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Posted Date: 8 February 2024

doi: 10.20944/preprints202402.0500.v1

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Clinical and Structural Biological Studies of Central Nervous System Inflammatory Demyelinating Diseases Related to COVID-19 Vaccines

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Abstract: Various vaccines have been developed in response to the SARS-CoV-2 pandemic, and the safety of vaccines has become an important issue. COVID-19 vaccines-related central nervous system inflammatory demyelinating diseases (CNS IDDs) have been reported recently. We present one case of AstraZeneca vaccine-related myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease and literature review another 78 patients published from January 2020 to October 2022. Patients were divided into three vaccine groups (viral vector, mRNA and inactivated vaccines) for further analyses. Among 79 patients with COVID-19 vaccines-related CNS IDDs, 49 (62%) cases received viral vector vaccines, 20 (25.3%) received mRNA vaccines and 10 (12.7%) received inactivated vaccines. Twenty-seven cases (34.2%) were confirmed with autoantibodies, including 15 patients (19%) with anti-MOG, 11 (13.9%) with anti-aquaporin 4 (AQP4), and one (1.3%) with both antibodies. Significantly, more males developed CNS IDDs post viral vector vaccines compared to mRNA and inactivated vaccines. Patients receiving mRNA vaccines were older than other groups. Furthermore, mRNA and inactivated vaccines correlated more with anti-AQP4 antibodies, while viral vector vaccines showed higher MOG positivity. The research suggests potential associations between COVID-19 vaccines-related CNS IDDs and gender, age, and autoantibodies, contingent on vaccine types. Protein sequence analysis implies similarities between the S protein and AQP4/MOG. Further studies may elucidate the mechanisms of CNS IDDs, aiding vaccine selection for specific groups.

Keywords: acute disseminated encephalomyelitis; central nervous system inflammatory demyelinating diseases; COVID-19 vaccines; myelin oligodendrocyte glycoprotein antibody-associated disease; neuromyelitis optica spectrum disorders; transverse myelitis

1. Introduction

Diseases of myelin sheaths in the central nervous system (CNS) can be divided into two categories including genetic dysmyelinating diseases with abnormal myelin formation and acquired inflammatory demyelinating diseases, so called central nervous system inflammatory demyelinating diseases (CNS IDDs). CNS IDDs include multiple sclerosis (MS), neuromyelitis optica spectrum

 doi:10.20944/preprints202402.0500.v1

disorders (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), acute disseminated encephalomyelitis (ADEM), optic neuritis (ON) and transverse myelitis (TM) [1].

Among CNS IDDs, MS is the most common one disorder. The worldwide incidence rate of MS is 2.1 per 100,000 person-year, and the prevalence is estimated 35.9 per 100,000 people [2]. MS has been considered as a T cells and B cells-mediated disease, while NMOSD and MOGAD are both related to autoantibodies, which target aquaporin 4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG), respectively. The incidence and prevalence of NMOSD is about 0.28–0.73 per 100,000 person-years and 0.52–10 per 100,000 people, respectively [3]. The epidemiological data of NMOSD ranged widely might be due to different study designs, regions, and ethnicity. NMOSD is more common in East Asian, African and Latin American than other Western populations, and the prevalence is 2.3 to 7.6 times higher in women than in men [4]. Previous studies in Europe estimated that the incidence of MOGAD is around 0.16–0.34 per 100,000 person-years, and the prevalence is 2 per 100,000 people [5,6]. The median age of onset is from early to mid-thirties with a slight predominance in females (57–68%) [7-9]. The clinical manifestations of MOGAD are diverse and can include one or a combination of the following diseases, such as ON, TM and ADEM [10]. ON was the most common symptom (54–68.5%), followed by TM (27–30%), and ADEM or ADEM-like presentation (18–25%) [7,9,11]. The initial presentations of MOGAD in children and adults were also different, that ADEM was the most common in children and ON was primarily found in adults [8].

ADEM is characterized by monophasic multifocal neurologic symptoms, and its diagnosis requires exclusion of MS, NMOSD, MOGAD or other demyelinating diseases [12]. ADEM is primarily regarded as a post-infectious disease, whereas vaccines related ADEM is a rare condition. It has been published that < 5% of ADEM cases were related to vaccination for diseases such as rabies, measles, mumps, smallpox, or Japanese B encephalitis [13]. However, a recent study in the United States reported that there were no statistically significant increased risks of ADEM after vaccination for 5–28 days, except for tetanus, reduced diphtheria, and acellular pertussis (Tdap) [14]. Another study further demonstrated that there was no association between ADEM and various types of vaccines, including Tdap [15]. The controversial relationship between vaccination and ADEM remains ambiguous, and large-scale epidemiologic data and clinical studies are required to confirm their association.

During the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, vaccines are currently one of the most effective ways to prevent infection. The mechanisms of COVID-19 vaccines include viral vectors (AstraZeneca, Janssen, Sputnik V, CanSino), mRNA (Pfizer-BioNTech and Moderna), inactivated vaccines (Sinovac, Sinopharm, Covaxin), and protein subunit vaccines (Medigen). Various side effects of COVID-19 vaccines have been widely reported recently. Although the distinct mechanism has not yet been elucidated, some adverse events may be related to specific groups of vaccines. For example, vaccines-induced immune thrombotic thrombocytopenia (VITT) and Guillain–Barre syndrome are generally considered to be related to the viral vector COVID-19 vaccines [16-19]. An elevated risk of myocarditis was observed in a population of young men who received mRNA COVID-19 vaccines [20]. CNS IDDs, such as TM, NMOSD, ADEM or ON, have been reported after receiving AstraZeneca [21-28], Janssen [29], Sputnik V [30], Pfizer-BioNTech [31-35], Moderna [36-40], Sinovac [41,42], Sinopharm [43,44] and an unknown inactivated vaccine [45].

We speculate that the COVID-19 vaccines may induced CNS IDDs in a small subset of populations. Additionally, different types of COVID-19 vaccines may lead to different clinical manifestations, laboratory or imaging characteristics of CNS IDDs. We now present a patient who developed MOGAD following COVID-19 vaccination and recruit relevant cases from the update literature in details for comparison and analysis.

2. Materials and Methods

2.1. Case presentation

 doi:10.20944/preprints202402.0500.v1

Our report describes a 50-year-old man who has chronic hepatitis B virus (HBV) hepatitis and with no other comorbidities. After the first dose with COVID-19 vaccine (AZD1222, AstraZeneca), the patient experienced mild headache and general weakness that persisted for 2 days and then spontaneously subsided. On the 13th day following vaccination, he experienced acute onset of headache which was exacerbated upon waking up in the morning. In addition, fever, bilateral lower limb numbness, low back pain, confusion, slow response, unsteady gait, constipation, and urine retention requiring insertion of a Foley catheter developed over the following 4 days. Neurologic examination revealed Glasgow coma scale E4V5M6, but with episodic lethargy and obtunded. Impaired proprioception over the bilateral lower limbs causing ataxic gait and a dermatome level with a pin-prick sensation decreased below the T4 level were found. Motor function and deep tendon reflexes were normal, and the Babinski reflex was bilateral plantar flexion. Autonomic dysfunction led to constipation and urine retention. Cervical and thoracic spinal MRI revealed T2-hyperintensity in the spinal cord at the T3 to T4 level without contrast enhancement, resembling focal myelitis (Figure 1a and 1c, 19th day post-vaccination). Brain MRI revealed symmetric, poorly demarcated hyperintensities involving the brainstem, bilateral pulvinar thalami, putamen, centrum semiovale, and subcortical white matter on FLAIR and T2WI without gadolinium enhancement (Figure 2, 20th day post-vaccination). Blood tests revealed leukocytosis (11,000 cells/uL) with neutrophil predominance (85%) and elevated CRP (48.49 mg/L). Urinalysis for intoxication was negative. CSF analysis showed lymphocytic predominant pleocytosis (175 cells/μL, 99% lymphocytes), elevated total protein (78.1 mg/dL), and low CSF/serum glucose ratio (0.47).

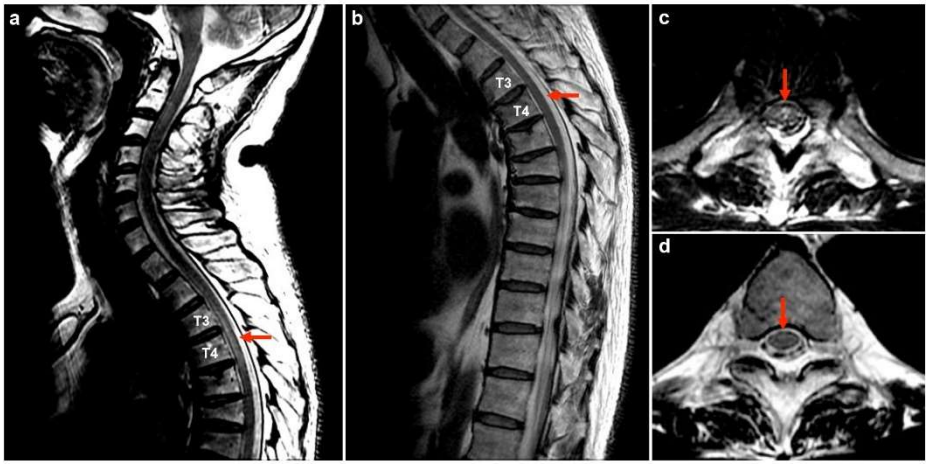

Figure 1. Spinal MRI: On the 6th day after onset, an intramedullary spotty lesion with T2-hyperintensity at T3 to T4 was showed (red arrows. a: sagittal view. c: axial view). Five months later, the lesion over T3 to T4 was totally resolved on T2 FLAIR images (red arrows. b: sagittal view. d: axial view).

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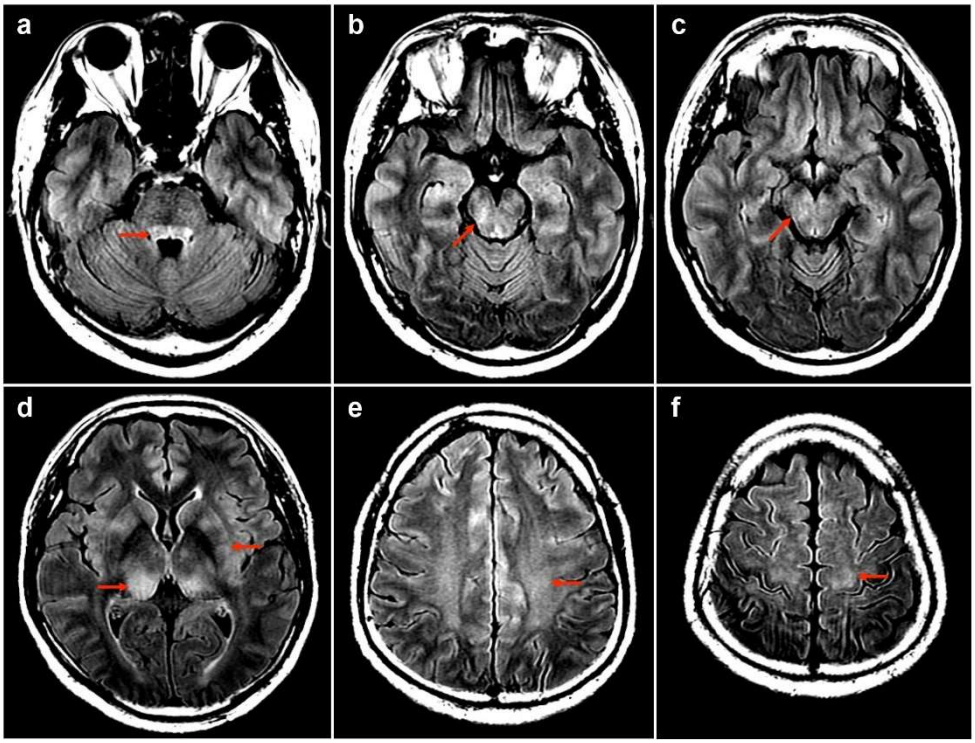

Figure 2. Brain MRI: Bilateral poorly demarcated T2 FLAIR hyperintensities at brainstem (a, b, c), pulvinar thalami (d), putamen (d), centrum semiovale (e) and subcortical white matters (f) were marked by red arrows in the image.

He was administered empiric antibiotics (ceftriaxone and vancomycin) and antiviral (acyclovir) treatment initially which were discontinued because bacterial culture and viral examination of CSF and blood were negative results. Other pathogens, including COVID-19 (nasopharyngeal swab for SARS-CoV-2-RT-PCR), Japanese encephalitis virus, herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), human immunodeficiency virus (HIV), cryptococcus, tuberculosis, syphilis, hepatitis C, and mycoplasma, were all negative. Further tests for vitamin B12 deficiency, vasculitis, connective tissue diseases, and tumor markers were unremarkable findings. Anti-AQP4 antibodies and oligoclonal bands were not found, but anti-MOG antibodies were detected in serum by cell-based assay (CBA) (Figure 3).

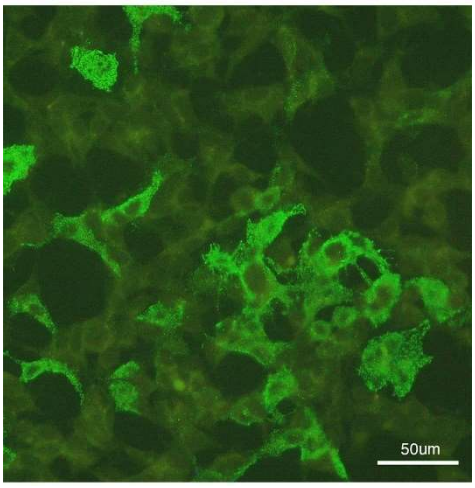

Figure 3. Cell-based immunofluorescence assay (Euroimmun Lübeck, Germany): Indirect immunofluorescence test was used on HEK-293 cells transfected with plasmids containing MOG. After applying diluted (1:10) patient's serum, a positive fluorescent reactivity was indicated over cell membrane and cytoplasm in transfected HEK-293 cells.

 doi:10.20944/preprints202402.0500.v1

Pulse therapy with methylprednisolone (1 g per day for 5 consecutive days) was administered, followed by oral prednisolone (1 mg/kg/day) with gradual tapering. His consciousness and response became clear, and proprioception and pin-prick sensation gradually improved since the 2nd day after pulse therapy. The patient was discharged with total recovery of proprioception, pin-prick sensory level receding to T10 level, and improvement in constipation. The Foley catheter was successfully removed on the 38th day post-vaccination. Spinal MRI 5 months after vaccination revealed total resolution of T3 to T4 myelitis (Figure 1b and 1d). All neurological deficits have fully recovered. Anti-MOG antibodies in serum remained positive after 7 months of follow-up.

2.2. Literature review

To analyze the clinical presentations and MRI findings of patients with CNS IDDs after COVID-19 vaccination, a literature review of studies published in English was conducted using PubMed, EMBASE, Google Scholar, Ovid, and SCOPUS. Published articles and preprint of cases between January 2020 and October 2022 were included to obtain sufficient data, particularly brain and spinal MR imaging. The Medical Subject Heading (MeSH) terms "acute disseminated encephalomyelitis (ADEM)," "myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)", "neuromyelitis optica spectrum disorders (NMOSD)", "optic neuritis" and "myelitis" with "COVID-19 vaccines" were used to retrieve all accessible articles. We aimed to identify cases with first onset of CNS IDDs related to COVID-19 vaccination. Those diagnosed with relapses of MS and NMOSD, SARS-CoV-2 infection, and CNS infection were excluded. We recorded the clinical features, past history, laboratory findings, brain/spinal MR imaging, treatment, and outcomes of our index patient in addition to previously reported cases of CNS IDDs after receiving COVID-19 vaccines. The lesions on brain MRI were classified as cortical, deep gray matters, white matters (periventricular, subcortical, periaqueductal), brainstem, and with or without gadolinium enhancement. The lesions on spinal MRI were divided into long cord (≥3 segments) or short cord (<3 segments), and with or without gadolinium enhancement.

2.3. Statistical analysis

SPSS 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. One-way analysis of variance (ANOVA) was used to compare unpaired groups. An independent samples *t*-test was applied for continuous variables. The level of significance was set at $P < 0.05$. All tests were two-tailed.

3. Results

In total, there were 79 cases (including our index case of MOGAD) diagnosed with CNS IDDs after COVID-19 vaccination. Among them, the proportion of female (54.4%) was higher than that of males (45.6%), with average ages of 46.2 and 48.5 (p=0.524), respectively (Table 1). The majority of patients developed symptoms after the first dose (77.2%) or second dose (21.5%) of the COVID-19 vaccination, while one patient (1.3%) developed CNS IDDs after the third dose. The mean time of onset from vaccination to clinical symptoms was approximately 12.2 days (range 1-42 days). Twenty-four patients (30.4%) presented with ADEM or ADEM-like, 21 cases (26.6%) with myelitis, 17 (21.5%) with ADEM with myelitis, 13 (16.5%) with NMOSD, and four (5.1%) with ON. A total of 27 patients (34.2%) had autoantibodies, including 15 patients (19%) with anti-MOG antibodies, 11 patients (13.9%) with anti-AQP4 antibodies, and one patient (1.3%) with both anti-MOG and anti-AQP4 antibodies. In the CSF examination of the 79 cases, the average WBC was 63.5 cells/μL with lymphocyte predominant, and the average total protein was 69.5 mg/dL. Additionally, oligoclonal bands were positive in 13 cases (16.5%).

Table 1. Demographic, clinical features, and laboratory data of 79 patients with CNS IDDs after COVID-19 vaccines.

			Dx	Serum	CSF	MRI	Tx		Ref

 doi:10.20944/preprints202402.0500.v1

No	Age/sex/PH	Vaccine / interval (D)		AQP4	MOG	OCB	WBC	Lym (%)	Neut(%)	TP	Glu ratio	OCB	Brain	Spine(myelitis)		Outcome	
1	50M/HBV carrier	1st AZ/13	MOGAD	-	+	-	175	99	0	78.1	0.47	NA	Bil thalami, pu, subcortical WM, brainstem	T3-T4	PT	R	Index case
2	45M	1st AZ/12	ADEM+ SSM	-	-	NA	44	P	NA	N	NA	+	Pons, R MCP, R thalamus; C+	Cervical, thoracic and conus medullaris;C+	PT	R	[21]
3	63M/DM, HL, IHD, Af	1st AZ/12	ADEM	-	-	NA	2	NA	NA	69	N	+	Bil WM, bil CC, L thalamus, IC, L midbrain, lower pons, R MCP	N	PT + PP	E(D20)	[22]
4	45M/atopic dermatitis	1st AZ/8	LETM	-	-	NA	481	NA	67	140	0.43	-	N	C3-T2	PT	I	[23]
5	25F	1st AZ/12	LETM	-	-	NA	NA	NA	NA	54.6	0.55	-	N	T3-T5, T7-T8, T11-L1 ;C+ in T7-T8	PT	I	[24]
6	58M/DM, pulmonary sarcoidosis	1st AZ/7	LETM	-	-	+	11	100	0	162	0.54	+	NA	C1-T10; C+ in T3-T4, T9-T10	PT + PE	I	[25]
7	41M/DM	1st AZ/14	LETM	-	NA	NA	11	100	0	44.3	NA	NA	N	T1-T6; C+	PT	R	[26]
8	44F	1st AZ/4	SSM	-	-	NA	↑	P	NA	76.7	NA	-	N	T7-T8, T10-T11; C+ in T7-T8	PT	R	[27]
9	36M	1st AZ/8	SSM	-	-	NA	NA	NA	NA	54	NA	NA	N	C6-C7; C+	PT	R	[28]
10	44F	1st Janssen/10	LETM	-	NA	NA	227	96	0	43	N	-	N	C2 to upper thoracic	PT + PE	R	[29]
11	34M	2nd Sputnik V/21	NMOSD	+	-	NA	↑	P	NA	↑	NA	-	Lateral, 3rd and 4th ventricles, thalamus, CC, optic chiasma	N	PP	I	[30]
12	88F/DM, AD	2nd Pfizer/29	ADEM	NA	NA	NA	NA	NA	NA	NA	NA	-	Bil MCPs	NA	PT	R	[31]
13	56F/Post-infectious rhombencephalitis	1st Pfizer/14	ADEM-like	-	-	-	N	NA	NA	N	N	-	L cerebellar peduncle and L centrum semiovale	NA	Oral steroid	R	[32]
14	64M	1st Pfizer/18	NMOSD	+	NA	NA	N	NA	NA	N	N	-	CC, L frontal and parietal WM; C-	Cervical to the conus; C+	PT + PE + RTX	I	[33]
15	38M	1st Pfizer/2	SSM	NA	NA	NA	NA	NA	NA	62.1	N	NA	NA	T11-T12; C+	NA	NA	[34]
16	69F/cervical ca, HL, hypothyroidism	1st Pfizer/2	LETM	-	-	+	N	NA	NA	N	N	+	N	C3-C4 to T2-T3	PT	I	[35]
17	19F/atopic dermatitis, depression	1st Moderna/14	ADEM+ LETM	-	-	-	294	91	1	64.8	NA	-	Bil hemispheres, pons, medulla, cerebellum; C+	Medulla to T11; C+	PT + PE	R	[36]
18	46F/c	1st Moderna/2	NMOSD	-	NA	NA	NA	NA	NA	NA	NA	NA	N	C6-T2	PT	R	[37]
19	76F/HTN, vit B12 deficiency	1st Moderna/2	LETM	-	NA	NA	15	NA	73	57.2	NA	-	N	C2-C5; C+ in C3	PT	I	[38]
20	67F/CAD, CKD, neuropathy	1st Moderna/1	LETM	-	-	+	2	NA	NA	56	0.61	+	Nonspecific WM	C1-C3; C+	PT + PP	I	[39]
21	63M	2nd Moderna/1	SSM	-	-	NA	3	NA	NA	37	N	NA	Nonspecific bil corona radiata	Conus medullaris; C+	IVIG + PT	I	[40]
22	46F/Hashimoto's thyroiditis	2nd Sinovac/30	ADEM-like	-	-	NA	0	0	0	45	NA	-	L thalamus, bil corona radiata, L diencephalon, R parietal cortex	NA	PT	R	[41]
23	78F/DM, HTN, breast ca	2nd Sinovac/21	LETM	-	-	NA	2	NA	NA	56	0.69	-	N	C1-T3	PT	I	[42]

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24	24F	1st Sinopharm/14	ADEM	-	-	-	51	NA	NA	NA	NA	-	Bil temporal	NA	IVIG	I	[43]
25	71M/DM, HTN, IHD	1st Sinopharm/5	LETM	-	-	NA	0	0	0	N	N	-	N	Cervico-medullary junction to C3	PT	I	[44]
26	50F	1st inactivated/3	NMOSD	+	-	NA	31	NA	NA	N	N	-	Area postrema , bil hypothalamus	N	PT	I	[45]
27	65M	1st AZ/8	LETM	-	-	NA	N	NA	NA	70	NA	-	NA	C4-C6	PT	R	[52]
28	68F/HTN, pancreatic ca	2nd Moderna/14	MOGAD	-	+	NA	0	0	0	32	NA	+	R lateral pons, trigeminal nerve, MCP	NA	PT	I	[53]
29	59M	1st AZ/14	MOGAD	-	+	NA	110	NA	NA	625	N	+	N	T7-L1	PT + PE	I	[54]
30	45M/allergic asthma	1st AZ/7	MOGAD	-	+	NA	43	NA	NA	40.6	N	-	Bil subcortical and gray-white matter	T10-conus	PT	I	[55]
31	26M	1st AZ/20	MOGAD	-	+	NA	184	NA	NA	88	NA	-	Bil MCPs, pons	C3-C6	PT	I	[56]
32	56F/HTN	1st AZ/2	ADEM-like	NA	NA	NA	NA	NA	NA	NA	NA	NA	L parietal WM, body of CC	NA	Oral steroid	I	[57]
33	81M	1st Moderna/13	ADEM	NA	-	NA	69	83%	NA	52	N	NA	R dorsal medulla, L pons, midbrain, thalami	NA	PT + IVIG + PP	E(D26)	[58]
34	63F/HL, hypothyroidism	1st Pfizer/7	NMOSD	+	-	NA	33	91%	NA	57	NA	-	L thalamus	T6-T12	PT + PP	R	
35	54F/ITP	2nd Moderna/3	NMOSD	+	-	NA	26	86%	NA	71	NA	-	N	T2-T9	PT	I	
36	55M	1st mRNA/21	ADEM	NA	NA	NA	200	95%	NA	75	N	NA	Bil WM	NA	PT	R	[59]
37	36F	1st AZ/14	ADEM	-	-	+	59	NA	NA	40	N	+	Subcortical WM, PIC, pons and L MCP	N	PT	R	[60]
38	37M	1st Sinopharm/30	ADEM	NA	NA	NA	2	NA	NA	56	0.61	-	L cerebral peduncle, bil pons, medulla	N	PT	R	[61]
39	27F/Recto vaginal fistula	2nd Pfizer/4	LETM	-	-	NA	7	NA	NA	43	N	-	N	C5-C7	PT	I	[62]
40	61F/HTN, anxiety	1st Pfizer/5	ADEM	NA	-	NA	N	NA	NA	61	N	-	Deep WM, brainstem, cerebellum	N	PT + IVIG	I	[63]
41	64M	1st AZ/10	ADEM	-	-	NA	25	P	NA	NA	N	NA	Bil mesial temporal, hippocampus, MCPs	NA	PT + PP + RTX	R	[64]
42	64M	2nd AZ/20	ADEM+ SSM	-	-	NA	N	NA	NA	N	N	NA	Bil perirolandic cortex, corona radiata	T8-T9 dorsal	PT + IVIG + RTX	I	
43	46M	1st AZ/5	ADEM + LETM	-	-	NA	63	NA	NA	52	N	NA	Bil MCP, pontine tegmentum, R paramedian medulla, L thalamocapsular	LETM	PT + PE	I	
44	42F	1st AZ/5	ADEM-like	-	-	NA	N	NA	NA	N	N	NA	R temporal	NA	Oral steroid	R	
45	56F	1st AZ/10	ADEM-like	NA	NA	NA	1	16%	20%	↑	N	NA	Subcortical WM, basal ganglia	NA	PT	R	[65]
46	44F/HL, hypothyroidism, renal stone, anxiety	1st mRNA/6	ADEM+ LETM	-	NA	NA	105	NA	NA	98	N	-	Multifocal PV lesions; C+ in L frontal WM	C3-C4 to thoracic with sparing C5-C6; C+ in T7-T8	PT + PP	I	[66]
47	70F	3rd Sinovac/7	NMOSD	+	NA	NA	N	N	N	N	N	-	NA	C1-C7 and T1-T3	PT + PE + CP	E(M2)	[67]
48	26F	1st Sinovac/10	NMOSD	+	NA	NA	N	N	N	N	N	-	N	C4-C5	PT + PE + RTX	I	[68]
49	46F	1st AZ/10	NMOSD	+	NA	NA	N	N	N	N	N	-	R lateral medulla, PV	C2-C3	PT +AZT	I	

 doi:10.20944/preprints202402.0500.v1

50	80M	2nd Pfizer/2	NMOSD	+	+	NA	39	93%	NA	N	N	-	N	T3-T10	PT + PE + MMF	I	[69]
51	43F	2nd Pfizer/1	NMOSD	+	-	NA	6	NA	NA	40.1	N	+	R ON, R periatrium, L crus cerebri	C1 to mid-thoracic	PT + PE + RTX	R	[70]
52	29F	1st AZ/11	MOGAD	NA	+	NA	0	NA	NA	18	N	-	Long intraorbital segment of R ON	NA	PT + PP	NA	
53	26F	1st Covaxin /11	LETM	-	-	NA	207	NA	P	95.8	N	NA	NA	C2-L1	PT + PP	NA	
54	54F	1st AZ/14	ADEM-like	-	-	NA	8	P	NA	77	N	NA	CC, PV, subcortical WM, infratentorial	NA	PT + PP	NA	
55	44M	1st AZ/7	MOGAD	NA	+	NA	130	P	NA	38	N	NA	NA	Cervical and dorsal cord, conus	PT + PP	NA	
56	50F	1st AZ/28	SSM	-	-	NA	2	P	NA	28	N	NA	NA	C6	PT	NA	
57	39M	1st AZ/14	MOGAD	NA	+	NA	NA	NA	NA	NA	NA	NA	Long intraorbital segment of R ON	NA	PT	NA	
58	54M	1st AZ/14	MOGAD	NA	+	NA	NA	NA	NA	NA	NA	NA	R pons	N	PT	NA	
59	34M	1st AZ/1	ON	-	-	NA	2	P	NA	26	N	NA	R ON	NA	PT	NA	
60	35M	1st AZ/9	MOGAD	NA	+	NA	58	P	NA	47.4	N	NA	Midbrain, pons, L MCP, PICs, thalamus, bil centrum semiovale	Cervical to conus	PT	NA	
61	20F	1st AZ/3	ADEM-like	-	-	NA	NA	NA	NA	NA	NA	NA	Pericallosal, callososeptal, PV, fronto-parietal	NA	PT	NA	
62	31M	1st AZ/14	LETM	-	-	NA	370	NA	P	174	N	NA	NA	Cervico-dorsal long segment	PT + PP + RTX	NA	
63	20F	1st Covaxin /1	ADEM+ SSM	-	-	NA	8	P	NA	24.9	N	-	Juxtacortical	C5	PT + PP	NA	
64	45F	1st AZ/21	MOGAD	NA	+	NA	2	P	NA	52.3	N	+	Bil ON	N	PT + PP	NA	
65	33F	1st AZ/14	MOGAD	NA	+	NA	105	P	NA	28.12	N	NA	Bil fronto-parietal	NA	PT	NA	[71]
66	53F	2nd AZ/1	ADEM+ LETM	-	-	NA	6	P	NA	54.2	N	NA	Bil subcortical, PV WM, insular, cerebellum, brainstem	C5-C7 and T6-T7	PT	NA	
67	38M	2nd AZ/6	ADEM-like	-	-	NA	6	NA	NA	67.8	N	NA	L MCP, R corona radiata	NA	PT	NA	
68	30M	1st AZ/14	ADEM+ ON	-	-	NA	4	50	NA	26.8	N	+	Bil subcortical lesions, bil ON	NA	PT + PP + RTX	NA	
69	30F	1st AZ/15	ADEM+ SSM	-	-	NA	4	NA	NA	36	N	+	CC	C3	PT + PP + MMF	NA	
70	36M	2nd AZ/32	MOGAD	NA	+	NA	720	80	NA	144.4	N	NA	Bil trigeminal n, pons	Obex to conus	PT + PP	NA	
71	27F	1st AZ/8	ADEM-like	-	-	NA	Clear	NA	NA	27.7	N	NA	Bil PV WM	N	PT	NA	
72	60M	2nd AZ/14	ADEM	-	-	NA	9	90	NA	68.3	N	-	R pons, midbrain, temporal, parietal, CC	NA	PT + MMF	NA	
73	23F	2nd AZ/7	ADEM+ LETM	-	-	NA	NA	NA	NA	NA	NA	-	R frontal horn and bil lateral ventricles	C2-C5 and T4 myelitis	PT	NA	
74	40M	1st AZ/10	MOGAD	NA	+	NA	8	100	0	32	N	+	Pons, bil thalami and R frontal cortex	C4-T3	PT + MMF	NA	
75	45M	1st AZ/10	MOGAD	-	+	NA	44	44	NA	90.9	N	NA	Brainstem, supratentorial	Cervicodorsal cord	PT + PP	NA	
76	34F	2nd AZ/36	NMOSD	+	-	NA	1	NA	NA	15.3	N	-	Dorsal aspect of medulla	NA	PT + PP + RTX	NA	
77	31M	1st AZ/42	ADEM+	-	-	NA	32	100	0	49.2	N	NA	Cervico-medullary junction, R	C2-C5	PT + PP + MMF	NA	

 doi:10.20944/preprints202402.0500.v1

			LETM									frontal subcortical				
78	52F	1st AZ/35	ADEM-like	-	-	NA	2	NA	NA	40.5	N	NA	L frontal, insular, midbrain	NA	PT + PP + RTX	NA
79	65F	1st AZ/42	NMOSD	+	-	NA	17	NA	NA	49	N	NA	Frontal subcortical WM	T2-T11	PT + PP + MMF	NA

Abbreviations: Af: atrial fibrillation. AD: Alzheimer's disease. AZT: azathioprine. C+: with contrast enhancement. CC: corpus callosum. CKD: chronic kidney disease. CP: cyclophosphamide. DM: diabetes mellitus. E: expired. HBV: hepatitis B virus. HL: hyperlipidemia. HTN: hypertension. I: improvement. IC: internal capsule. IHD: ischemic heart disease. ITP: immune thrombocytopenic purpura. MCP: middle cerebellar peduncle. MMF: *Mycophenolate* mofetil. N: normal. NA: not available. ON: optic neuritis. P: predominant. PIC: posterior limb of internal capsule. PP: plasmapheresis. PT: steroid pulse therapy. PU: putamen. PV: periventricular. R: complete recovery. RTX: rituximab. WM: white matter.

[a] Oxford-AstraZeneca, marketed as Covishield. A kind of viral vector (chimpanzee adenovirus) vaccine. [b] Johnson & Johnson's Janssen, a kind of viral vector (human adenovirus) vaccine. [c] A kind of viral vector (human adenovirus) vaccine. [d] Pfizer-BioNTech, marketed as Comirnaty. A kind of messenger RNA vaccine. [e] A kind of messenger RNA vaccine. [f] Marketed as CoronaVac. A kind of inactivated vaccine. [g] Also known as BBIBP-CorV. A kind of inactivated vaccine. [h] Clinical and MRI features are compatible with ADEM, but without presentation of encephalopathy

COVID-19 vaccines with different mechanisms of action may lead to different manifestations of CNS IDDs. We categorize the vaccines into three major groups, including viral vector (49 cases, 62%), mRNA (20 cases, 25.3%) and inactivated vaccines (10 cases, 12.7%), to analyze their clinical presentations and laboratory examinations of CNS IDDs (Table 2). Compared to viral vector vaccines, CNS IDDs were more commonly observed in female patients receiving mRNA or inactivated vaccines ($p = 0.027$). The mean age of onset of patients received mRNA vaccines was much older than those receiving viral vector or inactivated vaccines ($p = 0.002$). The vast majority of patients in the viral vector vaccine group developed CNS IDDs after the first dose. Approximately two-thirds of the mRNA vaccine group experienced CNS IDDs after the first dose, and one-third after the second dose. In the inactivated vaccine group, there was one patient developed CNS IDDs after the third dose. The time interval between vaccination and clinical presentations of CNS IDDs in patients receiving mRNA vaccines appears to be shorter than the other two groups, although it is not statistically significant. There was no significant difference in the clinical presentations of CNS IDDs among these three groups. Patients receiving mRNA or inactivated vaccines were more commonly found to have anti-AQP4 antibodies, while those receiving viral vector vaccines were frequently associated with anti-MOG antibodies ($p = 0.044$). On the other hand, a higher rate of CSF pleocytosis with lymphocyte predominant was observed in patients administered viral vector and mRNA vaccines ($p = 0.004$). Spinal cord lesions with gadolinium enhancement were most commonly found in patients who received mRNA vaccines ($p = 0.015$). There was no significant difference in the distribution of brain lesions or LETM (>= 3 contiguous vertebral segments) between the three groups. In past history, hypertension and diabetes were the most common, with 6 patients each (Table 1). The next most common diseases were hyperlipidemia and autoimmune diseases, with 4 patients each. Nevertheless, there was no statistically significant correlation between past history and the occurrence of CNS IDDs due to receiving different groups of vaccines (data not presented in Table 2).

The majority of patients (86%) received the first-line immunotherapy, including steroid pulse therapy, plasmapheresis/plasma exchange, or IVIG. Ten patients (13%) underwent additional second-line immunotherapy, such as cyclophosphamide or Rituximab. Except for the three mortality cases (3.8%), the rest of the patients had either totally recovered (20 patients) or shown improvement (27 patients).

Table 2. Differences between three major vaccine groups.

	Vaccine types			
	Viral vector (n=49)	**mRNA (n=20)**	**Inactivated(n=10)**	**P value**
Sex, n (%)				0.027*
Male	28 (57)	6 (30)	2 (20)	
Female	21 (43)	14 (70)	8 (80)	
Mean age of onset (S.D.)	44.3 (12.2)	58.1 (17.9)	44.8 (21.8)	0.002*
Doses (1st/2nd/3rd)	41/8/0	13/7/0	7/2/1	0.042*
Post-vaccination onset time (days)	13.6	8.1	13.6	0.086
Clinical presentations, n (%)				0.200
ADEM	15 (31)	6 (30)	3 (30)	
ADEM with myelitis	14 (29)	2 (10)	1 (10)	

 doi:10.20944/preprints202402.0500.v1

4.

Pure myelitis	12 (24)	6 (30)	3 (30)	
ON	4 (8)	0 (0)	0 (0)	
NMOSD	4 (8)	6 (30)	3 (30)	
Serum Autoantibodies, n				0.044*
Negative	31	14	7	
MOG	14	1	0	
AQP4	4	4	3	
MOG+AQP4	0	1	0	
CSF, n				
WBC count	74.2	57.1	30.1	0.605
Lym predominant (yes/no)	23/3	6/2	1/4	0.004*
Elevated total protein (yes/no)[@]	24/19	10/8	4/5	0.817
CSF/serum glu ratio (<0.6/>0.6)	4/33	0/13	0/8	0.295
Oligoclonal bands (+/-)	9/13	4/11	0/9	0.071
Brain MRI lesions, n				
Cortex (+/-)	7/33	1/16	2/5	0.329
Deep grey matters (+/-)	8/32	2/15	2/5	0.598
Subcortical white matters (+/-)	18/22	5/12	2/5	0.454
Periventricular white matters (+/-)	16/24	6/11	1/6	0.424
Periaqueductal white matters (+/-)	3/37	0/17	0/7	0.389
Brainstem (+/-)	20/20	7/10	2/5	0.532
Gadolinium enhanced (+/-)	1/9	2/9	0/5	0.562
Spine MRI, n				
Segments of cord lesions (≥ 3/< 3)	20/8	12/2	4/2	0.143
Gadolinium enhanced (+/-)	6/6	7/1	0/4	0.015*
Treatment, n				0.754
1st line immunotherapy	43	17	8	
1st and 2nd line immunotherapy	6	2	2	
Outcome, n				0.762
Recovery	11	7	2	
Improved	11	11	5	
Expired	1	1	1	

*Pearson chi-squared test, p<0.05

[#] Independent t test, p<0.05

[@] Elevated total protein defined as total protein > 45 mg/dL

Discussion

During the global SARS-CoV-2 pandemic, universal vaccination is a key factor in preventing infection and avoiding critical illness. The overall safety and tolerability of COVID-19 vaccines has been shown to be generally acceptable in patients with underlying CNS IDDs, but there were still some patients (16.7%) reported worsening of their symptoms after vaccination during the first week, with rapid resolution within 3 days [46]. The cases we reviewed in our study resulted from exposure to COVID-19 vaccines and they did not have a past history of CNS IDDs. The decision whether to receive the 2nd or booster shots of COVID-19 vaccines, or to shift to another kind of vaccine, are important clinical issues.

According to statistics from the Centers for Disease Control in Taiwan, as of April 2023, the COVID-19 vaccine coverage rate was 94% for the first dose, 89% for the second dose, and 76.7% for additional doses. Most people received mRNA or viral vector vaccines, including Moderna (42.7%), Pfizer-BioNTech (29.2%), AstraZeneca (22.5%), Medigen (4.5%, a type of protein subunit vaccine produced in Taiwan), and Novavax (0.9%). Various adverse effects were reported. Six ADEM (not included our index case), two NMOSD, 13 ON, and four myelitis cases were suspected to be related to COVID-19 vaccination been reported on Taiwan CDC website, but they had not been formally published [47]. Thrombosis with thrombocytopenia syndrome (TTS, also known as VITT) was suspected in 74 cases (86% of them received AstraZeneca, 8% received Moderna, 4% received Pfizer and 1% received Medigen) [47]. In Taiwan, the first case of VITT after the AstraZeneca vaccination was diagnosed in May 2021 at Chang Gung Memorial Hospital, a tertiary medical center. The patient presented with severe headaches, thrombocytopenia, and abdominal pain without neurological deficit. Brain CT revealed lacunar infarction in the right centrum semiovale. His platelet count

 doi:10.20944/preprints202402.0500.v1

normalized after treatment with high-dose IVIG (2 g/kg for two consecutive days) and he was discharged without further thrombotic or hemorrhagic events [48].

The pathophysiology of vaccines-induced CNS IDDs remains unclear. Many studies have suggested the molecular mimicry theory. For example, amino acid similarities between small HBV surface antigen (SHBsAg, the ingredient of HBV non-infectious viral subunit vaccine) and MOG have been analyzed, displaying 66–100% homology in several sequences [49]. This finding suggests the possibility of immunological cross-reactivity. H1N1 and HPV vaccines have been identified with suspicious overlapping targets, which may result in certain autoimmune diseases [50]. Although there is no evidence of molecular mimicry regarding COVID-19 vaccines to date, the positive findings of anti-MOG antibodies and anti-AQP4 antibodies after receiving COVID-19 vaccines imply the possible similar amino acid sequences of MOG, AQP4, and spike (S) protein of SARS-CoV-2 virus or other unidentified immunological mechanisms. Through protein sequence analysis, it is possible that the S protein shares similar protein sequences with AQP4 and MOG (Figure 4). Once the definite pathological mechanisms have been elucidated, CNS IDDs induced by COVID-19 vaccines may be avoided by the development of safer vaccines. These results have limitations because of a short follow-up period and a small number of patients. A larger database is required for further investigation into the relationship between demographics and vaccine types. The occurrence of CNS IDDs may be reduced by employing more precise indications for each kind of COVID-19 vaccines.

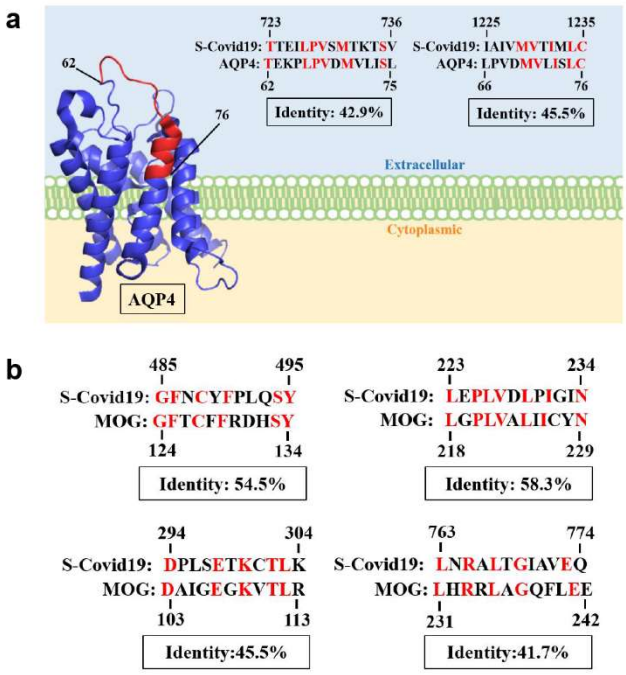

Figure 4. S-Covid 19 refers to the spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), retrieved from the Protein Data Bank (PDB) under the accession number 6X29. Aquaporin 4 (AQP4) has a well-documented 3D structure with established structural domains, sourced from the PDB with the accession number 3GD8 (a). Notably, the extracellular loop of the AQP4 transmembrane protein could function as an antigen or be recognized by antibodies. The 3D structure of MOG is unknown (b). The Expasy SIM protein sequence alignment tool was utilized for analysis (https://web.expasy.org/sim/). Additionally, we employed PyMOL for protein structural analysis. The red-highlighted structure represents regions of high similarity between the two proteins.

The rare complication of CNS IDDs after vaccination should not restrain the use of vaccines during the COVID-19 pandemic. For those who develop vaccines-related neuroimmunological adverse effects, further treatment strategies should be considered. Although the short-term outcomes were primarily ideal among the patients listed in our review following appropriate treatment, the possibility of long-term sequelae or recurrence of CNS IDDs still exists. To our knowledge, NMOSD

and MOGAD patients have a higher risk of relapse if persistent seropositivity, and prolonged immunotherapy should be considered to prevent relapse [10,51]. Therefore, patients initially positive for autoantibodies are recommended for regular follow up MRI and antibody testing. Attention is also required for seronegative cases because of the possibility of seroconversion or the existence of other yet undefined autoantibodies.

5. Conclusions

We observed that there were more male patients with CNS IDDs in the viral vector vaccine group and they were often accompanied with anti-MOG antibodies. Patients receiving mRNA vaccines were older and more commonly positive for anti-AQP4 antibodies. The current consensus is that the rare occurrence of CNS IDDs is not a contraindication to vaccination. More extensive studies with larger cohorts are necessary to elucidate the pathological mechanisms of vaccines-related CNS IDDs and can provide physicians to select safer and more appropriate vaccines for each individual group to reduce the risk of adverse effects.

Author Contributions: *All authors contributed to the study conception and design. Data collection and analysis were performed by Mei-Yun Cheng,* Hsuan-Chen Ho, Jung-Lung Hsu, *and* Ming-Feng Liao. Protein sequence analysis was undertaken by Yi Wang and Lin-Yi Chen. *The first draft of the manuscript was written by Mei-Yun Cheng and* Hsuan-Chen Ho. Long-Sun Ro supervised the editing of the writing. A*ll authors critically reviewed the manuscript and approved the final version for submission.*

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (No: 202200651B0) of Chang Gung Memorial Hospital for studies involving humans.

Informed Consent Statement: Patient consent was waived due to retrospective medical chart reviews.
Data Availability Statement: *The datasets generated during and/or analyzed during the current study are available from the corresponding author.*

Acknowledgments: The cell-based immunofluorescence assay was performed and photographed by Yang-Hsuan at Chang-Gung Memorial Hospital in Linkou, Taiwan.

Conflicts of Interest: The authors declare no conflicts of interest.

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