MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Acute central nervous system inflammation following COVID-19 vaccination: An observational cohort study

Multiple Sclerosis Journal
2023, Vol. 29(4-5) 595–605
DOI: 10.1177/13524585231154780

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Abstract

Background: Reports suggest a potential association between coronavirus disease 2019 (COVID-19) vaccines and acute central nervous system (CNS) inflammation.

Objective: The main objective of this study is to describe features of acute CNS inflammation following COVID-19 vaccination.

Methods: A retrospective observational cohort study was performed at the BARLO MS Centre in Toronto, Canada. Clinicians reported acute CNS inflammatory events within 60 days after a COVID-19 vaccine from March 2021 to August 2022. Clinical characteristics were evaluated.

Results: Thirty-eight patients (median age 39 (range: 20–82) years; 60.5% female) presented within 0–55 (median 15) days of a receiving a COVID-19 vaccine and were diagnosed with relapsing remitting multiple sclerosis (MS) ($n=16$), post-vaccine transverse myelitis ($n=7$), clinically isolated syndrome ($n=5$), MS relapse ($n=4$), tumefactive demyelination ($n=2$), myelin oligodendrocyte glycoprotein antibody disease ($n=1$), neuromyelitis optica spectrum disorder ($n=1$), chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids ($n=1$) and primary autoimmune cerebellar ataxia ($n=1$). Twenty-two received acute treatment and 21 started disease-modifying therapy. Sixteen received subsequent COVID-19 vaccination, of which 87.5% had no new or worsening neurological symptoms.

Conclusion: To our knowledge, this is the largest study describing acute CNS inflammation after COVID-19 vaccination. We could not determine whether the number of inflammatory events was higher than expected.

Keywords: COVID-19, vaccination, demyelinating diseases, neuroinflammatory diseases, multiple sclerosis, central nervous system

Date received: 24 October 2022; revised: 8 January 2023; accepted: 15 January 2023

Introduction

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became available in late 2020 and remains a critical measure to control the coronavirus disease 2019 (COVID-19) pandemic.[1] Four COVID-19 vaccines are authorized for use in Canada and include Pfizer-BioN-Tech (BNT162b2), Moderna (mRNA-1273), Oxford-AstraZeneca (ChAdOx1S/nCoV-19, AZD1222) and Johnson & Johnson/Janssen (JNJ-78436735).[2] Although the vaccines differ in their mode of delivery, all of them use the viral spike protein as an immunogen.[3] Each vaccine has been shown to be remarkably effective and safe.[4,5]

Upon global uptake of COVID-19 vaccines, a number of reports have described various presentations of acute central nervous system (CNS) inflammation in individuals shortly after vaccination. This includes new onset multiple sclerosis (MS),[6–8] MS relapse,[6,9] transverse myelitis (TM),[4,10–13] myelin oligodendrocyte glycoprotein antibody disease (MOGAD),[14,15] neuromyelitis optica spectrum disorder (NMOSD),[6,16–18] acute disseminated encephalomyelitis (ADEM),[19–21] leucine-rich glioma-inactivated protein 1 (LGI1) antibody encephalitis,[22] and seronegative autoimmune limbic encephalitis.[23]

Vaccination has long been speculated to increase the risk of CNS inflammatory events, most notably demyelinating diseases such as ADEM.[24] A large case–control study published in 2014 suggested that vaccination of any type may accelerate the transition from

subclinical to overt demyelinating disease, but a longer-term association between vaccination and demyelinating disease was not found, arguing against a causal association.[25] More recently, a disproportionality analysis using the World Health Organization's pharmacovigilance database observed a weak association between the Pfizer-BioN-Tech, Moderna and Oxford-AstraZeneca vaccines and CNS demyelinating disease, but this risk was low and similar to that of other viral vaccines.[26]

Several questions remain about the relationship between COVID-19 vaccines and acute CNS inflammation. There is a need to define the clinical spectrum of acute CNS inflammatory events occurring in temporal relation to COVID-19 vaccination and to assess outcomes in response to immunotherapy. It is also unclear whether subsequent vaccination against COVID-19 is associated with recurrent adverse events in this population. We report 38 patients with or without pre-existing neuroinflammatory disease who experienced an acute CNS inflammatory event within 60 days of receiving at least one dose of a COVID-19 vaccine. We describe their clinical, laboratory and imaging features, as well as their treatment outcomes and response to subsequent vaccination against COVID-19.

Materials and methods

Study design, setting and participants

We performed a retrospective observational cohort study using clinical data from the BARLO MS Centre, a tertiary care centre in Toronto, Ontario, Canada. Patients were identified by their treating clinician for inclusion in the study. Eligible patients were age 18 years or older and experienced an acute CNS inflammatory event within 60 days of receiving at least one COVID-19 vaccine from March 2021 to August 2022. The 60-day range was chosen based on reports of acute CNS inflammation occurring mostly within 30 days and less commonly up to 90 days after vaccination.[27,28] Patients with or without pre-existing neuroinflammatory disease were included. Data of interest were retrospectively obtained from patients' electronic health records and included only information already collected in clinical practice. Patients underwent investigation, received treatment and were seen in follow-up at the discretion of their treating clinician and not for the purpose of the study. The study was approved by the Unity Health Toronto Research Ethics Board with a waiver of informed consent.

Exposures and outcomes

We collected demographic data including age at symptom onset and sex. The type and dose of COVID-19 vaccine received most recently prior to symptom onset was recorded. Information was collected on the type and duration of acute treatment, the continuation or initiation of disease-modifying therapy (DMT) and whether a subsequent COVID-19 vaccine was administered at any time after the acute CNS inflammatory event.

Outcome data included the number of days between vaccination and symptom onset. Neurological symptoms and corresponding neurological syndromes were evaluated. We recorded the duration of follow-up and diagnosis at last follow-up. Neurological and functional disability was measured using the expanded disability status scale (EDSS) at symptom nadir and at last follow-up. The EDSS was either documented by the examiner at the time of the clinical visit or retrospectively calculated by the authors based on the available clinical documentation. Clinical outcome was based on reported symptoms and neurological examination at last follow-up and defined as 'return to baseline', 'partial recovery' or 'worsening'. Subsequent vaccination against COVID-19 was documented and patient charts were reviewed for symptom recrudescence or disease relapse.

Radiological data included magnetic resonance imaging (MRI) brain and spinal cord results. Patients seen at the BARLO MS Centre are geographically dispersed across the province of Ontario, and neuroimaging was sometimes obtained at an outside hospital, with results made available to the treating clinician. Therefore, MRI protocols varied among patients in the study. Images were reviewed directly by study personnel. T2 and fluid-attenuated inversion recovery (FLAIR) sequences were examined for new or enlarging T2 hyperintense lesions in the brain and spinal cord. T1 sequences with gadolinium were evaluated for enhancing lesions in the brain and spinal cord. T1 sequences were reviewed for T1 'black hole' lesions in the brain. All abnormal lesions were included, regardless of whether they were located in regions that meet criteria for MS as outlined in the 2017 McDonald Criteria.[29] Repeat MRI brain and spinal cord images were reviewed if available and compared to the initial studies. 'Stable' was defined as no change in the number or size of lesions, 'improvement' was defined as a decrease in the number or size of lesions, and 'worsening' was defined as an increase in the number or size of lesions.

Laboratory data comprised antibody positivity for MOG and aquaporin 4 (AQP4) IgG in serum. Cerebrospinal fluid (CSF) results were reviewed for white blood cell (WBC) count, WBC differential, red blood cell (RBC) count, glucose, protein, oligoclonal bands and IgG index.

Statistical analysis

Descriptive statistics were reported as frequency counts and percentages for categorical variables and as median and range for continuous variables.

Results

Thirty-eight patients were identified for inclusion in the study. The median age at symptom onset was 39 years (range 20–82) and 23 were female (60.5%, ratio 1.5:1). Four (10.5%) patients had a pre-existing diagnosis of relapsing remitting multiple sclerosis (RRMS), and three of them were on DMT at the time of receiving a COVID-19 vaccine. One (2.6%) patient had a retrospective history of neurological symptoms in keeping with an MS relapse but did not have a known diagnosis at the time of receiving a COVID-19 vaccine. One (2.6%) patient had a pre-existing diagnosis of overlap syndrome with rheumatoid arthritis and systemic lupus erythematosus. The remaining 32 (84.2%) patients had no known history of neuroinflammatory or autoimmune disease. Prior to symptom onset, individuals received the Pfizer-BioN-Tech ($n=26$), Moderna ($n=10$), Oxford-AstraZeneca ($n=1$) or unknown ($n=1$) COVID-19 vaccines. Although the Johnson & Johnson/Janssen COVID-19 vaccine was available in Ontario at the time of the study, it was not commonly used and we did not encounter any individuals who received this vaccine.

Within 0 to 55 days (median 15) of receiving either the first ($n=13$), second ($n=16$), third ($n=7$) or fourth ($n=2$) vaccine dose, patients developed a variety of neurologic symptoms that localized to the CNS. This included numbness ($n=25$), weakness ($n=19$), sphincter dysfunction ($n=8$), vision loss ($n=6$), ataxia ($n=6$), dysarthria ($n=5$), diplopia ($n=1$), aphasia ($n=1$) and vertigo ($n=1$). Median EDSS at symptom nadir was 2.5 (range 0–7). The predominant clinical syndrome was TM ($n=24$), followed by hemispheric ($n=7$), optic neuritis (ON) ($n=6$), brainstem ($n=4$), cerebellar ($n=3$) and thalamic ($n=1$). Six (15.8%) patients had a multifocal presentation, with neurological symptoms localizing to more than one region of the CNS. Of those with a multifocal presentation, 5 (83.3%) had corresponding lesions on neuroimaging. Demographic and clinical characteristics are summarized in Table 1a. Given that most cases reported in the literature presented within 30 days of receiving a COVID-19 vaccination, we re-examined the demographic and clinical characteristics of our cohort, limiting the time window from 60 to 30 days (Table 1b). The demographic and clinical characteristics were similar for the 30 day group ($n=24$) when compared to the cohort as a whole ($n=38$).

Thirty-six patients underwent MRI brain (Table 2). Twenty-two (61.1%) had T2 hyperintense lesions. This included all four patients with pre-existing RRMS, who had new lesions when compared to previous MRI brain. Twenty-seven patients had an MRI brain with contrast, and 10 (37.0%) had enhancing lesions. T1 sequences were available for review in 30 patients, and 11 (36.7%) had T1 hypointense 'black hole' lesions, including 3 with pre-existing RRMS and 8 with no prior history (6 new diagnosis of RRMS, 1 CIS, 1 MOGAD). Thirty-five patients underwent MRI spinal cord. T2 hyperintense lesions were observed in 27 (77.1%). This included 2 patients with pre-existing RRMS, who had new lesions when compared to previous MRI spinal cord. Two (7.4%) patients had a longitudinally extensive spinal cord lesion (1 NMOSD and 1 post-vaccine TM) and 3 (11.1%) had a lesion involving the conus medullaris (1 MS relapse, 1 CIS and 1 post-vaccine TM). Twenty-six patients had an MRI spinal cord with contrast and 9 (34.6%) had enhancing lesions. One patient with a final diagnosis of primary autoimmune cerebellar ataxia (PACA) did not have any T2 hyperintense lesions on MRI brain or spinal cord, but was found to have mild cerebellar atrophy. Figure 1 shows representative MRI images.

Serology for MOG IgG was performed in 33 patients, and 2 (6.1%) were positive (1 with unknown titre, 1 with high titre). The patient with unknown titre MOG IgG had clinical and radiologic features in keeping with a diagnosis of MOGAD. The patient with high titre MOG IgG had a pre-existing diagnosis of RRMS and no prior testing for MOG IgG. Clinical and radiologic features were in keeping with an MS relapse, rather than a new diagnosis of MOGAD. Serology for AQP4 IgG was performed in 34 patients, and 2 (5.9%) were positive (1 with high titre, 1 with weak titre). The patient with high titre AQP4 IgG had clinical and radiologic features in keeping with a diagnosis of NMOSD.[18] The patient with weak titre AQP4 IgG presented with short segment TM and was positive for MOG IgG (unknown titre as indicated above). This patient received a diagnosis of MOGAD and repeat AQP4 IgG was negative.

Table 1.

(a) Demographic and clinical characteristics of patients presenting within 60 days of COVID-19 vaccination	Patients with CNS inflammatory event, $n = 38$
Age at symptom onset, median years (range)	39 (20–82)
Female, *n* (%)	23 (60.5)
Pre-existing immune-mediated disease, *n* (%)	
RRMS	4 (10.5)
Retrospective MS relapse	1 (2.6)
Overlap syndrome (RA/SLE)	1 (2.6)
None	32 (84.2)
Vaccine received, *n* (%)	
Pfizer-BioN-Tech	26 (68.4)
Moderna	10 (26.3)
Oxford-AstraZeneca	1 (2.6)
Unknown	1 (2.6)
Symptom onset following, *n* (%)	
First dose	13 (34.2)
Second dose	16 (42.1)
Third dose	7 (18.4)
Fourth dose	2 (5.3)
Time of symptom onset post-vaccine, median days (range)	15 (0-55)
Presenting symptoms, *n* (%)	
Numbness	25 (65.8)
Weakness	19 (50.0)
Sphincter dysfunction	8 (21.1)
Vision loss	6 (15.8)
Ataxia	6 (15.8)
Dysarthria	5 (13.2)
Diplopia	1 (2.6)
Aphasia	1 (2.6)
Vertigo	1 (2.6)
EDSS at symptom nadir, median (range)	2.5 (0–7)
Clinical syndrome, *n* (%)	
Transverse myelitis	24 (63.2)
Hemispheric	7 (18.4)
Optic neuritis	6 (15.8)
Brainstem	4 (10.5)
Cerebellar	3 (7.9)
Thalamic	1 (2.6)
Multifocal presentation, *n* (%)	6 (15.8)
(b) Demographic and clinical characteristics of patients presenting within 30 days of COVID-19 vaccination.	**Patients with CNS inflammatory event, $n = 24$**
Age at symptom onset, median years (range)	44 (20–82)
Female, *n* (%)	15 (62.5)
Pre-existing immune-mediated disease, *n* (%)	
RRMS	3 (12.5)
Retrospective MS relapse	1 (4.2)
Overlap syndrome (RA/SLE)	1 (4.2)
None	19 (79.2)
Vaccine received, *n* (%)	
Pfizer-BioN-Tech	16 (66.7)
Moderna	6 (25.0)

(Continued)

Table 1. (Continued)

(b) Demographic and clinical characteristics of patients presenting within 30 days of COVID-19 vaccination.	Patients with CNS inflammatory event, $n = 24$
Oxford-AstraZeneca	1 (4.2)
Unknown	1 (4.2)
Symptom onset following, *n* (%)	
First dose	11 (45.8)
Second dose	9 (37.5)
Third dose	4 (16.7)
Time of symptom onset post-vaccine, median days (range)	7 (0–30)
Presenting symptoms, *n* (%)	
Numbness	18 (75.0)
Weakness	10 (41.7)
Sphincter dysfunction	6 (25.0)
Vision loss	4 (16.7)
Dysarthria	4 (6.7)
Ataxia	2 (8.3)
Vertigo	1 (4.2)
EDSS at symptom nadir, median (range)	2.5 (0–7)
Clinical syndrome, *n* (%)	
Transverse myelitis	16 (66.7)
Hemispheric	4 (16.7)
Optic neuritis	4 (16.7)
Brainstem	3 (12.5)
Cerebellar	2 (8.3)
Multifocal presentation, *n* (%)	4 (16.7)

Abbreviations: CNS: central nervous system; RRMS: relapsing remitting multiple sclerosis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; EDSS: expanded disability status scale.

Table 2. Neuroradiological findings.

	Patients with CNS inflammatory event, $n = 38$[a]
MRI brain, *n* (%)	
Normal	13/36 (36.1)
T2 hyperintense lesions	22/36 (61.1)
Enhancing lesions	10/27 (37.0)
T1 “black hole” lesions	11/30 (36.7)
Cerebellar atrophy	1/36 (2.8)
MRI spine, *n* (%)	
Normal	8/35 (22.9)
T2 hyperintense lesions	27/35 (77.1)
LETM	2/27 (7.4)
Lesion of the conus medullaris	3/27 (11.1)
Enhancing lesions	9/26 (34.6)
Time of repeat MRI from symptom onset, median days (range)	180 (39–405)
Repeat MRI, *n* (%)	
Improvement	10/28 (35.7)
Stable	9/28 (32.1)
Worsening	9/28 (32.1)

Abbreviations: CNS = central nervous system; MRI = magnetic resonance imaging; FLAIR = fluid-attenuated inversion recovery; LETM = longitudinally extensive transverse myelitis.
[a]Imaging not available for all patients, with sample size shown for each variable based on available imaging.

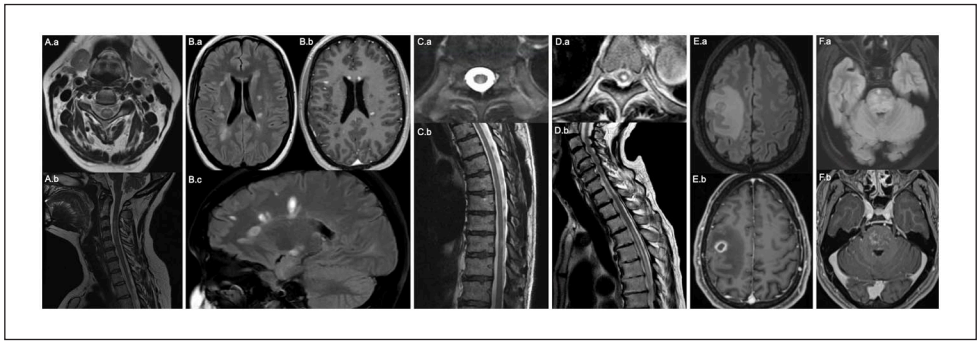

Figure 1. Select MRI brain and spinal cord images of patients with acute CNS inflammatory events following COVID-19 vaccination. (A) Post-vaccine transverse myelitis. (A.a) Axial and (A.b) Sagittal T2 of the cervical spine reveal an intramedullary T2 hyperintense lesion at the level of C3–C4. (B) New onset relapsing remitting MS. (B.a) Axial and (B.c) Sagittal FLAIR reveal multiple ovoid T2 hyperintense lesions in the supratentorial white matter, including periventricular and juxtacortical involvement. (B.b) Axial T1 post-contrast shows enhancement of several lesions, as well as multiple T1 black hole lesions. (C) Myelin oligodendrocyte glycoprotein antibody disease. (C.a) Axial and (C.b) Sagittal T2 of the thoracic spine reveal an intramedullary T2 hyperintense lesion at the level of T10. (D) Neuromyelitis optica spectrum disorder. (D.a) Axial T2 of the thoracic spine at the level of T6 and (D.b) Sagittal T2 of the cervical and thoracic spine reveal a longitudinally extensive intramedullary T2 hyperintense lesion from T3–T4 to T9–T10 (thoracic spine only visualized to T8). (E) Post-vaccine tumefactive demyelination. (E.a) Axial FLAIR reveals a right frontal mass lesion with vasogenic edema and (E.b) Axial T1 post-contrast reveals associated ring-enhancement. (F) Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. (F.a) Axial FLAIR reveals diffuse, patchy increased T2 signal in the pons and (F.b) Axial T1 post-contrast reveals associated nodular enhancement.

Table 3. Serologic and cerebral spinal fluid results.

	Patients with CNS inflammatory event, $n=38$[a]
Serologic results, *n* (%)	
Positive MOG IgG	2/33 (6.1)
Positive AQP4 IgG	2/34 (5.9)
CSF results, *n* (%)	
Elevated WBC (WBC > 5 per mm^3)	8/20 (40.0)
Lymphocytic pleocytosis (WBC > 5 per mm^3 with lymphocytic predominance)	8/20 (40.0)
Elevated protein (>0.45 g/L)	8/20 (40.0)
Elevated protein (adjusted for age)	5/20 (25.0)
Normal glucose (>60% serum glucose)	20/20 (100.0)
CSF specific oligoclonal bands	7/17 (41.2)
Elevated IgG index (>70)	3/15 (20.0)

Abbreviations: CNS = central nervous system; MOG = myelin oligodendrocyte glycoprotein; IgG = immunoglobulin G; AQP4 = aquaporin 4; CSF = cerebral spinal fluid; WBC = white blood cell.
[a]Serum/CSF results not available for all patients, with sample size shown for each variable based on available data.

Twenty patients underwent a lumbar puncture for CSF analysis (Table 3). This revealed a lymphocytic pleocytosis (WBC > 5 per mm^3 with lymphocytic predominance) in 8 (40.0%). All 20 (100.0%) patients had normal CSF glucose (>60% serum glucose). Eight (40.0%) had elevated CSF protein (>0.45 g/L), but only 5 (25.0%) had elevated CSF protein when adjusted for age.[30] Oligoclonal bands were tested in 17 patients and 7 (41.2%) had CSF specific oligoclonal bands (3 new diagnosis of RRMS, 3 post-vaccine TM, 1 MS relapse). CSF IgG index was assessed in 15 patients and elevated in 3 (20.0%).

Patients were followed for a median of 299 days (range 6–473). Diagnoses at last available follow-up were new onset RRMS ($n=16$), post-vaccine TM ($n=7$), clinically isolated syndrome (CIS) ($n=5$), MS relapse ($n=4$), post-vaccine tumefactive demyelination ($n=2$), MOGAD ($n=1$), NMOSD ($n=1$), PACA ($n=1$) and chronic lymphocytic inflammation with

pontine perivascular enhancement responsive to steroids (CLIPPERS) ($n=1$). All four patients with pre-existing RRMS had an MS relapse. Twenty-two (57.9%) received acute treatment with intravenous (IV) methylprednisolone ($n=16$), high-dose pulse oral prednisone ($n=5$) or oral dexamethasone ($n=1$). The remaining 16 (42.1%) did not receive acute treatment. Of those who received acute treatment, eight had an inadequate response and went on to receive plasma exchange therapy (PLEX) ($n=5$), repeat IV methylprednisolone ($n=2$) or IV immunoglobulin ($n=1$). Sixteen (42.1%) patients completed a tapering course of oral prednisone. At the time of last follow-up, 78.9% had partial recovery ($n=30$), 18.4% returned to baseline ($n=7$) and 2.6% had worsening ($n=1$). The median follow-up EDSS score was 2 (range 0–6.5) and was performed at a median of 141 (range 6–473) days from symptom onset.

At the time of last follow-up, 21 (55.3%) were on DMT. This included three patients with pre-existing RRMS, who were switched to a different DMT (glatiramer acetate to ofatumumab ($n=1$), interferon beta-1a to ocrelizumab ($n=1$) and ocrelizumab to cladribine ($n=1$)) and 17 with a new diagnosis of MS/CIS who were started on a range of DMTs (Table 4). The patient with PACA was started on cyclophosphamide. One patient with NMOSD was initially started on mycophenolate mofetil, but this was discontinued due to oral ulcers. At the time of last follow-up, the patient was waiting to start rituximab. The remaining 16 (42.1%) did not start long-term treatment (7 post-vaccine TM, 3 CIS, 2 tumefactive demyelination, 1 RRMS, 1 MS relapse, 1 MOGAD and 1 CLIPPERS). Table 4 outlines diagnosis, treatment and outcome data.

Repeat MRI brain and/or spinal cord was performed in 28 patients at a median of 180 days (range 39–405) from symptom onset (Table 2). Compared to the initial MRI, 35.7% had improvement ($n=10$), 32.1% had worsening ($n=9$), and 32.1% had stable lesion burden ($n=9$).

Data on subsequent vaccination were available for 34 patients (Table 5). Sixteen (47.1%) went on to have subsequent COVID-19 vaccination (10 had one additional vaccine and 6 had two additional vaccines) (12 RRMS, 2 CIS, 1 MOGAD and 1 tumefactive demyelination). Following subsequent vaccination, 14 (87.5%) had no adverse events and 2 (12.5%) experienced new or recurrent neurological symptoms (both had new diagnosis of RRMS after a prior vaccine). The first patient developed focal numbness of the fifth digit 21 days after a second vaccine dose. It was unclear if this represented a relapse, symptom recrudescence or focal nerve injury, but given the mild nature of symptoms the patient did not require acute therapy. The second patient experienced recurrent right eye pain, vision loss, bilateral leg weakness, bilateral foot numbness and cognitive disturbance 2 days after receiving a second vaccine dose. Repeat MRI did not reveal radiologic evidence of disease activity, and this event was suspected to be symptom recrudescence, rather than a new demyelinating attack.

Discussion

We identified 38 patients with acute CNS inflammation following COVID-19 vaccination. To our knowledge, this represents the largest cohort study to date describing clinical, radiologic, laboratory and outcome data. Our study revealed a female predominance and median age of 39 years, which is similar to previous reports.[6,7] Unlike previous studies, our cohort included only a handful of patients with pre-existing immune-mediated disease.[27] Although our inclusion criteria allowed the identification of patients presenting with neurological symptoms up to 60 days following COVID-19 vaccination, patients in our cohort presented after a median of only 15 days. The Pfizer-BioN-Tech vaccine was the most common vaccine received prior to symptom onset, followed by Moderna and AstraZeneca. This likely reflects differences in the availability of COVID-19 vaccines in Ontario at the time of the study and does not imply that CNS inflammatory events are more likely to occur with the Pfizer-BioN-Tech vaccine.[2]

Numbness and weakness were the most common symptoms in our cohort, and TM was the predominant clinical syndrome. It is unclear if post-vaccination CNS inflammatory events are more likely to affect the spinal cord than the brain or if inflammatory events involving the spinal cord are more likely to result in symptoms that bring patients to medical attention. Our cohort had a median follow-up duration of 299 days. The most common diagnosis at last follow-up was new onset RRMS, followed by post-vaccine TM, CIS, MS relapse, post-vaccine tumefactive demyelination, MOGAD, NMOSD, PACA and CLIPPERS. Although CLIPPERS has been reported following influenza vaccination, this is the first report of CLIPPERS following COVID-19 vaccination that we are aware of.[31] To our knowledge, this is also the first report of PACA following COVID-19 vaccination; however, vaccination against several agents has been known to precede the development of other cerebellar disorders, namely paediatric acute cerebellar

Table 4. Diagnosis, treatment and outcome.

	Patients with CNS inflammatory event, *n* = 38
Duration of follow up, median days (range)	299 (6–473)
Diagnosis at last follow up, *n* (%)	
RRMS	16 (42.1)
Post-vaccine TM	7 (18.4)
CIS	5 (13.2)
MS relapse	4 (10.5)
Post-vaccine tumefactive demyelination	2 (5.3)
MOGAD	1 (2.6)
NMOSD	1 (2.6)
PACA	1 (2.6)
CLIPPERS	1 (2.6)
Acute treatment 1, *n* (%)	
IV methylprednisolone	16 (42.1)
High dose pulse PO prednisone	5 (13.2)
PO dexamethasone	1 (2.6)
None	16 (42.1)
Acute treatment 2, *n* (%)	
PO prednisone taper	16 (42.1)
PLEX	5 (13.2)
IV methylprednisolone	2 (5.3)
IVIG	1 (2.6)
None	14 (36.8)
EDSS at last follow up, median (range)	2 (0–6.5)
Time of last EDSS from symptom onset, median days (range)	141 (6–473)
Outcome at last follow up, *n* (%)	
Partial recovery	30 (78.9)
Baseline	7 (18.4)
Worsening	1 (2.6)
DMT by diagnosis at last follow up, *n* (%)	
RRMS	
Ocrelizumab	4/16 (25.0)
Dimethyl fumarate	4/16 (25.0)
Ofatumumab	3/16 (18.8)
Glatiramer acetate	2/16 (12.5)
Natalizumab	1/16 (6.3)
Unknown	1/16 (6.3)
None	1/16 (6.3)
Post-vaccine TM	
None	7/7 (100.0)
CIS	
Glatiramer acetate	2/5 (40.0)
None	3/5 (60.0)
MS relapse	
Ofatumumab	1/4 (25.0)
Cladribine	1/4 (25.0)
Waiting to start ocrelizumab	1/4 (25.0)
None	1/4 (25.0)
Post-vaccine tumefactive demyelination	
None	2/2 (100.0)

(Continued)

Table 4. (Continued)

	Patients with CNS inflammatory event, $n=38$
MOGAD	
None	1/1 (100.0)
NMOSD	
Waiting to start rituximab	1/1 (100.0)
PACA	
Cyclophosphamide	1/1 (100.0)
CLIPPERS	
None	1/1 (100.0)

Abbreviations: CNS = central nervous system; RRMS = relapsing remitting multiple sclerosis; TM = transverse myelitis; CIS = clinically isolated syndrome; MOGAD = myelin oligodendrocyte glycoprotein antibody disease; NMOSD = neuromyelitis optica spectrum disorder; PACA = primary autoimmune cerebellar ataxia; CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; IV = intravenous; PO = by mouth; PLEX = plasmapheresis; IVIG = intravenous immunoglobulin; EDSS = expanded disability status scale; DMT = disease-modifying therapy.

Table 5. Subsequent COVID-19 vaccination.

	Patients with CNS inflammatory event, $n=38$[a]
Received subsequent COVID-19 vaccine, *n* (%)	
Yes	16/34 (47.1)
No	18/34 (52.9)
Outcome following subsequent COVID-19 vaccine, *n* (%)	
No adverse events	14/16 (87.5)
New or recurrent neurological symptoms	2/16 (12.5)
Symptom recrudescence	1/16 (6.3)
Unknown	1/16 (6.3)

Abbreviations: CNS = central nervous system.
[a]Not available for all patients, with sample size shown for each variable based on available data.

ataxia.[32] Patients in our cohort generally responded well to high-dose oral or IV steroids; however, some required additional acute treatment. At the time of last follow-up, most patients had partial recovery, with some returning to baseline and only a couple with worsening symptoms. Just over half of the patients started DMT, which was determined by their diagnosis and disease severity.

We assessed the effects of subsequent COVID-19 vaccination in our cohort, which was given to patients with a range of diagnoses including RRMS, CIS, MOGAD and tumefactive demyelination. Although two patients with RRMS experienced new or recurrent neurological symptoms, there was no definitive new inflammatory activity associated with subsequent vaccination. This reflects existing data demonstrating that COVID-19 vaccination is safe in MS and MOGAD, with no increased risk of relapse activity following vaccination compared to other time periods.[33,34] None of the patients with post-vaccine TM received subsequent vaccination in this study. Given the absence of features to suggest MS or other neuroinflammatory disease in this group, it was felt that an isolated TM was more likely to be related to the vaccine, which may have prevented patients from receiving subsequent vaccination in clinical practice.

There are limitations to our study. This was a retrospective observational study at a single centre. We cannot determine whether the rate of CNS inflammatory events was higher than expected. The rate of COVID-19 vaccination in the eligible general population was high during the time of the cases, with 90.5% having received one dose, 87.0% having received two doses, and 51.0% having received three doses in Ontario by 15 September 2022.[35] The BARLO MS Centre is a tertiary referral centre, and we could not capture an accurate denominator for the cases in this study. Furthermore, we could not accurately compare

the incidence of cases in our study to the usual incidence of cases seen at our centre prior to March 2021 due to several factors that have increased referral rates over time. Importantly, our study cannot determine a causal relationship between the COVID-19 vaccines and CNS inflammatory events. The presence of T1 black hole lesions in six patients with a new diagnosis of RRMS and one with CIS suggests that these individuals may have had pre-existing clinically silent disease activity. Similarly, the COVID-19 vaccine may have unmasked previously silent disease in patients with a new diagnosis of RRMS or CIS who met dissemination in space criteria on MRI but did not have a multifocal clinical presentation. This hypothesis is supported by prior studies suggesting that in general, vaccines may accelerate the transition from subclinical to overt demyelinating disease without a longer-term or causal association[25] and that COVID-19 vaccines only have a weak association with CNS demyelinating diseases, with a low risk similar to other viral vaccines.[26] The BARLO MS Centre evaluates patients from a diverse population across Toronto and Ontario. However, data were not readily available on race, ethnicity or socioeconomic status, which may limit generalizability. The inclusion of patients presenting within 60 days after vaccination may underestimate or overestimate the number of individuals with a CNS inflammatory event that is temporally related to the vaccine.

In summary, we present 38 cases of acute CNS inflammation following COVID-19 vaccination. Clinical, laboratory and imaging features were heterogenous, and most patients had a favourable outcome. Repeat COVID-19 vaccination was not associated with recurrent CNS inflammatory events in our cohort. Our study could not determine whether the rate of CNS inflammatory events was higher than expected, and large prospective controlled studies are needed to evaluate for a relationship between COVID-19 vaccines and acute CNS inflammation. Currently, it seems that the benefits of vaccination against COVID-19 outweigh the risk of developing CNS inflammatory disease.

Acknowledgements

The authors thank the BARLO MS Centre and its clinicians for the identification of study participants and access to clinical records.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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