DOI: *http://dx.doi.org/10.18502/cjn.v23i1.16430*

Current Journal of Neurology

Original Paper

Curr J Neurol 2024; 23(1): 21-38

New diagnosis of multiple sclerosis in the setting of recent Sinopharm COVID-19 vaccine (BBIBP-CorV) exposure: A series of clinical cases and updated review of the literature

Received: 05 Sep. 2023
Accepted: 06 Nov. 2023

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Keywords
COVID-19; COVID-19 Vaccines; Multiple Sclerosis; CNS Demyelinating Autoimmune Diseases; Safety; Demyelinating Diseases

Abstract

Background: Multiple sclerosis (MS) is the most common cause of non-traumatic disability in young individuals. There are limited reports of developing demyelinating events following the coronavirus disease 2019 (COVID-19) vaccination.

Methods: We reported all individuals (n = 8) with new MS diagnoses with recent exposure (≤ 6 weeks) to the Sinopharm (BBIBP-CorV) vaccine between September 2021 and June 2022. We also reviewed the related literature published as of September 2023.

Results: Of 338 newly diagnosed patients with MS who attended our tertiary referral MS center during the study period, 8 (2.36%) had their first demyelinating attack with a median interval of 2 [2.0, 4.0] weeks following the Sinopharm vaccine (sex ratio 1:1, median age: 20.5 [18.0, 27.0] years). No personal or family history of autoimmune/neurological disorders was documented, except for one patient's history of a previous potential demyelinating event and another's family history of immune thrombocytopenic purpura (ITP).

How to cite this article: Paybast S, Jameie M, Shahbazi M, Habibi MA, Mohammadianinejad SE, Harirchian MH. New diagnosis of multiple sclerosis in the setting of recent Sinopharm COVID-19 vaccine (BBIBP-CorV) exposure: A series of clinical cases and updated review of the literature. Curr J Neurol 2024; 23(1): 21-38.

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All patients had demyelinating brain MRI lesions, and 4 had cervical spinal cord involvement. The brain areas most commonly affected were the periventricular and subcortical regions. Positive oligoclonal bands (OCBs) in all patients supported the MS diagnosis. All patients were diagnosed with relapsing-remitting MS and received intravenous methylprednisolone (IVMP) alone or in combination with plasma exchange (3/8). Rituximab was the most frequently used disease-modifying treatment (3/8).

Conclusion: This study provides preliminary evidence of a potential association between the Sinopharm vaccine and the initial manifestations of MS. However, further larger-scale studies with control groups and long-term follow-ups are needed to confirm this association and determine the underlying mechanisms.

Introduction

Coronavirus disease 2019 (COVID-19), a highly contagious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was initially reported in December 2019.[1] Since the onset of the COVID-19 pandemic,[2] it has been linked to significant mortality and morbidity,[3-7] profoundly impacting the mental and physical well-being of both patients and healthcare professionals.[8-10] There have also been reports of associated neurological manifestations.[11] In response to these challenges, vaccination has emerged as the most effective strategy for the mitigation of the associated mortality and morbidity.[12]

Multiple sclerosis (MS) is a demyelinating inflammatory disease of the central nervous system (CNS).[13] Genetic variants and environmental factors, including vitamin D deficiency, obesity, smoking, and the Epstein-Barr virus are the factors associated with MS.[14,15] Notably, several studies have explored the potential involvement of viral infections in the pathogenesis of MS.[15-18] Recent reports on the co-occurrence of SARS-CoV-2 infection and neuroimmunological disorders have raised questions about their potential association.[19-21] A similar discourse has emerged concerning the impact of SARS-CoV-2 vaccination on neuroimmunological disorders.[22-30]

The relationship between vaccines and the potential risk of demyelinating diseases has long been an area of research interest,[31-36] with controversy surrounding this association.[34,35] However, except for the yellow fever vaccine,[36] there is no sufficient evidence to indicate a causal association between most vaccines, including hepatitis B, human papillomavirus (HPV), influenza, and "measles, mumps, and rubella" (MMR), and MS activity.[31,33-35] Recently, concerns regarding neurological adverse events following immunization (AEFI) with SARS-CoV-2 vaccines have arisen,[26-28,37,38] including limited reports of the CNS demyelinating events potentially associated with these vaccines.[22-25,28,30,39-43]

In this case series, we have reported 8 individuals who experienced the initial manifestations of MS within a temporal relationship (≤ 6 weeks) with the Sinopharm vaccine exposure. This case series is unique for two primary reasons. Firstly, while studies evaluating MS relapse following SARS-CoV-2 vaccination among patients with established MS have been conducted,[29,44,45] reports regarding the new onset of the disease in seemingly healthy individuals still remain limited. Secondly, the existing literature predominantly concentrates on vaccines other than the Sinopharm (BBIBP-CorV) vaccine.[22-25,28,30,39-41] Notably, except for one case series,[46] we are not aware of any previously published article concerning a new diagnosis of MS after vaccination with Sinopharm (BBIBP-CorV).

Materials and Methods

Study design and ethics statement: This is a single-center case series of prospectively collected data on 8 consecutive individuals with their first CNS demyelinating event following SARS-CoV-2 vaccination. These individuals attended an academic hospital affiliated with the Tehran University of Medical Sciences, Tehran, Iran, between September 2021 and June 2022. This study was approved by the institutional review board (IRB) of the Tehran University of Medical Sciences, Tehran, Iran, and followed the CAse REports (CARE) guideline.[47] According to the declaration of Helsinki, patients' anonymity and confidentiality were protected, and informed consent was obtained.[48]

Study population: All individuals attending the hospital (whether they were referred to the hospital or self-referred) during the study period with the following criteria were eligible for inclusion: (a) new onset CNS demyelination symptoms, (b) SARS-CoV-2 vaccination in the past 6 weeks, lack of infection with SARS-CoV-2 during this interval, (c) a neurologist-confirmed diagnosis of MS.[49] A 6-week time frame was chosen based on the typical time frame suggested

for neurological AEFI (Table 1).[50] No limitations were imposed regarding patients' age, or the type of vaccine received.

Study measures: The following information was collected by a neurology resident (M.SH.) and double-checked by 3 MS specialists (S.P., MH.H., and SE.M.) to validate the accuracy of the collected data: (a) demographics, past medical history (PMH), familial, and habitual history through the in-person interview, (b) vaccine-related characteristics according to the COVID-19 vaccination cards (type, dose, and the received date), (c) MS-related clinical, laboratory, and neuroimaging characteristics [initial presentations and severity of MS attack, the interval between vaccination and the disease onset, cerebrospinal fluid (CSF) oligoclonal bands (OCBs) and IgG index, as well as brain, cervical spine, and thoracic spine magnetic resonance imaging (MRI) findings], (d) acute phase management, and the chosen disease-modifying therapy (DMT).

MS diagnosis was established based on the McDonald criteria 2017 and confirmed by an expert in the field, according to the presence of typical MRI lesions and positive OCBs, as well as the absence of clinical or MRI red flags supporting alternative diagnoses.[49] Attack severity was defined based on increase in the Expanded Disability Status Scale (EDSS) on the day of maximal worsening: mild (< 1.0), moderate (1.0-2.5), and severe (≥ 3.0).[51]

Quantitative and qualitative data are presented as median (interquartile range [IQR]), and number (percentage), respectively.

Results

Of the 338 newly diagnosed patients with MS during the study period, 8 (2.36%) had their first MS demyelinating attack in temporal association with the Sinopharm vaccine. Moreover, 4 of the 8 patients were women, and their median age was 20.5 [18.0, 27.0] years. Except for a history of a probable previous demyelinating event in 1 patient and a familial history of immune thrombocytopenic purpura (ITP) in another, no personal or familial history of autoimmune or neurological conditions was reported. In addition, 6 patients reported symptom onset after the 2nd vaccine dose, and the median interval between the 1st (v1)/ 2nd (v2) dose and symptom initiation was 2.0 [2.0, 4.0] weeks. Initial presentations varied from mild sensory syndrome to severe multifocal disseminated demyelination. Attack severity was moderate in most patients (5/8).

Brain MRI revealed demyelinating lesions in all (8/8) patients. Periventricular and subcortical regions were the most frequently affected brain regions, with lesions observed in 7 and 6 patients, respectively. Other affected brain regions include juxtacortical (3/8), cortical (2/8), and the brain stem (3/8). Spinal cord involvement was seen in 4, with the upper and lower cervical spine involvement in 2 and 2 patients, respectively. Gadolinium-enhanced lesions were observed in 4 patients (patients 2, 5, 6, and 8). Notably, apart from 1 patient (patient 3) who exhibited multiple hypointense lesions in T1 sequences (black holes), no other patients displayed such findings in their T1 images.

Table 1. Suggested criteria for labelling causality in immune-associated neurological adverse events following immunization (AEFI) suggested by Butler et al.[50]

Causality	Time frame*		Risk factor		Alternative etiology	Notes
Probable	< 6 week	AND	No risk factors	AND	No indication of an alternative etiology	Ruling out other risk factors or etiologies identified by clinical, laboratory, radiological and electrophysiological assessment, as indicated
Possible	6-12 week	AND/ OR	There may be an indication of an alternative etiology, but unlikely to explain the event	AND /OR	There may be an indication of an alternative risk factor, but unlikely to explain the event	e.g., presence of a previous episode of Bell's palsy in a patient with post-vaccination Bell's palsy
Unlikely	< 24 hour or > 12 week	AND/ OR	Alternative etiology fully explains the event	AND /OR	Alternative risk factor fully explains the event	e.g., Campylobacter diarrhea preceding Guillain-Barré syndrome

AEFI: Adverse events following immunization
*Time interval between immune-associated AEFI and vaccination

Thoracic MRIs were unremarkable in all patients. Positive OCBs supported MS diagnosis in all patients. With a relapsing-remitting MS (RRMS) diagnosis, all patients received intravenous methylprednisolone (IVMP) with oral tapering. Of the 8 patients, 3 required therapeutic plasma exchange (TPE). All patients achieved marked clinical recovery. Rituximab (3/8) and dimethyl fumarate (DMF) (2/8) were the most frequently prescribed DMTs (Table 2).

According to the criteria proposed by Butler et al. for labeling causality in immune-associated neurological AEFI[50] (Table 1), 7 out of 8 patients were classified as "probably" related (AEFI occurring within 6 weeks after vaccination with no indication of an alternative etiology or no risk factors). Patient number 3 was deemed "unlikely" to be associated with the vaccine, since, although the event occurred within 6 weeks, it could be explained by an alternative etiology and/or risk factors.

Patient 1 was a 17-year-old man with a 5-day history of left facial numbness, initiated 2 weeks after v2. Neurological examination revealed decreased light touch sensation in the facial area innervated by the left trigeminal nerve's second (V2) and third (V3) divisions, and an EDSS score of 1.0. CSF analysis revealed 4 OCBs. Serum and CSF evaluations were negative for inflammatory, metabolic, and infectious diseases. Neuromyelitis optica-antibody (NMO-antibody) and anti-myelin oligodendrocyte glycoprotein (anti-MOG) IgG were negative. Brain MRI demonstrated a few non-enhancing ovoid T2 periventricular and subcortical lesions and 1 cortical lesion.

A cervical MRI revealed no specific findings. With RRMS diagnosis, IV-MP (1 gr/day, 3 days) was given, leading to a complete symptom recovery. DMF was then initiated (120 mg daily, titrated to 240 mg twice a day).

Patient 3 was a 39-year-old female smoker with a 7-day history of right upper limb paresis 2 weeks after v2. She reported a history of 3 days of right facial numbness 15 years ago. Neurological examination revealed generalized hyperreflexia and right upper limb mono-paresis (power 3/5 according to the Medical Research Council [MRC] muscle strength scale). EDSS was estimated to be 2.5. Extensive laboratory assessments revealed no abnormal findings in the serum and CSF except for 5 OCBs restricted to the CSF. The brain and cervical spine MRIs demonstrated slight, generalized atrophy, multiple non-enhancing hyperintense lesions, predominantly in juxtacortical and periventricular locations, and a short-segment, non-enhancing C2 lesion (Figure 1). Moreover, multiple black hole lesions were observed in T1 sequences. With a diagnosis of RRMS, IV-MP (1 gr/day, 5 days) was commenced, followed by rituximab (1 gr biannually). A previous history of facial numbness and MRI alterations (atrophy and black holes) suggest a latent demyelinating process initiated years ago. She achieved a significant recovery and was discharged with an EDSS score of 1.0.

Patient 4 was a 29-year-old male smoker with left leg debility initiated a week after v2. Neurological examination exhibited a muscle strength of 4/5 in his left lower limb with an upward plantar reflex and EDSS score of 2.5. CSF analysis demonstrated a mildly elevated IgG index (0.78) and 9 unique OCBs. Brain MRI revealed a few non-enhancing periventricular and subcortical demyelinating lesions. A cervical MRI revealed 2 short-segment lesions without gadolinium enhancement. With a diagnosis of RRMS, IV-MP (1 gr/d, 3 days) was started, markedly improving his symptoms. Subsequently, fingolimod (0.5 mg) was started under 6 hours of cardiac monitoring.

Patient 5 was a 14-year-old girl with acute diplopia 2 weeks after v1. Neurological examination revealed right 6th nerve palsy, with an EDSS of 1.5. Except for 11 unique CSF OCBs, serum and CSF analysis did not indicate other abnormalities. Brain MRI showed numerous ovoid T2 periventricular, subcortical, cortical, and brain stem lesions, some of which showed abnormal gadolinium enhancement. The cervical spine MRI was normal (Figure 2). With a diagnosis of RRMS, IV-MP (1 gr/day, 5 days) and TPE were started (5 exchanges daily with 1.5-liter plasma volume, using 5% albumin as a replacement fluid). Rituximab was chosen as DMT (1 gr biannually). She achieved a complete recovery at discharge.

Patient 6 was a 16-year-old girl with acute onset painful blurred vision 5 weeks after v2. Neurological examination revealed a reduced right-side visual acuity of "light perception" with a relative afferent pupillary defect (RAPD). Fundal examination showed pink disks with sharp margins. CSF analysis revealed an elevated IgG index (0.92) and 6 OCBs on isoelectric focusing.

Brain MRI revealed a few T2 subcortical, midbrain, and MCP lesions, one of which demonstrated nodular gadolinium enhancement.

Table 2. Part I: Demographic, vaccine-related, MS-related, and management-related characteristics of patients with a new diagnosis of MS

Variable	Case 1	Case 2	Case 3	Case 4
Age	17	25	39	29
Sex	M	M	F	M
PMH	Neg	Neg	Facial numbness	Neg
HH	Neg	Neg	Smoking (20 PY)	Alcohol, Smoking (15 PY)
FH	Neg	Neg	Neg	Neg
Vaccine	Sinopharm	Sinopharm	Sinopharm	Sinopharm
Vaccine dose	v2	v1	v2	v2
Interval*	2 W	4 W	2 W	1 W
Manifestation	Lt. facial numbness	Quadri-paresthesia	Rt. upper limb paresis	Lt. lower limb paresis
Attack severity	Mild	Moderate	Moderate	Moderate
Laboratory	4 OCBs (CSF)	6 OCBs (CSF)	5 OCBs (CSF)	Elevated IgG index, 9 OCBs (CSF)
Brain MRI	Few non-enhancing PV and SC lesions, One cortical lesion	One enhancing lesion in the Rt. MCP, Few non-enhancing PV lesions	Slight generalized atrophy, Multiple non-enhancing lesions, predominantly in JC and PV, Multiple black hole lesions in T1 sequences imaging	Few non-enhancing PV and SC lesions
Cervical MRI	Normal	One ss lower cervical, non-enhancing lesion	One ss C2 non-enhancing lesion	Two ss non-enhancing lesions
Thoracic MRI	Normal	Normal	Normal	Normal
Acute management	IVMP (3 gr)	IVMP (5 gr)	IVMP (5 gr)	IVMP (3 gr)
DMT	DMF	DMF	RTX	FG
Causality**	Probable	Probable	Unlikely	Probable

Table 2. Part II: Demographic, vaccine-related, MS-related, and management-related characteristics of patients with a new diagnosis of MS

Variable	Case 5	Case 6	Case 7	Case 8
Age	14	19	20	21
Sex	F	F	M	F
PMH	Neg	Neg	Neg	Neg
HH	Neg	Neg	Smoking (15 PY)	Neg
FH	Neg	Neg	ITP	Neg
Vaccine	Sinopharm	Sinopharm	Sinopharm	Sinopharm
Vaccine dose	v1	v2	v2	v2
Interval*	2 W	5 W	2 W	4 W
Manifestation	Acute diplopia, Rt. 6th nerve palsy	Acute onset blurred vision, Rt. declined VA (light perception), RAPD^{+}	Acute onset blurred vision, Rt. Declined VA (6/10), RAPD^{+}	Rt. facial numbness, Impaired ocular movement, Rt. 6th nerve palsy, Walking difficulty, Ataxia
Attack severity	Moderate	Severe	Moderate	Severe
Laboratory	11 OCBs (CSF)	IgG index ↑, 6 OCBs (CSF)	5 OCBs (CSF)	6 OCBs (CSF)
Brain MRI	Numerous PV, SC, cortical, and brain stem lesions, Some of which enhanced with gadolinium	Few SC, midbrain, MCP lesions, One of which demonstrated nodular gadolinium enhancement	Few non-enhancing lesions within the PV, JC, and SC	Two JC lesions, Numerous PV and SC lesions, some of which enhanced with gadolinium

Table 2. Part II: Demographic, vaccine-related, MS-related, and management-related characteristics of patients with a new diagnosis of MS (continue)

Variable	Case 5	Case 6	Case 7	Case 8
Cervical MRI	Normal	Normal	Normal	Two non-enhancing, ss upper cervical lesions
Thoracic MRI	Normal	Normal	Normal	Normal
Acute management	IVMP (5 gr), TPE (5 sessions)	IVMP (7 gr), TPE (5 sessions)	IV-MP (5 gr)	IV-MP (5 gr), TPE (5 sessions)
DMT	RTX	GA	INF-β 1a	RTX
Causality**	Probable	Probable	Probable	Probable

CSF: Cerebrospinal fluid; DMF: Dimethyl fumarate; DMT: Disease-modifying treatment; F: Female; FG: Fingolimod; FH: Familial history; GA: Glatiramer acetate; HH: Habitual history; INF-β 1a: Interferon-beta 1a; ITP: Immune thrombocytopenic purpura; IV: Intravenous; IVMP: Intravenous methylprednisolone; JC: Juxtacortical; Lt: Left; M: Male; MCP: Middle cerebellar peduncle; MP: Methylprednisolone; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; Neg: Negative; OCB: Oligoclonal band; PMH: Past medical history; PV: Periventricular; PY: Pack-years; RAPD: Relative afferent pupillary defect; Rt: Right; RTX: Rituximab; SC: Subcortical; ss: Short segment; TPE: Therapeutic plasma exchange; VA: Visual acuity; v1: 1st vaccine does; v2: 2nd vaccine dose; W: weeks

*The interval between MS symptoms onset and SARS-CoV-2 vaccination

**According to the causality criteria suggested by Butler et al.[50]

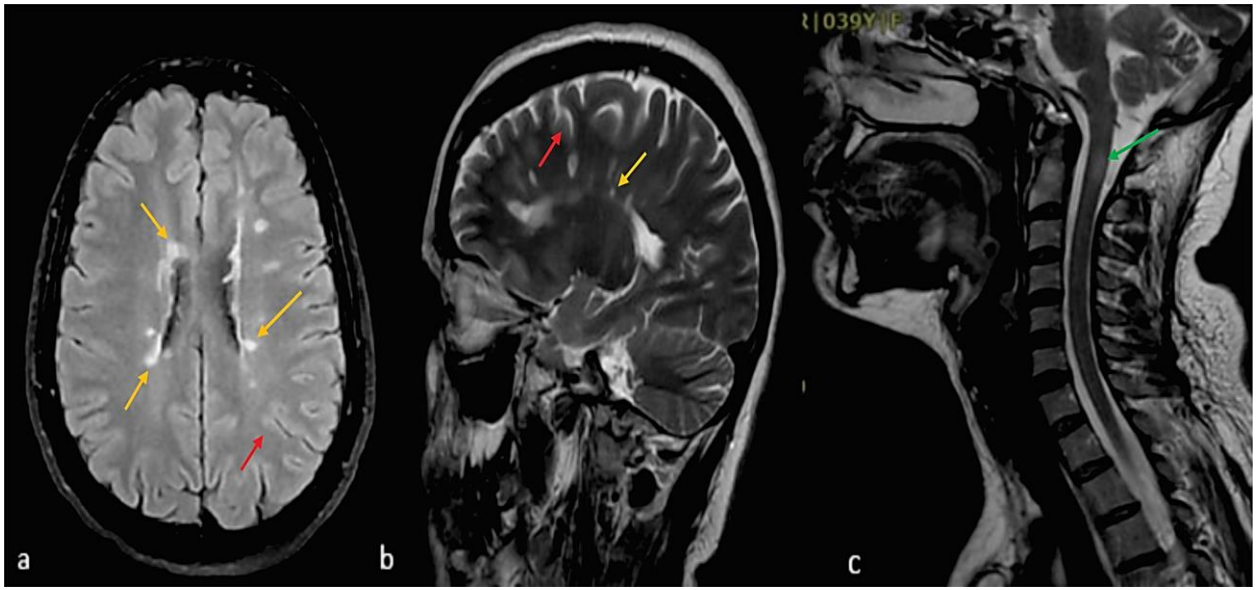

Figure 1. Patient 3; (a, b) multiple ovoid hyperintense lesions predominantly in juxtacortical (red arrows) and periventricular (yellow arrows) locations in axial T2-weighted fluid-attenuated inversion recovery (FLAIR) (a) sagittal T2, (b) sequences, (c) small T2 higher cervical hyper-intense lesion (green arrow) in the sagittal image

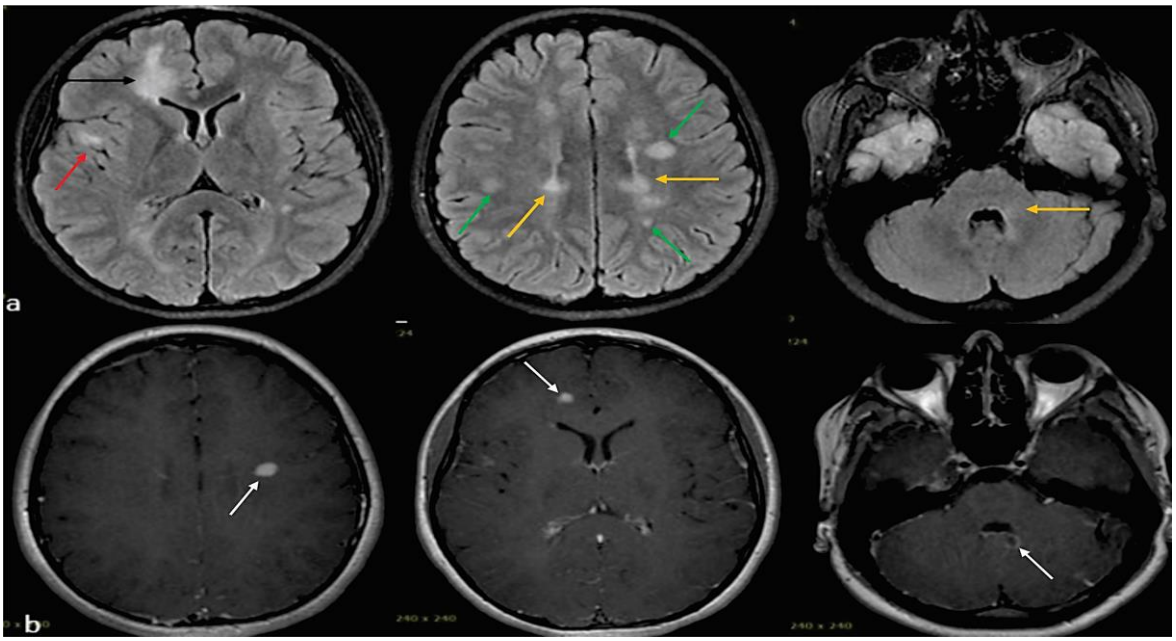

Figure 2. Patient 5; (a) multiple ovoid hyperintense lesions in juxtacortical (red arrow), subcortical (green arrows), and periventricular (yellow arrows, third and fourth ventricle) locations in axial T2-weighted fluid-attenuated inversion recovery (FLAIR), and one tumefactive-like lesion (black arrow), (b) evidence of gadolinium enhancement in some of the lesions (white arrows)

Orbital and cervical MRIs were unrevealing (Figure 3). The patient was diagnosed with RRMS, with an EDSS of 3.0, and initially treated with IV-MP (1 gr/day, 7 days), which failed to improve the visual acuity. Subsequently, she underwent 5 full-volume TPE courses, significantly improving her visual acuity (7/10). Glatiramer acetate was then initiated (40 mg/ml).

Patient 7 was a 20-year-old male smoker with acute blurred vision and pain in eye movements 2 weeks after v2. Familial history was positive for ITP. Neurological examinations revealed reduced visual acuity (6/10) and RAPD on the left side (EDSS of 1.5). Extensive evaluation covering the differential diagnostic possibilities was normal except for 5 unique CSF OCBs.

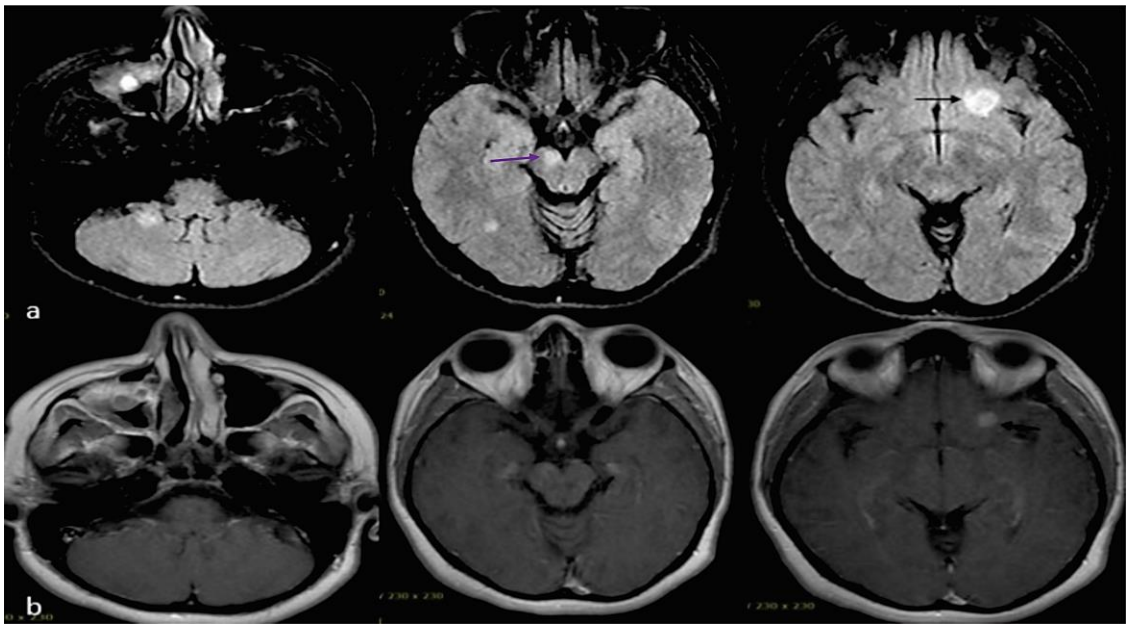

Figure 3. Patient 6; (a) few T2 midbrain (purple arrow) lesions, (b) evidence of nodular gadolinium enhancement in the tumefactive lesion (black arrow)

Brain MRI demonstrated a few demyelinating lesions within the periventricular, juxtacortical, and subcortical locations without gadolinium enhancement. Orbital and cervical MRIs were unrevealing. With RRMS diagnosis, he underwent a course of 3 g IV-MP (1 gr/day), leading to a complete clinical recovery. Interferon-beta 1a (INF-β 1a) was the chosen DMT (44 mg/ml).

Patient 8 was a 21-year-old woman with progressive right facial numbness, impaired ocular movement, and walking difficulty for 3 days. Symptoms developed 4 weeks after v2. Neurological examinations indicated right-side facial numbness, right abducens (VI) nerve palsy, generalized hyperreflexia, right ataxia, and positive left-side Babinski sign, with an EDSS of 4.0. Routine biochemistry, CSF assay, and autoimmune-related antibodies revealed no abnormalities except 6 CSF OCBs. Brian MRI showed 2 juxtacortical demyelinating lesions, as well as numerous periventricular and subcortical T2 demyelinating lesions, some of which were enhanced with gadolinium. A cervical MRI revealed two non-enhancing, short-segment upper cervical plaques. With a diagnosis of RRMS, she received IV-MP (1 gr/day, 5 days) along with 5 full-volume courses of TPE, which improved her symptoms considerably, albeit not completely (EDSS score of 1.0). DMT was planned with rituximab (1 gr biannually).

Discussion

In this series of clinical cases, we have reported 8 patients who had presented the first manifestations of MS in a close temporal relationship (≤ 6 weeks) to receiving the Sinopharm (BBIBP-CorV) vaccine.

The Sinopharm (BBIBP-CorV) vaccine, which is the most widely available SARS-CoV-2 vaccine in our country, Iran,[52] obtained the Emergency Used Listing in May 2021.[12,53] A retrospective cohort study, based on self-reported data from 517 vaccinated and 174 unvaccinated Iranian patients with MS, suggested that the BBIBP-CorV vaccine does not appear to affect short-term MS activity.[45] Although studies have shown acceptable SARS-CoV-2 vaccine safety profiles,[53-58] concerns regarding neurological AEs have begun to emerge, with vaccine-attributed headaches being the most frequently reported.[59] However, more serious neurological AEs, including Guillain-Barré syndrome,[60] Bells' palsy,[61] cerebral venous sinus thrombosis, ischemic stroke, and convulsive disorders, were also reported following SARS-CoV-2 vaccination.[62] A self-controlled case series on nearly 32 million vaccine receivers suggested an increased risk of some neurological AEFI, including Guillain-Barré syndrome, Bells' palsy, and hemorrhagic stroke, within 28 days of receiving ChAdOx1nCoV-19 or BNT162b2.[27] Remarkably, the author found no association between these vaccines and hospital admissions due to acute CNS demyelinating events.[27]

A general PubMed search using the following search query ((covid 19 vaccines [MeSH Terms]) AND ((multiple sclerosis [MeSH Terms]) OR (Demyelinating Autoimmune Diseases, CNS [MeSH Terms]))) AND (((((("initial"[Title/Abstract]) OR ("first"[Title/Abstract])) OR ("new"[Title/Abstract])) OR ("onset"[Title/Abstract])) OR ("new onset"[Title/Abstract])) revealed that as of September 5, 2023, there are very few studies specifically addressing the new diagnosis of MS following SARS-CoV-2 vaccination, and are primarily limited to case reports and case series.[22-25,30,40,42,43,46] A systematic review of patients with CNS demyelinating events after SARS-CoV-2 vaccination suggested that MS-like presentations were among the most frequently reported.[28] According to the authors' findings up until September 2021, 12 individuals were reported with MS-like presentations following SARS-CoV-2 vaccination, of which 6 were MS relapses and 4 were diagnosed with the first MS episode without any previous history of neurological dysfunction.[28] In a more recent case-report-based systematic review, the authors presented 11 reported individuals with new diagnoses of MS following SARS-CoV-2 vaccination as of March 1st, 2022.[63] For comprehensive insights, in table 3, we have provided detailed characteristics of 7 related studies published as of September 5, 2023, collectively encompassing a total of 26 reported cases with new MS diagnoses following immunization with SARS-CoV-2 vaccines.[22-25,30,40,42,43,46]

Most of the patients (22/26) were women and the age at MS diagnosis ranged from 19 to 66 years. PMH was reported in all patients except 3 (p5 in the study by Toljan et al.,[22] p2 and p4 in the study by Nistri et al.[43]). Accordingly, 9/26 patients had no remarkable PMH, 1/26 had unknown background,[24] and 7/21 had a previous history of non-neurological conditions (hypothyroidism [n = 2],[30,46] hyperthyroidism [n = 1],[46] thyroid cancer [n = 1],[42] hypertension [n = 1],[46] asthma [n = 1],[46] obsessive-compulsive disorder [n = 3],[46] depression [n = 1],[46] and iron-deficiency anemia [n = 3][46]).

Table 3. Part I: Studies specifically addressing the new diagnosis of MS following SARS-CoV-2 vaccination

Study	Design	N	Sex	Age (year)	PMH, FH	Vaccine type (dose)	Int.
Fujimori et al.[25]	Case report	1	F	40	recovered Lt. facial palsy (4 years ago) FH: N/A	BNT162b2 (v2)	2w
Havla et al.[24]	Case report	1	F	28	Unknown background likely pre-existing subclinical inflammatory, CNS disease, unremarkable history of previous relapses, FH: MS in a paternal cousin	BNT162b2 (v1)	6d
Khayat-Khoei et al.[23]	Case series‡ (n = 7)	p2	F	26	PMH: Neg FH: N/A	mRNA-1273 (v2)	14d
		p5	M	33	PMH: Neg FH: N/A	BNT162b2 (v2)	1d
Mathew and John[41]	Case report	1	F	24	PMH: Lt. facial numb., Lt. upper limb weakness (4 years ago, self-improved in a week), FH: N/A	AZD1222 (v2)	5d
Nistri et al.[43]	Case series (n = 16)##	p2	F	48	PMH: N/A FH: N/A	AZD1222 (v1)	8d
		p4	F	66	PMH: N/A FH: N/A	AZD1222 (v1)	7d
		p9	F	39	first clinical CIS episode in 2019 with a complete recovery, FH: N/A	BNT162b2 (v1)	3d
Tagliaferri et al.[40]	Case report	1	F	32	PMH: Neg FH: N/A	BNT162b2 (v1)	7d
Toljan et al.[22]	Case series (n = 5)	p1	F	29	PMH: migraines FH: N/A	BNT162b2 (v1)	1d
		p2	M	37	PMH: Neg FH: N/A	Initiated: BNT162b2 (v1), Develope: BNT162b2 (v2)	v1 3d v2 3w
		p3	M	41	PMH: Neg FH: N/A	mRNA-1273 (v2)	~ 1m
		p4	F	46	unilateral optic neuritis at 38, previously unremarkable brain MRI FH: N/A	Initiated: mRNA-1273 (v1), Developed: mRNA-1273 (v2)	v1: N/A v2: 3d
		p5	F	43	N/A	BNT162b2 (v2)	5w
Watad et al.[30]	Case series*** (n = 27)	p7	F	45	PMH: Controlled hypothyroidism FH: N/A	BNT162b2 (v1)	7d
Kim et al.[42]	Case series‡‡ (n = 10)	p1	F	28	PMH: Neg FH: N/A	BNT162b2 (v2)	28d
		p2	F	29	PMH: thyroid cancer FH: N/A	BNT162b2 (v2)	8d
Ebrahimi et al.[46]	Case series (n = 12)	p1	M	24	PMH: Headache FH: Neg	BBIBP-CorV (v2)	14d
		p2	F	46	PMH: OCD, IDA, depression FH: Neg	BBIBP-CorV (v2)	3d

Table 3. Part I: Studies specifically addressing the new diagnosis of MS following SARS-CoV-2 vaccination (continue)

Study	Design	N	Sex	Age (year)	PMH, FH	Vaccine type (dose)	Int.
Ebrahimi et al.[46]	Case series (n = 12)	p3	F	42	PMH: hyperthyroidism, hypertension, Asthma FH: Neg	BBIBP-CorV (v1)	20d
		p4	F	21	PMH: IDA FH: MS in mother and cousin	BBIBP-CorV (v2)	2d
		p5	F	20	PMH: Neg FH: Neg	BBIBP-CorV (V2)	60d
		p6	F	23	PMH: Neg FH: MS in sister	BBIBP-CorV (v1)	10d
		p7	F	19	PMH: IDA, hypothyroidism, OCD FH: Neg	BBIBP-CorV (v2)	10d
		p8	F	50	PMH: OCD FH: Neg	AZD1222 (v2)	11d
		p9	F	30	PMH: Neg FH: Neg	BBIBP-CorV (v3)	6d

Table 3. Part II: Studies specifically addressing the new diagnosis of MS following SARS-CoV-2 vaccination

Study	Initial symptoms, signs	EDSS	MRI	Labs and CSF analyses	Treat., response	Notes
Fujimori et al.[25]	Rt. hand: numbness and sensory imp, ascended to Rt. Shoulder, Rt. cervical 5th-8th dermatome sensory imp	N/A	Brain: several PV or SC T2 hyperintense white matter lesions w/o Gad enhancement no brainstem lesions Cervical: a T2 hyperintense right spinal cord lesion with Gad enhancement at C5/C6 Thoracic: N/A	mildly elevated leukocytes protein and glucose: NL, OCB: pos, IgG index: 1.04, MBP < 102 pg/ml, IL-6 < 4.0 pg/ml, MOG-IgG: Neg	IVMP (3 g) recovered	The patient possibly had pre-existing subclinical inflammatory CNS disease before vaccination, since the patient already had several asymptomatic non-gadolinium enhanced brain lesions and oligoclonal IgG band on admission. Although she had a history of left peripheral facial nerve palsy that resolved after steroid therapy, we could not confirm the episode as her initial clinical manifestation of MS.
Havla et al.[24]	Lt. abdominal neuropathic pain sensory imp below the T6 level, Rt. abdominal wall and genital hypoesthesia, Lt. leg paresis	N/A	Brain: > 20 partially confluent lesions with spatial dissemination w/o Gad enhancement Cervical: NL Thoracic: a contrast-enhancing lesion at T6	Mild pleocytosis, OCB: pos, IgG index: N/A	IVMP (1st cycle: 5 g, 2nd cycle:10 g), TPE (No complete remission*)	Assuming that some of these vaccines do carry a small risk of autoimmune exacerbation, it is still unclear whether and how this might differ between the different vaccines and whether patients with pre-existing inflammatory CNS disease should be prioritized for any particular vaccine.
Khayat-Khoei et al.[23]	Rt. eye visual symptoms mild blurring, progressed over the next few days pain with eye movement OD, relative RAPD, decreased visual acuity, color desaturation OD, monocular central/inferior monocular deficit	0#	Brain: multiple (9) T2 hyperintense, PV, SC, posterior fossa lesions, with one Gad enhancement Spinal cord: multiple (> 2) T2 lesion, with one Gad-enhanced lesion	IgG index: 1.27, elevated cell count, protein and glucose: NL, OCB: Neg	IVMP (5 g) recovered	Our report is anecdotal and does not prove a cause-and-effect relationship between SARS-CoV-2 mRNA vaccines and active CNS demyelinating disease. We do not know the number of people with MS who were vaccinated against COVID-19 in the communities from which these cases were derived.
	Unilateral painless vision blurring, visual acuity (20/50 OS)	0	Brain: multiple (7) T2 hyperintense white matter lesions with a single gadolinium-enhancing lesion Spinal cord: one new T2 lesion, w/o Gad-enhancement	OCB: pos (> 5), elevated IgG index, normal CSF cell count, protein, and glucose. NMO antibody: Neg	IVMP (3 g) recovered	
Mathew and John[41]	Lt. upper and lower limbs paresthesia, Lhermitte's sign	N/A	lesions in the brain and spinal cord (not described), Two lesions in the brain and one in the spinal cord were enhancing	N/A	IVMP (5 g) partially improved**	She was diagnosed with MS in view of two episodes of neurological dysfunction four years apart (Dissemination in time) and multiple lesions on MRI in the brain and spinal cord (Dissemination in space) with a probable vaccine induced second relapse.

Table 3. Part II: Studies specifically addressing the new diagnosis of MS following SARS-CoV-2 vaccination (continue)

Study	Initial symptoms, signs	EDSS	MRI	Labs and CSF analyses	Treat., response	Notes
Nistri et al.[43]	Rt. eye visual acuity deficit	2.0	Brain: enhancing lesion in the corpus callosum, multiple white matter unenhanced lesions, and lesions in the occipital lobe Spine: NL	N/A	IVMP (N/A) marked improvement	Although the evidence of an association between vaccination and MS activity is still debated, a link between them has been suggested, within the first 30 days after immunization, given the possibility that vaccines may accelerate the transition from subclinical to clinical disease through a stimulation of the immune system.
	Visual disturbance, Rt. sided postural instability	2.5	Brain: multiple white matter lesions, four of them enhancing in the left para-trigonal and PV white matter Spine: NL	OCB: pos	IVMP (N/A) partial improvement	
	Rt. limbs dysesthesia	1.0	Brain: a new enhancing lesion in the mesencephalon Spine: NL	N/A	IVMP (N/A) good recovery	
Tagliaferri et al.[40]	Rt. sided weakness, Rt. hand fine motor weakness, word slurring, gait instability, diffuse Rt. sided weakness, Rt. upper and lower EXT diminished strength and sensation	N/A	Brain: multiple round hyperintensities in the white matter with restricted diffusion in the left pons Cervical: N/A Thoracic: N/A	elevated myelin basic protein, OCB: pos (> 6), IgG index: N/A	IVMP (3 g) response: N/A	Although it remains completely unclear, we associated the MS incidence with the vaccine based on the temporal relationship between receiving the vaccine and onset of symptoms. The purpose of this paper is not to definitely associate the COVID vaccine with the disease; rather, we aim to shed light on the possibility of this rare occurrence.
Toljan et al.[22]	Lt. leg acute onset weakness and numbness, Rt. arm paresthesia, Lt. arm weakness, orbiting sign, mild pronator drift, Lt. leg weakness, Lt. EXT marked hyperreflexia, Lt. leg: diminished vibratory sensation	N/A	Brain: multiple brain lesions, including several PV and JC white matter lesions with one enhancing lesion in the right centrum semiovale Cervical: NL Thoracic: N/A	Pleocytosis, IgG index: 0.71, OCB: pos (10)	IVMP (5 g) significant improvement	The association cannot be determined to be causal, as latent CNS demyelinating disease may unmask itself in the setting of an infection or a systemic inflammatory response.
	Lt. hand: paresthesia, paresthesia spread over the entire Lt. arm, urinary urgency, gait imbalance, Rt. sided internuclear ophthalmoplegia, Lt. arm isolated hyperreflexia	N/A	Brain: multiple PV non-enhancing T2/FLAIR hyperintensities Cervical: a C3-C4 cord T2 and STIR hyperintense lesion Thoracic: N/A	OCB: N/A, IgG index: N/A, Serum AQP4-IgG: Neg, MOG-IgG: Neg	High dose oral PSL, taper over 12 days, 3 days of 600 mg oral PSL, response: N/A	
	Bilateral foot numbness, progressive paraparesis, difficulty initiating voiding, Rt. Hemiparesis, Rt. facial droop	N/A	Brain: multiple intracranial PV and JC T2/FLAIR hyperintensities, with most lesions demonstrating contrast enhancement	Pleocytosis, IgG index: 5.82, OCB: pos (6), Serum AQP4-IgG: NegMOG-IgG: Neg	IVMP (5 g), TPE (5 sess) Oral PSL, No complete remission[¥]	

Table 3. Part II: Studies specifically addressing the new diagnosis of MS following SARS-CoV-2 vaccination (continue)

Study	Initial symptoms, signs	EDSS	MRI	Labs and CSF analyses	Treat., response	Notes
Toljan et al.[22]			Complete spinal cord: additional multifocal enhancing and non-enhancing T2 and STIR dorsal cord hyperintensities			
	Rt. leg intermittent numbness, bilateral arm pain, Lt. lateral abdomen burning sensation, Lt. foot drop, mild anisocoria, Rt. eye red desaturation w/o RAPD, symmetrically reduced strength in lower EXT, diffuse hyperreflexia with bilateral extensor response	N/A	Brain: PV and JC intracranial lesions with enhancement of the PV lesion Cervical and thoracic spine: multiple enhancing lesions in the spine	index: 1.83, OCB: pos (20), herpes viruses (HSV, VZV, EBV, CMV), WNV, Borrelia burgdorferi IgG and IgM: Neg VDRL: Neg MOG-IgG: Neg AQP4-IgG: Neg	IVMP (5 g) response: N/A	
	distal Rt. arm weakness, Rt. periorbital and palatal numbness	N/A	Brain: enhancing and non-enhancing temporal and callosal PV ovoid lesions, enhancement of the proximal Rt. trigeminal nerve Cervical: NL Thoracic: NL	OCB: pos (8), CSF cell counts: NL	IVMP (3 g), Symptoms, Improved	
Watad et al.[30]	Lt. leg weakness, Disequilibrium, lower limbs distal numbness	N/A	Brain: Multiple PV white matter changes Cervical: N/A Thoracic: N/A	OCB: pos IgG index: N/A	IVPM (5 g), Rapid improvement	Most of the reported disease were flares, which supports the idea of the delicate balance of immune homeostasis in such cases being momentarily tipped into a pro-inflammatory state by vaccination.
Kim et al.[42]	Unilateral optic neuritis	N/A	Orbit: Rt. optic nerve T2 HSI with enhancement Brain: Multiple T2 HSI on PV, brainstem with enhancement Spine: NL	WBC: 5, OCB: pos, IgG index: 0.48	IVMP (3 g), Complete recovery	There is no definitive way to link the onset of CNS-IDDs with COVD- 19 vaccination, but the close temporal association may suggest a pathogenic link.
	Unilateral optic neuritis	N/A	Orbit: Lt. optic nerve T2 HSI with enhancement Brain: Multiple T2 HSI on PV, JC with enhancement Spine: ss myelitis (T11-12 level)			
Ebrahimi et al.[46]	Balance disturbance	3	N/A	N/A	IVMP (3 g), marked improvement	We see both old and new lesions meaning that this excessive immune response may contribute to the unmasking of these diseases following vaccination in those who already have a weakened immune system.
	Rt. hand paresthesia	2.5	N/A	N/A	IVMP (3 g), partial response[###]	
	Lt. hand paresthesia to complete numbness	2	N/A	N/A	IVMP (3 g), complete recovery	

Table 3. Part II: Studies specifically addressing the new diagnosis of MS following SARS-CoV-2 vaccination (continue)

Study	Initial symptoms, signs	EDSS	MRI	Labs and CSF analyses	Treat., response	Notes
Ebrahimi et al.[46]	Lt. hand paresthesia	N/A	N/A	N/A	IVMP (3 g), partial response¥¥	
	Lt. hand paresthesia, Lhermitte sign	2.5	N/A	N/A	IVMP (3 g), partial response	
	Rt. sided facial paresthesia, Rt. hand tingling	1.5	N/A	N/A	IVMP (3 g), complete recovery	
	Lt. sided numbness	1.5	N/A	N/A	IVMP (3 g), complete recovery	
	Numbness in Lt. hand and foot	2.5	N/A	N/A	IVMP (3 g), EDSS improved	

AQP4-IgG: Aquaporin 4-IgG; CIS: Clinically isolated syndrome; CMV: Cytomegalovirus; EBV: Epstein–Barr virus; EXT: Extremities; FH: Family history; g: Gram; HIS: High signal intensity; HSV: Herpes-simplex virus; IDA: Iron deficiency anemia; IMP: Impairment; INT: Interval; m: Month; JC: Juxtacortical; MBP: Myelin basic protein; MOG-IgG: Myelin oligodendrocyte glycoprotein-IgG; MS: Multiple sclerosis; Neg: Negative; NL: Normal; Numb.: Numbness; OCB: Oligoclonal band; OCD: Obsessive-compulsive disorder; pos: Positive; PMH: Past medical history; PSL: Prednisolone; PV: Periventricular; RAPD: Relative afferent pupillary defect; SC: Subcortical; sess: session(s); ss: Short-segment; STIR: Short-tau inversion recovery; Treat.: Treatment; v1: 1st vaccine dose; v2: 2nd vaccine dose; VZV: Varicella-zoster virus; WNV: West Nile virus; w/o: Without; CNS: Central nervous system

*Complete remission of symptoms did not occur even after a second cycle of glucocorticoid therapy (2000 mg IVMP for 5 days) and escalating the relapse therapy with plasma exchange treatment was performed, which resulted in further improvement.

**At six weeks she had improved 80% with mild distal paresthesia and persisting Lhermitte symptom.

***In this case series, 27 patients with new-onset or flare of immune-mediated diseases were included, one of which was diagnosed with new-onset multiple sclerosis (patient 7).

‡In this series, 7 patients who developed neurologic symptoms and MRI findings consistent with active CNS demyelination of the optic nerve, brain, and/or spinal cord were reported. The final diagnosis was exacerbation of known stable MS (n = 4, two were receiving disease-modifying therapy (DMT) at the time of vaccination), new onset MS (n = 2), or new onset neuromyelitis optica (NMO) (n = 1). In this table only data for the 2 patients with new onset MS is reported (patients 2 and 5).

‡‡In this study, among 117 cases, 10 had their first disease manifestation within one month following COVID-19 vaccination, two of which were diagnosed with MS.

‡‡‡In this case series, 12 patients developing MS, clinically isolated syndrome (CIS), and NMOSD following COVID 19 vaccines were reported, 9 of which were diagnosed with MS (patients 1 to 9).

#At baseline and after treatment

##In this study, 16 patients received a diagnosis of MS, three of which had a first episode after COVID-19 vaccination (patients 2, 4, and 9).

###Forty-two days after her diagnosis, numbness was resolved, but she experienced frequent urination and urinary incontinence one to three times a week. After a four-month follow-up, she said that her urinary dysfunctions were no longer an issue and that she was seldom bothered by them.

¥Residual Rt. upper extremity weakness and symmetric hyperreflexia with sustained clonus in both ankles, residual decreased sensation to all sensory modalities over the entire Lt. arm, left half of trunk below T4 level dermatome, and over the entire Lt. leg.

"Mild right wrist extensor weakness and ipsilateral hip flexor and knee flexor weakness persist after a week.

¥¥She feels no numbness in her fingers anymore, but as she bends her neck, she still feels some trembling in her back.

After two months, she still feels a light electric shock passing down her neck, but her numbness and tingling have gone away.

Remarkably, 6/26 patients had a previous history of neurological conditions, including headaches/migraine (n = 2),[22,46] recovered facial palsy (n = 1),[25] recovered facial numbness with left upper limb weakness (n = 1),[41] unilateral optic neuritis with previously unremarkable brain MRI (n = 1),[22] and the first episode of the clinically isolated syndrome (CIS) with complete recovery (n = 1).[43] Only 2/7 studies, accounting for 10 individuals, provided information about the patient's family history.[24,46] While family history was unremarkable in 7/10, 3/10 patients had positive family histories, with MS present in a paternal cousin,[24] in both mother and cousin,[46] and in a sister.[46]

MS symptoms manifested within 1 day to 3 months after receiving BNT162b2 (n = 11; v1: 6, v2: 5),[22-25,30,40,42,43] mRNA-1273 (n = 3; v1: 1, v2: 2),[22,23] BBIBP-CorV (n = 8; v1: 2, v2: 5, v3: 1),[46] or AZD1222 (n = 4, v1: 2, v2: 2).[41,43,46] The duration between the symptoms onset and vaccination was less than 6 weeks in 24/26 patients (≤ 7 days in 12/26), more than 6 weeks in 1/21 (p5 in the study by Ebrahimi et al.),[46] and remained unspecified in 1/21 (p4 in the study by Toljan et al.).[22] It is noteworthy that 2/21 patients (p2 and p4 in the study by Toljan et al.) experienced MS-related symptoms after both vaccine doses.[22] One patient (p2) experienced initial symptoms 3 days after receiving v1, with further progression observed 3 weeks after the subsequent dose.[22] While the authors did not specify the duration between the other patient's (p4) initial symptoms and v1 administration, they did note that the symptoms, which had previously commenced, progressed 3 days after the administration of v2.[22]

Brain MRI results were available in all studies except one.[46] In line with our findings, periventricular lesions were the most frequently observed lesions,[22,23,25,30,42,43] followed by subcortical[23,25] and juxtacortical lesions.[22,42] Spinal cord MRI findings were reported in all studies except 3,[30,40,46] with lesions detected at C3-C4,[22] C5-C6,[25] T6,[24] and T11-T12.[42] MS-related laboratory evaluation results were reported for all patients except 3.[41,43,46] In most cases, the diagnosis of MS was supported by CSF pleocytosis, positive OCBs, and elevated IgG index. All patients received 3-5 gr of IVMP, except for 1 patient (p2 in the study by Toljan et al.), who received high-dose oral prednisolone.[22] Additionally, 2/26 patients underwent TPE.[22,24] At the last follow-up, all patients showed partial to complete symptom recovery. Response to treatment was not reported for 3 patients.[22,40]

Although the exact pathophysiology behind some autoimmune sequelae in the context of vaccine exposure is currently unknown, there is a hypothesis that COVID-19 vaccines might trigger an excessive inflammatory immune reaction in a subgroup of vulnerable individuals. This could potentially accelerate the transition from subclinical to clinical disease and reveal a previously concealed demyelinating condition within the CNS,[32] which is not surprising due to the involvement of neuroinflammation in various neurological conditions such as MS.[64,65] Notably, a combination of old and new MRI lesions in many of the reported patients could indicate a clinically latent disease, which was masked before the vaccination-induced immune response.[22-25] Although only 1 of our patients showed evidence of a latent demyelinating process, we cannot exclude possible genetic susceptibility in others. Other suggested mechanisms include molecular mimicry (similarities between self-antigens and vaccine), aberrant immune response, vaccine-related factors (i.e., adjuvants), and an already altered immune response in susceptible individuals.[28]

Determining whether these observations imply causality (the development of a new disease) or mere temporal coincidence (the manifestation of an existing, previously subclinical neuroinflammation) requires thorough consideration of various issues. Firstly, although there have been reports of autoimmune diseases occurring after vaccination, only a limited number have been definitively labeled as "vaccine-induced".[66,67] Butler et al. have proposed specific criteria for establishing "probable causality" in cases of neurological AEFI, including a typical time frame (< 6 weeks), no indication of an alternative etiology, and no other risk factors[50] (Table 1). Secondly, even when considering the possibility of a small risk of autoimmune exacerbation associated with SARS-CoV-2 vaccines, research has indicated a substantially higher risk of neurological AEs, including CNS demyelinating disease, following infections as opposed to vaccination.[27,28,68] Eventually, our understanding of this will only be enhanced when forthcoming studies investigate whether COVID-19 vaccines raise the likelihood of MS beyond the anticipated, usual background rate of such incidents.

Conclusion

This study is the second case series to report MS

incidence following the administration of BBIBP-CorV in a temporal relationship. Apart from our patients, we conducted a thorough review of the relevant published literature. Among our 8 patients, 1 case was deemed unlikely to be vaccine-related due to a prior history of facial numbness together with brain atrophy and black holes in MRI. Nevertheless, an association of < 6 weeks with ictus and evidence of OCBs along with the MRI findings suggests the possibility of a latent disease that may have been triggered by vaccination. It is worth mentioning that the occurrence of MS onset following vaccination is still extremely rare when compared to the vaccinated population. As with previous reports, due to their descriptive nature, lack of a comparison group, and limited sample, it is not possible to establish a causal relationship between vaccination and any specific AEFI based on single case reports;[69] hence, the findings should be interpreted with caution. Causality can change when additional information about the same or similar cases becomes available. Although the short interval between the exposure and event might reduce the possible role of potentially confounding factors, several steps should be taken to establish a causal relationship beyond a mere temporal association between exposure and the event. Strength of the association, dose-response relationship (higher likelihood of the outcome with higher exposures), replication, biological plausibility, coherence (consistency of the association with existing knowledge), and analogy are among the most important criteria to establish a causal relationship.[70] Statistical analyses also play a crucial role in establishing causality in research by identifying correlations, estimating the strength of the association, and controlling for confounding variables.[70] Collectively, the current evidence strongly suggests that the benefits of vaccination outweigh the plausible risks.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

We thank all patients and the staff in our center for their kind assistance.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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