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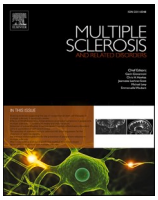

Onset of various CNS inflammatory demyelination diseases following COVID-19 vaccinations

Ki Hoon Kim, Su-Hyun Kim, Na Young Park, Jae-Won Hyun, Ho Jin Kim *

Department of Neurology, Research Institute and Hospital of National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 10408, South Korea

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ABSTRACT

Background: Since the start of COVID-19 vaccination worldwide, there have been several reports of inflammatory demyelinating diseases of the central nervous system (CNS-IDDs) following vaccination.
Methods: We prospectively collected cases of new-onset CNS-IDDs with a temporal relationship between disease onset and COVID-19 vaccination and investigated their proportion among newly registered cases of CNS-IDD over the past year.
Results: Among 117 cases, 10 (8.5%) had their first disease manifestation within one month following COVID-19 vaccination: 2 multiple sclerosis, 2 neuromyelitis optica spectrum disorder, 3 MOG antibody-associated disease, and 3 unclassified CNS-IDDs.
Conclusion: This observation suggests that COVID-19 vaccination may trigger the onset of various CNS-IDDs in susceptible individuals.

1. Introduction

At the end of 2019, the coronavirus disease 2019 (COVID-19) emerged and rapidly spread worldwide, leading to a global pandemic. Multiple studies have shown that COVID-19 vaccination is the most effective tool to prevent the disease and reduce mortality.

With an increased number of people undergoing COVID-19 vaccination, neurological complications after vaccination have been reported in the clinical trial and real-world settings (Voysey et al., 2021). An interim study reported three cases of transverse myelitis after ChAdOX1 nCoV-19 vaccination (Knoll and Wonodi, 2021; Voysey et al., 2021). A recent systematic review screened published articles, and demonstrated a temporal relationship between the disease onset of inflammatory demyelinating diseases of the central nervous system (CNS-IDDs) and COVID-19 vaccination in 32 cases: 12 cases with myelitis, 12 cases with multiple sclerosis (MS), 5 cases with acute disseminated encephalomyelitis (ADEM), and 3 cases with neuromyelitis optica spectrum disorder (NMOSD) (Ismail and Salama, 2021). However, case studies of CNS-IDDs following COVID-19 vaccination are still lacking, especially in the Asian population (Eom et al., 2022; Gao et al., 2021; Hsiao et al., 2021), and the proportion of CNS-IDDs cases having a temporal relationship with COVID-19 vaccination has not been assessed.

We prospectively collected data on patients with CNS-IDD showing a temporal relationship with COVID-19 vaccination, and investigated its proportion among newly registered cases with CNS-IDDs at the National Cancer Center (NCC) since the start of COVID-19 vaccination in Korea. Over the past year, four COVID-19 vaccines have been administered in Korea: ChAdOx1 nCoV-19 vaccine (AstraZeneca, Total 20,318,526 doses [16.8%] by the end of March 2022), BNT162b2 (Pfizer-BioNTech, 74,500,895 doses [61.7%]), mRNA-1273 (Moderna, 24,255,886 doses [20.1%]), and JNJ-78436735 (Johnson & Johnson/Janssen, 1,542,722 dose [1.3%]). The vaccination completion rate is 86.6%, and the third vaccination (booster shot) was completed by 63.7% of the population as of March 31, 2022. The majority of Koreans have received COVID-19 vaccinations for a short period, and it is a great opportunity to observe the frequency of post-vaccinal CNS-IDDs among newly registered cases of CNS-IDDs in the NCC registry.

2. Method

We prospectively collected data from ten CNS-IDD patients with a temporal relationship between the disease onset and COVID-19 vaccination at the NCC, from March 2021 to March 2022. All patients developed the first neurologic symptom after vaccination, and were diagnosed with new-onset CNS-IDDs supported by magnetic resonance image findings suggestive of active CNS demyelination. Patients with a

* Corresponding author.
E-mail address: hojinkim@ncc.re.kr (H.J. Kim).

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previous history of COVID-19 infection were excluded. Disease onset within a month from each dose of vaccination was defined as having a temporal relationship between COVID-19 vaccination and the onset of acute CNS demyelinating events. In addition, the proportion of cases with a temporal relationship between disease onset and COVID-19 vaccination, among newly registered patients with CNS-IDD who first visited the NCC during the same study period, was investigated.

Patients were categorized as having MS according to the 2017 McDonald criteria (Thompson et al., 2018), NMOSD according to the 2015 criteria (Wingerchuk et al., 2015), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) according to the recent international recommendations for diagnosis (Jarius et al., 2018). The remaining patients who did not fulfill the above diagnostic criteria were categorized as having unclassified CNS-IDDs. Serologic tests for anti-aquaporin4 (AQP4) and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies were performed in all patients using a live cell-based assay (Kim et al., 2020, 2017).

The institutional review board of the NCC approved this study (NCC2014-0146), and written consent was obtained from all participants.

3. Results

During the study period, 117 patients were newly registered in the CNS-IDD cohort, comprising MS, NMOSD, MOGAD, and unclassified CNS-IDDs in 47, 22, 12, and 36 patients, respectively. Of these patients, ten (8.5%) were diagnosed with CNS-IDDs, with a temporal relationship with COVID-19 vaccination, and all of them had new-onset disease: two with MS, two with AQP4-IgG-positive NMOSD, three with MOGAD, and three with unclassified CNS-IDDs (two with seronegative isolated optic neuritis (ON), and one with seronegative myelitis). No patient had a previous history of CNS demyelinating events. They developed neurological symptoms after the first ($n = 4$), second ($n = 5$), or third ($n = 1$) dose of COVID-19 vaccination (BNT162b2, $n = 4$; mRNA-1273, $n = 4$; ChAdOx1 nCoV-19, $n = 2$), with a median interval of 6.5 (range, 3–28) days after vaccination. At onset, the mean age was 36.5 years (range, 22–67) years, and the male-to-female ratio was 4:6.

The most common phenotype in patients with CNS-IDD after COVID-19 vaccination was isolated ON ($n = 6$, 60%), and the remaining four presented with encephalomyelitis, longitudinal extensive transverse myelitis (LETM), multifocal short-segment myelitis, and a single demyelinating CNS lesion (medulla). The neurologic symptoms responded well to intravenous methylprednisolone (IVMP) treatment in seven patients with MS, NMOSD, or MOGAD: six patients completely recovered after IVMP, but mild gait disturbance persisted in one patient with NMOSD due to the loss of vibration sense (the expanded disability status scale 3.0). The remaining three patients with unclassified CNS-IDD only partially recovered despite two of them receiving additional intravenous immunoglobulin treatment after IVMP administration: the best visions of the affected eye in these two patients with isolated ON were 0.4 and 0.2, respectively. Mild gait disturbance and tingling sensation in the lower extremities remained in one patient with seronegative myelitis.

Two patients with MS, and two with NMOSD received maintenance immunotherapy, whereas three patients with MOGAD, and three with unclassified CNS-IDD were monitored without additional immunotherapy. No further clinical episodes occurred during the median 5-months (range, 1–6) follow-up. In addition, two patients (one with MS and the other with NMOSD) subsequently completed additional vaccinations (BNT162b2) without specific complications.

The radiological and clinical findings of the ten patients are summarized in Table 1 and Fig. 1. The description of each case is provided below.

4. Case descriptions

4.1. New-onset multiple sclerosis (MS): two cases

4.1.1. Case 1

A previously healthy 28-year-old woman presented with right optic neuritis (ON), 28 days after receiving the second dose of BNT162b2 vaccine. Orbit magnetic resonance imaging (MRI) performed on the 14th day after ON onset demonstrated T2 high signal intensity (HSI) in the right optic nerve with contrast enhancement (Fig. 1a1). Simultaneously, multiple periventricular and middle cerebellar peduncle lesions, suggestive of MS, were detected on brain MRI (Fig. 1a2–a4). The Spine MRI was normal. Cerebrospinal fluid (CSF) examination revealed a normal pressure, total nucleated cell count of 5/uL, and protein level of 29 mg/dL. The IgG index value was 0.48, and the CSF-specific oligoclonal bands (OCBs) were positive. The visual evoked potential test (VEP) revealed a pre-chiasmatic conduction defect on the right side. Anti-AQP4 and myelin oligodendrocyte glycoprotein (MOG) antibodies were negative. This patient satisfied both the dissemination in space (DIS) and time (DIT) criteria based on the 2017 McDonald criteria and was treated with high-dose methylprednisolone (1 g/day) for 3 days. After a month, the patient showed complete recovery from decreased visual acuity (VA) in the right eye, 0.5 (20/40 on Snellen chart) at nadir. She participated a clinical trial (Bruton's tyrosine kinase inhibitor (BTKi) vs. Teriflunomide), and is in progress without further relapses.

4.1.2. Case 2

A 29-year-old woman presented with eyeball pain and decreased VA in the left eye, 8 days after the second dose of the BNT162b2 vaccine. She underwent total thyroidectomy for underlying thyroid cancer in 2012 and had been taking thyroxine. At the nadir, the VA of the left eye decreased to 0.5 (20/40). Orbit and brain MRI showed T2 HSI in the left optic nerve (Fig. 1b1), and multiple juxtacortical and periventricular lesions with contrast enhancement (Fig. 1b2), which were suggestive of ON-onset MS. In addition, subtle T2 HSI without contrast enhancement was detected at the level of T11 on spine MRI (Fig. 1b3). Mild pleocytosis (total nucleated cell count: 8/uL) and elevated protein levels (68 mg/dL) were noted in the CSF study. OCBs were positive, and the IgG index value was slightly elevated at 0.74. High-dose methylprednisolone was administered for 5 days, and her symptoms completely resolved with subsequent oral steroid tapering. Dimethyl fumarate was initiated as maintenance therapy.

4.2. New-onset AQP4-IgG-positive neuromyelitis optica spectrum disorder (NMOSD): two cases

4.2.1. Case 3

A 57-year-old woman with suspected Sjogren's syndrome presented with mild constipation and paresthesia in both legs, predominantly on the left side, 11 days after the first dose of mRNA-1273 vaccine. Her symptoms progressed over the next 1 week, but she could walk independently unassisted for more than 500 m without despite mild gait disturbance. Neurological examination showed hypoesthesia below the T12 dermatome, decreased position sensation on the left side, and absence of vibration sensation with spasticity in both legs. The expanded disability status scale (EDSS) score was 3.0. Spine MRI conducted 1 week after symptom onset demonstrated T2 HSI at the level of T5-9 with patchy gadolinium enhancement (Fig. 1c1,c2), which is suggestive of longitudinal extensive transverse myelitis (LETM). Non-specific T2 HSIs were observed on brain MRI. The results of the CSF study were unremarkable, and the OCBs were negative. This patient was seropositive for the anti-AQP4 antibody; the semi-quantitative grade of the staining intensity was 4+. The patient was diagnosed with AQP4-IgG-positive NMOSD and was treated with high-dose methylprednisolone for 5 days. Her symptoms partially recovered with subsequent oral steroid tapering and azathioprine as maintenance therapy.

Table 1
Characteristics of patients with new-onset CNS-IDDs following COVID-19 vaccination.

New-onset CNS-IDDs	MS		Seropositive NMOSD		MOGAD			Unclassified CNS-IDD Seronegative isolated optic neuritis		Seronegative myelitis
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Presenting symptom	Unilateral optic neuritis	Unilateral optic neuritis	Left leg tingling sensation	Hiccup, gait disturbance	Unilateral optic neuritis	Unilateral optic neuritis	Headache, urinary difficulty	Unilateral optic neuritis	Unilateral optic neuritis	Both leg hypesthesia and weakness
Sex	F	F	F	F	M	M	M	M	F	F
Age	28	29	57	47	33	40	22	67	53	24
Underlying disease	–	Thyroid cancer	Sjogren's syndrome	–	–	–	–	HTN	–	–
Vaccine	BNT162b2, 2nd dose	BNT162b2, 2nd dose	mRNA-1273, 1st dose	ChAdOx1 nCoV-19, 1st dose	mRNA-1273, 2nd dose	mRNA-1273, 2nd dose	mRNA-1273, 2nd dose	ChAdOx1 nCoV-19, 1st dose	BNT162b2, 1st dose	BNT162b2, 3rd dose
Time interval	28 days	8 days	11 days	22 days	3 days	20 days	3 days	5 days	3 days	5 days
Orbit MRI	Rt optic nerve T2 HSI with enhancement	Lt optic nerve T2 HSI with enhancement	–	–	Rt optic nerve T2 HSI with enhancement	Lt optic nerve T2 HSI with enhancement	–	Lt optic nerve T2 HSI without enhancement	Lt optic nerve subtle enhancement	–
Brain MRI	Multiple T2 HSI on PV, brainstem with enhancement	Multiple T2 HSI on PV, JC with enhancement	Non-specific white matter change	Multiple T2 HSI on SCWM, medulla with enhancement	–	Normal	Multiple T2 HSI on internal capsule, pons, middle cerebellar peduncle, and SCWM	Non-specific white matter change	Non-specific white matter change	Non-specific white matter change
Spine MRI	Normal	Short-segment myelitis (T11-12 level)	T2 HSI at the level of T5-9 with enhancement, suggesting LETM	T2 HSI at lower posterior medulla with enhancement	Normal	–	Multifocal T2 HSI at the level of upper and mid T spine, with enhancement	–	–	Multifocal T2 HSI at the T10-11 and L1 level
Evoked potentials (EP)	Visual EP (VEP): Rt pre-chiasmatic conduction defect/ Sensory EP (SEP): normal	VEP: Lt pre-chiasmatic conduction defect/ SEP: normal	VEP: normal	VEP: normal	VEP: Rt pre-chiasmatic conduction defect/ SEP: normal	VEP: Lt pre-chiasmatic conduction defect/ SEP: normal	VEP: bilateral pre-chiasmatic conduction defect/ SEP: normal	VEP: Lt pre-chiasmatic conduction defect	VEP: Lt pre-chiasmatic conduction defect	VEP: normal/ SEP: normal/ Motor EP: prolonged central conduction defect on left side.
CSF finding	Protein 29, WBC 5, OCBs positive, IgG index 0.48	Protein 68, WBC 8, OCBs positive, IgG index 0.74	Protein 31, WBC 0, OCBs negative	Protein 27, WBC 0, OCBs negative, IgG index 0.44	–	–	Protein 37, WBC 51, OCBs negative	–	Protein 31, WBC 5, OCBs negative	Protein 30, WBC 13, OCBs positive
AQP4-IgG or MOG-IgG	Not detected	Not detected	AQP4-IgG 4+	AQP-IgG 2+	MOG-IgG 1+	MOG-IgG 2+	MOG-IgG 1+	Not detected	Not detected	Not detected
Acute treatment	IVMP 3 days	IVMP 5 days	IVMP 5 days	IVMP 5 days	IVMP 5 days	IVMP 3 days	IVMP 5 days	IVMP 5 days + IVIG 5 days (total 2 g/Kg)	IVMP 5 days	IVMP 5 days + IVIG 5 days (total 2 g/Kg)
Maintenance therapy	Clinical trial (BTKi vs. Teriflunomide)	Dimethyl fumarate	Azathioprine	Azathioprine	–	–	–	–	–	–
Clinical outcome	Complete recovery	Complete recovery	Partial recovery	Complete recovery	Complete recovery	Complete recovery	Complete recovery	Partial recovery	Partial recovery	Partial recovery

HSI: high signal intensity; OCB: CSF-specific oligoclonal bands; PV: periventricular lesion; JC: juxtacortical lesions; SCWM: subcortical white matter lesions; IVMP: high-dose intravenous methylprednisolone; IVIG: intravenous immunoglobulin; BTKi: Bruton tyrosine kinases inhibitors; LETM: longitudinally extensive transverse myelitis.

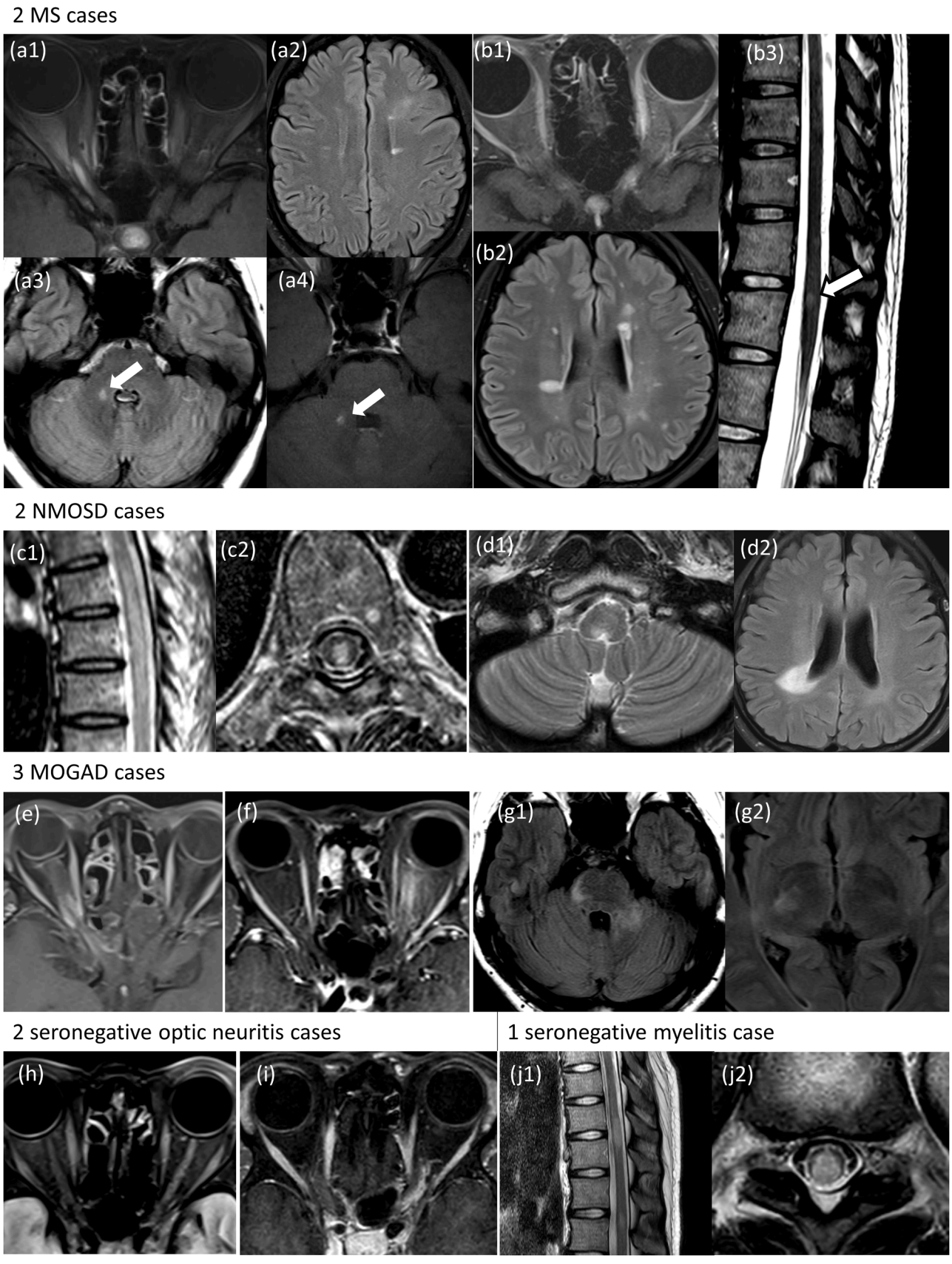

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Fig. 1. Magnetic resonance image (MRI) findings in patients diagnosed with CNS-IDDs after COVID-19 vaccination. Two patients with MS following COVID-19 vaccination (a1-4 and b1-3): gadolinium-enhanced T1-weighted (Gd-T1) images show optic nerve enhancements (a1, b1) in both patients. In the patient with MS, axial fluid-attenuated inversion recovery (FLAIR) images show T2-hyperintense periventricular and middle cerebellar peduncle lesions (white arrow) (a2-3), and gadolinium enhancement is accompanied by a middle cerebellar peduncle lesion (white arrow, a4). The other patient with MS demonstrates T2-hyperintense lesions in the periventricular region (b2) and spinal cord at the T11 level (white arrow, b3). Two patients with NMOSD following COVID-19 vaccination (c1-2 and d1-2): A sagittal T2-weighted image demonstrates a longitudinally extensive T2-hyperintense lesion (T5-9 level) with gadolinium enhancement in the patient with NMOSD (c1-2). The other patient with NMOSD shows T2-hyperintense lesions in the medulla around the 4th ventricle with contrast enhancement (d1), and the right parietal area without contrast enhancement (d2). Three patients with MOGAD following COVID-19 vaccination (e, f, g1-2): two patients presenting with optic neuritis show optic nerve enhancements on Gd-T1 images (e, f). In another patient with MOGAD, multifocal T2 hyperintense lesions involving the right thalamus, pons, and left cerebellar peduncle without definite contrast enhancement are noted on FLAIR images (g1-2). Three patients with unclassified CNS-IDDs after COVID-19 vaccination: in two patients with seronegative optic neuritis, orbital magnetic resonance imaging demonstrates a T2-hyperintense lesion with a subtle enhancement of the left optic nerve (h and i). In the patient with seronegative myelitis, spine MRI demonstrates multifocal T2 hyperintense lesions (T10-11 and L1 level) (j1-2).

4.2.2. Case 4

A 47-year-old woman without underlying disease developed intractable hiccups 22 days after the first dose of the ChAdOx1 nCoV-19 vaccine. Despite taking medications for symptomatic treatment, the hiccups persisted, and 2 weeks later, she experienced dysarthria, dysphagia, hoarseness, and gait disturbance. On brain MRI, T2 HSI with contrast enhancement was noted in the medulla around fourth ventricle with contrast enhancement (Fig. 1d1). Considering persistent hiccups for several days and dorsal medulla lesions, this patient had typical area postrema syndrome (APS), one of the core clinical features described in the 2015 diagnostic criteria for NMOSD (Wingerchuk et al., 2015). In addition, a large periventricular lesion in the right parietal area was observed on FLAIR MRI images without contrast enhancement (Fig. 1d2). There was no signal abnormality on the spinal MRI. Anti-AQP4 antibody was determined to be seropositive for semi-quantitative grade 2+. After 5 days of high-dose methylprednisolone, her symptoms gradually improved, and she completely recovered with oral steroid and azathioprine use.

4.3. New-onset MOG antibody-associated disease (MOGAD): three cases

4.3.1. Case 5 – ON phenotype

A 33-year-old healthy man developed eyeball pain and visual disturbance in the right eye 3 days after the second dose of the mRNA-1273 vaccine. The VA of the right eye declined to 0.1 (20/200), and then gradually recovered to 0.5 (20/40) after a week without acute treatment. However, 2 weeks later, his visual disturbance deteriorated again, and orbital MRI demonstrated T2 HSI in the canalicular portion of the right optic nerve with contrast enhancement (Fig. 1e). VEP was also suggestive of a right pre-chiasmatic conduction defect. There were no signal abnormalities in the brain parenchyma or spine. Anti-MOG antibodies were of a semi-quantitative grade of 1+. Under the diagnosis of MOGAD with an ON phenotype, high-dose methylprednisolone was administered for 5 days, and his vision completely recovered. Currently, this patient is undergoing follow-up without maintenance immunotherapy, and the serological test for MOG-IgG will be repeated after 6 months.

4.3.2. Case 6 – ON phenotype

Similar to Case 5, a 40-year-old man presented with left eyeball pain and visual disturbance 20 days after the second dose of the mRNA-1273 vaccine. The VA of the left eye decreased to a finger count of 30 cm at nadir, and orbital MRI performed on the third day after symptom onset demonstrated T2 HSI with contrast enhancement on the left optic nerve (Fig. 1f), which was consistent with the VEP result of the left pre-chiasmatic conduction defect. Brain parenchyma was normal. High-dose methylprednisolone was initiated for 3 days, and his VA completely recovered with subsequent oral steroid tapering. The anti-MOG antibody was determined to be seropositive with semi-quantitative grade 2+, and he was also diagnosed with MOGAD presenting with ON. As it still shows a monophasic course and the previous symptoms have recovered well, the patient is being monitored without additional immunotherapy.

4.3.3. Case 7 – encephalomyelitis phenotype

A 23-year-old man with no significant medical history received a second dose of the mRNA-1273 vaccine. Three days after the second dose, the patient developed a headache and urinary difficulty, and these symptoms gradually deteriorated (requiring catheterization). One month later, he experienced a decreased sensation below his belly, and his vision in his right eye decreased along with right eyeball pain. Brain MRI performed 44 days after symptom onset demonstrated multiple T2 HSIs in the right thalamus, pons, and left cerebellar peduncle, without definite contrast enhancement (Fig. 1g1,g2). Multifocal T2 hyperintense lesions involving the mid-thoracic level were noted on spinal MRI, suggesting an active demyelinating process. CSF studies showed normal pressure, total nucleated cell count of 140/uL, protein level of 50 mg/dL, and negative OCBs. The serum MOG antibody level was 1+. The patient was treated with high-dose methylprednisolone for 5 days. One month after steroid therapy, all symptoms recovered, except for mild residual urination, and right eye VA improved to 0.8 (20/25), which was 0.5 (20/40) at nadir. This patient is also being monitored without long-term immunotherapy.

4.4. New-onset unclassified CNS-IDDs: three cases

4.4.1. Case 8 – seronegative isolated ON

A 67-year-old man with underlying hypertension developed eyeball pain and decreased visual acuity in the left eye 5 days after the first dose of the ChAdOx1 nCoV-19 vaccine. At nadir, the visual acuity of the left eye decreased to a finger count of 40 cm. Orbit MRI showed T2 HSI in the left optic nerve (Fig. 1h), and a non-specific white matter change was found on brain MRI. VEP showed a pre-chiasmatic conduction defect on the left side, which was compatible with a left ON. Anti-AQP4 and anti-MOG antibodies were not detected in the serum, and CSF analysis was not performed. High-dose methylprednisolone was administered for 5 days, and the visual acuity in the left eye partially improved to 0.2 (20/100) over 2 months. Due to poor recovery of VA, additional intravenous immunoglobulin (IVIG, total 2 g/kg) was administered, but there was no significant response. This patient is being regularly followed up without long-term immunotherapy or oral steroids.

4.4.2. Case 9 – seronegative isolated ON

Similar to Case 8, a 53-year-old woman presented with left eyeball pain and visual disturbance 3 days after the first dose of the BNT162b2 vaccine. The VA of the left eye decreased to 0.1 (20/200) at nadir, and orbit MRI demonstrated the T2 HSI with subtle enhancement on the left optic nerve (Fig. 1i), which was compatible with the VEP result of the left pre-chiasmatic conduction defect. High-dose methylprednisolone was initiated for five days, and her VA partially recovered to 0.4 (20/50), with subsequent oral steroid tapering. A CSF study revealed normal pressure, total nucleated cell count of 5/uL, and protein level of 31 mg/dL. VEP showed a pre-chiasmatic conduction defect on the left side, and anti-AQP4 and anti-MOG antibody results were negative. Under a diagnosis of seronegative ON, the patient is being monitored without additional immunotherapy.

4.4.3. Case 10 – seronegative myelitis

A 24-year-old woman presented with paresthesia and weakness in both legs, 5 days after the third dose of BNT162b2 vaccine. Her symptoms including sphincter dysfunction slowly progressed over the next 10 days, and she could walk independently unassisted for less than 300 m at nadir. Neurological examination revealed hypoesthesia below the T12 dermatome, paraplegia of lower extremities (motor grade 4 by the Medical Research Council scale), and decreased vibration sensation with mild spasticity in both legs. The expanded disability status scale (EDSS) score was 5.0. Spine MRI conducted 10 days after symptom onset demonstrated multifocal T2 HSI at the level of T10- and L1 (Fig. 1j1,j2). Non-specific T2 HSIs were observed on brain MRI. The CSF study showed a total nucleated cell count of 13/uL, protein 30 mg/dL, and positive OCBs. This patient was seronegative for both anti-AQP4 and anti-MOG antibodies, and was diagnosed with seronegative myelitis. After administration of high-dose methylprednisolone for 5 days, paraplegia partially improved, but gait disturbance and sphincter dysfunction remained. Due to partial response of steroid therapy, additional IVIG (total 2 g/kg) was administered. Two weeks after steroid and IVIG therapy, symptoms markedly recovered, except for mild residual urination and tingling sensation on lower extremities, with a follow-up EDSS score of 2.0. This patient is being monitored without long-term immunotherapy.

5. Discussion

Herein, we report ten cases of new-onset CNS-IDD following COVID-19 vaccination in the past year. Among the newly registered patients with CNS-IDDs in the NCC cohort, 8.5% of them showed a temporal relationship between the disease onset and COVID-19 vaccination, and they manifested diverse types of CNS-IDDs, regardless of the vaccine type or order.

Previous studies showed five cases of MS with the first episode developing after COVID-19 vaccination: two patients after ChAdOx1 nCoV-19 vaccine, two after BNT162b2 vaccine, and one after mRNA-1273 vaccine (Khayat-Khoei et al., 2022; Nistri et al., 2021; Watad et al., 2021). New-onset AQP4-positive NMOSD was reported in two patients, for whom neurologic symptoms started 18 days after BNT162b2 vaccination and two months after the inactivated virus vaccine (unknown) for COVID-19, respectively (Chen et al., 2021; Khayat-Khoei et al., 2022). Case studies have also been published about autoimmune encephalitis and ON events after COVID-19 vaccination (García-Estrada et al., 2022; Shin et al., 2022; Zuhorn et al., 2021). Recently, the first case of MOG-positive LETM after ChAdOx1 nCoV-19 vaccination was described (Dams et al., 2022). In addition to the pre-existing cases, our study adds new-onset CNS-IDDs following COVID-19 vaccination.

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. The potential antigenic cross-reactivity by molecular mimicry and the activation of pro-inflammatory cytokines in delivery process of mRNA can lead to vaccine-associated autoimmunity (Talotta, 2021). The mRNA-containing lipid nanoparticles and adjuvants may also induce the up-regulation of immune response, contributing to the breakdown of the immunological balance (Cabanillas et al., 2021; Teijaro and Farber, 2021). Whether this occurs in predisposed patients who would eventually develop CNS-IDDs remains unknown. To the best of our knowledge, studies on the incidence of CNS-IDDs during the COVID-19 pandemic have not yet been conducted. It is yet to be addressed whether COVID-19 vaccination increases the occurrence of CNS-IDDs. Of note is that clinical relapses with a temporal relationship to COVID-19 vaccination were not observed in our total cohort with CNS-IDDs, including a few hundreds of patients with MS or NMOSD during the same study period. This observation is in line with recent studies that reported no increase of relapse rate after mRNA vaccination in patients with MS compared with that before vaccination (Achiron et al., 2021; Di Filippo et al., 2022). Thus, COVID-19 vaccination may not significantly increase disease activity in patients undergoing disease-modifying immunotherapy, whilst it may provoke the onset of CNS-IDD in susceptible individuals.

Interestingly, the proportion of MOGAD cases ($n = 3$) having a temporal relationship with COVID-19 vaccination was relatively higher in the entire MOGAD registry ($n = 12$) than in the other types of CNS-IDDs. Currently, there are few case reports of MOGAD developing after COVID-19 vaccination (Dams et al., 2022). However, given that MOG-positive myelitis has been found after other types of vaccinations (influenza and DTaP) (Amano et al., 2014; Loos et al., 2020) and MOGAD cases after COVID-19 infection have been described with diverse phenotypes (Kogure et al., 2021; Sinha et al., 2021; Žorić et al., 2021), more MOGAD cases following COVID-19 vaccination may be reported. Our three patients with MOGAD improved completely after high-dose steroid administration, and remained with no disability, and without further relapses; these patients are being monitored without maintenance immunotherapy. Due to the lack of long-term observational data on new-onset MOGAD after COVID-19 vaccination, it is necessary to regularly examine the serostatus of MOG antibodies and observe further clinical relapses, throughout long-term follow-up.

Given that this study was conducted at a single referral center, this observation cannot be generalizable. Additionally, the time interval of one month after vaccination, defined for the temporal relationship in this study, has not been agreed upon by expert consensus. Further discussion is required regarding an ideal period to determine the temporal relationship between vaccination and symptom onset in CNS-IDDs. Despite the above-mentioned shortcomings, our study provides the proportion and diversity of CNS-IDDs following COVID-19 vaccination. Further investigations are warranted to uncover a possible link between COVID-19 vaccination and CNS-IDD onset, including a nationwide comparative study to reveal changes in the annual incidence of new CNS-IDDs following COVID-19 vaccinations.

CRediT authorship contribution statement

Ki Hoon Kim: Resources, Visualization, Writing – original draft, Writing – review & editing. **Su-Hyun Kim:** Resources, Supervision, Writing – review & editing. **Na Young Park:** Resources, Writing – review & editing. **Jae-Won Hyun:** Resources, Writing – review & editing. **Ho Jin Kim:** Resources, Supervision, Writing – review & editing, Conceptualization.

Declaration of Competing Interest

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