaccination was 42 days.

patients with available data was 229 days (IQR 175–304). In remaining patients with MS without a date of SARS-CoV-2 infection, infection occurred prior to first sampling which took place a median of 216 days (IQR 185–231) prior to the first vaccination.

Before the first vaccination, 65% (26/40) of all participants with prior SARS-CoV-2 infection had anti-RBD IgG titers above the threshold of 4 AU/mL; however, titers were low [median titer 10.9 AU/mL (IQR 6.5–17.8)].

At day 28 after the first vaccination, 85% (23/27) of patients with MS and prior SARS-CoV-2 infection had anti-RBD IgG titers above the threshold of 4 AU/mL vs. 68% (21/31) of patients with MS without SARS-CoV-2 infection (p: 0.14, Table 1). In patients with MS on natalizumab, patients without DMTs, and healthy controls, the anti-RBD antibody titer after the first vaccination was higher in participants with prior SARS-CoV-2 infection than in participants without prior infection to vaccination (p: 0.04, $p < 0.01$, and $p < 0.001$, respectively,

Table 1). In contrast, no difference was identified in anti-RBD titers after the first vaccination in patients with MS on ocrelizumab with or without a prior SARS-CoV-2 infection (p: 0.07, Table 1).

At day 28 after the second vaccination, all individuals were seroconverted (anti-RBD titer >4 AU/mL 28 days after the second vaccination), with an exception of ocrelizumab-treated patients (36%, 5/14). Antibody titers in patients with MS on natalizumab, without DMTs, and healthy controls, were all higher after the second vaccination compared with the first vaccination (Table 1). In patients on natalizumab and without DMTs, no significant differences in titer were observed in patients with and without prior SARS-CoV-2 infection (p: 0.73 and p: 0.48, respectively, Table 1), whereas for healthy controls, the median anti-RBD antibody was higher by 1.6-fold ($p < 0.01$, Table 1). In ocrelizumab-treated patients, seroconversion and anti-RBD antibody titers remained low after vaccinations, also in the group with prior SARS-CoV-2 infection.

SARS-CoV-2 breakthrough infections in 6 months (180 days) after the second vaccination were reported by 3% (3/102) of participants, all females without prior SARS-CoV-2 infection. These breakthrough infections occurred in one 53 years old healthy control who had mild symptomatic disease (no assistance needed), one 50 years old patient without DMT who had mild symptomatic disease (no assistance needed), and one 50 years old ocrelizumab-treated patient who had moderate disease (hospitalization with oxygen). The patient on ocrelizumab was hospitalized for supportive treatment including oxygen suppletion for 10 days after which she recovered and was discharged.

Discussion

In this study, in patients with MS on natalizumab and without DMTs and healthy controls with prior SARS-CoV-2 infection, higher SARS-CoV-2 antibody titers were found 28 days after the first vaccination compared with matched individuals without SARS-CoV-2 infection. In these patients, further increase of anti-RBD titer was limited after the second vaccination. Our results are in agreement with Shenoy et al. who reported an increase in antibody titers after vaccination in convalescent patients with autoimmune rheumatic diseases compared with non-convalescent patients (8). In this study, part of the patients who experienced COVID-19 did not show seroconversion when tested prior to vaccination. As immunity and seroconversion after infection or vaccination against SARS-CoV-2 wanes over time, a full vaccination cycle is also recommended following international guidelines in patients with MS andprior SARS-CoV-2 infection. Our data show no difference in SARS-CoV-2 antibody titers after a full vaccination cycle between convalescent and non-convalescent patients with MS. Therefore, patients with MS and hybrid immunity (including a full vaccination cycle) might have comparable immunity compared with non-convalescent patients, although the potency and breadth of SARS-CoV-2 antibodies could be different after vaccination or infection, which was not evaluated in this current study.

In ocrelizumab-treated patients, we found low seroconversion rates and anti-RBD antibody titers in patients with and without prior SARS-CoV-2 infection. Anti-CD20 therapies greatly impair the antibody response after SARS-CoV-2 infection and vaccination in patients with MS (1, 9). Therefore, patients are offered additional vaccinations to increase humoral responses. The majority of these patients, however, remain seronegative after the third vaccination (10). Decreased humoral responses are shown to increase the risk of SARS-CoV-2 breakthrough infection, but severe breakthrough infection is rare likely due to intact T cell responses (4).

Our study has limitations, the most important one being the limited sample size. In addition, we were unable to study patients on sphingosine 1-phosphate receptor modulators, a therapy known to inhibit the humoral and cellular responses after SARS-CoV-2 vaccination, as only five patients on fingolimod with a SARS-CoV-2 infection were identified in the COMS-19 study who did not complete follow-up after vaccination (5). Another limitation was missing data regarding the timing of COVID-19 prior to vaccination in half of our patients, as the timing influences antibody titers and level of immunity. Furthermore, our results might not be translatable to later variants of SARS-CoV-2. The strength of this study was the prospective design and sampling at pre-specified time points after vaccination.

In conclusion, prior SARS-CoV-2 infection increases anti-RBD antibody responses after the first vaccination in patients with MS. However, in ocrelizumab-treated patients, humoral responses remained low and also in convalescent participants.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethical Committee of the VU University Medical Center/Medical Ethical Committee of the Amsterdam Medical Center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZK, KD, TK, AB, SH, TR, FE, and JKi contributed to the conception and design of the study. ZK, LH, EWS, EMS, MS,

LK, KD, Jke, and LW contributed to the acquisition and analysis of the data. KD performed the statistical analyses. ZK and KD drafted a significant portion of the manuscript or figures. All authors revised the manuscript critically for intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

FE reports consulting fees from UCB Pharma and CSl Behring; honoraria from Grifols. TR reports consulting fees from Novartis. Jki reported speaking and consulting relationships with Biogen, Genzyme, Merck, Novartis, Roche, Sanofi, and TEVA. Amsterdam UMC, location VUmc, MS Center Amsterdam has received financial support for research activities from Biogen, Celgene, Genzyme, Merck, Novartis, Roche, Sanofi, and TEVA.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Multiple sclerosis-disease modifying therapies affect humoral and T-cell response to mRNA COVID-19 vaccine

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Background: The mRNA vaccines help protect from COVID-19 severity, however multiple sclerosis (MS) disease modifying therapies (DMTs) might affect the development of humoral and T-cell specific response to vaccination.

Methods: The aim of the study was to evaluate humoral and specific T-cell response, as well as B-cell activation and survival factors, in people with MS (pwMS) under DMTs before (T0) and after two months (T1) from the third dose of vaccine, comparing the obtained findings to healthy donors (HD). All possible combinations of intracellular IFNγ, IL2 and TNFα T-cell production were evaluated, and T-cells were labelled "responding T-cells", those cells that produced at least one of the three cytokines of interest, and "triple positive T-cells", those cells that produced simultaneously all the three cytokines.

Results: The cross-sectional evaluation showed no significant differences in anti-S antibody titers between pwMS and HD at both time-points. In pwMS, lower percentages of responding T-cells at T0 (CD4: p=0.0165; CD8: p=0.0022) and triple positive T-cells at both time-points compared to HD were observed (at T0, CD4: p=0.0007 and CD8: p=0.0703; at T1, CD4: p=0.0422 and CD8: p=0.0535). At T0, pwMS showed higher plasma levels of APRIL, BAFF and CD40L compared to HD (p<0.0001, p<0.0001 and p<0.0001, respectively) and at T1, plasma levels of BAFF were still higher in pwMS compared to HD (p=0.0022).According to DMTs, at both T0 and T1, lower anti-S antibody titers in the depleting/sequestering-out compared to the

enriching-in pwMS subgroup were found (p=0.0410 and p=0.0047, respectively) as well as lower percentages of responding CD4+ T-cells (CD4: p=0.0394 and p=0.0004, respectively). Moreover, the depleting/sequestering-out subgroup showed higher percentages of IFNγ-IL2-TNFα+ T-cells at both time-points, compared to the enriching-in subgroup in which a more heterogeneous cytokine profile was observed (at T0 CD4: p=0.0187; at T0 and T1 CD8: p =0.0007 and p =0.0077, respectively).

Conclusion: In pwMS, humoral and T-cell response to vaccination seems to be influenced by the different DMTs. pwMS under depleting/sequestering-out treatment can mount cellular responses even in the presence of a low positive humoral response, although the cellular response seems qualitatively inferior compared to HD. An understanding of T-cell quality dynamic is needed to determine the best vaccination strategy and in general the capability of immune response in pwMS under different DMT.

KEYWORDS

SARS-CoV-2 mRNA vaccine, T-cell, MS, DMTs, flow-cytometry, BAFF, April, CD40L

Introduction

In the last two years, the coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2), has emerged with a severe global health impact and difficult clinical management (1, 2). SARS-CoV-2 vaccines with different designs have been approved and authorized in many countries, Italy included, and vaccine campaigns have been launched (3). Among them, the mRNA vaccine mRNABNT162b2 (Comirnaty®) has been widely employed in the Italian population (4). Several studies showed that mRNA vaccines help protect from severe COVID-19 disease, hospitalization and death in immunocompetent individuals and in frail populations (5, 6). However, multiple sclerosis (MS) disease modifying therapies (DMTs) might affect COVID-19 disease severity as well as the development of humoral and cellular immunity after SARS-CoV-2 exposure or vaccination (7, 8). Indeed, Sormani et al. (9) showed a propensity toward a more severe COVID-19 disease in people with MS (pwMS) under certain DMTs, such as anti-CD20 treatments.

MS is an inflammatory demyelinating disease affecting the central nervous system (CNS), thought to result from the interaction of genetic and environmental factors that remain only partially understood (10). Several DMTs have been developed and are now currently available (11). These drugs act at different levels on the immune system causing (I) depletion and/or cytolysis of immune cells, such as anti-CD20 humanized monoclonal antibody (ocrelizumab), anti-CD52 monoclonal antibody that depletes CD52+ T- and B-cells (alemtuzumab) and purine analogue that interferes with DNA synthesis inducing prolonged lymphocyte depletion (cladribine), and (II) an impairment of immune cell migration, such as α4-integrin antibody that prevents lymphocytes blood–brain barrier (BBB) crossing (natalizumab) and a non-selective sphingosine 1 phosphate (S1P) receptor modulator that prevents lymphocyte egress from lymph nodes (fingolimod) (2, 11). Despite the remarkable effectiveness, DMTs are usually associated to an increased risk of infections, such as tuberculosis, hepatitis B, John Cunningham (JC) virus, herpes viruses reactivation (12–20) and an attenuation of responses to vaccination, that seems to be related to the drug's mode of action (21–24).

B-cell activating and survival factors, like B-cell activating factor (BAFF), A-proliferation inducing ligand (APRIL) and CD40L ligand (CD40L), are mainly implicated in B-cell survival, proliferation and antibody production and T-cell dependent and independent antibody class switching (25–27). After vaccination their concentrations increases enhancing B-cell activation (28, 29), and their expression is a prerequisite for activation of adaptive immune response to vaccination, while their absence may result in a reduced magnitude of response (27). Being involved in B-cell differentiation and survival, the three cytokines are target for immune modulation in the context of vaccine design and have been recently studied as molecular adjuvants to improve vaccine outcome (30).

The aim of the study was to evaluate humoral and specific T-cell response, as well as B-cell activating and survival factors in pwMS under different DMTs.

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Materials and methods

Ethics statement

The study was approved by Ethics Committee of Policlinico Umberto I, Sapienza University of Rome (protocol numbers 0062/2022). All patients gave written consent for participation in the study.

Study design and participants

To evaluate humoral and specific T-cell response to mRNABNT162b2 (Comirnaty®) vaccine, pwMS under different DMTs and age- and sex-matched healthy donors (HD) were enrolled. Prior history of symptomatic SARS-CoV-2 infection was considered as exclusion criterion. Both pwMS and HD received two dose of mRNABNT162b2 (Comirnaty®) vaccine according to schedule proposed by the current Italian national vaccination program (4). For both groups, two time-points were considered: before (T0) and after two months from the third dose of mRNABNT162b2 vaccine (T1).

All enrolled pwMS were stratified according to the drug's mechanism of action on peripheral blood cells into two subgroups: depleting/sequestering-out, including those patients treated with alemtuzumab, cladribine, fingolimod and ocrelizumab, and enriching-in, including those patients treated with natalizumab. The blood samples from pwMS treated with cladribine, ocrelizumab or alemtuzumab were taken at least 3 months after last drug administration. The differences in humoral and specific T-cell response as well as in B-cell activating and survivor factors, among the two subgroups were evaluated.

SARS-CoV-2 anti-N and anti-S antibodies

To exclude possible pre-exposure to asymptomatic natural SARS-CoV-2 infection, specific SARS-CoV-2 anti-Nucleocapsid (N) antibodies were measured on serum using the KT-1032 EDI TM Novel Coronavirus COVID-19 IgG Enzyme Linked Immunosorbent Assay (ELISA) Kit (Epitope Diagnostics, Inc. 7110 Carroll Rd, San Diego, CA 92121, USA) and performed according to the manufacturer's instructions. The average value of the absorbance of the negative control is less than 0.25 optical density (OD), and the absorbance of the positive control is not less than 0.30 OD.

Specific SARS-CoV-2 total anti-Spike antibodies were evaluated in serum, for all time-points, using a commercial chemiluminescence immunoassay (CLIA) (The DiaSorin Liaison SARS-CoV-2 TrimericS IgG; DiaSorin S.p.A) according to manufacturer's instructions. The test detects SARS-CoV-2 Spike S1/S2 protein specific IgG antibody levels, expressed in binding antibody unit (BAU/ml) according to World Health Organization international Reference Standard (NIBSC code. 20/268). A positive serologic response was defined as having detectable IgG antibodies against SARS-CoV-2 over the cut-off value of 33.8 BAU/ml.

T-cell stimulation with SARS-CoV-2 specific peptide libraries

T-cell specific response was assessed using a multiparametric flow cytometry after overnight stimulation with SARS-CoV-2 peptide libraries on isolated peripheral blood mononuclear cells (PBMCs), as previously described (12, 21, 31). Pools of lyophilized peptides, consisting mainly of 15-mer sequences with 11 amino acids overlap, covering the immunodominant sequence domains of the Spike glycoprotein (S) (GenBank MN908947.3, Protein QHD43416.1) and the Nucleocapsid phosphoprotein (N) (GenBank MN908947.3, Protein QHD43423.2) of SARS-CoV- 2 were purchased from Miltenyi Biotec. Specifically, PepTivator SARS-CoV-2 Prot_S1 covered the N-terminal S1 domain of the spike protein (amino acids [aa] 1–692). PepTivator SARS-CoV-2 Prot_S covered selected immunodominant sequence domains of the spike protein (aa 304–338, 421–475, 492–519, 683–707, 741–770, 785–802, and 885–1273). PepTivator SARS-CoV-2 Prot_N covered the complete sequence of the N phosphoprotein of SARS-CoV-2. For each patient, an unstimulated and a positive phytohemagglutinin (PHA) 5µg/ml control was also included. Brefeldin A at a final concentration of 5µg/ml was added in the culture after 1 hour of incubation.

PBMCs were stained with an appropriate combination of fluorochrome-conjugated antibodies (PacificBlue-conjugated anti-CD45, APC-Cy7-conjugated anti-CD4, APC-conjugated anti-CD8, BioLegend, San Diego). Fix/Perm solution (BioLegend, San Diego) was used prior intracellular staining (FITC-conjugated anti- IFNγ, PerCp-Cy 5.5-conjugated anti-TNFα and PE-Cy7-conjugated anti-IL2, BioLegend, San Diego), according to manufacturer's instructions. Fixable viability kit (Zombie Aqua™ BioLegend, San Diego) was used to exclude dead cells. Samples were acquired using MACSQuant (Miltenyi Biotec, Germany) and analyzed using FlowJo™ v10.8.1 software. Specifically, cytokine background obtained from the unstimulated condition was subtracted to the stimulated ones. All possible combinations of intracellular expression of IFNγ, IL2 and TNFα in cytokine-producing T-cells were evaluated using the Boolean gate. "Responding T-cells" were defined as those cells that produce any of IFNγ, IL2 and TNFα, while "triple-positive T-cells" were defined as those simultaneously producing all three cytokines. Display and analysis of the different cytokine combinations was performed with SPICE v6.1.

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Measurement of BAFF, APRIL and CD40L

In both pwMS and HD, plasma levels of BAFF, APRIL and CD40L were measured using a commercial cytometric bead-based multiplex panel immunoassay (CBA) (BioLegend, San Diego), acquired using MACSQuant (Miltenyi Biotec, Germany) and analyzed using FlowJo™ v10.8.1 software (Figure 1). B-cell activating and survival factors were expressed as plasma concentration (pg/ml).

Statistical analyses

All data are reported as median and interquartile range (IQR). Differences between pwMS and HD were assessed using a two-tailed Mann-Whitney test for quantitative variables. Differences among pwMS subgroups and HD were assessed using a non-parametric Kruskal-Wallis test with Dunn's multiple comparison post-test for quantitative variables. Two-point longitudinal assessment was performed using a non-parametric Wilcoxon test. Results were considered statistically significant if the p value was <0.05. Statistical analyses were performed using GraphPad Prism 9. Finally, distributions of different cytokine combinations were performed by the nonparametric Wilcoxon rank test using SPICE, distributed by the National Institute of Allergy and Infectious Diseases, NIH.

Results

Study population

From October 2021 to June 2022, 18 pwMS (female/male: 12/6; 43 [35-56] years) and 18 HD (female/male: 13/5; 30 [30-53] years) were enrolled (Table 1). All pwMS were under DMTs and the median time (IQR) from starting the current treatment was of 3 [2-4] years. As reported in Table 1, among pwMS 5.5% were alemtuzumab-treated, 11.1% cladribine-treated, 11.1% fingolimod-treated, 33,3% natalizumab-treated and 38.9% ocrelizumab-treated. Given that, we stratified pwMS according to the drug's mechanism of action on peripheral blood immune cells into two subgroups: depleting/sequestering-out (n=12; female/male: 7/5; 46 [35-57] years) and enriching-in (n=6; female/male: 5/1; 40 [34-44] years) (Table 1).

The cross-sectional evaluation of humoral and specific T-cell response, and B-cell activating and survival factors

The cross-sectional evaluation of humoral and specific T-cell response, as well as B-cell activating and survival factors was performed at T0 comparing 18 pwMS (female/male: 12/6; 43 [35-56] years) and 12 HD (female/male: 8/4; 42 [33-53] years), and at T1 comparing 16 pwMS (female/male:11/5; 42 [34-49] years) and 15 HD (female/male: 12/3; 38 [30-52] years).

The evaluation of specific SARS-CoV-2 anti-N antibodies performed both T0 and T1 showed negative results for all enrolled pwMS and HD.

Overall, a positive serological response to vaccination was observed in 77.8% (14/18) and 88.0% (14/16) of enrolled pwMS, at T0 and T1, respectively. Conversely, a positive serological response at both time-points in 100% (12/12 and 15/15, respectively) of enrolled HD was found.

The cross-sectional evaluation of anti-S antibody titers showed no statistically significant differences between pwMS and HD at both time-points (T0: 199 [60-1120] and 369 [189-700.50] BAU/ml, respectively; T1: 1930 [225-5895] and 1660 [1520-9400] BAU/ml, respectively) (Figure 2A).

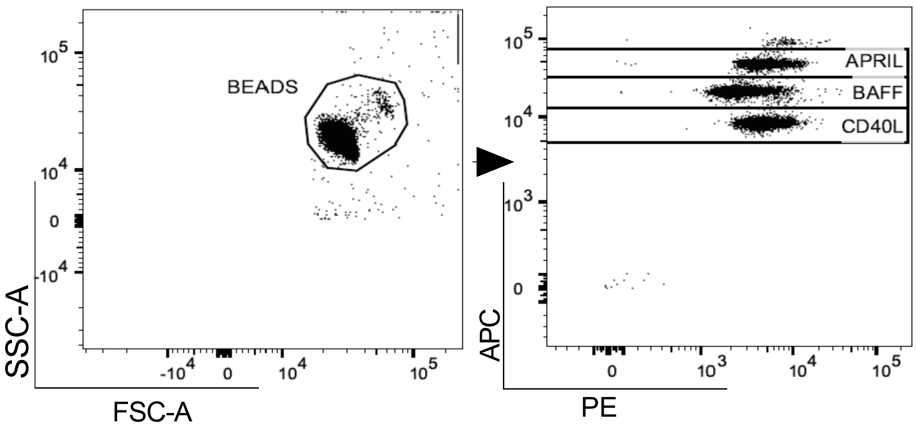

FIGURE 1
Gating strategy. A. Representative flow cytometry plot for the evaluation of plasma APRIL, BAFF and CD40L levels after bead-based multiplex assay panel. APRIL, A-proliferation inducing ligand; BAFF, B-cell activating factor; CD40L, CD40 ligand.

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TABLE 1 Demographic and clinical features of study population.

	HD	pwMS	depleting/sequestering-out	enriching-in
Female/Male	13/5	12/6	7/5	5/1
Age, median (IQR)	30 (35–53)	43 (35–56)	46 (35–57)	40 (34–44)
Years of disease, median (IQR)	–	7 (3–14)	7 (5–15)	5 (1–9)
EDSS, median (IQR)	–	3 (1–4)	3 (1–6)	2 (1–3)
Previous MS treatment (yes/no)	–	5/13	3/9	2/6
Years of current treatment, median (IQR)	–	2 (2–4)	3 (2–4)	1 (1–4)
Current MS treatment	–			
alemtuzumab (n)		1		
cladribine (n)	–	2		
fingolimod (n)	–	2		
natalizumab (n)	–	6		
ocrelizumab (n)	–	7		

MS, multiple sclerosis; pwMS, people with multiple sclerosis; HD, healthy donors; n, number; IQR, interquartile range; EDSS, expanded disability status scale.

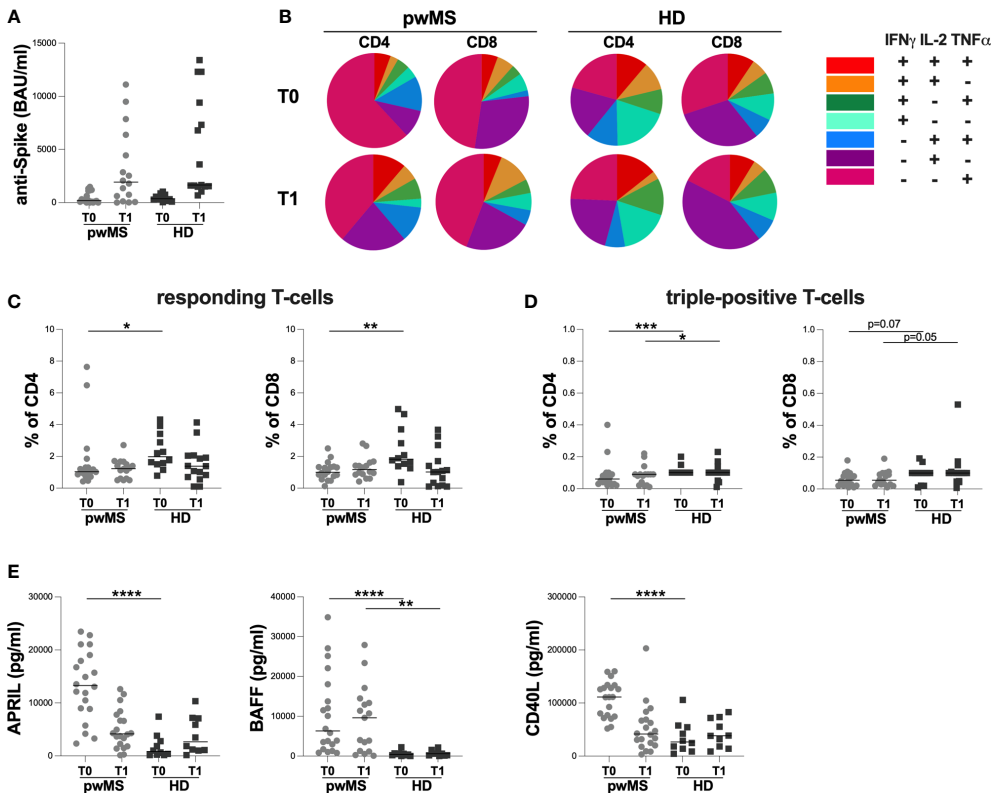

FIGURE 2
Cross-sectional evaluation of humoral and specific T-cell response in pwMS and HD, and overview of cytokine-producing T-cells. **(A)** The evaluation of anti-S antibody titers in pwMS and HD. **(B)** Overview of intracellular IFNγ,IL2 and TNFα production by CD4+ and CD8+ T-cells at T0 and at T1 in pwMS and HD. **(C)** Evaluation of percentage in responding CD4+ and CD8+ T-cells in pwMS and HD. **(D)** Evaluation of percentage in triple-positive CD4+ and CD8+ T-cells in pwMS and HD. **(E)** Evaluation of plasma levels of APRIL, BAFF and CD40L in pwMS and HD. APRIL, A-proliferation inducing ligand; BAFF, B-cell activating factor; CD40L, CD40 ligand; pwMS, people with multiple sclerosis; HD, healthy donors; T0, before third dose of vaccine; T1, after two months form third dose of vaccine. *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001.

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As reported in Figure 2B, at both time-points, we observed a different T-cell subset distribution in pwMS and HD, with a more heterogeneous production of the three cytokines in the latter (Figure 2B).

At T0, a lower percentage of responding CD4+ and CD8+ T-cells in pwMS compared to HD was observed (CD4: 1.04 [0.85-1.44] and 1.98 [1.52-3.29], respectively, p=0.0165; CD8: 1.00 [0.71-1.34] and 1.82 [1.42-3.48], respectively, p=0.0022) (Figure 2C). Otherwise, at T1, not statistically differences in the percentage of responding T-cells were found (CD4:1.23 [0.60-1.63] and 1.39 [0.70-2.05], respectively; CD8: 1.17 [0.86-1.56] and 1.02 [0.17-1.70], respectively) (Figure 2C).

At both T0 and T1, lower percentages of triple-positive T-cells were seen, although only a trend for CD8+ T-cells was observed (CD4: 0.06 [0.03-0.09] and 0.10 [0.10-0.10], respectively, p=0.0007; 0.09 [0.03-0.09] and 0.10 [0.10-0.10], respectively, p=0.0422; CD8: 0.06 [0.02-0.09] and 0.10 [0.04-0.10], respectively, p=0.0703; 0.06 [0.03-0.10] and 0.10 [0.05-0.11], respectively, p=0.0533) (Figure 2D).

Finally, at T0, pwMS showed higher plasma levels of APRIL, BAFF, and CD40L compared to HD (APRIL: 13296 [8890-18759] and 833 [220-3042] pg/ml, respectively, p<0.0001; BAFF: 6330 [2015-16971] and 429.3 [154-631] pg/ml, respectively, p<0.0001; CD40L:111275 [75329-132373] and 26664 [12457-55197] pg/ml, respectively, p<0.0001) (Figure 2E). Otherwise, at T1, only plasma levels of BAFF were still higher in pwMS compared to HD (9616 [1204-13922] and 594 [143-1097] pg/ml, respectively, p=0.0022) (Figure 2E). No significant differences in plasma levels of APRIL and CD40L were observed (Figure 2E).

The longitudinal evaluation of humoral and specific T-cell response, and B-cell activating and survival factors

The two-point longitudinal evaluation of humoral and T-cell response, as well as B-cell activating and survival factors was performed in 16 pwMS (female/male: 11/5; 42 [34-49] years) and 9 HD (female/male: 7/2; 44 [33-53] years).

At T1, both pwMS and HD showed an increase in anti-S antibody titers compared to T0 (pwMS: 1930 [245-5895] and 198.5 [81-1140] BAU/ml, respectively, p=0.0006; HD: 3590 [1575-10850] and 320 [124-662] BAU/ml, respectively, p=0.0039) (Figure 3A). Concerning specific T-cell response, an increase in the percentage of responding CD8+ T-cells in pwMS was observed (1.17 [0.86-1.56] and 1.00 [0.60-1.33], respectively, p=0.0136) (Figure 3B). Conversely, no differences in the percentages of responding CD4 + T-cells neither in the percentages of triple-positive T-cells in both pwMS and HD were found (responding CD4+ T-cells: 1.23 [0.60-1.63] and 1.03 [0.80-1.28], respectively; triple-positive CD4+ T-cells: 0.09 [0.03-0.09] and 0.05 [0.03-0.09], respectively; triple-positive CD8+ T-cells: 0.06 [0.03-0.10] and 0.05 [0.02-0.09], respectively) (Figure 3B, C).

In pwMS, the evaluation of B-cell activating and survival factors showed a significantly reduction in plasma levels of APRIL and CD40L at T1 compared to T0 (APRIL: 4173 [1926-7510] and 13296 [8890-18759] pg/ml, respectively, p=0.0001; CD40L: 41546 [21284-68397] and 111275 [75329-132373] pg/ml, respectively, p=0.0012) (Figure 3D). Conversely, in pwMS no differences in plasma levels of BAFF were observed (Figure 3D) as well as in the longitudinal evaluation of APRIL, BAFF and CD40L plasma levels in HD (Figure 3D).

Two-point cross-sectional evaluation of humoral and T-cell response, and B-cell activating and survival factors in pwMS stratified according to DMTs

Stratifying pwMS according to DMTs, at both T0 and T1, a lower anti-S antibody titer in the depleting/sequestering-out compared to the enriching-in subgroup was found (T0: 100 [1-292] and 871 [175-1360] BAU/ml, respectively, p=0.0410; T1: 370 [50-1975] and 5410 [2655-9893] BAU/ml, respectively, p=0.0047) (Figure 4A). Moreover, only at T1, the depleting/sequestering-out subgroup showed a lower anti-S antibody titer compared to HD (370 [50-1975] and 1660 [1520-9400] BAU/ml, respectively, p=0.0244) (Figure 4A). No significantly differences in anti-S antibody titers between the enriching-in subgroup and HD ween seen (Figure 4A).

Interestingly, at both time-points, in the enriching-in subgroup, a heterogeneous cytokine production was observed (Figure 4B). Conversely, an unusual T-cell subset distribution in the depleting/sequestering-out subgroup at both time-points was found (Figure 4B). Specifically, the depleting/sequestering-out subgroup showed a higher percentage of IFNγ-IL2-TNFα+ CD4 + T-cells compared to the enriching-in one at both time point, although at T1 the differences were not statistically significant (T0: 1.31 [0.38-3.76] and 0.20 [0.08-0.32], respectively, p=0.0187; T1: 0.51 [0.23-2.40] and 0.27 [0.16-0.41], respectively). Likely, a higher percentage of IFNγ-IL2-TNFα+ CD8+ T-cells in the depleting/sequestering-out subgroup compared to the enriching-in one at both time-points was observed (T0: 0.72 [0.45-0.82] and 0.04 [0.02-0.06], respectively, p=0.0007; T1: 0.52 [0.33-0.74] and 0.06 [0.01-0.55], respectively, p=0.0077).

At both T0 and T1, a lower percentage of responding CD4+ T-cells in the depleting/sequestering-out compared to the enriching-in subgroup was seen (0.92 [0.73-1.15] and 1.30 [1.16-2.01], respectively, p=0.0394; 0.85 [0.50-1.22] and 1.68 [1.48-1.96], respectively, p=0.0004) (Figure 4C). No differences in the responding CD8+ T-cell percentages between the depleting/

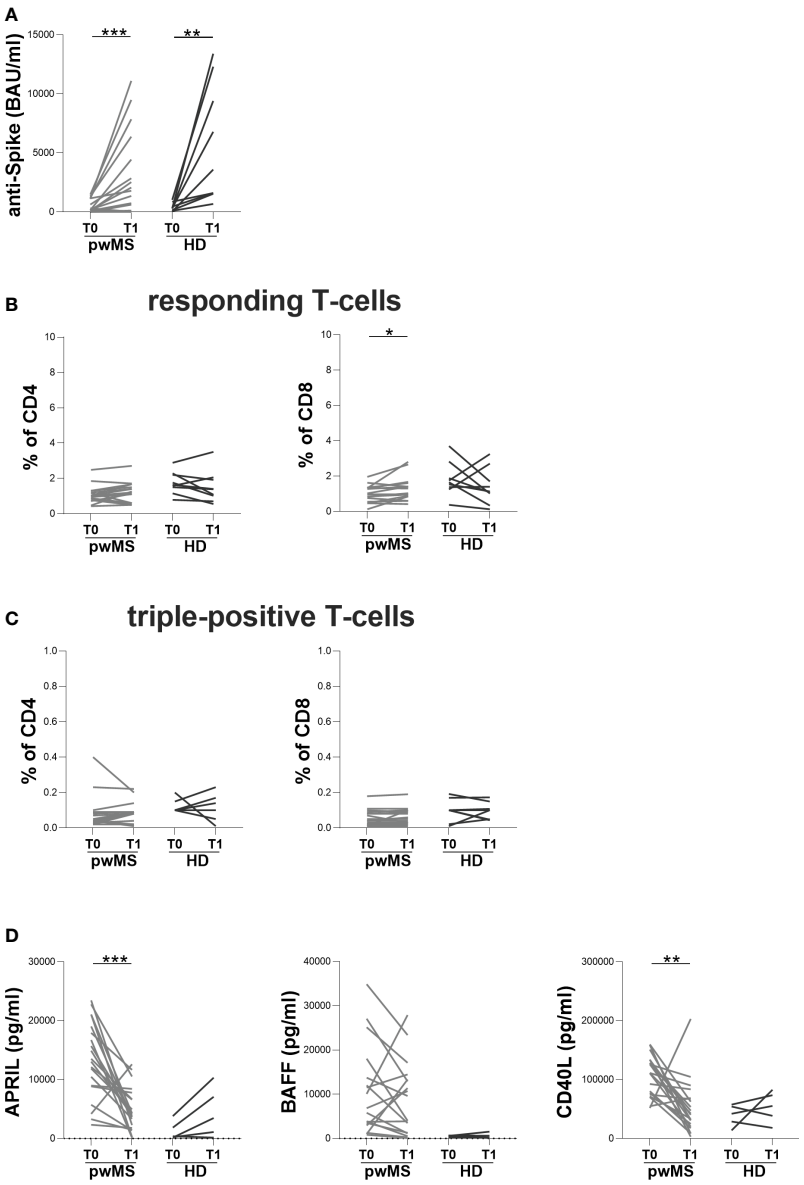

FIGURE 3
Longitudinal evaluation of humoral and specific T-cell response in pwMS and HD. **(A)** The longitudinal evaluation of anti-S antibody titers in pwMS and HD. **(B)** The evaluation of responding CD4+ and CD8+ T-cells in pwMS and HD. **(C)** The evaluation of triple-positive CD4+ and CD8+ T-cells in pwMS and HD. **(D)** The longitudinal evaluation of plasma levels of APRIL, BAFF and CD40L. APRIL, A-proliferation inducing ligand; BAFF, B-cell activating factor; CD40L, CD40 ligand; pwMS, people with multiple sclerosis; HD, healthy donors; T0, before third dose of vaccine; T1, after two months from third dose of vaccine. *p < 0.05; **p < 0.01; ***p < 0.001.

sequestering-out and the enriching-in subgroups were observed (T0: 0.91 [0.60-1.32] and 1.31 [0.75-1.72], respectively; T1: 0.97 [0.60-1.41] and 1.54 [1.00-2.70], respectively) (Figure 4C). Conversely, at T1, a lower percentage in triple-positive CD8+ T-cells in the depleting/sequestering-out compared to the enriching-in subgroup was observed (0.04 [0.02-0.07] and 0.10 [0.08-0.13], respectively, p=0.0082) (Figure 4D).

Finally, at T0, a lower percentage of responding T-cells in the depleting/sequestering-out subgroup compared to HD was found (CD4: 0.92 [0.73-1.15] and 1.98 [1.52-3.29], respectively, p=0.0116; CD8: 0.91 [0.60-1.32] and 1.82 [1.42-3.48], respectively, p=0.0049) (Figure 4C). A both T0 and T1, a lower percentage in triple-positive CD4+ T-cells in the depleting/sequestering-out subgroup compared to HD was seen, although

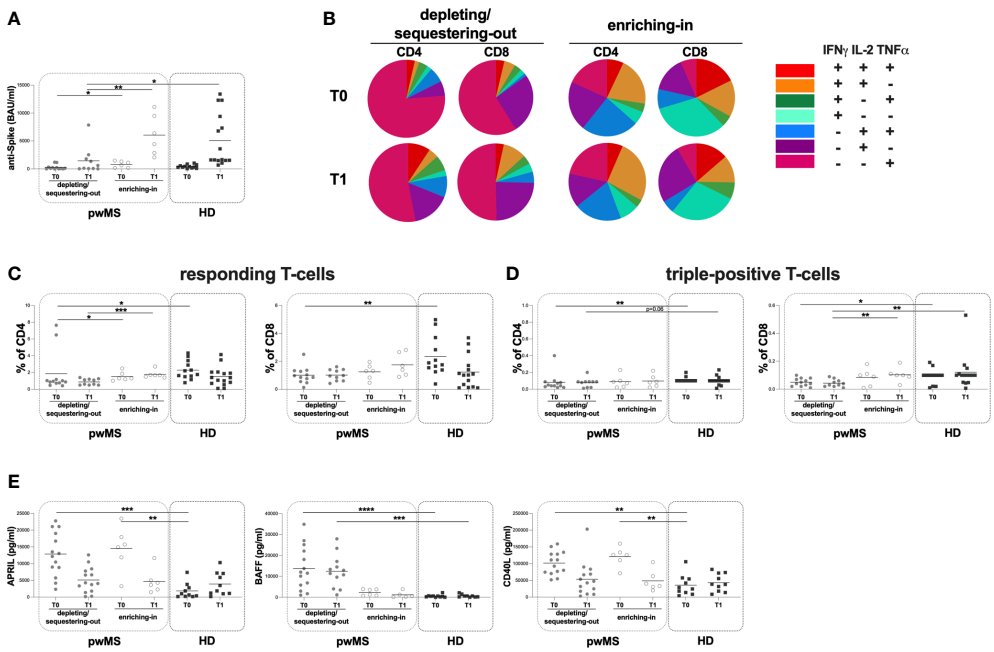

FIGURE 4
Cross-sectional evaluation of humoral and specific T-cell response is pwMS subgroups and HD, and overview of cytokine-producing T-cells. **(A)** The evaluation of anti-S antibody titers at two time-points: T0 and T1 in the depleting/sequestering-out and the enriching-in subgroups, and HD. **(B)** Overview of intracellular IFNγ, IL2 and TNFα production by CD4+ and CD8+ T-cells at T0 and at T1 in the depleting/sequestering-out and the enriching-in subgroups. **(C)** Evaluation of responding CD4+ and CD8+ T-cells in pwMS subgroups and HD. **(D)** Evaluation of triple-positive CD4+ and CD8+ T-cells in pwMS subgroups and HD. **(E)** Evaluation of plasma levels of APRIL, BAFF and CD40L in the depleting/sequestering-out and the enriching-in subgroups, and HD. APRIL, A-proliferation inducing ligand; BAFF, B-cell activating factor; CD40L, CD40 ligand; pwMS, people with multiple sclerosis; HD, healthy donors; T0, before third dose of vaccine; T1, after two months form third dose of vaccine. *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001.

not statistically significant at T1 (T0: 0.05 [0.03-0.09] and 0.10 [0.10-0.10], respectively, p=0.0024; T1: 0.09 [0.02-0.09] and 0.10 [0.10-0.10], respectively, p=0.0645) (Figure 4D).

Moreover, at both T0 and T1, lower percentages of triple-positive CD8+ T-cells in the depleting/sequestering-out subgroup compared to HD was found, although not statistically significant at T0 (T0: 0.05 [0.02-0.08] and 0.10 [0.04-0.10], respectively, p=0.0588; T1: 0.04 [0.02-0.07] and 0.10 [0.05-0.11], respectively, p=0.0048) (Figure 4D).

At both time-points, no differences in the plasma levels of APRIL and CD40L between the depleting/sequestering-out and the enriching-in subgroups were observed (APRIL T0: 12603 [8077-19540] and 15312 [9740-11670] pg/ml, respectively; T1: 4173 [1706-7957] and 3965 [2082-6646] pg/ml, respectively; CD40L T0: 101855 [73681-129802] and 125967 [101016-140260] pg/ml, respectively; T1: 45043 [15469-72595] and 36953 [28036-73177] pg/ml, respectively) (Figure 4E). Otherwise, at T0 and T1, a higher plasma level of BAFF in the depleting/sequestering-out compared to the enriching-in subgroup was seen (T0: 11768 [5094-228865] and 2412 [836.30-3807] pg/ml, respectively, p=0.0064; T1: 12146 [5409-164509] and 504.90 [163.30-2578]pg/ml, respectively, p=0.0023) (Figure 4E).

At T0, a higher plasma level of APRIL in both the depleting/sequestering-out and the enriching-in subgroups compared to HD was observed (the depleting/sequestering-out: 12603 [8077-19540] and 832.70 [220.10-3042] pg/ml, respectively, p=0.0005; the enriching-in: 15312 [9740-11670] and 832.70 [220.10-3042] pg/ml, respectively, p=0.0017) (Figure 4E). At T1, no differences were observed (Figure 4E). Otherwise, at T0 and T1, a higher plasma level of BAFF in the depleting/sequestering-out subgroup compared to HD was observed (T0: 11768 [5094-228865] and 429.30 [154.20-630.80] pg/ml, respectively, p <0.0001; T1: 12146 [5409-164509] and 594.10 [142.50-1097] pg/ml, respectively, p=0.0004) (Figure 4E). No differences in the plasma level of BAFF between the enriching-in subgroup and HD were found (Figure 4E). Finally, at T0 a higher plasma level of CD40L in both the depleting/sequestering-out and the enriching-in subgroups compared to HD was observed (the depleting/sequestering-out: 101855 [73681-129802] and 26664 [12457-55197] pg/ml, respectively, p=0.0013; the enriching-in: 125967 [101016-140260] and 26664 [12457-55197] pg/ml, respectively, p=0.0012) (Figure 4E). No differences in plasma level of CD40L between pwMS subgroups were seen (Figure 4E).

Two-point longitudinal evaluation of humoral and T-cell response, and B-cell activating and survival factors in pwMS stratified according to DMTs

At T1, the longitudinal evaluation of anti-S antibody titer showed a significant increase in the enriching-in subgroup compared to T0 (5410 [2655-9893] and 871 [175.30-1360] BAU/ml, respectively, p=0.0313) (Figure 5A).

In both pwMS subgroups, no differences in the percentages of responding and triple-positive T-cells were observed (Figure 5B, C). Finally, at T1, a significant reduction in plasma levels of APRIL and CD40L in both pwMS subgroups compared to T0 was observed (the depleting/sequestering-out subgroup: APRIL: 4173 [1706-7957] and 12603 [8077-19540] pg/ml, respectively, p=0.0031; CD40L: 45043 [15469-72595] and 101855 [73681-129802] pg/ml, respectively, p=0.0245; the enriching-in subgroup: APRIL: 3965 [2082-6646] and 15312 [9740-19322] pg/ml, respectively, p=0.0313; CD40L: 36953 [28036-73177] and 125967 [101016-140260] pg/ml, respectively, p=0.0313) (Figure 5D).

Discussion

In this observational, monocentric, and prospective study, we investigated the immunogenicity before and after the third dose of BNT162b2 mRNA vaccine in pwMS under different DMTs, evaluating both humoral and specific T-cell response as well as B-cell activating and survival factors and comparing the obtaining findings with a control group.

In line with other studies involving different pwMS (8, 32–34), the first main result of our study was that pwMS treated with DMTs develop a positive humoral immune response to the mRNA vaccine, which does not differ significantly from that

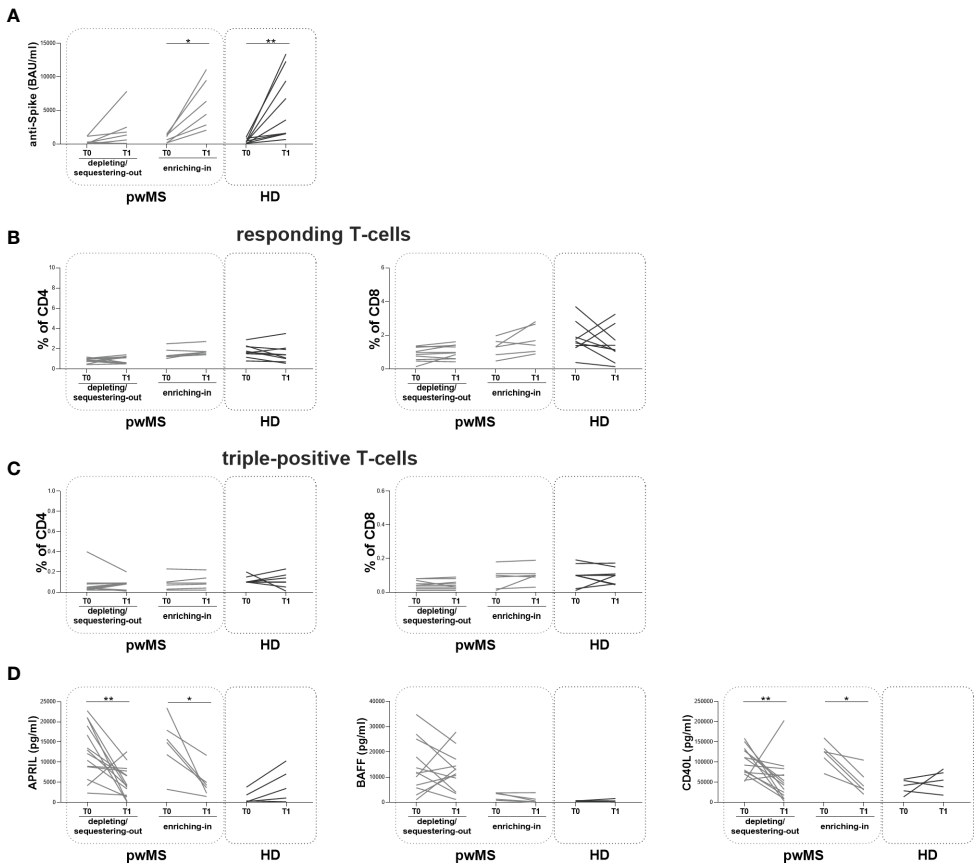

FIGURE 5
Longitudinal evaluation of humoral and specific T-cell response pwMS subgroups and HD. **(A)** The longitudinal evaluation of anti-S antibody titers between T0 and T1 in the depleting/sequestering-out and in the enriching-in subgroups compared to HD. **(B)** The evaluation of responding CD4+ and CD8+ T-cells in pwMS subgroups. **(C)** The evaluation of triple-positive CD4+ and CD8+ T-cells in the depleting/sequestering-out and in the enriching-in subgroups. **(D)** The longitudinal evaluation of plasma levels APRIL, BAFF and CD40L. APRIL, A-proliferation inducing ligand; BAFF, B-cell activating factor; CD40L, CD40 ligand; pwMS, people with multiple sclerosis; HD, healthy donors; T0, before third dose of vaccine; T1, after two months from third dose of vaccine. *p < 0.05; **p < 0.01.

observed in HD. Moreover, an increase in humoral response in pwMS following the third dose of BNT162b2 mRNA vaccine was seen. However, as reported by Sabatino et al. (32), humoral response to SARS-CoV-2 vaccine appears to be influenced by different DMTs mechanism of action. Indeed, in our study, pwMS belonging to the depleting/sequestering-out subgroup (including alemtuzumab-, cladribine-, fingolimod- and ocrelizumab-treated) showed a significantly lower humoral response to vaccination when compared to HD and to the enriching-in subgroup (natalizumab-treated). This is in agreement with several published studies in which a pattern of low humoral response to SARS-CoV-2 vaccination, with respect to healthy subjects, has been previously reported, mainly for patients receiving B-cell depleting drugs (35–37) and fingolimod (32, 38). Even though the depleting/sequestering-out subgroup displayed lower anti-Spike antibody titers, most patients had near-normal total anti-Spike IgG levels, while only few did not seroconvert. This particular phenomenon could be due, as already proposed by Hausler et al., to an incomplete depletion of B-cells by anti-CD20 treatment, that mainly act on circulating B-cells, leaving a smaller number of these cells that may persist in secondary lymphoid tissues (32, 39).

Although the first line of protection against SARS-CoV-2 includes pre-existing antibodies, induced by vaccination or infection, great safeguard can also be attributed to the T-cell response (40, 41). Indeed, as shown by Agrati et al. (42), in immunocompetent subjects the BNT162b2 mRNA vaccine is able to elicit a coordinated spike-specific T-cell response characterized by a production of all Th1 cytokines, with IFNγ correlating with both TNFα and IL2. Given that, we performed in pwMS a broad characterization of the functional profiles of specific T-cells, comparing the obtaining findings with HD. One strength of our study was the evaluation of all possible combination of intracellular expression of IFNγ, IL2 and TNFα by T-cells. T-cells that produce more than one of the three cytokine of interest have been considered as to be important in response to viral infections, including influenza (43, 44). Moreover, in convalescent COVID-19 patients this polyfunctional cytokine profile has been observed suggesting a possible rapid recall response (45–47).

In our study, pwMS showed lower percentages in responding and triple-positive T-cells compared to HD. Interestingly, when stratifying pwMS according to DMTs, lower percentages in responding and triple-positive T-cells were seen mainly in the depleting/sequestering-out subgroup. Different results have been reported in pwMS, with an extensive T-cell response in natalizumab-treated patients, an adequate T-cell response in ocrelizumab-treated and an impaired one in fingolimod-treated ones (2, 21, 32, 48, 49). The lower T-cell mediated response to vaccination that we observed in the depleting/sequestering-out subgroup is in accordance with published studies in which a reduction or even absence of adaptive cellular response has been reported in patients treated with fingolimod (50, 51). An explanation to this phenomenon could be the mode of action of fingolimod itself, that may result in trapping relevant T-cells in secondary lymphoid tissues blocking *in vitro* responses (51).

Moreover, in our study, pwMS included into the depleting/sequestering-out subgroup showed a higher percentage of IFNγ-IL2-TNFα+ T-cells at both time-points, compared to the enriching-in subgroup and HD in which a more heterogeneous cytokine profile was observed. These data suggest an inferior quality of response in pwMS included into the depleting/sequestering-out subgroup. This is in line with results from Picchianti-Diamanti et al. (52), showing a production of only one cytokine by T-cells in fragile patients and suggesting a potential dysfunction in T-cell response in frail subjects.

Lastly, due to B-cell involvement in vaccination immune response and in mounting an immunological memory (28), we evaluated plasma concentration of B-cells activating and survival factors, BAFF, APRIL and CD40L (25, 53, 54). Higher plasma levels of BAFF, APRIL and CD40L were seen at baseline in pwMS when compared to HD, difference that lasted in the depleting/sequestering-out and in the enriching-in subgroups. This is in accordance with some studies in which higher plasma levels of the three cytokines are reported in pwMS when compared to HD, due to their involvement in worsening of MS pathogenesis and in its regulation (55–58). A reduction over-time in APRIL and CD40L plasma concentration was seen in pwMS and the two subgroups, supporting their involvement in immune response to vaccination (59–61). However, no differences in plasma levels of BAFF over-time were observed. Being involved in B-cell survival and promotion, BAFF receptor expression is critical in enhancing an immune response and antiviral immunity (62). These results suggest that, event tough it is lower than healthy subjects', a humoral response is still elicited in pwMS.

Our study has some limitations such as the small sample size and the extremely heterogeneous pwMS DMTs included. On the other hand, an alemtuzumab-treated patients was included into the study, a treatment difficult to include due to the reduced use of this drug.

Conclusion

In summary, our data underline that the third dose of BNT162b2 mRNA vaccine provides additional benefit to pwMS. However, according to DMT mechanism of action, pwMS should be addressed toward the use of pre-exposure monoclonal antibodies, that have been proved to be effective in mounting an adequate humoral response (63), and to other therapeutic strategies to prevent SARS-CoV-2 infection, when necessary. T-cell and antibody titer testing of patients under

certain DMTs may allow a more individualized counselling of their infection risk. Finally, an understanding of T-cell quality dynamic is needed to determine the best vaccination strategy and in general the capability of immune response in pwMS under different DMT.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The study was approved by Ethics Committee of Policlinico Umberto I, Sapienza University of Rome (protocol numbers 0062/2022). The patients/participants provided their written informed consent to participate in this study.

Author contributions

MZ, MT, MC, AC: Designed the study. MZ, FD, MG, ET, AN, VP: Performed laboratory testing, analyzed data, performed statistical analysis, and wrote the manuscript. MC, AC, CM, ML: Assisted in designing the study. MZ, AC, MC, ML: Discussed results and critically revised the manuscript. MT, LM, PP, FC, VB, AG: Provided clinical samples and clinical data. MZ, MC, AC, ML: Discussed results, read, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CNS inflammatory demyelinating events after COVID-19 vaccines: A case series and systematic review

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Background: Vaccinations provided the most effective tool to fight the SARS-CoV-2 pandemic. It is now well established that COVID-19 vaccines are safe for the general population; however, some cases of rare adverse events following immunization have been described, including CNS Inflammatory Demyelinating Events (CIDEs). Although observational studies are showing that these events are rare and vaccines' benefits highly outweigh the risks, collecting and characterizing post-COVID-19 vaccine CIDEs might be relevant to single out potential risk factors and suggest possible underlying mechanisms.

Methods: Here we describe six CIDEs, including two acute transverse myelitis (ATM), three multiple sclerosis (MS), and one neuromyelitis optica spectrum disorder (NMOSD), occurring between 8 and 35 days from a COVID-19 vaccine. Moreover, we performed a systematic literature search of post-COVID-19 vaccines CIDEs, including ATM, ADEM, MS, and NMOSD/MOGAD, published worldwide between December 2020 and December 2021, during 1 year of the vaccination campaign. Clinical/MRI and CSF/serum characteristics were extracted from reviewed studies and pooled-analyzed.

Results: Forty-nine studies were included in the systematic review, reporting a total amount of 85 CIDEs. Considering our additional six cases, 91 CIDEs were summarized, including 24 ATM, 11 ADEM, 47 MS, and nine NMOSD/MOGAD. Overall, CIDEs occurred after both mRNA (n = 46), adenoviral-vectored (n = 37), and inactivated vaccines (n = 8). Adenoviral-vectored vaccines accounted for the majority of ADEM (55%) and NMOSD/MOGAD (56%), while mRNA vaccines were more frequent in MS new diagnoses (87%) and relapses (56%). Age was heterogeneous (19–88) and the female sex was prevalent. Time from vaccine to symptoms onset was notably variable: ADEM and NMOSD/MOGAD had a longer median time of onset (12.5 and 10 days) compared to ATM and MS (6 and 7 days) and further timing differences were observed between events

following different vaccine types, with ATM and MS after mRNA-vaccines occurring earlier than those following adenoviral-vectored ones.

Conclusion: Both the prevalence of vaccine types for certain CIDEs and the heterogeneity in time of onset suggest that different mechanisms—with distinct dynamic/kinetic—might underly these events. While epidemiological studies have assessed the safety of COVID-19 vaccines, descriptions and pooled analyses of sporadic cases may still be valuable to gain insights into CIDE's pathophysiology.

KEYWORDS

ADEM, transverse myelitis, multiple sclerosis, NMOSD, MOGAD, COVID-19, vaccines

Introduction

The Coronavirus disease 19 (COVID-19) vaccination campaign has no precedent in history for magnitude and speed. Randomized Control Trials (1–4) (RCTs) and real-world studies (5, 6) provided clear-cut evidence of vaccines' effectiveness in reducing infections, severe COVID-19, and deaths, resulting as the major tool to fight the pandemic. Up to now, 40 COVID-19 vaccines have been approved for emergency use by at least one regulatory authority (7) and several are under development (8). These include mRNA/DNA, adenoviral-vectored, protein-based, and whole virus inactivated/live attenuated formulations. Currently, the four vaccines licensed for use in the highest number of countries are the mRNA-based BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), and the adenoviral-vectored ChAdOx1 nCoV-19 (Vaxzeviria) and Ad26.COV2.S (Janssen). Phase 3 RCTs have demonstrated their safety in the general population (1–4). However, as the global vaccination campaign advances, data are being collected for Rare Adverse Events (RAEs), negligible from a statistical viewpoint but potentially helpful to suggest candidate risk factors and possible underlying mechanisms. Among RAEs, some cases of CNS Inflammatory Demyelinating Events (CIDEs) following COVID-19 vaccines have been described in literature from December 2020 (9), including both acute syndromes, such as acute transverse myelitis (ATM) and Acute demyelinating encephalomyelitis (ADEM), and relapses of chronic CNS inflammatory demyelinating diseases, such as multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Although an increasing amount of studies are showing that these events are rare and COVID-19 vaccine benefits highly outweigh the risks (10–13), collecting and characterizing post-COVID-19 vaccine CIDEs might still be relevant to gain insights about CNS inflammatory demyelinating diseases pathophysiology.

Here we report six CIDEs occurring after COVID-19 vaccines and present the results of a systematic review and pooled descriptive analysis of an additional 85, published worldwide from 1 December 2020 to 31 December 2021, during 1 year of the vaccination campaign.

Case series

Case 1

A 34-year-old man, with unremarkable past medical history, presented with numbness in his arms 8 days after receiving the first dose of Ad26.COV2.S vaccine. His condition worsened in a few days: numbness extended to his trunk and legs, and he progressively developed lower limb weakness and urinary retention. He entered our unit 4 days later. On neurological exam, he had light touch/pin-prick hypoesthesia below C4 level, four limbs weakness, and sphincter disturbances requiring catheterization. A spinal cord MRI showed a T2-weighted hyperintensity irregularly extending from C3 to medullaris conus (appearing swallowing from C4 to C7) with no gadolinium enhancement on T1-weighted images (Figures 1A,B); brain MRI resulted negative. Blood count, erythrocyte sedimentation rate, and C-reactive protein were normal. Cerebrospinal fluid (CSF) analysis revealed marked lymphocytosis (310 leucocytes, 90% mononuclear cells) and a slightly elevated protein level. No infectious agent was detected at CSF PCR testing for extensive infectious panel (Herpesviruses, Enterovirus, Parechovirus, i K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae,* and *Cryptococcus neoformans/gattii*). CSF immunoelectrophoresis (IEP) showed no oligoclonal bands (OCB). Serum anti-AQP-4 and anti-MOG antibodies were negative, as well as an antibody panel for connective tissue diseases. The patient was administered a 5-day course of high-dose IV methylprednisolone (IVMP) followed by oral tapering. After 2 weeks, he showed an almost complete motor recovery in the arms while lower limb weakness and sphincter disturbances

partially improved. He started rehabilitation treatment and after 4 months he reported marked amelioration of leg strength and further recovery of limb hypoesthesia. At 8 months of control, he remained clinically stable and MRI showed the complete resolution of the cervical swelling, with the extended T2-hyperintensity appearing fragmented in multiple shorter lesions, barely visible (Figure 1C); brain MRI was still negative.

Case 2

A 19-year-old man with a negative past medical history presented with numbness and weakness in his right arm in December 2018, 3 months after receiving Diphtheria/Tetanus/Pertussis (Tdap) and Poliovirus (IVP) vaccine booster doses. Symptoms spontaneously resolved in 2 weeks. Three months later, he underwent a spinal cord MRI showing a T2-weighted hyperintensity from C5 to C7, with swelling and blurred contrast-enhancement (Figures 1D,E); the brain MRI was negative. CSF analysis revealed normal cell count/protein level and IEP showed the presence of three OCBs (pattern II, OCB exclusively in CSF). CSF PCR testing for the extensive infectious panel was positive for Enterovirus, but this result was not considered significant due to the absence of prodromal respiratory/gastroenteric illness and clinical/MRI/CSF findings not suggestive of Enterovirus-related ATM. Serum antibodies panel for infectious diseases (including HIV, Herpesviruses, and Borrelia) was unremarkable as well as anti-AQP-4/MOG and connective tissue diseases antibodies. At 6-months of MRI control the cervical lesion appeared shrunk in volume, with no more contrast-enhancing, and no other lesions were detected in the spinal cord and brain (Figures 1F,G). He remained stable at clinical and radiological follow-ups for the next two years, with the last MRI performed in February 2021. On 3rd June 2021, he received the first dose of the BNT162b2 vaccine and the second dose on 28th June. After 8 days, he underwent a brain and spinal cord MRI follow-up, showing the swelling and gadolinium enhancement of the previously detected cervical lesion (Figures 1H,I). He did not complain of any symptoms, except for a mild right-hand numbness occurring 3 weeks after the second dose and lasting for a few days. At a brain and spinal cord MRI performed 4 months later, the cervical lesion appeared reduced in dimension and did not show enhancement (Figures 1J,K). On 22nd December 2021, the patient received the third dose of BNT162b2. After 35 days, he reported numbness in his right arm followed by his right limb weakness. He was admitted to our neurology unit and a new spinal cord MRI showed the swelling and contrast enhancement of the pre-existing cervical lesion (Figures 1L,M); the brain MRI was still negative. A new lumbar puncture showed normal cell count/protein level with no infectious agent detected at PCR, while IEP revealed again the presence of three OCBs (pattern II). Serum anti-AQP-4/anti-MOG and antibodies panel for connective tissue diseases were still unremarkable. The patient was administrated a 5-day course of high-dose IVMP followed by Oral Corticosteroid (OCS) tapering, showing complete recovery after a week. At 4-months of control, he was clinically stable and did not report relapses. He is currently under clinical/radiological follow-up.

Case 3

A 40-year-old woman, with a history of renal cell carcinoma and no other comorbidities, received the first dose of the BNT162b2 vaccine on 5th May 2021, and the second dose 5 weeks later. Ten days after the first dose, she presented with numbness in her hands progressively extending to all the upper limbs. On 4th July −25 days after the second dose—she developed diplopia in her left horizontal gaze. She was admitted to the emergency unit and an abduction deficit in her left eye was found. A brain and cervical spinal cord MRI showed a T2-weighted hyperintensity with blurred enhancement in the left paramedian mid-pons (Figures 2A,B) and a non-enhancing cervical spinal lesion at C2–C3 level (Figure 2C). She was administered a 5-day course of high-dose IVMP and almost completely recovered within 1 week. Two months of the brain and spinal cord MRI control showed two new enhancing supratentorial lesions—one juxtacortical in the left frontal hemisphere and one periventricular abutting the right lateral ventricle occipital horn—and two spinal lesions at the dorsal level, with no contrast enhancement (we cannot define their time of onset as the first MRI lacked a dorsal study; Figures 2D–H). Blood counts and C-reactive protein were normal. Anti-AQP-4/anti-MOG and antibodies for connective tissue diseases were negative. Serum panel for infectious diseases was unremarkable, except for Epstein-Barr Virus (EBV) serology resulting positive for anti-EBV VCA IgM (titer 75.3 U/ml), VCA IgG (>750 U/ml), EBNA IgG (239 U/ml), while EBV EA IgG was negative (9 U/ml). CSF analysis revealed normal cell count, protein, and glucose, and no infectious agent (including EBV) was detected at CSF PCR; CSF IEP showed the presence of 12 OCB (pattern II). She was diagnosed with MS and Natalizumab was started.

Case 4

A 27-year-old woman, with no previous clinical history, received the first dose of BNT162b2 vaccine on 16th June 2021 and the second dose after 21 days. One week later she reported mild weakness in her left leg spontaneously resolving in 10 days. A few days later, she developed a right facio-brachial motor deficit and dysarthria. She was admitted to the emergency unit and a brain MRI revealed T2-weighted hyperintensities in both centra semiovale (CSO) and left thalamus/posterior limb of the internal capsule (IC); lesions in the right CSO and left IC showed

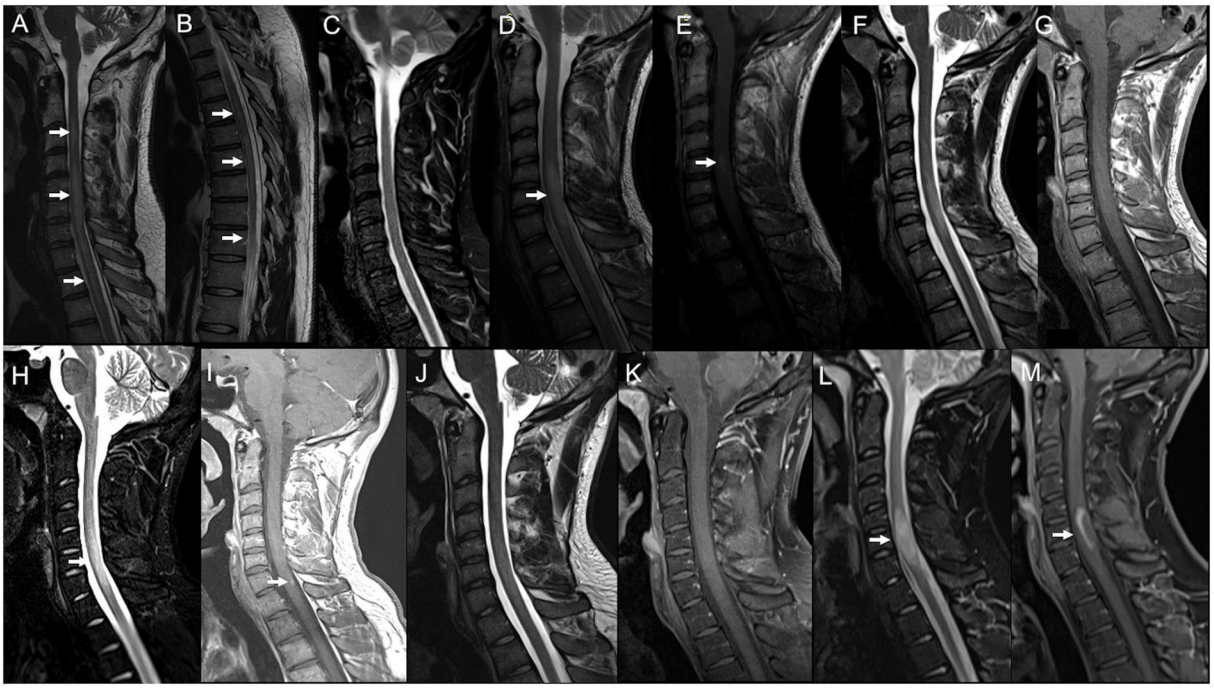

FIGURE 1
Serial spinal cord MRI scans in Case 1 **(A–C)** and Case 2 **(D–M)**. Case 1: Cervical **(A)** and thoracic **(B)** spinal cord MRI obtained 10 days after Ad26.COV2.S first dose showed a T2-weighted hyperintensity irregularly extending from C3 to medullaris conus with swelling from C4 to C7 (arrows) and no gadolinium enhancement (not shown). **(C)** 8-months MRI follow-up showing the complete resolution of the swelling and marked amelioration of the signal abnormality, barely visible on Short Tau Inversion Recovery (STIR) images. Case 2: **(D)** Spinal cord MRI performed 3 months after Tdap and IVP vaccine administration, showing a T2-weighted hyperintensity from C5 to C7 (arrow) with swelling and blurred contrast-enhancement on T1-weighted sequence **(E)** (arrow). **(F)** 6-months MRI control showing the cervical lesion shrinkage on T2-weighted sequences and no more contrast-enhancement **(G)**. **(H)** Spinal cord MRI obtained 8 days after the BNT162b2 second dose, showing swelling on STIR (arrow) and gadolinium enhancement [**(I)**; arrow] of the previously detected lesion. **(J)** 4-months MRI showed showing marked reduction of the signal abnormality and no more enhancement on the T1-weighted image **(K)**. **(L)** Spinal cord MRI obtained 62 days after the BNT162b2 third dose, showing a new swelling (arrow) and gadolinium ring enhancement **(M)** of the known cervical lesion.

blurred contrast enhancement (Figures 2I–L); spinal cord MRI was negative. CSF analysis revealed normal cell count/protein level and a negative extensive infectious panel, while IEP showed the presence of OCB (pattern II). Serum anti-AQP-4/anti-MOG antibodies resulted negative as well as connective tissue diseases panel except for the positivity of anti-nuclear antibodies (titer 1:160), considered a non-specific finding. Visual evoked potentials did not show abnormalities. She was administrated a 5-day course of high-dose IVMP, with complete recovery. One week later, she complained of right side weakness again—this time involving her leg also—and dysarthria. She started assuming OCS with no improvement. A new brain MRI revealed a new active lesion in the right peritrigonal area and an increase in the size of the previously detected lesions in the left CSO—this time gadolinium-enhancing—whereas areas in right CSO and left IC showed no more enhancement (Figures 2M–P). A spinal cord MRI—performed 10 days after—revealed the presence of three not enhancing cervical areas (at C2, C3, and C5–C6 levels; Figure 2Q). She was diagnosed with MS, and a second 5-day course of high-dose IVMP followed by OCS tapering was administrated. Poor clinical response was obtained and five plasma exchange (PEX) sessions were performed, with a resolution of dysarthria and slight recovery of right hemiparesis. At 2-months of MRI control, the left CSO and right peritrigonal lesions were still contrast-enhancing and a 3-day course of high-dose IVMP was administrated. She promptly started physical therapy with marked improvement in motor performance. She received the first cycle of Cladribine in October 2021. At the three-month follow-up, she almost fully recovered, only showing right-side brisk reflexes and mild oscillations at the position test in her right leg [Expanded Disability Status Scale (EDSS) score 1].

Case 5

A 53-year-old woman was diagnosed with MS at age 32 when she presented with paresthesia to her left limbs and a brain/spinal cord MRI showed dissemination in space and time. She was placed on interferon beta-1a with clinical and

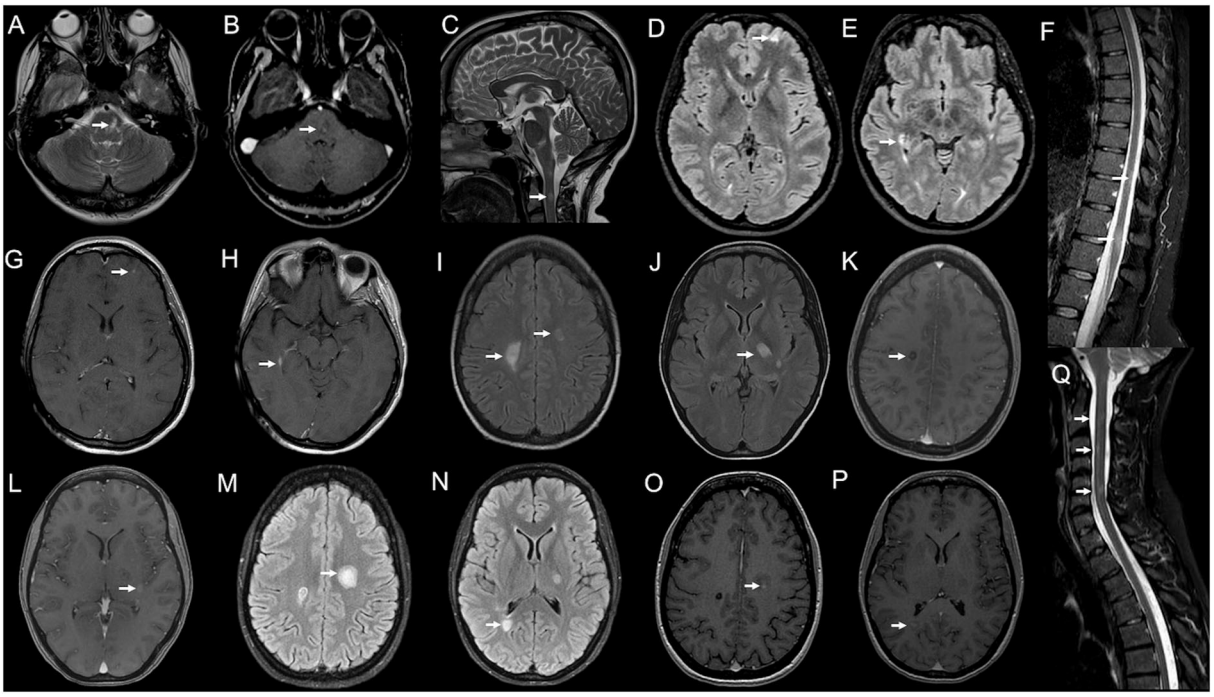

FIGURE 2
Serial brain and spinal cord MRI scans in Case 3 **(A–H)** and Case 4 **(I–Q)**. Case 3: **(A)** Brain MRI performed 25 days after BNT162b2 second dose, showing a T2-weighted hyperintensity (arrow) in the left paramedian mid-pons with blurred enhancement on T1-weighted images [**(B)**; arrow] and a non-enhancing spinal lesion at C2–C3 level [**(C)**; arrow]. **(D–H)** 2-months MRI follow-up showing two new brain lesions—one juxtacortical in the left frontal hemisphere [**(D)**; arrow] and one periventricular abutting the right lateral ventricle occipital horn [**(E)**; arrow], both with contrast-enhancement [**(G,H)**; arrows] and two spinal lesions at the dorsal level [**(F)**; arrows], with no contrast enhancement (not shown). Case 4: **(J–L)** Brain MRI obtained 10 days after BNT162b2 second dose, revealing T2-weighted hyperintensities in both centra semiovale (CSO) [**(I)**; arrows] and left thalamus/posterior limb of the internal capsule (IC) [**(J)**; arrow]; lesions in the right CSO [**(K)**; arrow] and left IC [**(L)**; arrow] showed blurred contrast enhancement on T1-weighted images. **(M–P)** 20-days MRI control showing the enlargement of the left CSO lesion [**(M)**; arrow] and a new lesion in the right peritrigonal area [**(N)**, arrow], both with gadolinium-enhancement on T1-weighted images [**(O,P)**; arrows]. **(Q)** Spinal cord MRI—obtained 10 days after the brain exam—showing three blurred areas at C2, C3, and C5–C6 levels on STIR sequences, with no enhancement (not shown).

radiological stability over the next 10 years. In 2010, she developed numbness in her right arm and a new enhancing cervical lesion was detected in a spinal cord MRI. She was switched to Fingolimod with no evidence of disease activity until 2014 when she reported dysesthesia in her left face and a brain MRI revealed a new active lesion in the left frontal lobe. She was administrated a 5-day course of high-dose IVMP with full recovery. Since then, she remained stable at an EDSS of 2.5 at 6-month clinical controls and annual MRI follow-up. On 31st May 2021, she received the first dose of BNT162b2 vaccine and the second dose 35 days later. Two weeks after the first dose administration, she complained of gait imbalance and marked fatigue. A brain/spinal cord MRI—performed 14 days after symptoms onset—revealed a new left lateral periventricular T2-weighted hyperintensity with contrast enhancement (Figures 3A,B). Compared to the previous neurological exam, she showed moderate gait ataxia leading to an EDSS increase by 1 point. She was administrated a 5-day course of IVMP and clinically improved in a few weeks. At 6-months of control, she reported complete recovery (with EDSS returned to baseline) and the resolution of the new lesion enhancement at MRI. She continued with her current disease-modifying therapy (DMT).

Case 6

A 75-year-old woman presented with right optic neuritis at age 60, partially resolved after OCS administration. Five years later she developed bilateral optic neuritis, treated with OCS with almost complete recovery. No brain/spinal cord MRI was performed at that time, and she started assuming chronic OCS with clinical stability over the following years. She developed Diabetes Mellitus and osteoporosis, complicated by a lumbar vertebral fracture for which she underwent surgical fixation in May 2021. Since then, she started using the right unilateral assistance in walking. On 3rd June 2021, she received the first dose of BNT162b2 vaccine and the second dose

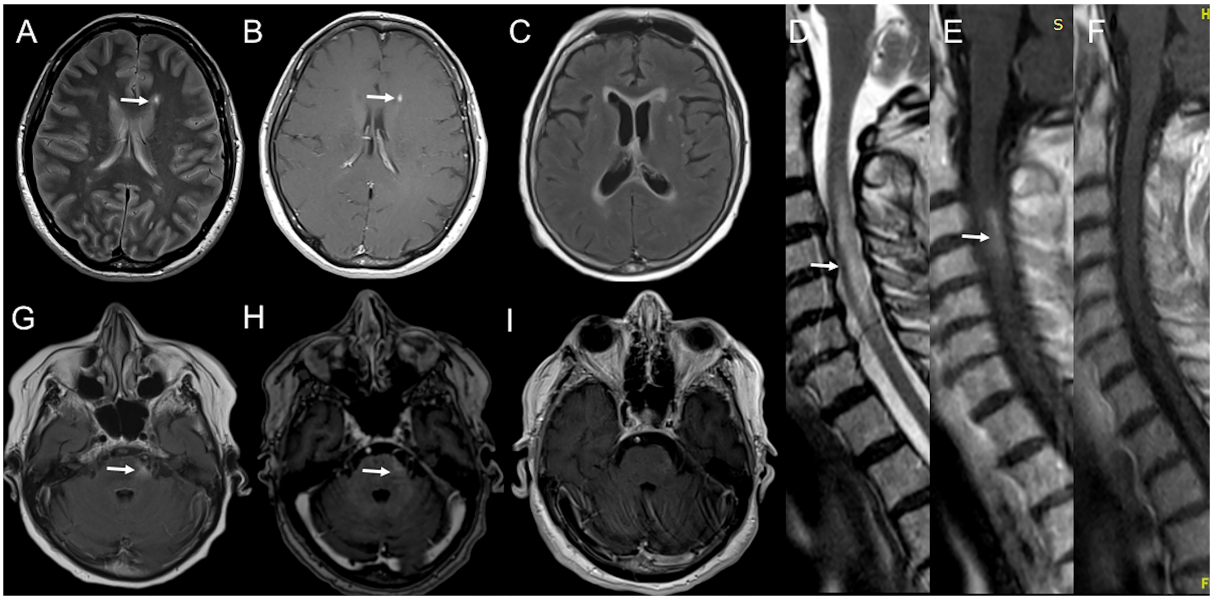

FIGURE 3
Serial brain and spinal cord MRI scans in Case 5 **(A,B)** and Case 6 **(C–I)**. Case 5: **(A)** Brain MRI performed 28 days after BNT162b2 first dose, showing a new left lateral periventricular T2-weighted hyperintensity (arrow) with contrast enhancement [**(B)**; arrow]. Case 6: **(D)** Spinal cord MRI obtained 12 days after BNT162b2 second dose, showing a T2-weighted hyperintensity from C2 to C7 with swelling (arrow) and gadolinium enhancement [**(E)**; arrow]. **(G)** Brain MRI performed few days later showed a T2-weighted hyperintensity in left lateral pons (arrow) with blurred contrast enhancement [**(H)**; arrow] and confluent supratentorial bilateral periventricular hyperintensities on FLAIR images **(C)**. **(I)** 7-days MRI controls revealed the complete resolution of gadolinium enhancement of the left pontine lesion and the volume shrinkage of the cervical lesion with no more contrast enhancement on T1-weighted images **(F)**.

on 1st July. After 10 days, she developed dysesthesia and weakness in her right upper limb, followed by weakness in her legs. She was admitted to our emergency unit. On exam, she had four limbs weakness (with motor strength at MRC scale of grade 2/5 and 3/5 in her upper, and lower limbs, respectively), brisk osteotendinous reflexes, bilateral Babinski sign, and light touch hypoesthesia below D4 level. A spinal cord MRI showed a T2-weighted hyperintensity from C2 to C7 with swelling and gadolinium enhancement on T1-weighted images (Figures 3D,E). A brain MRI performed a few days later showed a T2-weighted hyperintensity in left lateral pons with blurred contrast enhancement and confluent supratentorial bilateral periventricular areas on FLAIR images (Figures 3C,G,H). Blood count, erythrocyte sedimentation rate, and C-reactive protein were normal. CSF analysis revealed normal cell count and protein level. No infectious agent was detected at CSF PCR, while IEP showed the presence of three OCBs (pattern II). Anti-AQP-4 antibodies were positive. Extensive serum panel for infectious diseases was unremarkable, as well as anti-connective tissue and anti-neural surface/onconeural antigens antibodies. Patient was administrated a 5-day course of high-dose IVMP. After 10 days, she showed improvement in limb motor performance, with strength at the MRC scale of grade 4/5 in all limbs. A new MRI revealed the complete resolution of enhancement in the left pontine lesion (Figure 3I) and the cervical area—also appeared significantly shrunk in volume (Figure 3F). The patient was planned to start physical therapy and a DMT (Rituximab/Eculizumab).

Systematic review

Methods

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Data were collected from PubMed, SCOPUS, and Google Scholar databases, considering records published from 1st December 2020 to 31st December 2021. Two reviewers (VR and GB) independently conducted the search using the following relevant medical subject headings (MeSH) and keywords: "myelitis," "encephalomyelitis," "multiple sclerosis," "neuromyelitis optica," "MOGAD," "COVID-19," "SARS-CoV-2," and "vaccine." After duplicates' removal, records were screened and selected for full-text assessment according to the following inclusion criteria: (i) records reporting a CNS Inflammatory Demyelinating Event (CIDE) occurred after a COVID-19 vaccine (ii) CIDE was either an acute CNS inflammatory demyelinating syndrome—including ATM and ADEM—or a new diagnosis/relapse

of a chronic CNS inflammatory demyelinating disease—including MS, NMOSD, and MOGAD. Additional relevant articles that were referenced in the included studies were hand-searched and underwent the screening process. Among eligible records, studies that were not peer-reviewed and not published in English were ruled out. Reviews, viewpoints, letters, and commentaries—unless reporting a case report—were not considered. Furthermore, studies that did not provide individual data or were not supported by positive MRI findings were also excluded. Once identified, included studies were full-text assessed and the following variables were extracted using a standardized form: authors and country of publication, subjects' age, gender, and past medical history, disease characteristics for patients with previously diagnosed MS, NMOSD, and MOGAD (including clinical disease phenotype and duration, time since last clinical/radiological relapse, most recent EDSS score and treatment with DMT), COVID-19 vaccine type and dose administered, time from vaccine to neurological symptoms onset, CIDE clinical presentation, MRI and CSF/serum analysis findings, administered treatment and recovery outcome. Cases were defined as ATM, ADEM, MS, NMOSD, or MOGAD according to the most recent relative diagnostic criteria (14–18). For MS, NMOSD, and MOGAD, it was specified whether the event led to a new disease diagnosis or consisted of a relapse of a previously defined disease.

Pooled descriptive analysis was performed considering data from both cases reported in the literature and described in our case series. Data were summarized using frequencies/proportions for categorical variables and median/Interquartile Range (IQR)/range for continuous variables. Statistical analysis was conducted using R and RStudio.

Results

A systematic search identified an initial amount of 851 records, of which, 549 resulted unique after duplicate removal (Supplementary Figure 1). Among them, 455 studies did not meet inclusion criteria. The remaining 94 articles underwent a full-text assessment and 45 records were ruled out according to exclusion criteria. Forty-nine studies were finally included in the systematic review. These accounted for 40 case reports and nine case series, reporting a total number of 85 CIDEs, published in 20 countries worldwide. Considering the additional six cases described in our case series, a total of 91 CIDEs were summarized, including 24 ATM, 11 ADEM, 47 MS (15 new diagnoses and 32 relapses), eight NMOSD (seven new diagnoses and one relapse), and one MOGAD. Data extracted from single cases are reported in Supplementary Tables 1–4. Cases characteristics resulting from the pooled analysis are summarized in Table 1 for acute syndromes (ATM and ADEM) and Table 2 for chronic inflammatory demyelinating diseases (MS and NMOSD/MOGAD).

TABLE 1 Characteristics of ATM and ADEM after COVID-19 vaccines.

	ATM ($n = 24$)	ADEM ($n = 11$)
Age median years (range)	52 (19–85)	46 (19–88)
Female sex *n* (%)	12 (50)	8 (73)
History of IMD *n* (%)*	3 (14)	4 (40)
Vaccine type *n* (%)	- mRNA: 10 (42) - AV: 11 (46) - Inactivated: 3 (12)	- mRNA: 3 (27) - AV: 6 (55) - Inactivated: 2 (18)
Time from vaccine to symptoms onset[a] median days (range)	6 (1–35) - mRNA: 2.5 (2–3) - AV: 8 (7.5–11) - Inactivated: 5 (5–21)	12.5 (2–30) - mRNA: 14 (13–29) - AV: 9 (2–12) - Inactivated: 22 (14–30)
Number of very early onset events[b] *n* (%)	9 - mRNA: 8 (89) - AV: 1 (11) - Inactivated: –	1 - mRNA: – - AV: 1 - Inactivated: –
MRI[c] *n* (%)	STM: 7 (29) LETM: 17 (71)	Brain: - Supratentorial: 9 (82) - Infratentorial: 4 (36) Spinal cord: - STM: 1 (9) - LETM: 2 (18)
CSF[d] *n* (%)*	Pleocytosis: 11 (48) ↑ protein level: 14 (8) OCB presence: 5 (29)	Pleocytosis: 5 (56) ↑ protein level: 1 (20) OCB presence: 1 (10)
Treatment *n* (%)	IVMP/OCS: 23 (96) PEX/IVIG: 8 (33)	IVMP/OCS: 10 (91) PEX/IVIG: 5 (46)
Recovery[e] *n* (%)	Complete/almost: 10 (42) Partial: 13 (54) Death: 1 (4)	Complete/almost: 6 (55) Partial: 3 (27) Death: 2 (18)

AV, adenoviral-vectored; DMT, disease modifying treatment; IMD, immune-mediated disease; IQR, interquartile range; IVIG, intravenous immunoglobulin; IVMP, high dose intravenous methylprednisolone; n/a, not available data; LETM, longitudinally extensive transverse myelitis; Mab, monoclonal antibody; OCB, oligoclonal bands; OCS, oral corticosteroids; PEX, plasma exchange; STM, short-segment transverse myelitis; TM, transverse myelitis.

*Proportions are based on cases with related data available.

[a]Timeframe between vaccine administration and onset of ATM/ADEM symptoms.

[b]Events occurred within 3 days of vaccine administration.

[c]Number of cases presenting different locations/extensions of the brain and/or spinal cord lesions at MRI.

[d]Number of cases presenting CSF-positive findings. CSF pleocytosis and increased protein level were defined as CSF WBC >5/μl and protein level >45 mg/dl, respectively.

[e]Recovery at the last available follow-up.

TABLE 2 Characteristics of MS and NMOSD/MOGAD after COVID-19 vaccines.

	MS ($n = 47$)		NMOSD/MOGAD ($n = 9$)
	New diagnoses ($n = 15$)	**Relapses ($n = 32$)**	
Age median years (range)	40 (26–36)	39 (22–60)	53 (26–75)
Female sex *n* (%)	12 (80)	24 (75)	6 (67)
Disease duration median years (IQR)	–	10 (0.25–28)	8[h]
Time from last relapse[a] median years (IQR)	–	7 (3–14.25)	n/a
EDSS[b] median (range)	n/a	2 (0–6)	n/a
DMT *n* (%)	None	Untreated: 10 (31) First-line: 9 (28) Second-line: 13 (41)	Azathioprine[h]
Vaccine type *n* (%)	- mRNA: 13 (87) - AV: 2 (13) - Inactivated: –	- mRNA: 18 (56) - AV: 13 (41) - Inactivated: 1 (3)	- mRNA: 2 (22) - AV: 5 (56) - Inactivated: 2 (22)
Time from vaccine to symptoms onset[c] median days (range)	7 (1–35) - mRNA: 7 (1–35) - AV: 5.5 (3–8) - Inactivated: –	7 (1–25) - mRNA: 6.5 (3–14) - AV: 10 (7–20) - Inactivated: 2	10 (3–21) - mRNA: 14 (10–18) - AV: 8 (7.5–11) - Inactivated: 6.5 (3–10)
Number of very early onset events[d] *n* (%)	6 - mRNA: 5 (83) - AV: 1 (17) - Inactivated: –	9 - mRNA: 6 (67) - AV: 2 (22) - Inactivated: 1 (11)	1 - mRNA: – - AV: – - Inactivated: 1
MRI[e] *n* (%)	Brain: - Supratentorial: 12 (80) - Infratentorial: 3 (20) Spinal cord: - STM: 6 (40) - LETM: 0 Optic nerve: 0	Brain: - Supratentorial: 17 (53) - Infratentorial: 7 (22) Spinal cord: - STM: 7 (22) - LETM: 1 (3) Optic nerve: 2 (6)	Brain: - Supratentorial: 3 (33) - Infratentorial: 4 (44) Spinal cord: - STM: 2 (22) - LETM: 4 (44) Optic nerve: 2 (22%)
CSF[f] *n* (%)*	OCB presence: 12 (92)	n/a	OCB presence: 2 (25)
Serum[f] *n* (%)*	anti-AQP4: 0 anti-MOG: 0	n/a	anti-AQP4: 6 (75) anti-MOG: 1 (13)

(Continued)

TABLE 2 (Continued)

	MS ($n = 47$)		NMOSD/MOGAD ($n = 9$)
	New diagnoses ($n = 15$)	Relapses ($n = 32$)	
Treatment *n* (%)	IVMP/OCS: 15 (100) PEX/IVIG: 3 (20)	IVMP/OCS: 29 (91) PEX/IVIG: 1 (3)	IVMP/OCS: 8 (89) PEX/IVIG: 5 (56)
Recovery[g] *n* (%)*	Complete/almost: 10 (77) Partial: 3 (23)	Complete/almost: 16 (62) Partial: 10 (39)	Complete/almost: 3 (33) Partial: 6 (67)

AV, adenoviral-vectored; DMT, disease modifying treatment; IQR, interquartile range; IVIG, intravenous immunoglobulin; IVMP, high dose intravenous methylprednisolone; LETM, longitudinally extensive transverse myelitis; Mab, monoclonal antibody; n/a, not available data; OCB, oligoclonal bands; OCS, oral corticosteroids; PEX, plasma exchange; STM, short-segment transverse myelitis; TM, transverse myelitis.
*Proportions are based on cases with related data available.
[a]Time from the last clinical and/or radiological relapse.
[b]Expanded Disability Status Scale at baseline.
[c]Timeframe between vaccine administration and onset of MS/NMOSD/MOGAD symptoms.
[d]Events occurred within 3 days of vaccine administration.
[e]Number of cases presenting different location/extension of new T2-weighted/gadolinium-enhancing brain and/or spinal cord lesions at MRI.
[f]Number of cases presenting CSF/serum positive findings.
[g]Recovery at the last available follow-up.
[h]Disease duration and DMT of the unique reported case of NMOSD relapse in a previously diagnosed patient (Case 8, Supplementary Table 4).

Acute transverse myelitis

Among the 24 ATM described (19–40), 11 followed an adenoviral-vectored (46%), 10 an mRNA-based (42%), and three an inactivated vaccine (12%; Figure 4A). Overall, the median time from vaccine to symptoms onset was 6 days (1–35) (Figure 4D), although cases following mRNA-vaccines showed a lower median time (2.5 days, IQR: 2–3) comparing to those after adenoviral-vectored ones (8 days, IQR: 7.5–11; Figure 4E). Moreover, out of nine very early onset ATMs (within 3 days from vaccine administration), eight occurred after an mRNA vaccine. The median age was 52 years and events were equally distributed between sex groups (Figures 4B,C). Three out of 22 reporting cases (14%) had a history of the immune-mediated disease (including atopic dermatitis, asthma, and pulmonary sarcoidosis). All patients presented with a typical clinical syndrome involving sensory, motor, and sphincter systems, while in three cases (Cases 5, 9 and 10; Supplementary Table 1)—all occurring after an adenoviral-vectored vaccine—ATM was also accompanied/followed within 2 weeks by a cranial nerve palsy. Longitudinally Extending Transverse Myelitis (LETM) was the most common MRI finding (71% of cases). CSF OCB resulted absent in 12/17 tested patients, whereas type IV ("mirror," homologous OCB in CSF and serum) and II (OCB exclusively in CSF) patterns were described in 3 and 2 cases, respectively. All but one patient were treated with a 3–6-day course of high-dose IVMP and a second-line therapy (PEX/IVIG) was administrated in one-third of cases. Complete or almost complete recovery was achieved in 10/24 patients (42%), while others partially recovered, and one patient died of poor general condition.

Acute demyelinating encephalomyelitis

Out of 11 ADEM (41–49), six occurred after an adenoviral-vectored (55%), three after an mRNA-based (27%), and two after an inactivated vaccine (18%; Figure 4A). The median time from vaccine to symptoms onset was 12.5 days (2–30) (Figure 4D), with all but one case occurring at least after 7 days. Median age was 46 years and the female sex was prevalent (73%; Figures 4B,C). Four out of 10 reporting cases (40%) had a previous history of immune-mediated disease (including atopic dermatitis, Hashimoto's thyroiditis, polymyalgia rheumatica, and post-infectious rhombencephalitis). Prodromal symptoms (including fever, malaise, headache, and nausea) were common, followed by polyfocal neurological symptoms and/or encephalopathy [defined as decreased level of consciousness/lethargy/behavioral disorders, systemic illness or post-ictal symptoms (15)]. Seizures were reported in three cases. MRI revealed a prominent supratentorial localization with typical -multiple, large, and poorly marginated lesions, whereas the spinal cord was involved in 27% of cases, mostly with a longitudinally extensive feature. CSF OCB was absent in 9/10 tested cases. Acute Hemorrhagic Encephalomyelitis (AHEM) was described in three patients (Cases 3, 4, and 5; Supplementary Table 2), all showing poor outcomes. Complete or almost complete recovery was reached in 6/11 patients (55%) after a 3–7-day course of high-dose IVMP/OCS. Among others, three cases showed partial recovery

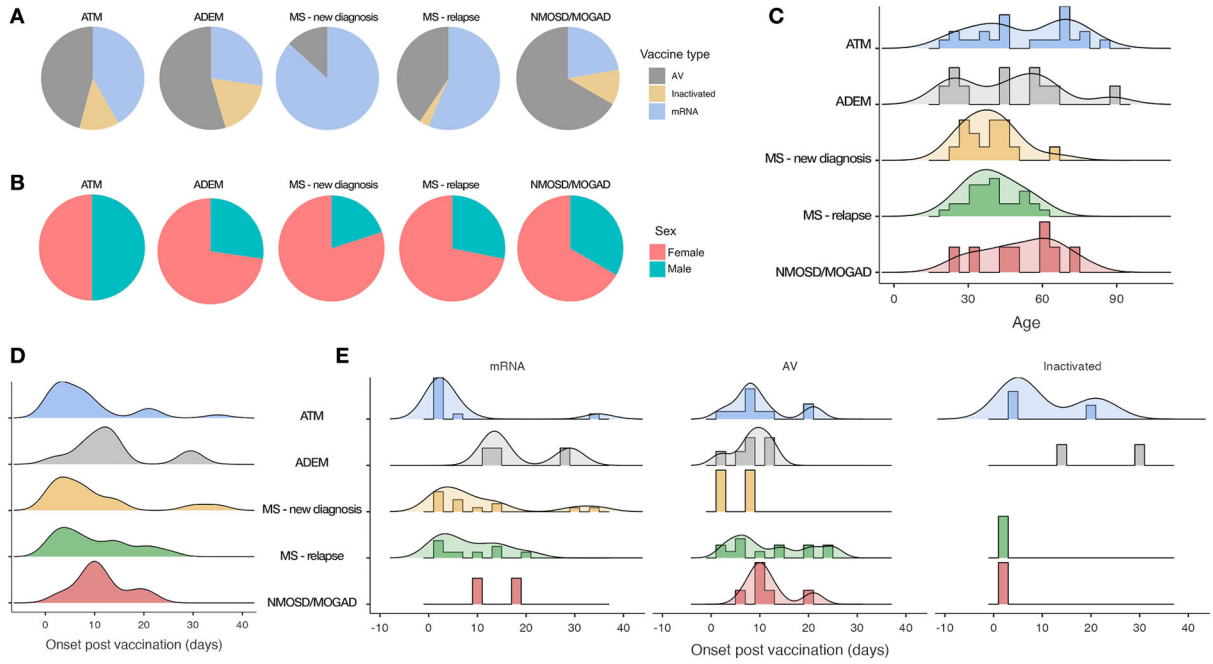

FIGURE 4
Demographical characteristics and time of onset among different CIDEs. **(A)** Proportions of different vaccine types. **(B)** Proportions of sex categories. **(C)** Age distributions. **(D)** Overall time from vaccine to symptoms onset. **(E)** Time from vaccine to symptoms onset by vaccine type. AV, adenoviral-vectored vaccines.

and two patients died—one presenting an AHEM variant and one due to a rapidly progressive clinical worsening.

Multiple sclerosis

Fifteen cases of MS new diagnoses and 32 relapses were described after a COVID-19 vaccine (50–62). Among new diagnoses, 13 occurred after an mRNA vaccine (87%) and two after an adenoviral-vectored one (13%; Figure 4A). Median time from vaccine to symptoms onset was 7 days (1–35) (Figure 4D). Patients were 80% women, with a median age of 40 years (Figures 4B,C). Sensory onset was the most common, followed by pyramidal, cerebellar, truncal, visual, and sphincter systems involvement. MRI showed typical supratentorial lesions (periventricular and/or cortical/iuxtacortical) in the majority of patients, while infratentorial and spinal cord locations were reported in 20 and 40% of cases, respectively. CSF OCB was present in 12/13 tested patients. All were treated with a 3–5 day course of IVMP (with further days of IVMP/PEX needed in just three cases) and recovery was mostly favorable.

Among MS relapses, 18 cases followed an mRNA (56%), 13 an adenoviral-vectored (41%), and 1 an inactivated vaccine (3%; Figure 4A). Overall, median time from vaccine to symptoms onset was 7 days (1–25) (Figure 4D), although relapses following mRNA-vaccines presented with a lower median time [6.5 days (IQR: 3–14)] compared to those after adenoviral-vectored vaccines [10 days (IQR: 7–20); Figure 4E]. Moreover, among nine very early onset events (within 3 days from vaccine administration), six followed an mRNA-vaccine. Median age was 39 years and the female sex was prevalent (Figures 4B,C). In cases reporting disease characteristics, the median EDSS was 2 and 75% had their last clinical and/or radiological relapse at least 3 years before. Ten out of 32 patients (31%) were not taking DMT, while 9/32 (28%) were on first-line DMT, and 13/32 (41%) were on second-line DMT (six of which receiving oral therapy and seven a monoclonal antibody). Active lesions were located exclusively in the brain on 11/28 and involved the spinal cord in 25% of cases. Corticosteroid therapy was performed in the vast majority of patients (followed by PEX in just one case), followed by complete or almost complete recovery in 16/26 reporting cases, while the others partially improved.

Neuromyelitis optica spectrum disorder and anti-MOG antibodies-associated disease

Eight cases of NMOSD and one case of MOGAD were reported after a COVID-19 vaccine (50, 58, 63–67). Five followed an adenoviral-vectored (56%), two an mRNA (22%), and two an inactivated vaccine (22%; Figure 4A), with a median time from vaccine to symptoms onset of 10 days (3–21) (Figure 4D). Median age was 53 years, and 6/9 cases were women (Figures 4B,C). Among NMOSD, seven cases were new diagnoses and one consisted in a relapse in a previously diagnosed patient, currently treated with

azathioprine (Case 8; Supplementary Table 4). The most frequent core clinical presentation was an acute medullary syndrome, followed by brainstem/area postrema/diencephalic syndromes and optic neuritis. MRI showed typical NMOSD characteristics in all cases (LETM and/or brain periependymal lesions) and anti-AQP4 were positive in all but one patient (Case 2; Supplementary Table 4), who fulfilled seronegative NMOSD diagnostic criteria reporting two clinical cores syndromes with typical MRI features. The unique case of MOGAD was described in a 59-years-old man, presenting an acute medullary syndrome with serum MOG-antibody positivity 13 days after receiving the first dose of ChAdOx1 nCoV-19 (Case 9; Supplementary Table 4). Overall, treatment consisted of IVMP in 8/9 NMOSD/MOGAD patients, followed by PEX in four of them. The outcome was commonly poor, with 6/9 patients not achieving complete recovery.

Discussion

Vaccinations and CIDEs

The magnitude and speed of the COVID-19 vaccination campaign allowed us to observe, on a large scale and in an extremely short time period, rare adverse events already described for other vaccines in a more scattered way. Among RAEs, post-vaccination CIDEs are a well-established entity and have been temporally associated with different vaccines. Karussis and Petrou (68) reported 71 cases of CIDEs published in literature from 1979 to 2013, including cases of ADEM, ATM, optic neuritis, MS, and NMOSD The most commonly associated vaccines included influenza, human papillomavirus (HPV), hepatitis A or B, rabies, measles, rubella, yellow fever, anthrax, meningococcus, and tetanus. However, apart from rare exceptions [e.g., ATM following the live attenuated Oral Poliovirus Vaccine (OPV) (69)], a causal link between vaccinations and CIDEs has not been formally confirmed and the association only relies on temporal relation (70).

CIDEs after COVID-19 vaccines

RCTs and observational studies

Phase 3 RCTs for COVID-19 mRNA vaccines—the first to be approved in December 2020—did not report CIDEs during the study period (1, 2), as well as RCT for the adenoviral-vectored Ad26.COV2.S (4). Interim analysis of the four RCTs for ChAdOx1 nCoV-19 reported three cases of ATM among 11,636 participants, two occurring in the treatment group and one in the control (meningococcal) arm (3). Among the first two, one case presented 14 days after the second dose and, although initially regarded as possibly related to vaccination, was eventually diagnosed as an idiopathic ATM. The second case occurred 10 days after the first dose and was instead considered to be related to a pre-existing—but not recognized—MS.

However, RCTs are hardly able to detect RAEs—for insufficient statistical power—and provide only limited information about population subgroups not included in trial protocols, such as persons with autoimmune diseases. Therefore, as long as the vaccination campaign advance, data have been acquired for RAEs through post-marketing surveillance systems, case reports, and observational studies—the latter allowing for a less biased risk assessment. Concerning CIDEs, a systematic review accounted for 32 events reported in the literature until September 2021 (9). Besides case descriptions, in a recent self-controlled case-series study—conducted from December 2020 to May 2021 on a cohort of more than 32 million people in England—Patone et al. (10) assessed the association between the first dose of a COVID-19 vaccine (ChAdOx1nCoV-19 or BNT162b2) and the occurrence of neurological complications, including CIDEs. Study findings showed an increased risk of Guillain–Barré syndrome and Bell's palsy after ChAdOx1nCoV-19 and of hemorrhagic stroke after BNT162b2, while CIDEs did not result associated to neither vaccine. However, a trend toward increased risk of encephalitis/meningitis/myelitis was reported after ChAdOx1nCoV-19 vaccine. Few other studies evaluated CIDEs risk more specifically in persons affected by a chronic CNS inflammatory demyelinating disease. Achiron et al. assessed the safety of BNT162b2 in an adult MS cohort ($n = 574$) in Israel, finding no increased risk of clinical relapses in a median time of 38 and 20 days, respectively, from the first and the second dose (11). Consistent results came from an Italian study ($n = 324$ patients) evaluating clinical relapse rates in a longer timeframe (2 months) after the first dose of an mRNA-based vaccine (12). Another Italian study conducted on a cohort of AQP4-positive NMOSD ($n = 26$) and MOGAD ($n = 30$) patients, showed no higher frequency of relapses in the month after an mRNA-vaccine administration (13). Although these studies did not include MRI data—detecting potential subclinical disease activity—they provide evidence supporting the COVID-19 vaccine's safety in patients affected by chronic inflammatory demyelinating diseases, encouraging their access to vaccination campaigns.

CIDEs characteristics

In our case series, we reported and characterized six post-COVID-19 vaccines CIDEs, including both acute syndromes (two ATM) and new diagnoses/relapses of chronic CNS inflammatory demyelinating diseases (three MS and one NMOSD). Among ATM, one case (Case 1) occurred 8 days after the first dose of Ad26.COV2.S and showed characteristics in line with the other 22 cases of ATM previously published in the literature. The other (Case 2) was instead a case of

recurrent ATM presenting multiple reactivations of the same spinal cord lesion after the administration of subsequent vaccine doses. Interestingly, the patient reported his first event 3 months after receiving Tdap and IVP vaccines, while the other two reactivations occurred after BNT162b2 second and third dose, as the mechanism driving those events would be shared across different vaccine types. Notably, the patient clinically and radiologically recovered within ATM recurrences and did not present any other spinal cord/brain lesion in the timeframes between vaccine administrations. These elements would argue against a diagnosis of a chronic inflammatory demyelinating disease such as MS, but—considering the presence of CSF OCB and the recent proposal of a new pure spinal MS phenotype (71)—a longer follow-up is needed to exclude any further disease activity. Our three MS cases (Cases 3–5) occurred after the BNT162b2 vaccine. In two patients (Cases 3 and 4), the event represented the clinical onset, and diagnosis was made according to the 2017-revised McDonald criteria. Intriguingly, in Case 3, the anti-EBV antibodies serum pattern was strongly suggestive of recent primary infection/reactivation. This is particularly remarkable considering the recent findings supporting the causal role of EBV in MS (72), pointing to a possible synergic effect between EBV infection and a simultaneous/strictly sequential vaccine administration in the priming of self-reactive lymphocytes (especially with regards to vaccine adjuvant component- as discussed below). In Case 5, we described the occurrence of a relapse in a previously diagnosed MS patient, showing demographic/disease characteristics consistent with the other 31 cases of MS relapses published in the literature. Last, we reported a newly diagnosed AQP4-positive NMOSD (Case 6), in a patient—with a previous history of two optic neuritis- presenting with LETM and brainstem involvement after BNT162b2 second dose.

Considering our cases ($n = 6$) and those collected from the literature ($n = 85$), we summarized the characteristics of 91 CIDEs. Overall, age was heterogeneous (Figure 4C), especially in ATM and ADEM, in line with recent evidence showing that differently from the post-infectious variant (more frequent in childhood) ADEM following vaccinations seems to occur at any lifetime (73). Apart from ATM where no sex prevalence was observed, females represent the majority in all other CIDEs (Figure 4B), as generally expected for CNS inflammatory demyelinating diseases [except for ADEM, known to have male predominance (15)]. Concerning past medical history, 40% of ADEM and 14% of ATM cases presented a previous diagnosis of immune-mediated disease, suggesting a possible predisposition to develop a dysfunctional immune response. The majority of MS patients were clinically/radiologically stable and with mild disability at the time of vaccination. Notably, 59% of them were either not assuming treatment or on first-line DMT and therefore possibly at higher risk of disease activity compared to patients receiving high-efficacy therapies. CIDEs outcome was generally favorable in MS and ADEM (except when a hemorrhagic variant occurred), while ATM and NMOSD more likely showed partial recovery.

Overall, CIDEs were described after both mRNA-based, adenoviral-vectored, and inactivated vaccines. In ATM, adenoviral-vectored and mRNA vaccines resulted in almost equal proportions (46 vs. 42%). Contrarily, adenoviral-vectored vaccines accounted for the greatest amount of ADEM (55%) and NMOSD/MOGAD (56%), while in MS cases mRNA-vaccines resulted in the majority of both new diagnoses (87%) and relapses (56%; Figure 4A). However, results for MS relapses could be biased by the fact that mRNA-based vaccines were mainly preferred for persons with autoimmune diseases, including MS. On average, ADEM and NMOSD/MOGAD presented a longer time of onset (12.5 and 10 days) compared to ATM and MS (6 and 7 days; Figure 4D); interestingly, ATM after mRNA-based vaccines occurred earlier than those following adenoviral-vectored ones (2.5 vs. 8 days), with a similar trend observed in MS relapses (Figure 4E). Moreover, 19/26 (73%) of very early onset CIDEs (within 3 days from vaccine administration) followed an mRNA-vaccine. Although these observations are limited by small numbers and potential recording bias, both the prevalence of vaccine types for certain CIDEs and the heterogeneity in time of onset could suggest that different mechanisms might underly these events.

Possible immunological mechanisms

Like all other vaccinations, anti-COVID-19 vaccines bear two components: a pathogen-specific antigen—against which neutralizing antibodies and specific T cells are desired, and an adjuvant— which is able to stimulate the innate immune response providing the second signal and pro-inflammatory cytokines to initiate the adaptive response. In mRNA-based vaccines, the mRNA itself constitutes both the immunogen (synthetizing the SARS-CoV-2 Spike glycoprotein) and the adjuvant (for the RNA intrinsic properties to be recognized by pattern recognition receptors (PRR), such as TLR3 and TRL7), while in adenoviral-vectored vaccines the antigen is encoded in the DNA of a recombinant Chimpanzee adenovirus and the adjuvant is provided by the virus particles itself (74). On these bases, several mechanisms—already advanced for other vaccines—could be proposed to explain post-COVID-19 vaccinations CIDEs (68, 69). For instance, vaccines, stimulating innate immune response through adjuvants and creating an inflammatory cytokines environment, could activate pre-existing self-reactive T and B cells, in a process known as bystander activation. This would occur rapidly in the early phase of the immune response and could therefore be involved in early-CIDEs presenting in the next few days after a vaccine administration, such as in early-onset ATM following mRNA vaccines. Other possible mechanisms include molecular mimicry (vaccine-derived antigens mimicking self-molecules

could prime cross-reactive T cells) and epitope spreading (after the initial activation of antigen-specific T cells against a dominant epitope, the immune response could react also against different epitopes of the same or other proteins of both self and non-self origin). Theoretically, all these mechanisms would involve both a cell-mediated and a humoral adaptive immune response. Interestingly, adenoviral-vectored vaccines have been previously associated with Guillain-Barré Syndrome (75)—which is largely driven by aberrant autoantibodies (29)—and thrombotic thrombocytopenia, mediated by platelet-activating antibodies against PF4 (76); from our analysis, adenoviral-vectored formulations resulted in major amounts in NMOSD cases and all ATM with a cranial nerve palsy. Altogether, these observations could suggest a higher tendency of adenoviral-vectored vaccines to trigger antibodies-mediated diseases, compared to mRNA-based formulations. Nevertheless, considering the rarity of these events both in the general population and in persons with immune-mediated diseases—beyond the possible immunological mechanisms involved—a genetic predisposition underlying an abnormal reaction to vaccine stimuli could play a key role. In this regard, polymorphisms in TLRs and other PRRs recognizing adjuvants could potentially affect the innate immune response to immunizations and represent risk factors for RAEs, as previously suggested by some authors (77).

CIDEs after the SARS-CoV-2 infection

Besides post-COVID-19 vaccines events, CIDEs have also been described after the SARS-CoV-2 infection itself. A systematic review reported 60 studies published from January 2020 to June 2021 describing 102 CNS demyelinating events temporally associated with COVID-19, including encephalitis/encephalomyelitis, ATM, and MS/NMOSD/MOGAD-like demyelination (78). More recently further studies reported cases of MS and NMOSD onset/relapses following SARS-CoV-2 infection (79–81), suggesting its possible ability to trigger inflammatory disease activity as previously considered for other viruses, especially with regard to MS (82, 83). In their large case-series study, Patone et al. (10) compared the risk of developing neurological complications after SARS-CoV-2 infection with that after COVID-19 vaccines, showing that the former was substantially higher. Taken together, these data further strengthen the favorable risk-benefits profile of COVID-19 vaccines, supporting their use both in the general population and in persons affected by chronic CNS inflammatory demyelinating diseases.

Limitations

Small numbers and potential recording/reporting bias of reviewed cases hampered the feasibility of performing inferential statistics and meta-analysis, limiting our study to a descriptive level. Moreover, we could not account for the number of persons administrated with different vaccine types in the population from which cases came from. Indeed, those data were highly variable among countries/times and difficult to estimate considering the worldwide source of reviewed cases and their occurrence in different time periods. We did not summarize the long-term follow-up outcomes and possible further events following vaccine booster doses (if administered), since data were missing in most of the reports. Whether a pre-existing CIDE would represent a risk factor for a future aberrant immune response to the same/another vaccine still remains an open question—with major implications in the clinical setting.

Conclusion

While epidemiological studies have assessed the safety of COVID-19 vaccines, detailed descriptions and systematic reviews of sporadic cases may still be valuable to gain insights into CIDEs pathophysiology and suggest candidate risk factors. From our pooled analysis, both the prevalence of vaccine types for certain CIDEs and the differences in time of onset might suggest that distinct mechanisms—with different dynamics and kinetic—could underly these events. Further large-scale observational studies are needed—both in the general population and in subgroups affected by chronic CNS inflammatory demyelinating diseases—to evaluate clinical and MRI data as well as other biomarkers (including genetic ones) potentially predicting CIDEs risk. These would help to optimize immunization strategies and tailor clinical management in patients with a history of post-vaccination CIDEs, as well as providing novel insights for future vaccine development.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

VR, GB, MS, and GR contributed to the conception and structure of the study. VR, MB, RR, MN, VZ, RN, RP, and AS contributed to clinical and MRI data collection of original cases described. VR and GB conducted the systematic literature search. VR performed pooled descriptive analysis and wrote the first draft of the manuscript. GB, VR, and AM contributed to figures and tables creation. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1018785/full#supplementary-material

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The relationship between chronic immune response and neurodegenerative damage in long COVID-19

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In the past two years, the world has faced the pandemic caused by the severe acute respiratory syndrome 2 coronavirus (SARS-CoV-2), which by August of 2022 has infected around 619 million people and caused the death of 6.55 million individuals globally. Although SARS-CoV-2 mainly affects the respiratory tract level, there are several reports, indicating that other organs such as the heart, kidney, pancreas, and brain can also be damaged. A characteristic observed in blood serum samples of patients suffering COVID-19 disease in moderate and severe stages, is a significant increase in proinflammatory cytokines such as interferon-α (IFN-α), interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6) and interleukin-18 (IL-18), as well as the presence of autoantibodies against interferon-α (IFN-α), interferon-λ (IFN-λ), C-C motif chemokine ligand 26 (CCL26), CXC motif chemokine ligand 12 (CXCL12), family with sequence similarity 19 (chemokine (C-C motif)-like) member A4 (FAM19A4), and C-C motif chemokine ligand 1 (CCL1). Interestingly, it has been described that the chronic cytokinemia is related to alterations of blood-brain barrier (BBB) permeability and induction of neurotoxicity. Furthermore, the generation of autoantibodies affects processes such as neurogenesis, neuronal repair, chemotaxis and the optimal microglia function. These observations support the notion that COVID-19 patients who survived the disease present neurological sequelae and neuropsychiatric disorders. The goal of this review is to explore the relationship between inflammatory and humoral immune markers and the major neurological damage manifested in post-COVID-19 patients.

KEYWORDS

long COVID syndrome, SARS-CoV-2, inflammatory response, neurodegeneration, autoantobodies, autoantigens

Introduction

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has increased morbidity and mortality rates worldwide (1, 2). According to various clinical reports and laboratory studies, it is known that the virus can affect different organs such as respiratory tract, lungs, heart, liver, pancreas, kidneys, muscles, and nervous system at different levels (3–5). During the pandemic course, several post COVID-19 effects have been observed that hinder total patient recovery. The World Health Organization (WHO) has denominated these symptoms as long COVID or COVID-19 condition, defining it as a condition that "occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time" (6–8).

Several follow-up studies in patients suffering long COVID have documented cardiovascular alterations, fatigue, dyspnea, chest pain, appetite loss and hair loss. Interestingly nervous system seems particularly affected after COVID-19 disease (9, 10). Patients have reported headaches and dizziness, as well as psychiatric disorders and motor discoordination (11–13). In a period of 7 months after viral infection, some patients have presented conditions that are mainly related to neuropsychiatric and neurological deficits, with a prevalence of 19.7% to 36% (4, 14, 15). The characteristic symptoms of these alterations are anosmia, hypogeusia, partial or total hyposmia (16, 17), myalgia, cerebral inflammation, cerebrovascular strokes (18), acute encephalopathy, seizures, Guillain-Barré syndrome (19), neurocognitive disorders, sleep disorders, delirium, memory deficit, concentration deficit, depression, psychosis, hallucinations, paranoia (20), chronic fatigue and partial or total apraxia (21).

Similar to the neurological alterations of SARS-CoV-2 post-infection, there are data from patients who were infected with SARS-CoV-1 and MERS. The clinical follow-up carried out on these patients recorded symptoms of depression, disorder of post-traumatic stress (PTSD), anxiety, sleep disorders, weakness, chronic fatigue and general pain, in a follow-up period covering 6 to 20 months post-infection (22, 23), symptoms set similar to the neurological alterations reported in SARS-CoV-2 post-infection. A meta-analysis of 120,970 patients infected with SARS-CoV-2 revelated that women are more susceptible to present moderate neurological and cardiovascular long-COVID symptoms. It also was reported that age is directly related to a higher incidence of psychiatric, respiratory, digestive and skin conditions. In addition, in a subgroup of 106,284 participants it was observed an incidence of 19.7% of neurological disorders, where the main manifestations included, concentration difficulty (14.6%), headache, disorders of the taste and smell, cognitive impairment, memory deficits, dizziness, and cramps. Furthermore, psychiatric conditions affected 20.3% of the participants, who presented PTSD, depression, sleep disorder and anxiety (14).

The analysis of cerebrospinal fluid (CSF) and peripheral blood samples of 127 patients, who were positive for SARS-CoV-2 and showed neurological damage symptoms after 7 days of infection, revelated that they suffered systemic inflammation and impaired blood-brain barrier (BBB). The neurological manifestations included encephalopathy, altered consciousness, delayed walking reaction, epilepsy-like electroencephalogram (EEG) changes, cerebral ischemia, myelitis, cerebellar ataxia, sensorimotor symptoms of unknown cause, cognitive impairment, peripheral neuropathy, anosmia, headache and nausea (24). Altogether these studies indicate a relationship between SARS-CoV-2 infection and neurological conditions observed in long COVID. The main goal of this review is to elucidate the role of the antiviral dysregulation response by the immune system and its relationship with the sequelae of damage to the central nervous system (CNS) in patients with long COVID.

Relationship between SARS-CoV-2 and nervous system

It has been documented that coronaviruses have the ability to affect the CNS (25). In this context, several investigations have discovered that β-coronaviruses such as MERS-CoV and SARS-CoV-1 can infect the CNS (25–29). Furthermore, traces of SARS-CoV-2 have been detected in the olfactory mucosa, trans olfactory mucosa, neuronal projections and neurons during and after the infection period (30–34). In some COVID-19 cases the first symptoms presented by patients is hyposmia or anosmia. This could be due to the olfactory epithelium damage caused by the coronavirus, which in turn affects the olfactory neural network that is connected with the primary olfactory cortex (35–37). To date there is no precise understanding about the dynamics of the initial antiviral response against SARS-CoV-2 that occur at the level of the olfactory epithelium. However, there are data from nasal samples that showed an increase of proinflammatory cytokines within two days after the first symptoms, compared with samples of same tissue that were taken at longer times (5 or more days after presenting the first symptoms), when the levels of proinflammatory cytokines decreased (17). This could indicate that the immune response produced in the olfactory epithelium associated with nerve cells occurs in a transient manner. However, this response is sufficient to generate some neuronal damage either by a direct action of the virus or by an indirect mechanism that involves the dysregulation of the immune response.

The BBB is the main physiological structural interconnection between the external environment and the brain whose main function is to protect central neurons. It also participates in the selective transit of cells, nutrients and brain cell metabolism toxic byproducts (38). When a systemic inflammation process occurs, the BBB induces a series of brain responses whose main objective is to promote brain survival, which is known as disease behavior (39). This response induces a set of physiological and behavioral changes, coordinated and executed by the brain, which protect the individual from the various phases occurring during an infection. For example, the induction of lethargy allows to fight infection through the induction of fever and anorexia (40, 41).

In patients who succumbed to COVID-19 and who had an exacerbated inflammatory response, presented BBB involvement manifested through multifocal vascular damage caused by autoantibodies. This process that induced serum proteins infiltration into the brain parenchyma, generalized endothelial cell activation, classical complement pathway activation, platelet aggregates and microthrombi adhered to endothelial cells throughout the vascular lumen. In addition, the infiltration of macrophages, T cells and B cells into brain structures has been reported, observing a greater presence of CD8+ T cells in the perivascular region compared to CD4+ cells. There are also reports of astrogliosis in perivascular regions and microglial nodule formation in the hindbrain, which is associated with focal neuronal loss and neuronophagia (42).

The SARS-CoV-2 induces a nuclear structure reorganization and the dispersion of the genomic compartments of the cell, which leads to the low expression of the genes *ADCY3*, *CNGA2*, *GN13*, *GFY*, *OMP*, *LHX2* and *ATF5*, which are key in the olfactory receptors signaling and this downregulation lead to anosmia (17). It has been proposed that once the virus enters the olfactory receptor neurons, the infection is propagated through the synaptic connections (43). In the case of the olfactory receptor neurons-mitral cells axis, there is an activation of the glial, which in turn promote the release proinflammatory cytokines such as IFN-α, TNF-α, IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-17A, IL-18, CXCL10, CXCL12, CCL1, CCL2, CCL3, CCL4, CCL5, CCL7, CCL11, GM-CSF and B cell-activating factor belonging to the TNF family (BAFF). These cytokines that have been detected at elevated levels in samples of CSF, brain tissue, and serum of peripheral blood from patients with severe COVID-19 (44–49). It should be noted that the upregulated production of these cytokines can cause serious damage to the CNS, since it promotes neuronal stress and apoptosis, as well as the interruption of the BBB (43). In a mild respiratory COVID mouse model, it was observed that these events eventually increase neuroinflammation cascades causing synaptic loss, demyelination, excitotoxicity and transcriptional downregulation of *Trem2*, *Sall3* and *Adrb1* genes in microglia, the latter gene being an indicator of white matter degeneration (48). Other cerebral regions can potentially be affected by a similar mechanism. For instance, midbrain dopamine neurons derived from human pluripotent stem cells are selectively permissive to SARS-CoV-2 infection. This triggers an inflammatory response at neuronal level and the expression of the insulin like growth factor binding protein 7 (IGFBP7) and LAMININ B1 genes associated with cellular senescence (32). The expression of these molecules leads to the overactivation of glia and trigger mechanisms of neuronal damage (50). Overall, the neuronal damage associated with the upregulation of proinflammatory cytokines could be the cause of the appearance of neurological symptoms related with long COVID (Table 1).

The effects that SARS-CoV-2 infection induces in brain structures was analyzed on 401 patients who suffered from COVID-19. Using the UK Biobank database, there was a selection of patients with brain imaging studies prior to COVID infection, and all patients were subject to brain imaging 38 months later. All the patients had at least one or more of the following affectations: significant reduction in gray matter thickness and tissue contrast in the orbitofrontal cortex, changes in diffusion measures, which are indicators of tissue damage, increase in CSF volume and overall size brain reduction (37). These changes were consistent and related to previously detected cognitive impairment in the study population. SARS-

TABLE 1 Upregulated cytokines associated at neurological damage observed in patients with long COVID.

Neurological affectation	Upregulated cytokines	References
Neurocognitive disorders	IFN-α, IL-1, IL-6, IL-17A, IL-18, CCL7	(51–59)
Sleep disorders	IL-1, IL-8, IL-18	(55, 56, 58, 60)
Memory deficit	IL-1, IL-18, CCL3, CCL7, BAFF	(54, 57, 60–63)
Concentration deficit	IFN-α, CCL7	(51, 57, 64)
Depression	IFN-α, TNF-α, IL-1, IL-2, IL-6, IL-8, IL-17A, IL-18, CCL1, CCL2, CCL5, CCL7, CCL11	(51, 52, 54–57, 65–71)
Psychosis	IFN-α, IL-6, BAFF	(51, 55, 63, 72)
Hallucinations	IFN-α	(51)
Systemic inflammation	IFN-α, TNF-α, IL-1, IL-2, IL-6, IL-8, IL-12, IL-17A, IL-18, CXCL10, CCL3, CCL4, CCL5, CCL7, GM-CSF	(51, 54–56, 60, 61, 73–78)
Peripherial neuropathy	TNF-α, IL-1, IL-2, IL-6, IL-8, IL-12, IL-17A, IL-18, CXCL10, CCL3, CCL4, CCL5, CCL7, GM-CSF	(54–56, 60, 61, 73–79)
Stroke	IFN-α, TNF-α, IL-1, IL-6, IL-8, IL-17A, IL-18, CXCL-10, CXCL12, CCL2, CCL3, CCL5, CCL11	(55, 56, 60, 75, 78, 80–82)
Anxiety	TNF-α, IL-1, CXCL12	(56, 67, 83)

CoV-2 infection also changes the vasculature of the brain, since one of the damages induced by the virus is ischemic and hemorrhagic cerebrovascular strokes (84). A postmortem study in patients who died from severe COVID-19 revelated the presence of viral inclusion structures, accumulation of inflammatory cells in the vascular endothelium (lymphocytic endotheliitis), and endothelial cell apoptosis (50). All these sequelae of SARS-CoV-2 infection in the CNS has been monitored in the serum and CSF of patients with long COVID who present neurological damage symptoms (encephalopathy, seizures, paraplegia, paresis, Guillain-Barré syndrome, ataxia and dysesthesia). These patients show a slight increase in white blood cells and an increase in the concentrations of total proteins and albumin, which indicates that the virus triggers a systemic dysfunction that can be detected at blood and CSF level (24).

Deciphering the process of neurological damage caused by the exacerbated innate immune response to SARS-CoV-2

Once a virus reaches the nerves and brain tissue, an inflammatory mechanism is activated which aims to limit the infection process, eliminate the virus, or repair cell damage. Depending on the activated immunological pathway and the magnitude with which it is activated, the response can have positive or negative consequences on the physiology and behavior of the individual (85). The complications of exacerbated neuroinflammation can include headache, ischemia, interstitial edema, cerebral vasodilatation, blood vessel injury, vomiting, visual loss, blood stasis, increased cerebral pressure, cognitive problems, and loss of consciousness (86–89). Neuroinflammation characterized by an early and brief inflammatory response is considered neuroprotective, and is initiated by the activation of glial and endothelial cells (90, 91). On the contrary, a prolonged neuroinflammatory activation induces damage to brain structures and tissues, which has been associated with several neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (92, 93).

The role of the microglia during resting conditions is to constantly examine the brain microenvironment to maintain homeostasis through the elimination of cellular waste (94). When there is a damage to neuronal structures, a process known as microglia activation occurs. This process is characterized by the release of cytokines, chemokines, and inflammatory molecules (95). However, when the immune response is dysregulated, the exacerbated release of proinflammatory cytokines occurs, which has been associated with high mortality in patients with COVID-19 (96). This type of patients show microglia hyperactivation through multisystem inflammatory syndrome (97, 98) and systemic inflammatory response syndrome (99).

Dysregulation of the immune response due to the SARS-CoV-2 infection has the ability to downregulate angiotensin converting enzyme 2 (ACE-2) expression, which influences the activation and balance of the inflammatory pathway (100). The decreased expression of ACE-2 increases the concentration of Ang-II favoring the ACE/Ang-II/AT1R pathway. This leads to the activation of the NF-κB transcription factor and the consequent activation of the production and release of proinflammatory cytokines (101). Altered cytokine concentrations have been observed in samples of both patients with acute SARS-CoV-2 and in patients with manifestations associated with long COVID (43, 102, 103). The increase in Ang-II concentration also favors the Ang-II/aminopeptidase-A/Ang-III/aminopeptidase-A/Ang-IV/AT4R pathway (104, 105). The increase in Ang-III concentration induces hormone overproduction such as vasopressin in the hypothalamus and aldosterone in the adrenal gland (105). These alterations result in increased peripheral vascular resistance and blood pressure. Moreover, Ang-III dysregulates Na+/K+ equilibrium which results in vascular damage, stroke and heart attack (106, 107). Both Ang-III and Ang-IV can bind to AT1R, thus induce the activation of this receptor and the activation consequently of the NF-κB transcription factor (105, 108, 109). The increase of Ang-IV dysregulates the vasodilatation process, increases the excretion of sodium, and the release of plasminogen activator inhibitor-1, favoring the development of thrombotic events both in lungs and in the brain (108, 110–113). According to transcriptome databases, ACE2 is expressed in excitatory and inhibitory neurons, astrocytes, oligodendrocytes, and endothelial cells (114). We believe that ACE-2 downregulation induced by SARS-CoV-2 infection, is one of the first pathways responsible for immunological response damage to the CNS.

An additional mechanism associated with pro-inflammatory cytokines induction occurs when the virus infects the cell, and the innate immune system detects viral RNA genome, either as ssRNA or one of dsRNA's intermediaries through the Toll-Like Receptors including TLR3, TLR7, and TLR8 (115, 116). These receptors are responsible for activation of transcription factors such as IRF3, IRF7, NF-κB, ISRE3, and API. This transcription factors are related to the expression of key proinflammatory cytokines in the antiviral response such as TNF-α, IFN-α, IFN-β and IFN-γ (115, 117). IFN-α and IFN-β activates genes involved in apoptosis processes, in the modulation of immune response, in cellular attraction and adhesion, and genes involved in antiviral and pathogenic detection (118). The balance that exists between IFN-α and IFN-β concentrations is key in the regulation of the inflammatory response. If there is any imbalance in their concentrations, the IFN-γ production is affected and therefore the anti-inflammatory process does not occur. In addition a chronic inflammation is promoted when the

humoral response is deficient (119). Interestingly, in samples of respiratory epithelial cells and plasmacytoid dendritic cells from patients with severe COVID-19, there is a decrease of type-I IFNs associated with self-recessive deficiencies in genes that code for the proteins involved in interferon production (e.g. TLR3, UNC93B, TRIF, TBK1, TBK1, IRF3, IRF7, IFNAR1/2, MYD88, GATA2 and IRAK4) (120–126). In CSF samples of patients with acute COVID-19 and sings of neurological damage, it was found a reduced interferon response, expansion of clonal T cells and a depletion of CD4+ T cells (127). Thus, it is possible that the interferon production during and after infection is a key point in the process of regulating systemic and neuronal inflammation.

The inflammatory response in the CNS system is mediated by resident microglia and astrocytes (128), which detects the presence of an exogenous or pathogenic agent such as SARS-CoV-2 (129). Besides its direct participation in the elimination of an infection, the microglia establish the balance between the innate immune response and the adaptive immune response (130, 131). During acute COVID-19, the exacerbated release of proinflammatory cytokines promotes the production of reactive oxygen species (ROS), which causes stress and cell damage at the systemic level, affecting brain tissue (129). In some COVID-19 patients these cellular events manifest in symptoms such as ischemia, inflammation of brain tissue, obstruction of blood flow, headaches, loss of consciousness, cerebral edema, and neuronal death (131–133).

Previous studies have reported that during influenza virus infection there is an increase in the levels of proinflammatory cytokines, such as IL-1β, IL-6, CXCL8, CXCL9, CXCL10, CCL2, and TNF-α, in the CSF of patients who present neurological alterations such as acute encephalitis and encephalopathy (134, 135). It is also known that patients infected with human orthopneumovirus and presenting neurological symptoms such as encephalitis and encephalopathies, have elevated levels of the proinflammatory cytokines IL-6, IL-8, CCL2, and CCL4 in CSF samples (136, 137). West Nile virus is also known to cause a neuroinvasive disease manifesting meningitis, meningoencephalitis, encephalitis, or acute flaccid paralysis, commonly associated with diarrhea/vomiting, weakness, impaired vision, confusion, or drowsiness, and shows elevated levels of proinflammatory cytokines IL4, IL6, and IL10 in serum samples (138). Finally, Zika virus can infect the CNS and induce microcephaly in fetuses and rare but serious neurological diseases in adults, which are associated with excessive production of IFN-α, IFN-β, IL-6, and TNF-α (139).

Interestingly, these neuroinflammatory pathological processes observed in long COVID patients, resemble those that occur in early phase of Parkinson's disease (PD and AD (92). For example, high levels of TNF-α and low levels of TNF-β have been detected in CSF samples from patients with mild cognitive impairment who progressed to AD, and the cytokines IL-1β, IL-6, and TNF-α, tend to increase slowly, while the cytokines IL-18, MCP-1, and IP-10 peak at a certain stage of the disease (140, 141). Activation of microglial cells has been detected in the substantia nigra of patients with PD, due to the fact that aggregated α-synuclein is released from the damaged dopaminergic neurons (142). The accumulation of α-synuclein leads microglia to a reactive proinflammatory phenotype in which TNF-α, nitric oxide, and IL-1β are produced, generating a neuroinflammatory state as recently shown in an *in vitro* model of PD (143).

Role of the dysregulated antibodies response against SARS-CoV-2 infection in neurological disorders

Part of neurological sequelae previously mentioned suffered by SARS-CoV-2 patients, were also reported in individuals who survived SARS-CoV-1 infection in 2004 who presented cerebrovascular disorders such as ischemic stroke (144). These affectations could be caused by abnormalities in coagulation and hyperinflammation promoted by the presence of antiphospholipid autoantibodies (eg. antiphosphatidylserine or antiprothrombin) produced by plasma cells (88, 145, 146). Autoantibodies are a type of antibodies that recognize epitopes present in organs or tissues of the same individual and are related to the development of autoimmune diseases including allergies and oncopathologies (147, 148). Much of the generation of these autoantibodies is caused by genetic mutations, infections or environmental factors (149). The autoantibody generation can result from an altered production of cytokines, stimulation of toll-like receptors, or pattern recognition receptors (150). Furthermore, they can also originate from an inadequate and dysregulated release of autoantigens by cells and tissues, and/or molecular mimicry (150, 151). In the case of COVID-19 infection, various studies indicate that the spike protein of SARS-CoV-2 is the causal agent of inducing the autoantibodies generation, which might be a common characteristic in coronavirus infections (147, 148, 150, 152). It has been reported that the antibodies produced by plasma cells against spike protein or receptor-binding domain of the SARS-CoV-2 can cross-bind with own antigens (153). In a follow-up study of 610 patients after 6 to 12 months post-infection with SARS-CoV-2, there were low concentrations of IgM and IgG3 that correlated with a predisposition to develop long COVID. Moreover, 71% of these patients presented severe COVID-19 and bronchial asthma at the same time (152). Regarding these immunoglobulins, it is known that both are induced by the controlled production of interferons and antagonized by IL-14 (154, 155). In addition, IgMs have a relevant role in the humoral response since it is the first immunoglobulin that participates in pathogen elimination (156). IgMs functions as a powerful complement activator, participate in the activation and regulation of the inflammatory response, opsonization, and destruction of pathogens present in

the circulatory system (155, 157). In addition, IgMs are associated with the protective mechanisms of the vasculature and mucous membranes (157). IgG3s, activate the complement system and have a great affinity with Fc receptors (158). The deficiency of IgG3s is related with the development of autoimmune diseases (159). This could indicate that the innate immune response dysregulation directly affects the humoral response activation process, which leads to a deficient, non-specific and delayed production of antibodies against SARS-CoV-2.

In a recent multicenter study it was proposed that a deficient and prolonged immune response in hospitalized severe COVID-19 patients promotes the adaptive immune response that attacks non-structural viral proteins and causes the development of IgG autoantibodies (160). Similarly, a proteomic profiling analysis revealed that the generation of certain autoantibodies (e.g. MUC1 or TNFRSF6B) is associated with the severity of the disease (147). Consistent with this notion, several investigations have also found that patients who had COVID-19 exhibit marked increases in autoantibody reactivity compared with uninfected individuals (160, 161). These individuals show a high prevalence of autoantibodies against immunomodulatory proteins (including cytokines, chemokines, complement components, and cell surface proteins) (162). The main consequence of these autoantibodies is the disruption of the immune function and the impairment of the virologic control by inhibiting immunoreceptor signaling and altering the composition of peripheral immune cells (163, 164).

There are cases where the presence of autoantibodies can be detected prior to any viral infection, suggesting a genetic predisposition to the generation of these autoantibodies (165). This could explain why some COVID-19 patients are more susceptible to produce autoantibodies that promote long COVID (166, 167). Recent studies have shown that some of these autoantibodies have an affinity for blood vessel and nervous system proteins, which could explain the neurological effects of long COVID by two mechanisms (168). First, autoantibodies could potentiate the cellular stress induced by proinflammatory cytokines. Second, autoantibodies could cause specific and long-term damage in patients suffering from post-COVID neurological sequelae (43, 168). In fact, COVID-19 patients with neurological sequelae produce autoantibodies that inhibit the function of key proteins involved in neuroprotection processes, neurite outgrowth, axogenesis, neuronal plasticity, neurotransmission, neuronal survival, and axonal regeneration (Supplementary Table 1) (167). The generation of these autoantibodies may aggravate the neuronal damage.

The dysregulation of the immune response and the deficient elimination of cells infected by SARS-CoV-2 promote the release of autoantigens towards the extracellular space and the

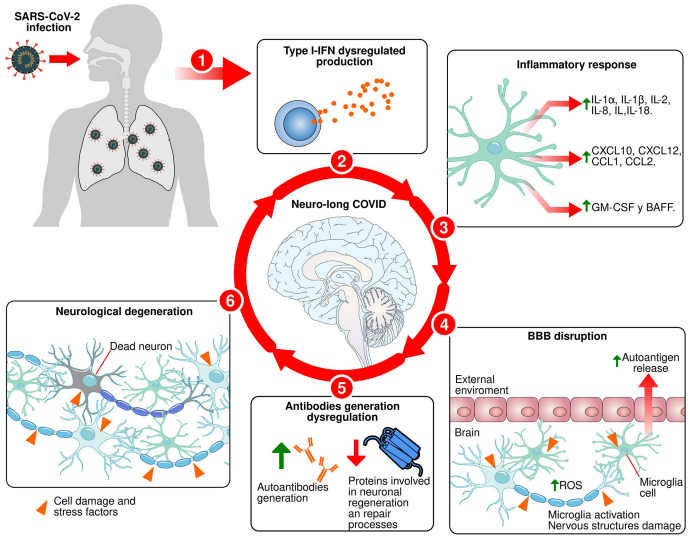

FIGURE 1
Proposed mechanism for neuro-long COVID. 1: SARS-CoV-2 infects olfactory epithelial and lungs. 2: Type-I IFNs production dysregulated during primary immune response process against SARS-CoV-2 infection. 3: Exacerbated release of proinflammatory cytokines. 4: The exacerbated and dysregulated inflammatory response causes the proinflammatory molecules release that damage the BBB, facilitate the infiltration of immune cells into brain tissue, activate microglia, and damaging brain tissue cells, causing the autoantigens release. 5: Innate immune response dysregulation affects the humoral response activation process and induce a nonspecific and delayed production of antibodies against SARS-CoV-2 and the generation of autoantibodies against key proteins involved in neuronal regeneration and repair processes. 6: Induction of neuronal death in specific areas.

consequent generation of autoantibodies (169, 170). The analysis of the "autoantigenicoma" in patients who suffered from COVID-19 through the detection of autoantigens bound to determatan sulfate (autoantigen-DS complex) seems to be helpful to predict the appearance of autoimmune diseases and neurological damage (171, 172). Using this strategy, 751 autoantigen candidates were found, of which 657 are directly altered by infection with SARS-CoV-2. Remarkably, 400 of those autoantigens are related to autoimmune diseases and cancer (162). Regarding the nervous system, 150 autoantigens of proteins are related to axon guidance, neuron projection, myelin sheath, axon growth cone, neuronal cell body, cerebellar Purkinje cell layer, peripheral nervous system axon regeneration, radial glial scaffolds and proteins related to the olfactory bulb. There were also 193 autoantigens of proteins related to neurological diseases such as neuronal infection with Japanese encephalitis virus, neuroblastoma, glioblastoma, neurodegeneration in Down syndrome, AD, schizophrenia, cerebral ischemia induced neurodegenerative diseases, PD, and neurodegeneration (Supplementary Table 2) (172). The mechanism by which coronaviruses could resemble conditions of early events of neurodegeneration should be explored considering the participation of the immune system and the uncontrolled generation of autoantibodies that deteriorate neuronal circuits.

Summary and proposal

The effects of long COVID on the CNS are increasingly evident. For this reason, in the present work we analyzed the role of the immune response against the coronavirus and its impact on neuronal structures. The SARS-CoV-2 infects olfactory epithelial cells through ACE-2 (173). Through genetic rearrangements, the virus downregulates the expression of proteins such as olfactory receptors and ACE-2 (17, 100). The latter is implicated in the production of proinflammatory cytokines (43). When the immune system detects the entry of the virus, it activates the primary response, which is characterized by the release of proinflammatory cytokines and the activation of immune cells. These processes are regulated by type-I INFs and together with IFN-γ (115, 117) induce the generation of antibodies (130, 131). However, due to the downregulation of ACE-2 and mutations in type I INFs, the inflammatory response is dysregulated, provoking the exacerbated release of proinflammatory cytokines (117). This response damages cellular structures and promotes the release of autoantigens (168, 169). At the same time, the dysregulation of the innate immune response affects the activation process of the humoral response (119, 169). This may lead to a nonspecific and delayed production of antibodies against SARS-CoV-2 and the generation of autoantibodies that recognize key proteins involved in neuronal regeneration and repair processes, thereby increasing neurodegeneration (167). We think this generates a cyclical process of recognition and destruction of neuronal structures (Figure 1). Depending on the region that is affected, this promotes the appearance of neurological symptoms observed in patients with long COVID.

Author contributions

JM-L and CM-N wrote the manuscript. JE-D and EM-M conceived and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2022.1039427/full#supplementary-material

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Third COVID-19 vaccine dose for people with multiple sclerosis who did not seroconvert following two doses of BBIBP-CorV (Sinopharm) inactivated vaccine: A pilot study on safety and immunogenicity

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Background: People with multiple sclerosis (pwMS) on anti-CD20 therapies (aCD20) and fingolimod have shown inadequate humoral responses to COVID-19 vaccines.

Objective: The objective of the study was to pilot larger studies by demonstrating the safety and comparing the immunogenicity of different types of third doses in seronegative pwMS after two doses of BBIBP-CorV inactivated vaccine.

Methods: In December 2021, subject to receiving their third dose, being COVID-19-naiive, and receiving no corticosteroid within two months, we measured the level of anti-SARS-CoV-2-Spike IgG in pwMS seronegative after two shots of BBIBP-CorV inactivated vaccine.

Results: We included 20/29 pwMS who received adenoviral vector (AV), 7/29 who received inactivated, and 2/29 who received conjugated third doses. No serious adverse events were reported two weeks post-third dose. The pwMS receiving AV third doses showed significantly increased IgG concentrations, while only the ones *not* on aCD20 and fingolimod responded to inactivated third doses. An ordinal logistic multivariable generalized linear model indicated that age (per year β: −0.10, P = 0.04), type of disease-modifying therapy (aCD20 β: −8.36, P <0.01; fingolimod β: −8.63, P = 0.01; others: reference), and type of third dose (AV or conjugated β: 2.36, P = 0.02; inactivated: reference) are predictive of third dose immunogenicity among pwMS who remain seronegative after two shots of BBIBP-CorV vaccine. Statistical significance was not achieved for variables sex, MS duration, EDSS, duration of DMT, duration of third dose to IgG test, and duration from last aCD20 infusion to third dose.

Conclusion: This preliminary pilot study highlights the need for further research to determine the optimal COVID-19 third dose vaccination strategy for pwMS living in areas where BBIBP-CorV vaccine has been used.

KEYWORDS

COVID-19, multiple sclerosis, vaccine immunogenicity, disease-modifying therapies (DMTs), BBIBP-CorV

1 Introduction

Among people with multiple sclerosis (pwMS) on sphingosine-1-phosphate receptor modulators (S1PRM) and anti-CD20 therapies (aCD20) primed with mRNA COVID-19 vaccines, evidence shows persistent vaccination failure after mRNA third doses (1), while data on third-dose immunogenicity remain scarce for those receiving other types of third doses—or any other primary series than adenoviral vector (AV) or mRNA. Given the vast global usage of inactivated vaccines as primary series, particularly in densely-populated developing areas, the determination of third dose safety and immunogenicity among immunocompromised people who fail to respond to the inactivated primary series is of relevance for future evidence-driven policy making and practice. Hence, in order to facilitate more research on the subject, we decided to reidentify from our previous study (2) the pwMS who remained seronegative after two doses of BBIBP-CorV, determine the frequency of serious adverse events, measure the anti-SARS-CoV-2 IgG levels among the ones who received their third dose, and investigate the effect of different variables on third-dose immunogenicity among them.

2 Methods and results

2.1 Design, settings, and participants

As an extension of an observational retrospective cohort study conducted in December 2021 in Isfahan, Iran, we identified 49 adults with definitive MS who received two doses of BBIBP-CorV but remained seronegative from our previous study (2) and contacted them, asking if they had received any kind of third dose of a COVID-19 vaccine. Among them, 21 women and eight men (mean age [SD]: 40 years [10.60]) were COVID-19-naiive—defined as having no history of: i) clinical illnesses compatible with COVID-19, ii) contact with suspected or confirmed COVID-19 patients, or iii) COVID-19 diagnosis based on the available laboratory and imaging methods—and did not receive corticosteroids within two months of their third dose. 12 were receiving aCD20, eight fingolimod, four teriflunomide, two glatiramer acetate (GA), and one dimethyl fumarate (DMF), without any change in DMT regimen in the past year. Their further demographics and MS-related characteristics are interpretable from Table 1.

Furthermore, information was collected regarding the date and type of their third dose and the development of any serious adverse events following their third dose, as defined by the US Food and Drug Administration (FDA) (3)[1]. A total of 20/29 of the participants received AV (ChAdOx1 nCoV-19, AstraZeneca), 7/29 inactivated (BBIBP-CorV, Sinopharm), and 2/29 conjugated (PastoCovac, Pasteur Institute of Iran) third doses. The participants receiving inactivated third doses had higher disease durations than the ones receiving AV/conjugated third doses (mean diff. 5.56 years, P = 0.03); their other known features were similar (Table 1).

2.2 Post-third dose safety and antibody responses

None of the participants reported any serious adverse events—including MS relapses or pseudorelapses—from the administration of their third dose until two weeks later. At least two weeks after their documented third dose, blood samples were obtained from the participants and used for quantification of post-third dose anti-SARS-CoV-2-Spike IgG—which corresponds to neutralizing activity against variants of concern (VOC) (4–6) with an ELISA kit (Pishtazteb Diagnostics, Iran), in accordance with manufacturer instructions (7) and with methods previously described (2). The

TABLE 1 Characteristics of participants.

Variable	Heterologous[1] third dose (n = 22)	Homologous[2] third dose (n = 7)	P-value
Mean Age (Years) [SD]	39.04 (11.28)	43 (8.08)	0.40#
Sex (n, %) [M:F]	7 (31.82): 15 (68.18)	1 (14.29): 6 (85.71)	0.36@
Mean MS duration (Years) [SD]	8.73 (5.98)	14.29 (4.57)	0.03#
Median EDSS (Range)	2.25 (1–4)	2 (1–3.5)	0.81*
DMT (n, %)			0.56@
* aCD20	8 (36.36)	4 (57.14)	
* Fingo	7 (31.82)	1 (14.29)	
* Other	7 (31.82)	2 (28.57)	
Median duration on current DMT (years) [Range]	5 (1–10)	5 (4–7)	0.27*

(Continued)

1 No data was collected on development of mild to moderate adverse events.

TABLE 1 Continued

Variable	Heterologous[1] third dose (n = 22)	Homologous[2] third dose (n = 7)	P-value
Median (Range) of weeks from:			
*2nd dose to 3rd dose	23.5 (16–28)	23 (11–25)	0.28*
* 2nd dose to subsequent IgG test	7 (2–18)	5 (3–9)	0.47*
* 3rd dose to subsequent IgG test	3 (2–6)	3 (2–6)	0.55*
* aCD20 infusion to 3rd dose (n = 12)	14.5 (5–22)	11 (9–12)	0.26*
Median anti-SARS-CoV-2-Spike IgG (Range)	31.75 (0.14– >100)	1.75 (0.17–47.10)	0.048*

#Student's T-test; @Pearson Chi^2; *Mann–Whitney U test. Assumptions of normality of distributions were tested using the Kolmogorov–Smirnov method; variables, the distribution of values of which passed the Kolmogorov–Smirnov test, are reported with mean and SD, and compared using parametric statistics; others are reported with median and range, and compared using non-parametric statistics.

1. AstraZeneca ChAdOx1 nCoV-19 (n = 20) and Pasteur Institute of Iran PastoCovac (n = 2).

2. Sinopharm BBIBP-CorV.

SD, standard deviation; M, male; F, female; MS, multiple sclerosis; EDSS, expanded disability status scale; DMT, disease-modifying therapy; aCD20, anti-CD20 therapies; Fingo, fingolimod.

IgG levels above the kit's upper limit of quantification (ULoQ) were regarded as >100 RU/ml without precise quantification due to restrictions in rerunning the assays with serial dilutions of samples.

2.2.1 Antibody responses in pwMS on aCD20

Among the pwMS on aCD20, 4/8 (50%) of the ones receiving AV/conjugated third doses and none of the four who received inactivated third doses seroconverted after their third dose. Anti-SARS-CoV-2-Spike IgG levels increased significantly in the aCD20-treated participants after receiving AV/conjugated third doses (P=0.01[2]) but did not differ significantly in the ones receiving inactivated third doses (P = 0.87[a]) (Figure 1).

2.2.2 Antibody responses in pwMS on fingolimod

Among the pwMS on fingolimod, 2/7 (28%) of those receiving AV/conjugated third doses seroconverted after their third dose. The only fingolimod-receiving participant who received an inactivated third dose did not seroconvert. Anti-SARS-CoV-2-Spike IgG levels increased insignificantly after AV/conjugated third doses among the

2 Wilcoxon matched-pairs signed rank test.

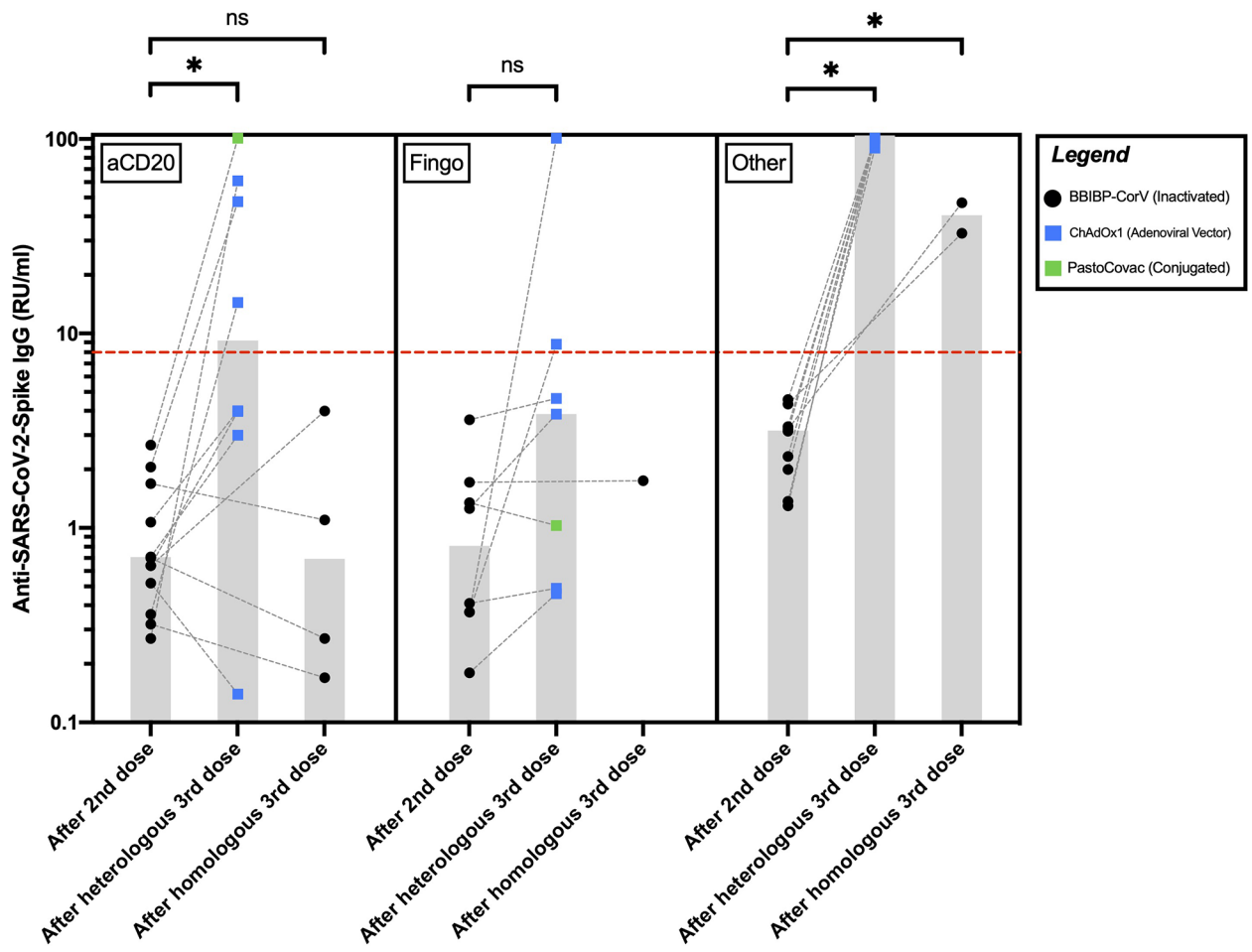

FIGURE 1
Anti-SARS-CoV-2-Spike IgG levels in pwMS receiving anti-CD20 therapies, fingolimod, or other disease-modifying therapies after their second and third COVID-19 vaccine doses. The red hyphenated line corresponds to the seropositivity cut-off index. The gray bars correspond to the median of IgG levels. *P <0.05; ns, P >0.05. aCD20, anti-CD20 therapies; Fingo, fingolimod; RU/ml, relative units per milliliter.

TABLE 2 Multivariable generalized linear model.

Variable (reference)	Multivariable GLM (n=29, ordinal logistic response, outcome: rank of increase in anti-SARS-CoV-2-Spike IgG [RU/ml] after third dose)	
	B (SE)	P-value
Age (per year)	-0.10 (0.05)	0.04
Female sex (male)	0.19 (0.92)	0.84
MS duration (per year)	-0.13 (0.11)	0.25
EDSS (per score)	0.62 (0.54)	0.25
DMT type (Other)		
–aCD20	-8.36 (3.01)	<0.01
– Fingo	-8.63 (3.48)	0.01
Duration of receiving DMT (per year)		
– aCD20	0.74 (0.43)	0.09
– Fingo	0.57 (0.53)	0.28
– Other	0.18 (0.31)	0.57
Heterologous third dose (homologous)	2.36 (1.02)	0.02
Duration from third dose to phlebotomy (per week)	-0.99 (0.54)	0.07

GLM, generalized linear model; B, beta coefficient; SE, standard error; MS, multiple sclerosis; EDSS, expanded disability status scale; DMT, disease-modifying therapy; aCD20, anti-CD20 therapies; Fingo, fingolimod.

fingolimod-receiving pwMS (P = 0.07[a]). Statistical significance was reached after excluding the single fingolimod-treated participant who received a conjugated third dose (P = 0.03[a]).

2.2.3 Antibody responses in pwMS on other DMTs

All the participants on other DMTs seroconverted following their third dose. Among them, compared to the ones receiving inactivated third doses, anti-SARS-CoV-2-Spike IgG levels were significantly higher in those receiving AV third doses (P = 0.03[b]) (Figure 1).

2.2.4 Further analysis

A multivariable generalized linear model controlling for the confounding effect of variables age, sex, MS duration, expanded disability status scale (EDSS), DMT, and the interaction term of DMT and duration of being on the DMT indicated a significant (P <0.05) effect of age, DMT type, and third dose type on the post-dose 3 increase in IgG levels (Table 2); the possible effects of other mentioned variables were not statistically confirmed (P >0.05).

3 Conclusion

Our study demonstrates that the immunogenicity of the third COVID-19 vaccine dose could be safely studied in adult pwMS who received two doses of an inactivated vaccine but remained seronegative. In line with studies among non-MS adults, which have consistently demonstrated the superiority of AV or mRNA third doses over inactivated ones in terms of humoral immunogenicity and clinical effectiveness against the VOC (8–12), our results hint that AV third COVID-19 vaccine doses may be of more benefit than inactivated ones for pwMS who received two doses of an inactivated vaccine but remained seronegative. Third dose studies are currently scarce among pwMS who received inactivated primary series; however, such studies among pwMS receiving mRNA or AV primary series have suggested that less time from the last aCD20 infusion and being on S1PRM and aCD20 DMTs blunt seroconversion rates (1, 13–15). The current study lacked adequate statistical power to support the former but could be considered supportive of the latter statement. Nevertheless, administration of third booster doses, although not as much as other pwMS, could be considered beneficial for pwMS on S1PRM and aCD20 (14) but its cost-effectiveness in the current state of the pandemic remains to be investigated.

4 Limitations

Although some of our findings are unlikely to be explained merely by chance as interpreted from hypothesis testing and statistical significance, our study was conducted on a limited number of participants; therefore, the certainty of our findings is very low. Also, due to our small sample size, the effect of the aCD20 infusion-to-third dose period could not be investigated. The results of the current study have implications for future larger studies on the subject; conclusions from our study that might affect real-world practices are subject to validation by studies with larger sample sizes. We encourage future researchers to account for the limitations of this study by recruiting a larger sample size, collecting data on mild to moderate adverse events, quantifying measures above ULoQ, using T cell and/or neutralization assays, and including previously-seropositive participants who might have been subject to immunity waning—especially the ones on aCD20, cladribine, and alemtuzumab.

Data availability statement

The datasets presented in this article are not readily available because of the privacy protection of the participants. The generated data in this study will be available to qualified investigators upon a reasonable request from the corresponding author and in context of a non-disclosure agreement. Requests to access the datasets should be directed to nahad.sedaghat@gmail.com.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee of School of Medicine, Isfahan University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

Author contributions

NS: writing - initial draft; formal analysis; conceptualization. ME: conceptualization; resources; supervision. NL: resources; supervision. FS: data curation, resources. AC: resources. MS: writing - review and editing. AG: data curation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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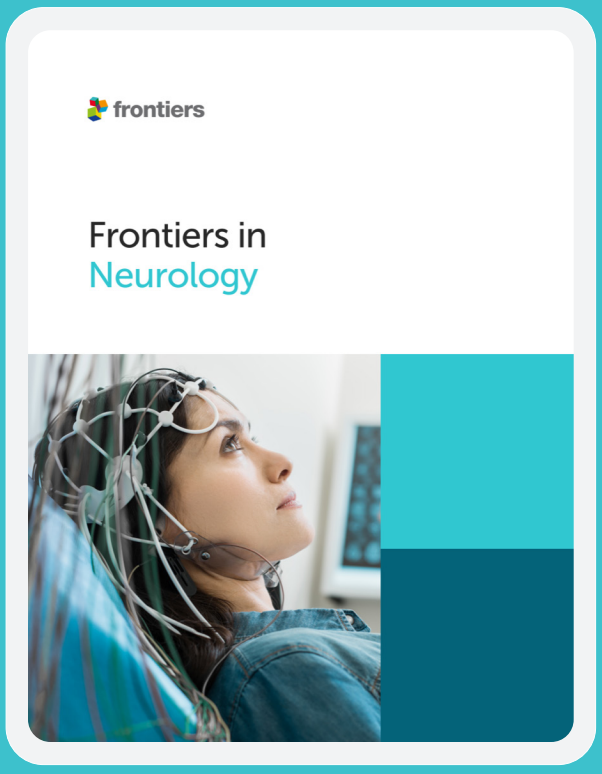

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