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Multiple sclerosis and neuroimmunology – case report collection, volume II

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CASE REPORT
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Case Report: Interferon-Alpha-Induced Neuromyelitis Optica Spectrum Disorder

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Background and Objectives: To describe a new case of neuromyelitis optica spectrum disorder (NMOSD) induced by the administration of interferon-alpha (IFNα) and to raise awareness of this rare drug-induced disease of IFNα treatment.

Methods: A single case study and comprehensive literature review of eight cases.

Results: A 24-year-old man was diagnosed with cerebral venous thrombosis and essential thrombocythemia. He had been undergoing IFNα treatment (IFNα-2b, 3 million IU per day) without any side effects for 18 months, at which point the patient developed persistent hiccups, nausea, urinary retention, and numbness. Spinal magnetic resonance imaging revealed a longitudinal abnormality extending from the medulla to the entire spinal cord. The patient was positive for anti-aquaporin-4 antibody (AQP4-IgG) in both the serum and cerebrospinal fluid (CSF), which confirmed the diagnosis of NMOSD. Thus, recombinant IFNα-2b was suspended immediately. Because his condition did not improve after 6-day treatment of methylprednisolone pulse therapy (1,000 mg for 3 days, then 500 mg for 3 days), intravenous immunoglobulin (0.4 g/kg/day for 5 days) was administered. The patient gradually improved. Low-dose prednisolone and mycophenolate mofetil were subsequently administered as a long-term treatment. The patient was discharged with subtle limb numbness and their expanded disability status score (EDSS) was 1. At the 1-year follow-up, the patient had not relapsed and tested negative for AQP4-IgG. We further identified the eight patients with IFNα-induced NMOSD. The median onset age was 59 years, and the median time of IFNα exposure was 18 months. Optic neuritis was the most common initial symptom (five, 55.6%), followed by myelitis in three patients and area postrema syndrome in one patient. More than half (five, 55.6%) of the patients were monophasic. After IFNα discontinuation and immunotherapy, most (seven, 77.8%) patients remained relapse-free. However, only one patient was free of sequelae.

Conclusion: This study highlights the potential pathogenic risk of NMOSD of IFNα treatment. Given the high disability rates of this rare drug-induced disease, it is crucial to monitor the early manifestations of NMOSD during IFNα treatment.

Keywords: NMOSD, AQP4 antibody, interferon, drug-induced disease, autoimmune disease, case report

INTRODUCTION

Neuromyelitis Optica spectrum disorder (NMOSD) refers to a spectrum of the central nervous system (CNS) neuroinflammatory demyelinating disease that predominantly attacks the spinal cord, optic nerves, and brain (1, 2). The NMOSD is usually associated with a significant reduction in patients' quality of life and heavy economic burden. In contrast to T-lymphocyte-predominant myelinopathy in multiple sclerosis (MS) (3), NMOSD is considered an autoimmune astrocytopathy mediated by anti-aquaporin-4 antibodies (AQP4-IgG) (2). Type I interferons (IFNIs), particularly interferon-alpha (IFNα), are widely used to treat various infectious, immunological, and oncological diseases (4). They are also moderately effective for restricting CNS autoimmunity and are currently recommended as first-line immunomodulatory therapy for MS (5, 6). However, their use in patients with NMOSD is associated with neurologic deterioration and increased AQP4-IgG production (7, 8), which suggests a possible link between the development of NMOSD and IFNI. Although various CNS side effects of IFNI treatment have been reported to date, NMOSD remains largely unrecognized as a drug-induced disease (DID) of IFNI therapy (9). Recently, NMOSD cases associated with IFNα treatment started arising sporadically in patients with hepatitis C (9–14), systemic mastocytosis (9), and malignant melanoma (15). However, the underlying diseases may contribute to the occurrence of NMOSD in such cases. The precise relationship between IFNα and NMOSD remains elusive.

Herein, we present a case where the patient developed NMOSD following the administration of recombinant IFNα-2b for essential thrombocythemia (ET). We also determined the clinical profile and potential mechanism of IFNα-induced NMOSD by reviewing previously published cases.

METHODS

This study was a single case report with a comprehensive literature review. The ethics committees waived institutional review and ethical approval. The patient provided written informed consent for publication. De-identified data are available upon appropriate request to the corresponding author.

We performed a systematic review of reported cases published between January 1, 2000, and December 31, 2021, by searching PubMed and China National Knowledge Infrastructure databases using the following search strategy: "NMOSD," "NMO," "AQP-4 antibody," "type I interferon," "interferon-alpha," and "interferon-beta." Reference lists of the identified publications were manually searched to find relevant publications not captured by the initial search strategy. Seven reports of eight cases were identified and reviewed.

Abbreviations: ANA, antinuclear antibody; ANCA, anti-neutrophilcytoplasmic antibody; APRIL, a proliferation-inducing ligand; APS, area postrema syndrome; AQP4, aquaporin-4; BAFF, B-Cell activating factor; CE-MRV, contrast-enhanced magnetic resonance venography; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; CVST, cerebral venous sinus thrombosis; DID, drug-induced disease; EAE, experimental autoimmune encephalomyelitis; EDSS, Expanded disability status score; ET, essential thrombocythemia; GAD, glutamate decarboxylase; GFAP, glial fibrillary acidic protein; HCV, hepatitis C virus; HLA, human leukocyte antigen; huC, human complement; IFN, interferon; IFNI, type I interferon; IFNAR, type-I IFN receptor; IgG, immunoglobulin G; IL-6, interleukin-6; NMOSD, neuromyelitis optica spectrum disorder; MRI, magnetic resonance imaging; MS, multiple sclerosis; mDC, myeloid dendritic cells; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; ON, optic neuritis; pDCs, plasmacytoid dendritic cells; SLE, systemic lupus erythematosus.

CASE PRESENTATION

A 24-year-old Chinese man presented with progressive headaches and right tinnitus for 3 months. He had no medical or family history relevant to his symptoms. He first visited the local hospital 2 weeks after onset, but no neurologic deficit was found. Brain MRI was performed 1 month later, which showed no abnormalities. He was admitted to our hospital after developing nausea and blurred vision. Neurological examination showed neck stiffness and bilateral optic disc swelling (ODS) (**Figure 1A**). Bilateral enlargement of the physiological blind spot was found in the visual field examinations (**Figure 1C**). Brain MRI with contrast showed no enhancement of the optic nerve (**Figure 1H**); however, the patient exhibited several imaging signs of intracranial hypertension (IH), which included the empty-sella sign (**Figure 1E**), perioptic subarachnoid space distension (**Figures 1F,G**), optic nerve tortuosity (**Figure 1G**), and posterior globe flattening (**Figures 1F,G**). A lumbar puncture was subsequently performed with an opening pressure of over 400 mm H_2O. The CSF analysis results were all within normal ranges. Therefore, the ODS was considered a result of IH rather than optic neuritis. Contrast MRI also showed filling defects in the right transverse-sigmoid sinus (**Figure 1I**), which were confirmed by contrast-enhanced magnetic resonance venography (CE-MRV) (**Figure 1J**). The diagnosis of cerebral venous sinus thrombosis (CVST) was then established. Thrombosis risk factors were screened, and laboratory analyses for acquired and genetic hypercoagulability states were performed. However, the patient showed no abnormalities except for thrombocytosis (402×10^9 /L). The patient underwent whole-exome sequencing, which revealed a mutation in JAK2-V617F (**Figure 2A**). Furthermore, a bone marrow biopsy showed increased numbers of megakaryocytes. Thus, ET with high thrombosis risk was established. The patient received low-molecular-weight heparin for 1 month, then, switched to indefinite 3-month warfarin treatment with an INR of 2–3. For patients with ET in the high-risk category, timely initiation of first-line cytoreduction therapies with recombinant IFNα or hydroxyurea are recommended. Therefore, IFNα-2b (3 million IU per day) was prescribed, and platelet count was controlled adequately. Headache and blurred vision gradually subsided within 2 months. Two months later, a repeat MRI showed partial recanalization of the right transverse-sigmoid sinus (**Figures 1K,L**), and the CSF opening pressure was 200 mm H_2O. Repeated fundoscopic examination showed mild improvement of ODS; thus, acetazolamide (250 mg twice a day) was administered to control IH.

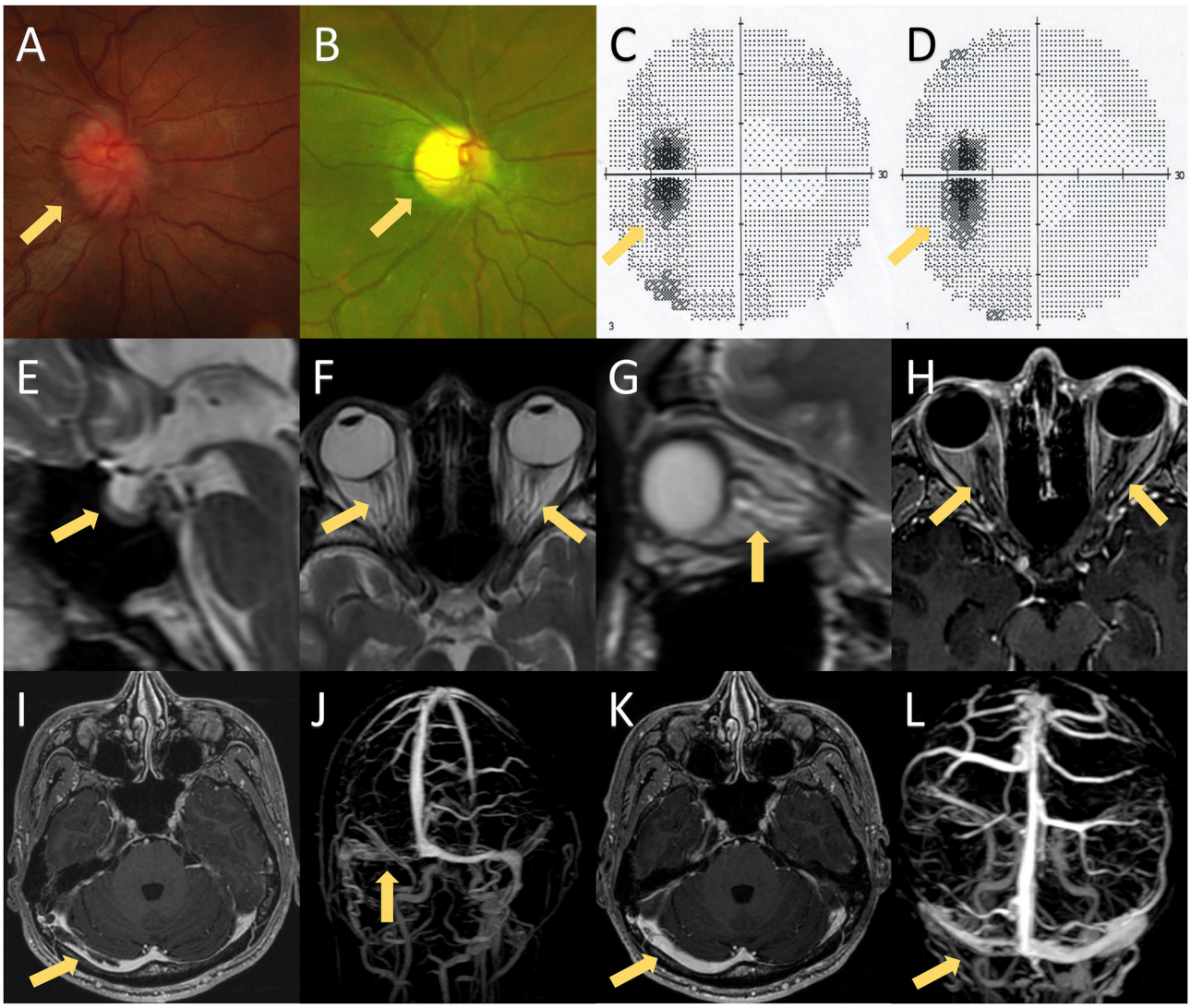

FIGURE 1 | MRI findings, fundoscopic findings, and visual fields of the presented case. **(A)** Fundoscopic examination on the first hospitalization showed bilateral papilledema. **(B)** Fundoscopic examination on the second hospitalization revealed bilateral optic atrophy, which was probably caused by bilateral papilledema. **(C,D)** Visual fields on the first and second hospitalizations showed bilateral enlargement of the physiological blind spot without any other visual field defect. **(E–G)** Brain MRI exhibited several imaging signs of intracranial hypertension, including the empty-sella sign **(E)**, perioptic subarachnoid space distension **(F,G)**, optic nerve tortuosity **(G)**, and posterior globe flattening **(F,G)**. **(H)** Brain MRI with contrast showed no enhancement of the optic nerve. **(I,J)** Post-contrast 3D GRE T1-weighted imaging and contrast-enhanced magnetic resonance venography (CE-MRV) showed filling defects of the right transverse-sigmoid sinus. **(K,L)** Brain MRI and CE-MRV after 3 months of anticoagulation showed partial recanalization of the right transverse-sigmoid sinus.

The patient had no side effects of IFNα treatment, and his condition remained stable. However, 18 months later, he complained of persistent hiccups, nausea, and vomiting for 8 days and was admitted to the gastroenterology department on the 9th day for gastrointestinal endoscopy and abdominopelvic CT. However, no abnormalities were observed. The patient presented with acute urinary retention on day 12. Neurological consultation was requested following the lack of relief from antiemetic therapy. Given the high clinical suspicion of CVST recurrence, MRI, CT venography, lumbar puncture, and fundoscopic examinations were suggested. Fundoscopic and visual field examination on the 12th day showed bilateral optic atrophy and enlarged blind spot, which were considered a result of prolonged IH rather than acute IH (**Figures 1B,D**). However, the lack of filling defects of the cerebral venous system in CT venography ruled out the recurrence of CVST on the 13th day (**Figure 2B**). The patient developed numbness of the extremities and tingling around both calves on day 14 and was transferred to the neurology department. Neurological examination showed that he was conscious and oriented with horizontal nystagmus toward the left side. He had grade 5/5 strength and normal muscle tone; however, tendon hyperreflexia was observed in

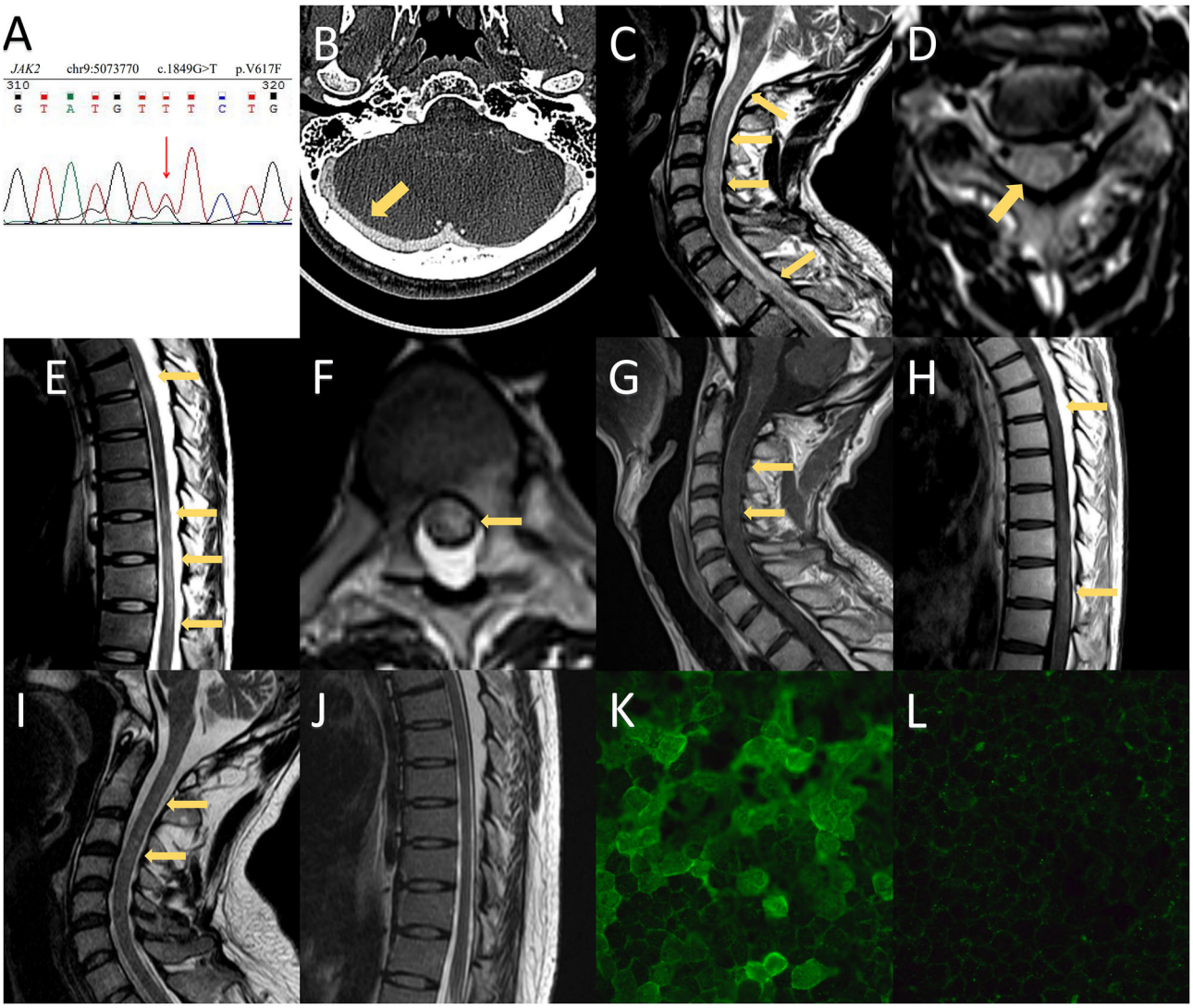

FIGURE 2 | MRI and CT findings and anti-aquaporin-4 antibody (AQP4-IgG) array of the presented case. **(A)** Whole-exome sequencing revealed a mutation in JAK2-V617F. **(B)** CT venography of the second hospitalization showed no filling defects of the cerebral venous sinus. **(C–H)** Spinal MRI demonstrated T2-weighted imaging abnormalities in the medulla as well as extensive spinal cord involvement extending from C1 to the conus. Spinal MRI with contrast showed mild enhancement in the cervical and thoracic spinal cord. **(I,J)** Follow-up MRI showed prominent regression of the hyperintense lesion, which included the medulla and spinal cord. **(K)** The serum titer of AQP4-IgG using a cell-based assay was 1:1,000 at the time of neuromyelitis optica spectrum disorder diagnosis. **(L)** The patient was negative for AQP4-IgG at the 1-year follow-up.

all four extremities. Sensory examination showed impaired proprioception sensations in both legs. Babinski and Hoffman's sign was positive bilaterally. Signs of meningeal irritation were absent. Repeated lumbar puncture was performed on the 15th day with a CSF opening pressure of 210 mm H_2O. The CSF examination showed only mild mononuclear pleocytosis (80/ul) without abnormalities in proteins, immunoglobulin G (IgG) index, or oligoclonal bands. Spinal and brain MRI with contrast was undertaken on the 17th day, which showed an extensive signal abnormality that extended longitudinally from the medulla to the entire spinal cord, with slight edema and gadolinium enhancement (**Figures 2C–H**).

Serology for rheumatoid factor, anti-neutrophil cytoplasmic antibodies (ANCA), antiphospholipid antibodies, anti-Sjögren syndrome A/B antibodies, paraneoplastic panel, human leukocyte antigen (HLA) B5, and HLA-B51 were all negative. Serum and CSF infection panels were also negative. Antinuclear antibody (ANA) was positive at a titer of 1:100. Cytokines panel showed elevated interleukin-6 (IL-6) at 19 pg/ml (normal range 0–3 pg/ml). The cell-based AQP4-IgG assay of serum and CSF were positive at 1:1,000 and 1:100 (**Figure 2K**), respectively. Moreover, myelin-oligodendrocyte-glycoprotein IgG and glial-fibrillary-acidic-protein IgG were negative. Thus, the diagnosis of NMOSD was established according to the 2015 NMOSD

criteria, and IFNα-2b treatment was suspended immediately. On the 18th day, the patient experienced weakness of both legs with an Expanded Disability Status Score (EDSS) of 3. However, neurological examination demonstrated only mild distal leg weakness (plantar flexion and ankle dorsiflexion, grade 4/5 strength). We administered a 12-day treatment plan with methylprednisolone (1,000 mg for 3 days, 500 mg for 3 days, 240 mg for 3 days, and 120 mg for 3 days). However, his clinical symptoms did not improve after 6 days of treatment. Intravenous immunoglobulin (0.4 g/kg/day for 5 days) was administered on the 23rd day, followed by mycophenolate mofetil (0.5 g twice a day) and oral prednisolone (60 mg per day, reduced to 20 mg per day step by step) as prophylaxis. In addition, hydroxyurea and aspirin were given instead of IFNα-2b to control ET.

The patient gradually improved, and urinary retention and lower limb weakness diminished on the 27th day. Hiccups and nausea subsided on the 31st day, and the patient was discharged on the 32nd day. The patient only had slight limb numbness at discharge, with an EDSS score of 1. On the follow-up visit 1 year later, the patient remained symptom-free and relapse-free, and his EDSS score was 0. Spinal MRI revealed that most foci had recovered (**Figures 2I,J**). Serum AQP4-IgG (**Figure 2L**) and ANA tests were negative. Long-term administration of mycophenolate mofetil and low dosage prednisolone was maintained. The patient remained symptom-, relapse-, and side-effect-free until December 2021.

REVIEW OF THE PUBLISHED LITERATURE AND THE PRESENT CASE

Our literature review identified six case reports and one small case series. Together with our patient, nine patients with IFNα-induced NMOSD, who met 2015 NMOSD criteria were included for the pooled analysis (1). The clinical summary is provided in **Table 1**. The median age of NMOSD occurrence in patients was 59 years (range: 24–65 years), and 55.6% (5/9) of patients were women. More than half of patients were characterized by relapsing NMOSD. Hepatitis C infection was the most common primary disease (six patients, 66.7%). The remaining two cases had malignant melanoma and systemic mastocytosis, respectively, whereas our patient had ET as the primary disease. Optic neuritis (ON) was the most common initial symptom (five patients, 55.6%), followed by myelitis in three patients and area postrema syndrome (APS) in one patient. Six patients presented with ON, six presented with transverse myelitis, and only one patient had APS. Four patients presented with brain lesions in MRI, of whom three were asymptomatic. Two patients were noted as having slight pleocytosis in the CSF. Correspondingly, these patients also had a slight-to-moderate increase in proteins in the CSF. Oligoclonal bands were not found in any patient. Serum AQP4-IgG was positively detected in all patients.

All patients received IFNα, and only two patients had transient exposure to IFNβ. The median time of IFNα exposure was 18 months (range 3–180 months). Notably, two patients developed NMOSD after discontinuation of IFNα (after 2 and 3 months, respectively). Autoimmune antibodies secondary to IFNα treatment were detected in two patients: ANA and an anti-glutamate decarboxylase (GAD) antibody. Less than half (4/9) of patients responded favorably to initial immunotherapy. Of the six patients who had available outcome data, only one patient showed no sequelae. After IFNα discontinuation and long-term immunotherapy, most (seven patients, 77.8%) patients remained relapse-free. Only two patients reported transverse myelitis relapse following immunotherapy.

DISCUSSION

Considerations of the Diagnostic Process of the Presented Case

We presented the first NMOSD case with ET, which is one of the myeloproliferative neoplasms (MPNs). Is MPN a potential cause of NMOSD? Immune dysregulation is an increasingly reported characteristic of MPNs (16). An association has already been reported between MPNs and several autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus (SLE) (16). Galimberti and colleagues found that 7.8% of patients with an MPN presented with an overt autoimmune disease (16). Moreover, the unusual concurrence of MS and MPN has been reported in a Roskilde MPN population. However, all five patients developed MPNs after MS. The authors concluded that chronic inflammation in MS patients may contribute to the development of MPNs (17). To date, there are no reports describing the occurrence of NMOSD in patients with MPNs. These results suggest that the presence of MPNs is not sufficient to cause NMOSD.

In addition, we presented a specific case of NMOSD, which developed following the administration of IFNα with a significant diagnostic delay. Thus, several considerations are warranted. The ODS was the most prominent presence in the early stages of our case. Thus, we question whether ODS is an early manifestation of NMOSD. The most common causes of ODS include papilledema (resulting from intracranial hypertension), inflammatory ON, and anterior ischemic optic neuropathy (18). The ODS of different etiologies usually appear ophthalmoscopically similar. Binocular involvement relatively preserved visual function, and symptoms, such as headache and tinnitus, can frequently help physicians distinguish papilledema from other diseases with ODS (18, 19). However, binocular ODS can emerge in ischemic and inflammatory optic neuropathies (18). Indeed, there are several case reports, in which bilateral ODS of NMOSD was misinterpreted as IH, even with marked elevated intracranial pressure. Furthermore, there are some cases, in which ODS with CVST was mistaken for ON. It can sometimes be challenging to determine the underlying cause of ODS (20); however, there are several helpful techniques. The optical coherence tomography (OCT) and OCT angiography (OCTA) provide non-invasive imaging of the optic circulation and can be used to identify ischemic ODS. The most sensitive diagnostic modality for ON is MRI with fat-saturated sequences and contrast enhancement (19). The abnormal enhancement of the optic nerve is direct evidence of ON. In addition, MRI of the orbits can reveal signs suggestive of IH, which include the empty-sella sign,

TABLE 1 | Characteristics of the patients with Interferon-alpha-induced neuromyelitis optica spectrum disorder (NMOSD).

Study (references)	Age/sex	Primary disease	IFNI type	IFNI exposure	Initial symptom	Clinical phenotype	MRI findings	CSF	Other antibody	Acute treatment	Long-term treatment	Relapse	EDSS	Outcome
Kajiyama et al. (14)	47/F	CHC	IFNα-2b	13 M	ON	ON+TM	Brain:periventricular WM Spinal: 4th thoracic TM	N/A	Negative	CS, CR	CS	No	N/A	N/A
Yamasaki et al. (11)	65/F	CHC	IFNα-2b IFNα-2a	34 M	ON	ON+ACS	Brain: callosum, WM, → cerebral pyramidal tract lesion Spinal: (–)	Negative	Negative	IVMP, CR	CS	Yes, 3 times	1	Visual defect
Kawazoe et al. (10)	60/F	CHC	IFNα IFNα-2b IFNα-1 IFNβ IFNα-2a	180 M	ON	ON	Brain: WM ON: left ON Spinal: (–)	Negative	Anti-GAD	1st: Oral CS, NE 2nd: IVMP, NE PE+IVMP, PR IVIG+CPM, PR	1st: MTX 2nd: monthly CPM	Yes, 2 times	1	Visual defect
Usmani et al. (12)	62/M	CHC	IFNβ-1a IFNα	7 M	TM	TM	Spinal: LETM from the medulla to upper thoracic Brain: (–)	Elevated protein (>500 mg/dL)	Negative	IVMP, NE IVIG, NE	CS	No	8	Lower extremities paralysis
Mangioni et al. (13)	32/M	CHC	IFNα-2a	3 M	ON	ON+TM	Spinal: LETM of the entire spinal cord and lower medulla Brain: (–)	Elevated protein; Pleocytosis (15/μL)	Negative	IVMP, NE PE+IVIG, PR	CS	No	6	Paraplegia, proprioceptive sensibility defect
Gao et al. (15)	40/M	MM	IFNα-2b	55 M	ON	ON	Spinal: (–) Brain: (–)	Negative	Negative	IV DXM, PR IVMP, NE	CS, rituximab	No	5	Visual defect
Williams et al. (9)	65/F	SM	IFNα	120 M	TM	ON+TM	Spinal: LETM thoracic	N/A	Negative	CS	Azathioprine, rituximab	Yes	N/A	N/A
	59/M	CHC	IFNα	12 M	TM	TM	Spinal: LETM thoracic	N/A	Negative	CS	Azathioprine	Yes	N/A	N/A
Present case	24/M	ET	IFNα-2b	18 M	APS	APS+TM	Spinal: LETM of entire spinal cord Brain: medulla	Pleocytosis (80/μl)	ANA	IVMP+IVIG, CR	CS, MMF	No	0	Symptom-free and relapse-free

ACS, acute cerebral syndrome; ANA, antinuclear antibodies; APS, area postrema syndrome; CHC, chronic hepatitis C; CR, complete remission; CS, corticosteroids; CPM, cyclophosphamide; DXM, dexamethasone; EDSS, expanded disability status score; ET, essential thrombocythemia; IFN, interferon; IFNI, type-I interferon; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; LETM, longitudinally extensive transverse myelitis; MM, malignant melanoma; MMF, mycophenolate mofetil; MTX, methotrexate; NE, not effective; ON, optic neuritis; PR, partial remission; SM, systemic mastocytosis; WM, white matter.

perioptic subarachnoid space distension, optic nerve tortuosity, and posterior globe flattening (21). Our case presented with headache, tinnitus, ODS, preserved visual function, and a CSF pressure of more than 400 mm H_2O, which strongly supported the diagnosis of papilledema. We also carefully re-analyzed the patient's neuroradiological data. Characteristic MRI findings for papilledema were identified without optic nerve enhancement. Therefore, in our case, bilateral ODS and secondary optic atrophyoptic atrophy were considered a consequence of CVST rather than the initial presentation of NMOSD.

In addition, our patient, who presented with APS as the initial symptom of NMOSD, was first admitted to the gastroenterology department. Intractable hiccups and vomiting are commonly encountered problems in the gastroenterology department or general medicine service (22). More than 70% of patients with APS are reported to visit a gastroenterologist or internist initially, and neurologic evaluation is not commonly pursued (22). However, intractable hiccups and vomiting can be a common clinical presentation of IH; although the absence of headache and papilledema made it an unlikely diagnosis. Thus, clinicians need to be aware of NMOSD as a diagnosable central cause for patients presenting with unexplained intractable nausea and vomiting.

Is NMOSD a DID of IFNα Treatment?

The IFNα, a member of the IFNI family, plays a critical role in linking innate and adaptive immunity (23). The IFNIs exert their anti-proliferative, anti-tumor, anti-angiogenic, and immunomodulatory properties by activating the Janus kinase signal transducer and activator of transcription signals *via* the common type-I IFN receptor (IFNAR) (23, 24). The IFNα is still widely used in the treatment of chronic viral infections, hematological malignancies, and certain cancers (25), whereas IFNβ preparations are recommended for multiple isoforms of MS (5, 6). Opposing the beneficial actions of IFNI treatment, IFNI has gradually been recognized as a pro-inflammatory molecule that may not only unmask and aggravate underlying autoimmune processes, but also induce *de novo* autoimmune disorders, such as type-I diabetes, vitiligo, SLE, Sjögren syndrome, and autoimmune thyroid disease (26–28). Various neuroautoimmune diseases, including myasthenia gravis, inflammatory demyelinating polyneuropathy, and polymyositis, are also occasionally induced by IFNα therapy (29, 30).

Notwithstanding, NMOSD is still not formally regarded as a DID of treatment with IFNα. To date, few cases of IFNα-induced NMOSD have been reported, and this condition has likely been ignored by clinicians. Only eight cases with NMOSD secondary to IFNα therapy have been described to date. A few cases of IFNα-induced CNS demyelinating disease, including two cases with ON, two with ON and myelitis, and two with MS-like demyelinating disease, have been reported previously (15). However, AQP4-IgG was not detected in these cases, which hindered definite diagnoses. The first AQP4-IgG seropositive case of IFNα-induced NMOSD was reported in 2007 by Kajiyama et al. (14). The patient developed bilateral ON, transverse myelitis, and multiple periventricular white matter lesions after undergoing 13 months of IFNα treatment for chronic hepatitis C (14). Since then, nine patients have been reported with NMOSD with HCV infection as the primary disease, although three patients were not treated with IFNI (31). A possible association between NMOSD and HCV infection is likely; clinical data suggest that extrahepatic diseases are present in 40–74% of patients with hepatitis C as a result of complex interactions between HCV and B lymphocytes (31, 32). The HCV may contribute to immune system dysregulation, lymphocytes activation, and autoimmune antibody production, which include anti-ANA, anti-ANCA, and AQP4-IgG (32). Therefore, IFNα may form the bridge between NMOSD and HCV infection. Unfortunately, IFNα concentration was not measured in the NMOSD patients who did not undergo IFNα treatment.

In the remaining patients without HCV infection, IFNα was considered the independent trigger for the occurrence of NMOSD (9, 15). In addition, Williams and colleagues reported two cases in which NMOSD was secondary to exposure to significantly elevated endogenous IFNα, which was constitutively produced by the underlying interferonopathic disease, including genetic interferonopathy and SLE (9). The above evidence strongly supports the notion that NMOSD is a DID of IFNα treatment.

Interestingly, IFNβ treatment can exacerbate NMOSD but rarely induces newly onset NMOSD. In terms of mechanistic aspects, both IFNα and IFNβ may contribute to the development of NMOSD. The capacity to penetrate the blood-brain barrier (BBB) is an essential factor for DIDs of the CNS. A previous study showed that peripheral IFNα was able to exert its effects across the BBB (33). However, peripheral IFNβ was reported to have no direct access to an intact BBB (34).

The IFNα-induced NMOSD shares heterogeneous disease process patterns with AQP-IgG seropositive NMOSD (35), where clinical data, neuroradiological data, treatment response, and outcome features are largely similar across both groups. This is unsurprising because both conditions share the common pathogenetic AQP4-IgG pathway to NMOSD. Notably, the onset of NMOSD in some patients occurs several months after discontinuation of IFNα (12, 15). In an *in vitro* model, astrocytes showed markedly increased reactivity and dysregulation of the downstream gene and cytokines after exposure to IFNα for 3 weeks. Notably, these effects were not restored even 7 days after withdrawal of IFNα (36). Therefore, the prolonged exposure of IFNα may lead to persistent activation of the neuroautoimmune cascade even after the cessation of IFNα exposure.

The Role of IFNI in the Immunopathogenesis of NMOSD

Over the last decade, research progress has contributed to the substantial expansion of our understanding of the critical role of IFNI in the immunopathogenesis of NMOSD. Both central and peripheral mechanisms of the IFNI pathway may contribute to the development of NMOSD. We provide a detailed picture of the underlying mechanism in **Figure 3**.

The Role of IFNI in Peripheral Immunity

The AQP4-IgG is generally believed to form peripherally before entering the CNS (2). It is well-established that

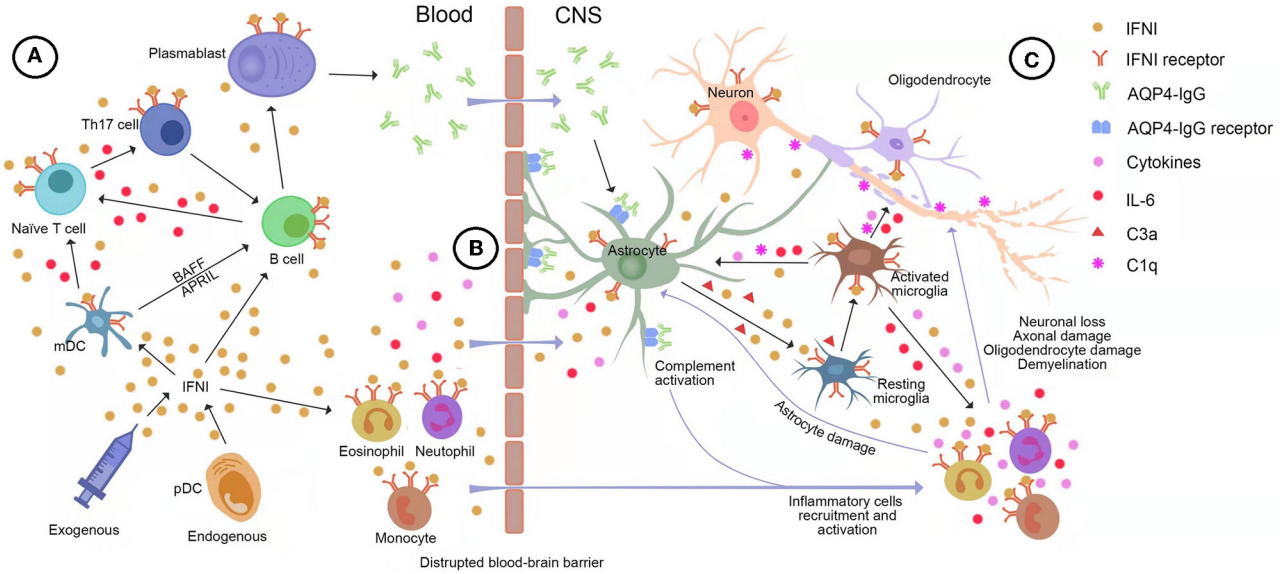

FIGURE 3 | The potential role of type-I interferon (IFNI) signaling in the immunopathogenesis of neuromyelitis optica spectrum disorder (NMOSD). **(A)** Both endogenous and exogenous IFNI can drive B cells and myeloid dendritic cells (mDC) to produce large quantities of interleukin (IL)-6, which stimulates naive T cells to transform into inflammatory Th17 cells. Moreover, plasmacytoid dendritic cells (pDC) secretes IFNI into mDC, facilitating the generation of BAFF and APRIL, which are essential for the survival and maturation of B cells. In turn, inflammatory Th17 cells help B cells differentiate into AQP4-IgG-secreting plasma cells. **(B)** IFNI drives IL-6 and other pro-inflammatory molecules to disrupt and increase the permeability of the blood-brain barrier (BBB), allowing AQP4-IgG, pro-inflammatory cytokines, and immune cells to infiltrate the brain. **(C)** The IFNI-dependent astrocyte-microglia interaction drives the development of NMOSD pathology. Astrocytes are highly responsive to IFNI and the predominant source of IFNI in the central nervous system (CNS). The binding of AQP4-IgG to astrocytes induces massive production of IFNI and complement C3a, which results in the IFNI-dependent activation of microglia. Microglia respond to astroglial IFNI with the subsequent production of nitric oxide, inflammatory factors, complements, and downstream ISGs, which leads to a heightened activation state of microglia, immune cell recruitment, and complement-mediated CNS destruction. In turn, microglia secrete pro-inflammatory factors into astrocytes, especially IFNI, IL-1, IL-6, and TNF-α, leading to astrocyte activation, C1q production, and release of other pro-inflammatory factors feeding back to microglia. AQP4, aquaporin-4; APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BBB, brain blood barrier; C1q, Complement component 1 q; C3a, Complement component 3 a; IFN, interferon; IFNI, type-I interferon; IL-6, interleukin-6; IL-11, interleukin-11; mDC, myeloid dendritic cells; pDC, plasmacytoid dendritic cells; Th17, T helper type 17 cell; TNF-α, Tumor necrosis factor-α.

IFNI is the most important immune mediator of peripheral immunity. Prolonged exposure to IFNI may lead to the breakdown of immune tolerance and the initiation of an autoimmune response. The IFNI, predominantly IFNα, is either endogenously produced by plasmacytoid dendritic cells (pDCs) or administered exogenously and modulates the functions of key inflammatory cells in NMOSD in the periphery. The following are the most important immune effects of IFNI (37, 38): (1) IFNI promotes the expression of MHC-I molecules, which facilitate the processing and presentation of exogenous antigens, including AQP4; (2) IFNα increases the expression of MHC-II molecules and the production of cytokines, which stimulates monocytes differentiating into myeloid dendritic cells (mDCs). Subsequently, mDCs facilitate B-Cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) generation, which are essential for the survival and maturation of B cells; (3) IFNI drives B cells and mDCs to produce large quantities of IL-6 and TGF-β, which are the key cytokines for the differentiation of Th17 cells and the suppression of Treg cell functions that lead to a protracted inflammatory response; (4) IFNI augments the differentiation of B cells into AQP4-IgG-secreting plasma cells *via* inflammatory Th17 cells and mDCs.

The IFNI also drives IL-6, CXCL10, and other pro-inflammatory molecules to disrupt and increase the permeability of the BBB, which allows AQP4-IgG, pro-inflammatory cytokines, and immune cells to infiltrate the brain.

The Role of IFNI in the CNS

The molecular and pathophysiological mechanisms involved in IFNI and NMOSD are being revealed *via* animal models of NMOSD. The most widely used animal models of autoinflammatory demyelinating disorders are referred to as experimental autoimmune encephalomyelitis (EAE) and can be divided into two clusters according to the passive transfer of myelin-specific TH1 or TH17 cells (TH1-EAE and TH17-EAE, respectively) (39, 40). Similar to NMOSD, TH17-EAE mice manifest ON and inflammatory demyelination in the CNS. Compared with effective treatment with IFNβ in TH1-EAE, IFNβ treatment of TH17-EAE shows significant deterioration of paralysis and increased spinal cord inflammation (39). Agasing et al. measured cytokines and inflammatory cells in TH17 mice treated with IFNβ and found that IFNI treatment of TH17-induced disease was associated with elevated serum IL-6 concentrations and TH17 cell numbers, but not with the number of neutrophils and inflammatory monocytes in the CNS. They

also found that IFNIs could induce IL-6 from activated B cells to drive the pathogenic TH17 cells that play a crucial role in the occurrence and formation of NMOSD (39).

Khorooshi et al. established an animal model of NMOSD brain lesions, where typical astrocyte pathology characterized by the loss of AQP4 and GFAP was induced in mouse brains by intracerebral AQP4-IgG and human complement (huC). They observed that astrocyte pathology and associated granulocyte infiltration were reduced significantly more in IFNAR-deficient knockout (KO) mice than in wild-type mice. This result highlighted the role of IFNI signaling in the development of NMO-like pathology (41). The same team recently established a novel animal model of NMOSD-ON using intrathecal AQP4-IgG and huC. Typical astrocytopathy and NMOSD-like lesions in the optic nerve were observed in wild-type mice after intrathecal injection (42). However, NMOSD pathology was absent in IFNAR-KO mice (42). This result also strongly supported the notion that the presence of IFNI signaling is required for the development of NMOSD.

The IFNI-dependent astrocyte-microglia interaction is currently recognized as the driver of the development of NMOSD pathology (43, 44). Astrocytes are highly responsive to IFNI and the primary cells that produce IFNα in the CNS (45). The binding of AQP4-IgG to astrocytic AQP4 initiates astrocytic injury and stimulates the production and secretion of inflammatory cytokines and complement components, particularly IFNI, IL-6, and complement C3a by C3 cleavage (2). In turn, IFNI activates astrocytes to produce further inflammatory cytokines. Microglia, a critical mediator of the classical complement pathway in NMOSD pathology, can directly exacerbate neuroinflammation and promote neuroglial damage (46). Previous studies have shown that AQP4-IgG cannot directly activate microglia without astrocyte involvement. Indeed, the binding of astrocytic C3a to C3aR on resting microglia promotes microglial activation. Microglia-astrocyte crosstalk and motor impairment were shown to be absent in C3aR-deficient mice receiving AQP4-IgG, which highlights the need for the C3-C3aR axis in NMOSD pathology. Microglia respond to astroglial IFNI and C3a with subsequent production of nitric oxide, inflammatory factors, complements, and downstream ISGs, which leads to a heightened activation state of microglia, immune cell recruitment, complement cascades boost, and complement-mediated CNS destruction (43, 44). In turn, active microglia secrete abundant inflammatory factors and complements into astrocytes, which include IFNI, C1q, and IL-6, leading to a positive feedback loop. Particularly in the initial phase when there is no evident leukocyte infiltration, strong microgliosis, which is dependent on IFNIs from AQP4-IgG-binding astrocytes, corresponds to the facilitation of NMOSD-like pathology. Activated microglia significantly increases after intrastriatal injection of IFNβ in NMO mice, which subsequently exacerbates NMOSD-like pathology. In contrast, NMO-like pathology, microglia activation, and immunoreactivity markers are absent in IFNAR-KO mice that receive AQP4-IgG. In addition, the percentage of $CD11c^+$ microglia was shown to be lower in IFNAR-KO mice than in control mice (46). Recent studies have found that microglia respond more strongly to IFNI than to other cell types in the CNS (33, 47). As mentioned earlier, IFNI drives the production of IL-6 and also exerts a pathogenic effect on NMOSD *via* the IL-6 pathway (39). The highly reactive microglia near the interface between the parenchyma and CSF has been identified to be closely associated with CSF IL-6 levels in patients with NMO. Correspondingly, the morphological characteristics of microglia in the IL-6 mice model are highly similar to those in patients with NMOSD (48). Therefore, it is reasonable to assume that IFNIs activate microglia *via* IL-6-driven pathology.

Taken together, IFNIs play a fundamental role in the immunopathogenesis and developmental process of NMOSD. The NMOSD is a severe neuroautoimmune disease of the CNS with high relapse and disability rates (1). Early diagnosis and rational immunotherapy strategies are crucial for improving the outcomes of patients with NMOSD. Insufficient awareness of NMOSD is a rare, yet life-threatening complication of IFNα therapy that may lead to misdiagnoses or delayed diagnoses associated with severe sequelae. Thus, screening for NMOSD should be performed as soon as possible, when patients present with early manifestations of NMOSD during IFNα treatment.

CONCLUSION

Our findings highlight the potential pathogenic risk of NMOSD of IFNα treatment. We present this case report and review of the published literature to alert physicians of this rare yet devastating consequence of IFNα. Monitoring early manifestations of NMOSD during or even after IFNα treatment is vital. Moreover, prompt suspension of IFNα treatment and early initiation of guideline-directed immunotherapy strategies are essential.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Deidentified data, including clinical manifestations, neuroimaging data, serum tests, and cerebrospinal fluid tests, are available upon appropriate request to the corresponding author.

AUTHOR CONTRIBUTIONS

FF and YL contributed to the design of the study, revised the manuscript, and are responsible for the integrity and accuracy of the data. JR and NX contributed to collecting clinical data, drafting the manuscript, and reviewing the published literature. JS was the attending doctor of the patient and contributed to the acquisition and analysis of the clinical data. All authors read and approved the final manuscript to be published.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.872684/full#supplementary-material

Supplementary Figure 1 | The timeline of the presented case.

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CASE REPORT
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Facial Palsy as Initial Symptom in Glycine Receptor Antibody Positive Progressive Encephalomyelitis With Rigidity and Myoclonus: A Case Report

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Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a rare and disabling syndrome characterized by painful spasms, myoclonic jerks, hyperekplexia, brainstem signs, and dysautonomia, which is considered to be a severe form of stiff person spectrum disorder (SPSD) and is mostly associated with glycine receptor antibodies. The PERM has an acute or subacute course, with complex and varied initial symptoms mainly manifest as stiffness and pain. The authors present the case of a male patient admitted for intractable stiffness and paroxysmal myoclonus of the lower extremities preceded by a 5-day history of facial weakness. After admission, his symptoms deteriorated rapidly. He developed progressive generalized hypertonia and painful spasms, which quickly spread to the upper extremities, and he suffered frequent paroxysmal myoclonus. Serum and cerebrospinal fluid (CSF) were tested by a cell-based assay, and both were positive for glycine receptor antibodies (GlyR-Abs). The patient developed complications, such as crushed teeth, lumbar vertebral compression fractures, and psoas major muscle abscess, during rapid disease progression, although he responded well after being treated with intravenous methylprednisolone and immunoglobulin. This report of PERM, initiated as facial palsy followed by acute progression, helps to expand the clinical spectrum of this rare autoimmune disorder and raise awareness of the prevention of complications.

Keywords: progressive encephalomyelitis with rigidity and myoclonus, glycine receptor antibody, facial palsy, autoimmune disease, complications, case report

INTRODUCTION

Stiff person spectrum disorder includes a group of immune-mediated disorders characterized by fluctuating muscle rigidity and painful spasms with pronounced stimulus sensitivity. The PERM is a more severe disease form of SPSD-exhibiting brainstem symptoms, long tract signs, and additionally autonomic features and is mostly associated with GlyR-Abs. The PERM has complex initial symptoms, which mainly present as limb stiffness and pain or brainstem symptoms, such as oculomotor disturbance, nystagmus, ptosis, and bulbar symptom (1). The report of facial palsy as an initial manifestation is rare. We report a case of acutely progressed PERM that led to severe complications, although responded well to immunotherapy. The GlyR-Abs were found positive both in CSF and in serum. No evidence for an underlying systemic neoplasm was found.

CASE PRESENTATION

A 61-year-old previously healthy male baker was admitted to the hospital for left-sided facial weakness (**Figure 1**). Neurological examination revealed lower motor neuron facial weakness of the left side without other abnormalities. The brain MRI showed lacunar infarction, and it was treated as a stroke. Treatments to improve cerebral circulation, anti-platelets, and lower lipids were tried, but his symptoms did not resolve, and the patient gradually developed right-sided ptosis during hospitalization. He did not complain of another discomfort. However, 5 days after the onset, the patient suddenly developed rigidity and intermittent involuntary tic-like jerks in the left lower extremity after returning home to take a shower. This rigidity and painful spasm expanded to the right-side lower extremity the next day. Pregabalin and cotrimoxazone were administrated without much relief, and the rigidity continued to deteriorate in the following 5 days, rendering a walking disability. The clinicians had no clue of his condition, so he was referred to our department.

On admission, he was well oriented. Neurological examination revealed contracted muscles in the spine and lower extremities; his spine was rigid and his ankle joints were fixed in a hyper-extended position. Paroxysmal painful myoclonic jerks of lower extremities were observed (**Supplementary Video 1**). He also had multiple cranial nerve dysfunctions: insufficient abduction, upward gaze diplopia, horizontal-gaze-evoked nystagmus of the left eye, eyelid ptosis, upward gaze paralysis of the right eye, and left-sided facial palsy. Also, petechiae on the left lateral calf were observed. The patient had a 20-year history of smoking and alcohol abuse. Trauma, infection, poisoning, drugs, psychiatric disease, and family genetic history were denied. He had no history of being scratched or bitten by dogs or cats. No insect bites were found.

Laboratory testing revealed creatine kinase: 1,600 U/L, creatine kinase isoenzyme: 111.5 U/L, lactate dehydrogenase: 1,578 U/L, white blood count, 20,000/mm^3 with neutrophil at 84.6%, lymphocytes at 7.4%, monocytes at 7.7%, hemoglobin: 15. g/dl, platelet counts: 173/mm^3, C reactive protein, 17.3 mg/L, IgE antibody, 393 IU/ml (0–100), granular type +, antiRo52 +, and HbeAb +, HBcAb +. Biochemical investigations, including liver and kidney function tests, thyroid function, blood glucose, blood ammonia, serum electrolytes, blood clotting function, tumor biomarkers, folate, vitamins B1 and B12, homocysteine, and electrolytes, were normal.

Clusters of herpes appeared in his mouth the night he was admitted. His symptoms deteriorated rapidly since admission; the rigidity and spasms spread to the upper extremities and masseter muscles on the next day, so he was transferred to the intensive care unit (ICU). He suffered frequent bouts of painful myoclonic jerks triggered by touch and spontaneously lasting about 30 s with an aura in the form of hallucinations and fear. He also exhibited emotional irritability and anxiety, as well as autonomic dysfunction, such as episodes of fever, tachycardia, and hypertension. Increased doses of diazepam (20 ml/h) and dexmedetomidine (10 ml/h) were administered only to cease the symptoms transiently. The rigidity was so severe that it was impossible to bend his knee or ankle joints passively, and some of his teeth were broken due to intense masticatory spasms. Based on the typical clinical features (the rapid onset, brainstem involved, and movement disorder), infectious or autoimmune encephalitis was considered as a high possibility.

Examinations were performed under anesthesia. The CSF examination revealed mild leukocytosis (12 lymphocytes/μL) (0–5 cells/μl), lymphocyte: 76%, mononuclear cell: 20%, plasma cells: 1%, protein: 355.7 mg/L (150–450 mg/L). The CSF cultures were negative for bacteria, tubercle bacillus, and fungi. No abnormalities in tumor markers were found. Brain MRI only showed a slightly high-signal on brainsteming T2/fluid-attenuated inversion recovery (FLAIR) (same with previous). Meanwhile, anti–GlyR antibodies were detected positive in serum (tilter 1:100) and CSF (tilter 1:100) through a cell-based assay. Antibodies for autoimmune encephalitis, including anti-GAD65, anti-Casper2, anti-DPPX, anti-mGluR1, anti-GABAB, anti-DRD2, anti-NMDA, anti-LGI1, anti-Neu3a, anti-AMPA1, anti-AMPA2, anti-IgLON5, and anti-mGluR5, were negative. Anti-GlyR antibody-associated PERM was suspected, and we started the intravenous methylprednisolone (Day 6 after admission) (1,000 mg/d and halve it every 3 days to an oral dose). (Day 6 after admission).

He showed transient remission with the recovery of oculomotor function and reduction of myoclonus bouts after 8 days of therapy of IV methylprednisolone. However, there was sudden paraplegia on the 9th day, while spasms and myoclonus were still severe; 5-day IV immunoglobulin (0.4 g/kg/d) was followed. He showed marked improvement, with only paroxysmal bouts of masticatory spasms remaining. Since the generalized pain was relieved, he complained of unbearable pain in his back and hip. Lumbar MRI showed an oval-shaped confined mass in the right-sided psoas major muscle and T4/5/7/12 compression fractures (**Figure 2**). The mass was confirmed to be an abscess by an ultrasound-guided puncture, and *Streptococcus constellatus* infection was proved by bacteria culture. The patient was transferred to the orthopedic department.

FOLLOW-UP AND OUTCOME

After discharge, the methylprednisolone was gradually reduced orally, and mycophenolate mofetil was prescribed. He was symptomatic for transient masticatory spasms, lasting about 1 s when blown by the wind or in emotional instability at 12-month follow-up, and the twitching disappeared 2 months later, but he still had a mild left-side facial weakness. After a year-long rehabilitation, the strength of the patient's lower limbs improved a bit, and he was able to move 20 m with the support of an assistive device.

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

DISCUSSION

The PERM is a variant of stiff person syndrome, usually presenting with classical symptoms of SPS (axial and limb

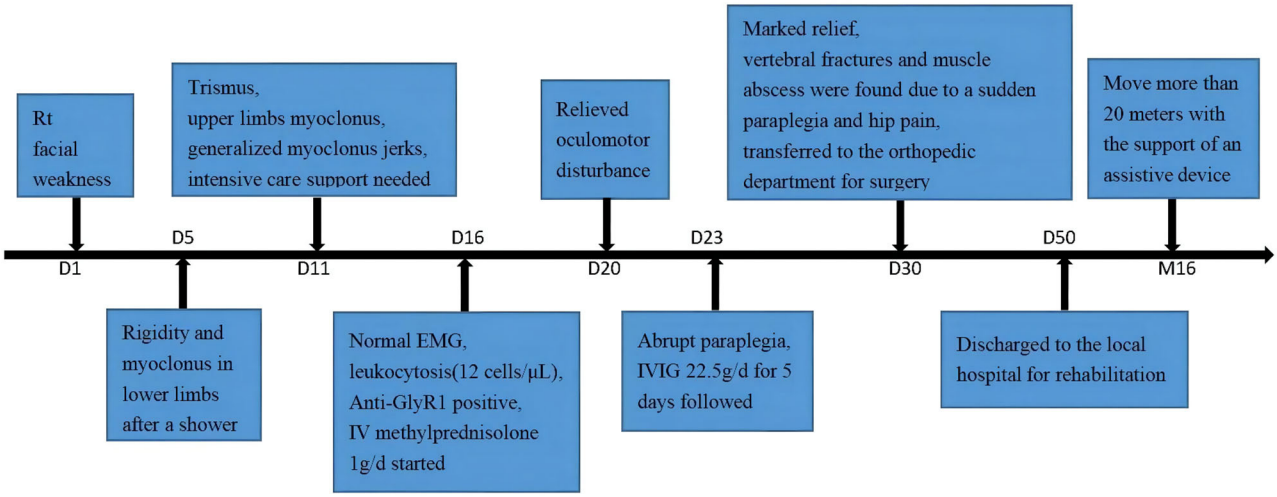

FIGURE 1 | Timeline with diseases' onset and course.

stiffness, painful muscle spasms) associated with myoclonus, hyperekplexia, brainstem signs, pyramidal signs, dysautonomia, and cognitive impairment with an aggressive course (1). GlyR-Abs was firstly reported to be related to PERM in 2008 by Hutchinson et al. (2), and they were most frequently found in patients with PERM (3). Glycine receptors are pentameric ligand-gated chloride channels present mainly in the adult brainstem and spinal cord, facilitating inhibitory signaling, and the stoichiometry has been recently proved to be 4 alpha: 1 beta subunits (4). Mutations of GlyRα1 result in hereditary hyperekplexia, a disorder characterized by excessive startle responses in infancy, which resembles the phenotype of PERM (5). Auto-antibodies against GlyRα1 show pathogenic characteristics *in vitro* such as complement activation and receptor internalization (1). Another study found that glycinergic currents are greatly disrupted by short incubations in patient IgG at room temperature, which suggests that the pathogenic mechanisms include direct antagonistic actions on glycine receptors (6). Whatever the mechanism is, the impairment of the GlyRs on the brainstem nuclei of spinal inhibitory interneurons may cause continuous firing of motor neurons, leading either to myotonia of the encephalomyelitis and rigidity seen in PERM.

Initial presentation of PERM can be very unspecific; 25% of patients may present with brainstem symptoms, such as oculomotor disturbance, nystagmus, ptosis, and bulbar symptom. Patients, then, progress acutely or subacutely to characteristic muscle stiffness and spasms; some may lead to death in the acute phase (1). Several reports mentioned facial weakness during disease progression, among which both lower motor neuron facial weakness and upper motor neuron weakness were described (7–13). Anti-GlyR1 is believed to be responsible for excessive muscle activation since it disrupts the function of inhibitory interneurons. However, the exact mechanism for cranial nerve palsy is not clear. Since congenital bilateral vocal cord paralysis has been experimentally shown to be associated with impaired glycine neurotransmission (14), we assume that they may share a similar pathophysiological mechanism. Neuron damage due to blood-brain barrier disruption or other potentially unknown pathogenic antibodies may play a role. A typical PERM presented 5 days post symptom initiation as facial palsy is unique and surely expands the clinical spectrum of PERM.

After the atypical onset, the patient developed typical PERM with an acute course. Although responded well to immunotherapy, he suffered skeletal fractures and teeth breakage due to severe spasms. A skeletal fracture happens in patients with SPSD (15, 16). It is difficult to discern whether hormonal shock therapy played a role in the fractures, but prompt differential diagnosis and timely intervention would certainly benefit, especially when the patient presents with an acute disease course on the basis that patients with GlyR-Abs usually show substantial and sustained improvement with immunotherapy (7). Besides, more thought should be given to the choice of treatment modality to avoid complications such as fractures in patients who are old-aged and have severe acute muscle contractions. Neurologic disorders, such as metabolic encephalopathies, himoto encephalopathy, tetanus, Isaacs' syndrome, malignant catatonia, and serotonin syndrome that manifest similar clinical presentations, should be considered as differential diagnoses. The medication history, blood tests, CSF findings, and brain MRI, especially auto-antibodies, are essential for differentiation.

The trigger of the autoimmune response is unknown. Tumors such as thymoma and Hodgkin's lymphoma are documented in approximately 20% of patients with PERM (17). In this case, the patient had no evidence of malignancy or thymoma on a CT scan. It is reported that the human herpes simplex virus (HSV) can trigger autoimmune encephalitis (18, 19). The patient experienced an attack of HSV, which lasted about 20 days. However, it is unknown whether the HSV infection acted as a trigger or a consequence of impaired immunity since no virological examination of CSF was performed. Besides, comorbid autoimmune diseases were not uncommon among patients with GlyR-Abs 13 of 45 that had another autoimmune

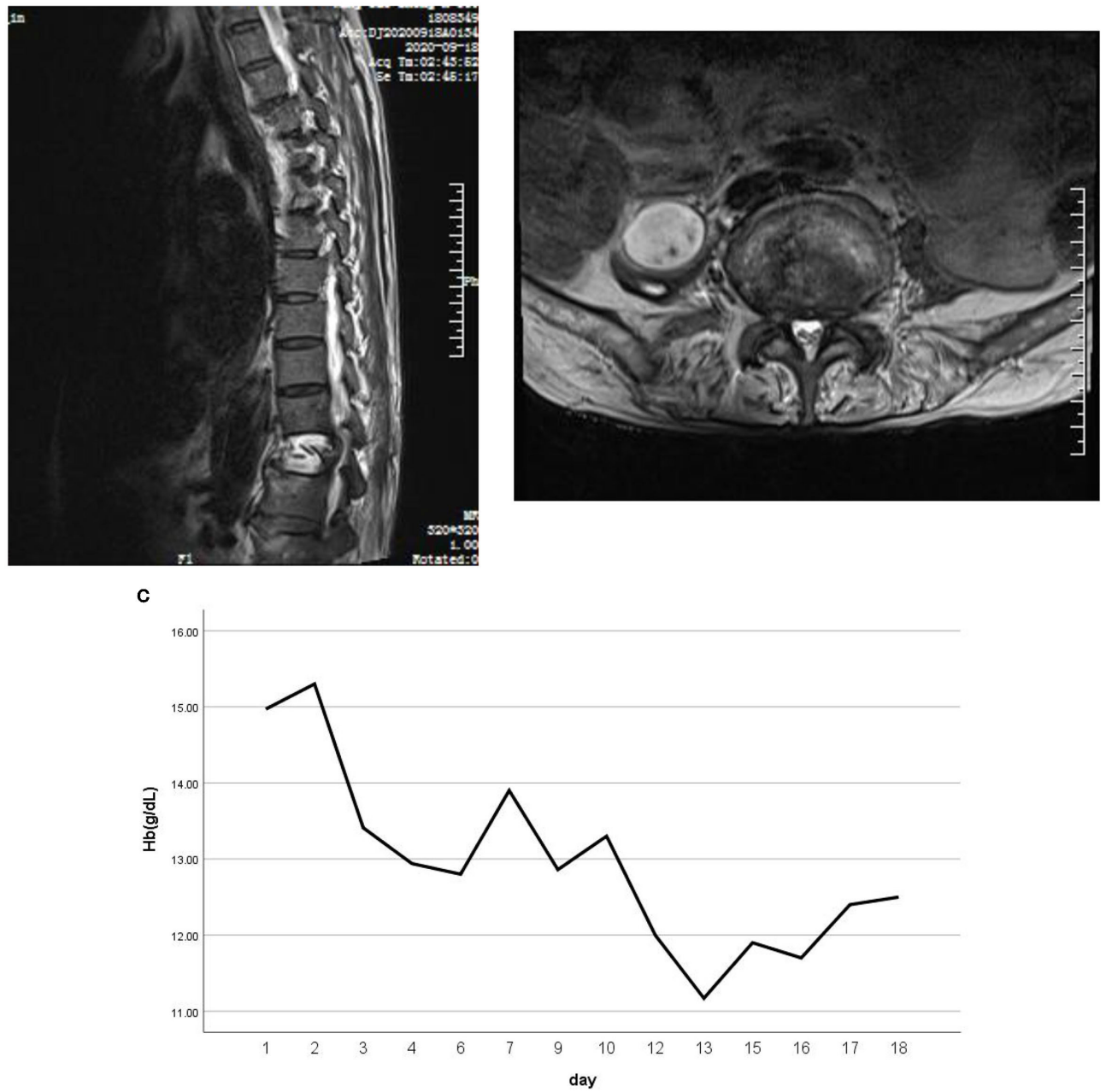

FIGURE 2 | Lumbar MRI showed an oval-shaped confined mass in the right-side psoas major muscle **(A)**. **(B)** T4/5/7/12 compression fractures. **(C)** A blood routine test suggested progressive anemia.

condition (1). Although there were auto-antibodies like Ro52 and granular type detected positive, the patient did not have a confirmed diagnosis.

The abscess of the psoas major muscle with *Streptococcus constellatus* cultivated positive is interesting. *Streptococcus constellatus* is a subgroup of viridans streptococci widely distributed in the oral cavity, nasopharynx, gastrointestinal tract, and vagina (20). These bacteria have the capability of causing pyogenic infections and abscess formations mainly in the respiratory tract, brain, liver, bone, and soft tissues on a rare occurrence (21). So, how did this patient's abscess of the psoas major muscle arise? Rui Shimazaki reported a case of PERM with anemia, complicated with bilateral iliopsoas hematomas (22), and he speculated that a simple microtrauma due to isometric muscle contraction could potentially result in muscle and capillary tears, subsequently leading to spontaneous muscle hematomas. He

also suggested a survey for intramuscular hematoma, including iliopsoas hematoma, when progressive anemia is present in patients with PERM. Our patient actually did have progressive anemia (**Figure 2C**). Therefore, it can be boldly speculated that the lumbar muscle abscess is an opportunistic pathogenic infection based on a hematoma caused by muscle contraction. This case illustrates that patients with PERM may develop multiple complications, among which some are unpredictable.

CONCLUSION

The PERM is a rare autoimmune disorder with complex symptoms. Patients may present an acute and severe disease course and lead to a variety of complications. Recognizing the atypical initial presentations of PERM is important for patients with an acute course for fast recognition and proper treatments are essential to prevent irreversible damage.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author/s.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

LW and RZ wrote the manuscript. KL, RZ, and BS examined and treated the patient. YaX and YuX participated in revising the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.866183/full#supplementary-material

Supplementary Video 1 | Broken teeth and difficulty opening the mouth due to facial muscular spasms and unhealed herpes on the tongue and around the mouth. Fixed ankle joints and upper extremities shaking. A bout of myoclonic jerks in lower extremities.

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CASE REPORT
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Case Report: Exacerbation of Relapses Following mRNA COVID-19 Vaccination in Multiple Sclerosis: A Case Series

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Quintanilla-Bordás C, Gascón-Gimenez F, Alcalá C, Payá M, Mallada J, Silla R, Carratalà-Boscà S, Gasque-Rubio R, Castillo J and Casanova B (2022) Case Report: Exacerbation of Relapses Following mRNA COVID-19 Vaccination in Multiple Sclerosis: A Case Series. Front. Neurol. 13:897275. doi: 10.3389/fneur.2022.897275

Introduction: mRNA coronavirus disease 2019 (COVID-19) vaccination has been widely used to arrest the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Rarely, autoimmune events such as relapses in patients with multiple sclerosis (MS) have been reported after vaccination. However, the possible effects of vaccination in a patient already experiencing the symptoms of a relapse represent an unusual scenario that has not been described.

Patients and Methods: This is a retrospective case series of four patients from three major tertiary referral centers that received mRNA COVID-19 vaccination after starting with symptoms of acute demyelination of the central nervous system due to non-recognized MS. A detailed description of each case, including MRI studies, serum light-neurofilament levels, and cerebrospinal fluid (CSF) cytokine profile, is provided.

Case Description: All patients presented exacerbation of ongoing symptoms after vaccination (range 14–112 days first dose). All patients presented MRI features suggestive of highly active MS and fulfilled McDonald 2017 criteria at the time of presentation. All patients presented high serum light-neurofilament levels and oligoclonal G bands restricted to the CSF. Higher levels of interleukin-6 in the CSF were present in the more severe cases.

Discussion: We describe exacerbation of relapses after mRNA COVID-19 vaccination. We hypothesize RNA sensors such as Toll-like receptor 7 may be activated and contribute to amplify the inflammatory response during a relapse.

Conclusion: Patients should seek medical attention if experiencing acute neurological symptoms, especially before vaccination. Fast diagnostic procedures and prompt treatment should be performed in these patients. Pharmacovigilance and further study are warranted to confirm causality.

Keywords: mRNA COVID-19 vaccine, vaccination, multiple sclerosis, relapses, exacerbation (symptom flare up)

INTRODUCTION

Widespread coronavirus disease 2019 (COVID-19) vaccination has dramatically changed the course of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. mRNA-based vaccines against COVID-19 are the first ones approved with this mechanism of action. To date, massive vaccination has shown that mRNA vaccines are safe and effective to arrest the spread of the pandemic (1).

However, as increasing number of people are being vaccinated, several reports have described infrequent associations between mRNA COVID-19 vaccine and onset of demyelinating diseases of the central nervous system (CNS) such as acute demyelinating encephalomyelitis (2), neuromyelitis optica spectrum disorders (3), and relapses in patients with multiple sclerosis (MS) (4, 5). In all cases, vaccination was administrated prior to the onset of any signs of disease, and therefore vaccine was thought to act as a trigger (6).

The possible effects of vaccination in patients *already* suffering from symptoms of acute demyelination represent a different and unusual scenario that has not been described.

We present four cases with similar temporal profile of events: onset of symptoms suggestive of acute demyelination of the CNS due to non-recognized MS, administration of mRNA COVID-19 vaccine, followed by unexpected worsening of symptoms and high inflammatory activity.

PATIENTS AND METHODS

This is a retrospective case series of four patients from three major tertiary referral centers that provide healthcare to a population of ∼800,000 people, collected between June and September 2021 during the COVID-19 vaccination campaign. Informed consent was obtained to publish their clinical reports. MRI studies were performed with 3.0 Tesla field strength machines. Cerebrospinal fluid (CSF) oligoclonal band (OCB) synthesis was determined by immunoelectrophoresis assay. Antibodies against aquaporin 4 channel (anti-AQP4) and myelin oligodendrocyte glycoprotein (anti-MOG) were determined with the commercially fixed cell-based assay (CBA) Euroimmun®. Anti-MOG was also determined in parallel using an in-home lived anti-MOG CBA, with anti-IgG1 as a secondary antibody. Levels of serum neurofilament light chain (sNfL) and CSF cytokines, including interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin 12p70 (IL-12p70), interferon gamma (IFN-γ), interleukin 17A (IL-17A), and tumor necrosis factor alpha (TNF-α), were determined using SR-X platform by Single-molecule array (SiMoA R) from Quanterix (Billerica, MA, USA) by Single-molecule array (SiMoA®).

CASE DESCRIPTION

All patients presented symptoms suggestive of demyelination starting within 60-21 days before the first mRNA vaccine dose. Patients received vaccination either before seeking medical attention (Cases 1 and 3) or while being studied for their symptoms on an outpatient basis (Cases 2 and 4). None of the patients had remarkable family history related to neurological or autoimmune conditions. No patient had prodromal symptoms, suggestive of viral illness prior to onset of symptoms.

Symptom aggravation occurred within 14-112 days after the first vaccine dose. All patients were admitted to the hospital, and in all, SARS-CoV-2 infection was excluded after reverse-transcription polymerase chain reaction (RT-PCR) assay of nasopharyngeal swab. Extensive workup that included the screening for systemic autoimmune and infectious diseases was performed in all patients. All patients had negative anti-AQP-4 and anti-MOG antibodies in serum. Lumbar puncture revealed the positive OCB IgG bands in CSF in all patients. Brain and spinal MRI showed demyelinating lesions, mostly well-demarcated, MS-typical periventricular lesions, affecting the callososeptal interface, and none had lesions in the thalamus or basal ganglia. Cortical involvement of demyelinating lesions was very rare. Also, lesions were of different age, with gadolinium-enhancing lesions (GELs) present in 30–80% of lesions at presentation and hypointensities suggestive of black holes in Case 3. No patient had fever at presentation or neck stiffness. Acute disseminated encephalomyelitis (ADEM) was considered in the differential diagnosis. However, after considering timeline and recurrence of symptoms and radiological activity extending well over 3 months, radiological features of lesions, and OCB positivity, patients were diagnosed with MS fulfilling McDonald 2017 criteria (7).

A summary of the cases showing the timeline of events, including the main clinical and radiological features in chronological order with respect to the day of vaccination, is shown in **Table 1**. Cytokine levels in the CSF are shown in **Table 2**. Cases 1 and 4, which reached a higher disability during the relapse, also presented the highest levels of IL-6.

Case 1

A 32-year-old female, with medical history of infectious mononucleosis 8 years before, presented 60 days before an episode of painful and diminished vision on right eye suggestive of optic neuritis that resolved spontaneously, and for which did not seek medical attention. Five days prior to vaccination, she started with tingling in her lower extremities. At this time, she received 2 doses of mRNA-1273 (Moderna) COVID-19 vaccine; 14 days following the first dose, she started to present increasing weakness. Her neurological examination 30 days later, upon hospital admission, revealed bilateral ophthalmoplegia, right facial palsy, dysarthria, tetraparesis (right upper limb 3/5 left upper limb 4/5, lower limbs 2/5,), pyramidalism, global hypoestesia, limb dysmetria, and severe gait ataxia, with an Expanded Disability Status Score (EDSS) of 7.0. MRI at this time showed multiple brain and infratentorial lesions and 2 cervical spinal cord lesions with more than 20 GELs suggestive of MS (**Figure 1A1,A2**). Lumbar puncture showed mildly elevated proteins and lymphocytic predominant pleocytosis (17 cells, 82% lymphocytes) and positive IgG OCBs.

The patient was started with 1,000 mg of IV methylprednisolone (MP) for 5 days. As no improvement was noted, the patient underwent five sessions of plasma exchange (PLEX) every other day combined with a single

TABLE 1 | Summary of the four cases showing the main clinical and radiological features in chronological order with respect to the day of vaccination.

	Age, sex	Time of symptom onset with respect to first dose of vaccine	Vaccine, 1st dose	Vaccine, 2nd dose	Vaccine manufacturer (codename)	Onset of symptom aggravation	Clinical course after vaccination	MRI: time performed and main radiological features	CSF findings	sNfL levels (pg/ml)	Treatment received in order of administration	Time of last follow-up	Clinical course at last follow-up
Case 1	32 y, female	Day −60: decreased vision and pain in left eye consistent with optic neuritis. Day−5: subtle sensory changes in lower limbs	Day 0	Day +28	Moderna (mRNA-1273)	Day + 14	Gait ataxia, tetraparesis, global sensory loss and decreased level of consciousness, reaching EDSS 9 on day +28 requiring ICU admission.	Day +30. More than 50 periventricular, juxtacortical and infratentorial lesions, 2 cervical spinal cord lesions. 20 GEL. Day +43: (worsening EDSS 9): 6 new GEL in subcortical and infratentorial locations. Day+55 (EDSS 8.5?): persistence of GELs and enlargement of T2 lesions	CSF: mild protein elevation (90 mg/dl), lymphocytic pleocytosis (17 cells, 82% lymphocytes), positive OCB bands.	92,6	MP 1 g IV for 5 days, 5 sessions of PLEX, rituximab 500 mg IV, cyclophosphamide 3 g/m² IV, MP 1 g IV for 5 days	Day +60	EDSS 8.5
Case 2	16 y, female	Day −12: left facial sensory loss		Day +21	Pfizer-BioNTech (BT162b2)	Day +112	Neurological exam day +60: left facial sensory loss, EDSS 2. Day +112: left facial sensory loss, mild left hemiparesis and mild left sensory loss her left limbs (EDSS 2.5) suggestive of a new relapse.	Day + 60. More than 100 demyelinating lesions, ovoid-shape and nodular in periventricular, subcortical, juxtacortical, infratentorial location. Multifocal involvement of the spinal cord. GEL of >50 lesions.	CSF: positive OCB bands, rest within the normal range*.	35,0	MP 1 g PO for 3 days after diagnosis, fingolimod 0.5 mg/d, MP 1 g PO for 5 days after symptom worsening.	Day +152	EDSS 2.0

(Continued)

TABLE 1 | Continued

	Age, sex	Time of symptom onset with respect to first dose of vaccine	Vaccine, 1st dose	Vaccine, 2nd dose	Vaccine manufacturer (codename)	Onset of symptom aggravation	Clinical course after vaccination	MRI: time performed and main radiological features	CSF findings	sNfL levels (pg/ml)	Treatment received in order of administration	Time of last follow-up	Clinical course at last follow-up
Case 3	41 y, female	Day −14: minor gait disturbance		Day +28	Moderna (mRNA-1273)	Day +39	Progressive gait ataxia, unable to walk unassisted, and mild encephalopathy (EDSS 6.5).	Day +15. More than 100 demyelinating lesions, most of them nodular, in subcortical, juxtacortical, periventricular, with tendency to coalesce, and to a lesser extent, in the brainstem. T1 hypointensities were also present. No lesions in the spinal cord. GEL enhancement in ∼80% of lesions. Day +178: 16 new T2 lesions, 13 GEL.	CSF: positive OCB bands (additional bands in CSF with respect to serum), elevated IgG index (1, 16). Rest within the normal range*.	198,5	MP 1 g IV for 5 days, 5 sessions of PLEX, cyclophosohamide 3 g/m^2 IV	Day +191	Encephalopathy resolved. Mild limb dysmetria and moderate gait ataxia. Walks 20 m unassisted. (EDSS 6).

(Continued)

TABLE 1 | Continued

	Age, sex	Time of symptom onset with respect to first dose of vaccine	Vaccine, 1st dose	Vaccine, 2nd dose	Vaccine manufacturer (codename)	Onset of symptom aggravation	Clinical course after vaccination	MRI: time performed and main radiological features	CSF findings	sNfL levels (pg/ml)	Treatment received in order of administration	Time of last follow-up	Clinical course at last follow-up
Case 4	33 y, male	Day −21: right-sided weakness and numbness, gait disturbance (EDSS 5.0).		None	Pfizer-BioNTech (BT162b2)	Day +14	Somnolence, brainstem locating symptoms (somnolence, dysarthria, dysphagia, hiccups, and severe nausea), increased right-sided weakness. On day +21 sudden aggravation: febrile peak and positive CSF for HSV-1 (EDSS 9).	Day −7: 10 demyelinating lesions: 8 supratentorial (including periventricular) 2 infratentorial. No spinal cord lesions. 3 GEL. Day +14: 4 new diffuse T2 lesions. 2 periventricular, one in the pons, and another in the medulla. 0 GEL. Day +21: new cortical hyperintensity of left temporal and medial frontal and occipital lobes consistent with HSV-1 encephalitis. Day +105: 3 new GEL (2 periventricular, 1 subcortical)	CSF of day−1: positive OCB bands, rest within the normal range*. CSF of day +21: normal glucose, 190 leukocytes (98% lymphocytes) Elevated protein (116 mg/dl). Positive PCR for HSV-1 (50.000 copies/ml).	578,6	MP 1 g PO for 5 days, acyclovir 10 mg/kg/8 h for 21 days IV, 6 sessions of PLEX, MP 1g IV for 5 days, two doses of rituximab 1 g IV separated by 2 weeks.	Day +105	Severe motor aphasia, right predominant tetraparesis, walks 20 m with a walker. (EDSS 7).

*CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Score; GEL, gadolinium-enhancing lesion; HSV-1, Herpes Simplex virus 1; ICU, intensive care unit; IV, intravascular; MP, methylprednisolone; OCB, oligoclonal band; PCR, polymerase chain reaction; PO, per os; PLEX, plasma exchange; y, years; sNfL, serum neurofilament light chain. *Normal CSF, except stated otherwise, refers to <6 cells, glucose > 60% with respect to plasma levels, proteins between 45 and 80 mg/dl.*

TABLE 2 | Cytokine levels in cerebrospinal fluid.

	IFN-γ (pg/ml)	IL-12p70 (pg/ml)	TNF-α (pg/ml)	IL-6 (pg/ml)	IL-17A (pg/ml)	IL-10 (pg/ml)
Case 1	0,06	0,05	0,50	27,24	0,09	1,72
Case 2	0,11	0,05	0,40	1,03	0,01	2,78
Case 3	0,15	0,03	0,57	4,70	0,02	0,41
Case 4 (1st sample)	1,53	0,09	1,48	25,02	0,06	5,67
Case 4 (2nd sample)	0,44	0,05	1,35	3,51	0,03	1,51

IFN-γ, interferon gamma; IL-12p70, interleukin 12p70; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; IL-17A, interleukin 17A; IL-10, interleukin 10.

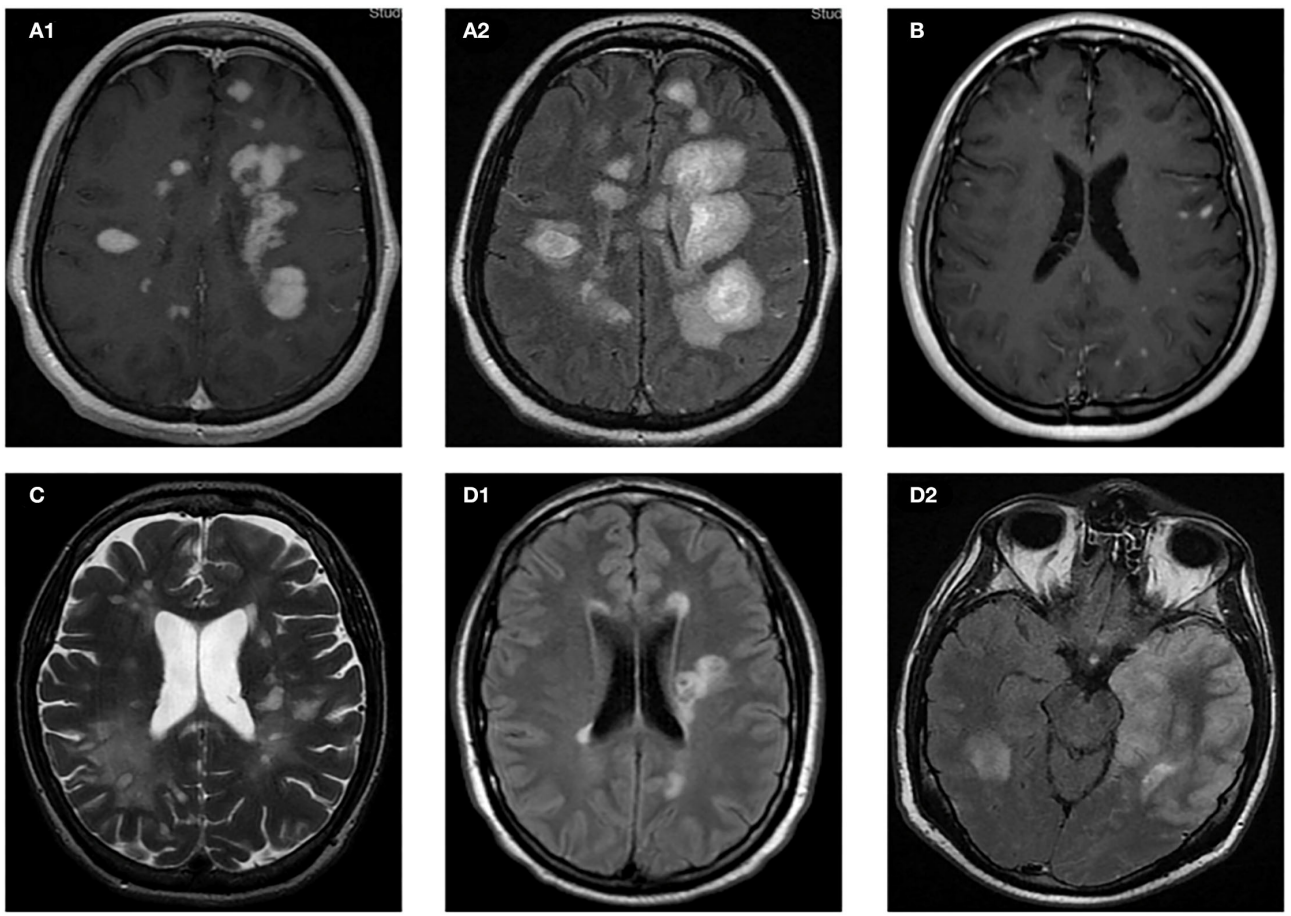

FIGURE 1 | Brain MRI of the cases. **(A)** Case 1: axial T1 post-gadolinium sequence **(A1)** and FLAIR sequence **(A2)**. **(B)** Case 2: axial T1 post-gadolinium sequence. **(C)** Case 3: axial T2 sequence. **(D)** Case 4: axial FLAIR sequence on day −1 **(D1)** and on day +21 **(D2)** with respect to vaccination.

dose of 500 mg IV rituximab 24 h prior to the first session. Still, the patient continued to worsen both clinically and radiologically over the following 14 days, reaching EDSS of 9 that required intensive care unit (ICU) admission. As a result, a myeloablative dose of 3 g/m² IV cyclophosphamide was administered. One week later, the patient had an EDSS of 8.5, but repeated MRI showed new lesions. An additional course of 5 days of 1,000 mg IV MP has been administrated.

Case 2

An otherwise healthy 16-year-old woman started with left-sided facial numbness; 12 days after symptom onset, she received two doses mRNA BNT162b2 Pfizer (Puurs, Belgium) COVID-19 vaccine 3 weeks apart. MRI performed 3 months after symptom onset revealed unexpectedly more than 100 demyelinating lesions, including ovoid-shaped lesions perpendicular to the lateral ventricles, nodular subcentimetric lesions in subcortical, juxtacortical, infratentorial locations, and patchy lesions over

the entire spinal cord. Gadolinium enhancement was found in more than 50 lesions (**Figure 1B**). She was admitted to hospital for rapid workup. During her stay, neurological examination was only remarkable for moderate left facial sensory loss (EDSS 2.0). The patient referred these symptoms remained unchanged since onset. She received 1,000 mg oral MP for 3 days, was discharged, and was started on fingolimod. Despite treatment, 4 weeks later she presented referring left-sided weakness. Her examination showed normal limb strength except for left hip flexion 4/5, diminished pinprick, and vibratory sensation over her left extremities suggestive of a relapse (EDSS 2.5). She was treated with a new course of 1,000 mg oral MP for 5 days. Four weeks later, she recovered partially, persisting left facial sensory loss and mild tingling in her left leg (EDSS 2.0).

Case 3

A 41-year-old-woman, with history of smoking and idiopathic acute pericarditis 7 years before, started with minor gait disturbance 4 months earlier for which did not seek medical attention. Two months after symptom onset, she received two doses of Moderna (mRNA-1273) vaccine separated by 4 weeks; 5 weeks after the first dose, symptoms started to aggravate. On week 12, gait unassisted was no further possible and she was admitted to the hospital. Upon admission, physical examination showed the signs of moderate encephalopathy, gaze-evoked nystagmus with saccadic intrusions, dysarthria, truncal and limb ataxia, right-sided weakness, and bilateral extensor plantar response (EDSS 6.5). MRI revealed more than 100 high intensity lesions in T2 and Fluid attenuated inversion recovery (FLAIR) sequences, most of them nodular in appearance, predominantly in subcortical, juxtacortical, and periventricular locations, with tendency to coalesce, and to a lesser extent in the brain stem (**Figure 1C**). T1 hypointense lesions were also present. Spinal MRI was normal. T1 post-gadolinium sequences showed enhancement in ∼80% of the lesions. CSF revealed OCBs and elevated IgG index. Total body CT scan did not detect any occult malignancy. Visual evoked potentials revealed increased latencies in her left eye. She received MP 1,000 mg orally for 5 days, followed by 5 sessions of PLEX every other day. After treatment, she improved clinically, as encephalopathy has resolved, and she was able to walk unassisted for 20 meters (EDSS 6.0). Still, an MRI performed 5 months after the first vaccine dose revealed 16 new T2 lesions and 13 GELs. However, the neurological examination was unchanged, but the patient was treated with cyclophosohamide 3 g/m^2 IV. Two weeks later, the patient referred subjective improvement of gait, although EDSS remained unchanged.

Case 4

An otherwise healthy 33-year-old male presented with a 3-week history of right-sided weakness and numbness. Neurological examination showed nystagmus, right-sided mild weakness, limb ataxia, and moderate hypoesthesia that interfered with normal gait (EDSS 5.0). Brain and spinal MRI performed at the time of presentation revealed a total of 10 lesions, most of them periventricular (**Figure 1D1**), ovoid-shape in appearance, >1 cm in size, and 2 infratentorial lesions (in right cerebellar peduncle and in the pons), 3 of which presented gadolinium enhancement. No spinal cord lesions were present. Patient was discharged and received a single dose of mRNA BNT162b2 (Pfizer) COVID-19 vaccine. Concomitantly, he also started high-dose oral steroids for 5 consecutive days. The patient was recovering until 2 weeks after, when he was readmitted to the hospital for new onset of somnolence, dysarthria, dysphagia, hiccups, severe nausea, and increased right-sided weakness. Repeated MRI revealed 4 new diffuse T2 lesions, none of which presented gadolinium enhancement. At this time, there were no other signs suggestive of infectious etiology (**Figure 1D1**). Seven days after admission, he presented a febrile peak and decreased level of consciousness (EDSS 9), requiring admission to ICU. Repeated lumbar puncture revealed positive PCR for Herpes Simplex Virus type 1 (HSV-1) with 50,000 copies/ml in CSF. A third MRI at this time showed increased number of demyelinating lesions in supra- and infratentorial locations, and a new diffuse left-temporal cortical hyperintensity. The latter finding was consistent with HSV-1 encephalitis (**Figure 1D2**). He was started on acyclovir, 6 sessions of PLEX every other day, 1,000 mg MP IV for 5 days, and two doses of 1,000 mg rituximab IV separated by 2 weeks. Two months later, MRI showed 3 new GELs (2 periventricular, 1 subcortical). However, the patient has partially recovered and is able to walk a few steps with a walker, but presents severe aphasia, dysphagia, and right predominant tetraparesis (EDSS 7).

DISCUSSION

Our report describes unusual cases of patients already suffering from symptoms of acute demyelination, yet still not diagnosed that received mRNA COVID-19 vaccination. These patients experienced after variable time unexpected worsening of symptoms with high inflammatory activity requiring highly intensive therapy. A final diagnosis of MS was made in all cases, after thorough exclusion of other causes. Despite the overlapping features with ADEM, the depiction of the cases showing long-lasting inflammatory activity (both clinically and radiologically), the pattern of MRI findings, and the presence of OCB bands in CSF make this diagnosis very unlikely.

Although controversial, a relationship between mRNA COVID-19 vaccine and the development of a neurological relapse leading to a diagnosis of MS, or to subsequent relapses in people previously diagnosed MS has been described by some authors (4, 8). These cases usually had good evolution after standard therapy. In addition, there have been reports of flares of other immune-mediated diseases following mRNA COVID-19 vaccination (9, 10). On the contrary, a cohort study of 324 patients with MS did not show statistical differences in the relapse rate within the first 2 months after BNT162b2 (Pfizer) COVID-19 vaccine (11). Therefore, whether the association between mRNA COVID-19 vaccine and relapses of demyelinating diseases is causative, or incidental, still remains a matter of debate.

However, our report describes a different scenario, as all patients were having symptoms at the time of the first vaccine dose. We suggest the possibility that mRNA-based vaccine did

not trigger a relapse, but rather acted as a booster of an already initiated immune process. The rationale behind this view takes into consideration the composition of the vaccine and its interactions with the innate and adaptive immune system (12).

mRNA and adenovirus-based vaccines enter dendritic cells, resulting in production of S protein, the primary target of neutralizing antibodies. Innate sensors are also triggered by the intrinsic adjuvant activity of these vaccines, resulting in the production of type I interferon and multiple pro-inflammatory cytokines and chemokines, responsible for the systemic side effects, and potentially, for the modulation of an ongoing inflammatory process such as a relapse.

The specific pathways triggered by each vaccine are different; while mRNA vaccines trigger RNA sensors such Toll-like receptor (TLR) 7 and MDA5 (13), adenovirus-based vaccines trigger TLR 9, the major dsDNA sensor. TLR 7 detects single stranded RNA, and it is expressed in monocytes, macrophages, plasmocytoid dendritic cells, B cells, and microglia. This receptor is upregulated in animal models of MS (14). TLR 7 induces secretion of IL-1, IL-6, and IL-12, and differentiation of naïve T cells to Th1 and Th17, which then secrete IL-17 and IFN-gamma, respectively (15). On the other hand, TLR 9 activation by adenovirus-based vaccines induces the production of interferon beta (IFN-β), which in turn activates T suppressor cells and inhibits the production of IL-17.

We therefore hypothesize that activation of TLR 7 by mRNA vaccines may upregulate IL-17, a cytokine of critical importance in the immunopathogenesis of MS. Thus, the vaccine might have acted to amplify the inflammatory process during a relapse in these patients (12, 16). This contrasts with TLR 9 signaling by adenovirus-based vaccines, and may account for the scarcity of severe relapses observed with this vaccine (12, 17). Interestingly, the most clinically aggressive cases had also the highest levels of IL-6, suggesting a major differentiation toward Th1 and Th17 (16, 18).

Nevertheless, the temporal association between mRNA COVID-19 vaccination and exacerbation of the relapses must be interpreted with caution. As any case series, we lack control group. Although the participating hospitals were reference centers for MS and were unaware of other cases, we cannot discard other cases that might have different outcomes.

CONCLUSION

Patients should be advised to seek medical attention if experiencing acute neurological symptoms, especially before vaccination. In such cases, fast diagnostic procedures and prompt treatment should be performed to potentially prevent exacerbation of the disease. Still, pharmacovigilance and further study of cases is warranted to establish causality in this unusual scenario.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CQ-B, FG-G, and BC: conception and design of the study, acquisition and analysis of data, and drafting a significant portion of the manuscript or figures. CA: conception and design of the study and drafting a significant portion of the manuscript or figures. MP, JM, RS, SC-B, RG-R and JC: acquisition and analysis of data and drafting a significant portion of the manuscript or figures. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Acute Necrotizing Encephalopathy Following COVID-19 Vaccine

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Objectives: Acute necrotizing encephalopathy (ANE) is a rare neurological disorder arising from a para- or post-infectious "cytokine storm. "It has recently been reported in association with coronavirus disease 2019 (COVID-19) infection.

Methods: A 56-year-old male with a diagnosis of ANE 48 h following the first dose of ChAdOx1 nCoV-19 vaccination was investigated. Cytokine analyses on serum and cerebrospinal fluid (CSF) were performed. The patient was treated with high-dose corticosteroids and followed clinically and radiologically.

Results: Favorable clinical and radiological outcomes were noted. There was an upregulation in serum levels of CXCL5, CXCL1, Il-8, IL-15, CCL2, TGF-B, and EGF, and up-regulation in CSF levels of CXCL5, IL-2, IL-3, and IL-8.

Discussion: As COVID-19 infection has been previously reported as a possible rare cause of ANE, we speculate on an aberrant immune response mechanism that was brought about by the vaccine. To increase our understanding of the pathogenesis of ANE in the context of COVID-19 vaccination and to better define its clinical features and outcomes, clinicians and scientists should continue reporting convincing cases of such entities.

Keywords: COVID, acute necrotizing encephalopathy, vaccine, Neuroimmunology, ANE, akinetic mutism, encephalopathy

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INTRODUCTION

We case report of a 56-year-old male who was found to have altered mental status upon awakening. The patient had no specific complaints the day prior aside from mild fatigue. He had received his first dose of the ChAdOx1 nCoV-19 vaccine 2 days prior. He had no viral prodrome in the weeks preceding his vaccination. His past medical history was significant for hypertension and a self-limited viral myocarditis 2 years before.

Upon his arrival to the emergency department, the patient's vital signs showed blood pressure at 160/100 mmHg and a rectal temperature of 38.3°C. His neurological examination was compatible with a state of akinetic mutism. Initial laboratories revealed white blood cell count (WBC) at 11.07 $\times$ 10^9/L. The toxicology screen workup was negative. The RT-PCR COVID-19 test was negative. Computed tomography angiography (CTA) with venous phase of the brain and neck was normal. Electroencephalogram (EEG) showed mild diffuse slowing but with no epileptiform discharges.

Magnetic resonance imaging (MRI) of the brain performed on day 1 (**Figures 1A-D**) showed hyperintensities involving bilateral thalami, with some diffusion restriction and microhemorrhagic components. Repeat brain MRI on day 3 showed relative stability of the FLAIR lesions, with increase in the hemorrhagic component within the thalami (**Figures 1E-H**). There was no enhancement post-gadolinium injection.

Cerebral spinal fluid (CSF) analysis on day 1 showed no WBC, and slightly increased proteins at 0.84 g/L. Multiplex PCR for infectious causes (HSV-1/2, HHV-6, HpeV, VZV, enterovirus, CMV, listeria, and cryptococcus) was negative. Repeat lumbar puncture on day 4 showed similar results. Oligoclonal bands were negative. In addition, rheumatological workup was non-contributory. Anti-aquaporin-4 and anti-myelin-oligodendrocyte antibodies were negative.

High-dose pulse intravenous corticosteroids (methylprednisolone 1g IV daily for 7 days) were started on day 4 and were followed by prednisone taper. Progressive clinical improvement was noted in the following days, with improvement in motor, visuospatial, language, and social skills.

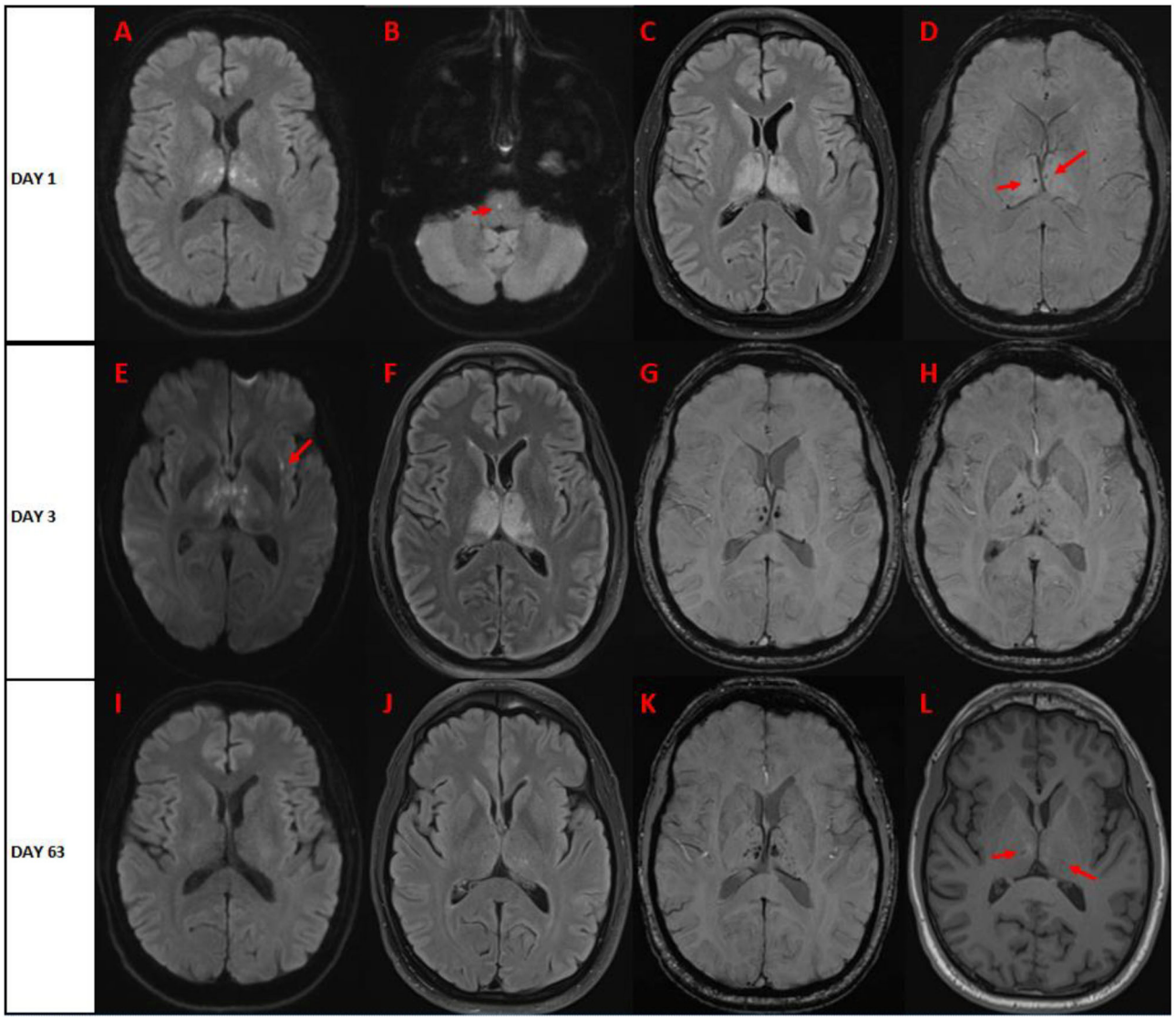

FIGURE 1 | Brain magnetic resonance on **(A–D)** *day* 1 **(E–H)** *day* 3, and **(I-L)** *day* 63 after symptom onset. **(A)** Diffusion-weighted imaging (DWI) shows bilateral symmetric punctiform restrictive lesions in bilateral thalami. **(B)** DWI shows single punctiform restrictive pontine lesion. **(C)** FLAIR imaging shows bilateral hyperintense lesions of the thalami, with no significant mass effect. **(D)** Susceptibility-weighted imaging (SWI) shows two punctiform hypointense lesions in bilateral thalami. On day 3, **(E)** DWI shows increase of the restrictive lesions of bilateral thalami, and new peri-insular restrictive lesions (arrow). **(F)** FLAIR imaging shows relative stability of bilateral hyperintensities involving thalami. **(G,H)** SWI shows increase hypointense microhemorrhagic lesions of bilateral thalami. On day 63, **(I)** DWI sequence shows resolution of restrictive lesions. **(J)** FLAIR imaging sequence reveals near resolution of thalamic hyperintensities. **(K)** SWI indicates persistence of hypointense microhemorrhagic bilthalamic lesions. **(L)** T1-weighted imaging shows subtle hypointense lesions in bilateral thalami (arrows).

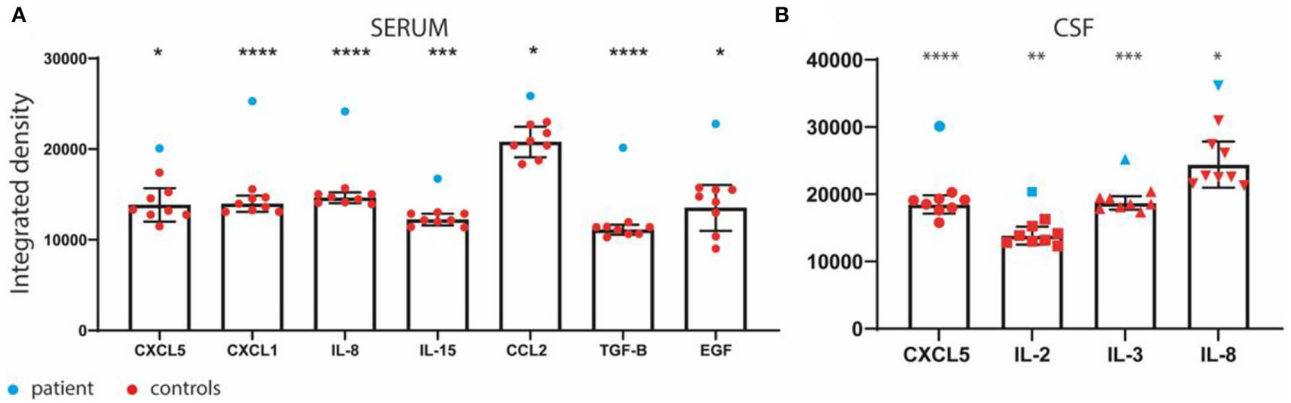

FIGURE 2 | (A) Serum and **(B)** cerebrospinal fluid (CSF) cytokine profile in the patient and eight healthy age-matched controls from a local biobank. *$p \leq 0.05$; **$p \leq 0.01$; *** $p \leq 0.001$; ****$p \leq 0.0001$.

He was discharged to the rehabilitation after 4 weeks. Prednisone was tapered off over a period of 5 weeks. On follow-up 6 weeks after discharge, the patient made a near-complete recovery, with no apparent sequelae. Favorable radiological evolution was noted (**Figures 1I-L**).

In total, the patient had three negative RT-PCR COVID-19 tests, as well as two negative COVID-19 serologies against spike and nucleocapsid proteins (performed 2 and 6 weeks after admission). Ran-binding protein 2 (RANBP2) gene sequencing with copy variant analysis was performed, as pathogenic mutations have been described to cause familial and recurrent forms of acute necrotizing encephalopathy (1). The results revealed a heterozygous c.8293-10C > T variant in intron 23. *In silico* splicing algorithms did not predict the adverse effect of this variant on splicing.

We analyzed the cytokine profile in blood and CSF drawn on day 4 of admission, thus prior to pulse corticosteroid therapy. We used an unbiased approach by cytokines array (Raybiotech) to study the protein levels of 42 cytokines. We compared these levels with eight healthy aged-matched controls from a local anonymized biobank. We observed upregulation in serum levels of CXCL5 ($p = 0.0173$), CXCL1 ($p < 0.0001$), Il-8 ($p < 0.0001$), IL-15 ($p = 0.0004$), CCL2 ($p = 0.0288$), TGF-B ($p < 0.0001$), and EGF ($p = 0.0117$) (**Figure 2A**). There was upregulation in CSF levels of CXCL5 ($p < 0.0001$), IL-2 ($p = 0.0026$), IL-3 ($p = 0.0004$), and IL-8 ($p = 0.0145$) (**Figure 2B**). We did not observe any significant changes in TNF-α, IFN-γ, IL-4-5-6-7-10, IL-1β, CCL1-5-17-22, and G-CSF, which were previously reported to be upregulated under similar conditions (2, 3).

TABLE 1 | Diagnostic criteria for acute necrotizing encephalopathy (ANE) contrasted to our patient's case.

Diagnostic criteria	Our patient
(1) Acute encephalopathy preceded by viral febrile disease; rapid deterioration in the level of consciousness or convulsions.	Fulfilled
(2) Increased CSF protein without pleocytosis.	Fulfilled
(3) CT or MRI evidence for symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum and cerebellar medulla. No involvement of other CNS regions.	Fulfilled
(4) Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia.	Unfulfilled
(5) Exclusion of other resembling diseases.	Fulfilled

DISCUSSION

Given the clinical and radiological evolution of the case, the patient's final diagnosis was established as being acute necrotizing encephalopathy (ANE). ANE is an extremely rare condition affecting mostly children and results from a para- or post-infectious "cytokine storm" that leads to breakdown of the blood-brain barrier and subsequent central nervous system (CNS) insult (1). The condition is frequently associated with signs of systemic inflammatory response syndrome (SIRS) and may evolve into shock, multiple organ failure (MOF), or disseminated intravascular coagulation (DIC). Proposed diagnostic criteria for ANE (4) are shown in **Table 1**. Our patient meets all the criteria except for elevation of serum aminotransferases. Such finding was frequently observed in case series of ANE and has, hence, been incorporated into the criteria as a marker of systemic symptoms that can arise from the immune response that leads to ANE. It is, however, not a universal feature, and we do not consider it to preclude the diagnosis. Furthermore, we note that our patient's case was not preceded by a viral febrile illness.

Radiologically, the hallmark feature of ANE is bilateral thalamic involvement, which is found in all cases of ANE (1, 4). Other multifocal brain lesions are usually present as shown in the diagnostic criteria. Such lesions have been described to have dynamic changes during the clinical course from edema to petechial hemorrhage and then to necrosis (5). Significant regression of these brain lesions has been reported in survivors

TABLE 2 | Cases presenting with altered level of consciousness following ChAdOx1 nCoV-19 vaccine.

Author/ country	Age/ gender	Relevant co-morbidity	Time from vaccination to symptom onset	Neurological presentation	Initial MRI findings	CSF findings	Diagnosis	Proposed mechanism	Management	Outcomes
Our case/Canada	56 y/M	Viral myocarditis 2 years prior	2 days after 1st dose	Fever and altered level of consciousness (akinetic mutism)	T2/FLAIR hyperintensities in thalami. Scattered punctate foci of diffusion restriction and petechial haemorrhage	Proteins at 0.84 g/L Normal cell count	ANE	Aberrant immune response	IVMP 1g/d × 7 days, followed by a 5-week prednisone taper	Full recovery after 6 weeks of rehabilitation
Siriratnam et al. (15)/Australia	75 y/F	Eosinophilic granulomatosis with polyangiitis; ceased all immunotherapy 12 months prior to illness Monoclonal gammopathy of unknown significance	2 days after 1st dose	Altered level of consciousness, dysarthria, followed by seizures	T2 hyperintensities in thalami and medial temporal lobes. Scattered punctate foci of diffusion restriction and petechial haemorrhage	Proteins at 2.98 g/L Normal cell count	ANE	None	IVIg 2 g/kg × days and intravenous methylprednisolone 1 g/d × 4 days, followed by prednisolone 1 mg/kg × 3 weeks	Death 1 month after disease onset
Permezel et al. (26)/Australia	63 y/M	Insulin-dependant type II diabetes mellitus Ischemic heart disease Atrial fibrillation	12 days after 1st dose	Vertigo, abdominal pain, fatigue, followed by decrease of consciousness after 4 days.	Bilateral white matter T2 hyperintensities in periventricular and juxtacortical areas	Initially no pleocytosis, protein 0.69 g/L. Subsequent CSF: 8 cells (mononuclear).	ADEM (proved by post-mortem neuropathology)	None	IVMP 1 g/d × days, followed by PLEX.	Death 20 days after admission
Ancau et al. (16)/Germany (case 1)	61 y/M	Hypothyroidism and polymyalgia rheumatica	2 days after 1st dose	Fever, headache and apathy followed by loss of consciousness and seizures	Bilateral confluent cortical and subcortical FLAIR lesions with hemorrhagic involvement of basal ganglia, specifically thalami	Normal cell count	AHEM	Molecular mimicry or re-infectious etiology	IVMP 1g/d × 5 days, followed by seven PLEX sessions with concomitant methylprednisolone 250 mg *via* nasogastric tube	Vegetative state after 14 weeks of rehabilitation
Ancau et al. (16)/Germany (case 3)	55 y/F	Unspecified	9 days after 1st dose	Nausea, dizziness and meningismus, progressing rapidly to spastic tetraparesis and coma	Multiple FLAIR hyperintensities with hemorrhagic lesions in the right parietal and temporal lobes, bilateral fronto-temporal regions, and right occipital lobe and left fronto-basal region	Lymphocytic pleocytosis (10 cells)	AE		IVMP 1g/d × 5 days followed by methylprednisolone 100 mg *via* nasogastric tube taper. Repeat treatment following deterioration of edema and increase of hemorrhagic lesions	Death

(Continued)

TABLE 2 | Continued

Author/ country	Age/ gender	Relevant co-morbidity	Time from vaccination to symptom onset	Neurological presentation	Initial MRI findings	CSF findings	Diagnosis	Proposed mechanism	Management	Outcomes
Chakrabarti et al. (27)/India	60 y/F	None	1 day after 2nd dose	Confusion, forgetfulness, hallucinations progressing over 5 days, followed by rigidity	FLAIR hyperintensities in bilateral caudate heads which showed diffusion restriction. Patchy diffusion restriction in left posterior parietal and occipital gyri. Deterioration of abnormalities on repeat imaging	Normal	Post-vaccinal prion-like neurodegeneration	Toxicity of S protein or toxicity of anti-S protein antibodies	Dexamethasone, antiepileptics, broad-spectrum antibiotics	Death 1 month after disease onset
Kwon et al. (19)/Korea	57 y/F	Hypertension	5 days after 2nd dose	Generalized seizure. Had fever and headache in the preceding days	Left insular and mesial temporal cortices restriction diffusion. 2 months after, encephalomalacia change in the affected temporal lobe	Initially normal 22 cells (91% lymphocytes) on repeat CSF 1-month after, with proteins at 88.3 mg/dl	AE	Central nervous system autoimmunity	Initially acyclovir and anticonvulsants. Methylprednisolone, IVIg and Rituximab after 1 month	Significant memory deficits
Maramattom et al. (28)/India (Case 1)	64 y/M	Unknown	10 days after 1st dose	Headache, fever, and drowsiness	FLAIR hyperintensities in mesial temporal lobe and middle cerebellar peduncles	Lymphocytic pleocytosis (value not provided)	AE (LE)	None	IVMP 1g/day × 5days and PLEX. Rituximab after 8 weeks	Discharged with no deficits; mRS 1
Maramattom et al. (28)/India (Case 2)	65 y/M	Unknown	10 days after 2nd dose	Behavioral changes. Developed jerky movement over the next 3 weeks	Unknown	Mild pleocytosis (10 cells)	OMAS	None	IVMP 1 g/d and IVIg for 5 days	mRS 1
Zuhorn et al. (18)/Germany (Case 1)	21 y/F	Obesity	5 days after 1st dose	Headache, attention and concentration difficulties. Seizures and stupor afterward	Normal	Lymphocytic pleocytosis (46 cells)	AE	Aberrant immune response	Dexamethasone 10 mg/d	Mild cognitive slowing at discharge with no functional impairment

(Continued)

TABLE 2 | Continued

Author/ country	Age/ gender	Relevant co-morbidity	Time from vaccination to symptom onset	Neurological presentation	Initial MRI findings	CSF findings	Diagnosis	Proposed mechanism	Management	Outcomes
Zuhorn et al. (18)/Germany (Case 2)	63 y/F	Deep vein thrombosis 2 days after vaccination	6 days after vaccination. Unspecified if 1st or 2nd dose	Gait deterioration with vigilance impairement and twitching, followed by opsoclonus-myoclonus syndrome	Normal	Lymphocytic pleocytosis (115 cells)	OMS		IVMP 1 g/d × 5 days.	Immediate improvement following treatment. Low-grade tremor as the only residual neurological deficit
Zuhorn et al. (18)/Germany (Case 3)	63 y/M	Unspecified	8 days after vaccination Unspecified if 1st or 2nd dose	Fever, headache and reduced alertness	Normal	Lymphocytic pleocytosis (7 cells)	AE		No treatment	Spontaneous improvement

AE, autoimmune encephalitis; ADEM, acute demyelinating encephalomyelitis; AHEM, acute hemorrhagic encephalomyelitis; ANE, acute necrotizing encephalopathy; CSF, cerebrospinal fluid; IVMP, intravenous methylprednisolone; LE, limbic encephalitis; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; OMS, opsoclonus-myoclonus syndrome; OMAS, opsoclonus-myoclonus ataxia syndrome; PLEX, plasmapheresis.

of ANE. Our case highlights these imaging findings and their evolution (**Figure 1**). Furthermore, differential diagnosis of acute bilateral thalamic lesions should be thoroughly assessed by clinicians. These include ischemic strokes ("top of the basilar" occlusion or artery of Percheron infarcts), deep venous occlusions, vasculitis, hypoxic-ischemic encephalopathy, acute disseminated encephalomyelitis (ADEM), Fabry disease, Wernicke encephalopathy, osmotic demyelination, viral encephalitis (Japanese encephalitis, West Nile virus, dengue virus, and others), neoplasms (lymphomas and astrocytomas), and Creutzfeldt-Jakob disease. Cases of autoimmune and paraneoplastic encephalitis harboring bilateral thalamic involvement are also increasingly being reported (6, 7). In children, differential diagnosis also includes Leigh Syndrome and inborn errors of metabolism.

ANE is distinct from inflammatory and demyelinating conditions that can occur in post-infectious or post-vaccinal states. Neuropathological cases of ANE demonstrated the absence of demyelination and important parenchymal abnormalities (perivascular hemorrhage and necrosis and vasogenic edema), with no significant inflammatory cell infiltration (4, 8, 9).

Previously reported cytokine profiles in influenza-associated ANE were mostly characterized by IL-6 and TNF-α increase (2), although this was not invariable (3). The immune response to the SARS-CoV-2 vaccine is driven by neutralizing antibodies and antigen-specific T cells. It was demonstrated that ChAdOx1 the nCoV-19 vaccine induces a Th1-biased response mostly characterized by production of interferon-y (IFN-y) and IL-2, and a small increase in IL-10 (10).

Some studies in ADEM suggested a CSF increase in Th1-related cytokines (TNF-α, IL-657 2, IFN-γ), Th2-related (IL-4, IL-5), macrophages-related (IL-1β, CCL4, IL-6, IL-8, G-CSF) and in chemokines (CXCL1-7-10 and CCL1-3-5-17-22) (11). Interestingly, the most consistent changes observed in our patient's serum and CSF samples were increase in CXCL5 and IL-8, which are both members of the ELR(+) CXC chemokine family. It was recently suggested that infection of human-induced pluripotent stem cell (iPSC) neural cultures by SARS-CoV-2 may induce IL-8 production (12). Although our patient's CSF and serum cytokine profile did not correspond directly to any previously described cytokine profile in ANE, it may suggest aberrant activation of mononuclear cells driving a CNS inflammatory process. The main limitations of our cytokine analyses include the fact that they were performed at only a single time point, and that they were performed 4 days after admission.

Several cases of ANE have been reported in adult patients with active COVID-19 infection (13, 14). Cases of CNS demyelination syndromes have been described in patients infected with SARS-CoV-2 (13). These include the clinically aggressive variant of ADEM, namely, acute hemorrhagic encephalomyelitis (AHEM). The interest in our case lies in the fact that the patient had no clinical or laboratory evidence of SARS-CoV-2 infection. The only potential precipitating factor was the administration of the ChAdOx1 nCoV-19 vaccine 2 days prior. Interestingly, there is a recently published case of a 75-year-old woman who developed ANE 2 days after receiving the ChAdOx1 nCoV-19

vaccine (15). Unlike our patient, however, the patient's outcome was unfavorable, as she died 1 month after disease onset despite corticosteroid treatment. Also, cases of AHEM within the first few days of the first shot of the ChAdOx1 nCoV-19 vaccine have been described (16). Although ANE and AHEM share clinical similarities in their aggressiveness and severity, key radiological, neuropathological, and laboratory differences allow for the distinction of the two entities (4, 17). Whether these rare conditions share a common pathophysiological basis remains a matter of debate, as some have considered them to occur as part of a continuum (13). Finally, cases of autoimmune encephalitis following ChAdOx1 nCoV-19 have been reported (18, 19). Such cases of altered sensorium following this vaccine are summarized in **Table 2**.

Although post-vaccinal CNS demyelination syndromes tend to occur at a mean of 14-days following vaccination (20), post-vaccinal timing of ANE is unclear because of its rarity. A case of ANE 6 days after diphtheria, tetanus toxoid, and whole-cell pertussis (DTPw) vaccination was reported in a previously healthy 6-month-old boy (21). Since our case shares similar timing to the previously reported case of ANE (15), and the fact that ANE is not considered a demyelinating condition, we consider the timing of the vaccine to be plausible. Furthermore, the ChAdOx1 nCoV-19 vaccine uses an adenovirus vector (22). Rapid induction of the innate immune system has been described with adenovirus viral vectors and could be IL-8-mediated (23). Hence, a hypothetical mechanism for ANE in our patient could include vector-induced aberrant immune response. However, since ANE has been reported as a rare manifestation of COVID-19, we can also speculate on a rapidly evolving aberrant immune response mechanism or even a molecular mimicry mechanism that could have been induced by the vaccine-contained SARS-CoV-2 spike protein epitope. Finally, the ChAdOx1 nCoV-19 vaccine does not contain adjuvants, ruling out such an immunopathogenic mechanism (22).

Our patient had negative COVID-19 serologies against spike and nucleocapsid proteins despite vaccination. We attribute the negative serologies to the administration of pulse corticosteroid therapy that was begun 5 days after vaccination, followed by high-dose prednisone taper. Immunogenicity data of the ChAdOx1 nCoV-19 vaccine show that antibodies against SARS-CoV-2 spike proteins significantly increase after 14 days and peak after 28 days, with no significant difference between day 0 and day 7 (24). Hence, with these elements, we suggest that our patient's treatment blunted the immune response to the vaccine and explains the negative serologies. Rapid treatment may have influenced the positive outcome in our patient's situation, as has been retrospectively shown in children with ANE (25).

Of note, RANBP2 mutations were found to predisposed to recurrent episodes of ANE in children (1). The mutation found in our case (c.8293-10C > T) has never been described in the literature to our knowledge. As an intronic point mutation with no expected splicing consequences, it is most likely to be unrelated to our patient's condition and is expected to be benign.

In summary, we report a case of ANE occurring after the first dose of the ChAdOx1 nCoV-19 vaccine. The patient was promptly treated with corticosteroids and had a very favorable outcome. To increase our understanding of the pathogenesis of ANE in the context of COVID-19 vaccination and to better define its clinical features and outcomes, clinicians and scientists should continue reporting convincing cases of such entities.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CER du CHU de Québec-Université Laval. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MB has done the required academic literature review for the conception of the article and drafted the article. VP-M has performed laboratory cytokine testing as well as critical revision of the article. FÉ, GS, and ND have performed critical revision of the article. PB has done a critical revision of the article and performed the final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: A Case Report of Neurosyphilis Mimicking Limbic Encephalitis

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Neurosyphilis (NS) is an infection of the central nervous system caused by Treponema pallidum. It mimics various neurological and psychiatric diseases. In recent years, there have been several NS cases that manifest as limbic encephalitis (LE). Therefore, the diagnosis of neurosyphilis in the early stages is difficult. Here, we present a case of an NS patient who presented with LE manifestation. The 62-year-old woman presented with acute clinical manifestations of gibberish speech, poor memory, and seizures. Brain MRI showed abnormal signals on the right medial temporal lobe. In addition, the patient had a positive serum leucine-rich glioma inactivated 1 (LGI1) antibody with a titer of 1:16. Therefore, an initial diagnosis of anti-LGI1 encephalitis was made. However, further tests carried out showed positive rapid plasma reagin (RPR), and treponema pallidum particle agglutination (TPPA) tests both in the serum and the cerebrospinal fluid (CSF). Therefore, uncertainty arose as to whether the patient had both anti-LGI1 encephalitis and NS or whether the LGI1 antibody and LE manifestations were due to the NS. The patient was initiated on the recommended dose of penicillin G sodium. Following treatment, the patient reported a significant improvement in clinical symptoms, normal signals in the right temporal lobe, and a negative serum LGI1 antibody. These findings suggested that NS induced the LE manifestations and the production of the LGI1 antibody. This case demonstrates that testing syphilis in patients with LE is important and positive autoimmune encephalitis (AE) antibodies in NS patients need to be viewed and interpreted with greater caution.

Keywords: neurosyphilis, encephalitis, leucine-rich glioma inactivated 1 protein, penicillin, case report

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INTRODUCTION

Syphilis is a sexually transmitted disease caused by the bacterium *Treponema pallidum*. It develops in four different stages: early syphilis (primary, secondary, and early latent syphilis) and late syphilis (latent and tertiary syphilis). Neurosyphilis (NS) is an infection of the central nervous system (CNS), which may occur at any stage of the infection (1). Syphilis outbreaks have been reported in some countries despite a fall in the reported incidence (2). The clinical manifestations of NS have had a dramatic change over the past 30 years. Compared with the pre-penicillin era, there has been a decline in cases of general paresis and tabes dorsalis. However, atypical forms (epilepsy, eye symptoms, stroke, confusion, or personality changes) have increased (3, 4). In recent years, several

NS cases which present as limbic encephalitis (LE) have been reported, thus making it more difficult to diagnose NS in the early stage(5). Here, we report a case of a patient with NS presenting with LE manifestation. Therefore, we suggest that patients with LE manifestations should be routinely tested for syphilis to avoid misdiagnosis of NS.

CASE PRESENTATION

A 62-year-old woman was admitted to the neurology department of Tianjin Huanhu Hospital. The patient complained of paroxysmal falls accompanied by impaired consciousness for the last nine days and paroxysmal limb twitch accompanied by gibberish speech for four days. Initially, the patient experienced tonic-clonic seizures, accompanied by impaired consciousness. Later, the patient experienced tonic seizures with head turning to the right and retained consciousness similar to faciobrachial dystonic seizures (FBDS) (**Supplementary Materials S1**). These incidences occurred more than ten times in a day. The patient was first seen in another hospital, and a brain MRI was done. The MRI showed no abnormalities. The patient was started on sodium valproate, diazepam, and levetiracetam (drug doses unknown). Due to no clinical improvement, the patient was referred for further management. The patient had no previous history of hypertension, coronary heart disease, diabetes, cerebrovascular disease, mental illness, hepatitis, tuberculosis, and no family history of any hereditary disease.

On admission, the patient had a body temperature of 36.3°C, a heart rate of 91 beats/min, a respiratory rate of 20 breaths/min, and a blood pressure of 162/85 mmHg. The neurological assessment revealed that the patient had cognitive dysfunction (poor memory and poor calculation ability). However, other categories of the neurological examination, including cranial nerves, motor system, reflexes, sensation, coordination, movement, gait, and signs of meningeal irritation, were normal.

The serum testing of routine blood tests, coagulation profile, liver function and kidney function tests, blood sugars, lipid profile, and serological testing for hepatitis B, syphilis, and HIV were negative. In addition, the results of anti-nuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factors, thyroid-stimulating hormone receptor antibodies, anti-thyroglobulin antibodies, and serum tumor markers, including carcinoembryonic antigen, squamous cell carcinoma antigen, cytokeratin-19 fragment, carbohydrate antigen 199, carbohydrate antigen 125, and neuron-specific enolase were normal. The patient had abnormal serum chloride levels of 95mmol/L. Further, the serum AE-related antibodies determined with both tissue-based and cell-based indirect immunofluorescence (IIF) assay in V-Medical Laboratory (Guangzhou, China), including anti-N-methyl-D-aspartate receptor (NMDAR), anti-leucine-rich glioma-inactivated 1 (LGI1), anti-contactin-associated protein-like 2 (CASPR2), anti-gamma-aminobutyric-acid B receptor (GABABR), anti-dipeptidyl-peptidase-like protein-6 (DPPX), and anti-glutamic acid decarboxylase 65 (GAD65) and paraneoplastic neurological syndrome (PNS)-related antibodies including anti-Hu, anti-Ri, anti-Yo, anti-Ma2, anti-CV2, and anti-amphiphysin, was remarkable only for positive anti-LGI1 antibody with a titer of 1:16 (normal<1:10). The CSF showed slight leukocytosis of 10×10^6 / L with lymphocytic predominance. However, the pressure, color, turbidity, glucose levels, chloride levels, Gram staining, acid-fast staining, ink staining, metagenomic next-generation sequencing (mNGS), AE-related antibodies which were also determined with both tissue-based and cell-based IIF assay in V-Medical Laboratory (Guangzhou, China), and PNS-related antibodies of the CSF were normal. The patient had a positive RPR with a serum titer of 1:16 and a positive TPPA. Subsequently, TPPA and RPR in CSF were tested, and both results were positive.

The electroencephalography (EEG)showed irregular slow waves with medium to high amplitudes in the right temporal lobe, which spread to the other lobes and showed sharp waves (**Figure 1**). The brain MRI showed increased signals on T2-weighted and FLAIR imaging in the medial temporal lobe (**Figure 2A**). The gadolinium-enhanced MRI of the brain showed mild to moderate cord enhancement in the right temporal lobe (**Figure 2B**). Syphilis can cause multiple system damage. Therefore, magnetic resonance angiography (MRA) was carried out to investigate vascular stenosis or vasculitis-like changes. However, the results revealed no abnormalities (**Figure 2C**). Moreover, CT of the chest, echocardiography, abdominal ultrasound, urinary tract ultrasound, electromyography, and nerve conduction velocities of the limbs were normal.

Therefore, uncertainty arose as to whether the patient had both anti-LGI1 encephalitis and NS or whether the LGI1 antibody and LE manifestations were due to the NS. The patient received intravenous penicillin sodium 3.5 million units every 4 h for 14 days to treat the NS. Furthermore, the patient was initiated on intravenous sodium valproate 400 mg two times daily and oral levetiracetam 500 mg two times daily. The drugs were then changed to oral sodium valproate 500 mg two times daily and oral levetiracetam 750 mg two times daily. Improvement was noted with no convulsions and normal cognitive function. Two months later, the serum TPPA was still positive. In addition, the serum RPR was still positive with a titer of 1:8, while the serum LGI1 antibody was positive with a titer of 1:10. Furthermore, a revaluation of the CSF showed that the CSF TPPA and RPR were positive. However, the other CSF tests remained negative. In addition, a repeat of the EEG showed no epileptiform wave emission (**Figure 3**). Moreover, a repeat of the brain MRI showed no abnormality (**Figure 2D**). A second course of intravenous penicillin G sodium 3.2 million units every 4 h for 14 days was started. After another four months, the serum TPPA was still positive, the serum RPR test was positive with a titer of 1:8, while the serum LGI1 antibody was negative. Changes in TPPA, RPR, and LGI1 antibodies during the syphilitic treatment are shown in **Figure 4**. A repeat of the EEG and brain MRI showed normal findings. The third course of intravenous penicillin G sodium 3.2 million units every four hours, was given for 14 days. In

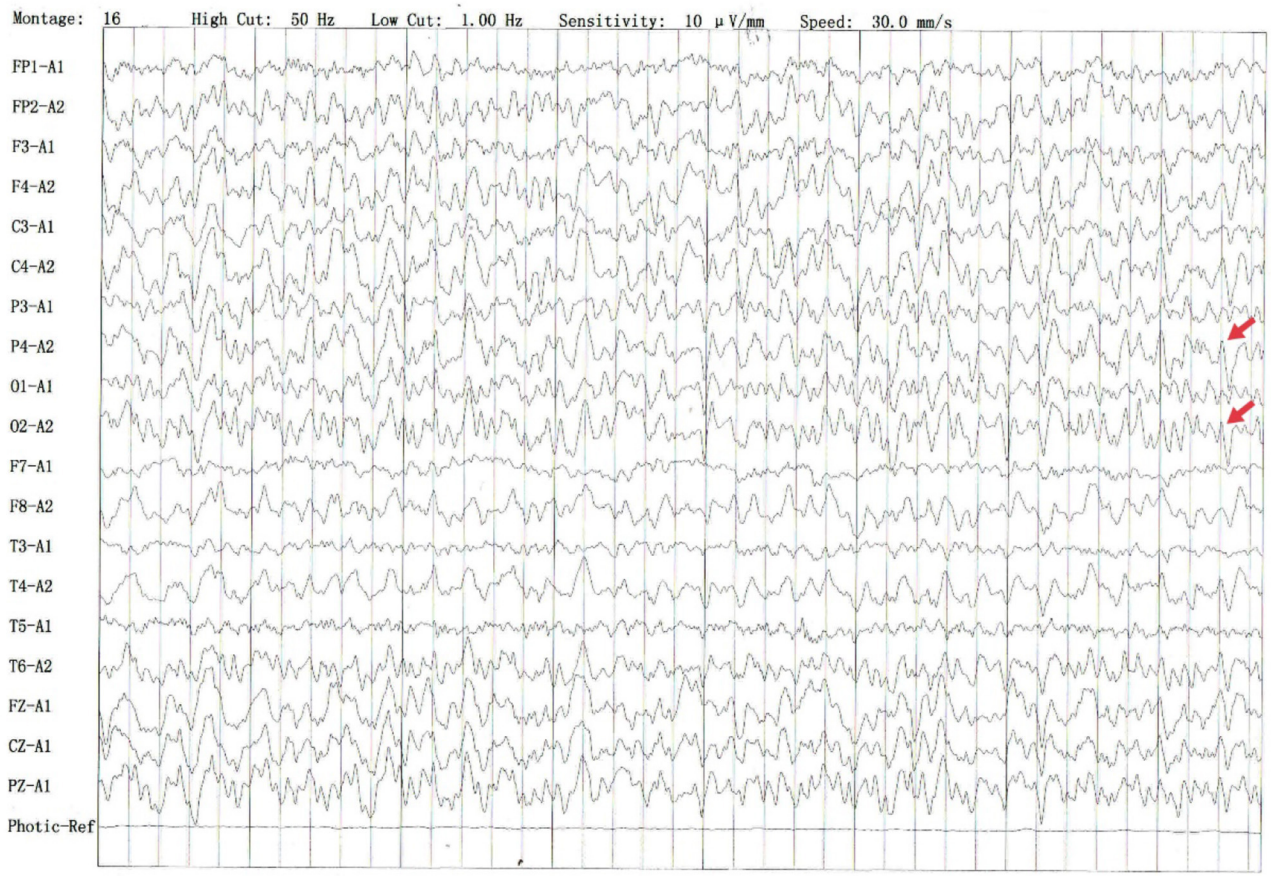

FIGURE 1 | Several irregular slow waves with medium to high amplitudes were recorded in the right temporal leads, which spread to other leads and showed sharp waves (shown by the red arrow).

addition, oral doses of sodium valproate 500 mg two times daily and levetiracetam 750 mg two times daily were continued. The patient was then followed up for additional three months. The patient reported no further convulsive episodes. In addition, the memory and calculation ability were noted to be normal.

DISCUSSION

We describe an unusual case of NS mimicking LE which has rarely been reported in literature. Based on the clinical manifestations and features of brain MRI, this particular case is identified as a limbic encephalitis. Limbic encephalitis is an inflammatory process of the limbic structures, with polymorphic clinical features, caused by paraneoplastic and nonparaneoplastic conditions and infections. In this case, it was important to consider some relevant differential diagnoses including paraneoplastic LE, herpes simplex encephalitis (HSE), and anti-LGI1 encephalitis.

Paraneoplastic LE is a paraneoplastic syndrome associated with antineural antibodies produced by tumors against intracellular antigens. The classical clinical presentation is characterized by subacute cognitive deterioration, especially short-term memory loss, seizures, and psychosis, suggesting involvement of the limbic system (6). PNS-related antibodies include anti-Hu, anti-Ri, anti-Yo, anti-Ma2, anti-CV2, and anti-amphiphysin. In this case, the diagnosis of Paraneoplastic LE was excluded by exclusion of cancer and the negativity of PNS-related antibody in both serum and CSF.

Herpes simplex encephalitis mainly presents with a subacute progression of fever, hemicranial headache, behavioral abnormalities, focal seizure activity, and focal neurological deficits (7). Mesiotemporal T2-weighted hyperintensity with an asymmetrical pattern also can be found in HSE. The diagnosis of HSV encephalitis was excluded by the clinical presentation and the negativity of mNGS for herpes simplex in CSF.

Anti-LGI1 encephalitis commonly present with seizures especially FBDS and cognitive decline mainly including memory and behavioral disturbance (8). Ancillary testing features of anti-LGI1 encephalitis, include mild to moderate hyponatraemia, normal CSF test results, or a slightly increased cell count in CSF, unilateral or bilateral hyperintensities in the medial temporal lobes in brain MRI and focal slowing or epileptic discharges in EEG (9). According to the patient's clinical symptoms including FBDS-like manifestation and cognitive

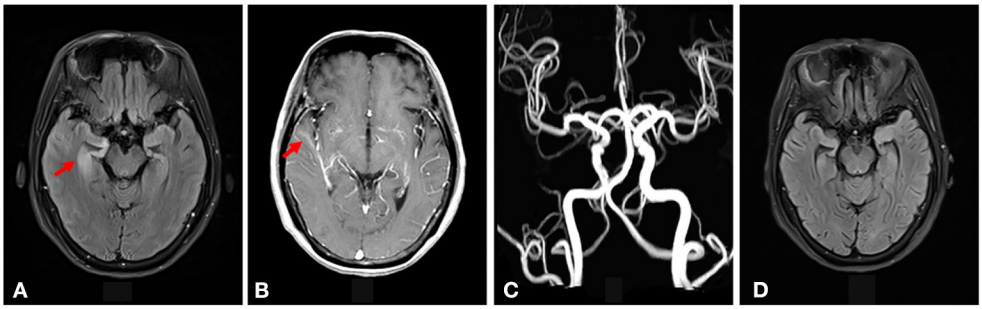

FIGURE 2 | (A) Increased signal intensity was seen on the T2-weighted FLAIR imaging in the right medial temporal lobe (shown by the red arrow). **(B)** Gadolinium-enhanced MRI of the brain showed mild to moderate cord enhancement in the right temporal lobe (shown by the red arrow). **(C)** The brain MRA did not show vascular stenosis or vasculitis-like changes. **(D)** The increased signal intensity on T2-weighted FLAIR imaging in the right medial temporal lobe disappeared after syphilitic treatment.

deficit, a slightly increased cell count in CSF, hyperintensity in the medial temporal lobes in brain MRI and serum positive LGI1, we initially considered diagnosis of anti-LGI1 encephalitis.

However, the serum was positive for TPPA and RPR, followed by positive TPPA and RPR in CSF. Therefore, there was uncertainty whether the patient had both anti-LGI1 encephalitis and NS or whether the NS induced the LE manifestations and the production of the LGI1 antibody. Treatment with penicillin G sodium according to the latest European guidelines(10), showed a significant improvement in the clinical symptoms, a decreased signal intensity on T2-weighted FLAIR imaging in the right medial temporal lobe, and a decrease in the LGI1 antibody titer. Therefore, it was assumed that the NS induced the LE manifestations and the production of the LGI1 antibody.

Neurosyphilis is an infection of the CNS caused by *Treponema pallidum*. It damages the meninges, blood vessels, or parenchyma of the brain and the spinal cord. The estimated incidence of NS is about 0.47 to 2.1 per 100,000 people (3, 11). Our patient's exclusive partner of more than 30 years tested seropositive for syphilis, and he admitted occasional sexual activity outside of this relationship. It is therefore possible that the patient contracted syphilis from her long-term partner in the course of sexual activity

The clinical manifestations of NS are related to the duration of the infection (12). Early-stage neurosyphilis usually is characterized by asymptomatic meningitis, but it can be symptomatic with headache, meningismus, cranial-nerve palsies, and blindness or deafness. Meningo-vascular syphilis is seen in early and late NS and involves the small and medium-sized arteries of the central nervous system leading to vasculitis, stroke, and several types of myelopathies. Late neurosyphilis occurs decades after the initial infection and is generally characterized by general paresis including progressive dementia, psychiatric syndromes, personality change, manic delusions, tremor, dysarthria, Argyll Robertson pupils in fewer than half of patients and tabes dorsalis including ataxic gait, prominent Romberg's sign, lightning pains in legs and trunk, greatly impaired deep and proprioceptive sensation, Charcot joints, Argyll Robertson pupils in most patients, paraparesis with leg areflexia, sphincter dysfunction (12). Currently, NS presents with atypical clinical forms due to incomplete doses of antibiotics for the treatment of other infections (4). In our case, the patient presented with gibberish speech, cognitive impairment, and seizures, characteristic of LE.

In the presented case, the serum and CSF RPR and TPPA tests were positive, suggesting a positive diagnosis for NS. NS is usually accompanied by CSF pleocytosis with 97% specificity and 95–100% sensitivity, and CSF elevated protein with less than 50% specificity and 90-95% sensitivity (12). A repeat white blood cell count in the CSF is used to determine the effectiveness of treatment. Re-treatment is recommended if the cells in the CSF do not decrease within six months of treatment (13). According to a previous study, there is no need to repeat treatment if the serum RPR titer is reduced four times or is negative(14). In this case, a slight increase in the white blood cells count was noted in the first CSF examination. Then, the patient's CSF white blood cell count decreased to normal and the serum titer of RPR decreased four times after treatment.

The common imaging manifestations of NS show abnormalities in the branches of the middle cerebral artery and basilar artery (15). Moreover, it has been reported that brain MRI in NS is often characterized by atrophy, white matter lesions, cerebral infarction and edema (4). So far, only a few cases have reported high signal intensity of the medial temporal lobe structure similar to LE on brain MRI (16–18).

The most prominent feature of this case is that both the first and second LGI1 antibody tests are positive, based on tissue-based and cell-based IIF assay, so that it is almost misdiagnosed as anti-LGI1 encephalitis. Ultimately, the patient's clinical symptoms improved significantly in the absence of glucocorticoids and gamma globulin therapy help us to rule out the diagnosis of LGI-1 encephalitis. In our view, NS may not only show LE manifestations but also cross-react with AE, leading to false-positive LGI1 antibodies. In our case, the effectiveness of antibiotic therapy suggests that NS may lead to a secondary immune response to LGI-1 antibody. It has been reported that the deterioration in neurological function after several weeks of treatment in HSE or its recurrence after viral clearance is related to the immune response associated with the production of NMDAR antibodies. Patients may

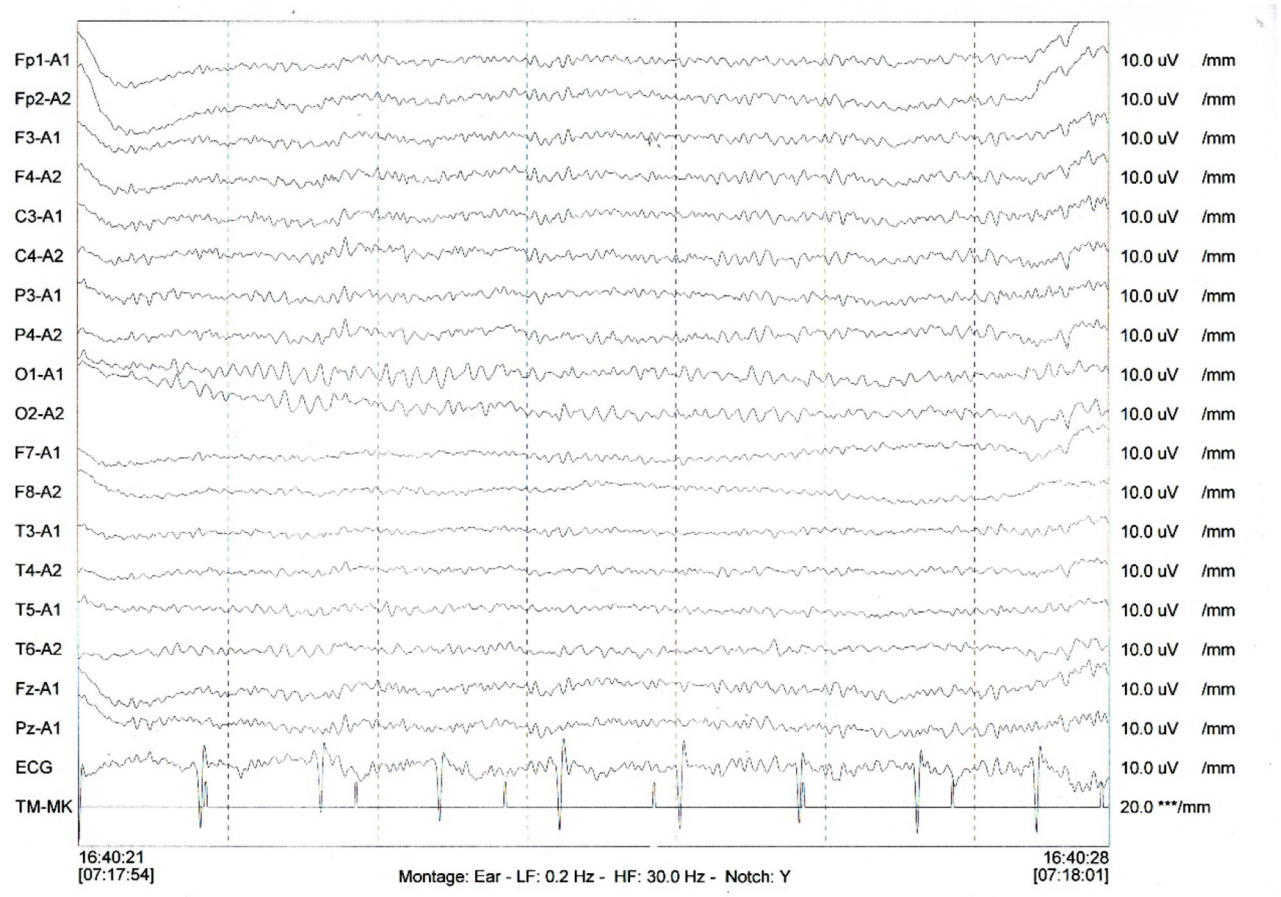

FIGURE 3 | A repeat of the EEG showed no irregular slow waves and sharp waves emission. *** means uV, the unit of measurement of electromyography (EMG).

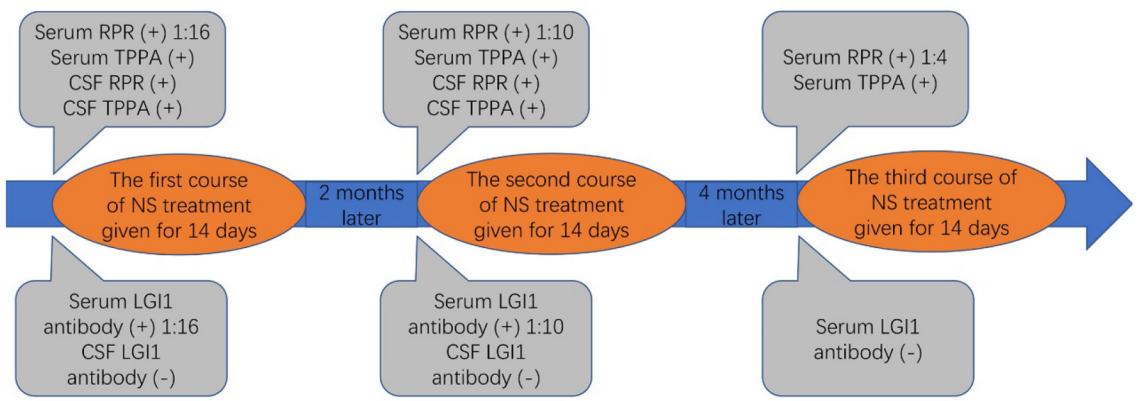

FIGURE 4 | The changes in syphilis and LGI1 antibodies over the course of syphilitic treatment.

present with deterioration in clinical manifestations, including abnormal mental status, cognitive dysfunction, and seizures similar to limbic encephalitis (19, 20). Therefore, we proposed that *Treponema pallidum* infection of the central nervous system may trigger an autoimmune response in the brain. Moreover, there is a need to investigate the presence of antibodies against synaptic receptors and intracellular antigens in patients with NS.

Based on this, we recommend that patients with LE, be tested for syphilis to avoid misdiagnosis in patients with atypical forms

of NS and positive AE antibody in NS patients need to be viewed and interpreted carefully.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

HL initiated the case report and drafted the manuscript. YZ consulted the relevant literature. WY were responsible for formulating the patient's treatment plan and revising the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.862175/full#supplementary-material

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CASE REPORT
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Case Report: Baló's Concentric Sclerosis-Like Lesion in a Patient With Relapsing-Remitting Multiple Sclerosis Treated With Dimethyl Fumarate

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Baló's concentric sclerosis (BCS) is a rare demyelinating disorder characterized by acute or subacute neurological symptoms associated with characteristic lesions of concentric onion skin appearance on MRI images and in pathology. The connection between BCS and classic MS is still a subject of debates. Our report presents a case of a patient who developed a symptomatic Baló-like lesion following several years of classical relapsing-remitting multiple sclerosis treated with dimethyl fumarate.

Keywords: multiple sclerosis, dimethyl fumarate, Baló concentric sclerosis, MRI, Baló disease

Baló disease, also known as Baló's concentric sclerosis (BCS), is a rare inflammatory and demyelinating disorder with a characteristic histopathological picture in which annular areas of demyelination alternate with rings of relatively preserved myelin. It is associated with loss of cerebral white matter oligodendrocytes resembling immunopathological pattern III of multiple sclerosis (MS) lesions. However, contrary to MS, the gray matter is spared. This typical pathology is reflected by magnetic resonance (MR) images of concentric lamellar-like zones of hyper- and hypointensities on T2-weighted sequences, corresponding to myelinated and demyelinated layers. The onion bulb (or wood grain) appearance is distinctive on gadolinium-enhanced T1-weighted sequences (1, 2).

BCS often affects young adults and is nearly two times more common in women and in people from East Asia. Patients may experience acute or subacute symptoms depending on the location of the lesion. In some cases, prodromal symptoms such as malaise, headache, and mild fever were reported. The most prominent features are behavioral changes, headache, muteness, cognitive deficits, aphasia, urinary incontinence, seizures, and hemiparesis that resemble those of intracerebral mass lesions (3). A fulminant disease course, resulting in death, is not uncommon and has recently been reported as 10%. However, complete recovery has also been described (2).

The overlap between BCS and MS is still not well defined. In one study, MRI images of more than half of the subjects revealed co-existence of Baló-like lesions with typical demyelinating MS lesions (4).

Our report is noteworthy, as it is one of the first that describe a patient who, after several years of typical relapsing-remitting MS treated successfully with dimethyl fumarate (and not other therapies previously associated with tumefactive lesions), developed a severe disease exacerbation associated with a new Baló-like lesion.

A 34-year-old female was admitted to the Department of Neurology, Poznan University of Medical Sciences in Poznan, Poland, with acute onset of left hemiparesis in November 2021. Her MS diagnosis was confirmed in April 2016 and was preceded by three relapses: right upper limb paresis in June 2015, cerebellar syndrome in November 2015, and left optic neuritis in February 2016. Her baseline pretreatment brain MRI in March 2016 revealed multiple supra- and infratentorial demyelinating lesions with one gadolinium-enhancing lesion in the cerebellum.

At that time, her cerebrospinal fluid (CSF) results were positive for type II oligoclonal bands. In November 2016, she was treated with dimethyl fumarate 240 mg twice daily; she remained relapse- and progression-free with a stable annual brain MRI scan.

One month before hospitalization, she noticed a weakness in the left lower limb, but the deficit resolved within 7 days without treatment, so she did not seek medical help.

Moreover, for 2–3 weeks, she reported general malaise and subfebrile temperature (37.7°C) without any upper respiratory tract or urinary tract infection symptoms.

Besides multiple sclerosis, she suffered from migraine with aura.

On admission her neurological examination revealed hemiparesis: left upper limb proximally MRC (Medical Research Council-muscle scale) grade 4, distally MRC grade 3, left lower limb proximally and distally MRC grade 2, with diminished sensation in the left limbs, positive Babinski and Rossolimo signs and exaggerated reflexes and mild spasticity in the left limbs.

The lymphocyte count on admission was 1.19 × 10Λ3/ul (normal range 1.1–4.5 × 10Λ3/ul), while 40 days before hospitalization, it was 1.47 × 10Λ3/ul. The white blood cell (WBC) count on admission was 5.96 × 10Λ3/ul (normal range 3.9–11 x×10Λ3/ul), and 40 days before hospitalization, it was 3.48 × 10Λ3/ul. The patient did not have lymphopenia; but had transient leukopenia in the past.

The clinical picture of this relapse was atypical, because the patient woke up with a fully developed left hemiparesis, which resembled a stroke onset and necessitated an urgent brain MRI.

The study showed a new Baló-like lesion in the right parietal lobe with a size of 27 mm leukopenia 27 mm and the characteristic "onion bulb" appearance. The lesion was partially enhanced after gadolinium contrast (**Figures 1A–C**). The remaining demyelinating lesions were comparable in terms of number and size with the previous brain MRI obtained in November 2020: 10 plaques in the right and 12 plaques in the left hemisphere.

The patient was treated with methylprednisolone (MPS) 1 g daily for 5 consecutive days without improvement, and the lower left limb deficit progressed to 1 MRC, rendering the patient dependent on a wheelchair.

Therefore, therapeutic plasma exchange (TPE) was implemented. However, the patient suddenly developed a significant clinical deterioration with fever (40°C), shock signs (blood pressure was 70/40 mmHg, tachycardia 150/min) and high inflammation parameters: CRP 156.6 mg/l (on admission 0.5 mg/L, normal range < 5 mg/L), white blood count 12.07 × 10^3/μl (on admission 5.96 × 10^3/μl, normal range 3.90–11 × 10^3/μl), and procalcitonin 21.7 ng/ml (on admission: 0.02 ng/ml, normal range < 0.5 ng/ml).

Chest X-ray was normal, and echocardiogram did not reveal endo- or myocarditis; urine test and antinuclear antibodies also remained also within normal values; COVID-19 antigen tests were negative.

Empirical therapy with ceftriaxone was started, and gradual clinical and laboratory improvement was observed.

Further steroid infusions and TPE were postponed because of signs of shock (possibly septic although blood cultures turned out negative), and the patient was discharged from the hospital to a rehabilitation center with moderate left hemiparesis: upper limb MRC grade 4, lower limb MRC grade 3, and Expanded Disability Status Scale (EDSS) 7 points.

In the 3-month follow-up, a substantial neurological improvement was observed. Her EDDS was 4.5, and the right parietal lobe lesion diminished slightly to a 24-mm size on MRI without gadolinium enhancement (refer to **Figures 1D,E**). Moreover, the lesion lost its "onion bulb" pattern. In the meantime, her therapy was switched to IV ocrelizumab.

It is still unclear whether BCS is a variant of MS, which typically has a type III immunopattern pathology, or a separate demyelinating disease (3). Data regarding BCS are based on individual cases and limited case series, and our report is an addition to this pool. Baló disease is considered a rare, usually monophasic variant of MS. However, Baló lesions have been shown to coexist with typical demyelinating lesions.

Several publications described patients with relapsing-remitting MS that began as BCS. Ayrignac et al. reported six patients with BCS, all of whom fulfilled MS criteria after 7 years of follow-up, with five of the patients positive for CSF oligoclonal bands (5). Pietroboni et al. described three cases with similar history, two of them fulfilled the MS criteria at baseline or in 10-month follow-up, and treatment with natalizumab or fingolimod was initiated (6). Behrens et al. presented 10 patients with BCS, three of them at baseline fulfilled the 2010 MS diagnostic criteria dissemination in space and in time (7).

On the other hand, the opposite scenario is unusual. There is only anecdotal data about patients who developed BCS after years of clinically stable MS. Moore et al. reported a young female whose third relapse was severe and associated with Baló-like lesions and akinetic mutism. She died 8 months later. Her CSF was negative for oligoclonal bands, which are more common in BCS than in classic MS (8). Barun et al. presented a case of a patient with RRMS who was treated with interferon beta 1a and suffered from aphasia related to a BCS lesion (9). Iannucci et al. described a 31-year-old patient who had both Baló- and MS lesions simultaneously (10). Our patient's relapse was not typical for classic MS, resembling rather a BCS course with a prodromal, subfebrile phase and stroke-like onset, which is

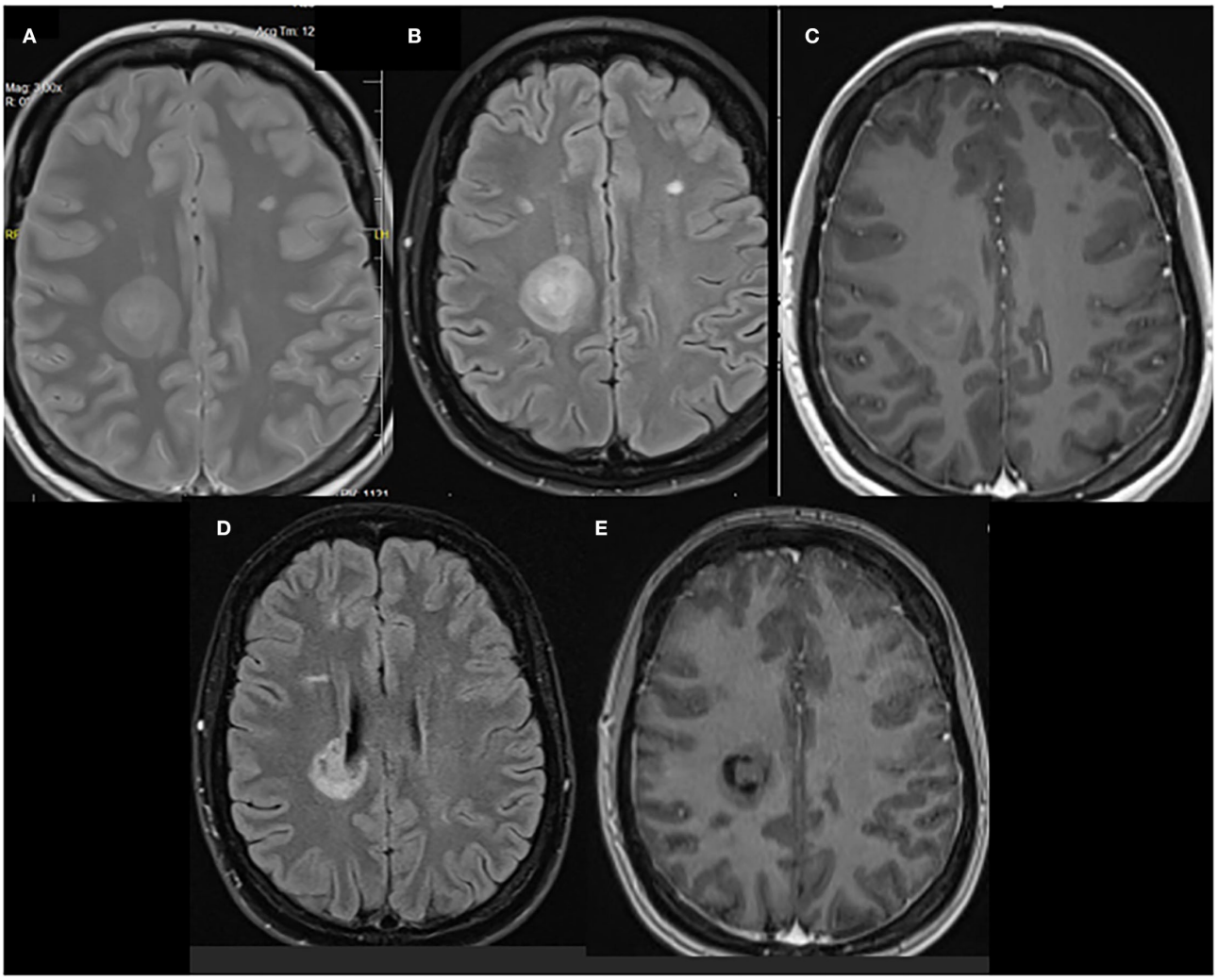

FIGURE 1 | (A) Proton density (PD) T2-weighted, **(B)** fluid-attenuated inversion recovery (FLAIR), and **(C)** gadolinium-enhanced T1-weighted images of a right parietal lobe lesion that shows a concentric lamellar appearance that is similar to that of a Balo-like lesion. MRI images 3 months after the treatment were **(D)** FLAIR and **(E)** gadolinium-enhanced T1-weighted.

consistent with a case series report of 17 patients with BCS, half of whom had prodromal symptoms of malaise, headache, and mild fever (1).

To our knowledge, it is one of the initial reports (2) of a patient with RRMS treated with dimethyl fumarate who developed a Baló-like lesion. However, the possible link between this therapy and tumefactive lesion development remains to be clarified.

The question about the appropriate disease-modifying treatment (DMT) modification for patients who develop Baló-like lesions during their DMT is still open. Our knowledge is based on occasional case reports, which have shown that alemtuzumab was not effective, but that cyclophosphamide, ocrelizumab, natalizumab, interferon beta-1a, and glatiramer acetate could be useful (11, 12). On the other hand, we know that the association between tumefactive lesions and fingolimod treatment is well documented (13–16).

Unfortunately, the cerebrospinal fluid examination was not repeated during the described exacerbation in our patient. This was because of combination of patient-related factors. We do realize this is a limitation, and we do acknowledge that lumbar puncture should be performed in such cases as ours, mainly to exclude the possible neuroinfections (especially in cases associated with lymphopenia or treated with DMTs linked to opportunistic infections). Having said that, based on the clinical picture alone, in our patient, neuroinfectious, especially progressive multifocal encephalopathy (PML), were not likely, as the patient improved significantly. Importantly, it has been shown that oligoclonal bands and IgG index in BCS are more similar to findings

in neuromyelitis optica spectrum disorders (NMOSD) than in MS, which could suggest a distinct immunological entity (17).

In conclusion, it seems that publishing all new cases of BCS on DMTs is essential to establish any potential link between MS therapy and rare variants of the disease.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

KK and WA drafted the manuscript. WK and AK revised the manuscript critically. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the study.

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CASE REPORT
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Anti-homer-3 Antibody Encephalitis in a 10-Year-Old Child: Case Report and Review of the Literature

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Objective: We present a rare case with anti-Homer-3 antibodies positive encephalitis in the youngest patient ever identified and reviewed the literature.

Case Report: A 10-year-old, Chinese boy came for evaluation of a 2-week history of cognitive impairment, irritability, dysarthria, and cautious gait. The neurological examination was consistent with the pan-cerebellar syndrome and encephalopathy. Cerebrospinal fluid (CSF) was inflammatory with increased leukocytes. Magnetic resonance imaging of the brain showed hyperintensities in both cerebellar hemispheres and vermis in Fluid-attenuated inversion recovery (FLAIR) and T2- weighted sequences. Infectious disorders were ruled out, but positivity for anti-Homer-3 antibodies was detected in the CSF, but not in the serum. Additionally, low titers of voltage-gated calcium channel (VGCC) antibodies were found in the serum. Treatment with intravenous (IV) corticosteroids did not provide meaningful clinical improvement; however, the patient achieved almost complete recovery (modified Ranking Scale score: 1) following IV immunoglobulin.

Conclusion: Anti-Homer-3 cerebellar ataxia with encephalopathy should be considered within the differential diagnosis of acute inflammatory cerebellar disease in children and it may coexist with VGCC antibodies.

Keywords: anti-homer-3 antibody, autoimmune encephalitis, antibodies, cerebellar ataxia, children

INTRODUCTION

Cerebellar ataxia may be associated with genetic and acquired causes. Among the latter, an autoimmune or paraneoplastic etiology should be considered within the differential diagnosis. Anti-Homer-3 antibody encephalitis is a rare cause of autoimmune cerebellar ataxia first described in 2007 by Zuliani and colleagues, in a patient with subacute cerebellar ataxia (1). Anti-Homer-3 cerebellar ataxia is mostly described in adult patients, with the youngest patient being 14 years old (2). In this manuscript, we report a case of anti-Homer-3 cerebellar ataxia in a 10-year-old child,

analyze the clinical profile of anti-Homer-3 autoimmunity, and contrast it with a closely related molecular disorder involving metabotropic glutamate receptor 1 (mGlutR1) autoimmunity.

CASE REPORT

A 10-year-old, right-handed, Chinese patient presented for clinical evaluation of a 2-week history characterized by impaired concentration, irritable mood, slurred speech, and slow, cautious gait. There was no recent history of an infectious disorder. The neurologic examination revealed bradypsychia, dysarthria, and downbeat nystagmus. The patient had dysmetria and dysdiadochokinesia. Tandem gait showed frank ataxia. Romberg's sign was negative.

Initial investigation showed normal blood cell count, lactic acid levels, d-dimer assays, and hepatic and renal function tests. Serology for hepatitis C and HIV type 1 and 2 were negative. A lumbar puncture revealed an opening pressure of 16.5 cm/H_2O. Cerebrospinal fluid (CSF) protein was 0.3 g/L (0.15–0.45 g/L), lactic dehydrogenase was 40.5 U/L ($\leq$ 70 U/L), granular leukocytes were 30 $\times$ 10^6/L (0–5 $\times$ 10^6/L), and glucose and chloride levels were normal. Ziehl-Neelsen staining for acid-fast bacilli and Cryptococcus neoformans smear test in the CSF were negative. We used tissue-based assay by indirect immunofluorescence in fixed rat brain slices to screen for antibodies reacting with central nervous system antigens. Then, we used a commercially available cell-based assay to check for interest antibodies. Anti-Homer-3 antibody was positive in the CSF (1:1) (**Figure 1**) cell-based assay; however, the test was negative in the serum. Other antibodies such as anti-NMDAR, anti-AMPA1, anti-AMPA2, anti-CASPR2, anti-DPPX, anti-DRD2, anti-GlyR, anti-GAD65, anti-$GABA_B$, anti-IgLON5, anti-LGI1, anti-mGlutR1, and anti-mGlutR5, as well as onconeural antibodies, were negative; however, low titers of anti-voltage gated calcium channel antibodies (VGCC-antibodies) were found in the serum: 41 pmol/L (normal value $\leq$ 30 pmol/L).

A detailed ultrasound examination of abdominal and pelvic structures was normal without evidence of tumor and a chest X-ray was unremarkable.

Brain magnetic resonance imaging (MRI) showed hyperintensities in both cerebellar hemispheres and vermis in FLAIR and T2-weighted (T2W) sequences (**Figures 2A,B**).

Initial treatment was carried out with intravenous boluses of methylprednisolone (1 g per day for 5 days), followed by oral prednisolone at decreasing doses for 15 days. No improvement was observed on day 10; for that reason, intravenous immunoglobulin (IVIg) was offered, but the patient's parents initially declined for personal reasons.

As no improvement in cognitive and motor condition was observed in the following weeks, the patient's parents accepted treatment with IVIg 1 month after the initial assessment. Slow but progressive clinical improvement was noticed with normalization of cognitive impairment and cerebellar syndrome a year later March 1, 2022, when only mild dysarthria was noticed, a score of 1 on the modified Rankin Scale was registered at that time. Follow-up MRI showed mild cerebellar atrophy (**Figures 2C,D**).

DISCUSSION

We report the youngest case ever with autoimmune encephalitis associated with anti-Homer-3 antibodies in a 10-year-old child, manifested by encephalopathy, cerebellar ataxia, and hyperintensities in the cerebellum. Acute and subacute cerebellar ataxia may follow diverse etiologies in children, including nutritional, toxic, post-infectious (e.g., Epstein-Barr, herpes simplex, measles, mumps, parvovirus B19, varicella, Mycoplasma, etc.), or autoimmune. Most of these causes do not show signs of inflammation in the cerebellum when assessed by MRI (3). However, few cases of post-infectious cerebellitis may present with cerebellar hyperintensities on MRI followed by cerebellar atrophy (4). Patients with post-infectious cerebellar ataxia usually show a prodromal period with a febrile illness, followed by frank cerebellar ataxia; this was not observed in our patient. Moreover, acute cerebellitis in children may be observed with metronidazole and vigabatrin therapy, these patients show a distinctive pattern on MRI with pons and dentate nuclei hyperintensities (5). While a paraneoplastic or an ischemic

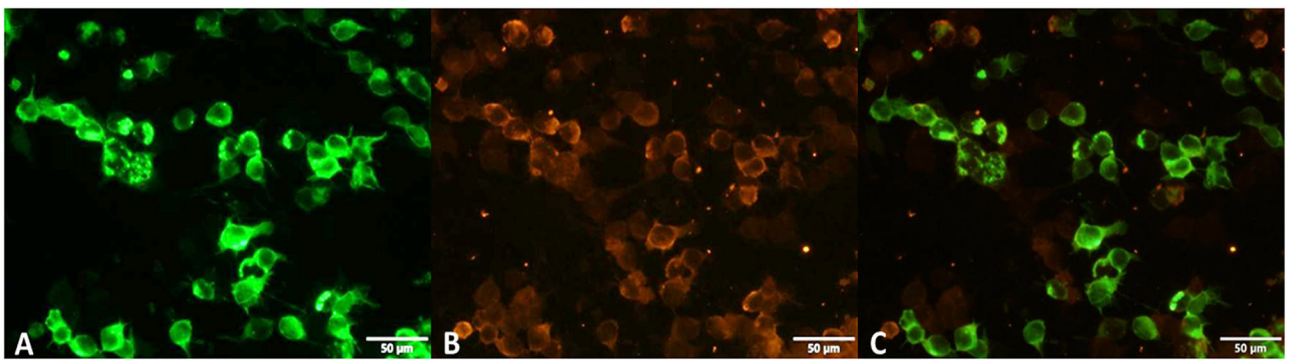

FIGURE 1 | The anti-Homer-3 antibody of CSF was positive. **(A)** The green marker represents Homer-3 antigen, **(B)** the red marker represents anti-Homer-3 antibody; **(C)** the third one is fluorescence overlap. The images were taken using Olympus IX73 microscopy. The scale bar is 50 µm.

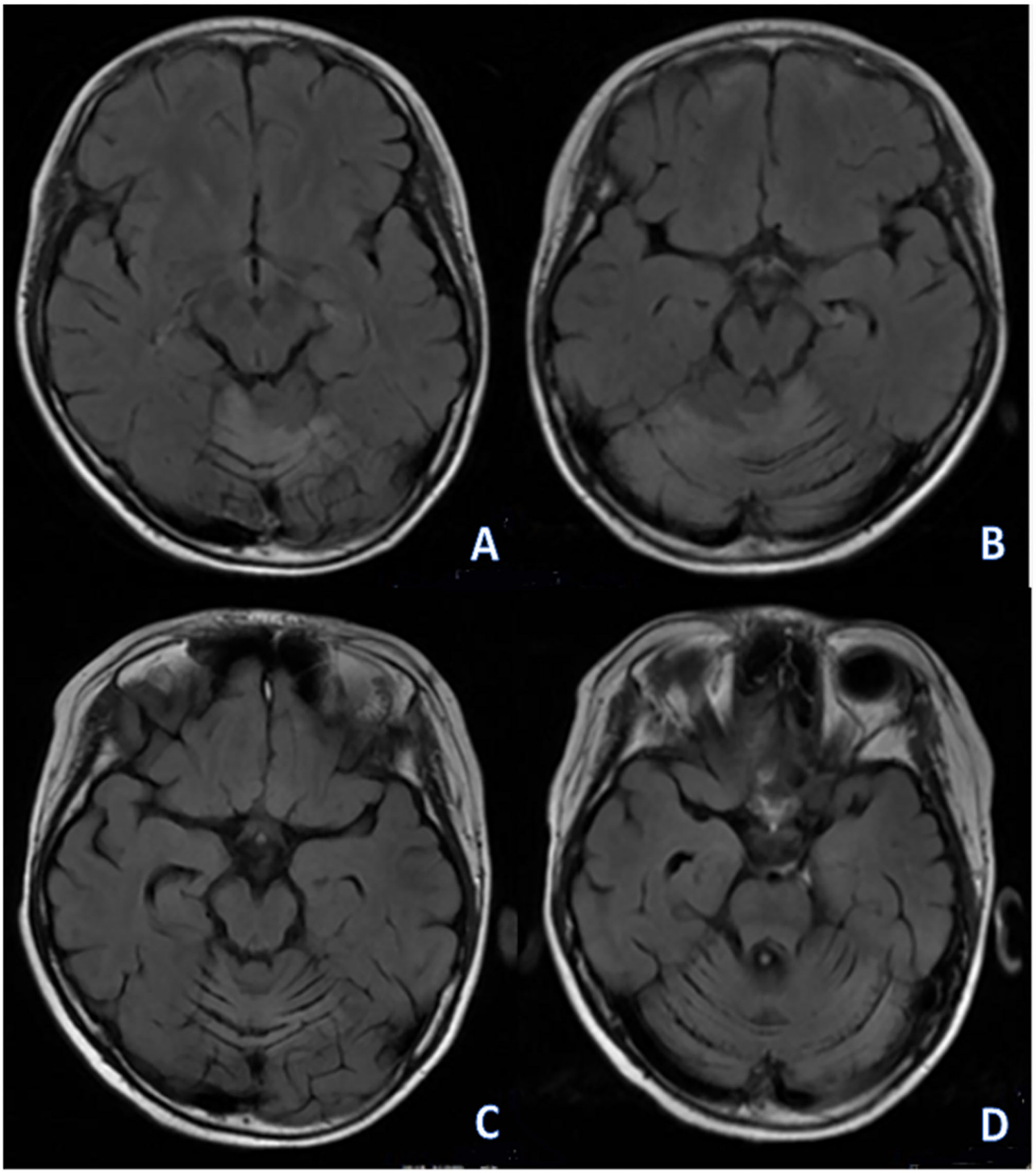

FIGURE 2 | (A,B) initial MRI: right cerebellar atrophy and multiple lesions in bilateral cerebellum and vermis. **(C,D)** follow-up MRI showed bilateral cerebellum and vermis atrophy, sulcus of left cerebellum was wider.

etiology is more commonly seen in adults with acute cerebellar ataxia, these etiologies are less common in children, which varies the clinical approach. Autoimmune cerebellar ataxia in children may be related to anti-glutamic acid decarboxylase (anti-GAD) antibodies, gluten ataxia, or the cerebellar variant of Hashimoto's encephalitis, but other etiologies have been rarely described (3).

Most patients reported with anti-Homer-3 autoimmunity are adults with cerebellar ataxia as the most common

TABLE 1 | Summary of reported clinical cases of anti-Homer-3 associated autoimmunity.

References	Sex/age (years)	Onset	Main manifestations	MRI findings	Treatment	Outcome
Zuliani et al. (1)	F/65	Subacute	CA, vertigo, vomiting	Normal	Steroids	No benefit
Höftberger et al. (6)	M/38	Acute	CA, encephalitis, seizures, papilledema vomiting	Cerebellar atrophy (f-u)	Steroids, IVIg	Partial recovery
Xu et al. (7)	F/51	Insidious	CA, dizziness, RBD	Cerebellar atrophy (f-u) Hot cross Bun sign	Steroids, MMF	Partial recovery
Liu et al. (8)	F/46	Insidious	CA	Cerebellar atrophy (f-u)	Steroids, MMF	Partial recovery
	M/14	Subacute	CA, encephalitis, myeloradiculopathy	Diffuse cerebellar T2W hyperintensities	Steroids, IVIg	Partial recovery with relapses
	M/65	Insidious	CA, RBD	Cerebellar and pons atrophy (f-u) Hot cross Bun sign	Steroids, IVIg, PE	No benefit with deterioration
	F/84	Subacute	CA	Normal	Steroids	Stability
	F/69	Subacute	CA, encephalopathy, radiculoneuropathy	Diffuse cerebral (FLAIR) hyperintensities	IVIg, steroids	Partial recovery with relapses
This report	M/10	Acute	CA, encephalopathy	Diffuse cerebellar T2W hyperintensities; cerebellar atrophy (f-u)	Steroids, IVIg	Almost complete recovery

CA, cerebellar ataxia; F-u, follow-up; MMF, mycophenolate mofetil; RBD, REM-sleep behavior disorder.

TABLE 2 | Differences between Homer-3 and mGluR1 autoimmunity.

	Homer-3	mGluR1
Age range (years)	10–84	6–81
Median age at onset (years)	51	55
Sex distribution (female)	55.5%	43%
Paraneoplastic association	0%	11%
Underlying neoplasm	None reported	Hodgkin lymphoma Cutaneous T-cell lymphoma
Main manifestations	CA isolated or combined with encephalopathy, RBD (MSA-like), myeloradiculoneuropathy	CA isolated, behavior/cognitive changes, dysgeusia. dysautonomia, MDS*
Imaging patterns on MRI	Cerebellar atrophy Cerebellar and brainstem atrophy Cerebellar hyperintensities	Normal Mild cerebellar atrophy Cerebellar hyperintensities
Cerebellar hyperintensities or meningeal enhancement	22.2%	16%
Treatment	Steroids, IVIg, PE, MMF	Steroids, IVIg, PE, Aza, RTx, HQQ
Outcome	Partial recovery sometimes with relapses. No improvement in some instances	Most patients have marked improvement

**MDS: chorea, dystonia, tremor. Aza, azathioprine; CA, cerebellar ataxia; HQQ, hydroxychloroquine; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; PE, plasma exchange; RBD, REM-sleep behavior disorder; RTx, Rituximab.*

presentation; however, other neurologic manifestations, such as encephalopathy, seizures, myeloradiculopathy, radiculoneuropathy, autonomic neuropathy, and REM-sleep behavior disorder (RBD), have been described (**Table 1**) (6–8). Although the number of reported cases in the literature is small, multiple system atrophy cerebellar subtype C (MSA-C)-like syndrome with brainstem and cerebellar atrophy along with RBD has been reported in adults; whereas inflammation with diffuse hyperintensities in the cerebellum has been only observed in young individuals: 14 and 10-year-old patients as described in this report (**Table 1**).

The Homer-3 antigen is enriched in the dendritic spines of cerebellar Purkinje cells and is also expressed in their cell bodies and axons (9). The cerebellar cortex, hippocampus, and non-neuronal tissues (e.g., thymus and lung) also express the Homer-3 antigen (9). Homer-3 interacts with the metabotropic glutamate receptor 1 (mGluR1) C-terminus in Purkinje cells to regulate its trafficking and clustering in the cell membrane to modulate its functional activity (9). Autoimmunity related to anti-mGluR1 antibodies has been described in a larger number of patients; there are several similar features between anti-Homer-3 and anti-mGlutR1 autoimmunity (**Table 2**), suggesting biological convergence between both disorders. However, it should be noticed, that while there is compelling *in vitro* and *in vivo* evidence that anti-mGlutR1 autoimmunity is related to pathogenic antibodies (1, 10), anti-Homer-3 autoimmunity

is more likely to be related to cellular toxicity as the antigen is intracellular.

Patients with anti-Homer-3 autoimmunity seem to have a worse prognosis and lower response rate to immunotherapy than patients with anti-mGlutR1 antibodies (**Table 2**), although direct comparisons are lacking (10, 11). A previous study reported that among six patients with anti-Homer-3 autoimmunity who received immunotherapy, four improved, but still showed residual disability with a modified Ranking Scale $\leq$2 at the last follow-up; moreover, relapses, might present following initial remission or improvement with immunosuppressant (8). However, whether all patients with anti-Homer-3 autoimmunity should undergo prolonged immunosuppression with medications, such as azathioprine or mycophenolate mofetil, is unclear.

Voltage-gated calcium channel antibodies are associated with Lambert-Eaton myasthenic syndrome, characterized by proximal muscle weakness, areflexia, and autonomic dysfunction; none of these features were observed in our patient (12). Anti-VGCC antibodies are paraneoplastic in about 90% of cases in the context of cerebellar ataxia, mainly associated with small cell lung cancer (SCLC); there was no evidence of underlying neoplasm in our patient. Some patients with positive anti-VGCC antibodies may present with non-paraneoplastic cerebellar degeneration, responding to immunotherapy (13). We cannot rule out that these antibodies contributed to the clinical manifestations in our patient; however, much higher serum titers between 500 and 648 pM/L have been reported in patients with paraneoplastic and non-paraneoplastic cerebellar ataxia (13, 14); moreover, we are not aware of VGCC autoimmunity presenting with signs of cerebellar inflammation in the MRI.

CONCLUSIONS

Autoimmunity related to anti-Homer-3 is mostly identified in adults, but may also present in children. Although data is scarce, it seems that in this age group, patients present with signs of cerebellar inflammation on MRI preceding cerebellar atrophy, contrasting with cerebellar, and brainstem atrophy observed at presentation and during the disease in adult patients. Anti-Homer-3 autoimmunity should be considered within the differential diagnosis of autoimmune cerebellar ataxia in childhood. Negative serum antibodies do not rule out the disorder as anti-Homer-3 antibodies may be present only in the CSF.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

YC, ZK, ZW, and SX conceived the study, gathered the data, and drafted the manuscript. JB-C and MM conceived the study, review, and critique. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Drug-Induced (Neuro) Sarcoidosis-Like Lesion Under IL4 Receptor Blockade With Dupilumab

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Dupilumab is a new monoclonal antibody inhibiting IL-4 and IL-13 signaling transduction through the blockage of the α-subunit of the IL-4 receptor. It is used to treat type 2 inflammatory disorders including atopic dermatitis, asthma, and chronic rhinosinusitis. Here we describe the case of a 79-year-old male presenting with visual hallucinations, disorientation, cognitive decline, and behavioral changes, evolving over 3 weeks. He had been under treatment with dupilumab for atopic dermatitis for the previous 4 months. Radiology and CSF analysis showed a granulomatous meningoencephalitis suspicious of sarcoidosis. Underlying infectious and antibody-mediated causes for meningoencephalitis were ruled out. Pausing Dupilumab and steroids (i.v. and oral) led to rapid clinical improvement. Inhibition of IL-4 and IL-13, key players in the differentiation and activation of Th2 cells, may shift the Th1/Th2- ratio toward an excessive Th1-mediated response, granuloma formation, and drug-induced (neuro)sarcoidosis reaction. Attention should be raised to this side effect.

Keywords: neurosarcoidosis, immune-related side effect, dupilumab, IL-4 receptor alpha, drug-induced sarcoid-like reaction

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BACKGROUND

Dupilumab is a human monoclonal IgG4-antibody, that blocks the α-subunit of the IL-4 receptor (IL-4R α). Through IL-4R α blockage, the IL-13 and IL-4 signaling pathways are modulated, leading to a decrease in Th2-biomarkers (1, 2). Dupilumab has shown clinical activity in the treatment of type 2 inflammatory disorders like atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP). It received approval from the United States Food and Drug Administration and the European Commission for moderate-to-severe atopic dermatitis and subsequently for asthma in 2018 and 2019, respectively (1–3).

The most common adverse reactions, reported so far, were local reactions at the injection site, conjunctivitis (2), and headache. Less frequently, nasopharyngitis, nausea, arthralgia, gastritis, insomnia, and toothache occurred (1, 2). However, with increased use, new nuances of the side effect spectrum may emerge.

CASE PRESENTATION

Here, we report the case of a 79-year-old male patient presenting with visual hallucinations, disorientation, difficulty finding words, cognitive decline, and behavioral changes including aggression, as well as burning sensations in both legs and arms, which had gradually evolved over

3 weeks before admission. Upon examination of temporal disorientation, reduced reflex levels of the lower extremities, symmetrical loss of sensation on both feet until below the knees, rigorously increased tone of the upper extremities, predominantly on the right side, and an uncertain gait with small steps, and the patient leaning forward was recorded. The remainder neurologic exam was unremarkable with no headache being reported.

He was under treatment with dupilumab injections every 2 weeks and 6 mg of prednisolone daily for his atopic dermatitis for the past 4 months. Apart from AD, he had undergone two surgeries for his lumbar spinal stenosis and a lumbar disc protrusion during the past year and was also suffering from cervical spinal stenosis, which explained his reduced reflex levels, sensory deficits, burning sensation, and gait impairment. Apart from the rigorously increased tone of his upper limbs, he showed no other signs of parkinsonism, so this was treated as an incidental finding upon examination. He was under treatment with tamsulosin for his prostate adenoma, and atorvastatin for hyperlipidemia and had recently been started on a low dose of pregabalin for his presumed neuropathic pain. His family history was clear for neurologic conditions.

His cognitive decline was objectified using the Montreal Cognitive Assessment (MoCA), which showed a pathological result of 21/30. His EEG showed a mild diffuse bilateral temporal encephalopathy with a focus on the left side. CSF analysis showed a meningitis syndrome with a lymphocytic pleocytosis (up to 48 cells/μl) and elevated protein (up to 261 mg/dl) with no signs of intrathecal antibody production and normal glucose level. A cranial MRI was performed and showed nodular, primarily sulcal, and pial contrast-enhancing formations. These were predominantly located in the right temporoparietal lobe and accompanied by brain edema, in anatomical correlation to the patient's neuropsychiatric symptoms, as well as his difficulties in orientation. Underlying infectious causes were ruled out through negative PCR results in the CSF for bacterial meningitis, tuberculosis, fungal infections, and viral meningitis including herpesviruses 1 to 6. Serology for cryptococcal and aspergillus antigens was negative. Aerobic and anaerobic bacterial cultures and mycobacterial cultures, as well as fungal cultures in the blood and the CSF, showed no growth. Serology for Lyme's disease, HIV, syphilis, hepatitis B, and C was negative. An extensive search for autoantibodies in the CSF inducing meningoencephalitis syndromes, including antibodies against sodium channels (AMPA1/2, NMDA-receptor, NMDA-NR1-receptor), chloride channels (GABA-B-receptor-1), the potassium channel-complex, including anti-CASPR2 and anti-LGI-1 antibodies, anti-amphiphysin-1, anti-GAD, and anti-Ma1/2-autoantibodies, also showed no positive results. Serological vasculitic parameters were unremarkable. A whole-body PET-CT showed no pathological findings largely ruling out a malignancy or granuloma formation outside the central nervous system. The Angiotensin Converting Enzyme (ACE) levels in blood and CSF were within the normal range. Pausing dupilumab and a 3-day-course of 1 g of methylprednisolone intravenously followed by an oral steroid course for 4 weeks led to quick clinical improvement and regression of his radiological findings on follow-up imaging and normalization of his EEG, as well as his CSF findings. His result on the MoCA also improved within <2 months to 24/30. The atopic dermatitis was treated with topical corticoids. **Figure 1** shows the dynamics of his CSF parameters before and after initiation of treatment, whereas **Figure 2** shows his findings on the MRI during his first hospitalization and on follow-up.

We postulate the diagnosis of a drug-induced neurosarcoid-like reaction caused by dupilumab, based on the typical imaging and CSF findings, as well as the prompt response to the withdrawal of the responsible drug and corticoid treatment. Normal ACE levels do not rule out the diagnosis given their low sensitivity for sarcoidosis (4).

DISCUSSION

In February 2020, Belhomme et al. reported the first case of systemic sarcoid-like granulomatosis induced by dupilumab occurring in a 28-year-old patient with atopic dermatitis (5). Drug-induced sarcoid-like reaction (DISRs) is a rare side effect of drugs but is described for immune checkpoint inhibitors, TNF-α antagonists, interferons, and highly active antiretroviral therapy (HAART) (6, 7). Retrospective studies demonstrate its occurrence in 0.2% of people treated with immune checkpoint inhibitors, or 0.04% of people treated with TNF-α inhibitors (6). Treatment of DISR is not always necessary as it can resolve spontaneously or with the withdrawal of the responsible drug. However, if symptoms persist or are severe, corticoids or other drugs used against sarcoidosis are recommended (6). Treatment is necessary depending on the causing agent in 40–60% of the cases and leads to resolution in 60–80% of treated cases (6).

It is not possible to distinguish a DISR from sarcoidosis clinically. Both may present with associations of bilateral hilar adenopathy, cutaneous lesions, uveitis, granulomatous infiltration of scars, hypercalcemia, elevated serum angiotensin-converting enzyme levels, and 18F-fluorodeoxyglucose uptake on PET scans (6). Temporal correlation of symptoms with the initiation of a specific therapy with drugs linked to DISR and resolution of symptoms when the drug is withdrawn are key factors in diagnosing a DISR.

Disturbance of the Th1/Th2 cell equilibrium, as well as their mediators in favor of a Th1 reaction, is thought to be the common underlying pathophysiological mechanism in all these cases (6).

The HAART has been associated with DISR in the setting of a rising CD4 count. An imbalance between Th1 and Th2 cells within this sudden rise with overweighing of the former is discussed to be leading to increased granuloma formation and DISR (8). Likewise, immune checkpoint inhibitors alleviate the immunosuppression of T-cells caused by tumors, prolonging T-cell activation, and restoring T-cell proliferation. Particularly ipilimumab, a CTLA-4 inhibitor linked to DISR, has been shown to lead to T-cell proliferation and an increase in Th1 markers (9, 10). TNF-α inhibitors, although used in the treatment of sarcoidosis, have also been paradoxically shown to cause DISR. In support of this, Etanercept, a soluble TNF-α receptor fusion protein, has been shown to increase the production of IFN-γ,

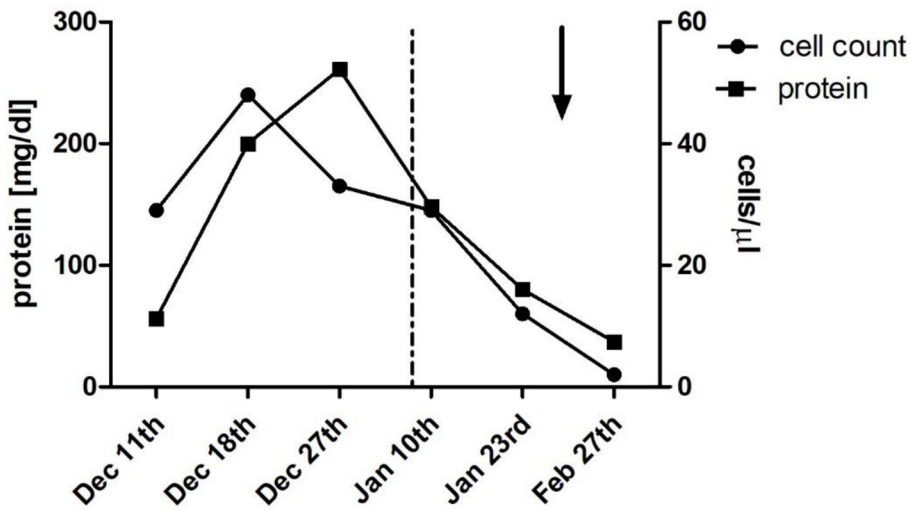

FIGURE 1 | Cerebrospinal fluid (CSF) analysis. Multiple lumbar punctures during hospitalization and outpatient follow-up showed initial lymphocytic pleocytosis (up to 48 cells/µl) and elevated protein (up to 261 mg/dl) which improved after discontinuation of dupilumab (dotted line; Jan 8th), followed by administration of 1g Methylprednisolone IV for 3 days (arrow; Jan 27th), and subsequent oral steroid treatment for 4 weeks.

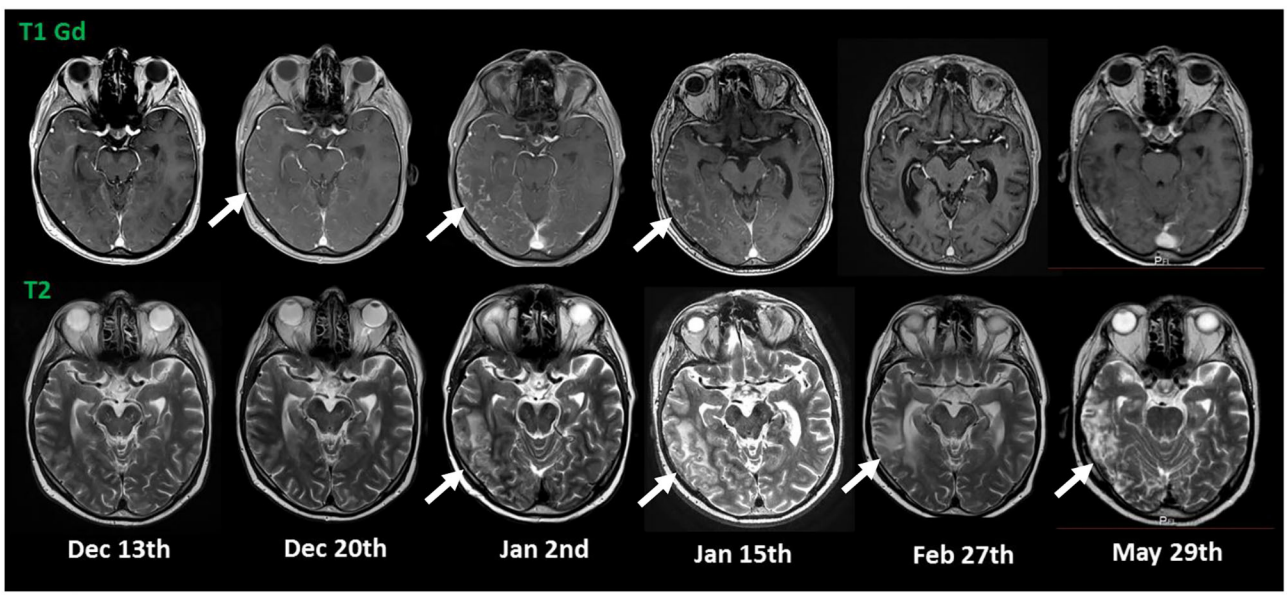

FIGURE 2 | MRI imaging. The initial MRI showed nodular, T1 contrast-enhancing lesions in the right temporo-parietal lobe (indicated by arrows in the upper row) suspicious for sarcoidosis with accompanying edema in T2 (indicated by arrows in the lower row). Discontinuation of dupilumab (Jan 8th) and initiation of a treatment with steroids (Jan 27th) led to quick regression of the nodular lesions and gradual regression of the brain edema.

a Th1 mediator, in T-cells (11). Monoclonal TNF-α inhibitors have similarly been shown to increase the Th1/Th2 ratio in the peripheral blood (12). Finally, interferons and particularly IFN-α have been linked to DISR. IFN-α has been associated with Th1 polarization and Th2 inactivation, as well as an increased level of granuloma-promoting cytokines (13). On the other hand, it has been shown that corticoids preferably affect Th1 cells by downregulating the chemokine receptors CCR10 and CXCR3 mainly expressed on Th1 cells, thus, preventing their migration to the site of inflammation. Furthermore, they reduce IFN-γ production in these cells. This may explain the generally good response to corticoids in DISR (14).

Dupilumab inhibits the action of IL-4 and IL-13. IL-4 leads to the differentiation of naive CD4 cells into Th2 cells, whereas

IL-13 is a cytokine of the Th2 pathway (15). Dupilumab, blocking the action of these agents, could, therefore, disturb the Th1/Th2 equilibrium leading to an increased Th1-response and granuloma formation, presenting as a DISR.

In summary, it is very important to consider this possible side effect of Dupilumab, especially, given the expected increasing application of the drug in the treatment of atopic dermatitis and asthma.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

LV conceived the original idea. PA, JM, and LV as well as ST and LN with the help of AS treated the patient and performed the diagnostic including imagery. ST and LN wrote the manuscript. LV and AS helped supervise the project. All authors contributed to manuscript revision, read, and approved the submitted version.

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CASE REPORT
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Case Report: Rapid Progression of Cognitive Dysfunction as an Initial Feature of Systemic Lupus Erythematosus With Leukoencephalopathy: A Case Report and Literature Review

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Neuropsychiatric systemic lupus erythematosus (NPSLE) has been considered to have high morbidity and mortality. Thus, earlier recognition and treatment are of great importance. However, the rapid progression of cognitive dysfunction with leukoencephalopathy as an initial presentation in SLE is rarely described. We report a case in which an elderly man experienced rapidly progressive cognitive impairment with bilateral, symmetric, and diffuse leukoencephalopathy with lasting diffusion-weighted image hyperintensity. An immunological workup showed low complement levels and positivity for antinuclear antibody -speckle and Coombs tests in the patient's serum samples. He had an appropriate improvement in cognitive function after receiving a combination of various immunotherapies. Long-term follow-up showed clinical improvement, including rheumatological labs and neuroimaging. A review of the literature on NPSLE with leukoencephalopathy and a summary of all reported cases to date are also presented. Our case indicated that isolated leukoencephalopathy in NPSLE, as an indicator of severe NPSLE, can be recognized early. Immunotherapy is warranted given the possibility of clinical improvement.

Keywords: neuropsychiatric systemic lupus erythematosus (NPSLE), leukoencephalopathy syndrome, rapidly progressive dementia (RPD), diffusion-weighted image (DWI), MRI

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disorder characterized by multiorgan involvement, the vast majority of whom are females of childbearing age (1). It presents clinically heterogeneous, usually involving in renal, dermatological, neuropsychiatric, musculo-skeletal and cardiovascular symptoms (1). Approximately 50 to 80% of patients have neuropsychiatric involvement in SLE (NPSLE) (2). NPSLE has been associated with an increase in the mortality rate and a lower quality of life (3, 4). Neuropsychiatric involvement occurs in the early stage of SLE and presents a variety of symptoms (4, 5). These include

psychiatric manifestations (mood disorders, cognitive impairment, and psychosis), stroke, seizures, myelopathy, chorea, and headaches (5). While neuropsychiatric events as initial symptoms in SLE patients are rare (4). Moreover, neuropsychiatric manifestations were classified into focal and diffuse neuropsychological syndromes (6). In the diffuse neuropsychological syndromes, isolated diffuse leukoencephalopathy with acute confusional state or cognitive dysfunction in lupus has rarely been reported and presents benign or malignant outcomes (7). Given the heterogeneity of the clinical manifestations, it is extremely difficult to recognize and treat early.

Here, our case report illustrates neuropsychiatric symptoms as an initial and only manifestation of SLE, with bilateral, symmetric, and diffuse leukoencephalopathy with lasting hyperintense diffusion-weighted images (DWI). We reviewed the literature on the clinical characteristics of and treatment responses for this condition. These characteristics are rare and make diagnosis challenging. Such a presentation represents a severe variant of NPSLE requiring aggressive immunosuppressive therapies.

METHODS AND RESULTS

Patient Data

A 58-year-old male initially presented to our hospital with cognitive dysfunction and gait disturbance. He started to have memory decline, impaired attention, and deficits in processing speed 2 months prior to his admission. Subsequently, he presented dysphagia and aphasia. His movement gradually became sluggish and even led to him being bedridden long-term. Meanwhile, he had never suffered from the malar, or butterfly rash, glomerulonephritis, arthralgias, and anemia etc.

The serological workup of immunology (**Table 1**) showed an increase in the erythrocyte sedimentation rate (ESR) (63 mm/h), anti-cardiolipin antibody IgM (42.9 MPL) level and C-reactive protein (CRP) (17 mg/L) level, a homogeneous antinuclear antibody-speckle (ANA) 320X test, Coombs test and anti-ribosomal P positivity and a decrease in C3 complement (C3) (0.60 g/L), C4 complement (C4) (0.06 g/L) and total completement activity (CH50) (1.0 U/mL) levels. Cerebral spinal fluid (CSF) analysis (**Table 1**) was negative under normal pressure, including for paraneoplastic antibodies (hu, ri, CV2, ANNA-3, PCA-2, YO, MA2, Amphiphysin, Tr, GAD) and autoimmunity encephalitis-associated antibodies (NMDA, AMPA1, AMPA2, IgLON5, GABA, LGI, CASPR2, MBP, MOG, AQP4). The leukodystrophy-associated gene panel testing results and exercise testing on serum lactate were negative.

Brain magnetic resonance imaging (MRI) (**Figure 1**) demonstrated symmetric abnormalities on fluid-attenuated inversion recovery (FLAIR) hyperintensity within the white matter of the corona radiata, brachium pontis, and basal ganglia, with T1-weighted associated hypointensity (T1WI), without enhancing lesions but with correlating areas of hyperintensity on DWI. MR spectroscopy showed increased choline and a decreased N-acetyl aspartate (NAA) peak, and positron emission computed tomography (PET-CT) showed decreased fluorodeoxyglucose (FDG) uptake of the corona radiata, suggesting demyelination of the white matter. Accordingly, a stereotactic biopsy for corona radiata excluded the possibility of lymphomas. The pathology showed hydropic degeneration, gliocyte proliferation, and perivascular lymphocyte infiltration in the white matter (**Figure 2**).

He received methylprednisolone (500 mg over 4 days) and had transient cognitive improvement. Due to progressive confusion, low-dose methylprednisolone (80 mg) combined with immunoglobulin G (10 g), plasma exchange (one cycle) and rituximab (500 mg, four cycles) was administered. His consciousness improved, and he could respond with simple body language to the doctor's orders after therapy. However, he remained dysphagic, aphasic and disabled at the time of discharge. The SLE disease activity index (**Table 1**) was improved throughout the course of immunosuppressive therapy. Repeated MRI showed a stable lesion without new changes after 3 months (**Figure 1**).

At his one-year follow-up visit, he could perform oral intake and communicate verbally but had difficulty walking alone. Meanwhile, the disease remained stable, without recurrence. He was maintained on 40 mg of methylprednisolone daily. His rheumatological lab results had recovered to a normal status (**Table 1**). Subsequently, he was treated with rituximab (500 mg, 1 cycles, every year) to prevent relapse. Repeat brain MRI at 1 year showed minimal residual hyperintensity on DWI and a small resolution of T2/FLAIR abnormalities, such as in the brachium pontis (**Figure 1**).

Literature Review

Twelve cases of leukoencephalopathy in NPSLE patients from 1991 to 2021 was searched by the online database PubMed utilizing the search strategies "NPSLE" and "leukoencephalopathy". Further searches were undertaken to identify articles by searching string "white matter", "intracranial hypertension", and "cerebral oedema". Additional cases not captured by the initial search method were found in the reference lists of identified cases. All cases that were selected presented leukoencephalopathy in the MRI. Data extracted from these case were age, sex, initial neurological symptoms, other previous organs involved, imaging findings-DWI, CSF, clinical treatment (outcomes), and follow up (**Table 2**). Our case has been rarely reported until now from the literature review. Most patient experienced aggressive treatment strategies earlier and had benign outcome.

DISCUSSION

This case report describes a male patient with a diagnosis of SLE with the initial and only onset of diffuse leukoencephalopathy

Abbreviations: SLE, Systemic lupus erythematosus; NPSLE, neuropsychiatric involvement in SLE; DWI, diffusion-weighted images; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibody - speckle; CH50, total completement activity; CSF, Cerebral spinal fluid; MRI, Brain magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; T1WI, T1-weighted associated hypointensity; NAA, N-acetyl aspartate; PET-CT, positron emission computed tomography; FDG, fluorodeoxyglucose.

TABLE 1 | Lab results and normal values.

Lab test	Patient value (1 month)	Patient value (3 months)	Patient value (12 months)	Normal value
CRP	17 mg/L	10 mg/L	1 mg/L	<10 mg/L
ESR	63 mm/h	6 mm/h	5 mm/h	Male: 0-15 mm/h
Complements (C3, C4)	C3: 0.60 g/L	0.89 g/L	1.08 g/L	0.74–1.4 g/L
	C4: 0.06 g/L	0.35 g/L	0.34 g/L	0.1-0.4 g/L
Total completement activity (CH50)	1.0 U/mL	42.0 U/mL	44 U/mL	23.0-46 U/mL
β2-glycoprotein IgA	≤9.4 SAU	–	≤9.4 SAU	<20 SAU
β2-glycoprotein IgG	≤9.4 SGU	–	≤9.4 SGU	<20 SGU
β2-glycoprotein IgM	12.7 SMU	–	≤9.4 SMU	<20 SMU
Anti-cardiolipin antibody IgG	9.4 GPL	–	≤9.4 GPL	<16 GPL (Negative)
Anti-cardiolipin antibody IgM	42.9 MPL	–	≤9.4 MPL	>20 MPL (Positive)
Lupus anticoagulant	1.03	–	1.01	<1.2 (Negative)
ANA	0.2639	–	Negative	Negative, <1:80
Anti-dsDNA IgG	126.8 IU/mL	–	29.4 U/mL	<200 IU/mL (Negative)
Anti-Smith antibody	Negative	–	Negative	Negative
Anti-SSA antibody	Negative	–	Negative	Negative
Anti-SSB antibody	Negative	–	Negative	Negative
Anti-RNP antibody	Negative	–	Negative	Negative
Anti-Smith/RNP antibody	Negative	–	Negative	Negative
Anti-ribosomal P antibody	Positive	–	Negative	Negative
CSF chemistry		–		
Protein	436.17 mg/L	–	–	150-450 mg/L
Glucose	3.27 mmol/L	–	–	2.5-4.4 mmol/L
CSF cytology	1.00×10^6/L	–	–	$0\text{-}5.00 \times 10^6$/L
CSF microbial sequencing	Negative	–	–	Negative
Oligoclonal banding	Negative	–	–	Negative

on imaging, characterized symptomatically only by the rapid progression of cognitive dysfunction. He had a gradual, but incomplete, recovery with a stronger immunosuppression treatment. To the best of our knowledge, no case reports have been made associating these entities.

SLE affects women more frequently than men, with the preponderance of occurrence around childbearing age (15–44) (19). Similarly, 12 patients with leukoencephalopathy and NPSLE have been reported, largely involving women around a mean age of 34 years (**Table 2**). NPSLE is more frequent in the juvenile-onset SLE than in adults with SLE (20, 21). Moreover, nearly half of children with SLE will exhibit CNS involvement in the first year after initial diagnosis (20, 21). As shown in **Table 2**, three cases that were children has been reported with leukoencephalopathy as the first manifestation of juvenile-onset NPSLE. Additionally, men with SLE often have a more rapid progression in the clinical course with severe organ damage, resulting in a poorer prognosis than women (19).

Many patients already had a diagnosis of SLE and/or other systemic symptoms related to their disease prior to CNS involvement (22). In contrast, our patient made a diagnosis of SLE charactered by isolated CNS involvement. Lab testing reveals ANA at a titer of ≥1:80 and then SLE classification requires at least one clinical criterion and ≥10 points according to the 2019 EULAR/ACR criteria for SLE (23). Thus, our case shown ANA at a titer of 1:320, rapid progression of cognitive dysfunction (2 points), positive Coomb's test (4 points), an increase in anti-cardiolipin antibody IgM level (2 points), and low complement (C3 and C4) (4 points). On the above findings, a diagnosis of SLE was highly suspected. However, NPSLE was not specific, and a careful process of exclusion of causes was necessary. In the literature review about leukoencephalopathy, etiologies were warranted to be excluded, involving in metabolism, leukodystrophies and infection. Evidence suggests that SLE is strongly associated with B cell lymphoma (24, 25). In our case, an extensive workup was performed and these results were normal, including autoantibodies and sequencing of CSF, tandem mass spectrometry of blood and urine, exercise testing on serum lactate, cerebral MR spectroscopy, plasma ammonium, thyroid studies, folate, vitamin B12 and leukodystrophy-associated gene panel testing. Ultimately, our case ruled out a CNS infection, metabolism, tumors and genetics etc.

Most SLE patients with cognitive dysfunction have subtle or subclinical disease with a stable, improving or fluctuating course and rarely have a rapid progression to dementia (2). In addition, most SLE-related cognitive dysfunction occurs in the absence of active systemic lupus or major NPSLE events (2). MRI has shown lower hippocampal

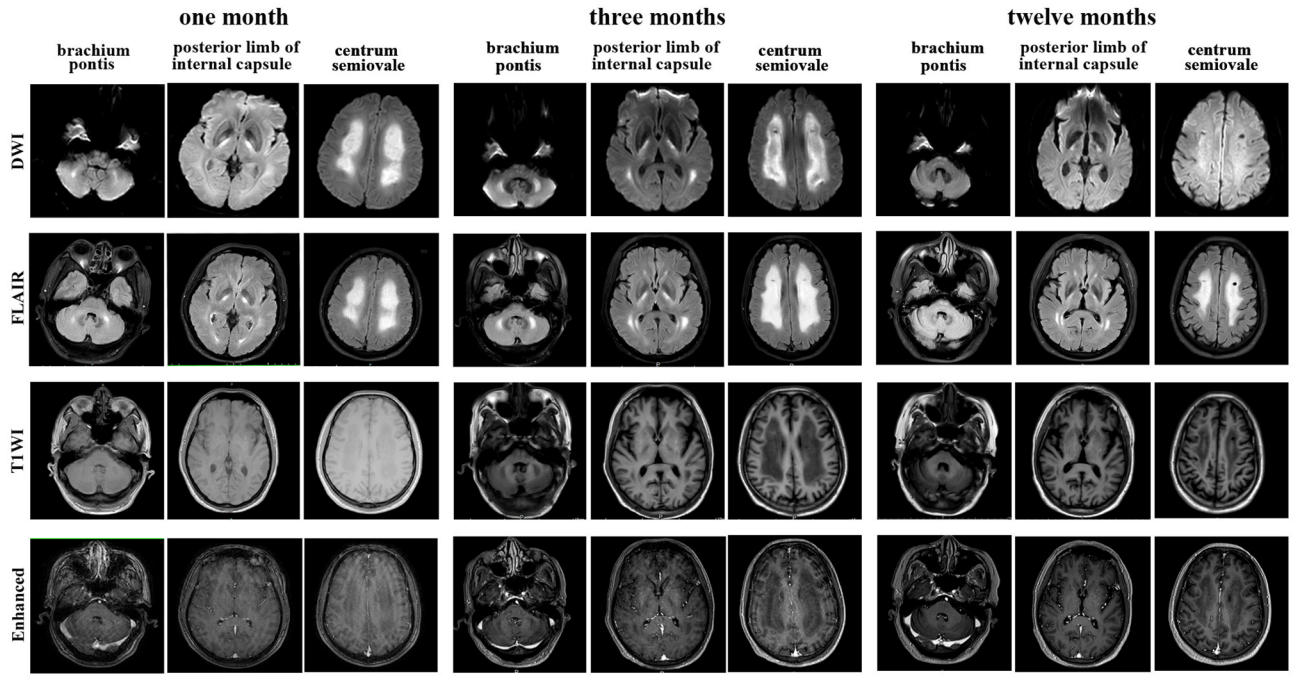

FIGURE 1 | Brain magnetic resonance imaging (MRI) performed at the 1-month, 3-month, and 12-month follow-ups showed T1-weighted, diffusion-weighted images (DWI), fluid-attenuated inversion recovery (FLAIR) and enhanced T1 MRI axial images of the centrum semiovale, brachium pontis and internal capsule lesions.

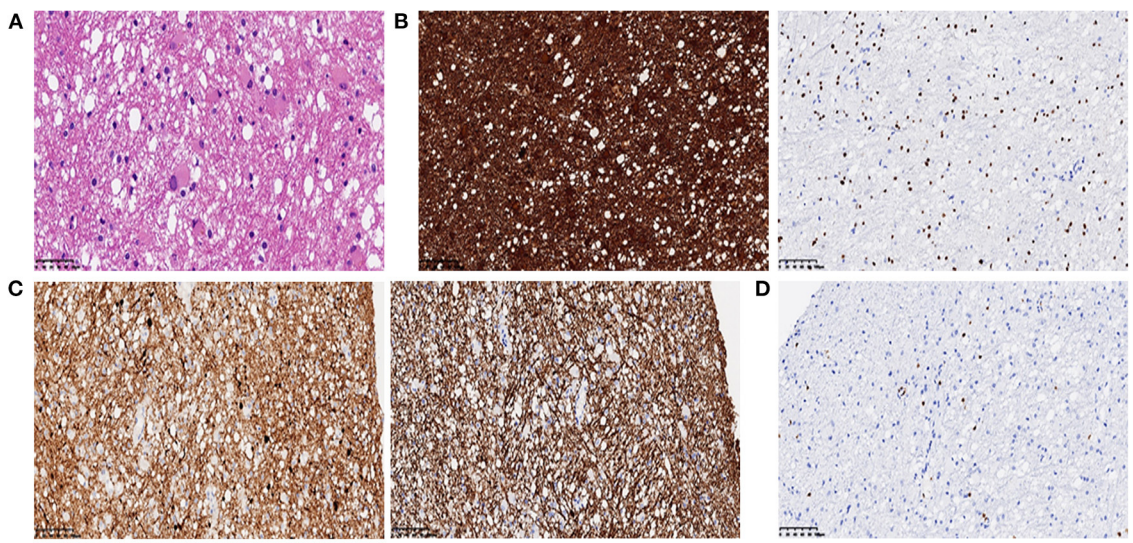

FIGURE 2 | (A) Histopathology showed mild hydropic degeneration and gliocyte proliferation of the lesion (H & E, 400×); **(B)** GFAP (left panel) and Olig2 (right panel) immunohistochemistry showed positive staining of reactive gliocytes (200×); **(C)** SYN (left panel) and NF (right panel) immunohistochemistry showed positive staining of neurofilaments. **(D)** Lymphocytes highlighted by CD3 showed a perivascular infiltration pattern.

volumes in SLE patients with cognitive dysfunction than in those without cognitive dysfunction (26). Interestingly, our patient presented dementia with a rapid course as the initial manifestation of active SLE with diffuse leukoencephalopathy, unlike two patients who had gradual cognitive decline and other organs involved, as shown in **Table 2**. This characteristic is extremely rare and makes early diagnosis difficult.

Common MRI changes in NPSLE patients include small punctate focal lesions in periventricular and subcortical white matter hyperintensity, brain atrophy, and infarcts (27). Indeed, there have been case reports of patients with T2/FLAIR

TABLE 2 | Summary of the clinical features of NPSLE patients with diffuse leukoencephalopathy.

Patient (ref)	Age/Sex	Initial neurological symptoms	Other previous organs involved	Neuro-imaging (DWI)	CSF	Treatment (outcome)	Follow up
1 (7)	38/F	Severe headache, syncope	Yes	Normal	Pressure ↑ chemistry: protein ↑ cytology: no cells OB(–)	IV steroid pulse (5 g over 3 days) –> 60 mg of oral prednisone and 200 mg of plaquenil daily (Marked improvement)	Relapse and death after one week
2 (8)	11/F	Generalized convulsions, prolonged unconsciousness	Yes	NA	Pressure: normal chemistry: protein 96 mg/dl ↑ cytology: no cells OB(–)	IV steroid pulse (1 g over 3 days) –>oral prednisolone (1 mg/kg) daily (Gradual improvement)	Stable rheumatological lab: normal MRI: T2 resolution (6 months later)
3 (9)	35/F	Headache, papilledema	Yes	NA	Pressure: 550 mmH_2O ↑	–	–
4 (10)	32/F	Nausea, vomiting, diplopia	No	NA	–	IV MP, plasmapheresis and CTX (Death)	–
5 (11)	56/F	Gradual cognitive decline	Yes	NA	Chemistry: normal cytology: no cells OB(–)	80 mg of prednisone daily (Gradual improvement)	Stable MRI: T2 resolution (29 months later)
6 (12)	41/M	Headache, vertigo, papilledema	Yes	NA	Pressure: 350 mmH_2O ↑ Pressure: 360 mmH_2O ↑	IV MP (Marked improvement)	–
7 (13)	14/F	Headache, abducens palsy	Yes	NA	chemistry: normal cytology: no cells	IV steroid pulse (1 g over 3 days) –> tapered to 5 mg of prednisone and 200 mg of plaquenil daily (Gradual improvement)	Stable
8 (14)	33/F	Headache, nausea, vomiting,inattention	Yes	NA	Pressure: 240 mmH_2O ↑	IV MP (1 g/day and tapered to 45 mg/day) (Marked improvement)	Relapse and death after two weeks
9 (15)	43/F	Gradual cognitive decline	Yes	NA	–	High doses of prednisolone (Gradual improvement)	–
10 (16)	13/F	Headache, blurry vision, neck pain	No	Normal	–	IV MP (1 g over 5 days), Rituximab and CTX –> 60 mg of prednisone daily and plaquenil (Marked improvement)	–
11 (17)	47/F	Headache	Yes	NA	Pressure: 250 mmH_2O ↑ chemistry: protein 682 mg/dl ↑	IV steroid pulse (1 g over 3 days) –> tapered to 30 mg of prednisolone daily (Marked improvement)	Stable rheumatological lab: normal MRI: T2 resolution (1 year later)
12 (18)	19/F	Headaches, diplopia, papilledema	Yes	NA	cytology: 91 mm^3 Pressure: 280 mmH_2O ↑ chemistry: normal cytology: no cells	IV MP (1 g over 5 days) –> prednisone 1 mg/kg/d, plaquenil 400 mg/d and rituximab (500 mg every 6 months) (Marked improvement)	Stable MRI: T2 resolution (3 months later)

Not available, NA; Methylprednisolone, MP; Cyclophosphamide, CTX; IV, Intravenous; OB, oligoclonal bands.

abnormalities with associated leukoencephalopathy, as shown in **Table 2**. However, we were unable to find an instance of a patient with a lasting DWI abnormality in leukoencephalopathy as the presenting sign of lupus upon initial diagnosis. Furthermore, patients have shown near-complete resolution of FLAIR abnormalities after immunosuppressive treatment. In contrast to these cases, our patient had a unique feature of hyperintense DWI and no reversible lesions at 3 months following a series of immunosuppressive therapies. There was a disappearance of hyperintensity on DWI after 1 year, while the FLAIR abnormalities remained. Hyperintensity on DWI MRI indicates that cytotoxic oedema has occurred and the damage is irreversible. This may be an indicator of severe NPSLE. What is more, inconsistent with most common findings, such as microinfarction and vasculitis in NPSLE (28), the pathology showed hydropic degeneration, gliocyte proliferation in our patient. Based on the relatively severe pathologic injury in brain, we might make an explanation on severe cognitive dysfunction in our patient.

Diagnosis of NPSLE is the lack of specific and sensitive CSF testing (6). As previous studies have shown, some autoantibodies have been suggested as a potential biomarker for

diagnosis and therapeutic decision, such as antineuronal, anti-ribosomal P, and ant-NR2 antibodies (6). Autoantibodies may be detected in the CSF as a result of the transfer of peripherally produced autoantibodies across a breached blood brain barrier or increased intrathecal production (2). In addition, these autoantibodies could be synthesized intrathecally, supported by studies reporting that CSF lgG index/oligoclonal bands (OB) are frequently elevated in patients with NPSLE (29). Nevertheless, three NPSLE patients with leukoencephalopathy (**Table 2**), besides our case, presented negative, and these mechanisms will be warranted to further explore. Idiopathic intracranial hypertension (IIH), defined by an increased intracranial pressure without hydrocephalus or lesions on the MRI and with normal CSF composition, has been reported in a few patients with NPSLE (30). IIH usually indicates a favorable outcome (30). According to **Table 2** findings, the increased intracranial pressure was a common manifestation in NPSLE patients with diffuse leukoencephalopathy. Therefore, difference from IIH, this subtype could be considered as vasogenic oedema and requires treatment aggressively to avoid death, especially combined immunotherapy with dehydrant usage, including acetazolamide, mannitol and furosemide.

High dose steroids have been a unifying treatment choice for neuropsychiatric lupus (31). In addition, due to patients' significant autoantibody loads and severe symptoms, rituximab and cyclophosphamide have been used to treat the severity of CNS involvement (32, 33). As **Table 2** shows, most patients with acute SLE leukoencephalopathy had a full clinical recovery after alone high-dose steroid therapy. Of course, others had experienced incomplete or no clinical response and combined immunotherapy was warranted, including rituximab and cyclophosphamide. Overall, there have been reports that a large of patients experienced a gradual or marked improvement of clinical symptoms after treatment at period of acute course. In the follow-up visit, oral prednisone was used to maintain therapy and, whether examination or symptom, some patients were under a stable state. But, in the patients with lupus relapse, the aggressive immunosuppressants, such as rituximab, immunoglobulin G, plasmapheresis and even autologous stem cell transplantation, is warranted to avoid death as soon as possible (34). In our patient, given the low response to steroids, various methods were used for treatment, including immunoglobulin G, rituximab, and plasma exchange. Meanwhile, his SLE disease activity index recovered to baseline, and his orientation was improved (**Table 1**), confirming the response to treatment. At his one-year follow-up visit, his symptoms had improved further without recurrence following low-dose oral prednisone.

CONCLUSION

NPSLE diagnosis is a challenge for clinicians, both at the diagnostic and therapeutic levels. Isolated leukoencephalopathy with hyperintense DWI on MRI in SLE, an indicator of severe NPSLE, has rarely been reported in the literature. Taken together, as a subtype of NPSLE, it is necessary to recognize severe NPSLE and provide aggressive immunosuppression therapy as soon as possible.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author/s.

ETHICS STATEMENT

The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YF, QX, and XY wrote the paper. TY implemented tissue staining. All authors read and approved the final manuscript.

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CASE REPORT
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Case Report: Paraneoplastic Tumefactive Demyelination Associated With Seminoma

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Paraneoplastic tumefactive demyelination (TD) is a rare disorder of the central nervous system that can be challenging to diagnose. Here, we describe a 32-year-old Japanese man with a TD associated with testicular seminoma. He presented with symptoms of right-sided motor and sensory impairment 2 days after vaccination for coronavirus disease 2019 (COVID-19). Brain magnetic resonance imaging (MRI) showed a high-intensity lesion in the left internal capsule. He had a 3-year history of enlargement of the left testicle. Blood examination showed tumor marker elevation and the presence of anti-amphiphysin antibodies. Whole-body computed tomography (CT) revealed mass lesions in the left testicle and enlargement of the retroperitoneal lymph nodes. Radical orchiectomy was performed. As the pathology showed testicular seminoma, chemotherapy was administered. After surgery, his neurological symptoms deteriorated. MRI revealed that the brain lesion had enlarged and progressed to a tumefactive lesion without gadolinium enhancement. The cerebrospinal fluid (CSF) examination was normal without pleocytosis or protein elevation. Steroid pulse therapy was added; however, his symptoms did not improve. A brain stereotactic biopsy was performed and the sample showed demyelinating lesions without malignant cells. As the initial corticosteroid therapy was ineffective, gamma globulin therapy was administered in parallel with chemotherapy, and the clinical symptoms and imaging findings were partially ameliorated. TD seldom appears as a paraneoplastic neurological syndrome. In addition, there are few reports of COVID-19 vaccination-associated demyelinating disease. Clinicians should recognize paraneoplastic TD, and the further accumulation of similar cases is needed.

Keywords: anti-amphiphysin antibody, COVID-19 vaccination, demyelinating disease, paraneoplastic syndrome, seminoma, stereotactic biopsy, steroid therapy, tumefactive demyelination

INTRODUCTION

Tumefactive demyelination (TD) is uncommon and its diagnosis is often difficult. Most instances of TD occur in the context of multiple sclerosis (MS), mainly associated with fingolimod and natalizumab (1). TD resembles a malignant tumor, and sometimes a biopsy is required for an accurate diagnosis. If TD appears as an isolated lesion without the context of MS, TD does

not usually progress to MS, and clinicians should consider other causes, such as malignancy-associated TD (2). Here, we describe a pathologically confirmed case of TD as a phenotype of seminoma-associated paraneoplastic disorder and post-COVID-19 vaccination. In our case, the clinical symptoms and imaging findings were partially improved by treatment of the seminoma and immunotherapy. This is the sixth case of pathologically confirmed TD associated with seminoma.

Case Presentation

A previously healthy 32-year-old Japanese man was admitted to our hospital due to right hemiparesis. He was aware that his left testicle had started to enlarge 3 years earlier, but he had not sought medical attention. He received a second vaccination for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Spikevax®; Moderna) in his left deltoid muscle. Two days after vaccination, he developed right hemiparesis and was admitted to our hospital.

On physical examination, he was alert and his body temperature was normal (36.4°C). He showed no headache or neck stiffness. He had no aphagia, apraxia, or agnosia. He showed right hemiparesis with a manual muscle test (MMT) score of 4/5, right hemihypesthesia, and right-sided hyperreflexia. His left testicle was enlarged to 15 cm in diameter. Blood examination showed elevated lactate dehydrogenase (3,520 U/L; normal: 124–222 U/L) and human chorionic gonadotropin (58.1 IU/L; normal: <2.7 IU/L) levels, but alpha-fetoprotein was within the normal limit (3.1 ng/mL; normal: <10 ng/mL). He was negative for anti-nuclear, -neutrophil cytoplasmic, and -SS-A antibodies. Among anti-paraneoplastic antibodies, he was positive for anti-amphiphysin antibodies by an immunoblotting method. He was negative for anti-CV2, -PNMA2, -Ri, -Yo, -Hu, -recoverin, -SOX-1, -titin, -zic4, -GAD65, and -Tr antibodies. We have not measured kelch-like protein 11 antibodies (3). Anti-aquaporin 4 antibody and anti-myelin oligodendrocyte glycoprotein antibody were negative. Whole-body CT showed enlargement of the left testicle and retroperitoneal lymph nodes (**Figure 1A**). Brain MRI revealed a T2 high-intensity lesion in the left internal capsule (**Figures 1B–D**) without gadolinium enhancement or a mass effect, which did not suggest brain metastasis.

At first, the brain lesion was suspected to be an infarct associated with a malignant tumor. The testicular mass was suspected to be a malignancy based on the retroperitoneal lesions and the serological tumor marker findings. Radical orchiectomy was performed, and after surgery, aspirin was administered as prophylaxis for brain infarction. The testicular tumor was pathologically diagnosed as a seminoma. At 3 days after orchiectomy, the right-side paralysis worsened to an MMT

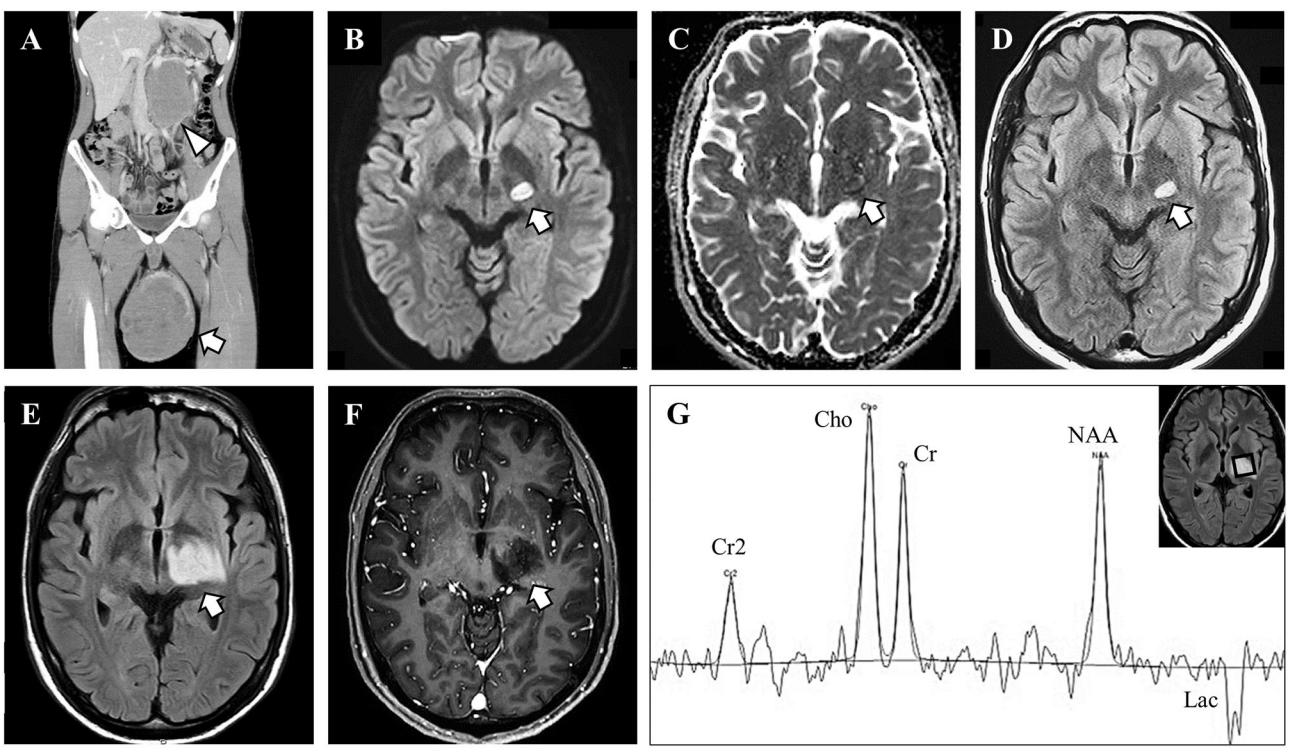

FIGURE 1 | Imaging and magnetic resonance spectroscopy findings. **(A)** Body trunk computed tomography showed enlargement of the left testicle with heterogeneous content (arrow) and retroperitoneal lymph node (arrowhead). **(B–D)** Brain magnetic resonance imaging (MRI) on admission showed a high-intensity lesion in diffusion-weighted and fluid-attenuated inversion recovery (FLAIR) images, with iso-intensity in apparent diffusion coherence images. **(E, F)** The brain lesion enlarged afterward, but with no gadolinium enhancement. **(G)** Magnetic resonance spectroscopy showed high choline (Cho) peak, preserved N-acetyl aspartate (NAA) peak, and lactate (Lac) peak. Cr, creatine.

score of 1/5, and right hemianopsia appeared. Follow-up MRI revealed enlargement of the brain lesion with invasion into the left optic tract. The brain lesion presented with slight edema and a mass effect showing a high-intensity lesion on fluid-attenuated inversion recovery and diffusion-weighted imaging. Gadolinium enhancement was still absent (**Figures 1E,F**). MR spectroscopy revealed an increased choline peak and an abnormal lactate peak, but the N-acetyl aspartate peak was preserved (**Figure 1G**). On suspicion of brain metastasis, encephalitis, or demyelinating lesions, a lumbar puncture was performed. CSF analysis demonstrated normal protein level (.37 g/L; normal:.15–.45 g/L) and cell count (1 cell/μL; normal: <10 cells/μL). The IgG index was also normal (.42; normal: <.72) and oligoclonal IgG bands were absent. CSF cytopathology showed no malignant cells.

As treatment for the seminoma, we started chemotherapy (bleomycin, etoposide, and cisplatin). We added corticosteroid therapy (1,000 mg/day methylprednisolone for 3 days) for the brain lesion, but there was no neurological or MRI improvement. We performed a stereotactic brain biopsy from the left thalamus because the brain lesion showed tumor-like enlargement even after corticosteroid therapy. The sampled specimen consisted of gliotic brain tissue with marked myelin loss and infiltration of inflammatory cells, including numerous macrophages, however, neither malignant tissue nor infarct lesion, was observed (**Figure 2**). The CD68-immunopositive macrophages were widely distributed without perivenous clustering. Some CD68-positive cells may be microglia, but it is difficult to differentiate by immunostaining. The nodular formation of CD 68 positive cells was absent, suggesting there were no microglial nodules. CD3 staining showed scarce infiltration of lymphocytes, so we did not perform CD8 immunostaining. Although axonal loss and degeneration were moderately observed, these findings of axonopathy seemed relatively mild than the degree of myelin loss. Together with these findings, we diagnosed the lesion as a TD, probably due to testicular seminoma.

As disease onset occurred 2 days after COVID-19 vaccination, the post-vaccination demyelinating syndrome was also suspected. In addition to chemotherapy, we added second and third corticosteroid pulse and intravenous immunoglobulin therapy. After four courses of bleomycin, etoposide, and platinum chemotherapy, enlargement of the retroperitoneal lymph nodes was reduced, and serum seminoma markers (lactate dehydrogenase and human chorionic gonadotropin) were decreased to within the normal range. After immunoglobulin therapy, the neurological symptoms showed partial improvement, and the right hemiparesis recovered to an MMT score of 3/5. Plasma exchange was not performed because it was anticipated to attenuate the effect of chemotherapy. The hemiparesis and hemianopia remained, and he was referred to a rehabilitation hospital with MRI amelioration (**Figures 3A–D**).

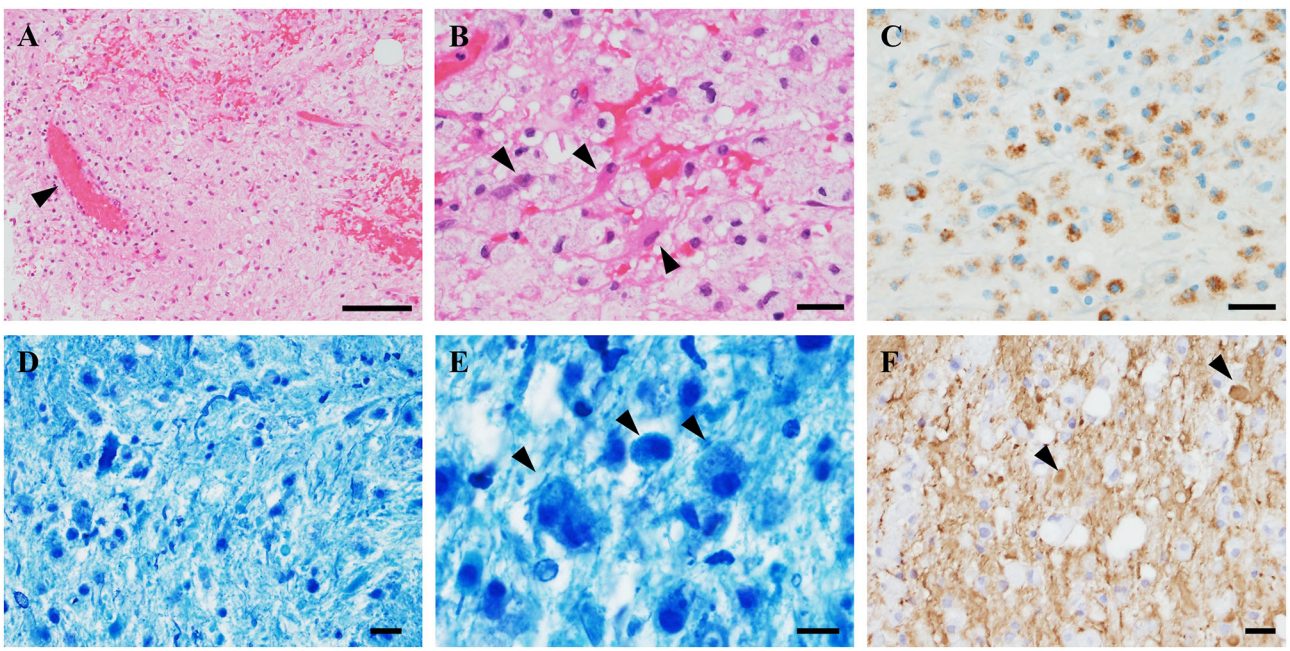

FIGURE 2 | Pathological findings of the brain biopsy. **(A)** Hematoxylin and eosin (HE) stains showed gliosis with widespread infiltration of inflammatory cells without neoplastic tissue. Perivascular inflammation was absent (arrowhead). **(B)** High-magnification HE showed diffuse foamy macrophage infiltration associated with reactive astrocytes (arrowheads). **(C)** CD68-immunostaining revealed clusters of macrophages. **(D,E)** Klüver–Barrera staining demonstrated myelin loss with myelin-laden macrophages (arrowheads). **(F)** Phosphorylated neurofilament immunostaining revealed axonal fragmentation and spheroids (arrowheads). The axonal loss was milder than myelin loss. Scale bars: **(A)** 100 μm. **(B–E)** 20 μm. **(F)** 10 μm.

DISCUSSION

Here, we report a case of a tumefactive demyelinating brain lesion accompanied by testicular seminoma. There are six previous case reports of TD associated with seminoma (4–9), of which five were diagnosed pathologically. To the best of our knowledge, this is the sixth pathologically diagnosed case report of paraneoplastic TD associated with seminoma. Not like previous cases, we could lead to the correct diagnosis before the lesion expands to the subcortical white matter because we confirmed the pathology by thalamic stereotactic biopsy.

Tumefactive demyelination (TD) mainly occurs in connection with MS and is commonly associated with disease-modifying drugs, such as fingolimod and natalizumab (1). When a demyelinating lesion is isolated and not associated with MS, neurologists should investigate other causes, including malignancy-associated TD (2). We could not rule out metastasis or malignancy because the brain lesion increased in size despite

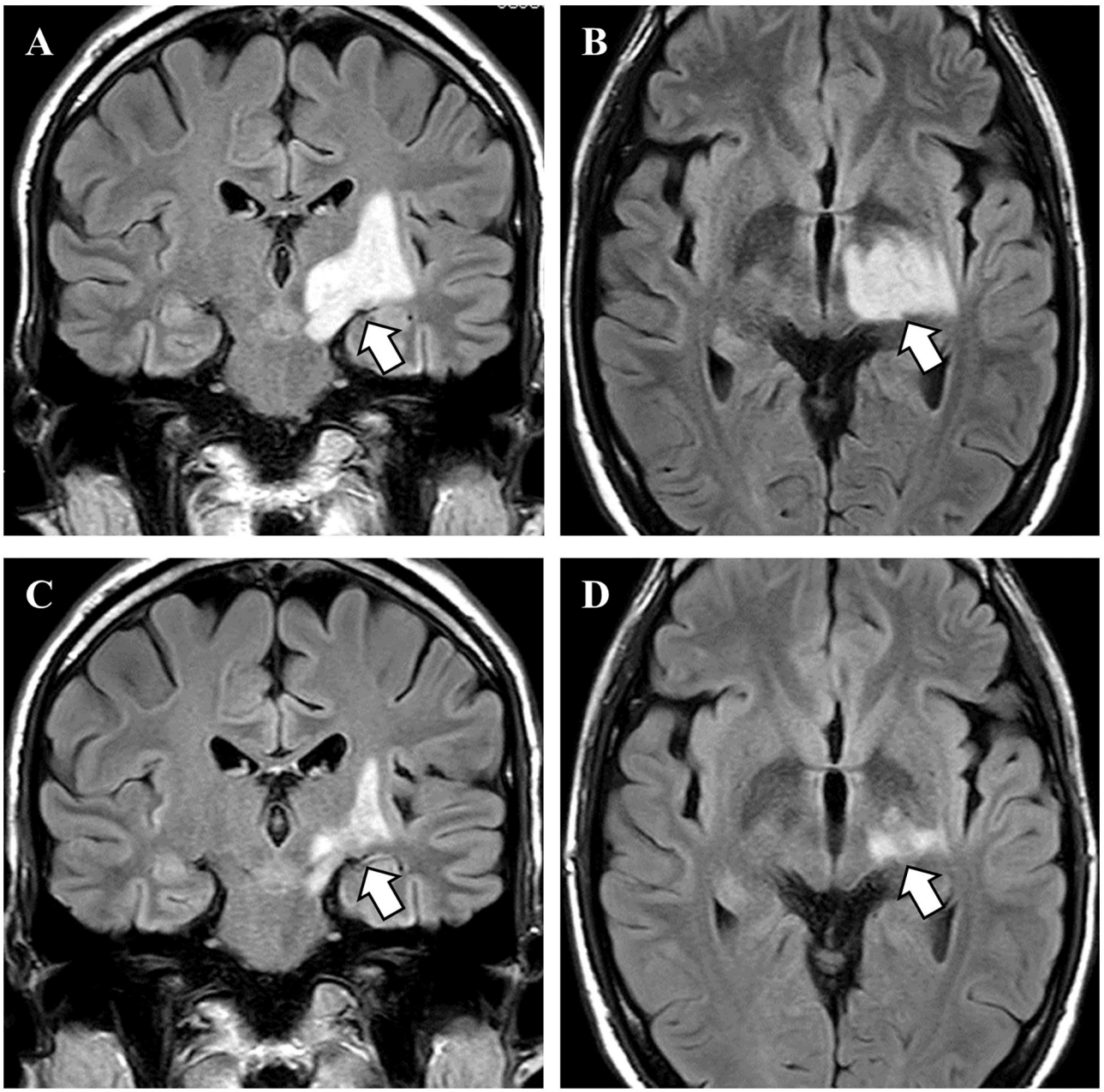

FIGURE 3 | MRI findings before and after treatment. **(A,B)** Before treatment, brain magnetic resonance imaging showed a high-intensity lesion in the left basal ganglia (arrows). **(C,D)** After chemotherapy and immunotherapy, the brain lesion was reduced in size (arrows).

the initial corticosteroid therapy and radical orchiectomy. A brain biopsy eventually led us to the correct diagnosis of TD, and we administered further immunotherapy, which resulted in a partial response. The MRI findings of TD are characteristic. Algahtani et al. reported that minor edema, a mass effect, open-ring enhancement, dilated veins, restricted diffusion, and low perfusion on brain MRI, and an increased choline peak, a relatively high N-acetyl aspartate peak, and an abnormal lactate peak on MR spectroscopy are highly suggestive for TD (1). Diffusion-weighted imaging is reported to show peripheral diffusion restriction with increased apparent diffusion coefficient, and perfusion imaging shows low relative cerebral blood volume (7). These imaging findings and careful management may lead clinicians to the diagnosis of TD without biopsy. Our case presented with a small mass effect without gadolinium enhancement on MRI. In addition, MR spectroscopy showed an increased choline peak, a preserved N-acetyl aspartate peak, and a lactate peak, which are consistent with TD. Sometimes, TD shows disease progression despite steroid therapy (8). Therefore, it is essential to note that resistance to initial steroid therapy does not always rule out demyelinating disease.

There are six previous case reports of TD with seminoma (**Table 1**). In all cases, the seminoma was discovered simultaneously or after the neurological symptoms had developed. All of these cases, except for the case of Plotkin et al., had pathologically confirmed demyelinating lesions. The brain lesions were predominantly in the white matter and corpus callosum with a tendency to increase in size. Concerning autoantibodies and paraneoplastic neuronal antibodies, only one case (6) was positive for autoantibodies, but all of the other cases were negative or not screened. Among these reports, Thebault et al. attempted serum antibody screening by immunofluorescence immunohistochemistry of rat brain sections and live neuronal cultures, but did not identify specific binding (9). Our case was positive for serum anti-amphiphysin antibodies. The most common neurological manifestations caused by anti-amphiphysin antibodies are stiff person syndrome, ataxia, neuropathy, and neuronopathy (10). In addition, an association between spinal lesions and the presence of anti-amphiphysin antibodies has been reported (11). However, to the best of our knowledge, intracranial demyelinating diseases associated with anti-amphiphysin antibodies, such as the present case, have not been reported. Therefore, it is difficult to conclude that there is an association between the presence of anti-amphiphysin antibodies and the pathomechanisms of this case. Also, there is the possibility of false-negative because generally, amphiphysin antibodies are not associated with seminoma (10, 12). Recently, new antibodies were discovered in cases of encephalitis complicated by seminoma (3). This kelch-like protein 11 antibodies positive encephalitis shows progressive brain-stem, cerebellar, or rhombencephalitis. We did not measure this antibody because the phenotype is different from our case. Further studies may detect antibodies shared by demyelinating diseases associated with seminomas.

As for the prognosis of TD, two previous cases showed favorable outcomes, while four showed poor outcomes. The treatment options are generally corticosteroid therapy and treatment of seminoma. Some cases, like our patient, did not respond to the initial steroid treatment and the lesions grew in size. Plasma exchange was used in one case. We treated our case with immunotherapy along with chemotherapy. Simultaneous plasma exchange with chemotherapy is considered to reduce the effectiveness of chemotherapy (11); therefore, to treat paraneoplastic demyelination without diminishing the therapeutic effect of chemotherapy, we used a combination of corticosteroids and gamma globulin therapy. However, there is no standardized treatment option for TD. Shah et al. reported a retrospective review of the treatment of TD, showing that the patients received steroid therapy, immunomodulatory drugs, biologics, intravenous immunoglobulin, anticonvulsants, and therapeutic plasma apheresis (13). They stated that there were no correlations between treatment and disease outcome. Vakrakou et al. suggested that when corticosteroids and plasma exchange are ineffective, cyclophosphamide can be an additional treatment option for TD (14).

Our patient showed neurological symptoms 2 days after the second COVID-19 vaccination. Generally, CNS demyelination after vaccination is rare (15). Although not common, there are some reports of CNS demyelinating diseases associated with COVID-19 vaccination (16). Ismail et al. reported that all types of COVID-19 vaccines could cause CNS demyelination, and the neurological symptoms commonly appear within the first 1–2 weeks after vaccination (16). In their study, CNS demyelination after receiving the Moderna vaccine was considered to be a relapse of MS and transverse myelitis, and there are no reports of new-onset TD, which was shown in our case, after COVID-19 vaccination. In addition, the pathological features of our case did not display the hallmarks of acute disseminated encephalomyelitis (ADEM), including perivenous demyelination, fever, headache, meningitis, and consciousness disturbance (17). The lack of these symptoms in our case indicated a primary demyelinating disease rather than ADEM. Therefore, paraneoplastic TD is a more appropriate diagnosis for our case than COVID-19 vaccine-associated ADEM. However, there remains the possibility that some kind of immune response to the vaccine triggered paraneoplastic demyelination. Ismail et al. reported that among 32 cases of demyelinating disease associated with the COVID-19 vaccine, two had cancer (16). One hypothesis of the immunoreaction according to COVD-19 vaccination is molecular mimicry. The similarity between the viral proteins used for the vaccine and self-antigens (e.g., myelin) triggers an unexpected immune response (18). A previous report showed that COVID-19 infection could cause demyelination *via* decreasing T cells, B cells, or NK cells. Another demyelination mechanism is provoked auto-immune reactions, resulting from excessive self-response and antigen-driven immune responses (19). It is not clear if the COVID-19 vaccination produces a similar response. Still, the details have not been clarified. Tumefactive demyelination has been reported to be associated with an immune response (1). Therefore, autoantibodies like anti-amphiphysin antibody, and vaccination may have been involved in the pathophysiology. At present, COVID-19 is still prevalent worldwide, and further accumulation of similar cases is necessary.

TABLE 1 | Previous cases of paraneoplastic tumefactive demyelination accompanied by seminoma.

Case	Age (years)	Sex	Symptoms	Imaging findings	Biopsy	Antibodies	Treatment	Response	Author
1	41	M	Depression, difficulty with concentration and memory.	Decreased T1-low and T2-high signals in the occipital lobes and corpus callosum, with some peripheral contrast enhancement.	Macrophage infiltration, reactive astrocytosis, demyelination, and preserved axons.	Negative for anti-Hu, –Yo, and –Ri antibodies.	Oral corticosteroid therapy and radiation to the seminoma.	Good response.	Jaster JH
2	54	M	Confusion and memory loss.	T1-low and T2-high signals on the corpus callosum and parieto-occipital white matter. Minimal mass effect and no contrast enhancement.	Foamy macrophages and reactive astrocytes. Complete myelin loss and moderate axonal loss.	Not assessed.	Chemotherapy and dexamethasone.	Partial response. Memory deficit remained.	Wong K
3	37	M	Left facial numbness and left-sided ataxia.	T1-low and FLAIR-high lesion in the left middle cerebellar peduncle. Irregular ring enhancement was present.	Not performed.	Elevation of anti-nuclear, –cardiolipin, and –double-stranded DNA antibodies. Negative for anti-Hu, –Ri, –Yo, and –Ma2 antibodies.	Dexamethasone and radiation therapy to the seminoma.	Good response. 4 years later, he became asymptomatic.	Plotkin SR
4	60	M	Memory loss and homonymous right upper quadrantanopia.	Large confluent lesion affecting both occipitoparietal lobes, crossing the splenium of the corpus callosum.	No evidence of neoplasia. Demyelination, CD68-positive macrophage infiltration containing myelin debris, and scattered $CD45^+$ and $CD3^+$ lymphocytes.	Negative for anti Yo, –Hu, and –Ri antibodies.	Cisplatin and etoposide for seminoma. Initial steroid pulse was ineffective. Repeated steroid pulse and five plasma exchanges were added.	Partial response. Left hemianopia and memory impairment remained.	Broadfoot JR
5	62	M	Headache, right-sided weakness, and receptive aphasia.	T1-low and T2-high lesion in the left frontoparietal area with a small mass effect and gadolinium enhancement. MRS showed an NAA/choline ratio of 0.42 with a lactate peak.	No evidence of neoplasia. Demyelination and infiltration of CD68-positive foamy macrophages.	Negative for anti-Ma2, –AQP4, and –MOG antibodies.	Steroid pulse, oral steroids, and radiotherapy to the seminoma.	Poor response. Severe right hemiparesis remained.	Thebault S
6	47	M	Motor aphasia and right facial and brachial paresis.	T1-low and T2/FLAIR-high lesion that expanded through the internal capsule to the left cerebral peduncle, imcomplete ring enhancement, and visualized central veins. Mass effect was small.	No evidence of neoplasia. CD68-positive macrophage infiltration and perivascular lymphocytic infiltration.	Negative for anti–Hu, –Yo, –Ri, –CV2, –Ma1, –Ma2, –Ta, –amphiphysine, –Zic, –SOX, –GAD65, –Tr, –ANNA3, –PCA2, and –cerebellum antibodies.	Sterod pulse, oral corticosteroid, and radical orchiectomy.	Partial response. Aphasia and paresis recovered. Behavioral problems remained.	Van Haver AS
Present case	32	M	Right hemiplegia and right hemianopia.	T1-low and T2/FLAIR-high lesion in the left thalamus. Enhancement was absent. Choline, NAA, and lactate peaks on MRS.	No evidence of neoplasia. Demyelination, CD68-positive macrophage infiltration with myelin debris, and axonal damage.	Positive for anti-amphiphysin antibodies. Negative for anti-nuclear, –AQP4, and –MOG antibodies.	Radical orchiectomy, bleomycin, etoposide, and cisplatin for seminoma. Steroid pulse and gamma globulin therapy for demyelination.	Partial response. Hemiparesis and hemianopsia remained.	Shiraishi W

ANNA, anti-neuronal nuclear antibody; AQP4, aquaporin-4; CD, cluster of differentiation; FLAIR, fluid-attenuated inversion recovery; GAD, glutamate decarboxylase; M, male; MOG, myelin oligodendrocyte glycoprotein; MRS, magnetic resonance spectroscopy; NAA, N-acetyl aspartate; PCA, Purkinje cell antibody.

To our knowledge, this is the sixth case report of pathologically confirmed paraneoplastic TD with seminoma. Our case exhibited unique and complicated pathomechanisms, including COVID-19 vaccination and anti-amphiphysin antibodies. In addition to brain biopsy pathology, peculiar MRI findings, such as a small mass effect and absence of gadolinium enhancement, and MR spectroscopy findings led us to the correct diagnosis. Finally, we administered steroid therapy and intravenous immunoglobulin, which ameliorated the disease. We hope that this case report provides helpful information for diagnosing and treating similar cases in the future.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

WS and TU participated in patient management, clinical data analysis, and writing of the article. YN participated in patient management and revision of the article. YY, MS, and TH participated in clinical data analysis and revision of the article. All authors contributed to the article and approved the submitted version.

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Case report: Variant-specific pre-exposure prophylaxis of SARS-CoV-2 infection in multiple sclerosis patients lacking vaccination responses

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Sphingosine-1-phosphate receptor modulators and anti-CD20 treatment are widely used disease-modifying treatments for multiple sclerosis. Unfortunately, they may impair the patient's ability to mount sufficient humoral and T-cellular responses to vaccination, which is of special relevance in the context of the SARS-CoV-2 pandemic. We present here a case series of six multiple sclerosis patients on treatment with sphingosine-1-phosphate receptor modulators who failed to develop SARS-CoV-2-specific antibodies and T-cells after three doses of vaccination. Due to their ongoing immunotherapy, lacking vaccination response, and additional risk factors, we offered them pre-exposure prophylactic treatment with monoclonal SARS-CoV-2-neutralizing antibodies. Initially, treatment was conducted with the antibody cocktail casirivimab/imdevimab. When the SARS-CoV-2 Omicron variant became predominant, we switched treatment to monoclonal antibody sotrovimab due to its sustained neutralizing ability also against the Omicron strain. Since sotrovimab was approved only for the treatment of COVID-19 infection and not for pre-exposure prophylaxis, we switched treatment to tixagevimab/cilgavimab as soon as it was granted marketing authorization in the European Union. This antibody cocktail has retained, albeit reduced, neutralizing activity against the Omicron variant and is approved for pre-exposure prophylaxis. No severe adverse events were recorded for our patients. One patient had a positive RT-PCR for SARS-CoV-2 under treatment with sotrovimab, but was asymptomatic. The other five patients did not develop symptoms of an upper respiratory tract infection or evidence of a SARS-CoV-2 infection during the time of treatment up until the finalization of this report. SARS-CoV-2-neutralizing antibody treatment should be considered individually for multiple sclerosis patients lacking adequate vaccination responses on account of their immunomodulatory treatment, especially in times of high incidences of SARS-CoV-2 infection.

KEYWORDS

multiple sclerosis, sphingosine-1-receptor modulators (S1PR), neutralizing antibody, prophylaxis, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease (COVID-19), vaccination, case report

Introduction

Many disease-modifying drugs are available for the treatment of multiple sclerosis (MS). Selected immunomodulatory agents like sphingosine-1-phosphate receptor (S1PR) modulators and anti-CD20 treatment limit the patients' ability to mount sufficient immune responses to vaccination (1). This is of special relevance in the context of the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.

MS patients at the MS Center Dresden, Germany, are screened for SARS-CoV-2-specific antibody and T-cellular responses after vaccination in order to detect those lacking an adequate immune response (2). Unfortunately, we found several patients under certain disease-modifying therapies who developed neither humoral nor T-cellular responses to SARS-CoV-2 vaccination, even after the application of three mRNA and/or vector vaccine doses. The lacking immune response to vaccination puts these patients at risk for contracting SARS-CoV-2 infection and for suffering a severe course of coronavirus disease (COVID-19). Additional factors like age > 50 years, cardiovascular disease, diabetes mellitus, obesity, chronic lung, kidney, or liver disease, can further increase the risk for severe COVID-19.

Fortunately, treatment options for patients who are not able to mount sufficient responses to active immunization are available. According to the recommendations of several German Medical Societies, passive immunization with neutralizing anti-SARS-CoV-2-antibodies as pre-exposure prophylactic treatment should be offered to those patients who have an increased risk for a severe course of COVID-19 due to immunosuppression (e.g. caused by hematooncological disease, immunotherapy, or hereditary immune defects) and who did not respond sufficiently to active immunization (3).

Here, we present a case series of six MS patients under immunomodulatory treatment who lacked antibody and T-cell responses to three SARS-CoV-2 vaccinations and who were thus prophylactically treated with SARS-CoV-2-neutralizing antibodies in our MS Center. In accordance with the prevalent SARS-CoV-2 variants at the time, treatment was started with casirivimab/imdevimab, subsequently switched to sotrovimab, and finally to tixagevimab/cilgavimab. To our knowledge, no cases of pre-exposure prophylactic SARS-CoV-2-neutralizing antibody treatment in MS patients have been reported yet.

Casirivimab/imdevimab

Casirivimab/imdevimab (Ronapreve/REGEN-COV; Roche Registration GmbH) is a monoclonal human IgG1 antibody cocktail with neutralizing activity against SARS-CoV-2. Each antibody binds to a distinct epitope on the receptor binding domain of the viral spike protein. The two antibodies are used in combination in order to enhance efficacy in the face of emerging virus variants and to decrease the risk of selection for viral escape mutations.

The neutralizing antibody cocktail first received emergency use authorization in the USA in November 2020. In November 2021, the European Commission granted marketing authorization for casirivimab/imdevimab for the treatment of selected patients with COVID-19 disease and for the prophylaxis of SARS-CoV-2 infection in adults and adolescents aged 12 years and older weighing at least 40 kg (4). In the case of pre-exposure prophylaxis, the antibodies casirivimab and imdevimab are initially administered at doses of 600 mg each as a single intravenous infusion or *via* subcutaneous injection. As long as prophylaxis is needed, treatment is repeated every four weeks at a dose of 300 mg each (4).

First results from trials evaluating the clinical efficacy of casirivimab/imdevimab in the treatment of COVID-19 and in the prophylaxis of SARS-CoV-2 infection have been reported. Published data from an ongoing clinical trial demonstrated that treatment with the antibody cocktail reduced hospitalization and death rates of non-hospitalized COVID-19 patients compared to placebo (5). Furthermore, the treatment led to a faster resolution of symptoms and to an accelerated decrease in viral load (5). In another analysis of the same clinical trial, the reduction in SARS-CoV-2 viral load mediated by casirivimab/imdevimab was more pronounced in previously seronegative patients (6). The rate of adverse events was similar between casirivimab/imdevimab and placebo (5, 6).

Concerning prophylaxis of COVID-19, the risk of asymptomatic SARS-CoV-2-infected patients to develop symptomatic disease was decreased in the group receiving casirivimab/imdevimab compared to the group receiving placebo (7). Moreover, the neutralizing antibody cocktail was able to prevent asymptomatic and symptomatic SARS-CoV-2 infection in individuals living in a household with infected persons (8). In the study participants who did contract SARS-CoV-2 in this setting, casirivimab/imdevimab treatment abbreviated the time of symptomatic disease and of high viral load (8). Preliminary data from a phase 1, double-blind, placebo-controlled study evaluating the repeated application of subcutaneous casirivimab/imdevimab every four weeks showed a significant risk reduction for the development of COVID-19 compared to participants receiving placebo treatment while there was no difference in serious adverse events between the two groups (9).

Casirivimab/imdevimab demonstrated effective neutralization of the SARS-CoV-2 Delta variant *in vitro*. Problematically, it was shown to insufficiently neutralize the SARS-CoV-2 Omicron variant (10, 11).

Sotrovimab

Sotrovimab (VIR-7831; GlaxoSmithKline/Vir Biotechnology) is an engineered human monoclonal IgG1 antibody produced in

Chinese Hamster Ovary cells. It neutralizes SARS-CoV-2 by binding to a highly conserved epitope on the viral spike protein located outside of the receptor-binding motif.

Sotrovimab was granted marketing authorization by the European Commission in December 2021 for the treatment of adults and adolescents aged > 12 years and weighing more than 40 kg who suffer from COVID-19, do not need oxygen supplementation, and have an increased risk of developing a severe disease course (12). It is recommended to start the treatment within five days after symptom onset. The antibody is administered at a dose of 500 mg intravenously.

An ongoing double-blind phase 3 trial compared disease progression to hospitalization or death between outpatients receiving sotrovimab or placebo. The analyzed population comprised non-hospitalized adults with symptomatic COVID-19 and at least one risk factor for a severe disease course. Patients were eligible if symptoms had begun within the previous five days and if they had mild-to-moderate COVID-19. An interim analysis of this trial showed that treatment with sotrovimab led to a significant risk reduction for hospitalization and death in comparison to placebo (13). Adverse events were similar between groups receiving sotrovimab and placebo, severe adverse events were less common in sotrovimab-treated patients compared to the placebo group (13).

Results of the double-blind, randomized TICO (Therapeutics for Inpatients with COVID-19) trial showed that sotrovimab did not improve clinical outcomes in adults hospitalized due to COVID-19 (14).

Several *in vitro* studies were able to show that sotrovimab and its parent monoclonal antibody, S309, fully or largely retain their neutralizing capacity also against the SARS-CoV-2 Omicron variant (10, 15, 16).

Tixagevimab/cilgavimab

Tixagevimab/cilgavimab (Evusheld/AZD7442; AstraZeneca AB) is a combination of two monoclonal antibodies with neutralizing activity against SARS-CoV-2 derived from B cells of SARS-CoV-2-infected persons. Modifications were added in order to prolong the antibodies' half-life and to decrease binding of the Fc receptor and complement component C1q. The antibodies are produced in Chinese Hamster Ovary cells. They are directed against distinct, non-overlapping epitopes of the receptor binding domain of the SARS-CoV-2 spike protein (17).

Tixagevimab/cilgavimab received marketing authorization in the European Union in March 2022 for pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg (18). The antibodies are administered as two separate intramuscular injections at a dose of 150 mg each in a 1.5 mL solution. Median terminal elimination half-life was estimated to be 89 days for tixagevimab and 84 days for cilgavimab. Protection is expected to last at least six months after one dose of tixagevimab/cilgavimab based on data from the PROVENT (Phase 3 Study of Efficacy and Safety of AZD7442 for Pre-exposure Prophylaxis of COVID-19 in Adults) trial so that injections can be repeated every six months (18).

Data from the ongoing double-blind PROVENT study showed a significant risk reduction for symptomatic COVID-19 disease in participants treated with tixagevimab/cilgavimab as compared to placebo within a median follow-up period of 83 days (17). The study population comprised individuals with an increased risk for inadequate responses to active SARS-CoV-2 vaccination or with an increased risk of exposure. Incidences of severe adverse events were not different between treatment and placebo groups.

According to several *in vitro* studies, the combination of tixagevimab and cilgavimab retains neutralizing activity against SARS-CoV-2 Omicron variants, however at a reduced level as compared to previous SARS-CoV-2 strains (19–21). Two studies evaluated the neutralizing capacity of sera obtained from immunocompromised patients after treatment with the antibody cocktail. Bruel et al. found an efficient neutralization of the Delta variant for all patient sera, but a reduced neutralizing activity against Omicron (22). Benotmane et al. reported that less than 10% of the analyzed patient sera were able to neutralize the Omicron BA.1 variant. They suggested that the antibody dose is probably insufficient and may need to be adapted (23). Correspondingly, the duration of protection after one application of tixagevimab/cilgavimab is likely shorter for the Omicron than for the other SARS-CoV-2 variants (18).

Case descriptions

The screening of patients at our MS Center in Dresden, Germany, for humoral and T-cellular responses to active SARS-CoV-2 immunization yielded several cases without detectable immune responses to three vaccine doses. For the respective patients, we evaluated the option of passive immunization with monoclonal SARS-CoV-2-neutralizing antibodies as pre-exposure prophylaxis.

Patient characteristics are summarized in Table 1. All reported patients received immunomodulatory treatment with S1PR modulators. Five of six patients had a diagnosis of relapsing-remitting MS (RRMS) and were treated with fingolimod, one received siponimod for therapy of secondary progressive MS. None of the patients had a history of suspected or confirmed status post SARS-CoV-2 infection before start of monoclonal antibody treatment.

The temporal sequence of vaccinations, analyses of immune responses, and initiation of neutralizing antibody treatment is depicted in Figure 1. All patients received two doses of SARS-CoV-2 vaccine in the time between February and June, 2021. Four of them were vaccinated with two doses of BNT162b2

TABLE 1 Patient characteristics.

Patient #	Age (y)	sex	MS type	DMT	EDSS	Comorbidities/other risk factors	1st/2nd vaccination date	Vaccine type	3rd vaccination date	Vaccine type	1st casirivimab/ imdevimab	2nd casirivimab/ imdevimab	1st sotrovimab	1st tixagevimab/ cilgavimab
1	63	m	SPMS	SIP	6.0	normocytic anemia	22 Feb 2021 15 Mar 2021	BNT162b2 BNT162b2	30 Jul 2021	BNT162b2	16 Dec 2021	13 Jan 2022	10 Feb 2022	7 Apr 2022
2	54	m	RRMS	FTY	2.0	wife with breast cancer on chemo- and radiotherapy	5 Apr 2021 26 Apr 2021	BNT162b2 BNT162b2	21 Sep 2021	BNT162b2	17 Dec 2021	14 Jan 2022	11 Feb 2022	8 Apr 2022
3	50	m	RRMS	FTY	2.0	suspected arterial hypertension	15 May 2021 5 Jun 2021	BNT162b2 BNT162b2	4 Nov 2021	mRNA-1273	10 Jan 2022	none	7 Feb 2022	4 Apr 2022
4	65	f	RRMS	FTY	4.0	arterial hypertension; hypercholesterolemia; autoimmune thyroiditis; slight overweight	5 May 2021 9 Jun 2021	BNT162b2 BNT162b2	3 Dec 2021	mRNA-1273	10 Jan 2022	none	7 Feb 2022	4 Apr 2022
5	64	m	RRMS	FTY	2.0	basal cell carcinoma, excision Sep and Oct 2021; hypercholesterolemia	2 May 2021 29 Jun 2021	AZD1222 BNT162b2	23 Nov 2021	BNT162b2	12 Jan 2022	none	9 Feb 2022	6 Apr 2022
6	44	f	RRMS	FTY	1.5	3 school-age children	22 Mar 2021 18 Jun 2021	AZD1222 BNT162b2	23 Sep 2021	mRNA-1273	14 Jan 2022	none	11 Feb 2022	8 Apr 2022

y, years; m, male; f, female; MS, multiple sclerosis; SPMS, secondary progressive MS; RRMS, relapsing-remitting MS; DMT, disease-modifying treatment; SIP, siponimod; FTY, fingolimod; EDSS, Expanded Disability Status Scale.

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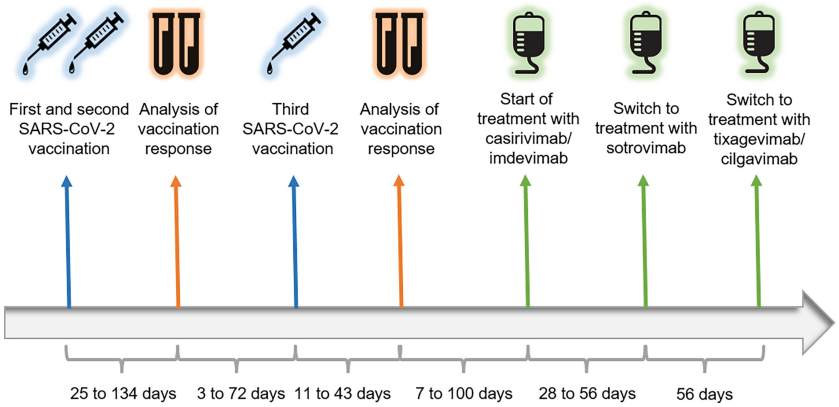

FIGURE 1
Timeline. Patients were vaccinated with two doses of SARS-CoV-2 mRNA and/or vector vaccine between February and June, 2021. Humoral and T-cellular responses to vaccination were analyzed 25 to 134 days after the second vaccine dose of each patient. All reported patients lacked SARS-CoV-2-specific antibodies and T-cells so that they received a third vaccination 3 to 72 days after the analysis of their immune response. After an interval of 11 to 43 days to the third vaccination, analysis of immune responses was repeated. Again, all patients did not have antibody and T-cellular responses to SARS-CoV-2. Neutralizing antibody treatment was discussed with the patients and initiated 7 to 100 days after the analysis. Initially, patients received infusions with casirivimab/imdevimab every four weeks. With rising incidences of infections with the SARS-CoV-2 Omicron variant, we switched treatment to sotrovimab 28 to 56 days after the first casirivimab/imdevimab infusion had taken place. As sotrovimab was formally approved only for the treatment of COVID-19 infection, we switched treatment to tixagevimab/cilgavimab as soon as it received marketing authorization in the European Union. This antibody cocktail is approved for pre-exposure prophylaxis of SARS-CoV-2 infection and has retained neutralizing capacity against the SARS-CoV-2 Omicron strain.

(BioNTech/Pfizer), two patients received a first dose of AZD1222 (Oxford-AstraZeneca) and a second dose of BNT162b2. Immune responses to vaccination were measured with an interval of at least 25 days after the second vaccine dose. Antibodies directed against the SARS-CoV-2 spike protein were initially measured *via* LIAISON® SARS-CoV-2 S1/S2 IgG quantitative chemiluminescence immunoassay (DiaSorin). Values < 12.0 AU/mL were considered negative as indicated in the manufacturer's instructions. From October 2021 onwards, antibodies were measured *via* LIAISON® SARS-CoV-2 TrimericS IgG quantitative chemiluminescence immunoassay (DiaSorin). For this assay, values < 33.8 BAU/mL were classified as negative according to manufacturer's information. T-cellular responses were measured *via* QuantiFERON® SARS-CoV-2 assay (Qiagen). Here, interferon-gamma secretion of T-cells after 18 to 24 hours of stimulation with SARS-CoV-2 spike protein peptide pools 1 and 2 was measured *via* enzyme-linked immunosorbent assay. Values < 0.15 IU/mL were considered negative in line with manufacturer's instructions. All reported patients showed negative SARS-CoV-2 spike-specific IgG antibodies and T-cellular responses after two doses of vaccination. Subsequently, all patients received a third SARS-CoV-2 vaccine dose. Three of them were vaccinated with BNT162b2, the other three with mRNA-1273 (Moderna). Control of vaccination responses took place 11 to 43 days after the third immunization and showed persistently negative antibody and T-cell responses to SARS-CoV-2 spike protein in all patients (Table 2).

Patient 1 is a 63-year-old male receiving siponimod for the treatment of secondary progressive MS. His degree of neurological disability is relatively high with a score of 6.0 in the Expanded Disability Status Scale (EDSS). His laboratory examination shows normocytic anemia as comorbidity.

Patient 2 is male and 54 years old. He takes fingolimod for the treatment of RRMS and has a lower degree of disability with an EDSS value of 2.0. His wife has been diagnosed with breast cancer and is receiving chemo- and radiotherapy posing her at risk for a severe COVID-19 disease course.

Patient 3 is a 50-year-old male with an EDSS score of 2.0, receiving medication with fingolimod for therapy of RRMS. Arterial hypertension is suspected as a comorbidity, but has not yet been confirmed at the time of preparation of this manuscript.

Patient 4 is a female RRMS patient who is 65 years old and takes fingolimod. She has an EDSS score of 4.0 corresponding to a limitation of her walking range. She has several cardiovascular risk factors comprising arterial hypertension, hypercholesterolemia, and slight overweight. Furthermore, she suffers from autoimmune thyreoiditis.

Patient 5 is a 64-year-old male patient taking fingolimod for treatment of RRMS with an EDSS value of 2.0. He was operated on a facial basal cell carcinoma in September and October, 2021. His laboratory exam displays hypercholesterolemia as cardiovascular risk factor.

Patient 6 is a female RRMS patient with an age of 44 years taking fingolimod. She has a low value of 1.5 in the EDSS and no

TABLE 2 Antibody and T-cellular response to SARS-CoV-2 vaccination in patients 1 to 6.

Patient #	Analysis of antibody and T-cell response to SARS-CoV-2 after second vaccination	S protein-specific antibody response	T-cell response to antigen pools S1/S2 (IU/mL)	Analysis of antibody and T-cell response to SARS-CoV-2 after third vaccination	S protein-specific antibody response	T-cell response to antigen pools S1/S2 (IU/mL)
1	27 Jul 2021	<3.8 AU/mL	0	7 Sep 2021	4.31 AU/mL	0.0065
			0			0
2	9 Aug 2021	<3.8 AU/mL	0	19 Oct 2021	25.8 BAU/mL	0
			0			0.003
3	13 Sep 2021	<3.8 AU/mL	0	13 Dec 2021	7.65 BAU/mL	0
			0			0
4	5 Oct 2021	<4.81 BAU/mL	0	14 Dec 2021	<4.81 BAU/mL	0.0045
			0.0205			0.014
5	12 Oct 2021	<4.81 BAU/mL	0.0595	5 Jan 2022	7.43 BAU/mL	0
			0			0
6	13 Jul 2021	4.62 AU/mL	0	1 Nov 2021	12.5 BAU/mL	0
			0			0

AU/mL, Antibody Units per milliliter; BAU/mL, Binding Antibody Units per milliliter; IU/mL, International Units per milliliter. SARS-CoV-2-specific antibody and T-cell responses were measured after the second and again after the third vaccination of each patient. IgG antibodies against the spike protein of SARS-CoV-2 were measured via LIAISON® SARS-CoV-2 S1/S2 IgG quantitative chemiluminescence immunoassay (DiaSorin; values < 12.0 AU/mL considered negative). From October 2021 onwards, antibodies were measured via LIAISON® SARS-CoV-2 TrimericS IgG quantitative chemiluminescence immunoassay (DiaSorin; values < 33.8 BAU/mL considered negative). T-cellular interferon-gamma secretion to SARS-CoV-2 spike protein peptide pools 1 and 2 was measured via QuantiFERON® SARS-CoV-2 assay (Qiagen; values < 0.15 IU/mL considered negative). All patients had negative antibody and T-cellular responses to SARS-CoV-2 spike protein after the second and third vaccination.

relevant comorbidities. She has three school-age children limiting her ability to reduce social contacts.

As casirivimab/imdevimab was granted marketing authorization for the prophylaxis of SARS-CoV-2 infection in adults by the European Commission in November 2021, we discussed this therapeutic option with eligible patients. The reported patients were in favor of a pre-exposure prophylactic treatment with the neutralizing antibodies and the first intravenous infusions with 600 mg each of casirivimab and imdevimab took place in our MS Center between 16th of December, 2021, and 14th of January, 2022. Patients 1 and 2 received their second casirivimab/imdevimab infusion at a dose of 300 mg each on January 13th and 14th, 2021, respectively. No severe adverse events occurred in our patients. Patient 1 and 6 reported chills and fatigue after the first casirivimab/imdevimab infusion. The former further reported more frequent occurrence of dizziness and headache than usual during the weeks up until the second infusion. During the first casirivimab/imdevimab infusion, hypertensive blood pressure was measured in patient 4 with a maximum of 165/105 mmHg and in patient 3 with maxima of 151 mmHg systolic and 107 mmHg diastolic. Arterial hypertension is known in the former and suspected in the latter, and the measurement before the start of the infusion already yielded hypertensive values similar to the ones during and after the infusion in both cases. Hence, a causal link between the medication and the hypertensive blood pressure seems unlikely. No abnormalities were documented for casirivimab/imdevimab infusions in the other two patients.

When the prevalence of the SARS-CoV-2 Omicron variant exceeded the Delta variant, we discussed a treatment switch to sotrovimab with our patients. Continued treatment with casirivimab/imdevimab was likely to become inefficacious for prophylaxis of SARS-CoV-2 infection in this context since the antibody cocktail's neutralizing activity against the Omicron strain had been demonstrated to be insufficient. As the European Commission granted marketing authorization for sotrovimab only for the treatment of early COVID-19, infusions had to be administered off-label for pre-exposure prophylaxis in our patients. All of them were in favor of the treatment switch. The first infusions with 500 mg sotrovimab were conducted four weeks after the last casirivimab/imdevimab infusion and took place between 7th and 11th of February, 2022. Hypertensive blood pressure was measured before, during, and after the infusion in patients 3, 4, and 5. Again, as the blood pressure was already high in all patients before the start of the infusion, a causal link to the infusion is unlikely. No other adverse events were recorded. Due to its longer half-life compared to casirivimab/imdevimab, sotrovimab was planned to be administered every eight weeks at a dose of 500 mg.

At the end of March, 2022, the antibody cocktail tixagevimab/cilgavimab received marketing authorization in the European Union. Because this antibody combination was shown to have retained, albeit reduced, neutralizing activity against the SARS-CoV-2 Omicron strain and was approved specifically for pre-exposure prophylaxis, we conducted another treatment switch. Again, all patients approved of the

switch and received their first injections eight weeks after their first sotrovimab infusion. No adverse events were recorded for tixagevimab/cilgavimab. Subject to the epidemiological situation, the next tixagevimab/cilgavimab injections are planned six months after the first dose.

The applied pre-exposure prophylactic treatment schedules for the different SARS-CoV-2-neutralizing monoclonal antibodies in our patients, the antibodies' marketing authorization status in the EU for pre-exposure prophylactic treatment, and their neutralizing capacity against the SARS-CoV-2 Omicron strain are summarized in Table 3.

Patients were regularly asked at routine clinical visits about occurrence of symptoms suggestive of an upper respiratory tract infection or positive SARS-CoV-2 testing. Data collected until the 2nd of June, 2022, were taken into account for this report, corresponding to a follow-up time between 139 and 168 days since the first neutralizing antibody infusion. Patient 1 had a positive RT-PCR for SARS-CoV-2 on the 8th of March, 2022, but was asymptomatic. His last sotrovimab infusion had taken place on the 10th of February. Unfortunately, data on the SARS-CoV-2 variant are not available. The five other patients did not develop symptoms of an upper respiratory tract infection or had a positive antigen or RT-PCR test for SARS-CoV-2 during follow-up.

Discussion

To our knowledge, no case reports on the use of monoclonal neutralizing antibodies for pre-exposure prophylaxis of SARS-CoV-2 infection in MS patients have been published yet. As mentioned above, several German Medical Societies recommend to consider treatment with SARS-CoV-2-neutralizing antibodies for patients who have an increased risk for severe COVID-19, for example due to immunotherapy, and who do not mount adequate immune responses to vaccination (3). These criteria are fulfilled by a relevant number of MS patients, especially those receiving immunomodulatory treatment with S1PR modulators or anti-CD20 antibodies. In order to identify affected individuals, it is necessary to screen MS patients on these disease-modifying therapies for immune responses to SARS-CoV-2 vaccination. In our Center, we conduct a screening not only for humoral, but also for T-cellular responses to the SARS-CoV-2 spike protein. The underlying rationale is that T-cells are able to confer protection against SARS-CoV-2 infection as well and that some patients, especially those on B-cell-depleting therapy, develop poor antibody, but good or even enhanced T-cellular responses to SARS-CoV-2 vaccination (24–26). We considered neutralizing antibody treatment only for those patients who lacked both humoral and T-cellular responses to SARS-CoV-2 after three doses of vaccination.

Treatment with S1PR modulators itself does not seem to increase the risk for severe COVID-19 disease (27–29). However, the lacking immune response to active SARS-CoV-2 vaccination caused by the S1PR modulator treatment does constitute a risk factor, and most of our patients who were treated with SARS-CoV-2-neutralizing antibodies had additional risk factors for severe COVID-19 beyond the lacking vaccination response. Patient 6, however, was 44 years old and did not have relevant comorbidities. Further, she had a low EDSS of 1.5 corresponding to no relevant neurological disability. She did have an increased risk of contracting SARS-CoV-2 because of the limited feasibility to reduce social contacts due to her three school-age children. According to the summary of product characteristics of casirivimab/imdevimab and tixagevimab/cilgavimab, their prophylactic use is not limited to defined groups of patients with certain risk factors so that treatment of patient 6 with these antibodies was possible within the marketing authorization. The patient felt much more secure on neutralizing antibody treatment which had a noticeable effect on her quality of life. On the other hand, it should be noted that several patients in our MS Center had similar constellations encompassing immunomodulatory treatment, a lack of vaccination responses, and no additional risk factors for severe COVID-19, and they were not treated with SARS-CoV-2-neutralizing antibodies. Treatment decisions need

TABLE 3 Pre-exposure prophylactic treatment schedules for the different SARS-CoV-2-neutralizing monoclonal antibodies in our patients, status of marketing authorization for pre-exposure prophylactic treatment in the EU, and neutralizing capacity against the SARS-CoV-2 Omicron strain.

SARS-CoV-2-neutralizing antibodies	Casirivimab/Imdevimab	Sotrovimab	Tixagevimab/Cilgavimab
Route of application	Single intravenous infusion or subcutaneous injection	Intravenous infusion	Two separate intramuscular injections
Dose	First treatment 600 mg/600 mg Repeat treatment 300 mg/300 mg	500 mg	150 mg/150 mg
Treatment interval	Every four weeks	Every eight weeks	Every six months
Approved for pre-exposure prophylaxis in EU	+	–	+
Neutralizing capacity against SARS-CoV-2 Omicron strain	None or insufficient	Fully or largely retained	Retained, but reduced

+, approved for pre-exposure prophylaxis in EU; -, not approved for pre-exposure prophylaxis in EU.

to be adapted to each patient's situation, in consideration of the individual risk profile for severe COVID-19 and the degree of exposure. Generally, MS patients lacking an immune response to active vaccination, but without any risk factors for severe COVID-19 or increased exposure, likely do not need pre-exposure prophylactic antibody treatment. This especially applies when the Omicron variant is the predominant circulating strain as it usually only causes mild disease.

For casirivimab/imdevimab, published data from clinical studies show that its application is efficacious and safe not only for the treatment of COVID-19 disease, but also for the prophylaxis of SARS-CoV-2 infection (5–9). An *in vitro* study showed potent neutralizing activity for the antibody cocktail against Delta virus-like particles making it a suitable treatment as long as the SARS-CoV-2 Delta variant was the predominant viral strain (11). However, no neutralizing capacity of casirivimab/imdevimab against Omicron virus-like particles was detected (11). Another *in vitro* study demonstrated that the Omicron spike protein is completely resistant to imdevimab and mostly resistant to casirivimab (10). Thus, casirivimab/imdevimab became an unsuitable treatment when the incidence of infections with the Omicron variant was rising. For sotrovimab, by contrast, two *in vitro* studies demonstrated sustained neutralizing capacity against the SARS-CoV-2 Omicron variant (10, 15). In another analysis, the neutralizing capacity against an infectious SARS-CoV-2 Omicron isolate was only marginally reduced for sotrovimab's parent antibody S309 (16). S309 had originally been derived from memory B cells of a convalescent individual infected with SARS-CoV in 2003. It binds a proteoglycan epitope on the viral spike protein distinct from the receptor-binding motif. The targeted epitope is highly conserved among sarbecoviruses explaining the antibody's ability to neutralize not only SARS-CoV, but also SARS-CoV-2 including its known variants (30). Therefore, we decided to switch our patients' pre-exposure prophylactic treatment to sotrovimab when the SARS-CoV-2 Omicron strain became prevalent. Because sotrovimab had not been granted marketing authorization by the European Commission for prophylactic use due to limited data on its efficacy in this context, the infusions remained an off-label treatment. Nonetheless, we assessed the treatment switch as the more sensible decision in the face of absent neutralizing activity of casirivimab/imdevimab against the SARS-CoV-2 Omicron strain. Tixagevimab/cilgavimab was the first monoclonal antibody combination with retained neutralizing activity against the Omicron variant approved for pre-exposure prophylaxis in the European Union. Treatment was hence switched in our patients as soon as this in-label treatment option was available. However, neutralizing capacity against the Omicron strain was shown to be reduced for tixagevimab/cilgavimab *in vitro* and also for sera obtained from immunocompromised patients after treatment with the antibody cocktail (19–23). It was suggested that higher treatment doses might be necessary in order to reach a greater degree of neutralization in the serum of treated patients. More data are needed in order to optimize treatment doses and to evaluate clinical efficacy.

Clearly, an intrinsic immune response to active immunization is favorable over continuous passive immunization. However, all patients reported here were not able to mount an immune response to vaccination with BNT162b2, mRNA-1273, and/or AZD1222. In the meantime, the European Commission has granted conditional marketing authorization for the protein-based adjuvanted vaccine Nuvaxovid (Novavax CZ). We recommend our S1PR modulator-treated patients lacking immune responses to SARS-CoV-2 mRNA and/or vector vaccination to get vaccinated with Nuvaxovid, now that it is available in Germany. Possibly, this vaccine will be more effective in eliciting an immune response in the respective patients due to the included immune adjuvant. If so, it will be possible to discontinue neutralizing antibody treatment.

In this case series, we present six MS patients who received pre-exposure prophylactic treatment with SARS-CoV-2-neutralizing antibodies due to their inability to mount an immune response to active SARS-CoV-2 vaccination on account of their immunomodulatory treatment. In times of a predominance of the SARS-CoV-2 Delta variant, casirivimab/imdevimab was a suitable treatment option which is authorized for prophylactic use. In times of higher incidences of the Omicron variant, we considered treatment with sotrovimab to be more suitable, but this antibody had to be administered off-label as no sufficient data on its prophylactic use are available yet. Tixagevimab/cilgavimab is the first monoclonal antibody combination approved for pre-exposure prophylaxis in the European Union with sustained neutralizing activity against the Omicron strain. In our opinion, it thus seems to be the best treatment option in patients who need pre-exposure prophylactic SARS-CoV-2-neutralizing antibody treatment in times of high incidences of infections with the Omicron variant. One patient in our case series had a positive RT-PCR for SARS-CoV-2 under sotrovimab treatment, but was asymptomatic. For the other patients, no symptoms typical of COVID-19 and no evidence of SARS-CoV-2 infection were recorded during the follow-up of 139 to 168 days under neutralizing antibody treatment. Importantly, we did not observe any significant adverse events. Neutralizing antibody treatment remains a treatment option that needs evaluation for and discussion with each individual patient according to their risk profile and individual preference. Of course, deductions on the efficacy and safety of SARS-CoV-2-neutralizing antibody treatment cannot be made from this case series. Hopefully, immunization with adjuvanted protein vaccines will be able to elicit adequate immune responses also in S1PR modulator-treated MS patients rendering neutralizing antibody treatment for pre-exposure prophylaxis of SARS-CoV-2 infection unnecessary.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Ethikkommission an der Technischen Universität Dresden. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Conception and design: CW, KA, and TZ. Writing the manuscript: CW. Creation of figure and tables: CW. Critical feedback and clinical management: UK. Revision for important intellectual content: KA and TZ. All authors approved the final version to be published.

Conflict of interest

CW received travel support from Novartis. KA received personal compensation from Roche, Sanofi, Teva, Merck, Alexion, BMS, and Celgene for oral presentations and consulting services. TZ received personal compensation from Biogen, BMS, Bayer, Merck, Novartis, Roche, Sanofi, Teva, and Viatris for consulting and speaking services. TZ received additional financial support for research activities from Biogen, Novartis, Roche, Teva, and Sanofi. TZ is principal investigator of the AMA-VAC and KYRIOS study.

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

Publisher's note

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Case report and literature analysis: Autoimmune cerebellar ataxia associated with homer-3 antibodies

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Objective: We present a case of autoimmune cerebellar ataxia (ACA) associated with Homer protein homolog 3 (Homer-3) antibodies. Then, a review of the literature was conducted to summarize its clinical spectrum to improve clinicians' understanding of this rare entity.

Case presentation: A 25-year-old man suffered from the subacute onset of cerebellar ataxia and psychiatric symptoms with abnormalities in the cerebellum on initial brain MRI and Homer-3 antibodies titers of 1:100 in the serum. His neurological symptoms did not improve after intravenous methylprednisolone but significantly improved following plasma exchange with a modified Rankin Scale (mRS) score of 1. However, 5 months later, he experienced relapse during oral prednisone tapering with enhanced cerebellar lesions and obvious cerebellar atrophy on repeated MRI. Various immunomodulatory approaches, including corticosteroids and plasma exchange, were utilized with no improvement. Then rituximab was given for the first time to treat Homer-3 autoimmunity with partial improvement of symptoms. However, the patient remained profoundly disabled with an mRS score of 4.

Conclusion: ACA associated with Homer-3 antibodies may have a suboptimal response to corticosteroid therapy. More intense immunotherapy such as rituximab may contribute to the improvement of cerebellar syndrome. Relapsing courses and presentation of cerebellar atrophy may suggest a poor prognosis in this entity.

KEYWORDS

autoimmune cerebellar ataxia, Homer-3 antibody, brain MRI enhanced abnormalities, relapse, rituximab

Introduction

Autoimmune cerebellar ataxia (ACA) associated with Homer protein homolog 3 (Homer-3) antibodies is a rare disease. To the best of our knowledge, only 11 cases have been reported in the literature (1–6). The whole clinical spectrum and potential treatment options remain obscure. Here, we present a well-characterized case of

Homer-3 autoimmunity, a 25-year-old man who experienced clinical relapse with enhanced abnormalities in the cerebellum on brain magnetic resonance imaging (MRI) that has not been reported in previous studies, and in whom rituximab was initiated for the first time with partial improvement of symptoms. Then, we reviewed and analyzed all ACA cases associated with Homer-3 antibodies, summarizing the clinical presentations, diagnostic considerations, imaging findings, treatment, and prognosis of this disease. Our purpose was to aid in the clinical understanding of this rare entity.

Case presentation

A 25-year-old man was admitted because of the subacute onset of vertigo, nausea, and vomiting for 2 weeks with slurred speech and unsteady gait for 1 week. He denied symptoms of previous infectious diseases. His past medical and family history was unremarkable. In the clinic, the patient was alert but unable to walk without help. Neurological examination demonstrated dysarthria, bilateral horizontal nystagmus, moderate limb dysmetria, and gait ataxia with a scale for the assessment and rating of ataxia (SARA) score of 20. The modified Rankin Scale (mRS) score on admission was 4. Initial brain MRI was performed and showed hyperintensities in the vermis and bilateral cerebellar hemispheres on fluid-attenuated inversion recovery (FLAIR) without enhancement (Figures 1A–F). Cerebrospinal fluid (CSF) study revealed an elevated opening pressure of 200 mmH_2O, mild pleocytosis (white blood cell count 50/ul, 88% lymphocytes; reference range: 0–8/ul), elevated protein level (0.63 g/L; reference range: 0.1–0.45 g/L) and increased CSF IgG index (74.7 mg/L; reference

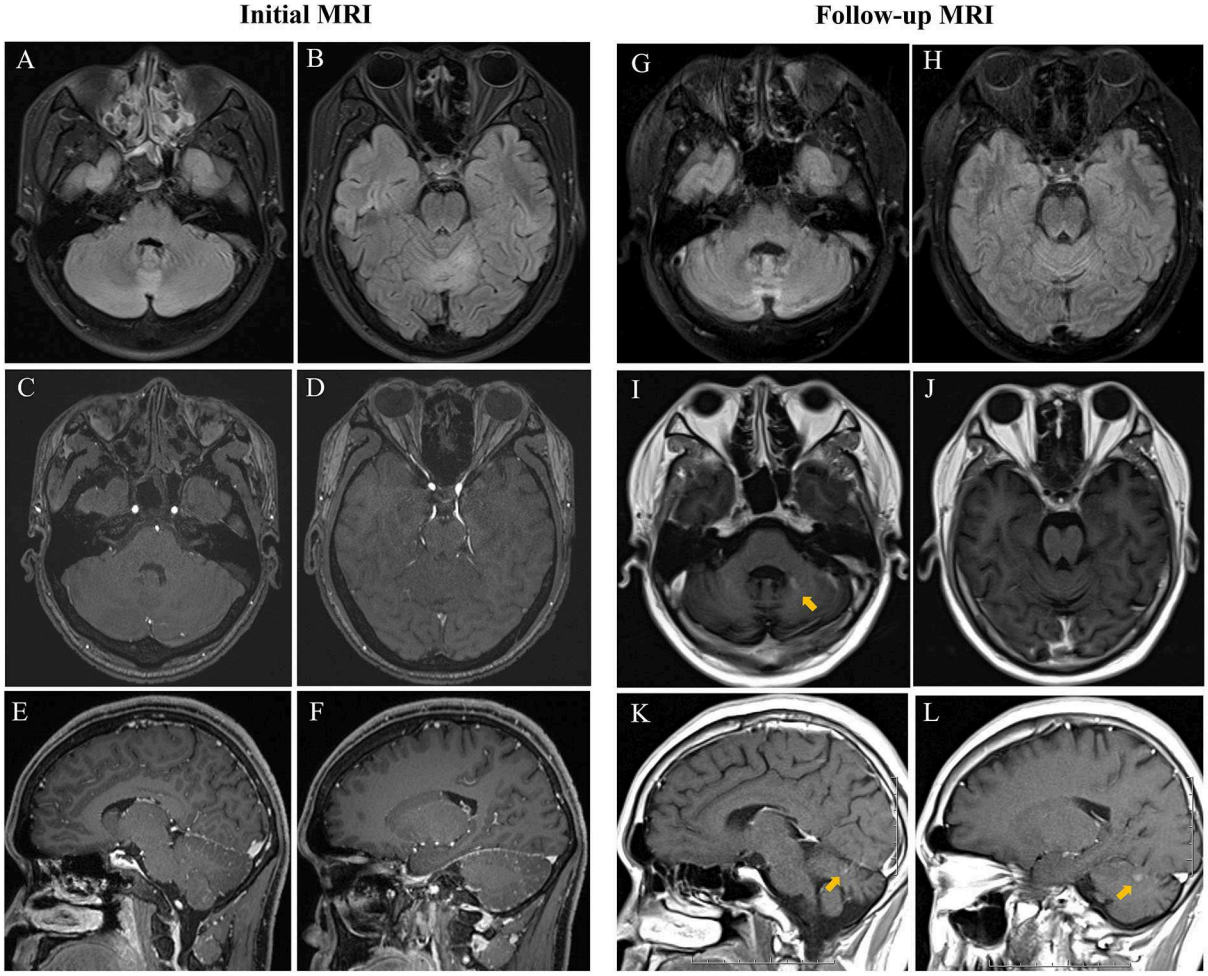

FIGURE 1
Initial cerebral MRI showed increased signal in the vermis and both bilateral cerebellar hemispheres on FLAIR **(A,B)** without enhancement on contrast-enhanced T1-weighted sequence **(C–F)**. Repeated MRI showed an increase of FLAIR hyperintensity of cerebellar lesions **(G)** and progression in size of the vermis lesions **(H)** with slightly enhanced T1-weighted signals on both axial and sagittal view and obvious cerebellar atrophy **(I–L)**.

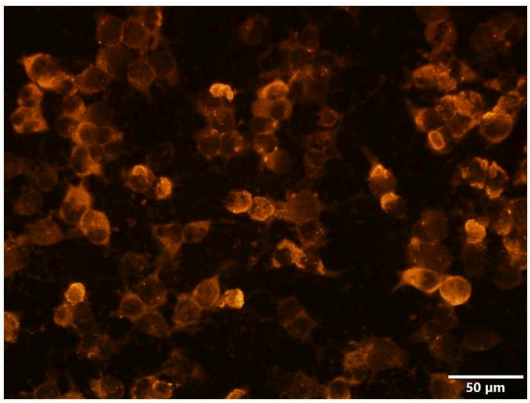

FIGURE 2
The Homer-3 antibody of serum was positive: the red marker represented Homer-3 antibodies (CBA, indirect immunofluorescence) (×400). The scale bar was 50 μm.

range: 10–40 mg/L). Oligoclonal bands (OCB) were negative. Peripheral blood cell counts, electrolytes, liver and kidney functions, and levels of lactate, ammonia, and vitamins B1 and B12 were all normal. Screening for viral and bacterial infections, tumors, and thyroid diseases was negative. The further laboratory workup of autoantibodies was notable for positive serum Homer-3 antibodies with a titer of 1:100, whereas the CSF sample was negative by using the indirect immunofluorescence technique (IIFT) employing transfected HEK293 cells (Figure 2). Serum and CSF paraneoplastic antibodies (anti-Hu, Yo, Ri, Ma1/2, CV2, Tr, SOX1, Zic4, and amphiphysin), autoimmune encephalitis antibodies (anti-NMDAR, AMPAR, LGI1, $GABA_B$, GAD65, CASPR2, IgLON5, DPPX, GlyR1, DRD2, and mGluR5) and serological markers specific for collagen diseases (antinuclear, anti-DNA, anti-Sm, anti-RNP, anti-SSA, anti-SSB, antineutrophil cytoplasmic antibodies) were either negative or in the normal range. Diagnosis of autoimmune cerebellar ataxia was made, and he was given intravenous methylprednisolone 1,000 mg for 3 days, followed by 500 mg for 3 days, and taped to oral prednisone 70 mg per day. However, no clinical improvement but a dysarthria deterioration was observed. His slurred speech could hardly be understood then with a score of 22 on SARA and a score of 4 on mRS. Moreover, he further developed psychiatric symptoms including difficulties with emotional control and impaired communication. Given these reasons, three circles of plasma exchanges (2,000 ml each time) were carried out at intervals of 2 to 3 days with significant improvement of psychiatric symptoms and slurred speech. And the patient could gradually walk alone. He was discharged with oral prednisone on a chronic basis and followed up at a local hospital. A score of 14.5 on SARA and a score of 1 on mRS were registered then.

However, 5 months later, the patient was admitted to our hospital again as he had severe head intention tremors and weakness in lower limbs for a month while he was currently on a daily dose of 30 mg of prednisone. He also complained of deterioration of slurred speech and gait instability. On neurological examination, he could barely stand with a SARA score of 28 and an mRS score of 4. CSF analysis revealed an increased protein level of 0.96 g/L. Repeated screening for neoplasia has been negative. Remarkably, repeated cerebral MRI indicated obvious cerebellar atrophy and worsened cerebellar lesions with gadolinium enhancement (Figures 1G–L). He received high-dose intravenous corticosteroids and cycles of plasma exchange with no response. Thus, an intravenous infusion of rituximab was subsequently administered. Progressive clinical improvement was noticed with near resolution of head intention tremor and weakness of lower limbs 6 weeks after rituximab. However, the gait instability was unchanged. After 5 months of follow-up, the patient was stable but remained profoundly disabled with an mRS score of 4 and a SARA score of 18 as he still required help when walking. The case report timeline is presented in Figure 3.

Discussion

ACA is an important cause of acquired cerebellar ataxia both in children and adults (7). Recent studies have identified several relevant antibodies serving as biomarkers of ACA, which were comprised of paraneoplastic antibodies such as anti-Hu, anti-Yo, Anti-Ri, amphiphysin, and other antibodies, and non-paraneoplastic antibodies including GAD65, AP3B2, neurochondrin, septin-5 and Homer-3 antibodies (2, 8–11). Homer-3 is expressed at a high level on Purkinje cell dendrites spines. It is the scaffold protein interacting with metabotropic glutamate receptor 1 (mGluR1) and intracellular calcium channel (ITPR1), thereby controlling the ability of the mGLuR1 receptor to trigger calcium responses (12). As a protein involved in calcium-related glutamate signaling pathways, Homer-3 has been recently identified as a new antigenic target of the immune response against Purkinje cells and causes cerebellar ataxia (1, 9). However, the direct effects of Homer-3 antibodies on cultured neurons have not yet been examined. Whether Homer-3 antibodies are directly attributed to the immunopathogenesis of Homer-3-associated autoimmunity or their pathogenicity is mediated by T lymphocytes is unclear so far (8).

Clinical presentations

A total of twelve cases, including ours, have been described in this study (Table 1) (1–6). Patients' age ranged from 10 to 84 years (mean ± SD: 43.92 ± 23.01), seven (58.33%) were women. Then, two patients had a history of prodromal infection. The onset was subacute/acute in nine and insidious in

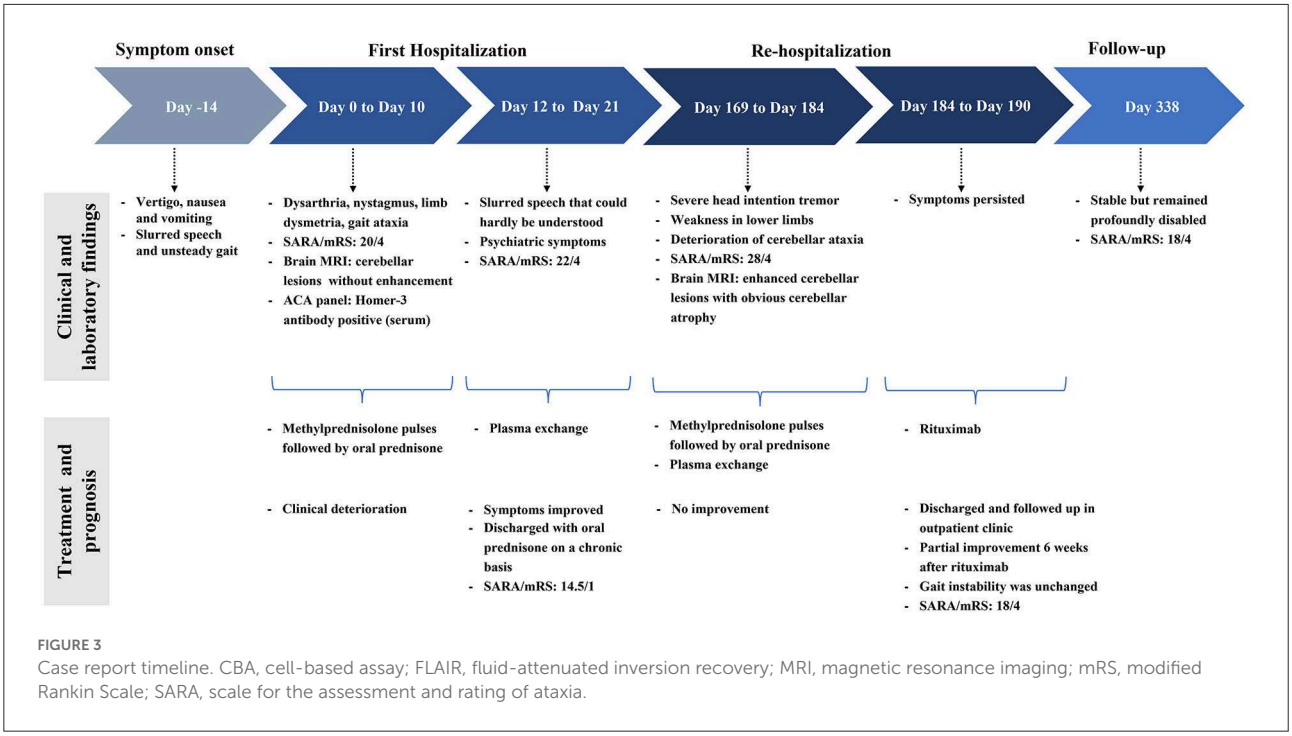

FIGURE 3
Case report timeline. CBA, cell-based assay; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; SARA, scale for the assessment and rating of ataxia.

three patients. Cerebellar symptoms were noted in all patients, including vertigo, nausea, vomiting, nystagmus, head intention tremor, speech dysarthria, limb dysmetria, and gait ataxia. A total of five patients exhibited symptoms of encephalopathy including psychosis ($n = 3$), seizures ($n = 2$), confusion ($n = 1$) and cognitive impairment ($n = 2$). Other extracerebellar features included myeloradiculopathy ($n = 2$), REM sleep behavior disorder (RBD) ($n = 2$) and autonomic dysfunction ($n = 2$). Except for one patient with pulmonary nodules of potential malignancy, extensive studies failed to reveal any tumor in these patients.

Diagnostic investigations

The detailed CSF data were available for all 12 patients with inflammatory changes: lymphocytic pleocytosis was noted in seven patients (cell counts 21–139/ul), elevated protein was noted in four patients (0.61–1.67 g/l), and intrathecal IgG synthesis was elevated in six patients. Besides, Homer-3 antibodies were detected in CSF of three patients (the CSF antibody panel was not performed in case 2, case 3, and case 4) and in serum of 11 patients, which indicated that serum and CSF testing is mandatory when ACA is considered. Ideally, both cell-based and tissue-based assays should be used to test for Homer-3 antibodies. However, we did not conduct a tissue-based assay, which was a limitation of this report.

Initial brain MRI was performed in all patients with variable manifestations, which were normal ($n = 4$), and showed bilateral cerebral/cerebellar abnormalities ($n = 5$) or cerebellar atrophy ($n = 3$). Repeated MRI was obtained in 10 patients on follow-up at 1.5–98 months. The cerebral/cerebellar lesions were reported to shrink after treatment in three patients. Nevertheless, the follow-up MRI in our patient showed enhanced cerebellar lesions which have not been reported in previous studies, indicating evidence of cerebellar inflammation. Moreover, it is important to note that in more than half of the patients (6 out of 10), the repeated MRI disclosed cerebellar or pontine atrophy after comprehensive immunotherapy, which is probably the result of the secondary degeneration of cerebellar circuits after cerebellar inflammation (4, 13, 14).

Treatment and prognosis

There are no standards for the treatment of Homer-3 autoimmunity. First-line immunotherapies in the acute phase including corticosteroids, intravenous immunoglobulins (IVIg), and plasma exchange may be beneficial (1–6). Besides, long-term immunosuppression such as oral prednisone and mycophenolate mofetil (MMF) was administered in some patients for the possibility of long-term clinical benefit, which was reported to halt and minimize cerebellar ataxia in Homer-3 autoimmunity (2–5). However, the response to immunotherapy was equivocal. In our patient, treatment with methylprednisolone did not improve the symptoms in the acute phase and maintenance therapy of oral prednisone did not prevent the occurrence of clinical relapse and cerebellar atrophy. In this situation, intravenous rituximab was given for the first time to treat Homer-3 autoimmunity, and partial

TABLE 1 Review all reported ACA cases with Homer-3 antibodies.

Case	Age/Gender	Onsetc	Neurological symptoms	Tumor	Initial/Follow-up MRI (months from onset)	Detection of Homer-3 antibodies	CSF WBC (/ul)/protein(g/l)/ intrathecal IgG synthesis	Treatment	Outcome/mRS (months from onset)
Case 1	25/M	Subacute	Cerebellar syndrome and psychiatric symptoms	No	FLAIR hyperintensities in cerebellar hemispheres and vermis/worsened cerebellar lesions with enhancement and obvious cerebellar atrophy (5)	Serum	50/0.63/increased IgG index	CS, PLEX, rituximab	Partially improved but relapsed/4(11)
Zuliani et al. (1)									
Case 2	65/F	Subacute	Cerebellar syndrome	No	Normal/NA	Serum*	27/NA/increased IgG index	CS	No improvement/NA(68)
Höftberger et al. (2)									
Case 3	38/M	Acute	Cerebellar syndrome and complex partial seizures	No	Normal/mild cerebellar atrophy (10)	Serum*	60/1.11/no	IVIg, CS	Partially improved/2(24)
Xu et al. (3)									
Case 4	51/F	Insidious	Cerebellar syndrome	No	Cerebellar atrophy/cerebellar atrophy (48)	Serum*	0/0.41/OCB positive	CS, MMF	Partially improved/3(12)
Liu et al. (4)									
Case 5	46/F	Insidious	Cerebellar syndrome	No	Cerebellar atrophy /worsened cerebellar atrophy (98)	Serum and CSF	0/0.41/OCB positive	CS, MMF	Partially improved/5(98)
Case 6	50/F	Subacute	Cerebellar syndrome and RBD	No	Normal/Cerebellar and pontine atrophy (16)	Serum	2/0.3/no	CS, MMF	Partially improved/2(31)
Case 7	14/M	Subacute	Cerebellar syndrome, cognitive impairment and myeloradiculopathy	No	Diffuse T2 hyperintensity in bilateral cerebral hemispheres /decrease of T2 hyperintensity (8)	Serum	21/0.61/OCB positive	IVIg, CS	Partially improved but relapsed twice/3(40)
Case 8	65/M	Insidious	Cerebellar syndrome and RBD	No	Cerebellar and pontine atrophy/worsened cerebellar and pontine atrophy (24)	Serum	30/1.136/NA	IVIg, CS, PLEX	Deteriorated/4(64)
Case 9	84/F	Subacute	Cerebellar syndrome	Potential malignant pulmonary nodules	Normal/normal (9)	Serum	6/0.48/NA	CS	No improvement/2(23)

(Continued)

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TABLE 1 Continued

Case	Age/Gender	Onsetc	Neurological symptoms	Tumor	Initial/Follow-up MRI (months from onset)	Detection of Homer-3 antibodies	CSF WBC (/ul)/protein(g/l)/ intrathecal IgG synthesis	Treatment	Outcome/mRS (months from onset)
Case 10	59/F	Subacute	Cerebellar syndrome, psychosis, seizure, confusion and radiculoneuropathy	No	FLAIR hyperintensity in bilateral cerebral cortex/normal (10)	Serum	2/0.17/no	IVIg, CS	Improvement followed by relapse/4(11)
Miao et al. (5)									
Case 11	20/F	Subacute	Cerebellar syndrome	No	T2 hyperintensities in the right cerebellar hemisphere/normal (1.5)	Serum and CSF	139/1.67/OCB positive	IVIg, CS, MMF	Obviously improved/3(2)
Kuang et al. (6)									
Case 12	10/M	Subacute	Cerebellar syndrome, cognitive impairment and irritability	NA	T2 and FLAIR hyperintensities in cerebellar hemispheres and vermis/NA	CSF	30/0.3/NA	IVIg, CS	Obviously improved/1(NA)

* The antibody panel was not performed in CSF.
ACA, autoimmune cerebellar ataxia; CS, corticosteroid; FLAIR, fluid attenuated inversion recovery; IVIg, IV immunoglobulin; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NA, not available; OCB, oligoclonal bands; PLEX, plasma exchange; WBC, white blood cell.

improvement was observed. This may indicate that more intense immunotherapy such as rituximab could be a second choice when the first-line treatment did not work out.

The overall outcome of this disease was poor. Only 4 patients were reported to achieve a good functional outcome (mRS $\leq$2) and almost all the patients ended up with neurological sequelae. This is partially explained by cerebellar atrophy, a possible complication of ACA associated with Homer-3 antibodies (1–6, 14). Moreover, it is important to highlight that three patients including our patient experienced clinical relapse during corticosteroid tapering or weaning or after they stopped IVIg infusion (4). The fact that these patients remained profoundly disabled may imply that relapsing courses can lead to a poor prognosis.

Conclusion

In patients with Homer-3 autoimmunity, extensive studies failed to reveal any tumor, MRI findings were variable, CSF always presented with inflammatory changes, Homer-3 antibodies were detected in serum or CSF and the response to immunotherapy treatment was equivocal. Intravenous rituximab may partially improve cerebellar symptoms, especially in relapsing cases. The neurologic prognosis depends on multiple factors. Relapsing courses and presentation of cerebellar atrophy may suggest that recovery will be incomplete.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QW made substantial contributions to study concept and design, interpretation of clinical data, drafting of the manuscript, and fund obtaining. BG made contributions to the acquisition, analysis, and interpretation of imaging data. AJ conducted the literature review and drafted the manuscript. QW and XQ were

involved in revising the manuscript critically and have given final approval for the version to be published. All authors read and approved the manuscript.

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Conflict of interest

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

Publisher's note

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Case report: Revealing a special and rare autoimmune GFAP astrocytopathy in the spinal cord succeeding Neurobrucellosis infection

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Brucellosis, a zoonosis, can cause an inflammatory response in most organs and continues to be a public health problem in some endemic areas, whereas neurobrucellosis is a morbid form of brucellosis that affects the central nervous system (CNS) with poor prognosis. Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is an autoimmune disease, and there have been no reports of a *Brucella* infection, leading to GFAP astrocytopathy. We report the case of a patient with a positive and high level of GFAP antibodies in the cerebrospinal fluid (CSF), following a *Brucella* infection. Although this patient did not show any responsible lesions in the diffusion sequence of the magnetic resonant imaging (MRI) scan, we found an evidence of thoracolumbar (T12) involvement on fluorodeoxyglucose (FDG) positron emission tomography (PET). The symptoms of spinal cord involvement were only partly relieved after initial treatment [doxycycline (0.1 g Bid) and rifampicin (0.6 g Qd) for 6 weeks]; however, they markedly improved after the subsequent immunosuppressive therapy [intravenous methylprednisolone (1,000 mg for 3 days)], followed by a 50% reduction from the preceding dose after 3 days, and subsequently, oral prednisone tablets (60 mg/day) was started, which was then gradually tapered [reduced to 10 mg/day every 1–2 weeks)]. The positive response to immunosuppressive therapy and treatment outcome strongly indicated the presence of an autoimmune neurological disease probably triggered by some infectious factors. Therefore, our findings reveal that a *Brucella* infection is one of the causes of autoimmune GFAP astrocytopathy, and when this infection is difficult to be identified by regular MRI, FDG PET can be used as a supplementary method for diagnosis and treatment.

KEYWORDS

case report, glial fibrillary acidic protein, GFAP astrocytopathy, neurobrucellosis, FDG PET

Introduction

Brucellosis is a zoonotic disease widely distributed around the world, which mainly infects the body from the skin, mucous membranes (of the respiratory tract, eye conjunctiva, and sexual organs), and digestive tract. It is an infection-led inflammatory disease, and the inflammatory response can be identified in most organs presenting clinical manifestations after infections such as endocarditis, arthritis, meningitis, joint lymphocytes, mononuclear cell infiltration, orchitis, nephritis, and liver granuloma (1). Like other manifestations of brucellosis, neurobrucellosis, a special form of brucellosis affecting the nervous system, also presents with signs and symptoms of inflammation. It primarily affects the central nervous system (CNS) and has a poor prognosis (2). Neurobrucellosis can manifest as meningitis, encephalitis, meningoencephalitis, meningeal vascular disease, brain abscess, demyelinating syndrome, and myelitis. Both encephalitis and myelitis are caused by bacteria that are present in the brain tissue and spinal cord. Moreover, reactive microgliosis and astrogliosis are involved in inflammatory responses. A *Brucella* infection and replication in the microglia, astrocytes, and brain endothelial cells lead to chronic infection in some patients, whereas the atypical clinical manifestations of neurobrucellosis can lead to misdiagnoses (3–5).

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is an inflammatory disease of the CNS. A specific immunoglobulin G (IgG) in the CSF that reacts with the intermediate filament protein GFAP in the cytoplasm of astrocytes is used as a biomarker. Clinical manifestations of the disease include fever, headache, encephalopathy, involuntary movements, myelitis, and abnormal vision (6, 7). The lesions often involve the subcortical white matter, basal ganglia, hypothalamus, brainstem, cerebellum, and spinal cord. A typical MRI feature is radial gadolinium enhancement perpendicular to the ventricles around the vessels of the brain in the white matter (8). Autoimmune GFAP astrocytopathy usually responds well to corticosteroids, although, in rare cases, long-term immunosuppression is required to alleviate the relapse course (6). Currently, there are no unified diagnostic criteria or consensus for autoimmune GFAP astrocytopathy, and it remains unclear how antibodies against GFAP are produced and whether they are involved in disease progression. Infectious pathogens may contribute to one of the major causes of GFAP astrocytopathy as triggering factors, although the underlying mechanisms still need to be clarified.

Here, we report the case of a patient who was infected with *Brucella* and tested positive for the GFAP antibody in the CSF. The symptoms of myelitis appeared throughout the disease phase, and initial antibacterial and successive immunosuppressive therapy relieved the symptoms in steps. Concurrently, concerns related to the diagnosis and treatment are discussed in detail, and potential relationships between the two diseases are explored.

Case representation

A 42-year-old man was admitted to our hospital with a chief complaint of fever for 1 month and bilateral lower extremity numbness, weakness, and difficulty urinating for 10 days. One month prior, the patient had developed fever, chills, and headache with no obvious cause and his temperature was up to 39.4°C. Cefixime was administered for 1 week at a local clinic. However, the patient's symptoms did not improve. The patient was then transferred to another local hospital. There were no positive findings in blood, urine, or stool cultures, among others. Ten days later, he developed a numbness and weakness of both lower limbs, unsteady walking, difficulty urinating, hearing loss in the left ear, and blurred vision. At the local the Centers for Disease Control, the serum agglutination test was positive for brucellosis at a titer of 1:100 (++), and the Rose Bengal Plate Test (RBPT) was positive (+). With the diagnosis of brucellosis, he was prescribed doxycycline (0.1 g Bid) and rifampicin (0.6 g Qd). His fever symptom was gradually relieved, but the weakness and numbness of the lower extremities and difficulty in urinating did not improve. The patient was admitted to our hospital for further treatment. This patient had a history of hypertension, coronary heart disease, and urticaria in the past. There was no previous history of infection or vaccination before the disease onset. His personal and family histories were unremarkable.

The examination revealed significant findings for both lower limbs with grade 4+ muscle power. Thermal and pain sensations diminished below the thoracic T11 level with an obvious tightness. The cremasteric reflex was not elicited. Romberg's sign was positive. The lymph node color Doppler ultrasound showed multiple lymphadenectasis in the bilateral axilla, groin, and right epididymis. The electromyogram and MRI of the head and spinal cord yielded normal results. In CSF, the white blood cell count was slightly increased, and lymphocytes and plasma cells were visible and were mainly observed. These findings suggested an inflammatory reaction. High titers of GFAP IgG antibodies (1:32) were detected in the CSF but not in the serum (Figures 1A–F). Tests for other autoantibodies in the CSF and serum, including AQP4-IgG, MBP-IgG, and MOG-IgG, were negative. Positive MRI evidence was absent, although symptoms and physical examination suggested spinal cord involvement. FDG PET was performed to identify possible lesions in the spinal cord and other parts of the nervous system. The abnormal concentration of FDG was mainly found in the thoracolumbar segment of the spinal cord, and the hypermetabolism region was located near the thoracic T12 level. The maximum standard

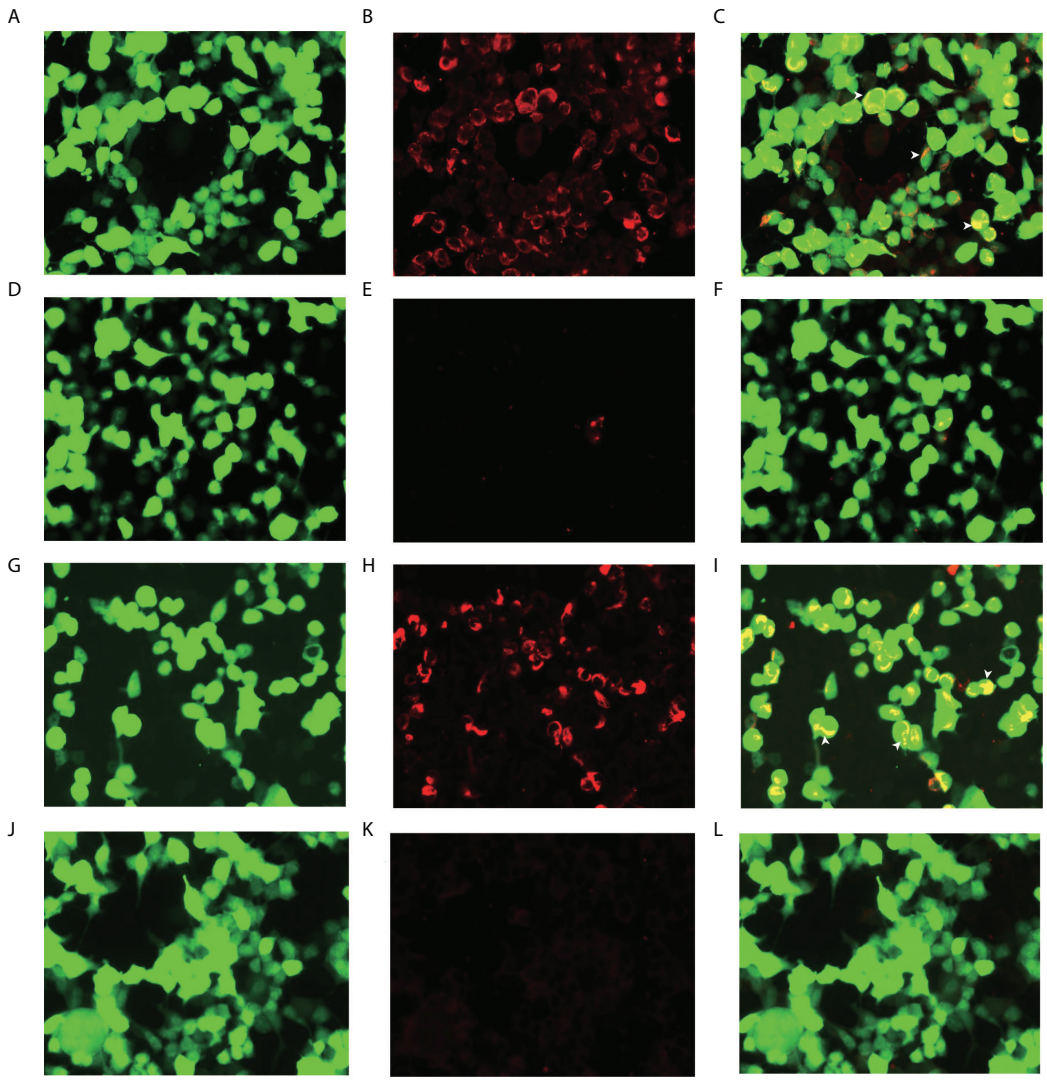

FIGURE 1
Glial fibrillary acidic protein (GFAP-IgG) by GFAP-transfected cell-based immunofluorescence assay. Cells were expressing green fluorescent protein-tagged GFAP (green) and immunostained (red if positive). **(A, B, C)** Examination of cerebrospinal fluid (CSF) in first admission. **(D, E, F)** Examination of serum in first admission. **(G, H, I)** Examination of CSF in second admission. **(J, K, L)** Examination of serum in second admission. **(C, F, I, L)** Merged images revealed the colocalization of the GFAP antibody and astrocyte (white arrows) (scale bar=50 μm).

uptake value (SUV_{max}) was 6.321, which was significantly higher than that in the normal area of the spinal cord (Figures 2A, B). FDG accumulation also occurred at other sites, such as the bilateral cervical lymph nodes, bilateral axillary lymph nodes, thoracoabdominal pelvic lymph nodes, and epididymis (Figures 2C–G).

Infective myelitis caused by neurobrucellosis is predominant in the initial stages of the disease, with coexisting autoimmune GFAP astrocytopathy. It is not reasonable to administer high-dose steroid pulse treatment in the case of the brucellosis infection spreading to multiple systems in the body. Therefore, plasma exchange and intravenous immunoglobulin combined with low-dose steroid therapy (prednisone tablets 30 mg Qd) were administered. Meanwhile, a first-line anti-infection regimen [doxycycline (0.1 g Bid) and rifampicin (0.6 g Qd)] and ceftriaxone (2 g Qd) were also added. The patient's numbness and weakness in the lower extremities did not worsen. Moreover, after plasma exchange, his symptoms stabilized, with a very slight trend toward alleviation. The patient was maintained on doxycycline, rifampicin, and prednisone after discharge from the hospital. However, the numbness and weakness of both lower extremities and waist tightness persisted. Difficulty in urinating occasionally occurs. The patient was readmitted to the hospital 1 month after

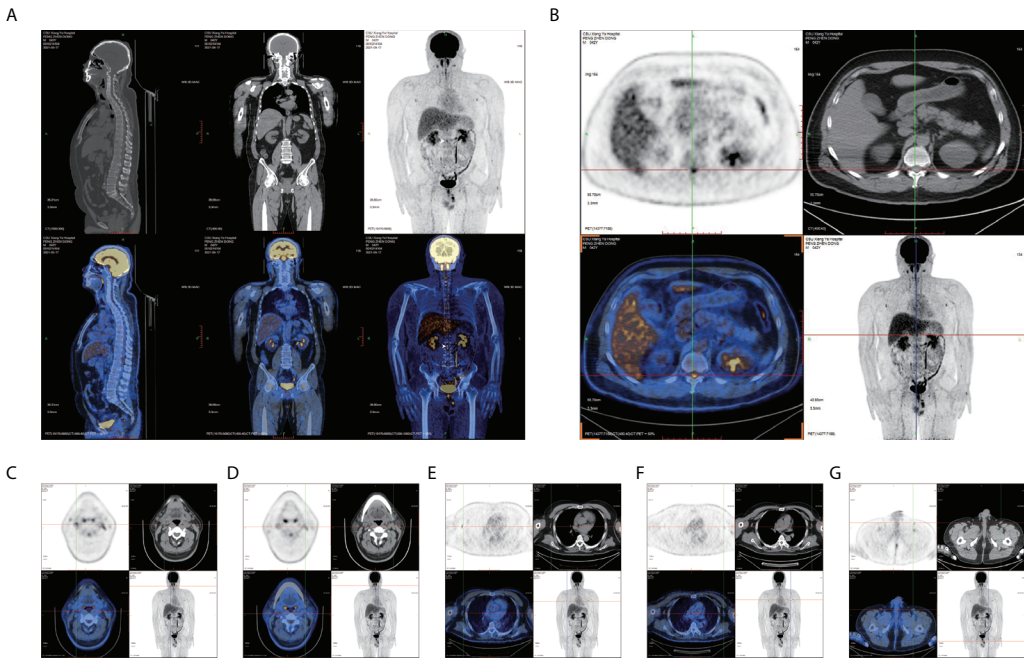

FIGURE 2
FDG PET images. **(A)** Sagittal and coronal PET/CT show a high concentration in the thoracolumbar segment (white arrow). **(B)** Axial PET/CT shows an extremely abnormal hypermetabolism of FDG near the T12 thoracolumbar segment (maximum standardized uptake value: 6.321). Axial PET/CT in **(C, D)** bilateral cervical lymph nodes, **(E, F)** bilateral axillary lymph nodes, and **(G)** epididymis.

discharge for further treatment. At readmission, all the brucellosis-related laboratory tests were negative. Spinal MRI findings were unremarkable. Higher titers of GFAP IgG antibodies (1:32) were detected in the CSF (Figures 1G–L). An elevated protein level of 89 mg/L (normal range: 10.0–30.0 mg/L) and oligoclonal bands (OCBs) (more than two bands) were detected in the CSF but not in the serum. In the second stage of the disease, autoimmune GFAP astrocytopathy occupied the predominant position and was responsible for the maintenance of symptoms and signs of the spinal cord, since the initial neurobrucellosis disappeared after first-line treatment with anti-infection therapy. Therefore, the patient was treated with intravenous methylprednisolone (1,000 mg for 3 days), followed by a 50% reduction of the dose after 3 days, followed by oral prednisone tablets (60 mg/day), were then gradually tapered (reduced to 10 mg/day every 1–2 weeks). All symptoms improved after high-dose steroid and oral tablet therapies.

Discussion

In the present case, the patient was diagnosed with autoimmune GFAP astrocytopathy secondary to a *Brucella* infection. However, the occurrence of autoimmune disease after a *Brucella* infection is comparatively rare; therefore, the identification and diagnosis of GFAP astrocytopathy are not as easy as expected. Our patient had persistent spinal cord involvement, presenting symptoms such as the numbness and weakness of both lower extremities as well as difficulty in urination. The patient's first condition improved slightly after anti-infection therapy, but the symptoms and signs of spinal cord involvement remained unresolved. Elevated levels of GFAP antibodies in the patient's CSF were confirmed using laboratory tests. Although the MRI scan did not show corresponding lesions, FDG PET demonstrated extremely abnormal hypermetabolism, indicating an infectious condition in the spinal cord and other body parts. As a result, anti-infection therapy, plasma exchange, IVIG, and low-dose hormone therapy were administered in the first stage. It is believed that the myelitis in the early stage was mainly attributed to a *Brucella* infection while in the later stage, myelitis was predominantly caused by autoimmune GFAP astrocytopathy. After one course of high-dose hormone methylprednisolone percussion therapy in the later stage, the numbness and weakness of both lower extremities, waist tightness, and labored urination were all ameliorated, which further confirmed the later predominance of GFAP astrocytopathy. Although the symptoms of our patient and the positive response to treatment established the diagnosis, unfortunately, the patient lacked complete epidemiological

investigations and pathological examination. Six months after being discharged from the hospital, we followed up the patient by telephone and found that all the symptoms of the patient continued to improve. Moreover, the patient adhered to taking the medication regularly, and no adverse and unanticipated events occurred during the treatment.

According to previous studies, GFAP antibodies can be found in the CSF after traumatic brain injury, certain tumors, viral infections (such as Herpes Simplex Virus), multiple sclerosis, diabetes, and idiopathic intracranial hypertension (9–14). There have been no reports of elevated levels of GFAP antibodies in the CSF after bacterial infection, and how GFAP antibodies are produced remains unclear. These signs led us to wonder why the intracellular protein GFAP causes an increase in autoantibodies. How does bacterial infection contribute to GFAP astrocytopathy? First of all, in the process of bacteria entering and egressing cells, it may cause the destruction of cell membranes and the release of cytoplasmic contents. This greatly increases the chance that the cytoplasmic contents will be falsely recognized by the immune system. Secondly, the infection of astrocytes and microglia with *Brucella* induces the secretion of proinflammatory mediators such as IL-6, IL-1β, and tumor necrosis factor (TNF)-α (15). On one hand, these proinflammatory mediators can lead to astrocytes apoptosis. During this period, GFAP in astrocytes has the potential to expose self-epitopes and may change its subcellular distribution through proteolytic cleavage, phosphorylation, or dephosphorylation (15–17). On the other hand, these proinflammatory mediators can disrupt the integrity of the blood–brain barrier and attract immune cells from the peripheral circulation into the CNS (15, 18). Moreover, consistent with the paraneoplastic origin of GFAP antibodies, it is unclear whether *Brucella* has antigens similar to GFAP, which causes an immune response after infection. Although the above evidence shows the possibility of the production of GFAP antibodies after a bacterial infection, some researchers still think that this specific IgG directed at intracellular antigens lacks pathogenicity to cell targets *in vivo*, and it is believed that the GFAP antibody can only be used as a marker for activated CD8+ cytotoxic T cells, whereas the real pathogenicity may be those unknown autoantibodies raised together with GFAP antibodies (7). As the exact mechanism is still debated, further experiments are required to confirm this.

In our case, it is also worth pointing out that we did not find responsible lesions in the MRI scan, but after using FDG PET as assistance, we identified the abnormal hypermetabolism of FDG near thoracic T12 thoracolumbar segment. According to previous cases, FDG metabolism can be extremely abnormal in infectious diseases, and the FDG uptake rate is higher than its counterparts in non-infectious chronic active inflammation. The maximum standardized uptake value (SUV_{max}) of infectious diseases can be significantly increased (up to 5.0–7.0, or even higher), whereas non-infectious inflammation shows moderate increases (generally <5.0, or insignificant increase) (19–21). Therefore, the maximum standardized uptake value (SUV_{max}) of the patient's spinal cord lesion was 6.321, indicating that the spinal cord lesion was caused by a *Brucella* infection. Due to some economic factors, FDG PET was not performed again at the time of readmission. Changes in the functional metabolic phase of CNS infectious diseases generally present earlier than changes in the anatomical structure phase, and the FDG PET manifestations of tiny and occult lesions are much more evident than lesions with obvious abnormal morphological structures. FDG PET helps detect early lesions that do not form structural abnormalities on MRI or small lesions that cannot be identified by MRI. These lesions can be identified through the functional metabolic phase, and changes in the metabolic function can be reflected in time. The advantage of the functional metabolic imaging of FDG PET is that it can compensate for the deficiency of regular MRI scans, and it possesses a real application value in clinical diagnosis and treatment.

In conclusion, autoimmune GFAP astrocytopathy should be considered for patients diagnosed with neurobrucellosis, and the presence of GFAP astrocytopathy should be confirmed by the detection of GFAP antibodies in the CSF and serum. Immunosuppressive therapy should be administered at a proper time and in a proper manner. The FDG PET provides an optional auxiliary method for patients who have no obvious abnormalities on MRI scans. Prompt identification and effective treatment can reduce the incidence of critical events.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Xiangya Hospital of Central South University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in the article.

Author contributions

KH designed the study, reviewed, and revised the manuscript. QH collected and analyzed data. JL drafted the manuscript. ZZ, YT,

and LL reviewed and revised the manuscript. All the authors read and approved the final manuscript.

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Conflict of interest

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

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Eculizumab for acute relapse of neuromyelitis optica spectrum disorder: Case report

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Introduction: Eculizumab has been shown to be an effective and typically well-tolerated medication in the treatment of neuromyelitis optica spectrum disorder (NMOSD) in maintaining disease remission in patients who are aquaporin-4 water channel autoantibody (AQP4-IgG) seropositive. The efficacy of eculizumab in an acute relapse of NMOSD however is still under review.

Case: We describe a 46 year-old female who presented with acute left monocular vision loss on a background of bilateral optic neuritis treated 15 years prior as suspected NMOSD. She had very poor vision from the right eye (6/60). On presentation she was not on any long-term immunosuppressive agents. Her serum was positive for AQP4-IgG and MRI brain and spine demonstrated areas of demyelination in the corpus callosum and thoracic spine. She was treated with high dose intravenous methylprednisolone and underwent plasmapheresis for five consecutive days, but continued to clinically deteriorate with ongoing blindness in her left eye (light perception only). She was subsequently administered eculizumab with weaning oral corticosteroids. Clinically her vision improved to counting fingers and she remains on maintenance eculizumab infusions in the community. At 3 months, there is a steady improvement but still significant loss of central vision from that eye.

Conclusion: The utility of eculizumab in NMOSD may assist with treating acute episodes. This theoretically accords with the mode of action in inhibiting conversion of C5–C5a/b, perhaps arresting the acute inflammatory process in this disease. Given that disease burden and mortality in NMOSD is almost entirely related to relapses, increased use of eculizumab acutely could potentially aid recovery from an attack in very severe attacks, and therefore minimize immediate stepwise accrual of disability.

KEYWORDS

neuromyelitis optica (NMO), demyelination, humanized antibody, case report, neuroimmunology

Introduction

Eculizumab is an effective medication approved for the treatment of NMOSD in maintaining disease remission. The efficacy of eculizumab in an acute relapse of NMOSD however remains unknown. We describe a female with NMOSD presenting with acute optic neuritis who continued to deteriorate despite plasmapheresis and intravenous

methylprednisolone. She was subsequently treated with eculizumab resulting in a steady improvement in her visual acuity. The clinical utility of eculizumab in NMOSD may extend further than reducing relapse risk and may assist with treating acute episodes. To our knowledge, there is no literature on its use in this setting, only in disease prevention. Given that disease burden and mortality in NMOSD is largely secondary to acute events, increased use of eculizumab earlier in the disease course for acute relapses could potentially minimize morbidity.

Case presentation

A 46 year-old Chinese female presented to a tertiary Emergency Department with acute left monocular vision loss over the preceding 24 h, associated with painful ocular movements and a severe headache. Her background was significant for suspected NMOSD with initial presentation 15 years previously with bilateral optic neuritis treated with 5 days of pulse intravenous methylprednisolone. At the time, serum AQP4-IgG antibody tests were positive but details lacking. She had migrated overseas and described a history of events concerning for area postrema syndrome with recurrent attacks of intractable nausea and hiccups that had spontaneously resolved. She also described recurrent optic neuritis, with her last episode 18 months previously whilst overseas that was not treated acutely and resulted in permanent significant visual impairment in her right eye. Despite these recurrent events, she was not on any long-term immunosuppression.

Physical examination revealed poor visual acuity in both eyes (6/60 right eye, light perception only left eye). There was a left relative afferent pupillary defect and fundoscopy was significant for right optic nerve head pallor. The remainder of her neurological examination was unremarkable and notably there were no signs of a myelopathic syndrome.

MRI brain and whole spine with gadolinium demonstrated a hyperintense T2/FLAIR signal with restricted diffusion in the left corpus callosum, as well as a hyperintense focus at the level of T5 that was also favored to represent demyelination, neither of which had evidence of active enhancement (Figure 1). High signal with enhancement was seen in the left optic nerve with chiasmal extension and the right optic nerve appeared to have significant atrophy (Figure 1). Repeat serum AQP4-IgG was positive at a greater than screening titer of 1:10 with cell-based indirect immunofluorescence assay (Euroimmun©), and the remainder of her blood tests were unremarkable. A lumbar puncture was not performed as the patient declined.

Given the typical clinical history and presentation, positive serum AQP4-IgG and neuroradiological findings, the patient was diagnosed with a likely acute relapse of her NMOSD and commenced on pulse intravenous methylprednisolone (IVMP) 1 g once daily for 5 days (Figure 2). Differential diagnoses of her optic neuritis initially considered on presentation included MOG antibody disease, infective etiologies such as bartonella, or other inflammatory conditions such as neurosarcoidosis. These diagnoses were deemed unlikely when her serum AQP4-IgG returned positive.

On her fourth day of IVMP, no improvement in her visual acuity was evident and plasmapheresis was commenced given she was now essentially blind in both eyes with significant disability. She continued to have no improvement in her visual acuity despite two cycles of plasmapheresis and completion of 5 days of IVMP. The main diagnostic challenge at this stage was whether the patient was having a delayed response to her current therapy warranting continuation of her current treatment approach and close observation vs. escalation of therapy.

On day twelve after presentation, she was subsequently administered intravenous eculizumab 900 mg weekly for 4 weeks, then 1,200 mg a week later and fortnightly thereafter. She was also commenced on a slow weaning regimen of

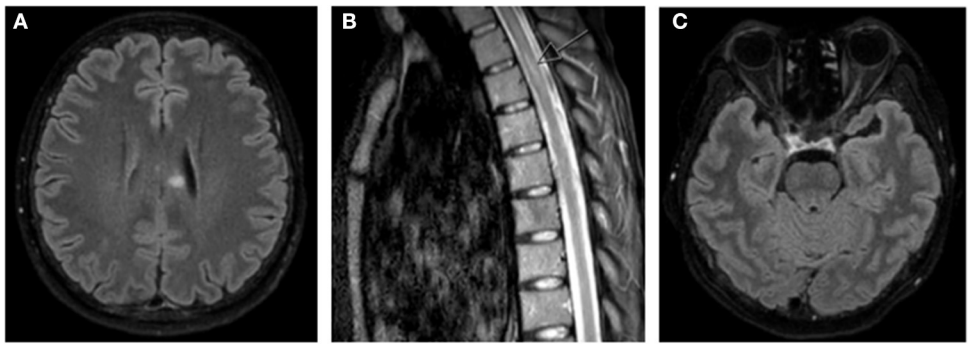

FIGURE 1
MRI brain and whole spine T2/FLAIR images demonstrating **(A)** hyperintense T2/FLAIR signal in left corpus callosum, **(B)** hyperintense foci in left side of thoracic spinal cord (arrow), and **(C)** hyperintense signal seen in left optic nerve with chiasmal extension with significant atrophy of right optic nerve.

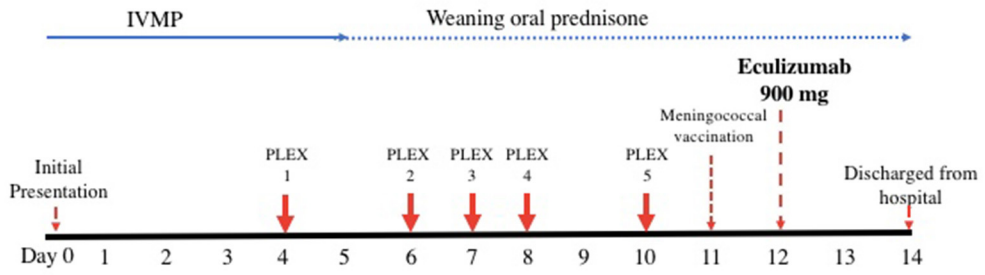

FIGURE 2
Timeline of acute therapy administered during hospital admission. IVMP, intravenous methylprednisolone; PLEX, plasmapheresis.

prednisolone, starting at 30 mg once daily, decreasing by 2.5 mg every week. On the day prior to administration of eculizumab, she was administered meningococcal vaccinations (MenACWY and MenB) in addition to streptococcal pneumoniae and haemophilus influenza vaccinations as she had not received these before. Amoxicillin 250 mg daily was commenced immediately as meningococcal chemoprophylaxis.

The patient's visual acuity promptly improved to counting fingers with her left eye 2 days after eculizumab commencement and she was able to be discharged home after her first infusion, 2 weeks following her initial presentation. At follow-up 2 and 5 months later, she remained on maintenance eculizumab without complications and there was evidence of ongoing improvement in her left eye visual acuity but still significant loss of central vision. Given the chronicity of her right eye visual impairment, no improvement was expected or found.

Discussion

NMOSD is a severe autoimmune demyelinating disorder of the central nervous system with a prevalence of 0.3–4.4 per 100,000 population (1). The characteristic features of NMOSD are recurrent episodes of optic neuritis and transverse myelitis, and such attacks typically result in significant disability if not treated promptly (2). Due to the natural progression of NMOSD being that of stepwise deterioration with recurrent attacks and accrued morbidity, long-term immunosuppressive therapy is indicated for the prevention of relapses as soon as the diagnosis is made (3). At present, the mainstay of maintenance therapy for NMOSD is with immunosuppressive therapies, with rituximab traditionally having collectively the greatest efficacy in relapse prevention (4–6). Of note however, there have been no randomized controlled trials comparing the clinical outcomes of different maintenance therapies for NMOSD to date.

Approximately 65–88 percent of patients with NMOSD have positive serum AQP4-IgG antibodies, and it is thought that these antibodies may have a direct pathological role by triggering complement-dependent cytotoxicity (7). Eculizumab is a long-acting humanized monoclonal antibody that binds to terminal complement protein C5 thereby inhibiting breakdown into C5a (which is pro-inflammatory) and C5b (which forms the membrane attack complex) (7). Eculizumab was the first monoclonal antibody to be approved for the treatment of NMOSD. The efficacy of eculizumab was demonstrated in the 2019 PREVENT randomized control trial (RCT) of 143 patients who were AQP4-IgG seropositive with NMOSD that found a significantly lower risk of relapse with eculizumab compared to placebo, with 96.4% of patients in the eculizumab arm relapse free vs. 51.9% in the control arm at 96 weeks (hazard ratio 0.06; 95% confidence interval 0.02–0.20, $p < 0.001$) (7). In comparison, in the RIN-1 RCT of 38 patients who were AQP4-IgG seropositive with NMOSD, no relapses occurred in the rituximab arm vs. seven relapses in the control (placebo) arm at 72 weeks (group difference 36.8%, $p = 0.0058$) (8). Whilst its efficacy has been recently demonstrated, cost remains a significant inhibitory factor for the healthcare system (9) and its efficacy as an acute therapy in NMOSD remains unknown.

Very few studies have compared conventional intravenous methylprednisolone monotherapy with methylprednisolone in addition to plasmapheresis. The response rate to plasmapheresis for NMOSD when high dose methylprednisolone has failed is estimated to be 50–89% (10). Given that the pathophysiology of NMOSD is largely due to a strong humoral response, plasmapheresis is typically deemed the most appropriate therapy in severe relapses (11). Risk factors for poor outcome include delayed presentation or delayed onset of treatment, likely due to these patients sustaining severe, irreversible axonal injury (12).

It is known that up to fifty percent of patients treated with plasmapheresis and/or high-dose intravenous methylprednisolone have a delayed response in improvement in function (10, 13, 14). Therefore, it is possible that the observed effects in our case study may have been at least partially attributable to delayed effect of this therapy, independent of eculizumab use. More studies are needed to explore this further. The use of eculizumab acutely theoretically accords

with the immediate mode of action in inhibiting conversion of C5–C5a/b, perhaps arresting the acute inflammatory process in this disease. Given that disease burden and mortality in NMOSD is almost entirely related to relapses, the use of eculizumab acutely could potentially aid recovery from an attack and therefore, minimize accrual of disability. However, this needs to be balanced against the present high cost of this drug, and the difficulty in deciding in the acute phase if there will be a delayed response to traditional first-line acute therapies. Consideration should be given in individual cases to the severity and potential consequence of a given attack, like in this patient, and if continuation of this expensive therapy as prophylaxis is warranted. The place of eculizumab in the treatment of acute attacks however, will require more detailed study, perhaps in a randomized controlled trial setting.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SC, JP, and KN: conceptualization and writing—review and editing. JP and KN: supervision. SC: roles/writing—original draft. All authors contributed to the article and approved the submitted version.

Conflict of interest

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Case report: A pediatric case of Bickerstaff brainstem encephalitis after COVID-19 vaccination and Mycoplasma pneumoniae infection: Looking for the culprit

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Bickerstaff brainstem encephalitis (BBE) is a rare, immune-mediated disease characterized by the acute onset of external ophthalmoplegia, ataxia, and consciousness disturbance. It has a complex multifactorial etiology, and a preceding infectious illness is seen in the majority of cases. Immune-mediated neurological syndromes following COVID-19 vaccination have been increasingly described. Here we report the case of a child developing BBE 2 weeks after COVID-19 vaccination. Despite nerve conduction studies and CSF analysis showing normal results, BBE was diagnosed on clinical ground and immunotherapy was started early with a complete recovery. Later, diagnosis was confirmed by positive anti-GQ1b IgG in serum. Even if there was a close temporal relationship between disease onset and COVID-19 vaccination, our patient also had evidence of a recent Mycoplasma pneumoniae infection that is associated with BBE. Indeed, the similarity between bacterial glycolipids and human myelin glycolipids, including gangliosides, could lead to an aberrantly immune activation against self-antigens (i.e., molecular mimicry). We considered the recent Mycoplasma pneumoniae infection a more plausible explanation of the disease onset. Our case report suggests that suspect cases of side effects related to COVID-19 vaccines need a careful evaluation in order to rule out well-known associated factors before claiming for a causal relationship.

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COVID-19 vaccination, immune-mediated diseases, Bickerstaff brainstem encephalitis, anti-GQ1b antibody, Mycoplasma pneumoniae

Introduction

Bickerstaff brainstem encephalitis (BBE) is a rare, immune-mediated disease characterized by the acute onset of external ophthalmoplegia, ataxia, and consciousness disturbance. In addition to this characteristic triad, areflexia, extremity weakness, sensory alterations, and bulbar and facial palsy are frequently reported (1, 2). Serum anti-GQ1b IgG antibodies (Abs) are detected at different frequencies in patients with BBE (3) and represent a feature common to Guillain–Barrè syndrome (GBS) and Miller Fisher syndrome (MFS) (4). Indeed, it is generally thought that BBE is not a distinct neurological entity but lies at one end of a spectrum of diseases known as the anti-GQ1b syndromes. A preceding infectious illness is seen in the majority of BBE cases (5, 6) and is considered a potential trigger of the autoimmune response. Epitopes present on Campylobacter jejuni (7) and Mycoplasma pneumoniae (8) share a marked similarity with human myelin glycolipids, including gangliosides. Therefore, Abs elicited by the aforementioned infective agents could cross-react with structurally similar gangliosides, leading to off-target immune-mediated tissue damage in susceptible individuals. Another possible trigger of autoimmunity is vaccination, which is thought to act through a strong induction of proinflammatory cytokines and T-cell response (9). The association between vaccination and immune-mediated neurological syndromes made a comeback during the Coronavirus Disease 19 (COVID-19) pandemic. Neurological complications following vaccination have been increasingly described (10). Here we report the case of a child developing BBE a few days after the second dose of COVID-19 vaccination (Pfizer-BioNTech).

Case description

A 15-year-old man was admitted to our Emergency Department for acute onset of asthenia, limb paresthesia, and gait unsteadiness followed in the next day by diplopia, dysarthria, and consciousness disturbance. Two weeks before the disease onset, he received the second dose of SARS-CoV2 vaccination. Ten days before admission, the patient had fever, coughing, and vomiting that resolved spontaneously within 3 days, and the nasopharyngeal swab test for SARS-CoV-2 was negative.

Neurological examination showed a stuporous state, dysarthria, vertical ophthalmoplegia, VI and VII left cranial nerve paresis with lateral-gaze diplopia, and limb hypotonia with normal deep tendon reflexes and no meningeal signs. The patient had no fever, and he resulted negative for SARS-CoV2 infection. Magnetic resonance imaging (MRI) of the brain and spinal cord with contrast was normal. Lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis showed normal results. CSF cultures and polymerase chain reaction (PCR) showed no evidence of infection. Oligoclonal bands resulted negative. The electroencephalogram (EEG) showed an alpha activity with poor regional differentiation consistent with an "alpha coma pattern". Nerve conduction studies, F-response, and H-reflex resulted normal while blink reflex showed an abnormal pattern suggesting brainstem dysfunction (Figure 1A). Routine laboratory examination was normal, and toxicological screening was negative. Anti-Mycoplasma pneumoniae IgM and low titer IgG (1.7 U/ml, normal value <0.9 U/ml) were detected in serum, while PCR for Mycoplasma pneumoniae resulted negative in throat specimen. Anti-SARS-CoV2 serological response was evaluated, and both anti-spike and anti-nucleocapsid Abs resulted positive, suggesting a previous unknown infection. Chest X-ray was normal. The tests performed on blood, cerebrospinal fluid, nasopharyngeal and urine samples are reported in Table 1.

Overall, these findings were consistent with BBE and the patient was treated with intravenous methylprednisolone 1,000 mg daily for 5 days plus intravenous immunoglobulins (IVIg) 2 g/kg with a rapid improvement of consciousness and gradual resolution of the ophthalmoplegia and facial palsy. Due to the persistence of gait ataxia, the patient was still unable to walk without assistance. MRI of the brain and spinal cord with contrast was repeated and showed a normal result, as well as EEG activity. Anti-ganglioside Ab testing revealed positive anti-GQ1b IgG in serum, confirming the diagnosis of BBE. The patient was transferred to the Pediatric Rehabilitation Unit. After 2 weeks, he was able to walk without assistance and the neurological examination was normal (Figure 2). Six weeks after disease onset, the blink reflex resulted normal (Figure 1B).

Discussion

Immune-mediated diseases have a complex multifactorial etiology, and many factors can contribute to their onset. Infectious agents are among the most important environmental triggers of autoimmunity, through various

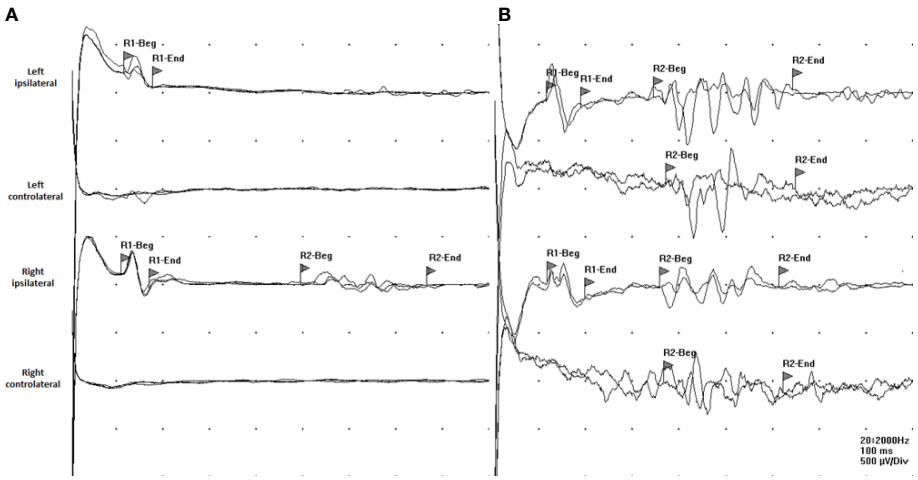

FIGURE 1
Recording from both orbicularis oculi muscles, stimulating the supraorbital nerve on each side. **(A)** Stimulating the left side results in a normal R1 response while ipsilateral and contralateral R2 components are absent. Stimulating the right side results in a normal R1 component, while the ipsilateral R2 response is delayed and the contralateral R2 component is absent. This feature is related to a bilateral alteration of the multisynaptic pathway between the nucleus of the spinal tract of V cranial nerve in the ipsilateral pons and medulla and interneurons forming connections to the ipsilateral and contralateral facial nuclei. **(B)** The blink reflex is normal.

mechanisms such as molecular mimicry, bystander activation, and polyclonal activation (11).

Two weeks before the disease onset, our patient received the second dose of SARS-CoV2 vaccination (Pfizer-BioNTech), a temporal relationship that may suggest a possible causal link. Neurological immune-related adverse events, especially GBS and its variants, have been reported after COVID-19 vaccination (10). GBS has been associated with some vaccination programs (e.g., for influenza), but the risk was shown to be very small when weighed against the benefits of immunization (12). A recent paper analyzed National Health Service (NHS) data on GBS cases and COVID-19 vaccination in England and found no increased risk in people receiving Comirnaty (Pfizer-BioNTech) (13). Furthermore, in the past, most associations between vaccines and nervous system autoimmune syndromes that have been reported as severe adverse events following immunization were no longer evidenced when well-conducted epidemiological studies were carried out (14). Notably, to improve the reliability of COVID-19 vaccination post-marketing surveillance and the causal relationship assessment of post-immunization adverse events, it is of outmost importance to exclude commonly associated causes and triggers of immune-mediated neurological syndromes (15). Mycoplasma pneumoniae is a major cause of respiratory tract infections in children and has been associated with BBE (16, 17). The similarity between bacterial glycolipids and host myelin glycolipids, including gangliosides, could lead to an

TABLE 1 Test performed on blood, cerebrospinal fluid, nasopharyngeal, and urine samples.

Sample	Test
Blood	Cell count, routine chemical exam, culture IgM and IgG: CMV, EBV, HSV, HHV-6, MV, Mumps virus, Rubella virus, SARS-CoV2, VZV, Mycoplasma pneumoniae, Chlamydia pneumoniae AE panel: Anti-NMDAr Ab, Anti-AMPAr Ab, Anti-CASPR2 Ab, Anti-LGI1 Ab, Anti-GABAr Ab, Anti-DPPX Ab, onconeural Abs
Cerebrospinal fluid	Cell count, protein, glucose, lactate, oligoclonal bands, cytological examination Culture, PCR for bacterial (Streptococcus pneumoniae and agalactiae, Neisseria meningitidis, Listeria monocytogenes, Haemophilus influenzae, Escherichia coli) and virus infection (CMV, EBV, Enterovirus, HSV, Rubella virus, VZV) AE panel: Anti-NMDAr Ab, Anti-AMPAr Ab, Anti-CASPR2 Ab, Anti-LGI1 Ab, Anti-GABAr Ab, Anti-DPPX Ab, onconeural Abs
Nasal and pharyngeal swab	PCR for virus (SARS-CoV2) and bacterial infection (Mycoplasma pneumoniae, Chlamydia pneumoniae)
Urine	Cell count, protein, glucose, blood cell count, leukocyte esterase, nitrites, culture Toxicological screening

Ab, antibody; AE, autoimmune encephalitis; AMPAr, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein-2; CMV, Cytomegalovirus; DPPX, dipeptidyl-peptidase-like protein 6; EBV, Epstein–Barr virus; GABA, gamma aminobutyric acid receptor; HHV, human herpesvirus; HSV, herpes simplex virus; Ig, immunoglobulin; LGI1, leucine-rich glioma inactivated 1; MV, measles virus; NMDAr, N-methyl-d-aspartate receptor; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

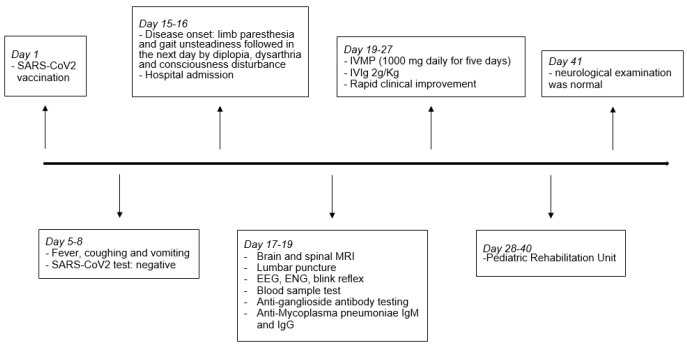

FIGURE 2
Timeline with selected events. EEG, electroencephalogram; ENG, electroneurography; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MRI, magnetic resonance imaging.

aberrantly immune activation against self-antigens (i.e., molecular mimicry) (8, 11). Our patient presented 10 days after a respiratory illness and had laboratory evidence of recent Mycoplasma pneumoniae infection, both supporting its role as a trigger of BBE. In conclusion, in the case reported here, even if there was a close temporal relationship between BBE onset and SARS-CoV2 vaccination, the aforementioned findings—providing a more plausible explanation—make a causal correlation unlikely.

Importantly, in our case nerve conduction studies and CSF analysis showed normal results, as already reported in the early stages of the disease. These findings should not delay treatment if the diagnosis is highly suspected on clinical grounds (18), given that the early use of immunotherapy is associated with a better outcome (2).

In conclusion, this case highlights the importance of prompt recognition and diagnosis of such rare disease to ensure effective management and treatment. Even if this is a single case report, we suggest that suspect cases of COVID-19 vaccine-related side effects should firstly be carefully analyzed to rule out well-known associated factors before claiming for a causal relationship. Overall, vaccination should still be advocated considering the markedly increased risk of complications—including postinfectious autoimmune disorders—after SARS-CoV2 infection.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

GM, FU, MF, RM, LP, GS and GB acquired the clinical data. SP performed neurophysiological studies. GM and MV drafted the manuscript. GM, MV, PP and FV critically revised the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

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The "hot cross bun sign" in patients with autoimmune cerebellar ataxia: A case report and literature review

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Objectives: The "hot cross bun sign" (HCBs) on magnetic resonance imaging (MRI) has been initially considered specific for multiple system atrophy with cerebellar features. However, a number of other conditions have since been described, which may be associated with this imaging sign. We herein describe a patient with anti-Ri and paraneoplastic cerebellar ataxia, and review the association of the HCBs on imaging with various neurological autoimmune conditions.

Methods: We report a 40-year-old woman with anti-Ri-associated paraneoplastic neurological syndrome and breast carcinoma, in whom brain MRI revealed the HCBs late in the disease course. We also reviewed similar cases reported in the literature.

Results: The patient presented with cerebellar ataxia, polyneuropathy, and pyramidal signs. Although brain MRI was initially unremarkable, the HCBs and T2-weighted hyperintensity of the bilateral middle cerebellar peduncles were observed at later follow-up. Anti-Ri was detected in the serum and cerebrospinal fluid. Breast adenocarcinoma was confirmed *via* an axillary lymph node biopsy. Her symptoms partially resolved after the first corticosteroid pulse. However, subsequent immunotherapy and tumor treatments were ineffective. Four autoimmune cerebellar ataxia cases with the HCBs (two paraneoplastic and two non-paraneoplastic) were identified in the literature.

Discussion: The HCBs can be associated with paraneoplastic and non-paraneoplastic cerebellar ataxia, which may reflect neurodegeneration secondary to autoimmune injury. Thus, the HCBs should not be considered a contraindication for autoimmune cerebellar syndrome.

KEYWORDS

hot cross bun sign, anti-Ri antibody, paraneoplastic neurological syndrome (PNS), autoimmune cerebellar ataxia, case report

Introduction

The "hot cross bun sign" (HCBs) refers to a characteristic cruciform pontine T2-weighted hyperintensity evident on brain magnetic resonance imaging (MRI) and is suggestive of multiple system atrophy with cerebellar features (MSA-C). MSA-C is a neurodegenerative alpha-synucleinopathy and a common cause of adult-onset sporadic cerebellar ataxia (1). The diagnostic specificity of the HCBs and middle cerebellar peduncular hyperintensity on MRI for MSA-C is as high as 98.5% (2). However, the HCBs has also been reported in patients with neurological autoimmunity. To help improve the differential diagnosis spectrum of the HCBs, here, we present a patient with anti-Ri-related paraneoplastic neurological syndrome (PNS) and breast cancer who showed the HCBs. We also provide a review of patients with the HCBs associated with autoimmune etiologies.

Case presentation

A 40-year-old woman presented with paresthesia and weakness in all four limbs for 2 years and an unstable gait for 1 year. Electromyography conducted 7 months after the disease onset showed neurogenic change, while brain MRI performed was unremarkable. Ganglioside antibodies in the serum and cerebrospinal fluid (CSF) were both negative. Empirical corticosteroids significantly improved her symptoms. However, the numbness and quadriplegia reappeared during corticosteroid weaning 4 months later, and she gradually developed dizziness, an unsteady gait, and diplopia. Brain MRI performed at 16 months after the disease onset revealed T2 hyperintensity in the middle of the pons (Figure 1). There was no improvement with pulse glucocorticoid therapy and intravenous immunoglobulin, and she developed slurred speech and dysphagia.

Physical examination revealed dysarthria, paresis of left eye adduction, diplopia, and nystagmus. The lower extremities exhibited weakness, hyporeflexia, and Babinski's signs. The finger-to-nose and knee-heel-shin tests revealed slowness and intentional tremors. She could not walk independently and was wheelchair-bound. Her sensation was intact. The Scale for the Assessment and Rating of Ataxia score was 33.5, and the modified Rankin Scale score was 4.

Complete blood count, biochemical tests, and screening for infection, toxins, and metabolic and systemic autoimmune diseases were unremarkable. There was an increased CSF white blood cell count (22 cells/μL) and positive oligoclonal bands. PNS autoantibody assays (for the Hu/Yo/Ri/Ma2/Ta/CV2/Tr/Zic4/SOX1/amphiphysin antibodies) revealed anti-Ri in the serum and CSF. Electromyography demonstrated sensory polyneuropathy. Spinal MRI was unremarkable. Hypermetabolism and enlargement of the left axillary lymph nodes were apparent on positron emission tomography-computed tomography. Biopsies revealed breast adenocarcinoma metastases [CK7 (+), ER (++), PR (−), HER-2 (+)]. No hypermetabolism in positron emission tomography-computed tomography was observed in the mammary glands, and pathological investigation after left mammectomy revealed no malignancy. 18F-fluorodeoxyglucose uptake of the cerebellum was decreased.

The patient was diagnosed with PNS with breast carcinoma. Endocrine therapy with goserelin and letrozole and plasma exchange were performed. However, her neurological symptoms worsened. Follow-up brain MRI revealed the HCBs, with signal change in the bilateral middle cerebellar peduncles and widened cerebellar sulci (Figure 1). Her symptom was stabilized by a repeated course of corticosteroid and mycophenolate mofetil treatment, after which CSF pleocytosis improved (white blood cell count, 2 cells/ul). However, CSF oligoclonal bands and anti-Ri in the serum and CSF remained positive. Her modified Rankin Scale score evaluated 34 months after the disease onset was 4. The clinical course of the patient is summarized in Figure 2.

Discussion

Herein, we report a patient with paraneoplastic cerebellar ataxia and polyneuropathy in whom brain MRI showed the HCBs and bilateral middle cerebellar peduncle hyperintensities, imitating MSA-C. To our knowledge, this is the first report of the HCBs in a patient with PNS related to anti-Ri antibodies.

As the targets of anti-Ri are intracellular RNA-binding proteins encoded by Nova-1 and Nova-2 genes, direct pathogenicity of anti-Ri antibodies is unlikely, and T lymphocyte-mediated neuronal damage is considered the main pathogenic mechanism (3). In pathological studies, lymphocytic infiltration was detected in the cerebellum, brainstem, and neocortex, with prominent Purkinje cell loss (4). Most patients with anti-Ri antibodies have unremarkable brain MRI findings, although some abnormalities have been reported, including signal changes in the brainstem, the medial temporal and insular lobes, and reversible lesions in the pontine tegmentum (3, 5). This seems in line with the multifocal neurological abnormalities involving cerebellar ataxia, opsoclonus-myoclonus syndrome, jaw dystonia, and Parkinsonism (3, 6, 7). As for the present case, peripheral neuropathy was frequently reported, although Ri is exclusively expressed in the central nervous system (3).

Historically, the HCBs was considered a marker of MSA-C (8). However, its diagnostic specificity is now being questioned

Abbreviations: CSF, cerebrospinal fluid; HCBs, hot cross bun sign; MRI, magnetic resonance imaging; MSA-C, multiple system atrophy with cerebellar features; PNS, paraneoplastic neurological syndrome.

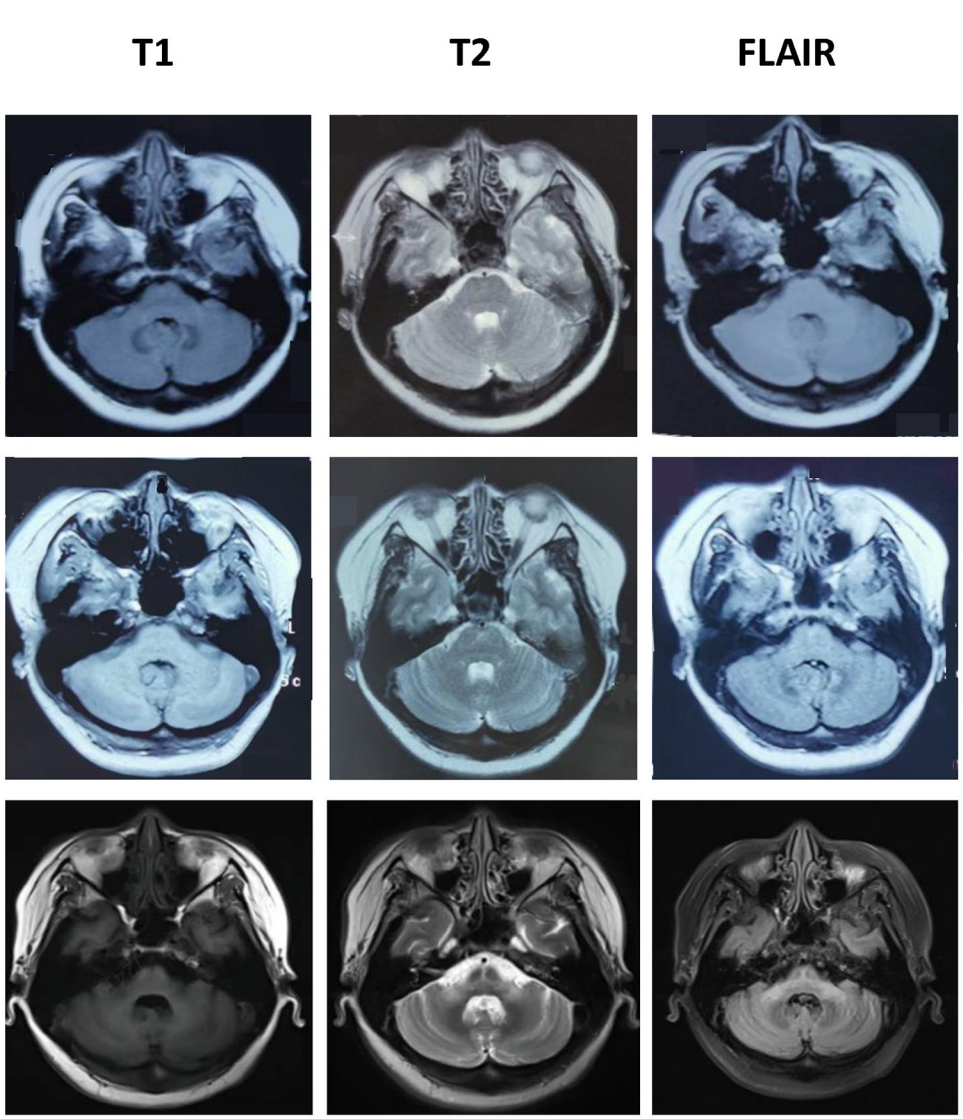

FIGURE 1
Brain MRI of our patient showing progressive atrophy of the cerebellum and the middle cerebellar peduncle. The hot cross bun sign and the abnormal signal in the middle cerebellar peduncles became more pronounced over time.

because of its identification in a range of other diseases. The pathogenic conditions underlying the HCBs include infectious (e.g., progressive multifocal leukoencephalopathy, Creutzfeldt-Jakob disease) (9–11), hereditary (e.g., spinocerebellar ataxia type 1, spinocerebellar ataxia type 3, cerebrotendinous xanthomatosis, oculodentodigital dysplasia, fragile X tremor ataxia syndrome) (12–16) or inflammatory (17) disorders. The HCBs secondary to leptomeningeal metastasis and infarction was also reported (18–20). The sign is thought to reflect Wallerian degeneration of the transverse pontocerebellar fibers and neuronal loss in the pontine raphe, with preservation of the pontine tegmentum, superior ventral cerebellar peduncles, and the bilateral corticospinal tracts (19, 21, 22). Gliosis of the reticular formation in the middle of the pontine and the pontocerebellar fiber also contributes to the HCBs (23).

In our systematic review, we searched the PubMed and EMBASE databases using "hot cross bun sign" OR "cruciform" OR "cruciate" and "autoimmune" OR "encephalitis" OR "rhombencephalitis" OR "paraneoplastic" as keywords. We excluded patients with central nervous system inflammatory demyelinating diseases because of their distinct pathogenicity. Four autoimmune cerebellar ataxia patients with the HCBs

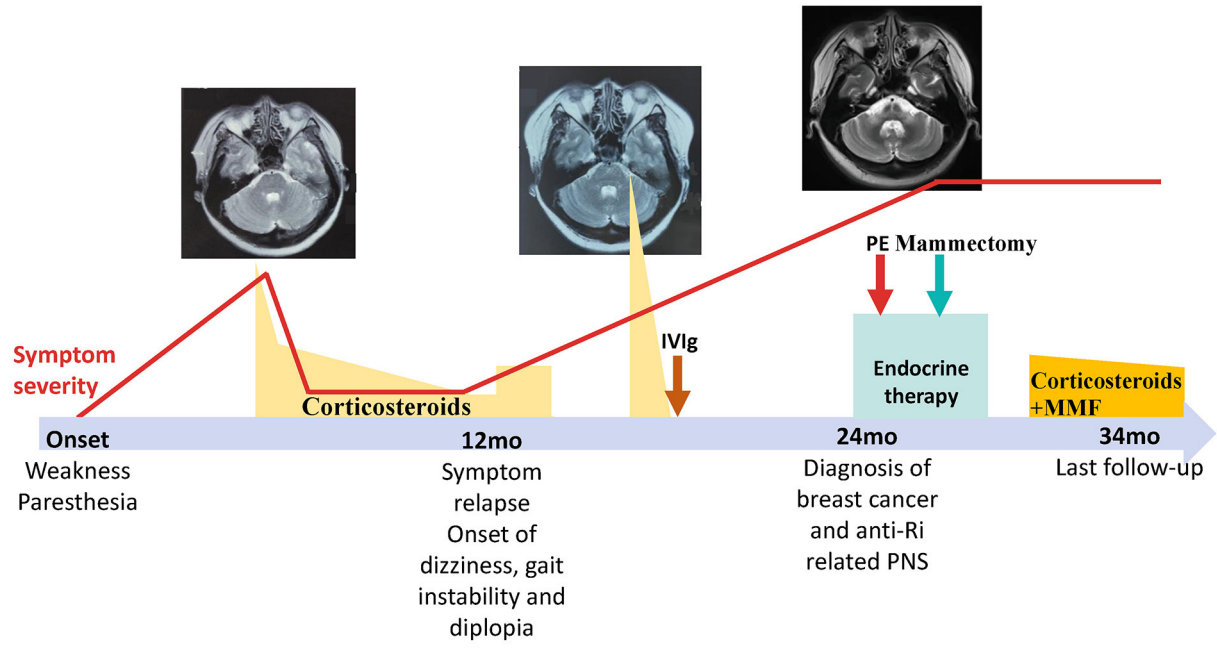

FIGURE 2
The timeline of the present case.

were identified in the literature (Table 1). Two of the patients were paraneoplastic, and two were non-paraneoplastic with anti-Homer 3 antibodies (24–26). All four patients presented with cerebellar ataxia, with or without other neurological abnormalities, including diplopia, pyramidal sign, rapid eye movement sleep behavior disorder, and sensorineural hearing loss. Notably, the HCBs usually appeared later in the disease course, with or without middle cerebellar peduncle lesions, while brain MRI at presentation was typically unremarkable or showed cerebellar atrophy. The patients generally had a poor outcome despite a wide range of immunological and oncological treatments.

In patients with PNS, the HCBs was first reported in a patient with kelch-like protein 11 (KLHL11) antibody (25). Interestingly, that patient and the present patient both presented with occult malignancies and lymph node metastases. Thus, a propensity toward lymphatic metastasis may facilitate the presentation of tumor autoantigens to the immune system, triggering cross reaction with the nervous tissue. The strong immune response may also promote regression of the primary tumor (27).

The patients with Homer 3 antibodies could show rapid eye movement sleep behavior disorder and cerebellar ataxia, in addition to the HCBs. Thus, it can be difficult to differentiate this disorder from degenerative MSA-C, particularly when the onset is insidious or an inflammatory CSF profile is absent (24, 28). Antineuronal autoantibody testing is important for identifying such potentially treatable etiologies.

The HCBs usually appears late in the disease course, and patients generally experience poor outcomes despite immunological and oncological treatments. In our patient, immunotherapy and tumor treatment failed to improve the cerebellar syndrome. Nevertheless, stabilization of the ataxia and alleviation of CSF inflammation support an immune-mediated etiology and treatment efficacy. In these circumstances, irreversible neuronal loss secondary to autoimmune destruction of the cerebellum and related structures may have already occurred, as suggested by the prominent cerebellar atrophy and the HCBs on brain MRI. However, there is some evidence that the HCBs can be reversed after immunotherapy, such as in neuromyelitis optica spectrum disorders (1).

Conclusions

This present case provides further evidence that the HCBs is not specific for MSA-C but, rather, can also appear in paraneoplastic or non-paraneoplastic autoimmune cerebellar ataxia, including PNS with anti-Ri. When this imaging characteristic is associated with the subacute/acute disease onset, an inflammatory CSF profile, and the absence of autonomic dysfunction (which were atypical for MSA-C), clinicians should consider the potential for autoimmune and paraneoplastic etiologies, and CSF examinations, neuronal

TABLE 1 A summary of patients with autoimmune cerebellar ataxia showing the HCBs.

Patient (sex/age at onset)	Onset	Neurological syndrome	Neuronal antibody/Malignancy	MRI at presentation/ at last follow-up	CSF WBC (/μL)/protein (g/L)/OCB	Treatment (outcome)	mRS/ SARA at last follow-up (mo from onset)
1 (F/38, this study)	Subacute	Cerebellar ataxia, diplopia, pyramidal sign, polyneuropathy	Anti-Ri/Breast cancer	Unremarkable/ Cerebellar atrophy, HCBs, T2-hyperintensity in MCPs	22/0.45/+	CS (improved initially but deteriorated later), IVIg, PLEX and endocrine therapy (deteriorated)	4/33.5 (28)
2 (51/F(26))	Subacute	Cerebellar ataxia	Anti-amphiphysin/ Breast cancer	HCBs, T2-hyperintensity in MCPs/ extension of MCP lesion to the midbrain	NA	NA	NA
3 (M/42(25))	Subacute	Cerebellar ataxia, sensorineural hearing loss	Anti-KLHL-11/ Seminoma	Cerebellar atrophy/ Cerebellar and brainstem atrophy, HCBs, T2-hyperintensity in MCPs, hypointensity on SWI in the substantia nigra, red nucleus and dentate nuclei	8/0.52/+	Tumor resection and chemotherapy (stabilization), CS and IVIg (stabilization)	4/21 (96)
4 (F/50(24))	Subacute	Cerebellar ataxia, RBD	Anti-Homer 3/None	Unremarkable/ Cerebellum and pons atrophy, HCBs	2/0.3/-	CS, MMF (partial recovery)	2/12(31)
5 (M/65(24))	Insidious	Cerebellar ataxia, RBD	Anti-Homer 3/None	Cerebellum and pons atrophy/ Cerebellum, pons and cerebellum peduncle atrophy, HCBs	30/1.136/- *	IVIg, CS, PLEX (deteriorated)	4/NA (64)

CS, corticosteroid; CSF, cerebrospinal fluid; HCBs, hot cross bun sign; IVIg, intravenous immunoglobulin; KLHL-11, kelch-like protein 11; MCP, middle cerebellar peduncle; MMF, mycophenolate mofetil; mo, month; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NA, not available; OCB, oligoclonal bands; PLEX, plasma exchange; SARA, Scale for the assessment and rating of ataxia; SWI, susceptibility-weighted imaging.

* Results affected by traumatic lumbar puncture.

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autoantibody assays, and malignancy screening should be considered.

Data availability statement

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

Ethics statement

This study was approved by the Ethics Committee of Peking Union Medical College Hospital (JS-891). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ML and HR drafted the manuscript for intellectual content and collected and analyzed the data. NL and YT collected and analyzed the data and revised the manuscript for intellectual content. SF and HG revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Anti-γ-aminobutyric acid-A receptor encephalitis with refractory seizures and cognitive impairment in a young woman: A case report

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Anti-γ-aminobutyric acid-A receptor ($GABA_AR$) encephalitis is an underappreciated cause of autoimmune encephalitis and remains refractory to antiepileptic therapies unless autoimmune responses are addressed. Herein, we reported a case of anti-$GABA_AR$ encephalitis in a young woman. A 29-year-old woman was admitted because of seizures for 10 months, memory decline for 7 months, and paroxysmal limbs jerking for 5 months. At admission, the patient showed mild cognitive impairment. Cell-based assays found no antibodies associated with common autoimmune encephalitis in the cerebrospinal fluid (CSF) and no antibodies in the plasma and CSF against central nervous system demyelination-associated proteins. MRI revealed multiple cortical-subcortical abnormalities and electroencephalography demonstrated periodic epileptiform discharges during paroxysmal clonus. A second test 1 month after admission detected antibodies against $GABA_AR$ α1/β3/γ2 in the plasma and CSF, leading to a diagnosis of anti-$GABA_AR$ encephalitis. The patient received intravenous immunoglobulin, prednisone, azathioprine, and levetiracetam and recovered from limb jerks and was no longer amnesic. A second episode occurred after an apparent cold and was managed by intravenous immunoglobulin, cyclophosphamide, and methylprednisolone with subsequent prednisone and levetiracetam. The patient was able to speak and ambulate after 15 days of treatment. Her MMSE, MoCA, and MRS scores improved. Physicians should harbor a high index of suspicion of anti-$GABA_AR$ encephalitis in refractory encephalitis patients with the manifestation of seizures or psychiatric disorders. Tests for a comprehensive panel of antibodies associated with anti-$GABA_AR$ encephalitis should be carried out in suspected cases and immunotherapy should be promptly initiated upon diagnosis to prevent irreversible neurological damage.

KEYWORDS

anti-$GABA_AR$ encephalitis, seizures, case report, encephalitis, neurology

Introduction

Encephalitis with the manifestation of seizures or psychiatric disorders can result from autoimmune responses induced by antibodies against excitatory or inhibitory synaptic receptors or associated cell-surface proteins (1). The γ-aminobutyric acid-A receptor ($GABA_AR$) is a ligand-gated chloride channel that mediates fast inhibitory synaptic transmission in the central nervous system (CNS) (2, 3). Antibodies to $GABA_AR$ have been associated with lengthy and refractory seizures (4). Seizures may be refractory to antiepileptic therapies unless the autoimmune responses are addressed, and epilepsy or recurrent seizures may impact cognitive ability (5). Therefore, it is critical that anti-$GABA_AR$ encephalitis be promptly recognized and treated in order to facilitate the recovery of neurological function. Herein, we reported a case of anti-$GABA_AR$ encephalitis in a young woman with refractory seizures, multifocal cerebral abnormalities, and positive $GABA_AR$ antibodies.

Case presentation

A 29-year-old woman was admitted to the Neurology Emergency Department of our hospital on 8 July 2020 because of seizures for 10 months, memory decline for 7 months, and paroxysmal limb jerk for 5 months. The patient had two episodes of generalized tonic-clonic seizures with concurrent fever and headache in September 2019. Cerebrospinal fluid (CSF) examination revealed leukocytosis ($16/mm^3$, reference range, $0–5/mm^3$), with 91% lymphocytes, 4% neutrophils and 2% eosinophils. In December 2019, she showed slowed response, impaired memory, and bradyphrasia (slowed speech). Two months later, paroxysmal myoclonic-like jerks appeared, successively involving the head, the left, and right arms. From September 2019 to February 2020, the patient was diagnosed with suspected autoimmune encephalitis at a local hospital and was treated with 3 cycles of intravenous immunoglobulin (400 mg/kg/d for 5 days) and 2 cycles of methylprednisolone (1,000 mg/d for 5 days). Antibodies associated with autoimmune encephalitis in the CSF were negative by cell-based assays on two occasions.

During physical examination at admission, the patient complained about recent insomnia and visual hallucinations. No remarkable physical findings were noticed. She scored 25/30 on the Mini-Mental State Examination (MMSE), 23/30 on the Montreal Cognitive Assessment (MoCA), and 2 on the Modified Rankin Scale (MRS), showing that the patient had mild cognitive impairment. A laboratory study showed elevated plasma ammonia at 41 mmol/L (reference range, 9–33 mmol/L), and the patient was positive for anti-rubella virus/cytomegalovirus/herpes simplex virus IgG. CSF cytology and biochemistry were within normal limits.

Cell-based assays were performed for antibodies against specific neuronal surface targets including NMDAR, AMPAR 1/2, LGI1, CASPR2, $GABA_BR$, $GABA_AR$α1/β3, DPPX, GlyR α1, mGluR5, D2R, IgLON5, and neurexin-3α, but yielded no positive findings. No antibodies were detected in the plasma and CSF against central nervous system demyelination-associated proteins including AQP4, MOG, and GFAP. A complete mitochondrial genome high-throughput sequencing of whole blood cells revealed no pathogenic or suspected pathogenic mutations.

MRI of the brain using fluid-attenuated inversion recovery (FLAIR) revealed multiple, asynchronous, cortical-subcortical abnormalities in the frontal, temporal, parietal, occipital, and insular lobes, and mismatched cerebrovascular distribution (Figure 1). Electroencephalography (EEG) demonstrated periodic epileptiform discharges in chains lasting for 2 min in the left frontal region when right arm paroxysmal clonus occurred (Figure 2A), which was nearly synchronously attenuated by intravenous midazolam (Figure 2B) A second test was performed on August 12, 2020, for antibodies in the plasma and CSF against $GABA_AR$ α1/β3 (4) and γ2 subunits (6) using live HEK293 cells expressing α1/β3/γ2 subunit and was positive (Figure 3). The patient was diagnosed with anti-$GABA_AR$ encephalitis.

Treatment

The patient was started with intravenous immunoglobulin (400 mg/kg/d for 5 days), prednisone (1 mg/kg/d PO), azathioprine (50 mg PO bid), and levetiracetam (0.5 g PO bid). One month later, azathioprine was withdrawn due to liver toxicities. At the outpatient follow-up visit in October 2020, the patient recovered from limb jerks and was no longer amnesic. In December 2020, following an occasional cold, she developed aphasia, with a clumsy right hand and blurred vision. Multiple cortical-subcortical T2/FLAIR MRI abnormalities appeared in the bilateral frontal and temporal lobes. Plasma and CSF $GABA_AR$ antibodies were positive. The

Abbreviations: $GABA_AR$, γ-aminobutyric acid-A receptor; NMDAR, anti-N-methyl-D-aspartate receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor; LGI1, leucine-rich glioma inactivated 1; Caspr2, contactin-associated protein-like 2; $GABA_BR$, γ-aminobutyric acid-B receptor; DPPX, dipeptidyl-peptidase-like protein-6; GlyR, glycine receptor; mGluR5, metabotropic glutamate receptor 5; D2R, dopamine-2 receptor; AQP4, aquaporin-4; MOG, myelin oligodendrocyte glycoprotein; GFAP, glial fibrillary acidic protein; MRI, Magnetic Resonance Imaging; FLAIR, Fluid attenuated inversion recovery; EEG, electroencephalogram; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRS, Modified Rankin Scale; AZP, Azathioprine; AEDs, anti-epilepsy drugs; CTX, cyclophosphamide; GTCS, generalized tonic-clonic seizures; CSF, cerebrospinal fluid; IVIg, intravenous immunoglobulin; MTP, methylprednisolone.

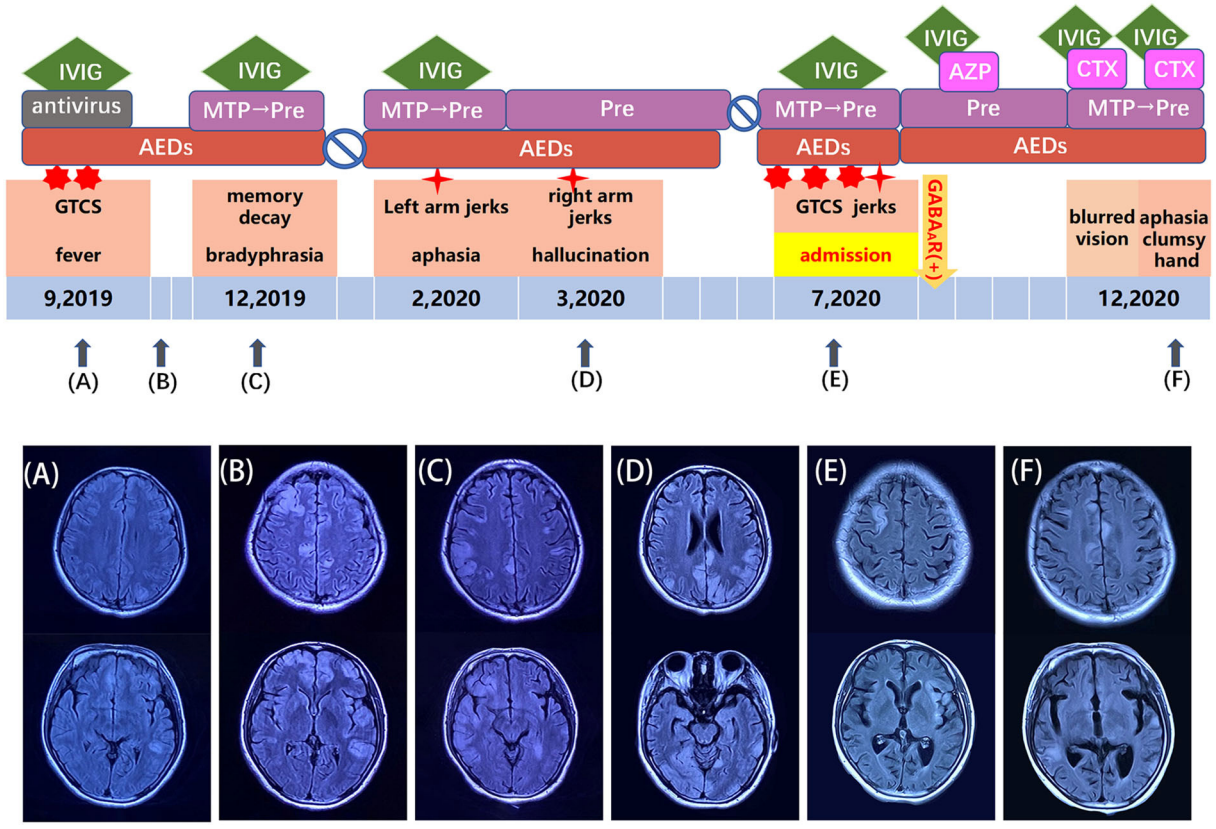

FIGURE 1
Schema for the disease course, treatments, and MRI manifestations of anti-$GABA_AR$ encephalitis in a 29-year-old woman. **(A–F)** Clinical manifestations and treatment options corresponding to each time point in the course of the disease. AEDs, anti-epilepsy drugs; AZP, azathioprine; CTX, cyclophosphamide; IVIG, intravenous immunoglobin; MTP, methylprednisolone.

patient was admitted to the hospital and treated with 2 cycles of intravenous immunoglobulin (400 mg/kg/d for 5 days), two cycles of cyclophosphamide (0.6 g twice a month), and 1 cycle of methylprednisolone (500 mg/d for 5 days) with subsequent oral prednisone (1 mg/kg/d). In addition, levetiracetam (0.5 g twice a day) was given. The patient could speak and ambulate after 15-day treatment. Her MMSE score was 27/30, her MoCA score was 27/30 and her MRS score was 1.

Discussion

Gamma-aminobutyric acid is one of the most important inhibitory neurotransmitters and plays biological roles through ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors. The $GABA_A$ receptor, which mediates fast-inhibitory neurotransmission in the brain as a pentamer in the order γ-β-α-β-α, has recently been identified as an autoantigen associated with limbic encephalitis (7). Antibodies to the α1 and β3 subunits of $GABA_AR$ with high serum and CSF titers were first reported in 6 patients with encephalitis and refractory seizures in 2014 (4) and later the β3 subunit was revealed to be the main target of plasma antibodies (8). Subsequently, the γ2 subunit was also found as a target for antibodies in autoimmune encephalitis (6). In the current case, antibodies to $GABA_AR$ were not detected on two occasions at the early stage by a specific $GABA_AR$ cell-based assay using live HEK cells expressing α1/β3 subunits. Plasma and CSF reactivities were demonstrated by HEK cells expressing α1/β3/γ2 subunits ~1 year later, allowing a final diagnosis of anti-$GABA_AR$ encephalitis. Therefore, we speculated that the omission of the γ2 subunit of $GABA_AR$ in the earlier assays may have led to missed diagnosis, suggesting that more attention should be paid to novel antibody subunit screening to avoid diagnostic delay in autoimmune diseases.

Anti-$GABA_AR$ encephalitis, which affects a very broad age range and both sexes, is characterized by severe seizures, cognitive impairment, consciousness decline, altered behavior, and movement disorders. Significantly, about 88% of the patients usually have seizures at presentation, which frequently progress to status epilepticus (9). In addition, lengthy and refractory epilepsia partialis continua are common. Children are more likely to develop generalized seizures than adults who predominantly develop focal seizures (4, 9, 10). Our case

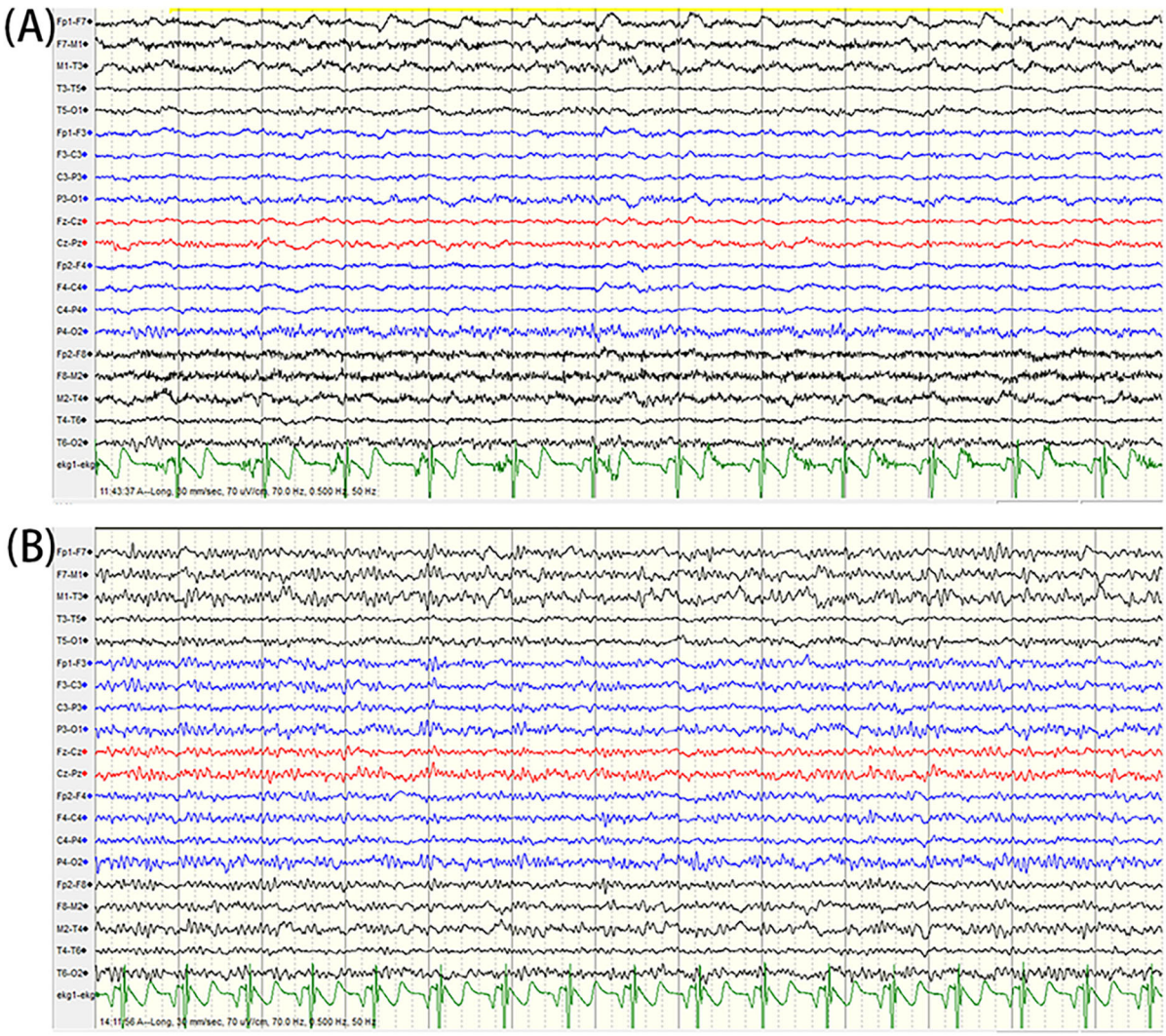

FIGURE 2
EEG manifestations at the time of right arm paroxysmal clonus occurrence **(A)** and after intravenous midazolam **(B)**.

had an acute onset and suffered from generalized tonic-clonic seizures, partial seizures, and cognitive disorder, which were aggravated after drug discontinuation or rapid reduction. This is consistent with previous studies (4, 9), indicating the possibility of autoimmune disease.

Given the extensive and age-related disease spectrum of anti-$GABA_AR$ encephalitis, we speculate that there might be pathophysiological links between subunit specificity and symptoms. For instance, receptor internalization occurs for α1-specific $GABA_AR$ antibodies (8). Direct receptor activation or complement deposition may be induced in other subunit-associated encephalitides. It appears that emotional or behavioral disturbances tend to be the main clinical manifestations in patients with α1-specific antibodies, and learning disabilities or spatial disorientation with γ2-specific ones, except for seizures (6). In the current case, the patient suffered from frequent episodes of seizures and memory decline.

Previous studies suggested that 40% of patients with anti-$GABA_AR$ encephalitis have tumors, mostly thymomas, and less commonly, other neoplasms that may impair the immune system (9). Interestingly, coexisting antibodies (LGI1 or CASPR2) were detected in patients suffering from both anti-$GABA_AR$ encephalitis and thymomas (8, 9). Type 1 diabetes mellitus and/or Hashimoto's thyroiditis were also reported in some adult patients (4).

Multifocal unilateral or bilateral cortical-subcortical T2/FLAIR MRI abnormalities occur in 80% of patients, predominantly involving temporal and frontal lobes, but also

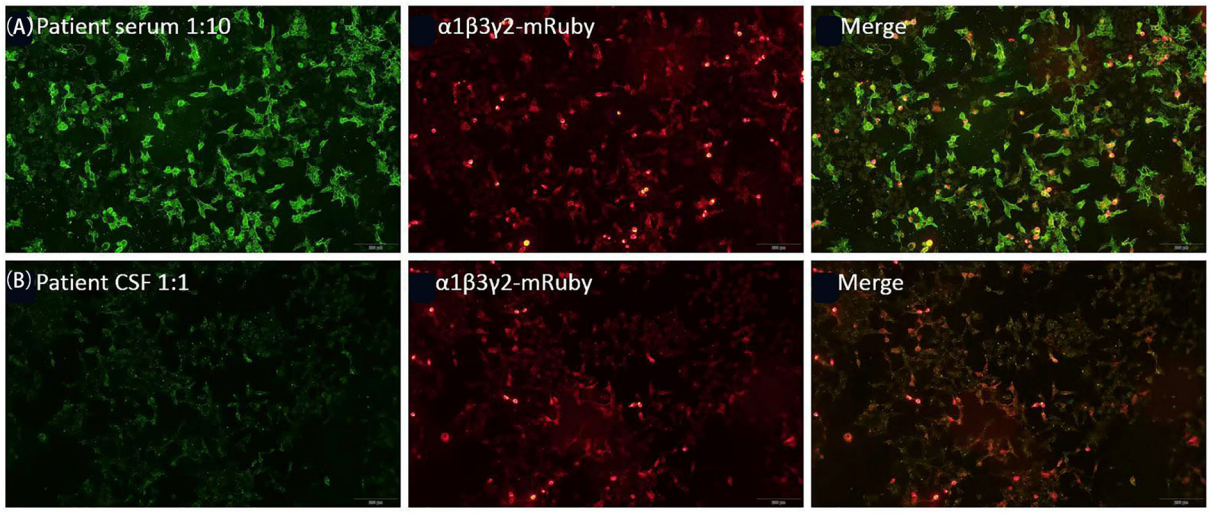

FIGURE 3
Reactivity of the patient's serum **(A)** and cerebrospinal fluid (CSF) **(B)** with live HEK293 cells expressing human α1/β3/γ2 subunits of $GABA_AR$.

basal ganglia, insular cortex, and other regions (8, 9, 11), which could asynchronously manifest during the disease (9). Interestingly, brain lesions tend to partly or completely vanish over weeks, leaving little or no residual findings after immune treatment (12).

The $GABA_AR$ antibodies cause a broad spectrum of symptoms, which seem less responsive to immunomodulatory treatment compared with other autoimmune encephalitides, and might be potentially lethal (6, 9). Therefore, prompt recognition and treatment of anti-$GABA_AR$ encephalitis are crucial to improving neurologic recovery in patients.

Moreover, anti-$GABA_AR$ encephalitis is characterized by multifocal and extensive brain MRI abnormalities. Our case showed that the immune response might have primarily contributed to cerebral damage. The distribution and severity of MRI abnormalities were inconsistent with the frequency and severity of seizures. In other autoimmune encephalitides, the MRI findings are often normal (NMDAR) (13), or predominantly involve the hippocampus (AMPAR, $GABA_BR$, LGI1) (14, 15), in which the patients also suffer from lengthy and frequent seizures.

Our case met the basic clinical, imaging, and laboratory performance of anti-$GABA_AR$ encephalitis, and achieved a satisfactory effect to immunomodulatory treatment. Notably, omission of the γ2 subunit of $GABA_AR$ resulted in a diagnostic delay, suggesting that comprehensive detection of antibody subunits should be performed at the early stage of the disease. The transient mild elevation of plasma ammonia was observed with no abnormal findings of abdominal-pelvic CT scan in the course, which was possibly attributed to diet or medication. Otherwise, there were several differential diagnoses to consider, such as mitochondrial encephalopathy lactic acidosis and stroke-like episodes, anti-MOG associated encephalitis with seizures, and so on.

Conclusion

In our case, although the patient was treated with several cycles of immunotherapy, recurrent neurological deficits occurred, and an MRI scan in December 2020 showed mild brain atrophy (Figure 1). We speculated that it might be related to rapid drug withdrawal and delayed immunosuppressive therapy before diagnosis. Therefore, suspected patients should be examined for a comprehensive panel of antibodies associated with anti-$GABA_AR$ encephalitis and immunotherapy should be promptly initiated upon diagnosis to prevent irreversible neurological damage.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by all procedures involving the human participant were in accordance with the ethical standards of Ethics Committee in Qilu Hospital of Shandong University. The

patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XY and XZ contributed to the study conception and design. All authors collected the data, performed the data analysis, contributed to the interpretation of the data, completion of figures and tables, drafting of the article, and final approval of the submitted version.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.954494/full#supplementary-material

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IgG4-related hypertrophic pachymeningitis with ANCA-positivity: A case series report and literature review

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Background: Hypertrophic pachymeningitis (HP) is a rare inflammatory disorder characterized by local or diffuse thickening of the intracranial or spinal dura mater. The most frequent cause of HP is antineutrophil cytoplasmic antibodies (ANCA), followed by IgG4. However, few cases of IgG4-HP coexpressing ANCA have been reported. Herein, we present three cases of IgG4-HP coexpressing ANCA and review the relevant literature to document the overlap of these two HP causes as a potential clinical pattern.

Methods: We retrospectively analyzed three patients with IgG4-HP coexpressing ANCA in our center and consulted the PubMed database to find other relevant cases reported in English from 1976 to April 2022. We used the following keywords: pachymeningitis, meningitis, dura, antineutrophil cytoplasmic antibody, myeloperoxidase, and proteinase-3. We analyzed the clinical, serological, radiological, and pathological characteristics of the obtained cases based on the ACR and Chapel Hill criteria and the exponential moving average (EMA) algorism for ANCA-associated vasculitis (AAV) and the IgG4-RD Comprehensive Diagnostic Criteria.

Results: We analyzed a total of 10 cases: seven literature reports and our three patients (52- and 61-year-old women and a 65-year-old man). The IgG4-related disease (IgG4-RD) diagnoses were definitive in four cases, and probable and possible in three cases. Eight patients had ANCA against myeloperoxidase (MPO), and two had ANCA against proteinase-3 (PR3). Two patients had both IgG4-RD and AAV, while the others only had ANCA seropositivity without additional clinical or pathological markers of AAV.

Conclusion: With regard to HP, we reconfirmed the existence of the IgG4-RD and AAV overlap syndrome. Meanwhile, our review does not support the hypothesis that ANCA positivity in IgG4-RD results from an excessive B-cell response. We speculate that IgG4-RD and AAV have similar or associated pathogeneses, although uncovering the role of IgG4 and ANCA in these pathophysiological processes requires further investigation.

KEYWORDS

hypertrophic pachymeningitis, IgG4-related disease, antineutrophil cytoplasmic antibody, ANCA-associated vasculitis, IgG4

Background

Hypertrophic pachymeningitis (HP) is a group of rare disorders characterized by local or diffuse thickening of the intracranial or spinal dura mater causing intracranial hypertension, cranial nerve palsy, or spinal cord dysfunction. Headache is the most common initial symptom of HP (1). The main pathological signs of HP include interstitial fibrosis and infiltration of inflammatory cells, mainly lymphocytes. The identifiable causes of HP are heterogeneous and include infections (i.e., *Mycobacterium tuberculosis*, fungi, or *Borrelia burgdorferi*), inflammatory diseases (i.e., IgG4-related disease (IgG4-RD), sarcoidosis, Sjogren's syndrome, rheumatoid arthritis, or Wegener's granulomatosis) (2). A nationwide investigation in Japan revealed that the most frequent cause of HP was antineutrophil cytoplasmic antibodies (ANCA) (30.2%), followed by IgG4 (8.8%) (1). ANCA-related HP comprises three underlying disorders: granulomatosis with polyangiitis (GPA) (1), microscopic polyangiitis (MPA) (3), and eosinophilic GPA (EGPA) (4), which is most commonly caused by GPA (5).

The IgG4-RD is a chronic inflammatory disorder with the following pathological characteristics: lymphoplasmacytic infiltration of numerous IgG4+ cells, storiform fibrosis, and obliterative phlebitis in various organs (e.g., the salivary glands, bile ducts, thyroid glands, lungs, and pancreas) (6). The characteristic features of IgG4-RD include elevated serum IgG4 and infiltration of IgG4+ cells; however, GPA, EGPA, pulmonary sarcoidosis, and lymphoma can cause similar pathological or serological manifestations (7). Therefore, the differential diagnosis of IgG4-RD includes neoplasms, infectious diseases, and autoimmune disorders such as ANCA-associated vasculitis (AAV).

An overlap between AAV and IgG4-RD has been described in some clinical patterns, such as tubulointerstitial nephritis, periaortitis, and prevertebral fibrosis. Therefore, we hypothesized that these two diseases could also overlap in the clinical pattern of HP. Herein, we present three new cases of patients with IgG4-HP coexpressing ANCA. In addition, we review the relevant literature to identify the clinical characteristics of IgG4-HP cases coexpressing ANCA and confirm whether the overlap of IgG4-RD and AAV also exists in HP.

Methods

Case presentation

Case 1

The first case was a 65-year-old man with paroxysmal bilateral temporal headache, a 20-kg weight loss over 3 months, hoarseness, dysphagia with paroxysmal diplopia, and intermittent fever for 1 month. A neurological examination revealed dysarthria, restricted right eye abduction, and left vocal cord paralysis. Laboratory tests yielded the following results: white blood cell count, 10,010/μl; hemoglobin, 6.9 g/dl; erythrocyte sedimentation rate (ESR), 140 mm/h; C-reactive protein (CRP), 131 mg/L. Tests for infections were negative, including blood bacteria cultures, *Mycobacterium tuberculosis* antibodies, respiratory viral antigens, human immunodeficiency virus, and fungi antigen. Rheumatologic assays were negative (such as antinuclear antibody, cyclic-citrullinated peptide IgG antibody, rheumatoid factor, anti-cardiolipin antibody, lupus anticoagulant, and angiotensin-1 converting enzyme), except for titers of serum cytoplasmic ANCA (1:32), myeloperoxidase antibodies (MPO-ANCA) (1:100) and elevated IgG4 (411 mg/dl; normal: 8–140 mg/dl), although the total IgG level was normal. Routine urinalysis was unremarkable. Cerebrospinal fluid (CSF) showed lymphocytosis (25 cells/mm^3), and three well-defined oligoclonal bands were present in both the CSF and serum. The CSF infectious disease test was negative. Chest and paranasal sinus CT found no abnormalities. Gadolinium-enhanced brain magnetic resonance imaging (MRI) revealed enhanced and thickened dura mater, predominantly in the posterior fossa (Figure 1). Intravenously administered dexamethasone (10 mg/day for 5 days) markedly relieved the patient's headache, but it recurred after the oral administration of prednisolone (28 mg/day). An additional intravenous cyclophosphamide administration (0.4 g once) achieved stable improvement. On discharge, fever and headache had disappeared, and dysarthria had significantly improved. The 6-month follow-up examination showed great clinical and radiological improvement, and intravenous cyclophosphamide administration at intervals allowed to taper prednisolone. The CRP and ESR also returned to normal levels.

Case 2

The second patient was a 52-year-old previously healthy woman with an ingravescent occipital headache for 6 months. The only notable neurological examination result was a right hypoglossal nerve palsy (Figure 2A). The gadolinium-enhanced brain MRI revealed pachymeningeal enhancement and thickening, predominantly in the posterior fossa and bilateral posterior cerebral hemispheres (Figures 2B–D). Infection tests were negative. Rheumatologic tests were also negative, except for the elevated rheumatoid factor (167.4 IU/ml) and CRP (87 mg/L). Urinary protein and occult blood tests were both negative. Serum levels of total IgG and IgG4 were 1,646 mg/dl (normal: <1,600 mg/dl) and 512 mg/dl, respectively, with an IgG4/IgG ratio of 31%. Serum was positive for perinuclear ANCA (titer, 1:10) and MPO-ANCA (titer, 1:100). The CSF showed lymphocytosis (33 cells/mm^3). The CSF infectious disease test was unremarkable. Chest

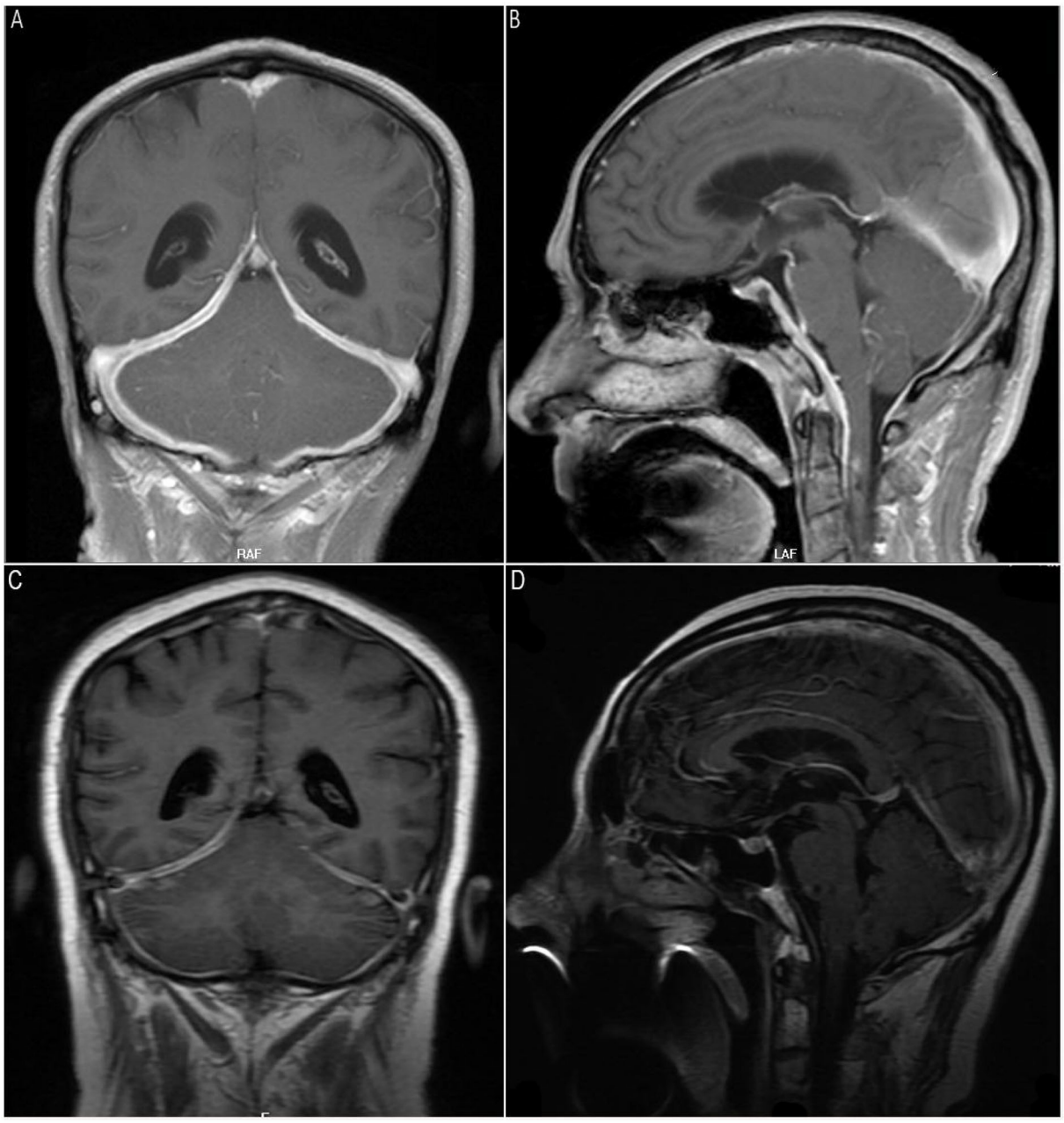

FIGURE 1
Magnetic resonance imaging (MRI) scan of the brain on admission. T1-weighted gadolinium-enhanced brain MRI revealed enhancement and thickening of dura mater predominantly in the posterior fossa **(A,B)**. Marked reduction of dura thickening and enhancement was evident at the 6-month follow-up **(C,D)**.

and paranasal sinus CT found no abnormalities. The patient received methylprednisolone pulse therapy (1 g/day, halved every 3 days until reaching 120 mg/day), followed by oral prednisone 60 mg/day, gradually reduced, and combined with oral cyclophosphamide 50 mg/day for about 3 months, with obvious relief of the headache and improvement of lingual symptoms.

Case 3

The third patient was a 61-year-old woman admitted for weakness and stiffness in both lower limbs for about 1 year, accompanied by thoracic back pain and constipation for 8 months. The neurological examination on admission revealed paresis in the bilateral lower limbs (3 to 4/5), decreased pain and thermal sensation in the trunk and lower limbs below

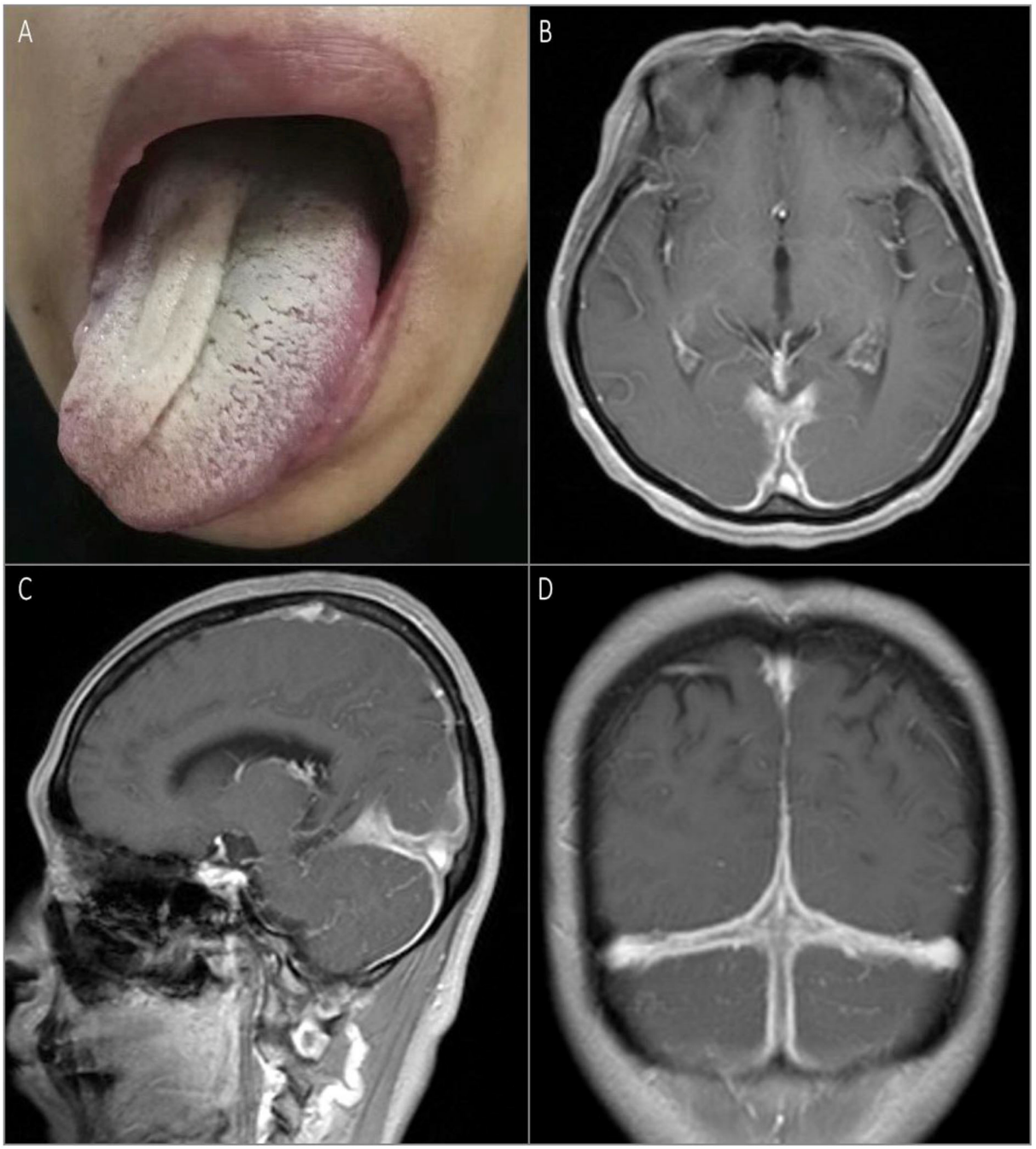

FIGURE 2
Physical examination and MRI scan of the brain on admission. Rightward tongue deviation upon protrusion and atrophy of right lingualis were observed on examination **(A)**. T1-weighted gadolinium-enhanced brain MRI showed pachymeningeal enhancement and thickening predominantly in the posterior fossa and bilateral posterior cerebral hemispheres **(B–D)**.

the T10 level, brisk bilateral knee and Achilles tendon reflexes, and bilateral extensor plantar response. The routine blood tests and inflammatory markers levels were normal. Infections assays were negative. Rheumatologic assays were negative, except for seropositivity for perinuclear ANCA (titer, 1:32), MPO-ANCA (titer, 1:100), and elevated IgG4 (441 mg/dl). Chest and paranasal sinus CT found no abnormalities. A spinal cord MRI revealed a ribbon-like thickening of the dura mater between vertebral levels T7 and T11 (which was moderately enhanced by gadolinium administration) and a compressed and flattened focal spinal cord (Figures 3A–C). Although the patient underwent emergent T7–T11 right

pediculectomy and partial corpectomy for decompression and resection of the dural lesion, her neurological deficits did not improve. The CSF analysis during the operation was negative for bacteria, tuberculosis, viruses, and fungi. A broad panel of immunohistochemical markers was assayed, such as S-100, EMA, CK-P, GFAP, Vim, CD20, CD68, CD38, CD138, CD34, and Ki67. A histopathology analysis showed lymphocyte infiltration, high IgG4+ cell infiltration, and a storiform pattern of fibrosis without granulomatous changes (Figures 3D,E).

Results: Review of the literature and our cases

We systematically searched the PubMed database for studies on humans, written in English, and published between 1976 and April 2022 using the keywords: "pachymeningitis, meningitis, dura, antineutrophil cytoplasmic antibody, myeloperoxidase, and proteinase-3." We excluded cases described in insufficient detail. Ultimately, we analyzed 10 cases (8–14), including our three cases. The patients' ages ranged from 48 to 79 years (median 61.5 ± 3.2 years), and the male/female ratio was 1:1. Table 1 summarizes the clinical, radiological, and pathological characteristics of all patients. We re-evaluated the cases according to the Comprehensive Diagnostic Criteria (CDC) for IgG4-RD (15). Possible IgG4-RD was defined by suggestive organ involvement associated with elevated serum IgG4 levels (>135 mg/dl). We identified probable IgG4-RD by looking for classical histopathological features (i.e., dense lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis, and mild-to-moderate eosinophil infiltration), IgG4/IgG positive plasma cell ratio >40% and >10 IgG4+ cells per high power field. Definitive IgG4-RD was identified by suggestive organ involvement associated with elevated serum IgG4 levels and histological features (15). For AAV, we used the American College of Rheumatology (ACR) 1990 criteria and the definitions from the 2012 Chapel Hill Consensus Conference and the EMA algorism for GPA, MPA, and EGPA (16–18). Due to a lack of histopathological examination, only a possible diagnosis of IgG4-RD was established in our two patients (Nos. 1, 2) according to the currently accepted criteria (6), although we cannot fully exclude the diagnosis of AAV in the current stage. We diagnosed four cases with definitive IgG4-RD and three with probable and possible Ig4-RD. Eight patients had anti-MPO ANCA, and two had anti-proteinase-3 (PR3) ANCA. Two cases (Nos. 7 and 10) fulfilled the CDC for IgG4-RD and the ACR and Chapel Hill criteria and the EMA algorism for AAV. One had biopsy results compatible with both GPA and IgG4-RD, and the other (No. 7) had a clinical overlap. Eight patients had documented symptom courses, and most of them had a diagnostic delay of several months before admission. In patients with intracranial dura mater involved, headache was the most common symptom, followed by cranial nerve deficits, such as hypoacusis, dysphagia, diplopia, vertigo, hypoglossal nerve palsy, and trigeminal nerve palsy. Headaches were often described as a sense of persistent local crushing with progressive exacerbation and refraction to drugs. Two patients (Nos. 4 and 5) had papilledema, most likely caused by intracranial hypertension. Patients with spinal hypertrophic pachymeningitis often experienced radicular pain and spinal cord compression symptoms (Nos. 3, 6, and 8), but rarely fever. MRI revealed focal pachymeningitis in eight cases, with the posterior fossa and occipital lobe most commonly involved, which might explain the neurological symptoms. Lymphocytosis and oligoclonal bands were commonly found in the CSF, as well as elevated blood non-specific inflammatory indicators, such as CPR and ESR. Eight patients had elevated serum IgG4 levels, while one displayed mild neutrophil-predominant leukocytosis, thrombocytosis, and normocytic anemia. The overall responses to immunosuppressants were good, with six cases attaining great clinical and radiological improvement; two cases suffered from one or two relapses, and only one patient expired from secondary infection.

Discussion

In our pooled analysis, two cases (Nos. 7 and 10) fulfilled the diagnostic criteria for both diseases, while the others only had ANCA seropositivity without additional clinical or pathological markers of AAV. Although IgG4-RD commonly involves multiple organs synchronously or metachronously, the clinical symptoms and radiological features of most patients in this study resulted from the involvement of a single organ (dura mater). They had elevated serum IgG4 levels (>135 mg/dl for most patients) and positive ANCA. Although AAV is an important differential diagnosis of IgG4-RD in both the 2019 ACR/EULAR classification criteria (19) and CDC for IgG4-RD, a recent report concluded that the presence of ANCA might not influence the pathomechanisms of IgG4-RD (20). Furthermore, an overlap of AAV and IgG4-RD has been reported in some clinical patterns, such as tubulointerstitial nephritis, periaortitis, and prevertebral fibrosis (21, 22). A prior case report also suggested that HP caused by GPA and IgG4-RD might be a disorder spectrum (12). However, controversy and counter-examples exist. A study with 62 patients diagnosed with IgG4-RD found no cases with overlapping AAV, challenging the coexistence of IgG4-RD and AAV (23). Meanwhile, our case review of IgG4-HP patients coexpressing ANCA is in line with the existence of the overlap syndrome.

Recently, Martin-Nares et al. (24) reported that IgG4-RD patients coexpressing ANCA often had the following characteristics: (1) constitutional symptoms with salivary glands, lymph nodes, and kidneys involved; (2) high levels of serum total IgG, IgG1, and IgG4; (3) low C3 and C4 levels; (4) high prevalence of antinuclear antibody positivity. The authors

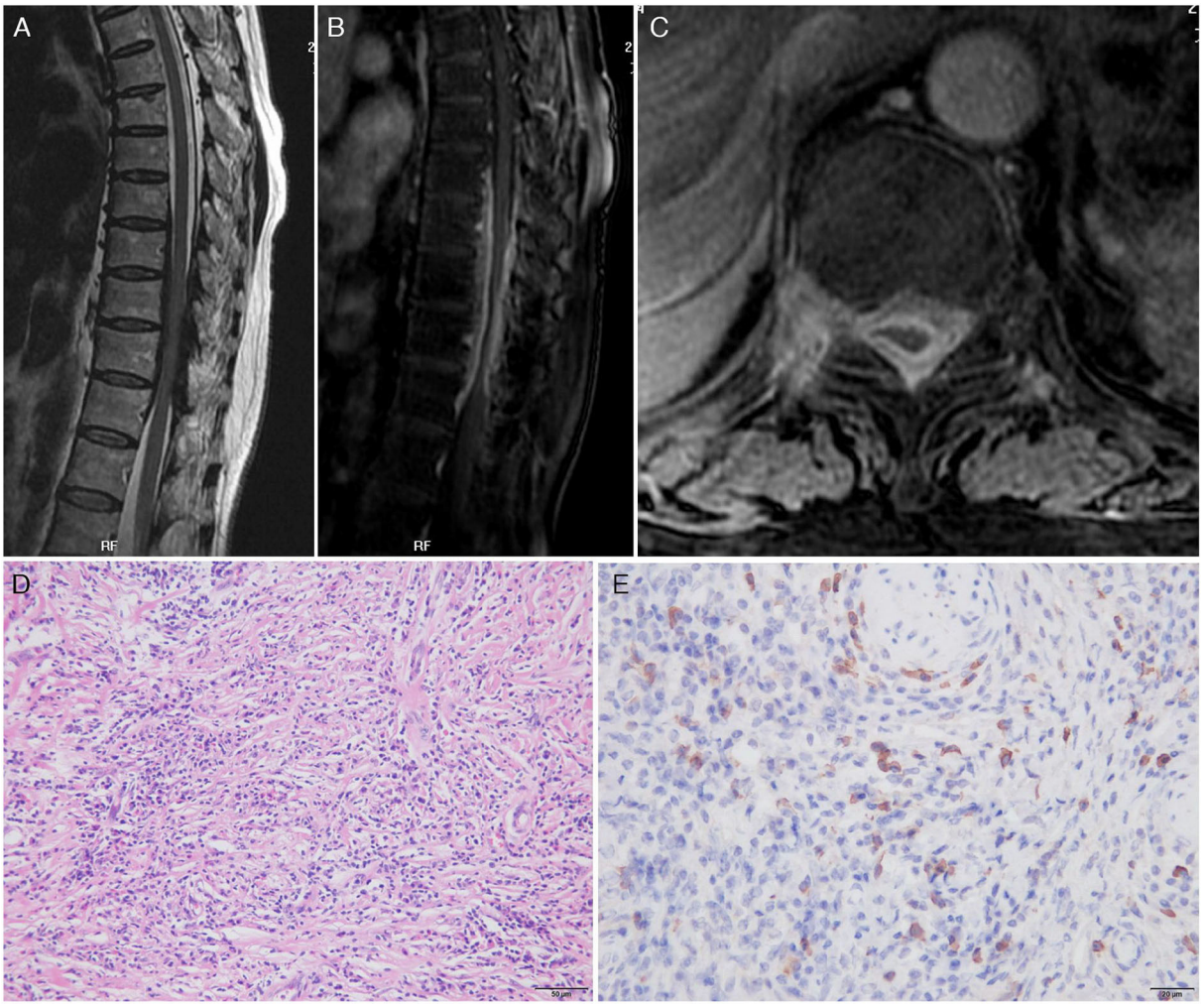

FIGURE 3
Magnetic resonance imaging scan of the thoracic spine on admission and pathology findings. Sagittal T2-weighted image **(A)** showed a low-signal intensity lesion in the anterior and posterior epidural spaces and high enhancement after gadolinium enhancement **(B)** at the thoracic canal between T7 and T11 vertebral body levels. Axial images showed that the lesion was located in the epidural space and extended to the neural foramen to the right. A fat-suppressed T1-weighted image with gadolinium enhancement demonstrated high enhancement of the mass **(C)**. Pathology findings: Hematoxylin and eosin stain of the epidural mass showed intense lymphoplasmacytic inflammatory cell infiltrate with fibrosis. Plasma cells and lymphocytes were also detected within the wall of a vessel as well as in the perivascular area **(D)**. IgG4 immunohistochemistry showed prominent IgG4+ cells within the inflammatory infiltration. Nearly more than half of the plasma cells exhibited IgG4 reactivity **(E)**.

interpreted these results as indicating that the ANCA detected in patients with IgG4-RD does not indicate an underlying AAV overlap but might instead represent an excessive B-cell response. However, our case review did not confirm these features in IgG4-HP patients coexpressing ANCA.

Currently, the pathogenesis of AAV and IgG4-RD is not entirely understood. Several studies have confirmed that many patients with EGPA do have elevated blood IgG4 levels. These levels are correlated with disease activity, suggesting that AAV and IgG4-RD have similar or associated pathogeneses. Several studies have shown that, in both disorders, T-follicular helper cell levels increase and become polarized toward T-follicular helper 2 subtype cells, enhancing IgG4-plasma cell polarization (25). Further investigation of the pathogenesis of these disorders may improve the understanding of the IgG4-ANCA coexistence. In addition, the close relation between GPA and IgG4-RD may be partly explained by the fact that, in GPA, ANCA belongs mainly to the IgG1 and IgG4 subclass. Thus, ANCA production could be induced after prolonged or repeated antigen exposures in the setting of a T-helper-2 cell immune response, where T-regulatory cells are activated and produce interleukins 4 and 10, which contribute to the shift of balance of IgG subclasses toward IgG4 (26). However, the pathophysiology of both AAV and IgG4-RD is complex and warrants further research.

Finally, the therapeutic approach remains also important. Current treatment strategies for IgG4-RD include

TABLE 1 Clinical, radiological, and laboratorial features of the patients.

No.	Age and sex	Onset	Clinical features	MRI dural thickening location	Serum IgG4 (mg/dL)	Findings about AAV	ANCA(+) status	Pathology	IgG4-RD based on CDC (15)	Tx
1	65M	Sub.	Headache, weight loss, dysphagia, diplopia, fever	Posterior fossa	411	No	C, MPO	na	Possible	CTC CTX
2	52F	Sub.	Headache, hypoglossal nerve palsy	Posterior fossa bilateral posterior cerebral	512	No	P, MPO	na	Possible	CTC CTX
3	61F	Chr.	Spinal cord compression symptoms	Spinal dura (T7 - T11)	441	No	P, MPO	IgG4+ cells rich infiltration, fibrosis	Definite	CTC
4. Popkirov et al. (8)	52M	Sub.	Headache, blurred vision, hearing impairment, tinnitus, and vertigo	Infratentorial	NA	No	P, MPO	IgG4+ cells rich infiltration	Probable	CTC AZA RTX
5. Massey et al. (9)	70M	Sub.	Headache, transient visual loss, syncope	Diffuse	233	No	P, MPO	Storiform fibrosis, IgG4+ cells rich infiltration	Definite	CTC
6. Maher et al. (10)	79F	Sub.	Thoracic back pain	Spinal dura (C6–L1)	↑	No	MPO,	Storiform fibrosis, IgG4+ cells rich infiltration, obliterative phlebitis	Definite	CTC RTX
7. Wyrostek et al. (11)	48M	Sub.	Headache, weight loss, hearing impairment, mastoiditis and pansinusitis, proteinuria, lung nodules	Posterior fossa bilateral posterior cerebral hemispheres	245	GPA	C, PR3	Increased IgG4+ cells (lung nodule and bone marrow)	Probable	CTC RTX
8. Cação et al. (12)	56F	Sub.	Lumbar pain, medullary symptoms	Dorsal and lumbar spinal dura	↑	No	MPO	na	Possible	CTC
9. Musto et al. (13)	59F	na	Headache neck pain	Foramen magnum	NA	No	C, PR3	Several IgG4+ cells	Probable	NA
10. Mori et al. (14)	73M	Chr.	Headaches, ophthalmalgia, blurred vision	Diffuse	156	GPA	MPO	Lymphocytes and rich IgG4+ cells infiltration, granulomatous inflammation	Definite	CTC

ANCA, anti-neutrophil cytoplasmic antibody; AZA, azathioprine; C, cytoplasmic; CDC, Comprehensive Diagnostic Criteria; Chr., Chronic; CTC, corticosteroids; CTX, cyclophosphamide; GPA, granulomatosis with polyangiitis; MPO, myeloperoxidase; na, not available; P, perinuclear; PR3, proteinase 3; RTX, rituximab; Sub., subacute; Tx, treatment.

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glucocorticoids and conventional steroid-sparing agents, such as low-dose cyclophosphamide and mycophenolate mofetil. Noteworthily, three patients used B-cell depletion therapy (Nos. 4, 6, and 7). Rituximab demonstrated efficacy against both AAV and IgG4-RD (27–29), including in overlapping cases (21). Patients with IgG4-RD may also benefit from 500 mg of rituximab every 6 months for at least 2 years (29), which is the standard approach to maintain clinical remission in AAV cases.

This study has several limitations. First, the inclusion and exclusion criteria in the selection of cases could not be rigorously applied according to the CDC and 2019 ACR/EULAR classification criteria for IgG4-RD, causing inevitable deficiencies in the literature cases. Second, we only performed a pathological examination on one of our cases and, therefore, cannot rule out other pathologies in the other two patients (such as lymphoma, inflammatory myofibroblastic tumor, Rosai Dorfman disease, Castleman's disease, ulcerative colitis, and rheumatoid meningitis). Third, not all patients had documented CSF levels of ANCA and IgG4. Those were increased in some reports of HP related to IgG4-RD (30) and AAV (31), making them valuable biomarkers for differentiating between IgG4-HP and ANCA-related HP.

Conclusion

In conclusion, we report three cases of IgG4-HP coexpressing ANCA. By analyzing them with previously reported cases, we confirmed the existence of an overlap syndrome for IgG4-RD and AAV in the clinical pattern of HP. Meanwhile, our results do not support the hypothesis that ANCA detected in IgG4-RD results from an excessive B-cell response in HP. Thus, we speculate that IgG4-RD and AAV have similar or associated pathogeneses, although further information is needed about the role of IgG4 and ANCA in their pathophysiological processes. Nevertheless, the question remains: do IgG4-RD and AAV belong to the spectrum of a single disease or simply overlap sometimes?

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethical Research Committee of General Hospital of Northern Theater Command. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CX: drafting/revision of the manuscript for content, including medical writing for content, major role in the acquisition of data, and analysis or interpretation of data. PL: study concept or design. All authors have read and approved the final manuscript to be published.

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Conflict of interest

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

Publisher's note

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Case report: IgG4-related intracranial lesions mimicking multiple sclerosis in a 14-year-old girl

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Objectives: IgG4-related disease (IgG4-RD) is distinguished by the infiltration of IgG4-positive plasma cells in a variety of tissues and organs. Even so, central nervous system lesions associated with IgG4-RD are scarce. We present a case of IgG4-related brain parenchymal lesions that mimics multiple sclerosis in a young girl.

Methods: The patient was followed by our neurology and rheumatology teams. Clinical information was recorded, and the brain was screened using magnetic resonance imaging (MRI). During follow-up, we examined serum IgE, IgG and IgG4 and lymph node biopsy.

Results: Here, we presented details of a 14-year-old Chinese girl suffering from diplopia, left eyelid ptosis, right facial numbness, and right lower limb weakness admitted to our institute. Brain MRI revealed multiple sclerosis-like lesions in the brain parenchyma and spinal cord. During the follow-up, she developed lymphadenopathy. Elevation of serum, IgG, IgG4 and IgE and lymph node biopsy favors a diagnosis of IgG4-RD. The patient had a good response to glucocorticoids and mycophenolate mofetil. The literature review summarized eight previously reported IgG4-RD involving brain parenchyma.

Discussion: Our case expands the known age spectrum of IgG4-RD. The intracranial IgG4-RD is rare and could mimic multiple sclerosis. Careful examination and dynamic review of disease history are crucial in the differential diagnosis.

KEYWORDS

multiple sclerosis, IgG4-related disease, magnetic resonance imaging, brain parenchyma, lymphadenopathy

Introduction

IgG4-related disease (IgG4-RD) is a syndrome that forms an inflammatory pseudotumor with densely infiltrated lymphocytes, including $IgG4^+$ plasmacytes along with storiform fibrosis and obliterative phlebitis (1, 2). The disease typically affects middle-aged and older people (55–59 years), preferentially prevalent more in men (1). It can involve virtually every organ in the body, including the lacrimal glands, the salivary glands, the pancreas, the biliary tree, the kidneys, and the retroperitoneum (2). However, intracranial IgG4-RD is rare and can present as a single pseudotumor or diffused lesion in the substance of the dura matter, the pia matter, the pituitary gland and stalk, and less likely brain parenchyma (3). Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) characterized by heterogeneity in clinical symptoms. MS plaques on magnetic resonance imaging (MRI) appear as multiple, well-demarcated, homogenous, small ovoid lesions lacking mass effect and are often oriented perpendicular to the long axis of the lateral ventricles (4). Differential diagnoses of IgG4-RD and MS can be challenging for both clinicians and radiologists as both diseases have various manifestations and lack specific markers. Here, we present a young girl with IgG4-related intracranial lesions that mimic multiple sclerosis (MS).

Case description

A 14-year-old girl presented with diplopia, left eyelid ptosis, right facial numbness, and right lower limb weakness since 1 month prior, which had progressively worsened. Physical examination revealed an impaired vision of both eyes, diplopia, left eyelid ptosis, right facial paresthesia, and hyperreflexia of both sides. There were no meningeal signs and no cervical, axillary, or inguinal lymphadenopathy. Routine blood tests, including blood cell counts, albumin level, transaminases, and C-reactive protein, were not significant. Brain MRI revealed multiple coin-like white matter lesions and one mesencephalon lesion (Figure 1A). Sagittal T2-weighted imaging of the brainstem and the spinal cord showed an enhanced lesion in the cerebral peduncle (Figure 2A) and in the spinal cord at the level of thoracic 12 (Figure 2B). Cerebral spinal fluid analysis showed leukocytes within the normal range, glucose was 6.25 mmol/L, albumin was 0.128 g/L, total Ig was 0.0563 g/L, IgG synthesis rate was 0 mg/day, and there were no detectable oligoclonal bands. The visual evoked potential (VEP) test was normal. She had a history of bilateral lacrimal gland enlargement about 6 months before, and a surgery was performed to correct this. Histological examination indicated lymphoproliferative changes, and the number of $IgG4^+$ cells was over 220/HPF. Serum IgG4 was elevated (3.45 g/L, normal range 0.049–1.35 g/L). The patient was diagnosed as "IgG4-RD" and received oral glucocorticoid combined with cyclosporin but stopped 3 months later. The patient's family history was not remarkable. Based on the symptoms and MRI findings, the patient was suspected of MS and was given prednisone and intravenous immunogloblin (IVIG). Her diplopia and ptosis improved significantly and was discharged. One month later, she was administered 1 g of methylprednisolone for 5 days, followed by 70 mg of prednisone daily since her abnormal gait and lower limb weakness persisted. The prednisone was tapered to stop while recombinant interferon (IFN) β-1b was given every 2 days subcutaneously for 6 months. She did not receive any treatment for over 1 year until the development of enlargement of lymph nodes in the submaxillary and inguinal areas. Fourteen milligrams of Teriflunomide was given daily; however, her symptoms persisted. Six months later, the patient came to our department with lymph node enlargement and right-side numbness and weakness, but she denied any fever, unintentional weight loss, fatigue, or change in appetite. Laboratory tests revealed normal counts of leukocytes and platelets, the hemoglobin level, the albumin level, the serum creatinine level, and C-reactive protein. Antinuclear antibodies, extractable nuclear antigen antibodies, anti-neutrophil cytoplasmic antibodies, and anti-phospholipid antibodies were all negative. Serum IgG was 70.7 g/L (normal range 8.0–15.5 g/L), IgG4 was 28.5 g/L, and IgE was 4,810 mg/L (normal range 5–150 mg/L), while IgA and IgM were within the normal range (Figure 3). Chest computerized tomography and abdominal ultrasonography were not significant. A biopsy of the left inguinal lymph node was performed. The histopathological evaluation of the biopsy specimen of the inguinal lymph node revealed mixed inflammation containing predominantly plasma cells (Figures 4A–C). No granuloma, prominent necrosis, "onion skin pattern" mantle zones, or "lollipop lesions" were found. Immunostaining showed an increased number of $IgG4^+$ plasma cells (>200/HPF) and an elevated ratio of $IgG4^+$ cells to $CD138^+$ plasma cells (∼80%) (Figures 4B,C). No mycobacteria, fungi, or parasites were noticed, and Epstein-Barr virus-encoded RNA 1/2 was negative. These findings were suggestive of an IgG4-RD involving the lacrimal glands, the brain parenchyma spinal cord, and the lymph nodes according to both the ACR/EULAR classification criteria (5) and the revised comprehensive criteria (6). She had a good response to oral prednisone 40 mg daily combined with mycophenolate mofetil 750 mg two times daily. In a consecutive 7-month follow-up, her lymphadenopathy and right-side numbness and weakness resolved. A repeated brain MRI revealed shrinkage of the intracranial lesions, and the lab tests showed a rapid drop in serum levels of IgG and IgG4 (Figures 1B, 3).

Discussion

Our case illustrates an intracranial IgG4-RD mimicking MS in a 14-year-old girl, which has been rarely reported in the literature. In this case, it is important to make differential

diagnoses among some relevant diseases including CNS tumor, infectious encephalitis, and immune-mediated encephalitis, such as MS.

Some mimickers, especially idiopathic multicentric Castleman's disease (CD), are sometimes difficult to be differentiated from IgG4-RD (7) and should be excluded before a diagnosis was made. The patient did not have a fever, large spleen or liver, serositis, angioma, or interstitial pneumonitis. Lab tests did not reveal anemia, thrombocytopenia, hypoalbuminemia, elevated CRP, or renal dysfunction. Elevated IgG and IgE but not IgA and IgM were found in the serum. The lymph node biopsy did not reveal "onion skin pattern" mantle zones, "lollipop lesions," or sheet-like mature plasma cell proliferation, which are characteristic findings of CD (8), and the enlarged lymph nodes resolved quickly with glucocorticoids. Therefore, the CD can be ruled out. Moreover, the negative autoantibody spectrum did not support other autoimmune diseases such as primary Sjogren's syndrome and systemic lupus erythematosus, whereas benign clinical features and histological findings ruled out lymphoma. Based on localized swelling of the lacrimal glands and the lymph nodes, elevated IgG4 level, and characteristic histological findings, the patient received a diagnosis of IgG4-RD.

IgG4-RD can affect almost every organ system, where 31% of patients were affected by hepato-pancreato -biliary diseases, 24% by retroperitoneal fibrosis and aortitis, 24% by head and neck-limited disease, and 22% by classic Mikulicz syndrome with systemic involvement (9). Nearly 40% of patients present with a clinically-evident disease in a single organ system, and it may evolve overtime, with new systems being involved in a metachronous manner (10). This patient showed different organ involvement at different stages, i.e., swelling of bilateral lacrimal glands at the beginning followed by intracranial and spinal cord lesions and recent lymph node enlargement, suggesting the complexity of this disease.

IgG4-RD can also involve the nervous system, including the central nervous system (CNS) and the peripheral nervous system. Neurological IgG4-RD has two main mechanisms: infiltration in the substance of the nervous system and compression of neurological structures by the mass effect of nearby diseased tissues (3). It most commonly manifests in the substance of the dura matter, followed by the pituitary gland and stalk, the peripheral nerves, the brain parenchyma, and occasionally the pia matter (3). So far, only a handful of cases of IgG4-RD involving brain parenchyma are reported (Supplementary Table 1). In these cases, most patients were middle-aged men (17–62 years old). Their neurological symptoms varied a lot, depending on the location and area of the intracranial lesions. The IgG4-related lesions were most likely found in the periventricular area or close to the meninges with MRI (Supplementary Table 1). To the best of our knowledge, this case, which starts to get symptoms at 13-year-old, is the youngest patient with histologically confirmed IgG4-RD.

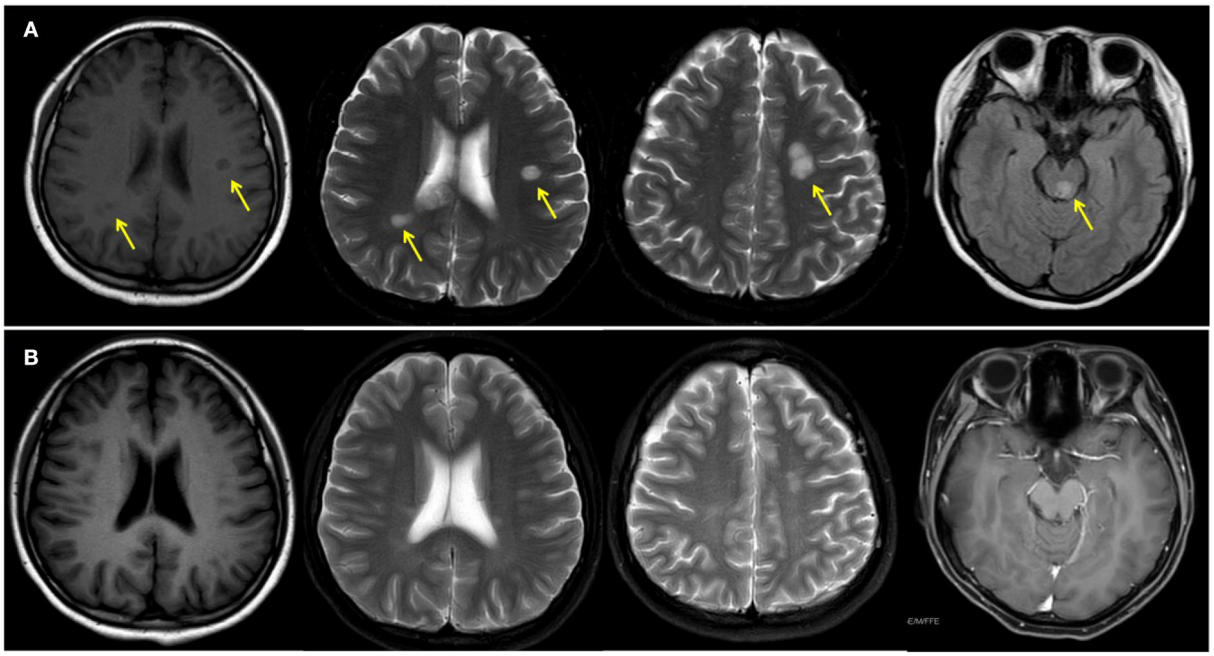

FIGURE 1
Magnetic resonance imaging of the brain before **(A)** and after **(B)** treatment. Yellow arrows indicate white matter lesions.

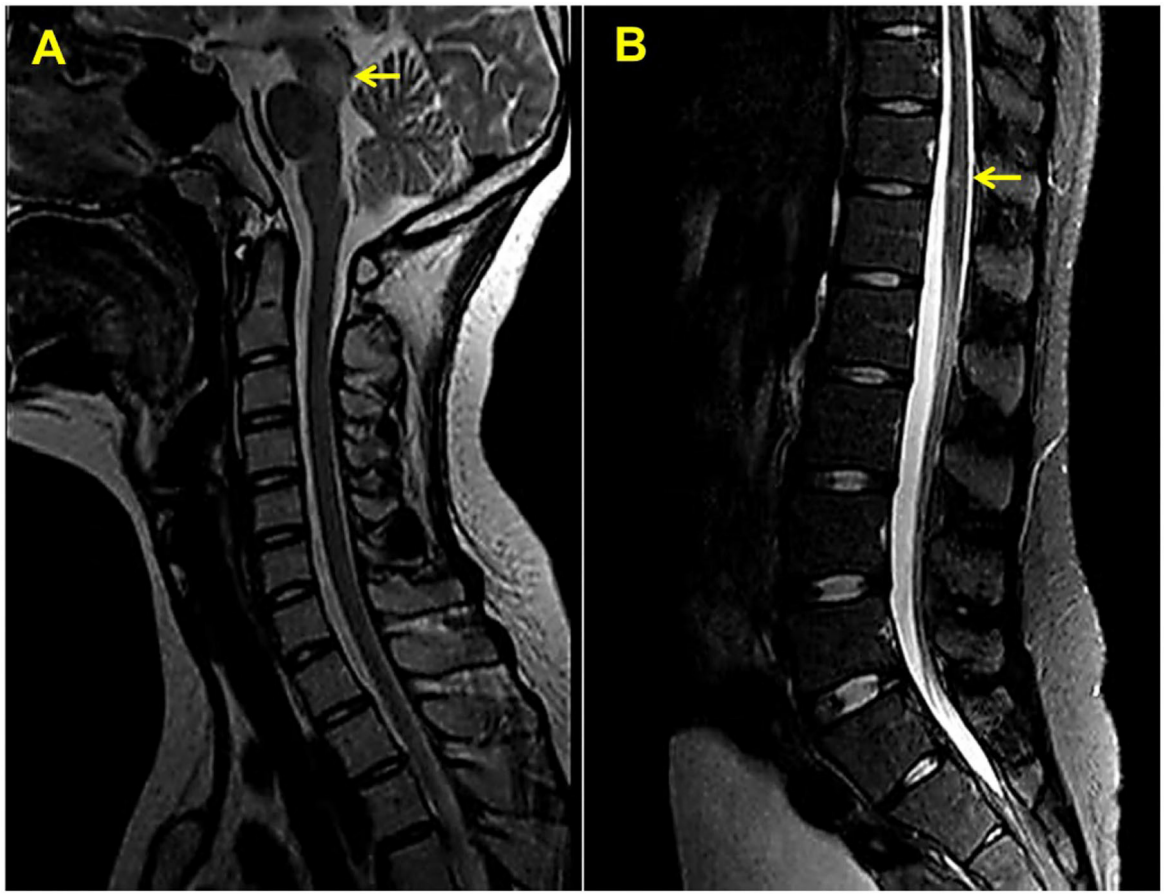

FIGURE 2
Sagittal T2-weighted magnetic resonance imaging of the upper **(A)** and lower **(B)** spinal cord. Yellow arrows indicate white matter lesions.

Neural symptoms and white matter plaques on MRI of this patient (Figure 1) usually prompt people to consider MS. MS attacks myelinated axons in the CNS, causing progressive neurological deterioration (11). This disorder usually presents in adults between the age of 20 and 45 years with female predominance (11). Its clinical symptoms are non-specific and usually include visual changes, numbness, weakness, and paralysis, depending on the amount and area of nerve damage. MS is usually diagnosed by demonstrating clinical and/or radiographic evidence of dissemination of disease in time and space (12). This disease is characterized by elliptical or ovoid lesions found in the white matter of the periventricular and juxtacortical regions, the cerebellar peduncles, the superficial pons, and the floor of the fourth ventricles (13). Spinal cord lesions are also commonly seen. T2-weighted imaging of the spinal cord demonstrates small and circumscribed high-signal lesions that are aligned with the long axis of the cord. The lesions are usually less than two vertebral segments in length and involve less than half the axial cord area (13). In this patient, MRI revealed multiple ovoid lesions in the white matter and mesencephalon, and an enhanced lesion in the spinal cord at the level of thoracic 12, which are similar to MS lesions. Because cerebral IgG4-RD and MS have distinct outcomes, distinguishing between these two entities is critical. However, clinical judgment is often required to make the classification given an absence of specific biomarkers and clear diagnostic criteria.

In addition to MS, the differential diagnosis of pseudotumoral brain lesions includes infection neoplastic, including primary CNS lymphomas and metastatic cancers; congenital, metabolic, or vascular diseases; and non-MS idiopathic inflammatory demyelinating diseases, which include neuromyelitis optica (NMO) spectrum disorders (NMOSD), opticospinal MS, and acute disseminated encephalomyelitis. NMOSD is characterized by simultaneous or consecutive attacks of acute optic neuritis and transverse myelitis (14). IgG autoantibodies against aquaporin 4 (AQP4) or myelin oligodendrocyte glycoprotein are widely present in these patients. In AQP4 positive NMOSD, whiter matter lesions are typically large, confluent, unilateral or bilateral subcortical and deep. Sometimes both brain and brainstem lesions can occur bilaterally, and brain lesions tend to be longitudinally

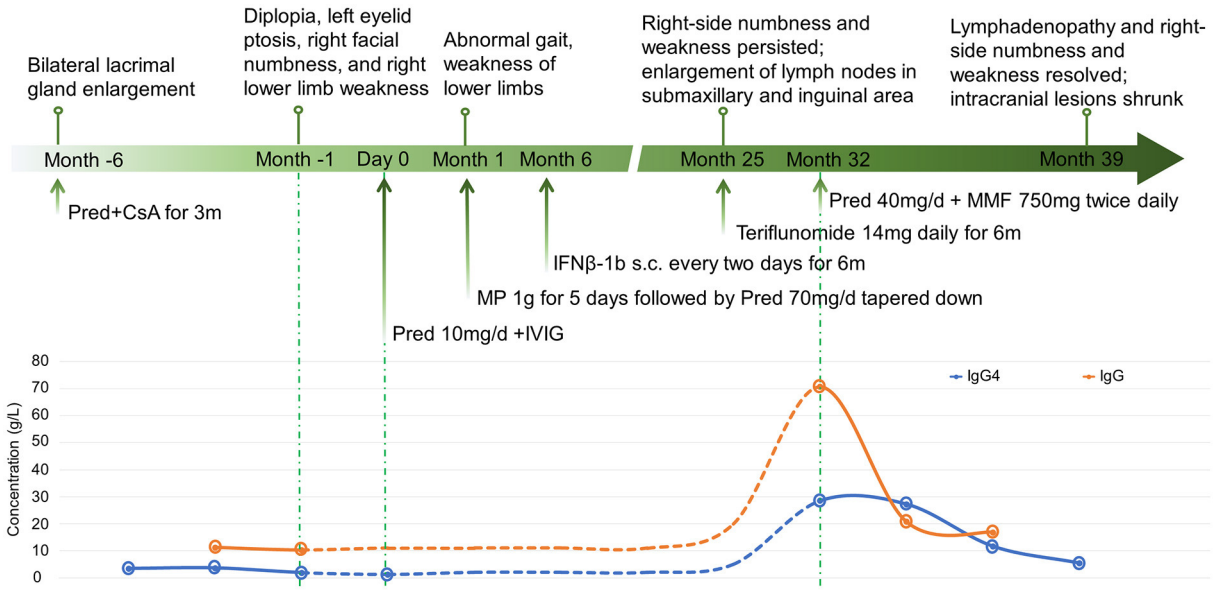

FIGURE 3
The disease course, treatments, and the changes of serum IgG and IgG4 of the patient.

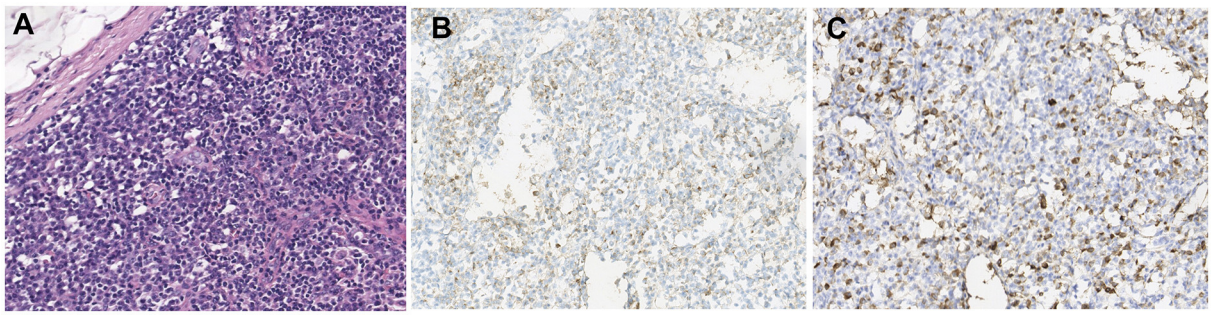

FIGURE 4
Histological examination of the biopsy of inguinal lymph node **(A)** H&E staining; **(B)** immunohistochemistry for CD138; **(C)** immunohistochemistry for IgG4; 200×).

extensive, involving the corticospinal tract and corpus callosum. Myelitis can manifest as a longitudinally intramedullary spinal lesion that extends over three vertebral segments. More than 50 cells/ul of white cell counts are frequently found in CSF of NMO. Prolonged P100 latencies in VEP were also present in 42–72% of NMOSD (14). The patient did not have an anti-AQP4 antibody test; however, the normal white cell counts in CSF and normal VEP with small and circumscribed lesions in the brain parenchyma and spinal cord on MRI can rule out the diagnosis of NMO. This patient had IgG4-RD involving the brain parenchyma, the lacrimal glands, and the lymph nodes, with distinct organ involvement present at different stages. Careful examination and dynamic review of medical history favor accurate diagnosis.

Similar to MS, the exact pathogenesis of IgG4-RD remains elusive but aberrant innate and adaptive immunity are considered to be involved (15, 16). B cells have been demonstrated to play a central role in IgG4-RD, while CD4+ cytotoxic T lymphocytes and T follicular helper cells contribute to the IgG4 isotype switching (16, 17). IgG4-RD is highly treatable with corticosteroids, but almost 40% either fail to achieve complete remission or relapse within 1 year even with a low dose of glucocorticoid (16). Some disease-modifying anti-rheumatic drugs (DMARDs), such as azathioprine and mycophenolate mofetil, were able to increase the rate of inducing remission and reduce disease flares (1, 10, 18). Other conventional steroid-sparing medications are also effective in this disease, but data are limited to retrospective analyses or case reports. B-cell depletion therapy including rituximab

can usually leads to disease remission in most cases, allowing early tapering of glucocorticoid therapy (19). Because IgG4-RD and MS have some common immunological abnormalities, several immunosuppressive treatments are shared between these two entities. In MS, immune cell activation and the blood–brain barrier breakdown cause demyelination and axon injury. IFN-β can improve the disease course of MS by reducing antigen presentation, reducing T-cell proliferation, decreasing the expression of cytokines, and reducing matrix metalloproteinase (20). However, a sustained elevation of type I IFN may accompany clinical manifestations and disease activity in systemic autoimmune disease, including systemic lupus erythematosus, primary Sjogren's syndrome, and systemic sclerosis (21). On the contrary, IFN-β was proved to be highly effective in a lupus mouse model (22). There is a strong IFN-γ signal in IgG4-RD immune cells (23); however, the role of type I IFN in the pathophysiology and outcome of the disease remains unknown. In this case, the disease relapsed during the usage of IFN-β-1b and discontinuance of prednisone. It is difficult to identify the causes of the disease flare.

This case report in conjunction with those in the literature indicates that IgG4-RD represents a great mimicker of many neoplastic, inflammatory, and infectious conditions. Histopathology remains critical to diagnosis because reliable biomarkers are lacking. IgG4-RD responds promptly to glucocorticoids and DMARDs, but prolonged courses are often needed because the disease relapses in most patients. This case illustrates the importance of dynamic monitoring and pathological examination to distinguish cerebral IgG4-RD from other CNS disorders and underscores the need for clear clinical guidelines to establish a diagnosis of IgG4-RD.

Data availability statement

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

Ethics statement

This study was approved by the Ethics Committee of West China Hospital of Sichuan University. Written informed consent was obtained from the patient and her parent for the publication of any potentially identifiable images or data included in this article.

Author contributions

PQ and BY collected the clinical information. CLiu interpreted the brain MRI findings. CLu made literature review and drafted the article. DF, YZ, YL, and CT interpreted the data and revised the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1007153/full#supplementary-material

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Case Report: Para-infectious cranial nerve palsy after bacterial meningitis

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A 27-year-old woman was admitted to our hospital for fever, associated with headache, nausea, and vomiting, and she rapidly developed mild left facial nerve palsy and diplopia. Neurological examination revealed mild meningitis associated with bilateral VI cranial nerve palsy and mild left facial palsy. As central nervous system (CNS) infection was suspected, a diagnostic lumbar puncture was performed, which revealed 1,677 cells/µl, 70% of which were *polymorphonuclear* leukocytes. Moreover, multiplex PCR immunoassay was positive for *Neisseria meningitidis*, supporting the diagnosis of bacterial meningitis. Finally, IgG oligoclonal bands (IgGOB) were absent in serum and cerebrospinal fluid (CSF). Therefore, ceftriaxone antibiotic therapy was started, and in the following days, the patient's signs and symptoms improved, with complete remission of diplopia and meningeal signs within a week. On the contrary, left facial nerve palsy progressively worsened into a severe bilateral deficit. A second lumbar puncture was therefore performed: the CSF analysis revealed a remarkable decrease of pleocytosis with a qualitative modification (only lymphocytes), and oligoclonal IgG bands were present. A new brain MRI was performed, showing a bilateral gadolinium enhancement of the intrameatal VII and VIII cranial nerves bilaterally. Due to suspicion of para-infectious etiology, the patient was treated with oral steroid (prednisolone 1 mg/kg/day), with a progressive and complete regression of the symptoms. We suggest that in this case, after a pathogen-driven immunological response (characterized by relevant CSF mixed pleocytosis and no evidence of IgGOB), a para-infectious adaptive immunity-driven reaction (with mild lymphocyte pleocytosis and pattern III IgGOB) against VII and VIII cranial nerves started. Indeed, steroid administration caused a rapid and complete restoration of cranial nerve function.

KEYWORDS

facial palsy, parainfectious disease, bacterial meningitis, parainfectious cranial nerve palsy, *Neisseria meningitidis*

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Introduction

Neisseria meningitidis is a Gram-negative diplococcus that can cause invasive meningococcal disease, such as bacterial meningitis. It is a member of the normal nasopharyngeal microbiome, and it can spread *via* aerosol or through oral and nasal secretions (1). Surveillance data from 25 European countries during 2004–2014 showed an annual incidence of invasive meningococcal disease ranging from 0.3 and 2.9 cases per 100,000, with a significantly decreasing annual trend in most countries (2). Nevertheless, *N. meningitidis* is associated with substantial mortality (5%–10%) and severe permanent disabilities, such as cognitive defects, hearing loss, vision deficits, and epilepsy (3–5).

Case description

A 27-year-old Italian woman living in London who returned to Italy recently suddenly presented fever, sore throat, headache, nausea, vomiting, and transient binocular diplopia (for the disease timeline see Figure 1). After 6 days, she went to the emergency department. At the first evaluation, she had no alteration of consciousness, and her vital signs were normal. Her previous medical history was unremarkable except for increased activity levels of coagulation factors (factor II, IX, and X) and vaccination for meningococcus C in 2009 and SARS-CoV-2 in August 2021 (two doses of RNA-based vaccine). Laboratory findings included increased leukocytes count (29,010 cells/µl), neutrophils especially (25,670 cells/µl), and a remarkable C-reactive protein (CRP) (390 mg/dl) and procalcitonin (2.70 ng/ml) increase. Neurological examination was normal, with no evidence of symptoms reflecting meningeal irritation. The head CT scan was normal. Therefore, the patient was admitted to an internal medicine division. However, the following day (7 days after the first symptom suggestive of infection), the patient rapidly developed progressive diplopia with evidence of bilateral abducens nerve palsy, mild left facial nerve palsy with involvement of both superior and inferior branches, nuchal rigidity, and *Lasègue's sign*. As meningitis was suspected, a diagnostic lumbar puncture was performed. At visual inspection, the collected cerebrospinal fluid (CSF) wasturbid and *cloudy*. Standard analysis showed the presence of pleocytosis (1,677 cells/µl, 70% of which were *polymorphonuclear* leukocytes), increased protein (0.90 g/L) and lactate concentrations (6.0 mmol/L), and decreased CSF glucose concentration (1.2 mmol/L). The diagnosis was bacterial meningitis, and antibiotic therapy based on ceftriaxone 4 g/day was started after the admission to our neurology unit. Based on the multiplex *PCR* immunoassay for the rapid diagnosis of infectious meningitis, which provided results in a few hours and showed the presence of *N. meningitidis* W135 serogroup, antibiotic therapy was confirmed. Isoelectric focusing did not reveal any IgG oligoclonal band (Pattern I). In the next few days, the patient's signs and symptoms started to rapidly improve, with complete remission of diplopia and meningeal signs within a week. Also, blood cultures resulted positive for *N. meningitidis*, further confirming the infection.

Brain magnetic resonance imaging (brain MRI) with gadolinium contrast was performed, with evidence of leptomeningeal T2/fluid-attenuated inversion recovery (FLAIR) signal hyperintensities at the level of transverse sinuses, with concurrent gadolinium-based enhancement at diffusion-weighted imaging (DWI) sequences; these findings were compatible with the presence of leptomeningeal purulent material. No cranial nerve enhancement was observed.

However, after the complete remission, left facial nerve palsy progressively worsened into a severe bilateral deficit. No serum antibodies against GM1, GM2, GD1a, GD1b, or GQ1b were detected. A second lumbar puncture was therefore performed on day 10 of hospitalization: the CSF was clear, and its analysis revealed a remarkable decrease of pleocytosis (103 cells/µl) with a qualitative modification (only lymphocytes) and reduced amount of protein (0.75 mg/dl). Interestingly, oligoclonal IgG bands (pattern III: oligoclonal IgG in CSF with additional identical bands in CSF and serum) were present (Figure 2). A follow-up brain MRI with gadolinium contrast was performed 11 days after the first MRI scan: a reduction of the hyperintensity of the leptomeninges at the level of the transverse sinuses and bilateral pathologically relevant gadolinium enhancement in VII and VIII cranial nerves' intrameatal tract bilaterally were observed. As a para-infectious process was suspected, oral steroid therapy was started based on prednisolone 1 mg/kg/day (weight 50 kg) for 5 days, followed by a subsequent decalage for the next 2 weeks, with complete and persistent regression of the symptomatology. Follow-up brain MRI with gadolinium contrast after 4 months showed no facial nerve abnormalities, and the patient did not develop any additional symptoms.

Discussion

The clinical onset of the patient's disease was quite slow and benign for *N. meningitidis*, which typically develops very rapidly. However, the initial presentation of meningococcal disease with a flu-like illness and prodromal symptoms (such as fever, headache, and respiratory and gastrointestinal symptoms) is often reported (6). Cranial nerve palsies during acute bacterial meningitis are not uncommon, as they can be present at the onset or during the infection in 9%–12% of adult patients (7–9). Particularly, oculomotor, abducens, facial, and glossopharyngeal cranial nerve disorders are often observed (7). Nevertheless, cranial nerve palsy in *N. meningitidis* infections is rarely described, and, to our knowledge, only a few cases in adult patients and one pediatric case have been reported in recent times (10–13).

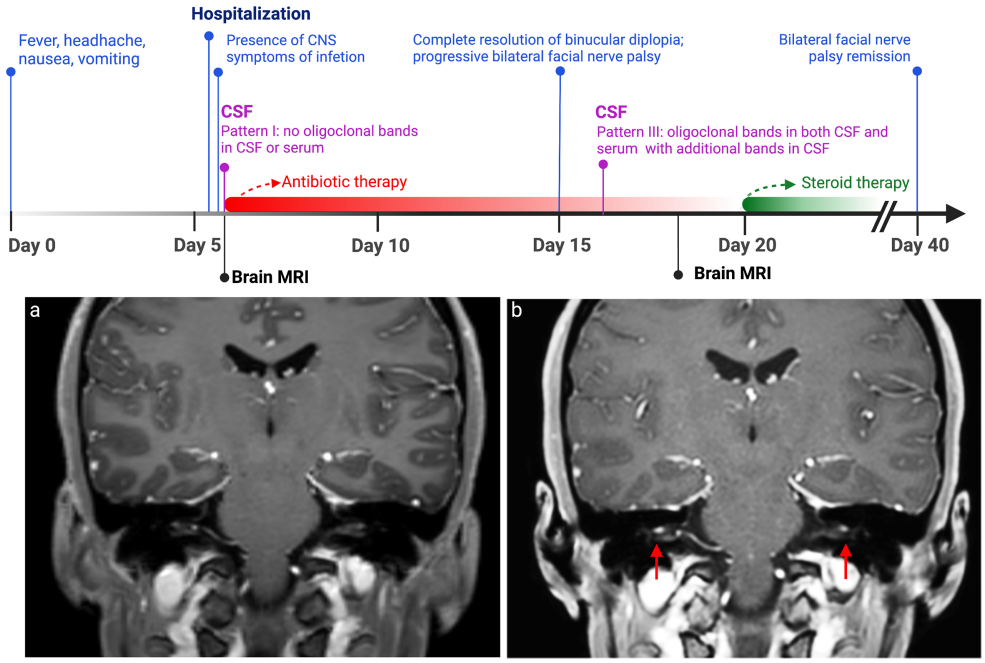

FIGURE 1
Disease timeline. In this timeline are displayed clinical (shown in blue) and CSF (in purple) changes in relation to antibiotic course (in red) and steroid therapy (in green). On the bottom, MRI T1-weighted imaging with gadolinium contrast performed after 18 days from clinical onset **(A)** demonstrated bilateral pathologically relevant gadolinium enhancement in VII and VIII cranial nerves' intrameatal tract bilaterally (red arrows), which was not present in the first MRI **(B)**. CSF, cerebrospinal fluid.

The pathological basis for cranial nerve palsies is not always clear, but it is believed that it might be determined by either the increased intracranial pressure or the meningeal inflammatory reaction adjacent to the cranial nerves (5). In our case herein reported, we first observed a bilateral abducens nerve palsy and associated binocular diplopia, present from the beginning of the infection, and improved when antibiotic therapy was initiated, suggesting a cause directly related to *Neisseria* infection.

The absence of any pathological findings along the VI cranial nerve observed by the MRI might suggest that its deficit might be determined by intracranial hypertension. On the contrary, bilateral facial nerve palsy developed with different characteristics. First, from a radiological point of view, the first MRI with gadolinium contrast performed at the beginning of the infection did not show T2/FLAIR signal intensities or contrast enhancement of the seventh cranial nerves, while pathological gadolinium enhancement was observed only after about 2 weeks from the clinical onset when the infectious process was almost remitted. The normal facial nerve can show various enhancement patterns in MRI sequences; however, intense enhancement of the intrameatal segment, as we observed in our case, can be considered pathological and is often described in Bell's palsy, owing to the breakdown of blood–peripheral nerve barrier and the subsequent diffusion of contrast into the endoneurial space (14).

Moreover, from an immunological point of view, oligoclonal bands were observed in the second analysis of the cerebrospinal fluid, while they were completely absent in the analysis performed in the diagnostic phase 9 days earlier. The presence of identical oligoclonal IgG bands in CSF and serum may be a common finding in acute bacterial meningitis, as a consequence of the systemic immune response; however, oligoclonal IgG band patterns suggestive of intrathecal immunoglobulin production are less common (15), although they are well characterized in chronic bacterial meningitis, such as lymphocytic meningoradiculitis due to *Borrelia burgdorferi* (16) and tuberculosis meningitis (17).

Finally, from a therapeutic point of view, although a mild left facial nerve deficit was already present during admission to our unit, it gradually worsened after ceftriaxone administration, with progression in severe left palsy and development of contralateral facial nerve deficit. Eventually, the bilateral deficit rapidly improved with oral steroid therapy, with complete remission of the symptomatology.

The Infectious Diseases Society of America (IDSA) guidelines recommend the use of dexamethasone (0.15 mg/kg) for 2–4 days with the first dose administered 10–20 min before, or at least concomitant with, the first dose of antimicrobial therapy in adults with suspected acute bacterial meningitis. The use of corticosteroid therapy administered in the initial phase of infection showed a

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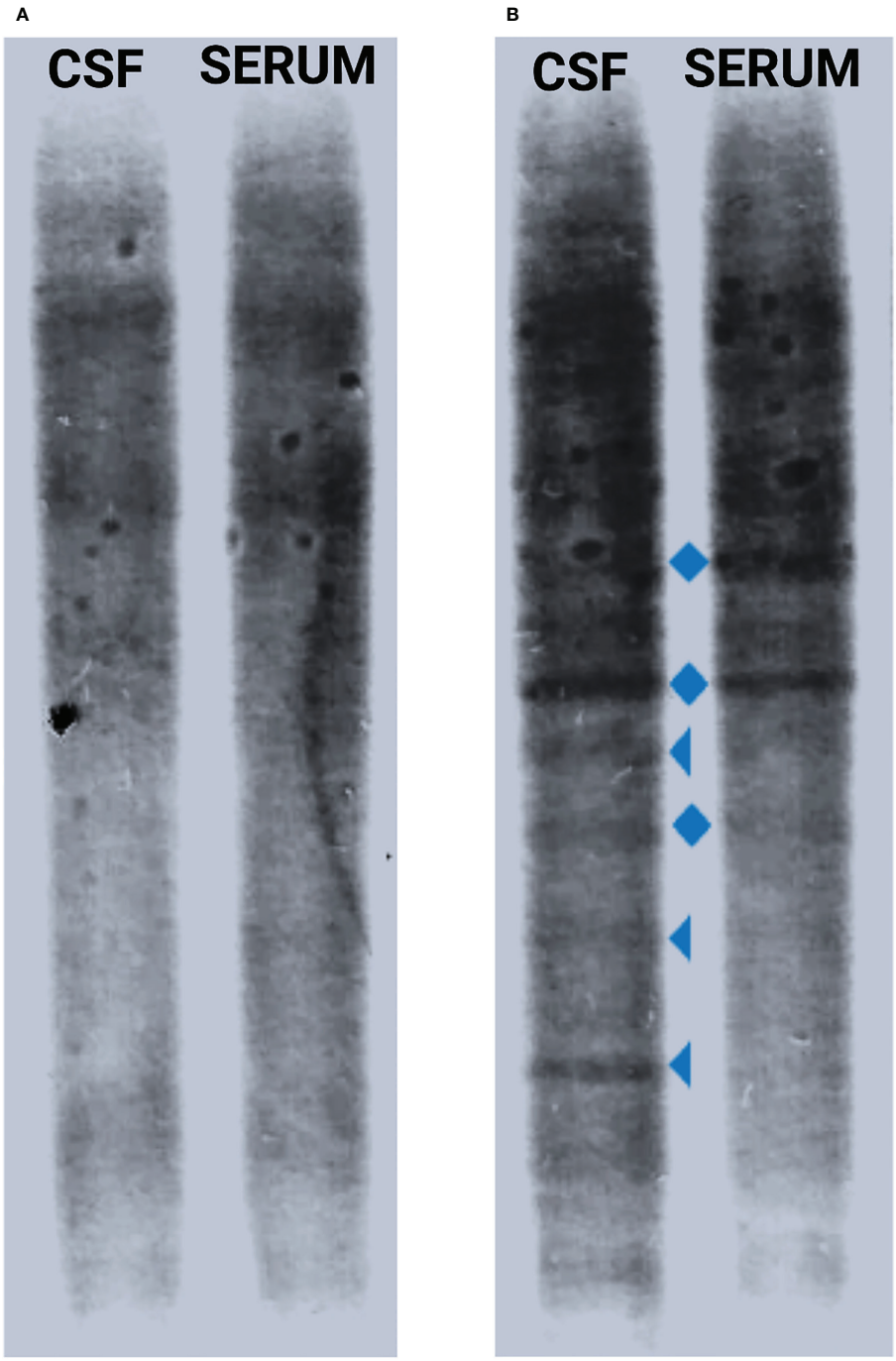

FIGURE 2
CSF IgGOB pattern modification. When the first lumbar puncture was performed at the beginning of the infection, no oligoclonal bands in CSF or serum were found (pattern I) **(A)**, while after 11 days of antibiotic therapy, there was presence of a few CSF-restricted oligoclonal bands (triangle) together with mirror serum–CSF bands (diamond) (pattern III) **(B)**. CSF, cerebrospinal fluid; IgGOB, IgG oligoclonal bands.

lower rate of neurological sequelae in adult patients (i.e., seizures and focal neurological deficits). Also, it is associated with reduced mortality in *Streptococcus pneumoniae* meningitis, but not in *N. meningitidis* or *Haemophilus influenzae* meningitis (18). In our case, the patient did not receive any steroids before starting antibiotic therapy. Although the use of corticosteroids in the early phase of the disease, through the downregulation of pro-inflammatory cytokine production, may be effective in decreasing

pathophysiologic consequences of the inflammation induced by bacterial meningitis (blood–brain barrier (BBB) permeability increase, which determines cerebral edema, intracranial hypertension, and neuronal injury) (19), the effect on BBB might limit or slow immunity recruitment within the CNS. In our case, since neurological symptoms rapidly improved, we decided to delay steroid administration. Despite that there was no evidence that the para-infectious mechanism would be prevented by steroid administration, we cannot exclude that in our case an early administration of dexamethasone would have prevented secondary transient autoimmune reactivity.

Taking into account all those findings, we believe that the bilateral involvement of the facial cranial nerve and the late clinical progression of its deficit may have been not directly related to meningeal inflammation or other acute infectious causes but to some indirect para-infectious inflammatory process.

Cranial nerve neuritis has been described as a rare para-infectious manifestation of viral diseases (20–22). To our knowledge, our case could be the first report of para-infectious cranial nerve palsy associated with acute bacterial meningitis. Interestingly, a full recovery from bilateral facial nerve palsy was achieved with oral steroid therapy, which exerts its effects through immunosuppressive action, suggesting a possible role of the immune response in the development of the nerve deficit, as the oligoclonal IgG bands' finding may also indicate. Since steroid administration in bacterial meningitis might prevent also para-infectious central and peripheral nervous system involvement, our case report suggests that steroid administration also rapidly improves meningitis.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the individual for the publication of this case report. All potentially identifiable images or data included in this article have been anonymized.

Author contributions

ZG and BL acquired clinical and radiological data and wrote the first draft of the manuscript. AM revised all the MRI sequences, radiologically followed up the patient, and wrote the manuscript. MA, RF, and PM supervised the clinical and therapeutic approach, conceptualized the manuscript, and wrote the final draft. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Anti-glycine receptor antibody-positive progressive encephalomyelitis with rigidity and myoclonus initially presenting with one-sided stiff face: A case report

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Background: Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a subtype of stiff-person syndrome, a rare cerebrospinal disease that causes brainstem symptoms, myoclonus, muscle rigidity, and hyperekplexia.

Case presentation: A 71-year-old man experienced left-sided stiff face, and was subsequently admitted to our hospital because of the appearance of left-dominant lower limb myoclonus. Muscle rigidity followed 3 days later. Magnetic resonance imaging revealed no abnormality. An electrophysiological examination showed a toughness of the antagonistic muscle following evocation of the Achilles tendon reflex, and a tonic phenomenon affecting the left facial muscles during the blink reflex. The patient's serum was positive for anti-glycine receptor (anti-GlyR) antibody, suggesting PERM. The patient was administered steroids, immunoglobulin therapy, and immunosuppressive drugs. He gradually improved after these therapies and became able to walk using a walker.

Conclusions: We conclude that this was a rare case of anti-GlyR antibody-positive PERM with unilateral brainstem symptoms, myoclonus, and muscle rigidity.

KEYWORDS

PERM, anti-GlyR antibody, stiff-person syndrome, myoclonus, rigidity, hyperekplexia

Introduction

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a subtype of stiff-person syndrome consisting of limb/trunk muscle rigidity, hyperekplexia, and myoclonus (1). Anti-glycine receptor (anti-GlyR) antibody has been implicated in its pathogenesis (2). In some anti-GlyR antibody-positive PERM cases reported to date, the initial symptoms were stiffness of the lower limbs and myoclonus. In others, brainstem symptoms preceded disease (3). Here, we encountered a case of PERM which initially manifested with trismus due to one-sided stiff face.

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Case presentation

A 71-year-old man whose past medical history was unremarkable experienced sudden trismus and left facial stiffness was admitted to the hospital. On the third day of the patient's hospitalization, left-dominant muscle rigidity, pain, and intermittent myoclonus appeared in both lower limbs, and he was transferred to our hospital. A neurological examination on admission revealed decreased pain and temperature sensation in the mandibular nerve area and muscle rigidity of the left face, in addition to trismus, hoarseness, muscle rigidity of the left lower limb, myoclonus, and hyperekplexia with left lower limb predominance. He had no sensory impairment and had enhanced deep tendon reflexes in his extremities, but no pathological reflexes. One day prior to transfer, dysautonomia appeared, including dysuria, constipation, and excessive sweating of the trunk and extremities. Laboratory tests, including hematological and biochemical analyses, revealed that levels of autoantibodies (anti-nuclear antibodies, anti-SS-A antibody, anti-SS-B antibody), hepatitis B virus antigen, anti-hepatitis C virus antibody, anti- human T-cell leukemia virus type I/II antibodies and tumor marker (carcinoembryonic antigen, colorectal carcinoma antigen 19–9), were normal. However, his erythrocyte sedimentation rate was elevated at 58 mm/h, as was his IgG level at 1981 mg/dl.

A cerebrospinal fluid analysis showed a normal cell count of 3/μL (100% mononuclear cells) and a normal protein level (30 mg/dL). No oligoclonal band was detected. We tested for the presence of the following serum anti-neuronal antibodies: amphiphysin, CV2/collapsin response mediator protein 5, Ma2/Ta, Ri, Yo, Hu, Recoverin, SRY-Box transcription factor 1, titin, Zic, glutamic acid decarboxylase65, Tr, and GlyR. Of these, only anti-GlyR antibody yielded positive reactions in serum and cerebrospinal fluid. Surface electromyogram of the left tibialis anterior and left gastrocnemius muscles revealed continuous, simultaneous co-contraction of both muscles on tapping the Achilles tendon with a reflex hammer. This is suggestive of rigidity in both the agonist and antagonist muscles of the Achilles tendon reflex (Figure 1A). Both the R1 and R2 components of the blink reflex showed higher amplitude on the left compared with the right after stimulation of either side, indicating hyper-excitability on the left side (Figure 1B). Head magnetic resonance imaging showed no structural abnormalities. A whole body computed tomography showed a gastric submucosal tumor, which was diagnosed

Abbreviations: anti-GlyR, anti-glycine receptor; PERM, progressive encephalomyelitis with rigidity and myoclonus.

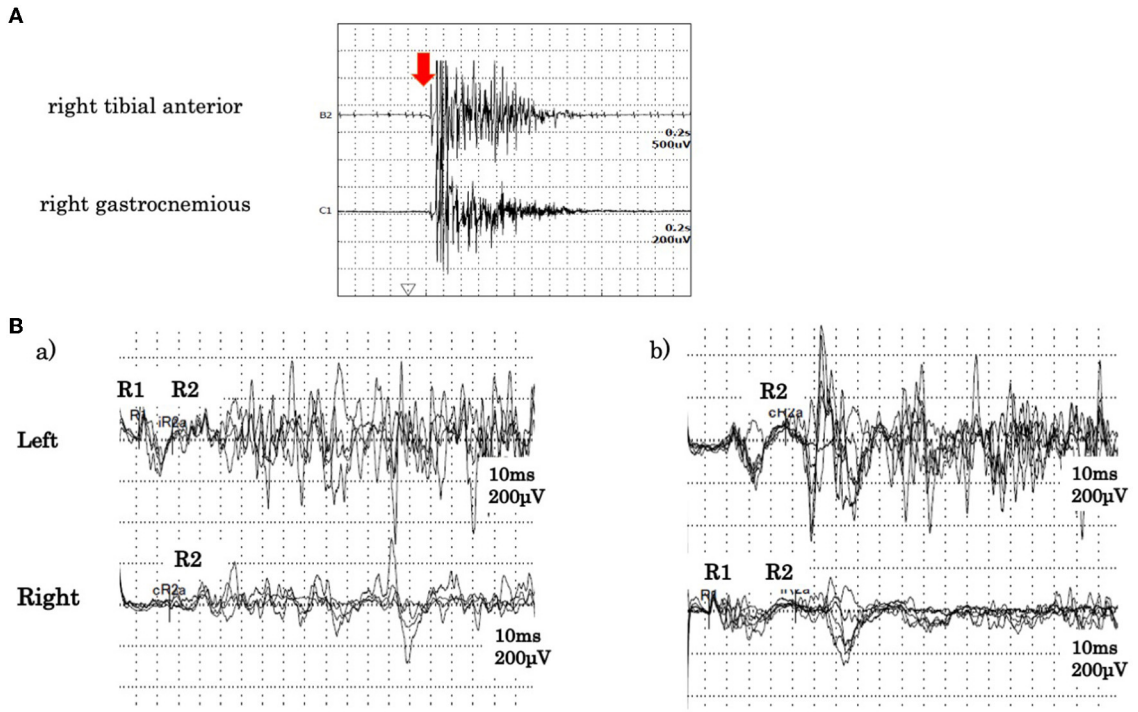

FIGURE 1
(A) Surface electromyogram findings. During the Achilles tendon reflex, tibialis anterior and gastrocnemius muscles exhibited continuous simultaneous co-contraction. The arrow indicates tapping of the Achilles tendon. **(B)** Blink reflex findings. (a) Record obtained on stimulation of the left side. (b) Record obtained on stimulation of the right side. In both (a,b), higher amplitude responses of R1 and R2 were observed from the left eyelid.

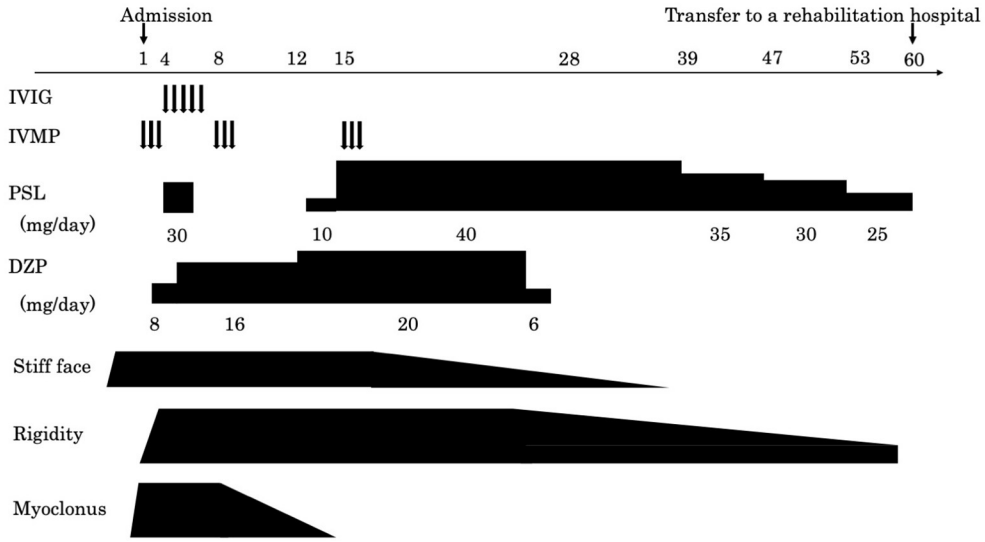

FIGURE 2
A graphical summary of symptom onset and clinical management for the current case. The arrow on the left indicates the date of admission and the arrow on the right indicates the date of transfer.

as a hyperplastic polyp by gastrointestinal endoscopy. We administered three courses of steroid pulse therapy with methylprednisolone (1,000 mg/day; duration 3 days) on the 1st, 8th, and 15th day after admission, as well as high-dose immunoglobulin (400 mg/kg/day; duration 5 days) on the 4th day. Following the third administration of steroid pulse therapy, we administered prednisolone (40 mg/day) and tapered. As symptomatic treatment, the patient was administered diazepam (20 mg/day, oral) and dantrium (75 mg/day, oral). After those steroid therapies, the muscle rigidity of the whole body and the myoclonus of both lower limbs gradually improved. The patient was then transferred for rehabilitation on the 60th day after admission. By the 90th day, his score on the modified Rankin Scale had improved from 5 to 3 (Figure 2).

Discussion and conclusions

Brown et al. first described PERM as a subacute disseminated encephalomyelitis with muscle rigidity and myoclonus, which has a distinct course and symptoms from classical stiff-person syndrome (1). The antibodies involved in PERM include anti-GAD antibody, amphiphysin antibody, anti-gephyrin antibody, and anti-GlyR antibody, all of which are involved in the inhibitory neurotransmission (4). In this case, we confirmed that the antibody was negative for amphiphysin and GAD antibodies, the cause of stiff person syndrome. Although leucine-rich glioma-inactivated 1 and contactin-associated protein-like 2 was not measured, the absence of fasiobrachial dystonic seizure, myotonia, and myokymia ruled out anti-voltage-gated potassium channels complex antibody-related disease. Ultimately, we diagnosed PERM based on positive anti-GlyR antibody in serum and cerebrospinal fluid. The glycine receptor is a pentameric ligand-gated chloride channel that is distributed throughout the brainstem and spinal cord. When glycine binds to these ionotropic receptors on a cell's surface, chloride ions flow into the cell, suppressing post-synaptic membrane excitation (5).

In the brainstem, the GlyR is expressed in the principal sensory nucleus and motor nuclei of the trigeminal nerve, the facial motor nucleus, and the dorsal motor nucleus of the vagus nerve. It is also found on the anterior and posterior horn cells of the spinal cord. While the mechanism of GlyR autoantibody action is not clear, suppression of GlyR function is assumed to induce excessive responses to sensory inputs, such as those from muscle spindles, somatosensory stimuli, and light and sound stimuli. As a result, these stimuli trigger symptoms including facial rigidity, hoarseness, myoclonus, and hyperekplexia of both lower limbs. Stiff-limb syndrome is characterized by the localized involvement of one limb, usually a leg. Unilateral cerebral and spinal cord lesions have been reported on MRI scans in these patients (3). This case presented with symptoms of unilateral brainstem dysfunction, which were followed by symptoms affecting the lower limb on the same side. This suggests that both spinal cord and brainstem lesions are confined to one side. In the electrophysiological examination, the amplitude of both the R1 and R2 components of the blink reflex was higher on the left side after stimulation of either side, and we could visually capture the moment at which the α motor neuron was released from suppression. The R1 response is mediated through the ipsilateral principal sensory nucleus of the trigeminal nerve, while the R2 response is mediated through

TABLE 1 A summary of published seropositive GlyR antibody positive PERM cases (including the current case).

References	Age of onset, sex	Days from onset to immunotherapy	Symptom of onset	Immunotherapy	Respiratory disturbance	mRS after immunotherapy	Outcome
Chang et al. (6)	46, M	1 months	Brain stem syndrome	IVIG, IVMP, PE Oral corticosteroid, AZP	+	5	No recurrence
Yao et al. (7)	52, M	45 days	Headache, dysarthria	IVMP, IVIG oral corticosteroid	+	1	No recurrence
Bernard et al. (8)	78, M	3 months	Seizure, cognitive imparement	IVMP, IVIG PE, AZP	-	4	He died of respiratory infection after 2.5 years
Fujino et al. (9)	62, M	7 weeks	Painful spasm in a leg	IVMP, IVIG Oral corticosteroid	+	1	No recurrence
Mizutani et al. (10)	59, M	2 weeks	Brain stem syndrome	IVMP, IVIG Dxazosin, Cyclosporine RTX, Cyclophosphamide	+	5	He remained bedridden with a tube feeding
Wang et al. (11)	61, M	11 days	Left facial weakness	IVMP, IVIG Oral corticosteroid, mycophenolate mofetil	-	5	No recurrence
Shimazaki et al. (12)	63, M	7 months	Painful stiffness in legs, dysphagia	IVMP, IVIG Oral corticosteroid	-	4	No recurrence
Borellini et al. (13)	60, M	3 months	Painful spasms of trunk and legs	IVMP, IVIG Oral corticosteroid	-	5	He improved after chemotherapy for Hodgkin's lymphoma
Ozaki et al. (14)	75, F	None noted	Rigidity of legs	PE	-	5	He died of respiratory failure after 10 months
Lee et al. (15)	41, F	2 weeks	Hypersomnia, dysphagia, gait disturbance	IVMP, IVIG Oral azathioprine and corticosteroid	-	Not noted	No recurrence
Gluck et al. (16)	63, M	5 months	Sleep requirements and disorganized behavior	High dose steroids, PE, rituximab	+	5	He remained bedridden with a tracheostomy. Modified Rankin scale score is 4 6 months after discharge.
Current case	71, M	3 days	Left stiff face	IVMP, IVIG Oral corticosteroid	-	5	No recurrence

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multiple pathways, including the spinal trigeminal nucleus and the bilateral lateral reticular formation *via* the trigeminal nucleus sensory nucleus. In the present case, both R1 and R2 showed high amplitude on the left side, suggesting hyperexcitability in the facial nucleus and the motor nucleus of the trigeminal nerve as opposed to the internuclear pathway. Additionally, the surface electromyograms of the left tibialis anterior and the left gastrocnemius muscles showed co-contraction and tonicity of both muscles during the Achilles tendon reflex. This indicates excessive excitability of the anterior horn cells of the spinal cord. Iizuka et al. reported that trismus was due to muscle stiffness induced by continuous excitation of alpha motor neurons in the brainstem (5). A summary of published seropositive GlyR antibody-positive PERM cases (including the current case) is provided in Table 1. In recent case reports, brainstem symptoms appeared initially, while myoclonus and rigidity of the lower limbs, hyperekplexia, and painful spasms appeared later. Therefore, there is often a delay between the onset of disease and subsequent diagnosis and treatment. In a case series of 45 glycine receptor antibody-positive PERM cases, most patients showed marked improvement with immunotherapies (17). As introducing immunotherapy within 2 months of onset has been reported to improve prognosis (6), early diagnosis is of great importance. In the present case, we administered immunotherapies from a relatively early stage, sparing the patient from ventilator usage and improving his symptoms promptly.

In conclusion, this is a rare case which presented with hemifacial stiffness (a symptom of unilateral brainstem dysfunction), before developing rigidity and myoclonus with dominance on the left side. Our ability to assess face stiffness and stiffness of the lower limbs electrophysiologically, thereby demonstrating the cause of these symptoms objectively, was key to this diagnosis. Despite the rare initial presentations of this case, the clinical outcome was positive due to early diagnosis and treatment.

Data availability statement

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

Ethics statement

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

Author contributions

K-II, TTat, and TTan made the study plan, conducted the research, and wrote the paper. TM, NS, and SK collected patient's samples and clinical data and supervised the analyses. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Neuromyelitis optica spectrum disorders associated with AQP4-positive-cancer—A case series

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Neuromyelitis optica spectrum disorders (NMOSD) are autoimmune, astrocytopathic diseases affecting the central nervous system (CNS), especially the central optic nerve and spinal cord. Aquaporin 4-immunoglobulin G (AQP4-IgG) is the dominant pathogenic antibody and can be detected in about 80% of patients with NMOSD. Although only a few cases were reported on NMOSD associated with cancer, they demonstrated the potential paraneoplastic link between cancer and NMOSD. In the present study, we report three NMOSD cases associated with cancer, which are teratoma and lung adenocarcinoma, teratoma, and transverse colon adenocarcinoma, respectively. Pathological staining of tumor sections revealed a high AQP4 expression. After tumor removal, all cases were stable and suffered no further relapses, which revealed the potential paraneoplastic mechanism between cancer and NMOSD. One of our patient's serum AQP4-IgG was transiently slightly elevated even though AQP4 was highly expressed in tumor cells, which indicates that AQP4 is not the main pathogenic antibody but might be induced by other underlying pathogenic antibody–antigen reactions.

KEYWORDS

neuromyelitis optic, autoimmune disease, neuro-oncology, aquaporin-4, cancer

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are autoimmune, astrocytopathic diseases affecting the central nervous system (CNS). Aquaporin 4 (AQP4) was identified as the main target protein of NMOSD in 2005 (1), which enabled NMOSD to be an independent entity, apart from multiple sclerosis. Aquaporin 4-immunoglobulin G (AQP4-IgG) can be detected in about 80% of patients with NMOSD (2). Among patients with AQP4-IgG-seronegative, antibodies to myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) account for 42% of all cases (3). Compared to AQP4-IgG-seropositive NMOSD, diagnostic criteria for AQP4-IgG-seronegative NMOSD are more stringent and require critical clinical criteria and additional neuroimaging findings (4). Although the incidence is extremely low, NMOSD were reported to be associated with different types of cancer, of which genitourinary, breast, and lung cancers are most frequently involved (5). NMOSD are

considered paraneoplastic neurologic syndrome (PNS) as NMOSD meets the diagnostic criteria (6). We reported three NMOSD cases associated with cancer, which are teratoma and lung adenocarcinoma, teratoma, and transverse colon adenocarcinoma, respectively. Immunohistochemistry staining of the tumor sections all revealed an AQP4 high expression.

Methods

This study reports three cases and was approved by the Ethics Committee of Soochow University, China. Written informed consent was obtained from all cases.

Case 1

A 30-year-old woman presented with transient loss of consciousness, blurred vision, binaural hearing loss, tinnitus, and slurring speech. Before presenting in our department, she kept visiting the gastroenterology department and was treated there for more than 3 years because of recurrent epigastric pain, nausea, and vomiting. She underwent peroral enteroscopy and transanal enteroscopy, and no obvious abnormalities were found. The patient underwent left ovarian teratoma ablation at the age of 23 years, and she was confirmed to have teratoma in the right ovary when she was 26 years old but did not receive any treatment (Figure 1A). Her cerebrospinal fluid (CSF) demonstrated 1 leukocyte/μL, moderately elevated protein (72 mg/dL), and negativity for oligoclonal immunoglobulin G (IgG) bands (OCBs), and no neoplastic cells were found. She tested for CSF and serum AQP4-IgG, MOG-IgG, glial fibrillary acidic protein antibody (GFAP-IgG), and the autoimmune encephalitis antibody panel (N-methyl-D-aspartate receptor (NMDAR)-IgG, leucine-rich, glioma-inactivated 1 protein (LGI1)-IgG, anti-contactin-associated protein-like 2 (CASPR2)-IgG, γ-aminobutyric acid receptor (GABABR)-IgG, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor 1 (AMPAR1)-IgG, Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor 2 (AMPAR2)-IgG, IgLON Family Member 5 (IgLON5-IgG), dipeptidyl aminopeptidase-like protein 6 (DPPX)-IgG, 65-kDa glutamic acid decarboxylase (GAD65)-IgG, metabotropic glutamate receptor 5 [mGluR5)-IgG, glycine receptor (GlyR)-IgG, and anti-dopamine-2 receptor (D2R)-IgG)], which were all negative (analysis with a cell-based assay). Brain magnetic resonance imaging (MRI) showed fluid-attenuated inversion recovery (FLAIR) hyperintense and contrast-enhancing lesions in the thalamus, hypothalamus, and area postrema (Figures 1E,F). MRI was also done on the spinal cord, but no lesions were remarkable. She presented with the negativity of sero-AQP4-IgG and two core clinical characteristics (optic neuritis and area postrema syndrome); therefore, she was diagnosed with AQP4-IgG-seronegative NMOSD. She was treated with intravenous immunoglobulins (IVIG) (0.4 g/kg/d*5 d) and subsequent methylprednisolone (400 mg*3 d, 200 mg*3 d, 80 mg*3 d, 40 mg*3 d) and maintained with oral steroids. Six months later, her visual and hearing symptoms progressively improved, and the lesions on the cerebral MRI disappeared (Figures 1G,H). The serum AQP4-IgG was slightly elevated [3.16 U/ml; normal, <3 U/ml; ELISA (ElisaRSR AQP4 Ab Version 2, RSR Ltd, United Kingdom)] and turned negative 1 month later. Immunosuppressive treatment was planned to be initiated. However, the treatment was postponed because of the nodule in her right lung (Figure 1B). She underwent resection of the nodule in the Department of Cardiothoracic Surgery and was pathologically proven to have a lung adenocarcinoma (Figure 1C) and a high AQP-4 expression (Figure 1D).

Case 2

This patient was a 39-year-old woman who developed numbness of lower limbs, dysuria, and defecation difficulty in 3 weeks. The cell numbers (white blood cells (WBC) 7 cells/μL) and protein (29 mg/dL) were normal in CSF and OCBs were negative. The AQP4-IgG was positive [87.94 U/ml, enzyme-linked immunosorbent assay (ELISA)] in serum while negative in CSF. She also proved positive for antinuclear antibody (ANA), anti-Sjögren's syndrome type A (SSA), and anti-Sjögren's syndrome type B (SSB) antibodies. The CSF and serum MOG-IgG and GFAP-IgG were also tested but both were negative. Spine MRI displayed T2 hyperintense segmental extensive lesions in the cervical and thoracic spinal cord (Figures 2A,B). An abdominal CT demonstrated a right ovary mass which was pathologically proved to be a mature teratoma (Figures 2C,D). Moreover, AQP-4 expression was detected in the teratoma by immunohistochemistry staining (Figure 2E). Given the positivity of sero-AQP4-IgG and transverse myelitis, she met the NMOSD diagnostic criteria. She completely recovered under intravenous methylprednisolone (500 mg*3 d, 250 mg*3 d, 120 mg*3 d, 80 mg*3 d) and was maintained with low-dose oral steroids. Serum AQP4-IgG was still positive but decreased to 21.10 U/ml 4 months later.

Case 3

A 25-year-old man presented with decreased visual acuity in both eyes for 2 months. Visual acuity of the right eye (VOD) was counted on fingers/before the eye, and visual acuity of the left eye (VOS) was 0.06 (best-corrected visual acuity was measured as Snellen decimal notation). The analysis of his CSF showed that the cell numbers were normal (WBC 6 cells/μL), the protein was moderately elevated (76 mg/dL),

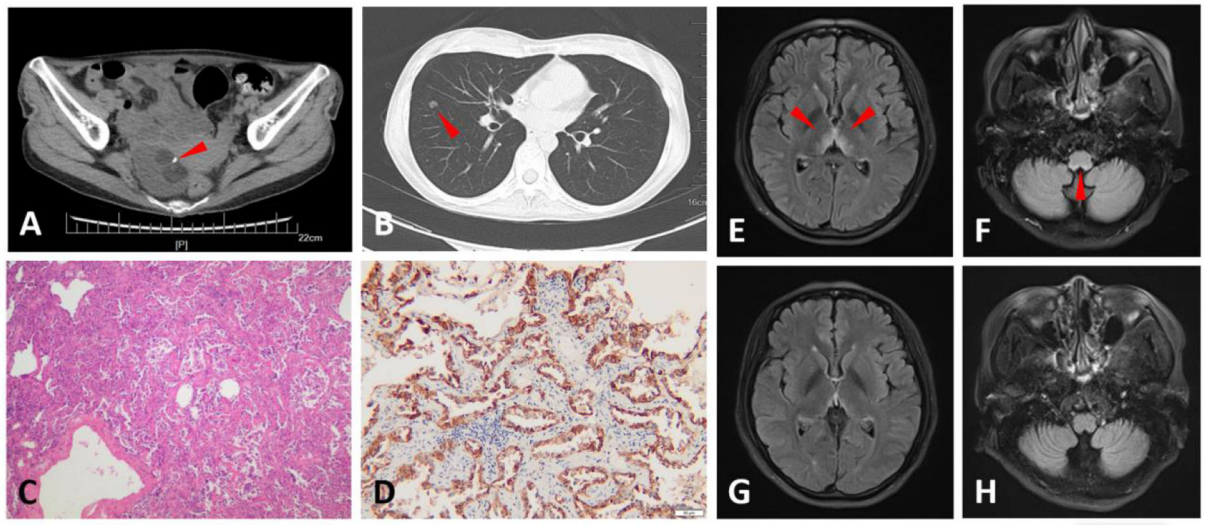

FIGURE 1
Computed tomography (CT), magnetic resonance imaging (MRI), and pathological findings of Case 1. An abdominal CT scan shows a tumor in the right ovary, in which calcification and fat were observed, and suggests an ovarian teratoma (arrowhead) **(A)**. Chest CT scan shows a nodule (9 mm in diameter) in the right lung (arrowhead) **(B)**. Hematoxylin and eosin (H&E) staining of the lung nodule section indicates adenocarcinoma **(C)**. The lung nodule section stained with aquaporin-4 (AQP-4)-specific monoclonal antibody (sc-32739, Santa Cruz, United States of America) shows intense immunoreactivity on adenocarcinoma cells **(D)**. Fluid-attenuated inversion recovery (FLAIR) images of the brain display hyperintense symmetrical lesions in the thalamus, hypothalamus **(E)**, and area postrema **(F)** when the patient was first present in our department (arrowhead). These lesions disappeared 6 months later **(G,H)**.

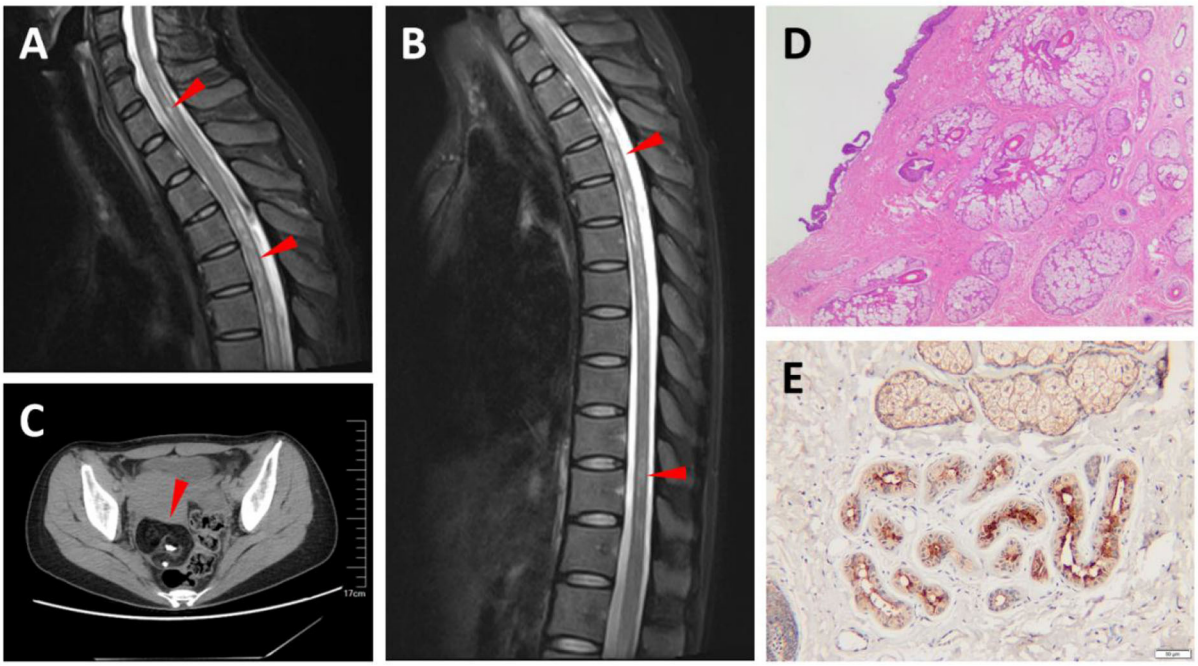

FIGURE 2
Magnetic resonance imaging (MRI) and pathological findings of Case 2. T2-weighted MRIs show abnormal signals in the cervical and thoracic spinal cord (arrowhead) **(A,B)**. An abdominal computed tomography (CT) shows a tumor in the right ovary, in which calcification and fat were observed, and suggests an ovarian teratoma (arrowhead) **(C)**. Hematoxylin and eosin (H&E) staining of teratoma section **(D)**. Teratoma section stained with aquaporin-4 (AQP-4)-specific monoclonal antibody shows intense immunoreactivity **(E)**.

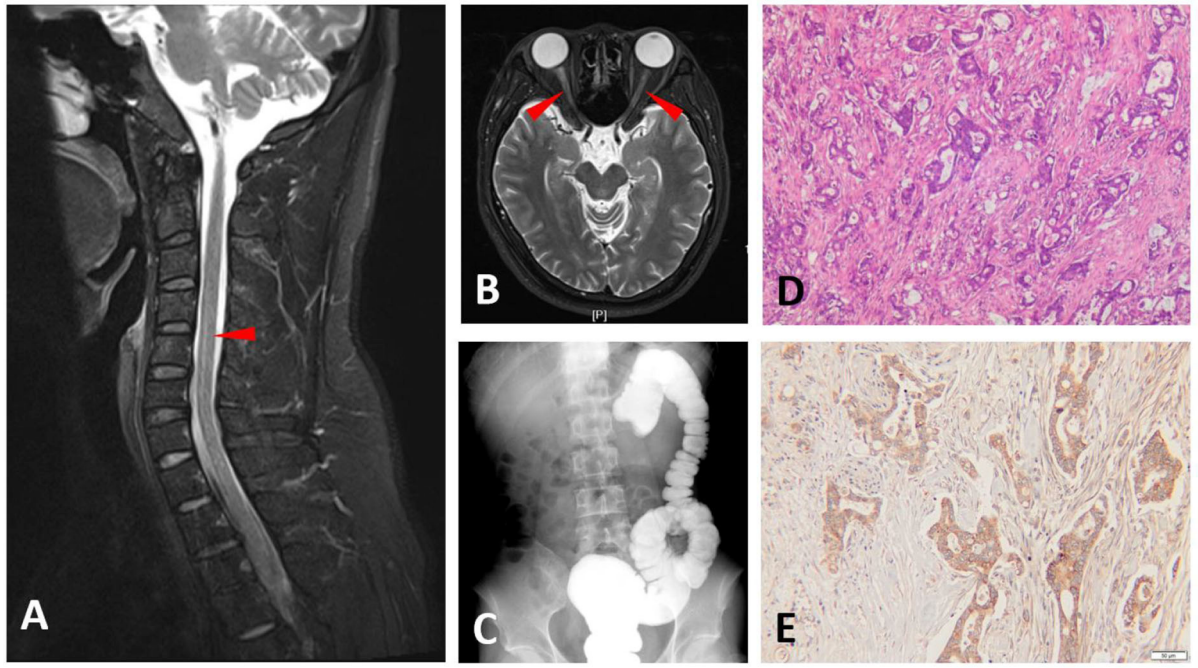

FIGURE 3
Magnetic resonance imaging (MRI), barium enema, and pathological findings of Case 3. T2-weighted MRIs show abnormal signals in the cervical spinal cord **(A)** and T2-weighted fat-suppressed MRI displayed hyperintensity in bilateral optic nerves **(B)** (arrowhead). Barium enema shows truncation of the transverse colon **(C)**. Hematoxylin and eosin (H&E) staining of the transverse colon tumor section **(D)**. Aquaporin-4 (AQP-4)-specific monoclonal antibody staining of the transverse colon tumor section shows intense immunoreactivity **(E)**.

and OCBs were negative. CSF- and Sero-AQP4-IgG were both positive (5.17 and 62.44 U/ml, respectively, ELISA). MOG-IgG was positive in the serum and negative in the CSF. He was also tested for sero- and CSF-GFAP-IgG, which were both negative. The MRI showed T2 hyperintense signals in the cervical spinal cord (C4-6) (Figure 3A) and hyperintensity of bilateral optic nerves on T2-weighted fat-suppressed MRI (Figure 3B). He was diagnosed with NMOSD, as he met the NMOSD diagnostic criteria (optic neuritis and AQP4-IgG-seropositive). He received IVIG (0.4 g/kg/d*5d), intravenous methylprednisolone (500 mg*3 d, 250 mg*3 d, 120 mg*3 d, 80 mg*3 d), and was maintained with oral prednisolone. He was treated with rituximab two and 11 months later, respectively (600 mg/time). However, the vision of both eyes progressively declined. Three weeks after the second rituximab treatment, the visual acuity was measured. VOD was light perception and VOS was 0.04. Besides, he developed abdominal distension, nausea, and vomiting. Abdominal CT showed a mass in the transverse colon and it was histologically proved to be a tubulovillous adenoma (these tests were done in another hospital and so the images were not available). Barium enema indicated local truncation of the transverse colon (Figure 3C). Radical resection was performed which was followed by anti-tumor chemotherapy. The biopsy of the tumor was consistent with that before (Figure 3D). AQP4 staining of the adenocarcinoma was positive (Figure 3E). Two months later, the sero-AQP4-IgG decreased significantly (32.17 U/ml vs 69.28 U/ml) and his condition remained stable.

Discussion

Paraneoplastic NMOSD cases are relatively rare, but they are considered as PNS (6), which are neurological disorders that might be triggered by antigen mimicking between tumor cells and nerve tissues followed by antibody cross-reacting. In 2021, Shahmohammadi and colleagues summarized NMOSD cases associated with cancer (5). There were 62 patients in total, of which lung adenocarcinoma ($n = 9$), gastrointestinal cancer ($n = 7$), and teratoma ($n = 5$) accounted for 14.5, 11.3, and 8.1%, respectively. After this review, two and one more paraneoplastic NMOSD cases associated with lung adenocarcinoma (7, 8) and teratoma (9) were reported respectively. Although mature teratomas are generally benign, malignant transformation occurs in 1.5%−2% of cases (10), and this makes teratoma a form of cancer.

Here, we report three NMOSD cases that were associated with AQP4-positive cancer. Case 2 and Case 3 are AQP4-IgG-seropositive, and the concentration of AQP4-IgG decreased after tumor resection and suffered no relapse. This highlights

the potential paraneoplastic mechanism between cancer and NMOSD. However, Case 3 received rituximab before the operation, which could also reduce the generation of AQP4-IgG. Aquaporins (AQPs) were found to be commonly expressed in various cancer types due to the feature of trafficking water and other small molecules, which facilitate cancer development and progression. According to Dajani and colleagues, AQP4 is mainly overexpressed in brain, lung, and thyroid cancers (11). However, AQP4 was also proved to be expressed in other cancers, and the total positive rate reached 80% (5). Positive AQP4 staining of lung adenocarcinoma, gastrointestinal cancer, and teratoma was detected to be 80% (4/5), 33.3% (1/3), and 100% (5/5), respectively. AQP4 is a self-antigen and AQP4-IgG should not be generated due to immune tolerance. However, sero-AQP4-IgG-positive in these patients reveals the breakdown of self-tolerance. The possibility for this breakdown may be attributed to the fact that the structure of AQP4 on tumor cells is changed and triggers the generation of corresponding antibodies (12). AQP4 is associated with tumor growth, angiogenesis, and metastasis (11). The generation of AQP4 antibodies can prevent cancer development and spread, but meanwhile it will cause NMOSD by targeting CNS. This might be the potential mechanism of paraneoplastic NMOSD.

Ontaneda reported the first and only paraneoplastic NMOSD case associated with different types of cancer (breast carcinoma and leiomyosarcoma) to date (13). To our knowledge, Case 1 is the first paraneoplastic NMOSD case associated with both recurrent teratoma and lung adenocarcinoma. The teratomas all showed AQP4 expression in six reported NMOSD cases associated with teratoma (5, 9); therefore, we infer that the teratomas of Case 1 are AQP4 positive. However, her serum AQP4-IgG was transiently positive and at a very low concentration, even though AQP4 was highly expressed in adenocarcinoma cells. The specificity and sensitivity of the serum AQP4-assay kit used in this study are 99% and 77%. The reason may be attributed to the fact that the concentration of AQP4-IgG is too low to be detected by the present method (14). Another possibility is that AQP4-IgG is not the main pathogenic antibody but it might be induced by other underlying pathogenic antibody–antigen reactions. According to Passeri, some newly described auto-antibodies (GFAP-IgG, anti-collapsin response-mediator protein-5, anti-amphiphysin, anti-neuronal nuclear antibody-1, DPPX-IgG, GAD65-IgG, anti-Yo, anti-Ri, and others) can also mimic NMOSD (15). Unfortunately, only a few common antibodies were tested in our cases.

To conclude, herein we report three NMOSD cases associated with different types of cancer. The histological analysis demonstrates AQP4 high expression on tumor cells in all cases. They all suffered no further relapses after tumor removal. The cross-talking between NMOSD and cancer remains a mystery and is worth further in-depth research.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Soochow University, China. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XW performed the immunohistochemistry staining and analyzed and interpreted the data. XD, HG, XJ, XX, and FZ collected and interpreted clinical data of patients. QX supervised the study and assisted with data interpretation and manuscript preparation. YD assembled the data and wrote the manuscript, which has been reviewed by all authors. All authors contributed to the article and approved the submitted version.

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Misdiagnosis of Susac syndrome as demyelinating disease and primary angiitis of the central nervous system: A case report

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Susac syndrome (SuS) is a rare neuroinflammatory disease that manifests with a triad of hearing loss, branch retinal artery occlusions, and encephalopathy. Patients with SuS are frequently misdiagnosed because the clinical trial is incompletely present at disease onset. In this report, we present a case of a 29-year-old man manifesting sleepiness, epilepsy, urinary dysfunction, and hemiparesis at the initial stage. Magnetic resonance imaging (MRI) revealed multiple abnormal signals located in the lateral paraventricular, corpus callosal, and pons. In addition, the patient had sustained elevation of CSF pressure and protein. ADEM was considered according to the clinical and radiographic findings. However, symptoms were not significantly improved after methylprednisolone therapy. He showed a vision decline in the third month after the disease onset. It was considered from intracranial hypertension or optic neuritis, and therefore retinal arteriolar impairment was ignored. As the disease progresses, cognitive decline was presented. Brain MRI exhibits multiple significant hyperintensities on the DWI sequence with speck-like gadolinium enhancement. Thus, PACNS was diagnosed. The SuS was not made until the presence of hearing decline in the 4 months after the disease onset. The case will be helpful for clinicians to better recognize the atypical initial manifestation of SuS.

KEYWORDS

Susac syndrome, demyelinating, primary angiitis of the central nervous system, acute disseminated encephalomyelitis, encephalopathy

Introduction

Susac syndrome (SuS) is a rare immune-mediated disease that predominantly involves the small arteries of the brain, retina, and inner ear, leading to endothelial cell damage and consequent vascular occlusion. It is characterized by acute encephalopathy, visual impairment, and sensorineural deafness. The disease mainly affects young women (male-to-female ratio of 1:3.2) (1). The rates of misdiagnosis are high, especially when rare clinical manifestations, including epilepsy (4%), urinary dysfunction (9%), and

hemiparesis (20%), occur (2). In this report, we present a case of a man with SuS showing these rare symptoms at the early stage of the disease, which was initially thought to be acute disseminated encephalomyelitis (ADEM) and subsequently considered to be primary angiitis of the central nervous system (PACNS).

Case description

A 29-year-old man visited the local hospital because of 3 months of sleepiness, hyporesponsive, dizziness, and left hemiparesis. Physical examination showed that the muscle strengths of the left and right limbs were 4/5 and 5/5, respectively. Brain magnetic resonance imaging (MRI) showed hyperintensities on T2-weighted imaging and sagittal fluid-attenuated inversion recovery imaging (subcortical, periventricular, corpus callosum, and brainstem), with a quasi-circular region of restricted diffusion (Figure 1). Cerebrospinal fluid (CSF) test results revealed 7×10^6/L white-cell count and 4.1 mmol/L glucose, 119.2 mmol/L chloride, and 1,241 mg/L protein levels. No antibodies against AQP4, MOG, GFAP, oligoclonal bands (OBs), autoimmune encephalitis-associated proteins, and paraneoplastic antibodies (anti-Hu, anti-Yo, anti-Ma2, anti-amphiphysin, anti-NMDAR, anti-VGKC, and anti-GABABR) were detected in the serum and CSF. Methylprednisolone was administered after diagnosing the case as possible acute disseminated encephalomyelitis (ADEM). However, the patient subsequently developed slurred speech and had simple-partial seizures (three times daily). Electroencephalogram exhibited median-high–amplitude (theta-delta) wave in the bilateral cerebral hemisphere. A re-examination using MRI revealed enlarged foci without gadolinium-enhanced lesions. CSF test results showed elevated initial pressure (320 mm H_2O) and protein level (1,598.9 mg/L). Moreover, the results of cell counts (0×10^6/L), smear analysis, and metagenomic next-generation sequencing revealed no abnormalities. After 5 days of immunoglobulin and methylprednisolone treatment, the symptoms were relieved. Brain MRI showed lesion shrinkage. The patient was prescribed low-dose oral prednisone and antiepileptic drugs post-discharge.

The patient presented with visual rotation, urinary dysfunction, nausea, and vomiting within a month post-discharge. Enlarged lesions involving the caudate nucleus and cortex were observed on brain MRI, particularly significant hyperintensity of foci on diffusion-weighted imaging (DWI). Therefore, PACNS was considered. The symptoms did not significantly improve upon treatment with immunoglobulin and rituximab (500 mg) to prevent relapse. Eventually, the patient was referred to the First Medical Center of Chinese PLA General Hospital. A review of his medical history revealed that the headache symptoms started 2 months pre-symptom-onset as intermittent pulsatile headaches in the right frontotemporal region. Physical examination showed a moderate cognitive decline (Mini-Mental State Examination score: 23/30, and Montreal Cognitive Assessment: 22/30). Other positive signs included pyramidal tract and meningeal irritation signs. Results of laboratory tests for routine blood parameters, biochemical factors, infection indicators, and tumor markers were normal. Furthermore, tests for demyelination-related antibodies, including those against AQP4, MOG, and GFAP, were negative. CSF findings showed 250 mm H_2O initial pressure and 1,028.7 mg/L protein level. Brain MRI results indicated that the lesion had diminished, with multifocal enhancement, compared with the MRI finding 1 month before. Therefore, the possibility of PACNS disease was considered. However, the symptoms continued to progress, and. the patient complained of decreased vision. Ophthalmic examination showed poor vision (20/125 and 20/32 in the left and right eyes, respectively; Snellen scale) and optic-disc edema in both eyes and cotton-wool-like lesions in the retina of the right eye. The patient experienced a hearing decline in both ears 4 months after the onset. Subsequently, a hearing test showed binaural sensorineural deafness (low-medium -frequency) (Figure 2). A re-test of visual acuity (naked eye) revealed scores of 20/200 and 20/32 in the left and right eyes, respectively. Fundus fluorescein angiography displayed branch retinal artery occlusion and leakage of the micro-arterial wall (Figure 1). Ultimately, the diagnosis of SuS was confirmed based on the above findings (Figure 1), and subsequently, methylprednisolone and infliximab were administered. No recurrence of symptoms was observed, and cognition ability was normal (MMSE score: 30/30, and MoCA: 29/30) at the latest follow-up (01. Nov. 2022).

Discussion

Susac syndrome is rare autoimmune microangiopathy that was first reported by Susac et al. in 1979 (3) and has an annual incidence of 0.024 per 100,000 (95% CI 0.010–0.047) (4). Only 13–30% of patients present with a full triad of vascular endothelium impairment in the brain, retina, and cochlea, and obstruction of small arteries during the initial stage (1). Thus, SuS may be easily misdiagnosed in the initial stage. In the present case, the patient showed rare clinical manifestations, including seizures and urinary dysfunction, as the initial symptoms, leading to misdiagnosis.

The diagnostic criteria established by the European Susac Association in 2016 include brain, retinal, and vestibulocochlear involvement (1). Although a central snowball-like lesion in the corpus callosum is a relatively characteristic image, it may not be present in the early stage, as was the case in our patient. He was initially misdiagnosed with ADEM because multiple lesions contributed to the white matter (particularly corpus-callosum and brainstem involvement), and he responded well to prednisone therapy. In the following stage, PACNS was

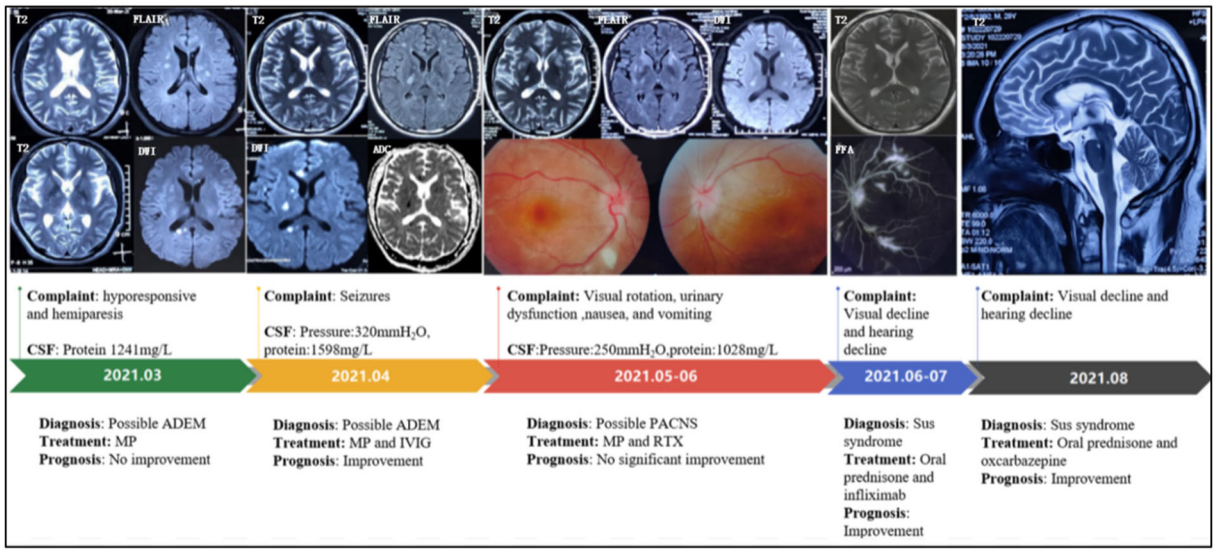

FIGURE 1
Disease progression map. CSF, cerebrospinal fluid; ADEM, acute disseminated encephalomyelitis; MP, methylprednisolone; IVIG, intravenous immunoglobulin; PACNS, primary angiitis of the central nervous system; RTX, rituximab; FFA, Fundus fluorescein angiography.

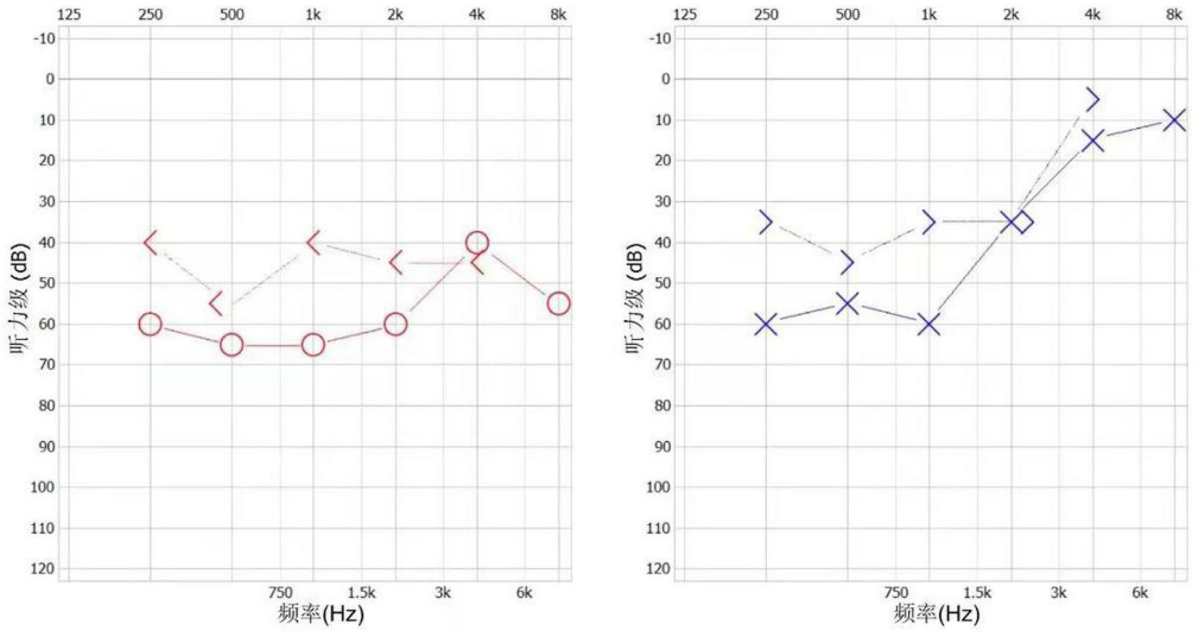

FIGURE 2
The patient's audiogram.

diagnosed based on the following points: (1) The patient with the encephalopathy-like presentation; (2) Clinical manifestations are severe; (3) MRI show acute ischemia-like hyperintensity on DWI sequence (Figure 1). Distinguishing SuS from PACNS is challenging when the early manifestations are hemiparesis and epilepsy. Increased intracranial pressure and CSF protein level and lesions with restricted diffusion on DWI can be observed in both PACNS and SuS (5). Seizures seem more common in patients with PACNS than in patients with SuS (8/15 vs. 1/13, $p = 0.035$) according to a multicenter study (5). A total of 42% of patients with PACNS have multiple disseminated lesions including cortex, caudate, and deep white

matter (6). Additionally, patients with SuS who manifested relapsing-remitting course with multiple periventricular T2 FLAIR hyperintensity may be easily misdiagnosed as multiple sclerosis (MS). A recent study found the diagnosis of MS was originally prioritized in 16% of patients with SuS (7). Nevertheless, for the present case, MS was not considered because encephalopathy-like episodes at the early stage rarely occur in patients with MS (8), especially with impairment in the caudate nucleus as well as significant hyperintensity of lesions on DWI. Unfortunately, the visual decline in the present case was considered to be caused by demyelination and intracranial hypertension. As the possible involvement of small retinal arteriopathy was ignored, fundus fluoroscopy was not performed in time, leading to an oversight in the differential diagnosis. Notably, SuS needs to be differentiated from lymphoproliferative disorders and specific infections. CSF examination, including evaluation of the inflammatory parameters and IL-10 levels and cytological assessment, can help with differential diagnosis.

Recently, the underlying pathogenesis of SuS is still far from clarification. An international multicenter study showed high-titer IgG1 and IgM anti-endothelial cell antibodies (AECA) in some patients with SuS, indicating that humoral autoimmunity may play a role in the pathogenesis of SuS (9). Patients with Sus were treated based on clinical experience. The latest treatment guidelines recommend stratified treatment according to the severity of the disease (1). For our patient, the symptoms improved after the administration of methylprednisolone combined with infliximab.

Conclusion

Susac syndrome is often misdiagnosed owing to its rarity, especially in patients manifesting epilepsy, urinary dysfunction, and hemiparesis with or without cortical functional decline, as the initial manifestation. Therefore, brain MRI, binocular vision assessment, and hearing tests must be performed as early as possible when patients show these symptoms. Given the high sensitivity to suspicious clinical findings, regular follow-up is extremely crucial for a correct diagnosis.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the First Medical Center of Chinese PLA General Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

GW and WJ collected the data and prepared the manuscript. ZL analyzed the data and created the figures. LW and DH designed and supervised the work. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Case report: Pain in anti-DPPX encephalitis

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Encephalitis due to antibodies targeting dipeptidyl-peptidase-like protein 6 (DPPX), a potassium channel subunit, is rare. The illness is typically characterized by a triad of weight loss, CNS hyperexcitability and cognitive symptoms, but recent reports suggest that the clinical picture may be more heterogeneous. Here, we describe the case of a 63-year-old female who was admitted to the hospital with severe extremity pain, which had been preceded by diarrhea and weight loss. She later developed cognitive changes, and her general condition rapidly deteriorated. Extensive workup did not reveal gastrointestinal illness or underlying malignancies. MRI of the brain was normal. Analyses of blood and cerebrospinal fluid showed normal cell counts but high titres of DPPX antibodies in blood and cerebrospinal fluid. The patient was treated with intravenous methylprednisolone followed by rituximab. At 1-year follow-up, she was without pain and had completely recovered. In this case, DPPX-associated autoimmune encephalitis was dominated by severe extremity pain, illustrating that sensory symptoms may be one of the main complaints in these patients. It is important for clinicians to be aware of the heterogeneous clinical picture in this serious condition, since correct diagnosis and treatment with immunosuppressants are associated with favorable prognosis.

KEYWORDS

anti-dipeptidyl-peptidase-like protein 6 (DPPX), autoimmune encephalitis, weight loss, extremity pain, rituximab

Introduction

Encephalitis associated with anti-dipeptidyl-peptidase-like protein 6 (DPPX) is a rare condition associated with weight loss, gastrointestinal symptoms, and neurological symptoms (1, 2). Major features include cognitive changes and central nervous system (CNS) hyperexcitability, as well as cerebellar symptoms and sleep disturbances (2). Symptoms are thought to arise due to antibodies that bind to the cell-surface antigen DPPX, which is a subunit of the Kv4.2. potassium channel (3). DPPX is expressed in many brain areas, including the hippocampus and cerebellum, as well as in the myenteric plexus (1). Reduced expression of DPPX and thus decreased Kv4.2 potassium channel activity in the gastrointestinal tract accompanied by neuronal hyperexcitability may be the cause of gastrointestinal symptoms and weight loss in these patients (2). In this paper,

we describe a case of DPPX antibody-associated autoimmune encephalitis in which severe extremity pain was the major complaint; the patient also suffered from diarrhea, weight loss, and cognitive changes.

Case presentation

A 63-year-old female was referred to Haukeland University Hospital after she developed painful, burning sensations and paresthesia, primarily in the extremities. A timeline of the symptoms and treatment are shown in Figure 1. The symptoms had progressed over 4 to 6 months prior to the hospitalization. In the same period, she had felt nauseous, had little appetite, and had developed diarrhea leading to a weight loss of 18 kg. The patient also complained of headache, dizziness, and insomnia. At night, she often walked on a cold floor to get some relief from her lower extremity pain. All her extremities felt heavy, and she complained of muscle ache. She also developed a red erythema on her chest and had slight general pruritus. Her earlier medical history included migraine, gout, gastroesophageal reflux, and cholecystectomy, however she was active and lived independently in her home.

The patient was extensively examined without findings of gastrointestinal illness. She had a normal gastroscopy and colonoscopy with normal biopsies and no signs of coeliac disease or a neuroendocrine tumor. In initial workup, blood tests were normal with only slightly elevated hemoglobin and ferritin levels. Tests were negative for antinuclear antibodies, and protein electrophoresis was normal. An infectious agent could not be identified. In addition, a broad endocrinology workup was normal. The patient was also screened for underlying malignancies. Total body CT scan showed multiple, partly cystic changes in the uterus, and further gynecological evaluation confirmed the presence of myomas with normal cervical cytology and endometrial biopsy samples. Whole body PET-CT scan and brain MRI were normal.

During the months after her first hospitalization, the patient's general condition worsened with progression of weight loss and increasing apathy. Throughout the course of the disease, she had persistent severe pain and allodynia as her major complaint, which restricted her daily life significantly. Clinical neurological examination at this stage was normal. Electromyography showed active denervation and nerve conduction study showed slight axonal and demyelinating motor and sensory changes in the lower extremity. Electroencephalography showed frequent focal low-frequency activity on the left frontotemporal area, both arrhythmic and single waves. There were also short second-long sequences with diffuse low-frequent activity.

5 months after the start of her diagnostic evaluation, the patient was unable to take care of herself. She was underweight with a BMI of 18, spent most of her days confined to the bed, and was not able to walk without support. At this stage, she showed reduced facial expressions, a low mood, and significant apathy and fatigue. She also had memory deficits with problems recalling details of her medical history. She repeated the same sentences, had difficulties changing topics during conversation, and had difficulties concentrating. Her gait was unsteady with some truncal ataxia but without tendency to fall. She had slightly increased tone in the extremities but no symptoms of cerebral hyperexcitability. Upper and lower extremity pain continued to be a major complaint.

Routine screening of blood was normal. Analysis of cerebrospinal fluid showed normal cell count and moderately increased level of protein. High titres of anti-DPPX antibodies were found in serum (10^6) and cerebrospinal fluid (10^3) (Figures 2A,B). The IgG subclass distribution of anti-DPPX in both serum and cerebrospinal fluid was: IgG4>>IgG2>IgG1=IgG3 (Figures 2C,D). No other encephalitis or paraneoplastic antibodies were detected using the Euroimmune autoimmune encephalitis mosaic 6 cell-based assay or the Ravo PNS 14 line assay. Her condition was assessed as probable DPPX antibody-associated autoimmune encephalitis with severe weight loss, and she was started on high-dose intravenous corticosteroids (methylprednisolone 1 g) for 5 days with subsequent slow dose tapering of prednisolone over several months. Initial treatment with methylprednisolone improved the patient's condition. She was subsequently treated with an infusion of rituximab (1,000 mg) beginning 1 month after discharge and with two additional rituximab treatments (500 mg each) at 6-month intervals. She was discharged from the hospital into a rehabilitation institution. After slow and gradual improvement, she returned to her home after several months. Serum tested 7 months after the initial antibody screening showed a decrease in the anti-DPPX titer (10^4). At a year after treatment initiation with corticosteroid, she had gained weight, completely recovered from the pain and other neurological complaints, and lived independently in her home performing all activities of daily living. Her neurophysiological changes were also normalized. She has since been without any immune therapy.

Discussion

Autoimmune encephalitis refers to a group of conditions with varying symptomatology caused by autoantibodies toward cell-surface antigens or synaptic antigens such as neurotransmitter receptors or ion channels (4). Encephalitis caused by antibodies that bind to the Kv4.2 potassium channel subunit DPPX was described by Boronat in 2013; symptoms reported included weight loss and gastrointestinal symptoms, CNS hyperexcitability, cognitive changes, sleep disturbances, and cerebellar symptoms (1). DPPX is expressed in areas such as the hippocampus, cerebellum, and myenteric plexus (1).

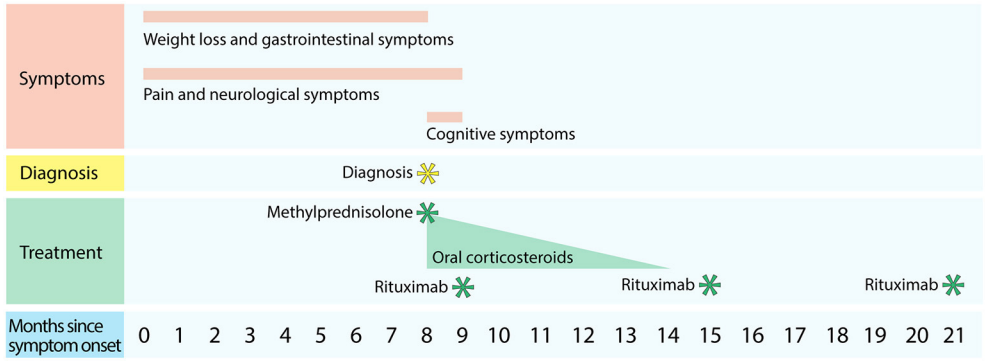

FIGURE 1
Time course of symptoms, diagnosis, and treatment.

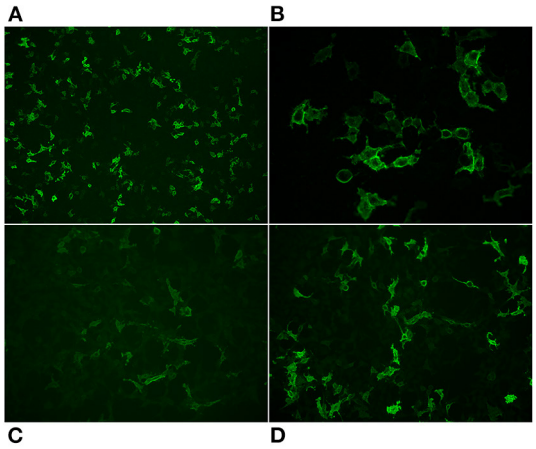

FIGURE 2
Representative images of the reaction of antibodies from the patients' serum with cells that express DPPX. Total IgG staining 10x **(A)** 40x **(B)**, IgG2 20x **(C)**, IgG4 20x **(D)**.

TABLE 1 Reported symptoms in 65 patients with DPPX antibody-associated encephalitis*) **).

Symptoms	Number of patients with symptom (%)	Female/male
Gastrointestinal symptoms and/or weight loss	47 (72 %)	15/31***)
Cognitive dysfunction	56 (86 %)	18/37***)
Psychiatric symptoms	24 (37 %)	12/12
CNS hyperexcitability (myoclonus, tremor, hyperreflexia seizures)	49 (75 %)	13/35***)
Paresis	1 (2 %)	1/0
Cerebellar dysfunction	29 (45 %)	12/17
Brain stem disorders	16 (25 %)	5/11
Dysautonomia	19 (29 %)	5/11****)
Sleep disorders	26 (40 %)	11/15
Sensory symptoms (allodynia, pruritus)	5 (8%)	0/5

*) Based on the following studies 1, 2, 5–23.
**) Details given in Supplementary Table S1.
***) Gender not reported for one patient.
****) Gender not reported for three patients.

To date, 65 patients with encephalitis caused by antibodies to DPPX have been described in the literature (1, 2, 5–23) (Table1 and Supplementary Table S1). The median age of these patients at diagnosis was 52 (range 13–80), and 66 % of the reported cases were male. The most commonly reported symptoms are cognitive, reported in 56 of 65 patients (86%). Also common were CNS hyperexcitability (49/65 patients; 75%) and weight loss and/or gastrointestinal symptoms (47 of 65 patients; 72%). A little less than half of the reported patients experienced cerebellar symptoms and sleep alterations, whereas dysautonomia and brain stem disorders were more seldom reported. Few papers have previously reported sensory symptoms, and only one has described pruritus as the main feature of this rare disease (2, 6, 18, 22). The case described here was a novel clinical presentation of DPPX antibody-associated encephalitis where altered pain perception was the primary symptom in addition to more common features such as weight loss and cognitive alterations. Our patient also complained of some pruritus, but to a much lesser degree than previously reported.

The Kv4.2. potassium channel is present in the dorsal horn neurons, and a previous study found that genetic elimination of the 4.2 potassium channel subunit in mice led to increased sensitivity to tactile and thermal stimuli (24). It has been shown in animal models that antibody-mediated or genetic ablation of

DPPX may result in neuronal hyperexcitability (5). Of interest is that our patient had electrophysiological changes of active denervation that normalized during treatment. However, since the patient did not show neurophysiological changes expected based on her pain levels, it is thus possible that alterations in spinothalamic signals also contributed to her pain sensitivity and pruritus.

Most reported patients with anti-DPPX mediated autoimmune encephalitis respond to immunotherapy, some many months after onset of symptoms (7). The most commonly used first-line therapy is corticosteroids (2). Other first-line therapies include intravenous immunoglobulin therapy (IVIg) and plasma exchange, which can be given alone or in combination with corticosteroids. Treatment with corticosteroids may in some cases result in complete recovery but relapses are also common (2). Second-line therapy with B cell-targeted agents such as rituximab is often needed to prevent relapse. Rituximab is especially effective in treatment of IgG4-mediated illnesses, and the antibodies toward DPPX are predominately IgG1 and IgG4, but also IgG2 (2, 25). We found that the main subclasses of anti-DPPX was IgG4 and IgG2. Our patient recovered completely after initiation of second-line therapy with rituximab, and a year after her first admission, she had completely recovered from the extremity pain and other neurological symptoms. This case thus shows that pain may be a prominent feature of encephalitis associated with anti-DPPX antibodies, and our patient is an example of the large variation of symptomatology in this rare disorder. It is important for clinicians to be aware of the clinical heterogeneity of the disorder to avoid delay in diagnosis and initiation of effective treatment.

Data availability statement

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

Ethics statement

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

Author contributions

TB and CV wrote the article with input from all authors. All authors contributed to the work-up, treatment of the patient, reviewed the manuscript, and approved the final version.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1091688/full#supplementary-material

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Progressive multifocal leukoencephalopathy genetic risk variants for pharmacovigilance of immunosuppressant therapies

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Background: Progressive multifocal leukoencephalopathy (PML) is a rare and often lethal brain disorder caused by the common, typically benign polyomavirus 2, also known as JC virus (JCV). In a small percentage of immunosuppressed individuals, JCV is reactivated and infects the brain, causing devastating neurological defects. A wide range of immunosuppressed groups can develop PML, such as patients with: HIV/AIDS, hematological malignancies (e.g., leukemias, lymphomas, and multiple myeloma), autoimmune disorders (e.g., psoriasis, rheumatoid arthritis, and systemic lupus erythematosus), and organ transplants. In some patients, iatrogenic (i.e., drug-induced) PML occurs as a serious adverse event from exposure to immunosuppressant therapies used to treat their disease (e.g., hematological malignancies and multiple sclerosis). While JCV infection and immunosuppression are necessary, they are not sufficient to cause PML.

Methods: We hypothesized that patients may also have a genetic susceptibility from the presence of rare deleterious genetic variants in immune-relevant genes (e.g., those that cause inborn errors of immunity). In our prior genetic study of 184 PML cases, we discovered 19 candidate PML risk variants. In the current study of another 152 cases, we validated 4 of 19 variants in both population controls (gnomAD 3.1) and matched controls (JCV+ multiple sclerosis patients on a PML-linked drug ≥ 2 years).

Results: The four variants, found in immune system genes with strong biological links, are: *C8B*, 1-57409459-C-A, rs139498867; *LY9* (alias *SLAMF3*), 1-160769595-AG-A, rs763811636; *FCN2*, 9-137779251-G-A, rs76267164; *STXBP2*, 19-7712287-G-C, rs35490401. Carriers of any one of these variants are shown to be at high risk of PML when drug-exposed PML cases are compared to drug-exposed matched controls: P value = 3.50E-06, OR = 8.7 [3.7–20.6]. Measures of clinical validity and utility compare favorably to other genetic risk tests, such as *BRCA1* and *BRCA2* screening for breast cancer risk and HLA-B*15:02 pharmacogenetic screening for pharmacovigilance of carbamazepine to prevent Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis.

Conclusion: For the first time, a PML genetic risk test can be implemented for screening patients taking or considering treatment with a PML-linked drug in order to decrease the incidence of PML and enable safer use of highly effective therapies used to treat their underlying disease.

KEYWORDS

immunodeficiency, JC virus, multiple sclerosis, natalizumab, pharmacovigilance, progressive multifocal leukoencephalopathy, PML, serious adverse event

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare brain disease caused by the reactivation of JC virus (JCV) in immunosuppressed individuals. As an aggressive demyelinating disorder, PML can be fatal and is often severe and debilitating; almost 70% of survivors experience ongoing neurological disability and there is no approved treatment once PML develops (1). While PML is quite rare, infection with JCV is common, with most patients being asymptomatic. Based on serological testing, JCV has an estimated worldwide prevalence of 40–70% (2). More recent studies in Asian populations showed even higher rates of seropositivity, ranging from 70 to 80% (3–5). We note that JCV is formally named human polyomavirus 2 (HPyV-2 or HuPyV2) (6, 7) but, for simplicity, will be referred to as JCV in the present study.

Immunosuppression in JCV-seropositive (JCV+) individuals that develop PML can be due to a wide range of underlying diseases and/or drugs but is broadly related to three underlying disease states (1, 8): Human Immunodeficiency Virus (HIV)-infected, hematological malignancies (i.e., lymphoproliferative diseases such as leukemias, lymphomas, and multiple myeloma); and autoimmune disorders, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). HIV-infected acquired immunodeficiency syndrome (AIDS) patients represent the largest proportion of PML cases (∼50%). Rates in this population substantially dropped after the 1996 introduction of highly active antiretroviral therapy (HAART), although at least 10% of HIV patients who are considered "immunological non-responders" to antiviral therapies (9) could continue to have elevated PML risk similar to the pre-1996 era. Conversely, iatrogenic PML (i.e., resulting from drug exposure) is on the rise with the growing number of immunosuppressant therapies used to treat various immune disorders (1, 10). Historically, iatrogenic PML risk was sufficiently high for psoriasis patients taking efalizumab (brand name Raptiva) that the therapy was withdrawn from the market worldwide in 2009 based upon a PML incidence rate of 0.158% or ∼16 in 10,000 (11). Today, multiple sclerosis (MS) patients on disease-modifying therapies are the largest proportion of iatrogenic PML cases (1).

There are over three dozen drugs that include a PML warning in their prescribing information (USA) and/or mention PML in their product characteristics (European Medicines Agency). Examples include alemtuzumab, brentuximab vedotin, dimethyl fumarate, efalizumab, fingolimod, ibrutinib, and

natalizumab; as well as anti-CD20 antibodies (also known as B cell depletion therapies) such as obinutuzumab, ocrelizumab, ofatumumab, and rituximab (12, 13). Of recent note, the PML warning in ocrelizumab's prescribing information was substantially expanded in August 2022.

Given the large number of drugs linked to the development of PML (1, 10, 14, 15), it is critical to identify additional risk factors that can be taken into consideration when patients and their clinicians are selecting a therapy for treatment of the underlying disorder. Since JCV infection is a requirement for developing PML (although most JCV-infected individuals will not develop PML), testing patients with a JCV antibody test (including assessing their index level) can be useful for informing PML risk (16, 17). For example, testing every 6 months (18) is recommended by the European Medicines Agency for patients on natalizumab who are JCV-negative or have a low index value. However, development of other PML risk biomarkers continues to be an area of high unmet need (19), especially since the specificity of the JCV antibody test is low (40–70% of the population are seropositive for JCV) (2, 20), the test's false negative rate is reported to be 3% (manufacturer's prescribing information for natalizumab, Dec-2021), and index levels may be unreliable for anti-CD20 therapies because of their mechanism of action (i.e., reduced antibody levels may result in lower anti-JCV antibody levels) (21, 22). Another suggested biomarker is serum neurofilament light chain (NfL) levels (23, 24), but it is only useful in verifying PML onset and resolution of the disease (in natalizumab-treated MS patients) as opposed to predicting who may get PML in the future (i.e., before a patient decides to take a PML-linked therapy). This is an important distinction given the seriousness of the condition and its limited treatment options once it develops.

Host genetic predisposition to PML (i.e., an individual has one or more genetic variants in their genome that increases their risk of developing PML) was proposed to be a significant risk factor (25); see also Mills and Mao-Draayer (26). This hypothesis is supported by a growing number of PML case reports (25, 27–42) in which the patients were found to have mutation(s) in known immunodeficiency disorder genes (43, 44). We previously explored the possibility of genetic predisposition to PML in the largest genetic study to date, whole-exome sequencing (WES) of 184 PML cases (45). That work identified 19 rare genetic variants in known immune-modulating genes that were significantly more common in PML patients compared to populations in the Genome Aggregation Database (gnomAD) database (46).

This study reports the frequency of these variants in additional PML cases (152 new, 336 total). By far, this is the largest ever assembled set of DNA samples from PML cases, providing a unique resource for studying germline genetic links to the disease. Importantly, this work, for the first time, compares 110 drug-exposed PML cases to 718 drug-exposed controls who took PML-linked drugs for ≥2 years. In this case-control analysis, four variants show a particularly strong association with PML; two of these variants only appear in cases and are never observed in the drug-exposed controls.

Due to the severity of PML as a serious adverse event, eight currently marketed drugs have PML in a Boxed Warning in their prescribing information (the FDA's strongest drug label

TABLE 1 Summary of PML cases and drug-exposed controls: primary disease group, MS drug exposure, and demographics.

		Drug-exposed	
	Total PML cases	**PML cases**	**Matched controls[a]**
Subjects	336	110	718
Primary disease[b]			
HIV	156	0	n/a
MS	94	94	718
Other	45	8	n/a
BC	41	8	n/a
Drug exposure[c]			
Natalizumab		86	604
Rituximab		13	25
Unknown[d]		4	0
Dimethyl fumarate		3	43
Alemtuzumab		1	0
Fingolimod		1	55
Glatiramer acetate		1	0
Mycophenolate mofetil		1	0
Ocrelizumab		0	12
TOTAL, non-redundant		110	718
Sex			
Male	184	31	194
Female	152	79	524
Primary ethnicity[e]			
EUR	281	109	645
AFR	55	1	73

[a]Drug-exposed matched controls are JCV+ MS patients on an MS drug ≥ 2 years who did not develop PML.
[b]Primary disease: BC, blood cancer; HIV, human immunodeficiency virus infected; MS, multiple sclerosis; Other, various. See Methods for list of diseases under the BC and Other subgroups.
[c]All drugs have PML listed in the prescribing information (Boxed Warning and/or Warnings and Precautions) with the exception of glatiramer acetate. Drug exposure times were unavailable for PML cases but are ≥ 2 years for controls (a subset were exposed to two or more drugs for ≥ 2 years). Of the 110 drug-exposed PML cases, four had multiple reported drug exposures: 1 glatiramer acetate (also exposed to interferon beta-1a, but no exposure to natalizumab) and 3 rituximab (also exposed to bendamustine, cyclophosphamide-fludarabine, or cyclosporine-methotrexate-mycophenolate mofetil-steroids-tacrolimus).
[d]Four PML cases had unknown drug exposures but were assumed to be drug-exposed since all were MS patients, a patient group that is not known to develop PML in the absence of treatment with a disease-modifying therapy.
[e]A primary ethnicity was assigned as AFR or EUR (see Methods) for statisical analyses. An Other ethnicity was annotated if > 5% of one or more other ethnicities was found: EUR, 62/281 PML cases and 128/645 drug-exposed controls; AFR, 33/55 PML cases and 67/73 drug-exposed controls.

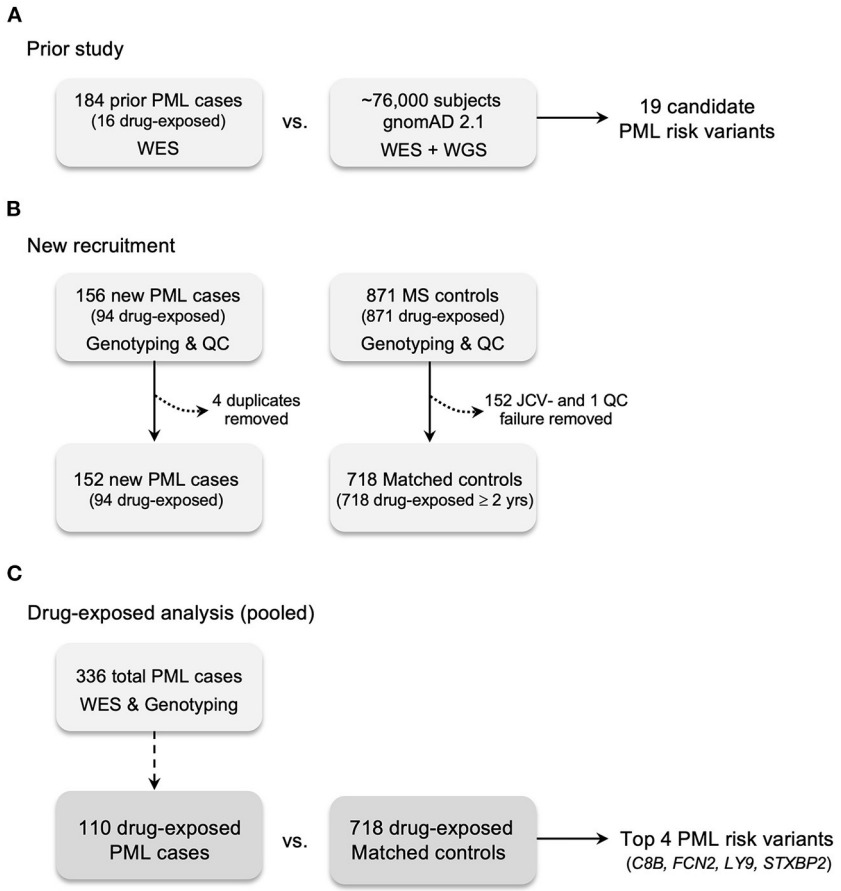

FIGURE 1
Case and control recruitment and study design. **(A)** Prior study for genetic discovery and validation using Whole Exome Sequencing (WES), 669 candidate immune response genes, and gnomAD 2.1 (WES + WGS) population controls (45). **(B)** New recruitment of PML cases and matched controls (JCV+ MS patients exposed to a PML-linked drug ≥2 years). All PML cases and matched controls were genotyped for the prior study's 19 candidate PML risk variants. Matched controls without JCV serostatus were assayed (see Methods). Excluded cases: four were found to be duplicates of the prior study (see Methods). Excluded controls: 152 JCV seronegative (JCV-) patients; one QC failure for genotyping assays due to low quality DNA. **(C)** Drug-exposed analysis is the pooled subgroup ($n = 110$) of total PML cases ($n = 336$) compared to matched controls. Drug-exposed study results are reported in Tables 2, 5 and genes for the top 4 variants are listed.

warning) and numerous other drugs have a warning about PML in their product labeling in the USA and similar warnings in the EU, while one drug was withdrawn from the market due to its PML risk. Our reported measures of clinical validity and utility for the identified four variants show that utilization of a simple and inexpensive genotyping test in patients considering treatment with PML-linked immunosuppressant therapies has the potential to reduce the incidence of PML and save lives.

Methods

IRB approvals

Written informed consent was obtained from all patients (PML cases and MS controls) participating in this study under IRB approved protocols from the following institutions: Accelerated Cure Project, Comitato Etico Provinciale of Brescia (PI Imberti), Beth Israel Deaconess Medical Center (PI Koralnik), Icahn School of Medicine at Mount Sinai (BioMe Biobank), NINDS/NIH (PIs Major and Cortese), Paris-Sud/INSERM (PI Taoufik), University of California San Francisco (PI Oksenberg), University of Münster (PIs Schwab and Wiendl), Université Toulouse (PIs Brassat, Martin-Blondel, and Liblau), and Vanderbilt University (BioVU Biobank).

PML cases

In addition to the 184 cases previously studied using WES (45), new cases were assembled for genetic validation via genotyping. A total of 156 new DNA samples were collected from the following collaborating institutions: Accelerated

TABLE 2 Association statistics[a] for PML risk variants: drug-exposed PML cases ($n = 110$) vs. drug-exposed controls and gnomAD 3.1 population controls.

			Drug-exposed controls[b] ($n = 718$)		gnomAD controls[c] ($n = 76,071$)	
Gene symbol	**dbSNP ID**	**Variant (GRCh37, hg19)**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
STXBP2	rs35490401	19-7712287-G-C	33.1 (1.6 - 694.4)	**0.0175**	6.8 (1.7 - 27.6)	**0.0373**
LY9	rs763811636	1-160769595-AG-A	19.6 (0.8 - 484.3)	0.1330	63.4 (8.1 - 495.5)	**0.0172**
C8B	rs139498867	1-57409459-C-A	6.7 (1.7 - 27.3)	**0.0135**	4.3 (1.6 - 11.8)	**0.0159**
FCN2	rs76267164	9-137779251-G-A	5.7 (1.7 - 18.8)	**0.0090**	7.0 (2.9 - 17.3)	**0.0001**

[a]The subset of total PML cases that were drug-exposed (110 of 336) were compared to drug-exposed controls and population controls (gnomAD). P values were calculated using Fisher's Exact Test; OR, odds ratio; CI, confidence interval. Variants are ordered by descending OR and bold-highlighted P values denote significance < 0.05.
[b]Drug-exposed (matched) controls are JCV+ MS patients on a MS drug ≥ 2 years who did not develop PML.
[c]All ethnicities in gnomAD 3.1 population controls were used (see Methods). Sample size (subject number) varies slightly by variant, n = 76,071 is an average of the 4 variants: *STXBP2*, n = 76,099; *LY9*, n = 76,054; *C8B*, n = 76,081; *FCN2*, n = 76,050.

TABLE 3 PML risk variant functional impact predictions.[a]

					gnomAD 3.1 *in silico* predictions		
Gene symbol	**dbSNP ID**	**Variant (GRCh37, hg19)**	**gnomAD 3.1 AF[b]**	**Consequence[c]**	**Polyphen**	**SIFT**	**CADD[e]**
STXBP2	rs35490401	19-7712287-G-C	0.001367	missense	probably damaging	deleterious	26.0
LY9	rs763811636	1-160769595-AG-A	0.000072	frameshift (pLOF)	n/a[d]	n/a[d]	22.8
C8B	rs139498867	1-57409459-C-A	0.004331	missense	possibly damaging	deleterious	23.1
FCN2	rs76267164	9-137779251-G-A	0.003393	missense	probably damaging	deleterious	24.0

[a]These PML risk variants are a subset of the 19 previously reported variants (45). Gray-shading denotes severity of functional predictions: no shading = low impact (none for these 4 variants), light gray, moderate impact, dark gray, high impact.
[b]AF, allele frequency of the variant in gnomAD 3.1 for all ethnicities (Total).
[c]Missense variants are amino acid substitutions; for the *LY9* variant, pLOF denotes protein loss-of-function.
[d]Polyphen and SIFT are prediction methods for missense variants and are not applicable (n/a) to other types of variants (e.g., the high impact frameshift for the *LY9* variant).
[e]CADD scores >20 are the highest category of deleteriousness in gnomAD 3.1 annotation.

Cure Project ($n = 1$), Comitato Etico Provinciale of Brescia ($n = 11$), NINDS/NIH ($n = 32$), Paris-Sud/INSERM ($n = 9$), Université Toulouse ($n = 57$), University of Münster ($n = 44$), and University of California San Francisco ($n = 2$). Potential cases were assessed using the consensus PML diagnostic criteria (47) and only "Definite" or "Probable" PML cases were retained. Wherever possible, drug exposures for immunosuppressant drugs (approved or used off-label) were noted. Primary underlying diseases were recorded and were then categorized as blood cancer (BC), HIV, MS, or Other. The BC subgroup includes: acute myeloid leukemia, anaplastic plasmacytoma, B-cell lymphoma, chronic lymphocytic leukemia, follicular lymphoma, Hodgkin lymphoma, leukemia, lymphoma, marginal zone lymphoma, myelodysplastic syndrome, multiple myeloma, and non-Hodgkin lymphoma. The Other subgroup includes: alcoholic cirrhosis, anti-synthetase syndrome, aplastic anemia, B-cell deficiency, Behcet's disease, cancer (non-hematological: colon and liver), common variable immunodeficiency, dermatomyositis, dermatopolymyositis, granulomatosis, idiopathic CD4 lymphocytopenia, immune thrombocytopenia, lymphopenia, microscopic polyangiitis, ocular pemphigoid, polycythemia vera, primary CD8 lymphopenia, psoriasis, RA, sarcoidosis (kidney, pulmonary, and unspecified), severe combined immunodeficiency, silicosis, thymoma with immunodeficiency, transplants (bone marrow, kidney, and liver), vasculitis, or unknown.

Control subjects

For comparison to drug-exposed PML cases, a set of drug-exposed controls with MS (called "matched controls") were assembled from two laboratories: Université Toulouse and University of California San Francisco (UCSF). Inclusion criteria for controls were as follows: 1) JCV seropositivity, 2) exposure to an immunosuppressant/PML-linked drug for at least 2 years as PML risk increases after 2 years in MS patients (17), and 3) absence of a PML diagnosis. The JCV antibody status was already determined to be positive for all Université Toulouse controls; for the UCSF controls, JCV antibody status experiments were performed by Lytic Solutions (Madison, WI, USA). Detection of anti-JCV IgGs in serum samples

TABLE 4 PML risk variant association with MS vs. drug-exposed PML cases.

Gene symbol	dbSNP ID	Variant (GRCh37, hg19)	Association with MS[a]		Association with PML[b]	
			OR	P value	OR	P value
STXBP2	rs35490401	19-7712287-G-C	1.0	0.6853	33.1	**0.0175**
LY9	rs763811636	1-160769595-AG-A	n/a[c]	n/a[c]	19.6	0.1330
C8B	rs139498867	1-57409459-C-A	1.0	0.0670	6.7	**0.0135**
FCN2	rs76267164	9-137779251-G-A	1.0	0.7088	5.7	**0.0090**

[a]MS association results (32,367 MS cases vs. 36,012 healthy controls) were previously reported (49), see Methods for details.
[b]Drug-exposed results (110 PML cases vs. 718 matched controls) are from Table 2 (as a comparator to the MS association results); P values were calculated using Fisher's Exact Test; OR, odds ratio.
[c]The *LY9* variant was not evaluated (n/a, not applicable) in the MS association study, likely because it is very rare in the general population (gnomAD 3.1 allele frequency = 0.000072) and therefore not included on the exome chip (Illumina Exome BeadChip).

TABLE 5 Clinical validity and utility of a 4-variant PML genetic risk test in drug-exposed cases vs. matched controls.

Association statistics[a]	
Frequency in PML cases (12/110)[b]	10.9%
Frequency in matched controls (10/718)	1.4%
P value	3.50E-06
OR (95% CI)	8.7 (3.7–20.6)
Clinical validity[c]	
Sensitivity	10.9%
Specificity	98.6%
PPV	19.5%
NPV	97.3%
Clinical utility[c]	
PAF	9.4%
NNT	6
NNG	355

[a]Frequencies and statistics for drug-exposed PML cases and drug-exposed controls testing positive with the 4-variant PML genetic risk test: P values were calculated using Fisher's Exact Test; OR, odds ratio; CI, confidence interval.
[b]Details for the 12 genotype-positive PML cases are as follows: *C8B* variant 1-57409459-C-A (4 total), 4 natalizumab-treated MS patients; *FCN2* variant 9-137779251-G-A (5 total), 2 natalizumab-treated MS patients, 1 dimethyl fumarate-treated MS patient (natalizumab-naïve), 1 rituximab-treated B cell lymphoma patient, and 1 rituximab-treated Behcet's disease patient that also had immune thrombocytopenia; *LY9* variant 1-160769595-AG-A (1 total), 1 natalizumab-treated MS patient; *STXBP2* variant 19-7712287-G-C (2 total), 2 natalizumab-treated MS patients.
[c]Clinical validity and utility (also known as population impact) measures were calculated as described in Tonk et al. (51): PPV, positive predictive value; NPV, negative predictive value; PAF, population attributable fraction; NNT, number needed to treat; NNG, number needed to genotype. Values were calculated using a 3% adverse event frequency (PML incidence rate): JCV+ patients taking natalizumab and receiving at least 72 infusions (17).

was performed according to manufacturer instructions using the ELISA-VIDITEST anti-JCV IgG diagnostic kit (Catalog # ODZ-450) from Vidia spol. s.r.o. (Vestec, Czech Republic; distributed by Boca Scientific Inc., Dedham, MA, USA). All serum samples (diluted 1:100) were run in duplicate and 96-well plates included control human serum samples of known JCV infection status. After color development (using kit-supplied stop solution), absorbance values at 450 nm (with a reference reading at 650 nm) were measured using a Molecular Devices Spectra Max Plus plate reader (San Jose, CA, USA). Background-subtracted values were averaged for each sample. The qualitative interpretation procedure for data analysis was performed according to the manufacturer instructions using the internal plate calibrator value and the plate lot correction factor. Samples with absorbances lower than 90% of the cut-off value were considered negative and samples with absorbances higher than 110% of the cut-off value were considered positive. Samples with values between these two cut-offs were considered indeterminable. Only JCV+ samples were retained for further analyses and all had MS as their primary disease.

To assess PML risk across all primary disease subgroups (BC, HIV, MS, and Other) in the context of population-level data, we used the most recent version (3.1) of gnomAD (46). This release consists of Whole Genome Sequencing (WGS) data for ∼76,000 genomes corresponding to a variety of ethnicities; results are also reported by ethnic subgroups for European (EUR, ∼34,000 non-Finnish European genomes), African (AFR, ∼21,000 genomes), and EUR plus AFR (∼55,000 genomes). In addition to the functional prediction methods PolyPhen and SIFT, gnomAD 3.1 also reports the results for other prediction measures of deleteriousness, such as CADD scores.

Genetic analyses

Ancestry and duplicate sample analyses were assessed for all PML cases and matched controls using previously described methods (45) with the exception that WGS (0.1x read depth) of newly acquired PML cases and matched controls was performed by Psomagen (Rockville, MD, USA). Ancestry analysis was performed by Gencove (New York, NY, USA) using 0.1x read depth WGS data based on implementation of a supervised version of the STRUCTURE model (48), which is trained on a panel of 7,345 individuals grouped in 49 populations. Primary ethnicities were assigned as AFR or EUR based on the majority percentage of ancestry.

For duplicate sample analyses, the low coverage WGS VCF files from Psomagen were filtered using bcftools (v1.10) to include only biallelic single nucleotide variants (SNVs) with exactly two alleles and PASS quality. The filtered variants were then annotated and evaluated for relatedness using plink (v1.9) and KING software (v2.2.6). Duplicate samples were excluded from further analysis.

Previously published WES data on the 19 PML risk variants (45) was reanalyzed in the context of new PML cases and JCV+ matched controls. We note that one of the previously published 185 PML cases was a bone marrow transplant patient whose DNA sample was acquired post-transplant; therefore we excluded this patient from the present analyses. For new PML cases and controls, the 19 variants were genotyped by a service provider (LGC Genomics, UK) with custom designed assays that use kompetitive allele specific PCR (KASP) chemistry. Sex was confirmed via genotyping.

To verify that previously published PML risk variants (45) were associated with PML and not with MS, we assessed 12 of 19 variants in a large genome-wide association study (GWAS) conducted by the International Multiple Sclerosis Genetics Consortium. This MS study used an exome chip (Illumina HumanExome Beadchip) containing 137,007 genome-wide common (12%) and rare (88%) variants to identify MS-associated loci in 32,367 MS cases vs. 36,012 healthy controls. The seven variants that were not assessed were either not found on the Illumina exome array or were not reported in the study (49).

Statistical and pharmacogenetic test analyses

Association statistics, Odds Ratio (OR) values and P values (two-tailed Fisher's Exact Test), were calculated as previously described (45). To avoid infinite ORs for variants that were not present in matched controls, 0.5 was added to all cells of the contingency table (50). The 19 previously identified variants for PML risk were evaluated in drug-exposed PML cases compared to drug-exposed controls and gnomAD population controls. Several PML cases had mixed ancestry (i.e., one or more other ethnicities present at >5%). Therefore, statistical analyses using gnomAD population controls included all ethnicities (i.e., all ~76,000 WGS data sets).

Following individual variant association testing, combinations of the highest-risk variants (as identified in the case-control analyses) were explored for use in a panel test. Pharmacogenetic test parameters (clinical validity and clinical utility) for this panel test were calculated using the method of Tonk et al. (51). Clinical validity measures are sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Clinical utility measures are population attributable fraction (PAF), number needed to treat (NNT), and number needed to genotype (NNG). As the incidence of drug-induced PML varies by drug type/exposure, for the adverse event frequency we used the best-established long term rate reported for JCV+ MS patients on natalizumab, which is 3% (17).

Results

Assembly of PML cases and matched controls to further validate candidate PML risk genetic variants

A total of 340 potential PML cases were assembled for the present study. Following ancestry and duplicate sample analyses, four newly acquired samples were found to be identical to previous samples and were therefore removed. The final PML cohort includes a total of 336 PML cases: 184 from our previous study (45) and 152 new, unique cases. Using consensus PML diagnostic criteria (47), 287 (85%) cases were Definite PML and 49 (15%) cases were Probable PML. Eleven PML cases (3.3%) had neither predominantly AFR nor EUR ancestry and were assigned EUR. Additionally, 60% (33/55) of AFR and 22% (62/281) of EUR cases had one or more other ethnicities present at >5%. Sex, primary ethnicity, primary disease, and drug exposures for these cases are summarized in Table 1 and a workflow of the recruitment and study design is shown in Figure 1. Of the assembled PML cohort, 110 of 336 (32.7%) PML cases were drug-exposed.

A total of 879 potential controls were assembled from Université Toulouse and UCSF. Of these, 152 samples (all from UCSF) were removed for lack of JCV seropositivity and 9 Toulouse samples were removed for either relatedness or incomplete drug-exposure data. This yielded a final drug-exposed control cohort of 718 individuals, all of whom had MS as a primary disease (hereafter referred to as drug-exposed controls). According to ancestry analysis, 24 (3.3%) controls had neither predominantly AFR nor EUR ancestry and were assigned as EUR (Table 1 and Figure 1).

Association of top PML risk variants in drug-exposed PML cases vs. matched controls

The presence of the 19 previously identified PML risk variants was assessed in drug-exposed PML cases (n = 110) vs. drug-exposed controls (n = 718) and vs. gnomAD population controls (n = ~76,000). As summarized in

TABLE 6 Distribution of genotype-positive PML cases[a] across ethnicities and primary diseases.

Gene symbol	dbSNP ID	Variant (GRCh37, hg19)	Primary ethnicity[b]	Primary disease[c]
STXBP2	rs35490401	19-7712287-G-C	4 EUR	1 HIV, 2 MS, 1 Other
LY9	rs763811636	1-160769595-AG-A	1 EUR, 2 AFR	1 HIV, 1 MS, 1 Other
C8B	rs139498867	1-57409459-C-A	7 EUR, 2 AFR	1 BC, 4 HIV, 4 MS
FCN2	rs76267164	9-137779251-G-A	9 EUR, 1 AFR	2 BC, 4 HIV, 3 MS, 1 Other

[a]Results are shown for all PML cases (n = 336). Results for each of the 4 variants in the drug-exposed PML cases (n = 110): *STXBP2*, 2 MS; *LY9*, 1 MS; *C8B*, 4 MS; *FCN2*, 1 BC, 3 MS, 1 Other.
[b]Number of genotype-positive PML cases assigned to European (EUR) or African (AFR) ancestry (see Methods).
[c]Number of genotype-positive PML cases assigned to 1 of 4 primary disease subgroups (see Methods): BC, blood cancer; HIV, Human immunodeficiency virus infected; MS, multiple sclerosis; Other, various other diseases/conditions (see Methods).

Table 2, four variants showed strong association with PML risk in this analysis. Variants in genes *C8B*, *FCN2*, and *STXBP2* were found to be significant (P value < 0.05) compared to both drug-exposed controls and gnomAD population controls. The *LY9* variant was only significant when compared to gnomAD controls, likely a consequence of its very low frequency (11 out of 76,504 subjects). Of note, the *STXBP2* and *LY9* variants were absent in drug-exposed controls and had large effect sizes (OR = 33.1 and 19.6, respectively).

As summarized in Table 1, natalizumab-exposed PML cases ($n = 86$) represent the largest subgroup of PML cases with a PML-linked drug exposure history in our study. Similarly, natalizumab-exposed controls ($n = 604$) were also the largest subgroup for matched controls. Therefore, we also assessed the association of the PML risk variants in the natalizumab subgroup (see Supplementary Table 6) and found comparable results to the full set of of drug-exposed cases and controls (Table 2 and Supplementary Table 5). The association statistics for three of the four top variants were slightly improved for the natalizumab subgroup (lower P values and higher ORs) but were less significant for the *FCN2* variant.

PML risk variants are rare and predicted to be pathogenic

All four variants are rare in the general population (Table 3), with gnomAD 3.1 allele frequencies $< 0.5\%$ and thus providing supporting evidence of their pathogenicity (52). Three variants are missense and are predicted to be probably or possibly damaging by PolyPhen and deleterious by SIFT. The *LY9* variant is a frameshift predicted to cause loss of function of the protein (pLOF). A third prediction method, the CADD score (as reported in gnomAD 3.1), is also reported in Table 3. The CADD score range was 22.8–26.0, indicating that all four variants are predicted to be detrimental (CADD score >20 is the highest category of deleteriousness in gnomAD 3.1 annotation).

No association of PML risk variants with MS

Since iatrogenic PML cases are on the rise and MS patients are one of the intended patient groups for a PML risk genetic test, we checked if any of our top four PML risk variants were associated with MS. Previously reported MS genome-wide association study (GWAS) data from a large international study (49) were used for this analysis and included 32,367 MS cases vs. 36,012 healthy controls. Table 4 shows the association results for the top four PML risk variants. Three of the four top variants in genes *C8B, FCN2,* and *STXBP2* show no association with MS. All three had an OR of 1.0 and uncorrected genome-wide P values of 0.07–0.71. The fourth top variant (in the *LY9* gene) is very rare in the general population (gnomAD 3.1 allele frequency = 0.000072) and has not been reported in the literature to be associated with disease (including MS).

Utilization of a genetic risk test to reduce the incidence of PML with immunosuppressant therapies

Based on the results of the association analysis in the drug-exposed PML cases, a panel of four rare variants in genes (*C8B*, *FCN2*, *STXBP2*, and *LY9*) with strong immune-linked biology was identified as being potentially useful to identify patients at high risk of PML (see Supplementary Table 9 for analysis of the four individual variants vs. the 4-variant panel test in three different groups of PML cases: All, any Drug-exposed, and Natalizumab-exposed). Clinical validity and population impact measures (i.e., clinical utility) are shown in Table 5. No subject in either cases or controls presented with more than one of the four variants in the panel. Presence of any one of these four variants was 10.9% in the drug-exposed PML cases vs. only 1.4% in the drug-exposed controls. Association statistics for the 4-variant panel were strong, with a P value of 3.50E-06 and high effect size (OR = 8.67). The population attributable fraction (PAF),

or percentage of drug-induced PML cases that could be avoided with preventative genetic testing, is 9.4%.

In the total cohort of PML cases (n = 336), three of the four variants were found in both EUR and AFR cases (Table 6). All four variants were distributed across multiple primary disease subgroups, further supporting their association with PML rather than any one of the underlying disease groups (BC, HIV, MS, Other). In the drug-exposed PML cases (n = 110), three of the variants were found only in the MS subgroup (Table 6, footnote a), likely due to the high proportion of MS cases (Table 1, 86/110). However, the *FCN2* variant was found in three primary disease subgroups (BC, MS, Other) and in PML cases exposed to one of three different drugs (1 dimethyl fumarate case, 2 natalizumab cases, and 2 rituximab cases; see Supplementary Table 8). Taken together, these results suggest that the 4-variant PML risk genetic test could be used for advising on PML risk in general and for preventing iatrogenic PML cases.

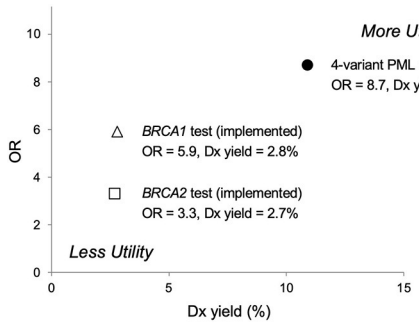

FIGURE 2
Predictive risk comparison to *BRCA* screening tests, odds ratio (OR) vs. diagnostic (Dx) yield. Results for a 4-variant PML risk test are shown in comparison to the *BRCA1*/*BRCA2* breast cancer risk prediction test. The proposed 4-variant PML risk test data point (●) is based on the total drug-exposed PML cases (Table 5). The *BRCA1* (△) and *BRCA2* (□) risk test data points are based on results for over 95,000 women reported in Kurian et al. (53). More Utility is defined as higher OR and higher Dx yield and Less Utility is defined as lower OR and lower Dx yield.

Discussion

Four actionable risk variants identified from case-control analysis

With the addition of 152 PML cases to our previously studied 184 PML cases (45), we have now assembled the largest collection of PML DNA samples (n = 336) for studying germline genetics to identify variants associated with PML risk. One crucial improvement to our previous work is the assembly of drug-exposed matched controls (n = 718), defined as JCV+ MS patients who did not develop PML after being exposed to an immunosuppressant therapy with PML risk for ≥2 years. This cohort enabled us to conduct a targeted, case-control analysis on the previously identified set of 19 PML genetic risk variants. From this analysis we demonstrate the clinical validity and utility of four immune-linked, high effect size, rare variants for use in an iatrogenic PML risk genetic test in the following genes: *C8B*, *FCN2*, *STXBP2*, and *LY9* (Tables 2–5).

Individually, the four variants show strong associations in the drug-exposed cases vs. matched controls and gnomAD population controls (Table 2). Notably, the *LY9* and *STXBP2* variants were absent in the 718 drug-exposed controls. There was no association with MS for three of the variants (Table 4) and the fourth variant was not evaluated in the study, presumably due to its rarity (49). When combined as a single PML risk test, the top four variants show robust statistical associations, with a P value = 3.5E-06 and OR = 8.7 (Table 5). They were present in 10.9% of PML cases vs. only 1.4% of drug-exposed matched controls. As such, testing for these four variants could prevent a substantial number of patients from developing PML without deterring most patients from their treatment plan. Finally, each of the four variants appears to be individually predictive of PML risk, as no PML case or matched control had more than one of these variants. This is consistent with the hypothesis that rare, deleterious variants in immune-regulating genes confer risk of PML.

Pharmacovigilance with a PML risk test is supported by clinical validity and utility measures

Clinical validity (sensitivity, specificity, PPV, NPV) refers to a test's ability to accurately predict a disorder while clinical utility (PAF, NNT, NNG), also referred to as population impact, measures its impact on the disorder (in this situation, PML cases prevented). See Tonk et al. (51) for further background information on pharmacogenetic test measures. The clinical impact of screening patients considering PML-linked drugs is shown in Table 5. The pharmacogenetic test measures shown are based on the results of this study and the rate of PML (3%) observed in JCV+ long duration natalizumab patients (17). One PML case would be prevented for every 355 patients genotyped (NNG). For every six patients (NNT) who carry one of these variants, one case of PML can be avoided. Additionally, the PAF of 9.4% suggests that nearly 10% of drug-exposed PML cases could be prevented. Taken together, preventative genotyping of patients considering treatment with a PML-linked drug would eliminate a significant portion of iatrogenic PML cases without deterring otherwise tolerant users (98.6% of the patient population who are not carriers of any of the top four variants) from starting or continuing treatment.

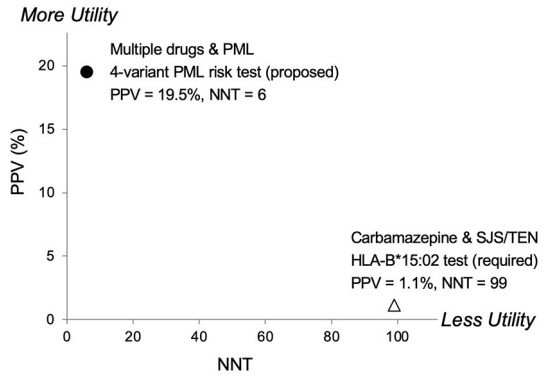

FIGURE 3
Predictive risk comparison to HLA-B*1502, positive predictive value (PPV) vs. number needed to treat (NNT). Results for a 4-variant PML risk test are shown in comparison to the HLA-B*15:02 test that is required in Asian populations before administering carbamazepine (CBZ). CBZ is a cause of the serious adverse event Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). The proposed 4-variant PML risk test data point (●) is based on the total drug-exposed PML cases (Table 5) and a PML incidence rate of 3% (17). The HLA-B*15:02 SJS/TEN risk test data point (Δ) is based on results reported in Shi et al. (54). More Utility is defined as higher PPV and lower NNT and Less Utility is defined as lower PPV and higher NNT.

Comparison to other clinically important genetic tests

Comparisons to other clinically important genetic tests suggest that pre-treatment screening with our PML risk test would be appropriate and could reduce the occurrence of PML for any therapy with known or suspected PML risk. As shown in Figure 2, the results of a large study (95,961 patients) published in 2017 (53) reports lower OR values for the association of breast cancer with all known pathogenic variants in either *BRCA* gene (OR = 5.9 for *BRCA1*, OR = 3.3 for *BRCA2*) than the proposed 4-variant PML risk test (OR = 8.7). Moreover, this PML risk panel test was positive for 10.9% of PML cases in our study (Table 5), which is higher than the presence of *BRCA1* and *BRCA2* variants in breast cancer patients (2.8 and 2.7%, respectively) (53).

Another relevant comparison is carbamazepine, an anticonvulsant drug. The FDA added a Boxed Warning to its prescribing information requiring pre-treatment genetic testing in certain populations for HLA-B*15:02 due to Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN) risks. In Figure 3, a comparison of pharmacogenetic testing measures (PPV vs. NNT) as indicators of clinical utility shows the proposed PML risk panel test has the potential to provide greater utility than the currently recommended test for carbamazepine's HLA-B*15:02 association with SJS/TEN (55). Also note that mortalities associated with SJS and TEN are estimated at 1–5% and 25–35%, respectively (56). Whereas PML-associated mortality is higher, reported as 23–65% (1, 15).

The top four variants are predicted to be pathogenic and have strong biological connections

In addition to being supported by strong statistical, clinical validity, and clinical utility measures, the four variants proposed for inclusion in the PML risk panel are predicted to be deleterious (Table 3) and their rarity further supports that they are pathogenic. All of the genes in which the four variants are located are linked to the immune system's viral defense mechanisms. Two genes (*C8B* and *FCN2*) are part of the complement system (lectin and terminal pathways) (57–60). The other two genes (*LY9* and *STXBP2*) cause or are linked to hemophagocytic lymphohistiocytosis (HLH) disorders, including macrophage activation syndrome (MAS) (61–65). Two genes (*C8B* and *STXBP2*) with PML risk variants are among the 437 genes designated by the International Union of Immunological Societies (IUIS) to cause inborn errors of immunity (43, 44), thereby supporting our original hypothesis (25) of host genetics as an additonal risk factor for development of PML.

Study limitations

A few areas of limitation are noted. Of the 336 PML cases, 49 had insufficient information to confirm them as Definite PML (47). Since PML is rare, assembling patient cohorts for research studies is very challenging and several of our cases were documented before consensus diagnostic criteria were implemented. Therefore, we decided to include both Definite and Probable PML cases in our study. Of note, Probable cases were almost entirely collected from PML centers of excellence, increasing the likelihood that they are in fact genuine PML cases.

The ethnic diversity for our PML cases is somewhat limited (Table 1 and Methods). While 11/336 (3%) PML cases assigned as EUR ancestry to simplify association analyses (see Methods) formally belonged to another majority ancestry, our study is lacking in predominantly East Asian, South Asian, and Latino/Admixed American ancestries. For example, studying germline genetics in East Asians may help to explain why PML incidence rates are about 8-fold higher in Japan for fingolimod-treated MS patients compared to the US and worldwide rates (66, 67). Presently, a higher rate of JCV seropositivity (2–5) and HLA-DRB1 alleles have been suggested as potential factors for this higher rate of PML development in fingolimod-treated Japanese MS patients (68).

We note that 95/336 (28%) PML cases had mixed ancestry (i.e., at least one other ancestry present at > 5%) and all four of our top variants are globally rare for all gnomAD ethnicities (allele frequency range 0.000072 to 0.004331). Furthermore, variant associations were significant whether analyzed by primary ethnicity (EUR or AFR) or using all ethnicities (All pooled analysis). While it is important to continue to study PML cases in underrepresented ancestries, we believe the global rarity of these variants—combined with the strength of the associations observed here—obviates the need to assess the variants in specific populations and enables the use of our PML risk test in the general population.

For iatrogenic PML cases, drug-specific association results may be informative but in our present work, this was only possible for the subgroup of PML cases and matched controls that were exposed to natalizumab (86 cases vs. 604 controls); see Supplementary Tables 6, 9. The next largest drug-specific subgroup for the drugs listed in Table 1 was rituximab (13 cases vs. 25 controls). However, given the consistent results (Supplementary Table 9) for our 4-variant PML genetic risk test among natalizumab-exposed and all drug-exposed cases and controls (110 cases vs. 718 controls), we would not expect dramatic differences across drug-specific groups. Furthermore, one of our PML risk variants (in the *FCN2* gene) was found in PML cases (see Table 5, footnote b) with three different underlying diseases (MS, B cell lymphoma, and Behcet's disease with immune thrombocytopenia), but also representing exposure to three different PML-linked drugs (dimethyl fumarate, natalizumab, and rituximab).

Finally, using matched controls for other underlying disorders besides MS (e.g., leukemia/lymphoma, other autoimmune conditions, or HIV-infected patients who did not develop PML) may provide additional support to the use of our proposed PML risk test in other clinical settings. Beyond the practical limitations of performing PML risk case-control studies for other underlying disorders and drug exposures, these results suggest it is likely unnecessary. All four top variants were found in PML cases representing at least three of four primary disease subgroups, with the *FCN2* variant found in all four subgroups (Table 6). This is consistent with the understanding that PML is the same clinical entity regardless of the patient's underlying disorder (1) and supports the use of our test in all patients considering the use of PML-linked therapies.

Conclusion

Identification of patients at risk of PML is an important area of unmet need given the growing number of PML-linked immunosuppressive therapies. Building on our previous work (45), this study represents what we believe to be the first case-control analysis of germline genetic variants that confer risk of PML. The association of PML risk with damaging variants in the immune-linked genes *C8B*, *FCN2*, *LY9*, and *STXBP2* is confirmed, with two variants being completely absent in the drug-exposed controls. High OR values and statistical significance support the use of this information when assessing patient risk of PML. The underlying genetic immunodeficiency conditions linked to these variants predispose carriers to uncontrolled JCV virus reactivation (i.e. PML), a serious infection. Simple, low-cost genetic screening in patients considering drugs with known or suspected PML risk will prevent future cases. Due to the seriousness of a PML diagnosis—particularly because it often leads to life-threatening outcomes (69) and the lack of treatment options once it develops—it would seem unethical not to test individuals considering immunosuppressive therapies with PML risk for our top four variants, and advising those with a positive result to consider an alternative therapy or treatment strategy.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: National Center for Biotechnology Information (NCBI) ClinVar, https://www.ncbi.nlm.nih.gov/clinvar/, SCV002572501.1, SCV002572502.1, SCV002572503.1, and SCV002572504.1.

Ethics statement

The studies involving human participants were reviewed and approved by IRB protocols from the following institutions: Accelerated Cure Project, Comitato Etico Provinciale of Brescia (LI), Beth Israel Deaconess Medical Center (IK), Icahn School of Medicine at Mount Sinai (BioMe Biobank), NINDS/NIH (EM and IC), Paris-Sud/INSERM (YT), University of California San Francisco (JO), University of Münster (NS and HW), Université Toulouse (DB, GM-B, and RL), and Vanderbilt University (BioVU Biobank). The patients provided their written informed consent to participate in this study.

Author contributions

EH, ES, and PE: conception and design of the study. EH, SJ, and DR: laboratory experiments. EH, ES, SJ, CB, TR, and PE: data analysis and interpretation. YT, HH-C, RL, DB, GM-B, HW, NS, IC, MM, LI, RC, JO, JG, BS, IK, BH, and EM: provision of study materials and clinical information for patients. EH, ES, CC, and PE: wrote the manuscript. All authors revised/approved the manuscript.

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Conflict of interest

Authors CB and CC are employed by Emerald Lake Safety LLC. Authors EH, ES, PE, and SJ are employed by Population Bio, Inc. Author TR is employed by Richmond Bioinformatics Consulting and author DR is employed by Lytic Solutions, LLC. Authors HW, IK, NS, and RL received funding from PML Screening, LLC to partially offset the costs for collection, and clinical characterization of patient samples used in the research. Authors EH, ES, PE, and YT are inventors of genetic screening methods for PML risk and have issued and pending patents related to this work. Applicants/Assignees on issued patents are: PML Screening, LLC, Newport Beach, CA (US), a joint venture between Population Bio, Inc. and Emerald Lake Safety LLC; Université Paris-Saclay, Gif sur Yvette (FR); The Assistance Publique-Hôpitaux de Paris (APHP), Paris (FR); and The Institut National de la Santé et de la Recherche Médicale (INSERM), Paris (FR). Author IC is a shareholder in Keires AG, Nouscom AG, and PDC*line Pharma.

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

The authors declare that this study received funding from PML Screening, LLC. The funders had the following involvement with the study: conception and design of the study, laboratory experiments, data analysis and interpretation, and wrote the manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1016377/full#supplementary-material

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Commentary: Progressive multifocal leukoencephalopathy genetic risk variants for pharmacovigilance of immunosuppressant therapies

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A Commentary on

Progressive multifocal leukoencephalopathy genetic risk variants for pharmacovigilance of immunosuppressant therapies

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a dreaded serious complication of immunotherapies. The drug with which it has been most frequently associated is natalizumab, a monoclonal antibody directed to alpha integrin that prevents the entry of lymphocytes to the central nervous system. It is approved for the treatment of relapsing multiple sclerosis (1, 2). As of 31 July 2022, 895 cases (892 in MS and 3 in patients with Crohn's disease) with a global overall incidence of 3.1 per 100,000, with 215 recorded deaths and 690 survivors with varying degrees of disability have been recorded (Biogen data on file). Previously, a number of risk factors were identified for the development of PML in patients on natalizumab: prior exposure to immunosuppressants, the duration of natalizumab treatment, and the presence of antibodies to the causative agent JC virus (human polyomavirus 2, HuPyV-2) (1, 2). There has been an intensive search to determine molecular factors governing susceptibility to this drug-related catastrophic CNS infection. Genetic variations have long been suspected to play an important role.

Genetic risk factors

In a refinement of an earlier study in which 19 genes were identified as increasing the risk of progressive multifocal leukoencephalopathy (PML) (3), Hatchwell et al. performed a case–control analysis that matched patients with PML to JCV antibody-positive patients with multiple sclerosis on natalizumab for 2 or more years who did not develop PML. This study demonstrated that four gene variants from those with natalizumab-associated PML are robustly linked to the risk of drug-associated PML (4). In total, two of these four genes only appeared in cases of drug-associated PML and were never observed in the drug-exposed controls. None of the drug-exposed PML cases was presented with more than one of the four genetic variants. The presence of any one of the four variants was observed in 10.9% of the drug-exposed PML cases vs. only 1.4% of the drug-exposed controls. When drug-associated patients with PML were compared to drug-exposed matched controls, the risk of PML with any one of these variants was exceptionally high (p-value 3.50 E-06, OR = 8.7 (3.7–20.6) (4).

All four genes (LY9, STXBP2, C8B, and FCN2) are involved in immune mechanisms, including viral defense mechanisms. LY9 encodes an immunomodulatory receptor on the surface of T-lymphocytes (5). STXBP2 encodes proteins that are involved in intracellular trafficking and the release of cytotoxic granules by natural killer cells and is associated with familial hemophagocytic lymphohistiocytosis (6). The other two genes (C8B and FCN2) are involved in complement activation. C8B codes for the late-acting complement proteins (C5-C9) that form the membrane attack complex (7), whereas, FCN2 is involved in the lectin pathway of complement (8).

Genetic risk factors related to host anti-pathogen defense mechanisms

These findings are not surprising. The immune system controls the response to infectious disease, conferring either vulnerability or resistance to a specific pathogen. Host adaptations to infectious pathogens have been among the strongest selective forces on the human genome (9). The expression of illness and its severity are simply the consequence of the combination of the offending organism and the host's response. The latter is determined by immunogenetics. Examples of this interaction are abundant. For instance, the Black Death of the middle ages that resulted from the bacterium *Yersinia pestis* led to an increase in salutary genetic variants in the human population that alters the cytokine response to *Y. pestis* and increase intracellular control of the pathogen in macrophages (10), thereby providing resistance to infection. CCR5-Δ32 deletion that confers resistance to HIV-1 infection has been attributed to this plague (11). In contrast, there are examples in which disease susceptibility is increased, such as deficiency of the membrane attack complex and properdin increasing the invasive nature of *Neisseria* infection; IL-12/23 and interferon-gamma deficiencies increasing the likelihood of disseminated tuberculosis; and signaling lymphocytic activation molecule (SLAM)-associated protein deficiency increasing the risk of X-linked lymphoproliferative disease with Epstein–Barr virus (12). More recently, the genetic variants of cytokine genes have been associated with COVID-19 disease susceptibility and cytokine storm (13). With respect to the genes identified in this study, the polymorphisms of FCN2 increase the risk of recurrent and severe streptococcal infections and rheumatic heart disease (14). Therefore, it should not be surprising that certain immune gene variants involved in the response to the JC virus (human polyomavirus 2) enhance the risk of PML.

Four PML epochs and risk factors

When considering the underlying risk factors for PML, four epochs of PML are identified. The first epoch was encompassed from the time of its framing as an illness in 1958 by Astrom et al. (15) to the beginning of the AIDS era in 1981. During this timeframe, the disease was associated chiefly, albeit not exclusively, with hematological malignancies, particularly B cell disorders (16). The second epoch began with the AIDS pandemic. PML was observed to be remarkably common with HIV infection ultimately occurring in 4–10% of patients with AIDS (17). HIV/AIDS became and remains the single greatest predisposing factor for PML. The third epoch of PML occurred with the introduction of highly active antiretroviral therapies in 1996 when the incidence of the disease in HIV/AIDS declined precipitously and almost invariably fatal disease is survived by about 50% of those with AIDS-associated PML (17). The next and most recent epoch of PML was initiated in 2005 with the observation of PML occurring with natalizumab (1, 18–20). While immunosuppressive agents had previously been linked to PML, their use in most individuals was for diseases that also increased the likelihood of PML. However, natalizumab was unique as it was not broadly immunosuppressive. Its α4β1 component prevented lymphocyte interaction with VCAM inhibiting lymphocyte entry into the brain and its α4β7 component interfered with lymphocyte binding to the gut endothelial cells through MAdCAM. Therefore, it is effective against MS and inflammatory bowel diseases. The former mode of action is believed to be responsible for the increased risk of PML with its use. Agents that inhibit α4β7 exclusively, such as vedolizumab, have a vanishingly small risk of PML, if any at all.

Risk mitigation

Although HIV/AIDS remains the most common predisposing cause of PML, a substantial and increasing number of patients are exposed to drugs that increase the risk of PML. As the authors highlight, a large number of drugs have been associated with PML risk, and eight drugs currently carry FDA black box warnings. These drugs have varied indications. While risk stratification methods have been developed for natalizumab-associated PML, this is not available for other agents that predispose to PML and would be very difficult to devise for a variety of reasons, including the relatively small numbers of patients who develop PML with some of these drugs and the difficulty excluding the contribution of the underlying disorder or concomitant therapies to the development of PML. Furthermore, despite the broader adoption of the risk mitigation

strategy employed with natalizumab, PML remains a substantial concern given the mortality, persistent disability, and the lack of established treatments.

Discussion

Testing for these genes will not eliminate the risk of PML but can be very helpful in identifying a subpopulation (∼10%) at particularly high risk for its occurrence when being treated with drugs that predispose to the disorder. The availability of a simple, relatively inexpensive test that can identify the genes that put one at risk for PML would be enormously helpful in the management of patients. The widespread use of such testing could potentially allow the physician to use alternative therapies that do not carry the same risk of PML, such as using alternative therapies for MS rather than using natalizumab in the JCV-positive individual. In those instances where alternative therapies do not exist, it would alert the treating physician to the importance of careful and frequent evaluation of PML. Tests for these genes would also be helpful for informing the patient and the family about relative risks.

Author contributions

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

Conflict of interest

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

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Case report: Anti-*N*-methyl-D-aspartate receptor antibody-associated autoimmunity triggered by primary central nervous system B-cell lymphoma

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Background: We herein detail our experience with a unique patient with a primary central nervous system (PCNS) B-cell lymphoma concomitant with anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies that satisfied the criteria of "probable anti-NMDAR encephalitis (ProNMDARE)" based on the Graus criteria 2016.

Case presentation: A 73-year-old Japanese woman presented with acute pyrexia, agitation, and disturbance of consciousness. She gradually developed a reduction in speech frequency and truncal dystonia causing abnormal posture. Brain magnetic resonance imaging (MRI) demonstrated high-intensity lesions in the bilateral frontal lobes, and her cerebrospinal fluid revealed mild pleocytosis. She was diagnosed with acute encephalitis and treated with acyclovir and intravenous dexamethasone; however, no improvement was observed. She was transferred to our hospital 6 weeks after the onset of her symptoms, and anti-NMDAR antibodies were identified in her cerebrospinal fluid through indirect immunolabeling with rat brain frozen sections and cell-based assays with NR1/NR2 transfected HEK cells. Follow-up MRI showed enlargement of the lesions in the right frontal lobe with gadolinium enhancement, suggesting a brain tumor. Stereotactic surgery was implemented, with subsequent pathological examination revealing that the tumor was consistent with diffuse large B-cell lymphoma (DLBCL) without evidence of systemic satellite lesions. Stereotactic irradiative therapies were then added to her treatment regimen, which partly improved her neurological symptoms with only mild cognitive dysfunction still remaining. A decrease in anti-NMDAR antibody titer was also confirmed after immunotherapy and tumor removal.

Conclusions: We herein report our experience with a novel case of PCNS-DLBCL masquerading as anti-NMDAR encephalitis that satisfied the diagnostic criteria of "proNMDARE." Treatment, including tumor removal, ameliorated disease severity and antibody titers of the patient. Our findings suggest that anti-NMDAR antibody-associated autoimmunity can be triggered by PCNS B-cell tumors, although primary brain tumors need to be excluded before establishing a diagnosis of autoimmune encephalitis.

KEYWORDS

primary central nervous system lymphoma, anti-NMDAR antibody, encephalitis, syndrome, diagnostic criteria

Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a well-characterized autoimmune encephalitis (AE) associated with immunoglobulin (Ig) G against the GluN1 subunit of the NMDAR (1). In 2016, Graus et al. (Graus criteria) proposed a syndrome-based diagnostic approach to AE that included NMDAR encephalitis (NMDARE) (2). The Graus criteria for probable NMDARE (ProNMDARE) comprises major groups of neuropsychiatric symptoms, laboratory study results, and reasonable exclusion of other disorders, whereas definite NMDARE requires the detection of the NMDAR IgG mainly in the CSF. In addition, associated teratoma, especially a systemic teratoma, is an important criterion for the diagnosis of NMDARE. Recently, primary central nervous system (PCNS) tumors, such as glioblastoma (3) and lymphomatosis cerebri (4), have been reported to occur concomitantly with NMDAR antibodies; however, the clinical significance of the antibodies associated with primary brain tumors has yet to be sufficiently discussed given that brain tumors need to be excluded before establishing a diagnosis of AE according to the criteria (2).

We herein report a patient with PCNS diffuse large B-cell lymphoma (DLBCL) concomitant with NMDAR antibodies in the CSF who developed acute encephalitis satisfying the diagnostic criteria of "proNMDARE."

Case presentation

A 73-year-old Japanese woman was admitted to another hospital for pyrexia, agitation, and mild disturbance of consciousness. She was initially diagnosed with a urinary tract infection, for which antibiotics were administered. However, her neurological condition gradually deteriorated. Brain MRI showed high-intensity lesions in the right temporal and bilateral frontal lobes on fluid-attenuated inversion recovery (FLAIR) images. CSF examination showed mild pleocytosis (47/mm^3, monocyte predominant). She was diagnosed with acute encephalitis and was started intravenous acyclovir and intravenous dexamethasone.

She was transferred to our hospital 6 weeks after the onset of her symptoms due to persistent disease despite treatment. Her medical history included hypertension. She had no family history of neuromuscular diseases. On admission, the patient had a height and weight of 154.0 cm and 56 kg, respectively. On physical examination, her body temperature was 37.4°C. Chest auscultation revealed normal respiratory sounds and a normal heart rate with no murmur. Neurological examination showed mild disturbance of consciousness: Glasgow Coma Scale (GCS) 13 (E4 V4 M5) with disorientation and agitation. She was able to answer some simple questions but showed a remarkable reduction in speech frequency. She presented with cervical and truncal dystonia causing abnormal posture. She did not experience seizures. Autonomic dysfunction and central hypoventilation were unremarkable. Electroencephalography (EEG) revealed a generalized slowness in activity (5–7 Hz) without epileptiform discharges. A cerebrospinal fluid (CSF) sample included 5 white blood cells/mm^3, 18 mg/dl of total protein, and 77 mg/dl of glucose (149 mg/dl of serum glucose). Her IgG index (0.50) was within normal range (cut-off < 0.67). Her CSF sample came back positive for oligoclonal bands. Brain MRI revealed high-intensity lesions in the right temporal and bilateral frontal lobes on FLAIR images, with the right frontal lesion demonstrating gadolinium (Gd) enhancement, which can be considered to indicate CNS inflammation or a high-grade brain tumor. Magnetic resonance spectroscopy of the right frontal lesion revealed an increase in the choline/creatine ratio and a normal N-acetyl aspartate level (Figure 1). Whole-body contrast-enhanced computed tomography showed no associated tumor and swelling of systemic lymph nodes. In addition, ^{67}Ga scintigraphy showed no abnormal uptake in the systemic organs and lymph nodes (Supplementary Figure 1).

In-house screening for anti-neuronal antibodies (5, 6) was performed using the patient's CSF and sera samples *via* indirect immunohistochemistry with frozen sections of rat brain. Patient's CSF immunolabeled neuropil of the

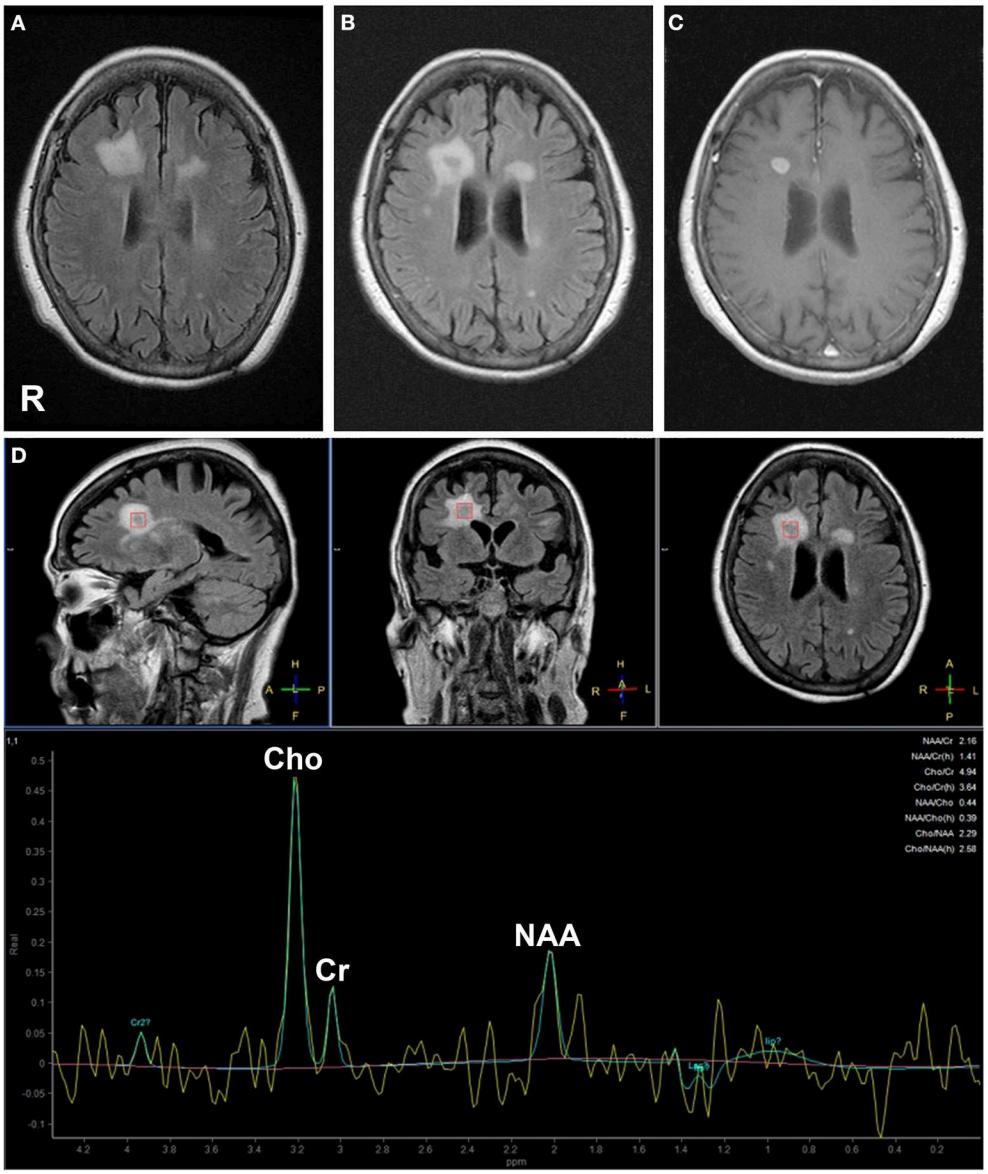

FIGURE 1
Brain magnetic resonance (MR) fluid-attenuated inversion recovery (FLAIR) images **(A, B)**, gadolinium (Gd)-enhanced T1-weighted image **(C)**, and MR spectroscopy **(D)** findings. Brain MRI FLAIR 7 days before admission revealed high-intensity lesions in the bilateral frontal lobes **(A)**. MRI FLAIR **(B)** and Gd-enhanced T1-weighted image **(C)** on admission revealed that high-intensity area in the right frontal lobe on MRI FLAIR showed round shaped on Gd enhancement. MR spectroscopy demonstrated an increase in choline/creatine ratio and decrease in N-acetyl aspartate levels in the Gd-enhanced lesion **(D)**.

rat hippocampus (Figure 2) and granular cell layers in the cerebellum (Supplementary Figure 2), which was consistent with the immunolabeling pattern of anti-NMDAR antibodies. In contrast, the patient's serum did not immunolabel the rat brain section. A cell-based assay with NR1/NR2-transfected HEK293 cells (BIOCHIP, Euroimmun, Labor Berlin) confirmed anti-NMDAR antibodies in the CSF alone (Figure 2, antibody titers were 1:32). No onconeural antibodies that included amphiphysin, Hu, Yo, CV2, Ri, Ma2/Ta, recoverin, Tr, GAD65, and others measured *via* line blot (EUROLINE, Euroimmun, Lübeck, Germany) were detected (details regarding autoantibody detection using in-house and commercially available assays are described in the Supplementary methods). Furthermore, autoantibodies associated with other AE were not detected, including Bickerstaff's brainstem encephalitis (anti-GQ1b antibody in the serum), Hashimoto's encephalitis (antibodies against thyroid peroxidase and thyroglobulin in the serum), and demyelinating disorders of the CNS (antibodies

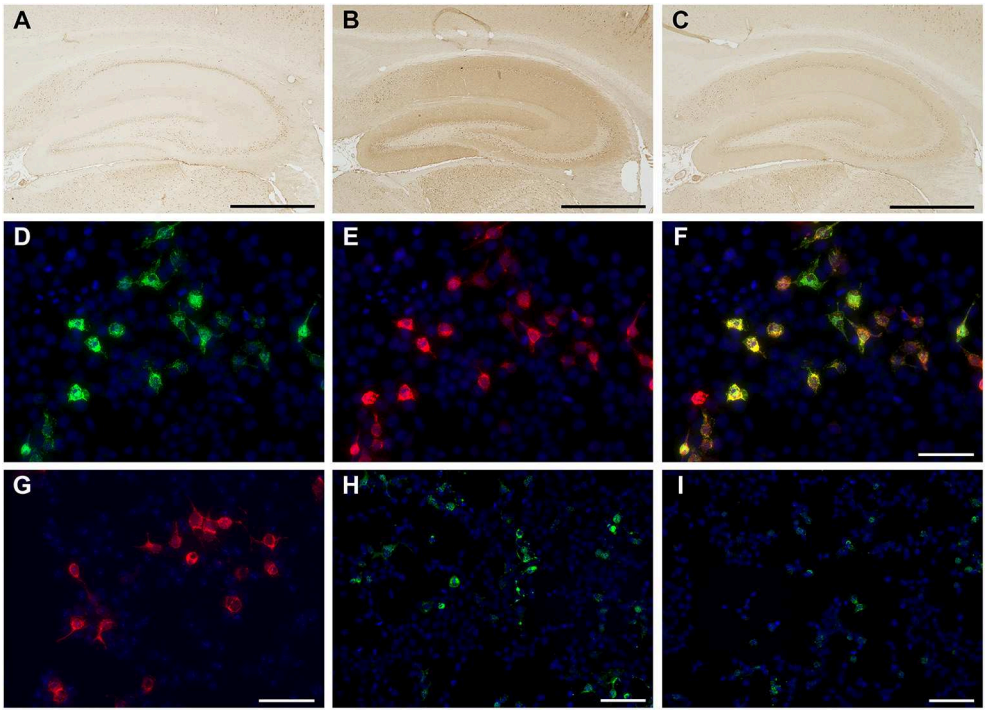

FIGURE 2
Immunolabeling of the patient's cerebrospinal fluid (CSF) sample with in-house tissue-based assay (TBA) **(A–C)** and cell-based assay (CBA) **(D–I)**. Control CSF did not react with in-house TBA **(A)**, whereas the initial patient's CSF immunolabeled neuropil on the rat hippocampus in the TBA **(B)**. The patient's CSF showed reactivity [green, **(D)**], with human embryonic kidney (HEK) cells expressing the *N*-methyl-D-aspartate receptor (NMDAR). The commercial antibody against NMDAR1 (clone EPR2480Y, ab68144, Abcam) [red, **(E)**] colocalizes with that of the patient's CSF [yellow, **(F)**], whereas a control CSF is negative **(G)**. Anti-NMDAR antibody titers (1:32) were confirmed using the fluorescent reactivity of CBA on the initial patient's CSF **(H)**. Following tumor removal and whole-brain irradiation therapy, immunosignals in TBA **(C)** and CBA decreased, as did antibody titers of anti-NMDAR antibody (titers 1:4) **(I)**. Nuclei were counterstained with 4′, 6-diamino-2-phenylindole. Bars = 1000 μm **(A–C)**, 50 μm **(D–G)**, and 100 μm **(H, I)**.

against anti-myelin oligodendrocyte and aquaporin-4 in both the CSF and serum).

The Gd-enhanced lesion accompanied by swelling of right frontal robe was required to rule out a high-grade brain tumor; thus, craniotomy was performed for tumor resection on day 15 of the hospitalization. Histopathological analyses showed a dense proliferation of atypical cells with large and irregular nuclei on hematoxylin-eosin (H&E) staining. Tumor cells were positive for CD20 (clone L26; Agilent Technologies, CA, US) and CD79a (clone JCB117; Agilent Technologies, CA, US) suggesting B-cell lymphoma with high Ki-67 (clone MIB-1; Agilent Technologies, CA, US) expression (90%). Immunological profiles of the tumor were consistent with primary central nervous system diffuse large B-cell lymphoma (PCNS-DLBCL) (Supplementary Figure 3). In addition, immunolabeling with biopsied brain sections using anti-NR1 antibodies (clone EPR23397-66; Abcam, Cambridge, UK) revealed that the tumor cells did not express the NR1 subunit of NMDAR (Figure 3).

After tumor removal, the patient underwent whole-brain stereotactic irradiation therapies (a total of 30 Gy). The antibody titers of anti-NMDAR antibodies in the CSF decreased as the volume of brain tumor reduced after surgical and irradiative therapies (Figure 2, titers were 1:4). Her consciousness and mental condition partially improved; however, she was discharged to another hospital for rehabilitation and long-term care due to limitations in performing activities of daily living. The clinical course of the patient is summarized in Supplementary Figure 4. Written informed consent was obtained from the patient and patient's kin for the publication of any potentially identifiable images or data included in this article.

Discussion

We herein describe a case of PCNS-DLBCL that clinically manifested as acute encephalitis associated with anti-NMDAR antibody. Fortunately, a combination of tumor removal and irradiative therapies was able to decreased her antibody titers. The present case satisfied the criteria for proNMDARE (four of the six major symptoms and abnormal EEG finding) proposed

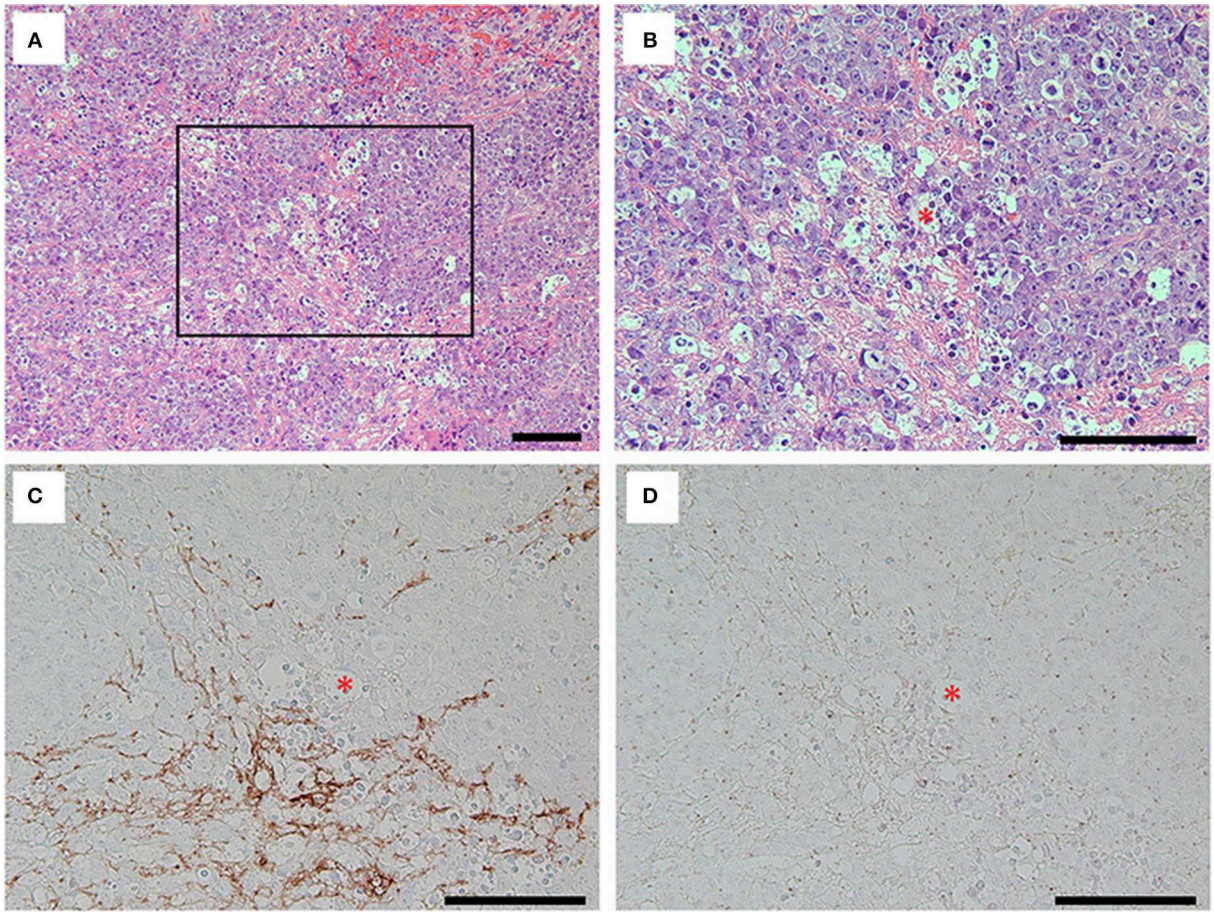

FIGURE 3
Hematoxylin and eosin (H&E) staining **(A, B)** and immunolabeling with the antibodies against grail fibrillary acidic protein (GFAP) (clone G-A-5; Sigma, MO, US) **(C)** and NR1 **(D)** for the tumor cells. Note that H&E staining of the removed brain specimens showed foci of highly proliferative atypical cells interposed with basophilic matrix **(A)**. The tumor cells with irregular nuclei and frequent mitoses [**(B)**, inset in **(A)**] were not immunolabeled with commercial antibodies against GFAP **(C)** nor NR1 subunit of NMDAR **(D)**, while the basophilic matrix on H&E staining was immunolabeled with commercial antibody against GFAP **(C)**. Asterisks in red **(B–D)** indicate the same blood vessel, and all bars = 100 μm.

by Graus et al. (2). In-house screening of the antibodies against neuronal surface antigens (5, 6), which included anti-NMDAR antibodies, could help with the early identification of antibodies in our patient. After testing positive for anti-NMDAR IgG in her CSF, she also satisfied the diagnostic criteria for definite NMDARE. However, systemic tumor analyses identified a DLBCL isolated in the CNS without radiological involvement of the systemic lymph nodes and organs. According to the aforementioned criteria (2), brain tumors are one of the diseases that need to be excluded before establishing a diagnosis of AE. Thus, we eventually diagnosed the patient with PCNS-DLBCL masquerading as NMDARE.

Recent studies have suggested the association between some types of neuronal surface antibodies (NSA) and hematologic neoplasms (7–10). For instance, Hodgkin lymphoma was associated with anti-NMDAR antibody (7) and mGluR5 antibody (8), whereas non-Hodgkin's lymphoma was associated with anti-DPPX antibody (9). Interestingly, Thomas et al. recently described a case with PCNS lymphoma mimicking anti-LGI1 limbic encephalitis. They mentioned that the case showed low serum anti-LGI1 antibody titers not detected in the CSF (10). In these reports (7–10), the patients were considered to have exhibited paraneoplastic syndrome considering that amelioration (8, 9) or deterioration (10) of the neurological syndrome was identified depending on the tumor condition. In addition, reports have also shown that the expression of the neuronal surface antigens was not confirmed on the surface of neoplastic lymphocytes (11, 12). In our case, the neurological syndrome partly improved, with only mild cognitive dysfunction remaining after the tumor removal following irradiative therapies. Furthermore, the tumor cells did not express NR1 subunits of NMDAR (Figure 3D), and no other associated tumors outside of the CNS (e.g., ovarian teratoma) were detected. Considering these facts and

TABLE 1 Literature review of brain tumors concomitant with anti-NMDAR antibodies.

	Fujii et al. (3)	Mariotto et al. (4)	Lu et al. (16)	Present case
Age/sex	54/F	54/M	67/M	73/F
Symptoms	Complex partial seizure with impaired consciousness	Depression and emotional lability, left hand dystonia, attention deficit, anosognosia, visuospatial impairment, constructional apraxia	Left limb convulsions without loss of consciousness	Cognitive dysfunction, reduction in speech frequency, abnormal postures, decreased level of consciousness
Associated tumor	Glioblastoma, Ovarian teratoma	Lymphomatosis cerebri	Brain astrocytoma	Primary CNS B-cell lymphoma
Major groups of symptoms on ProNMDARE	Seizures	Abnormal (psychiatric) behavior/cognitive dysfunction, Movement disorder	Seizures	Cognitive impairment, speech dysfunction, movement disorders, decreased level of consciousness
Main syndrome	Limited features	Limited features	Limited features	Anti-NMDAR syndrome
CSF cell count (mm^3)/TP (mg/dl)	2/30	Within normal limits	4/45	47/23
CSF NMDAR Abs	+	+	+	+
EEG findings	Focal slow activity, epileptic activity	Non-specific EEG changes	Slight abnormality	Diffuse slow activity
Treatments	Tumor resection (ovarian teratoma, glioblastoma), radiotherapy/chemotherapy (glioblastoma)	Plasma pheresis, cyclophosphamide	Dexamethasone, methylprednisolone, immunoglobulin, azathioprine, radiotherapy/chemotherapy	Dexamethasone, tumor resection/radiotherapy
mRS peak/latest	ND	6/6	6/6	5/5
Follow-up period, months	6	24	5	4

Abs, antibodies; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalogram; F, female; M, male; mRS, modified Rankin scale; NMDAR, anti-N-methyl-D-aspartate receptor; ND, not described; ProNMDARE, probable NMDAR encephalitis on Graus criteria.

aforementioned evidence, it is likely that the PCNS lymphoma in our case induced paraneoplastic NMDARE. However, it seems unreasonable that an ectopic expression of NMDAR on the tumor cells could yield anti-NMDAR antibodies as observed in patients with systemic teratomas and other associated tumors (13, 14).

Conversely, it is wellknown that anti-NMDAR antibody titers in the CSF corresponded to the severity of the disorder and that most patients experienced a decrease in the titers following treatment that included tumor removal (for paraneoplastic cases) and intensive immunotherapies (15). The serial CSF antibody titers throughout the disease course in cases reported to be associated with NSA accompanied by hematologic neoplasms have not been thoroughly discussed (4, 7). Interestingly, in our case, a decrease in the antibody titers in the CSF was confirmed after treatments for the PCNS lymphoma. This finding also suggests that the neurological syndrome of the present case behaved as a paraneoplastic NMDARE.

Thereafter, we reviewed previous cases with primary brain tumors concomitant with anti-NMDAR antibodies (3, 4, 16) (Table 1). Fujii et al. (3) reported a 54-year-old woman with glioblastoma and ovarian teratoma who presented with complex partial seizures and impaired consciousness. Lu et al. (16) also reported a 67-year-old man with a brain astrocytoma who developed partial seizures. Interestingly, encephalitis worsened as the tumor progressed, although alterations in antibody titers were not examined. Mariotto et al. (4) reported a 54-year-old man who developed various types of cognitive impairment and was treated with plasma pheresis and cyclophosphamide. She was diagnosed with lymphomatosis cerebri following an autopsy. All previous cases developed limited syndrome (3, 4, 16) of NMDARE based on the Graus criteria (2). In contrast, our case developed typical anti-NMDAR syndrome and satisfied the criteria for "proNMDARE" (4 of the 6 major symptoms and abnormal EEG finding) (2). Moreover, in-house screening immediately detected anti-NMDAR antibody in the CSF. The prognosis of the cases depended on the malignancy potential of the associated brain tumors, which was relatively poor compared to a typical NMDARE (17). In our case, anti-NMDAR syndrome partly improved; however, she could not return to baseline after having been debilitated by PCNS-DLBCL, including a series of treatments for the tumors.

Regarding the mechanism for the association between brain tumors and production of autoantibodies, Mariotto et al. (4) suggested that dysregulated lymphoma cells or exposure to specific antigens caused by brain damage yielded

autoantibodies. The aforementioned mechanism is similar to the mechanism proposed in NMDARE subsequent to herpes simplex encephalitis (post-HSE) (18, 19). Namely, viral-induced neuronal lysis of the CNS can induce autoimmune reaction to produce the NSAs that include anti-NMDAR antibodies in the patients with post-HSE (19–23). We challengingly speculated that the production of anti-NMDAR antibodies in the present case was mainly associated with antigen exposure of the damaged brain caused by tumor progression given that concomitant PCNS-DLBCL aggressively infiltrated the right frontal lobe with higher expression rate of Ki-67 (Supplementary Figure 3D), a marker for determining growth fraction (24). Further investigation is required to elucidate the precise mechanisms of NSA production induced by the brain tumors.

In conclusion, we herein report a unique case involving PCNS-DLBCL who developed acute encephalitis satisfying the diagnostic criteria for "probable NMDARE." The present case indicated that anti-NMDAR antibody-associated autoimmunity can be triggered by PCNS B-cell tumors, which are involved in anti-NMDAR syndrome presenting as a paraneoplastic NMDARE. Furthermore, brain tumor assessment even for patients suspected of AE can help prevent delays in the induction of appropriate treatment.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the individual(s) and/or minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

YY and MH drafted the manuscript. YY, MH, NO, TM, and HNa prepared patient's clinical data. HNi and HH performed the histological examination. MH, HH, and HNa supervised this study. All authors analyzed and interpreted the patient data and revised the manuscript for intellectual content. All authors approved the final manuscript.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1048953/full#supplementary-material

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Case report: First manifestation of multiple sclerosis temporally correlated with COVID-19 vaccination

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There are several case reports describing a temporal correlation between the first clinical manifestation of multiple sclerosis (MS) and the occurrence of relapses with vaccination against SARS-CoV-2. Here we report a case of a 33-year-old male who developed partial right upper and lower extremities numbness 2 weeks after receiving Johnson & Johnson's Janssen COVID-19 vaccine. The brain MRI performed during diagnostics in the Department of Neurology detected several demyelinating lesions, one with enhancement. Oligoclonal bands were present in the cerebrospinal fluid. The patient was treated with high-dose glucocorticoid therapy with improvement and the diagnosis of MS was made. It seems plausible that the vaccination revealed the underlying autoimmune condition. Cases like the one we reported here are rare, and—based on current knowledge—the benefits of vaccination against SARS-CoV-2 far outweigh the potential risks.

KEYWORDS

multiple sclerosis, autoimmune condition, vaccination, SARS-CoV-2, COVID-19, case report

Introduction

Among many environmental factors contributing to the pathogenesis of multiple sclerosis (MS), it is suspected that infectious agents play a triggering role. The most often implicated are the Herpesviridae family viruses, the John Cunningham virus, and human endogenous retroviruses (1). There are several case reports describing a temporal correlation between the first clinical manifestation of MS and the occurrence of relapses with vaccination against SARS-CoV-2 (2, 3). The data are still very limited, and the cause-and-effect relationship is vague, but those cases need to be noted. Furthermore, the COVID-19 pandemic is ongoing, and such data will be crucial for future analysis.

Case report

A 33-year-old male with a history of mild, well-controlled hypertension developed right upper and lower extremities numbness 2 weeks after receiving Johnson & Johnson's Janssen COVID-19 vaccine. In the prior period, the patient was not positive for coronavirus disease 2019 (COVID-19) infection and did not present any symptoms suggesting the presence of SARS-CoV-2 infection. Due to the above symptoms, the patient was admitted to the Department of Neurology. The examination revealed right side sensory impartment (loss of pain and temperature feeling) at the C5 level. Magnetic resonance imaging (MRI) scans

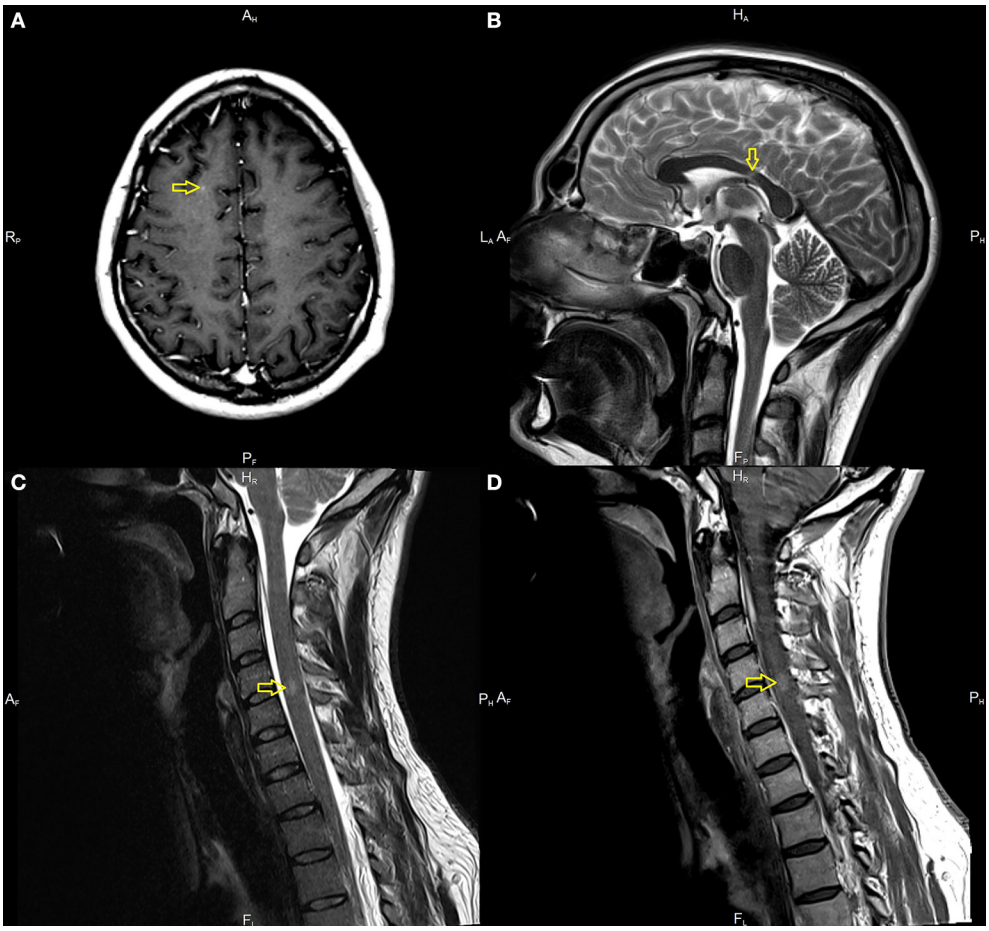

FIGURE 1
Magnetic resonance imaging (MRI) in the described case of multiple sclerosis (MS). Demyelination lesions are marked with yellow arrows, respectively. **(A)** T1-weighted subcortical Lesion with gadolinium enhancement on brain MRI on axial sequences. **(B)** T2-weighted images showing lesion located in corpus callosum. **(C)** T2 hyperintense acute lesion on cervical spinal cord on sagittal sequences. **(D)** Gadolinium enhancement of a lesion located in the cervical spinal cord.

of the brain and thoracic and cervical spine were performed. The brain MRI detected several demyelinating lesions, one with enhancement (in the subcortical region of the right frontal lobe). The spinal cord imaging showed an enhancing lesion consistent with demyelination at the fourth/fifth cervical vertebrae (C 4/5) and one smaller lesion at the level of the third/fourth cervical vertebrae (C3), without enhancement (Figure 1). Cerebrospinal fluid (CSF) analysis demonstrated moderate pleocytosis (25 leukocytes/μl; normal range 0–5 leukocytes/μl), elevated IgG index (0.84; normal range 0.0–0.7), and the presence of oligoclonal bands (serum unmatched CSF oligoclonal bands). Other evaluations from serum and CSF were unremarkable (serum: C-reactive protein, erythrocyte sedimentation rate, blood count were in the limits of the laboratory standard; CSF: glucose value 76 mg/dl with normal range of 50–80 mg/dl, protein value 44 mg/dl with normal range of 15–45 mg/dl). Diagnostic tests for infectious were negative. These included an examination of the presence of *Borrelia burgdorferi* and tick-borne encephalitis virus; the region of the patient living is endemic for both. Tests for the presence of anti-aquaporin-4 antibodies, myelin basic protein antibodies, and antibodies to myelin oligodendrocyte glycoprotein were negative. The evaluation for other autoimmune diseases was negative and included: rheumatoid factor, antiprothrombin, antinuclear, antiphospholipid, and antineutrophil cytoplasmic antibodies, antigens against :dsDNA, nucleosome, histosome, SS-A, Ro-52, SS-B, nRNP/Sm, Sm, Mi-2alfa, Mi-2beta, Ku, A, and B centromeres, Sp100, PML, PM-Scl100, PM-Scl75, Scl-70, RP155, gp210, PCNA, and DFS70.

The patient was treated with high-dose glucocorticoid therapy (1,000 mg of methylprednisolone i.v. for 3 days). A significant improvement in the patient's neurological condition was achieved but without complete recovery. A subtle disturbance of temperature sensation persisted (discharge EDSS = 1.0). The patient was diagnosed with MS according to the 2017 McDonald criteria and started treatment with dimethyl fumarate (4). In 1 year of observation, no relapses were present, there was no worsening of the patient's neurological state (EDSS = 1.0), and initial treatment with disease-modifying therapy has been continued. The follow-up MRI showed no new lesions and no enhancing lesions.

Discussion

In most countries, sanitary restrictions due to the spread of SARS-CoV-2 are now limited. However, the circulation of new variants of the virus is ongoing. Therefore, broad immunization is crucial for the further preservation of global health.

Vaccination against SARS-CoV-2 is recommended for individuals with MS (5). The serological response to SARS-CoV-2 vaccination is satisfactory in most patients treated with disease-modifying therapies (DMTs). Lower seroconversion is noted in individuals treated with anti-CD20 therapies and fingolimod (6).

In one of our previous works, we collected a database of more than 2000 individuals with MS from Poland, and the relapse rate after vaccination against COVID-19 was low (7). Similarly, low relapse incidence after vaccination was described by Kong et al. (8), including individuals with neuromyelitis optica spectrum disorder (NMOSD). In the analysis of patients with MS from Germany and the United Kingdom, the percentage of individuals manifesting deterioration after vaccination was significantly higher (19%), but not only relapses were taken into account (9). In the study of Stastna et al. (10), the relapse incidence was slightly higher in vaccinated individuals, but also in people with SM who had a history of COVID-19 infection. An interesting observation was made by Brunn et al. (11), where among about 300 vaccinated people with MS, worsening was mostly associated with symptom recrudescence (not new deficits). There are also case series showing the time relation of AstraZeneca vaccination to relapse in previously stable patients (12). However, studies with more people presenting worsening following immunization do not show the predominance of a particular vaccine (13). Based on currently available data, the potential for available vaccinations to induce autoimmune exacerbation, in general, is not significantly high. What is more, most authors agree, that the benefit of vaccination, for now, outweighs the potential risk of triggering relapse (14).

The presented case and similar cases reported by other authors are rare. The only link between the onset of symptoms and immunization is the time interval. It is impossible to state unequivocally that the vaccination triggered the onset of symptoms or that this was coincidental.

In the presented case, it seems plausible that the vaccination revealed the underlying autoimmune condition. The MRI scans showed dissemination in time. This indicates the presence of a latent autoimmune process before immunization. A case of exacerbation after vaccination with the Johnson & Johnson COVID-19 vaccine in an individual with MS, previously presenting neurological symptoms, is described in the literature (15). In the case we are presenting, the patient has never had any neurological symptoms before immunization. Other similar case reports (with new onset of the disease) in the literature followed the Pfizer-BioNTech COVID-19, Moderna COVID-19, and Oxford Astra Zeneca COVID-19 vaccines (3, 16, 17). There are reports of other CNS inflammatory demyelinating events (acute transverse myelitis, NMOSD, myelin oligodendrocyte glycoprotein antibody disease, acute disseminated encephalomyelitis) following vaccination against COVID-19 (18).

How the COVID-19 pandemic will unfold is difficult to predict. However, the current experiences have shown that broad immunization with currently available vaccines is safe and effective, reducing the risk of severe COVID-19, hospitalization, and death (19). Multiple studies have concluded that COVID-19 vaccines are safe for individuals with MS (20–22). Cases like the one we reported here are rare, and—based on current knowledge—the benefits of vaccination against SARS-CoV-2 far outweigh the potential risks.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Bioethics Committee at Medical University of Białystok. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AC, KK-T, JT, MC, JK, and AK contributed to conception and design of the article. ET performed analysis of the neuroimaging. AC wrote the first draft of the manuscript. KK-T, JT, and MC revised the final version of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

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

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FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures overlaying anti-N-methyl-D-aspartate receptor encephalitis: a case report and literature review

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Background: FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures (FLAMES) has been identified increasingly frequently in recent years. However, this rare MOG antibody disease may coexist with anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARe), in an overlap syndrome with unknown clinical features and prognosis.

Methods: We report a new case of this overlap syndrome and present a systematic review of similar cases in the literature to provide information on the clinical presentation, MRI features, EGG abnormalities, treatment, and prognosis of patients with this rare syndrome.

Results: A total of 12 patients were analyzed in the study. The most common clinical manifestations of FLAMES overlaid with anti-NMDARe were epilepsy (12/12), headache (11/12), and fever (10/12). Increases in intracranial pressure (median: 262.5 mmH_2O, range: 150–380 mmH_2O), cerebrospinal fluid (CSF) leukocyte count (median: 128×10^6/L, range: 1-610×10^6/L), and protein level (median: 0.48 g/L) were also observed. The median CSF anti-NMDAR antibody titer was 1:10 (1:1–1:32), while the median serum MOG antibody titer was 1:32 (1:10–1:1024). Seven cases exhibited unilateral cortical FLAIR hyperintensity, and five cases (42%) had bilateral cortical FLAIR hyperintensity, including four cases involving the bilateral medial frontal lobes. Of the 12 patients, five showed lesions at other sites (e.g., the brainstem, corpus callosum, or frontal orbital gyrus) before or after the development of cortical encephalitis. EEG showed slow waves in four cases, spike–slow waves in two cases, an epileptiform pattern in one case, and normal waves in two cases. The median number of relapses was two. Over a mean follow-up period of 18.5 months, only one patient experienced residual visual impairment, while the remaining 11 patients had good prognoses.

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Conclusion: FLAMES alone is difficult to distinguish from overlap syndrome based on clinical features. However, FLAMES with bilateral medial frontal lobe involvement suggests the presence of the overlap syndrome.

KEYWORDS

MOG ab-positive CCE, anti-N-methyl-D-aspartate receptor encephalitis, symptoms, demyelinating disease, FLAIR

Introduction

Myelin oligodendrocyte glycoprotein (MOG) is a protein expressed in the outermost layer of the myelin sheath of the central nervous system. MOG antibody-associated disease (MOGAD) is gradually becoming recognized as a new independent spectrum of disease. The most common clinical manifestations of MOGAD are optic neuritis (ON), myelitis, and acute disseminated encephalomyelitis, while cortical encephalitis, demyelination of the brainstem and cerebellum, and progressive white matter damage are rare (1). The term "FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures" (FLAMES) was introduced by Budhram in 2019. Although this was initially reported as unilateral cortical encephalitis, the presence of bilateral cortical involvement and meningeal inflammation in a subset of cases suggests a broader disease spectrum (2). Atypical manifestations of demyelination, such as fever, headache, epilepsy, and aphasia, are common in FLAMES.

Anti-NMDAR encephalitis is one of the most common types of autoimmune encephalitis and is associated with the presence of NMDAR subunit 1 (NR1) antibodies (3). Patients may experience abnormal mental behavior, involuntary movements of the mouth, and central hypoventilation. Between 4% and 7.5% of patients with anti-NMDARe have both glial and neuronal surface antibodies. A study of 215 anti-NMDARe patients, in which only 22 patients were positive for MOG-Ab, concluded that double antibody positivity is rare (4). In addition, Martinez-Hernandez (5) reported that patients with anti-NMDARe combined with MOG-Ab positivity have additional clinical radiological characteristics that may affect prognosis.

Despite previous case reports on the coexistence of FLAMES with anti-NMDARe, the clinical features, ancillary tests, treatment, and prognosis of these combined conditions have not been reviewed in detail. This paper reports a case of FLAMES combined with anti-NMDARe. In addition, we systematically review cases reported in the literature to provide information on the clinical symptoms, magnetic resonance imaging (MRI) findings, electroencephalographic (EEG) abnormalities, and treatment and prognosis of this rare overlap syndrome.

Materials and methods

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we searched the PubMed database for publications up to September 15, 2022 that contained the terms "NMDAR" and "MOG", or "NMDAR" and "Demyelination" and "MOG" and "Encephalitis", in order to identify articles reporting on patients with coexisting FLAMES and anti-NMDARe (Figure 1). The inclusion criteria were as follows: (1) patients were positive for anti-NMDAR antibodies in the CSF and MOG antibodies in the serum; (2) the course of the disease included an episode of FLAMES; and (3) complete data were available on clinical symptoms, imaging, and treatment. Patients lacking a detailed clinical course description or radiological and laboratory information were excluded from the study. One new case diagnosed in our hospital was also included in the study. Information on the enrolled cases, including our case, is listed in Table 1. The study was approved by the Ethics Committee of the First Hospital of Jilin University. Written informed consent was obtained from the patients for the release of data and accompanying images.

Case report

A 30-year-old man initially complained of headaches and memory loss. After 15 days, the patient suffered a generalized tonic–clonic seizure with a five-minute period of loss of

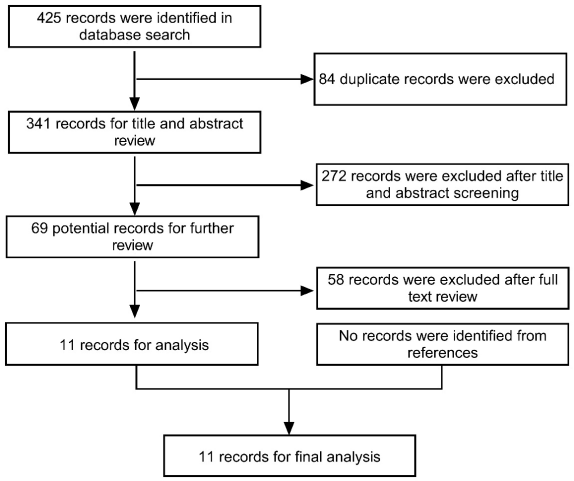

FIGURE 1
PRISMA flowchart.

TABLE 1 Summary of cases included in this study.

No.	Age	Sex	Clinical symptoms					CSF			MOG-ab		NMDAR		MRI		EEG	Relapse	Treatment
			Fever	Headache	Epilepsy	Visual impairment	Other symptoms	ICP	WC	Protein	CSF	Serum	CSF	Serum	Cortical FLAIR hyperintensity	Infratentorial lesion			
1	31	M	+	+	GTCS	+	Right hemiplegia, ataxia, ON		142	0.67		1:320	1:1	–	Right temporal, parietal, occipital	Midbrain, pons, medulla oblongata	Rt hemispheric-onset seizures	4	IVIG, IVMP, PSL/AZA, MMF
2	20	F	+	+	GTCS	+	Lower limb weakness, consciousness disorder, ON		29	0.38	1:16	1:128	+		Bilateral medial frontal lobe, cingulate	Pons	Diffuse slow wave (3HZ)	1	IVIG, IVMP, PE
3	36	F	+	+	Fas	–	Aphasia, disorientation, consciousness disorder, ataxia, central hypoventilation, involuntary movement during argument, delusion, depression		128	0.40		+	1:20		Bilateral medial frontal lobe	Cerebellum		1	IVIG, IVMP, PE
4	10	F	+	+	Fas	+	Involuntary movement during argument, consciousness disorder, ON	360	1	0.32		+	1:1	–	Right frontal, parietal		Spike and slow-wave discharges in the right hemisphere	4	IVIG, IVMP, PSL/RTM, MTX
5	21	M	+	+	GTCS	+	ON				–	1:32	1:32	+	Right frontotemporal lobe, meningeal enhancement		Normal	1	IVMP, IVIG,PSL
6	37	M	–	+	GTCS	–	Left limb weakness		11	0.48	1:10	1:10	1:1	1:1	Bilateral medial frontal lobe, meningeal enhancement		Normal	0	PSL
7	39	M	+	+	UEPC	–	Orientation, memory impairment, central hypopnea, delusions		112	0.44	+	1:1024	+		Bilateral medial frontal lobe, cingulate		Diffuse slow wave	2	IVMP, IVIG
8	38	M	+	+	GTCS	–	Restless	380	396	1.42	1:10	1:32	1:10	–	Left hemispheric		Left frontotemporal lobe apical–	0	IVMP, IVIG,PSL/MMF

(Continued)

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TABLE 1 Continued

No.	Age	Sex	Clinical symptoms					CSF			MOG-ab		NMDAR		MRI		EEG	Relapse	Treatment
			Fever	Headache	Epilepsy	Visual impairment	Other symptoms	ICP	WC	Protein	CSF	Serum	CSF	Serum	Cortical FLAIR hyperintensity	Infratentorial lesion			
9	28	M	+	+	GTCS	+	ON	250	610	1.28	1:32	1:10	1:10		Left frontal		Scattered slow wave	0	IVMP, PSL/MMF
10	20	M	+	+	GTCS	+	ON	240	590	0.82		1:32	1:10	1:10	Right parietal				IVMP
11	38	M	–	–	GTCS	+	Left hemiplegia, aphasia, consciousness disorder	275	88	0.48	+	+	+	+	Bilateral cerebral cortex	Brain stem		2	IVMP, IVIG,PSL/ MMF
12	30	M	+	+	GTCS	–	Consciousness disorder, aphasia, restless	150	268	0.37	1:100	1:1000	1:1 +	–	Right frontal, meningeal enhancement		Left temporal apical wave, right temporal slow wave	0	IVMP, IVIG,LEV, PSL/CTX

M, male; F, female; ON, optic neuritis; ICP, intracranial pressure; FAS, focal aware motor onset seizure; GTCS, generalized tonic–clonic seizure; RTM, rituximab; LEV, levetiracetam; AZA, azathioprine; MMF, mycophenolate mofetil; CTX, cyclophosphamide; PSL, prednisolone; IVMP, intravenous methylprednisolone; IVIG, intravenous human immunoglobulin, UEPC, unexplained epilepsia partialis continua; D, days; Y, years; M, months. Case1 (6); case2 (7); case3 (8); case4 (9); case5 (10); case6 (11); case7 (12); case8 (13); case9 (14); case10 (15); case11 (16).

consciousness. Neurological examination on admission showed no significant symptoms except for verbal confusion, agitation, and abnormal mental behavior. MRI showed a FLAIR-hyperintense lesion and abnormal enhancement in the right frontal cortex (Figure 2), while EEG revealed slow-wave activity in the right temporal lobe, sharp-wave activity in the left temporal lobe, and a limited decrease in brain function (Figure 3). A CSF examination indicated 100×10^6/L erythrocytes, 268×10^6/L leukocytosis, 98% mononuclear cells, and a protein concentration of 0.37g/L. CSF gram staining, ink staining, and bacterial and fungal cultures were negative. The patient was presumed to have viral encephalitis and was treated empirically with ganciclovir and levetiracetam. Five days after admission, the patient developed fever and persistent agitation. Cellular immunoassay results were positive for MOG antibodies (serum, 1:1000; cerebrospinal fluid, 1:100), autoimmune encephalitis-associated autoantibodies, and anti-NMDAR antibodies (serum, 1:10; cerebrospinal fluid, 1:10). autoimmune encephalitis-associated autoantibodies, and anti-NMDAR antibodies (serum: cerebrospinal fluid, 1:10). The patient was then administered intravenous immunoglobulin (0.4g/kg/d for 5 days) and intravenous methylprednisolone (1g/d for 3d, 0.5g/d for 3d, and 0.12g/d for 3d). This resulted in gradual improvement in the above symptoms. Repeat cerebral MRI 28 days after admission showed the disappearance of the FLAIR-hyperintense lesion in the right frontal cortex, while a CSF examination indicated 20×10^6/L leukocytes and 0.30 g/L protein. A fixed cell assay was positive for anti-NMDAR antibodies (CSF, 1:1+) and MOG antibodies (serum 1:10+, CSF 1:1+). In addition, results were negative for all of the following antibodies: anti-aquaporin-4 (AQP4), anti-NMDAR, anti-leucine-rich glioma inactivated 1 (LGI1), anti-contactin-associated protein-like 2 (CASPR2), α-amino-3-hydroxy-5-methyl-isoxazolepropionic acid receptor (AMPAR), and gamma-aminobutyric acid (GABA) receptor. After discharge, the patient was advised to take oral prednisolone and cyclophosphamide. We followed up with the patient after two years, and he had returned to work with no recurrence of symptoms.

Results of the literature search

Demographics and clinical characteristics

The search of the PubMed database identified a total of 425 studies, 11 of which were included in this study (n=12 patients with the addition of our case). Nine of the 12 patients were male (75%), with the age of onset ranging from 10 to 39 years (mean: 29 years).

The most frequent clinical manifestation of the overlay of FLAMES with anti-NMDARe was epilepsy (100%), followed by generalized tonic spastic seizures (75%), focal seizures (16.7%), and unknown forms of seizure (8.3%). Other common characteristics were headache (92%), fever (83%), decreased vision (58%), disorders of consciousness (42%), aphasia (33%), limb weakness (33%), psychiatric symptoms such as delirium, agitation, hallucinations, and babbling (33%), central hypoventilation (17%), cognitive impairment, disorientation, and ataxia (Table 2). Six patients also had ON. No patient had a teratoma or tumors.

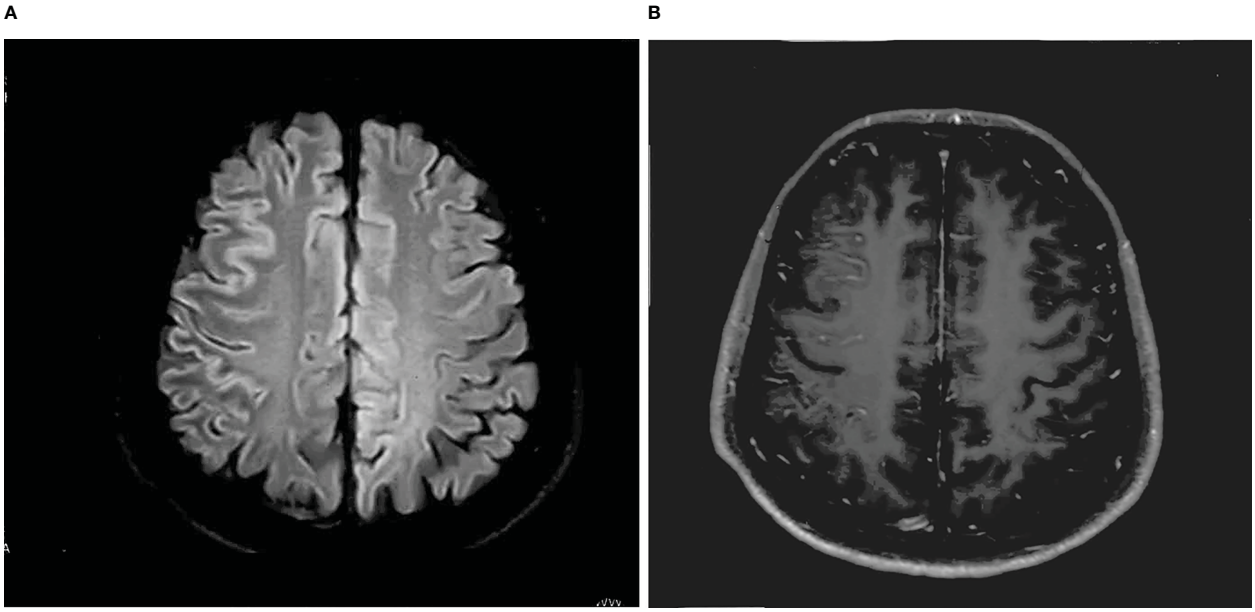

FIGURE 2
(A) T-2 FLAIR hyperintensity in the right frontal cortex, swelling of brain tissue, and shallowing of the cerebral sulcus. **(B)** Abnormal enhancement of the pia mater in the right frontal lobe.

Laboratory characteristics

CSF examinations showed leukocytes in the range of 1–610×10^6/L (median: 128×10^6/L), with this increase caused predominantly by monocytes. Protein levels were normal or slightly elevated, with a median of 0.48 g/L. Six patients had intracranial pressure results indicating CSF pressure ranging from 150 to 380 mmH_2O, with a median of 262.5 mmH_2O (Table 2).

All patients were positive for CFS anti-NMDAR antibodies and serum anti-MOG antibodies. CSF anti-NMDAR antibody titers ranged between 1:1 and 1:32 (median: 1:10), while MOG antibody titers in serum ranged from 1:10 to 1:1024 (median: 1:32). Some patients also tested positive for MOG antibodies in CSF, with titers ranging from 1:10 to 1:100 (median: 1:16). In one patient, mGluR5 antibodies were concurrently detected in the cerebrospinal fluid and serum.

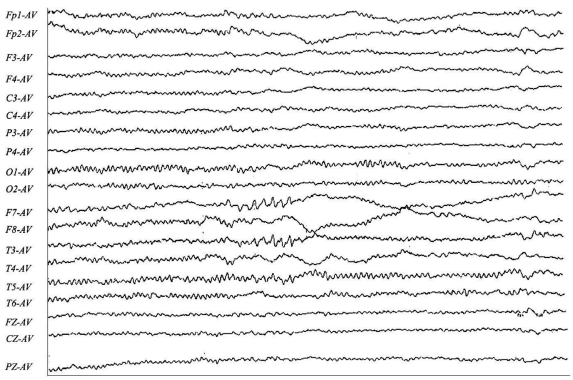

FIGURE 3
F7-AV, T3-AV, T5-AV: the left temporal region exhibits predominantly sharp-wave activity in the anterior and middle temporal regions, with some involvement of the posterior temporal region. F8-AV, T4-AV: The right anterior middle temporal region exhibits slow-wave activity.

EGG

EEG results were obtained for 9 patients, 4 of whom exhibited slow-wave activity; 2 exhibited pike-slow waves, 1 exhibited an epileptiform pattern, and 2 patients had normal EEG results. None of the patients exhibited the characteristic abnormal δ brush of NMDARe.

Neuroimaging findings

All 12 patients had a FLAIR-hyperintense lesion with anti-MOG-associated encephalitis, with seizures occurring during the disease episode. Seven patients presented with unilateral cortical FLAIR-hyperintense lesions, usually involving the frontal, temporal, and parietal lobes, some with meningeal enhancement. Five of the 12 patients had lesions at other sites (e.g., the brainstem, corpus callosum, and frontal orbital gyrus). Five patients (41.7%) showed bilateral cortical FLAIR-hyperintense lesions, four of which were in the bilateral medial frontal lobes. One patient had a hyperintense brainstem lesion before FLAME, and in 4 patients this occurred after the development of the disease.

Treatment and outcomes

First-line treatments included IVMP (11/12), IVIG (9/12), and plasma exchange (2/12). Eight patients received a combination of

TABLE 2 Demographic and clinical data on all patients.

Sex (male), n (%)	9 (75%)
Age (years), average	29
Clinical presentation, n (%)	
Epilepsy	12 (100%)
Headache	11 (92%)
Fever	10 (83%)
Vision loss	7 (58%)
Disorder of consciousness	5 (42%)
Aphasia	4 (33%)
Limb weakness	4 (33%)
Psychiatric symptoms	4 (33%)
Central hypoventilation	2 (17%)
CSF	
Pressure	262.5 mmH_2O
WBC, median	128 × 10^6 / L
Protein, median	0.48g/L
MOG, median	1:16
NMDAR, median	1:10
Serum	
MOG, median	1:32
FLAIR cortical hyperintensity	
Unilateral cortical	7 (58%)
Bilateral medial frontal lobes	4 (33%)
Infratentorial lesion	4 (33%)

IVMP+IVIG. Of the 12 patients, six recovered with first-line treatment. The second line of treatment included mycophenolate mofetil (4/12), azathioprine (1/12), cyclophosphamide (1/12), rituximab (1/12), and methotrexate (1/12). Seven patients relapsed during the disease episode, with the median number of relapses being two. Follow-up data were collected for four patients over a mean time period of 18.5 months. Only one patient experienced residual visual impairment, although this did not affect their daily work. The remaining 11 patients had no significant sequelae.

Discussion

FLAMES is a rare clinical phenotype of MOGAD that has been reported since 2017 (17). Fujimori et al. suggested that the specific role of MOG-ab in MOG cerebral cortical encephalitis (CCE) may have relevance to autoimmune encephalitis such as NMDARe, although its mechanism of action remains unclear (18). Vega's study on MOG-positive non-ADEM encephalitis showed that 40% of patients had concomitant NMDAR-abs in the CSF (19). Currently, many scholars consider positivity for both antibodies to be relevant to oligodendrocytes. Both MOG receptors and NMDAR can be expressed on the surface of oligodendrocytes, which may explain the double antibody positivity (20). In addition, the viral infection causes the blood–brain barrier to be disrupted, triggering subsequent inflammatory and immune responses. Mariotto's study (21) showed that 45% of patients with MOG antibody-related disease had prodromal symptoms or an infectious process. There is evidence that anti-NMDARe can be triggered by viral encephalitis, particularly the herpes simplex virus (22). Four patients in our study had flu-like symptoms before onset, and HHV-7 was detected in one patient using second-generation sequencing (14).

In this study, we have discussed the clinical features, neuroimaging features, and prognosis of 12 cases of coexistence of FLAMES and anti-NMDARe. Anti-NMDARe usually occurs in female patients, while the overlap syndrome is more common in male patients (75%). The common clinical manifestations of the overlap syndrome are epilepsy, headache, fever, vision impairment, psychiatric symptoms, aphasia, and (less frequently) central hypoventilation, involuntary chewing movements at the corners of the mouth, and loss of consciousness. ON is rare in anti-NMDARe patients but has been reported in overlap syndrome patients. Compared with classic anti-NMDARe, patients with the overlap syndrome have milder clinical symptoms (23). In our study, 10 patients initially had FLAMES while two patients had NMDARe. It is difficult to distinguish this overlap syndrome from FLAMES alone on the basis of clinical presentation. Previously, it had been concluded that anti-NMDARe in female patients was associated mostly with teratomas. However, no tumors were found in any of the patients in this study. Therefore, tumors are unlikely to be the primary trigger for NMDARe in FLAMES patients. Titulaer's study (11) concluded that the double positivity of the anti-NMDAR antibody and MOG-ab represented an autoimmune rather than a tumor trigger.

Overlap syndrome patients have CSF findings similar to those observed in patients with FLAMES alone. It is possible to observe elevated intracranial pressure, elevated leukocytes and erythrocytes, and mildly elevated protein levels. CSF titers of the anti-NMDAR antibody in overlap syndrome patients were in the range 1:1–1:32, with a median of 1:10. Overlap syndrome patients had lower antibody titers than seen in anti-NMDARe alone, which could explain the mostly mild symptoms of anti-NMDARe in these patients. Gresa-Arribas et al. (24) concluded that anti-NMDAR antibody titers are positively associated with poor prognosis. All the patients in our study with anti-NMDARe had mild clinical symptoms and achieved a good prognosis at subsequent follow-up. Anti-NMDARe is one of the most common types of autoimmune encephalitis, with the associated EEG abnormalities mainly being generalized slow waves, followed by focal slow waves in the frontal or anterior temporal regions (25, 26). The EEG abnormalities in FLAMES patients are seen in the central, parietal, posterior temporal, or occipital regions. The frontal and parietal lobes are usually involved in epileptic activity, whereas the limbic system is not (26). EEG may be normal during the interictal period, and in patients with FLAMES, EEG may differ from that

measured in other types of autoimmune encephalitis. In cases of focal epilepsy, FLAMES patients can exhibit slow waves or epileptic waves in the parietal and occipital lobes, which is rare in patients with other autoimmune encephalitides. These EEG characteristics can prompt clinicians to test for MOG antibodies. Tokumoto's (26) EEG study on FLAMES patients concluded that the abnormal slow waves mainly arose from the posterior temporal region and that no abnormalities were recorded in the anterior temporal region. This characteristic is distinct from the results observed for the patients in our study, whose EEGs suggested predominantly sharp waves in the left temporal region with some involvement of the posterior temporal region, while the right side exhibited slow-wave activity in the anterior middle temporal region. FLAMES in which EEG shows sharp–slow waves in the anterior temporal region may indicate anti-NMDAR antibody positivity. However, no reports relevant to this were identified in the current study, and further studies are therefore necessary.

The current study analyzed a total of 12 cases of FLAMES combined with anti-NMDARe. Four of the 12 patients showed bilateral medial frontal FLAIR-hyperintense lesions. Fujimori suggested that the presence of anti-NMDARe and MOG-ab may result in the onset of bilateral medial frontal lobe CCE almost simultaneously, and this possibility was confirmed in these four patients. Cherian et al. (24) pointed out that contrast enhancement in the bilateral medial frontal lobe, especially the bilateral cingulate gyrus, can be an imaging feature for the coexistence of dual antibodies to MOG and NMDAR. The four aforementioned patients in our study developed subtentorial demyelinating lesions during the course of the disease. Consistent with the hypothesis of Ren et al. (16), in patients with recurrent CNS demyelination, especially MRI brainstem lesions and cortical involvement, double positivity for MOG-ab and NMDAR antibodies should be considered. Furthermore, Vega's latest study showed that a significantly higher proportion of patients with FLAMES combined with non-ADEM encephalitis (13/25) presented with NMDAR antibodies in their CSF compared to the proportion among patients with FLAMES alone (2/13) (19). This further demonstrates that when FLAMES patients show infratentorial lesions on MRI, this represents an alert to check for the presence of the overlay syndrome. Such potentially unique imaging characteristics therefore provide clinicians with greater insight into the diagnosis of the overlap syndrome.

Vega's study concluded that patients with the overlay syndrome have a higher rate of relapse than patients with FLAMES alone (19). Patients with the overlay syndrome usually have a positive response to steroids, with the clinical symptoms of most patients being relieved within a short time after receiving IVIG and IVMP treatment. However, if steroids are discontinued, or reduced too quickly, a relapse may occur. Patients can then receive repeat first-line therapy, while second-line immunotherapy such as rituximab, mycophenolate, and azathioprine should be added. In general, it has been reported that all patients have recovered after appropriate treatment, with no significant sequelae remaining (6, 27). In addition, immunosuppression therapy may reduce relapse in patients.

Conclusion

The rate of coexistence of FLAMES and anti-NMDARe may be underestimated. It is difficult to distinguish patients with FLAMES alone from those with the overlap syndrome based on clinical characteristics. Patients diagnosed with FLAMES should be actively screened for anti-NMADR antibodies if MRI shows bilateral medical frontal lobe FLAIR-hyperintense lesions. Overlap syndrome patients should be treated with extended immunotherapy, which can reduce relapses and offer a good prognosis.

Ethics statement

Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

JC and J-XY: designed the study. J-XY, M-MY, C-HG, and Y-JH: interpreted the data. J-XY: drafted the manuscript. All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

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Case report: Persistent hypogammaglobulinemia in thymoma-associated myasthenia gravis: the impact of rituximab or Good's syndrome?

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Introduction: Rituximab (RTX) showed good efficacy and safety for patients with myasthenia gravis. However, the percentage of peripheral CD20+ B cell may be absent for years after low dose of RTX treatment. Persistent hypogammaglobulinemia and opportunistic infection may occur in patients under treatment of RTX with thymoma relapse.

Case representation: We report a case of refractory myasthenia gravis. After two doses of 100 mg rituximab, the patient developed transient neutropenia. The peripheral blood CD20+ B cell percentage was 0 more than 3 years. Eighteen months later, the patient's symptoms relapsed with thymoma recurred. She had persistent hypogammaglobulinemia and multiple opportunistic infections.

Conclusion: In MG patient under B cell depletion therapy had thymoma relapse, Good's syndrome may induce prolonged B cell depletion, hypogammaglobulinemia and opportunistic infections.

KEYWORDS

myasthenia gravis (MG), rituximab (RTX), hypogammaglobulinemia, infections, Good's syndrome (GS)

Introduction

Many studies have indicated that rituximab (RTX) is effective for myasthenia gravis (MG) (1). Although most studies have suggested that rituximab is safe, serious adverse events have been reported, including severe skin reactions, blood system diseases, hepatitis B reactivation, progressive multifocal leukoencephalopathy and other severe opportunistic infections (2). Conditions may become more complicated in patients with MG and thymoma.

Herein, we report a patient who received rituximab and radiotherapy for MG with thymoma. She suffered from transient severe agranulocytosis, persistent hypogammaglobulinemia, opportunistic infection and haemolytic anemia.

Case description

The patient is a 34-year-old female who was diagnosed with generalized myasthenia gravis 12 years prior. She underwent thymectomy and radiotherapy. Previously, she had three episodes of myasthenia gravis crises induced by infection. In addition to prednisone,

she received azathioprine and cyclosporine, which failed to control her symptoms. Her dose of tacrolimus was halved due to the high blood concentration.

Physical examination showed bilateral mild ptosis, and the distal muscle strength of the lower extremities was Grade IV. She was positive for anti-acetylcholine receptor (anti-AChR) antibody. The myasthenia gravis Foundation of America (MGFA) classification was IIb, and the Activities of Daily Living (ADL) and Quantitative Myasthenia Gravis Score for disease severity (QMG) score was 11 and 15, respectively. The baseline total T lymphocytes, total B lymphocytes, CD20+ B cells and CD22+ B cells were 79% (50–82%), 9.6% (5–21%), 9.5 and 9.6%, respectively. The patient was treated with rituximab (100 mg) intravenously in February 2019. After discharge, she continued to take prednisone (20 mg) daily. After 3 months, the percentage of CD20+ B cells in the peripheral blood was 0.1%. She was given another intravenous infusion of rituximab (100 mg) in May 2019, and the number of CD20+ B cells decreased to 0 on the second day. Her symptoms were quite stable, and she was prescribed 60 mg of pyridostigmine bromide and 20 mg of prednisone orally for maintenance therapy.

One month later, the patient presented with intermittent low fever, night sweats and herpes around the mouth, accompanied by ptosis of the right eyelid, dysarthria and chewing difficulty. The peripheral blood leukocyte count was significantly decreased to 1.65×10^9, and the neutrophil count was 0. Peripheral platelet count and red blood cell count were normal. The total peripheral blood B lymphocytes and CD20+ B cells were still 0. The immunoglobulin G (IgG) level was 8.51 (7.23–16.85) g/L. The immunoglobulin A (IgA) level was 0.78 (0.69–3.82) g/L. The immunoglobulin M (IgM) level was 0.83 (0.62–2.77) g/L. The patient's symptoms improved after empiric anti-infection treatment with cefatriaxone, acyclovir and colony stimulating factor. The peripheral counts of leukocytes and neutrophils returned to normal 3 months later. The dose of prednisone was tapered to 17.5 mg.

In August 2020, the patient's symptoms were aggravated. Her chest computed tomography (CT) showed that the thymoma recurred. She received intravenous infusion 20g of immunoglobulin (IVIG) for 5 days and 25 sessions of thymic intensity modulated radiotherapy, with total dose of 5000 gy in May 2021. Her immunotherapy regimen was adjusted to 20 mg and 12.5 mg of prednisone every other day, and her symptoms stabilized.

In August 2021, the patient had fever again. Her chest CT showed that both lungs had new multiple patchy ground glass foci. The percentage of total T lymphocytes was 96.5%, the percentage of CD4+ and CD8+ T cells was 23.7 and 72.5% respectively, and the percentage of B cells was still 0% in peripheral blood. The level of IgG was 29.3 g/L, the level of IgA was 0.49 g/L and the level of IgM was 0.58 g/L. Bronchoscopic alveolar lavage indicates pneumocystis pneumonia. IVIG (20 g) was administered intravenously for 5 days. Sulfamethoxazole tablets were given as treatment. Her prednisone dosage was reduced to 20 mg and 5 mg orally every other day. Two months later, the level of IgG was 7.86 g/L, the level of IgM returned to 0.65 g/L, and the level of IgA was still as low as 0.47 g/L.

In October 2021, the patient experienced decreased vision in her left eye, and she was diagnosed with cytomegalovirus infectious retinitis. Additionally, the IgG, IgM and IgA levels were all below normal limits (6.86 g/L, 0.43 g/l and 0.51 g/L). The patient received ganciclovir intravitreal injection, tobramycin and prednisone acetate eye drops, and the left eye vision of the patient was maintained at 0.15. Steroids were discontinued, and 20 g IVIG was administered every month. After 5 administrations, the interval was extended to 2 months, and the patient's immunoglobulin level was monitored monthly. The IgG level returned to normal, but IgM and IgA levels fluctuated between 0.45–0.5 g/L (0.63–2.77 g/L) and 0.27–0.4 g/L (0.69–3.82 g/L), respectively, for a long time.

In May 2022, the percentage of peripheral CD20+ B cells was 11.65% (5.0–21%). The patient's myasthenia symptoms were relatively stable, leaving only extraocular muscle paralysis and mild limb weakness. In August 2022, however, the patient felt fatigue and dizziness. Routine blood tests revealed anemia. HGB levels decreased to 50 mg/dl at minimum. Coomb's test was positive, and the patient was diagnosed with erythroblastic anemia. IVIG was given with 40 mg prednisone. HGB levels returned to 94 mg/dl. At present, the patient's symptoms are quite stable except for low immunoglobin levels. Her IgG level was 6.87 g/L, IgA and IgM was 0.39 g/L and 0.46 g/L, respectively. Her corticosteroids were tapered slowly, and IVIG was administered every 2–3 months. We summarized the patients clinical events and laboratory results in Figure 1.

Discussion

In the current case, transient neutropenia was induced by RTX and persistent hypogammaglobulinemia preceded by thymoma relapse, resulting in multiple opportunistic infections.

The incidence of neutropenia has been reported to be approximately 6.5% after RTX treatment in patients with rheumatoid arthritis. Most patients have a good prognosis without severe infections (3). Due to the low dosage of RTX and the patient was asymptomatic, the level of immunoglobin was not evaluated before and after treatment of RTX. Three months after thymoma relapse and radiotherapy, hypogammaglobulinemia was found, while peripheral B cell was still 0. These leads to

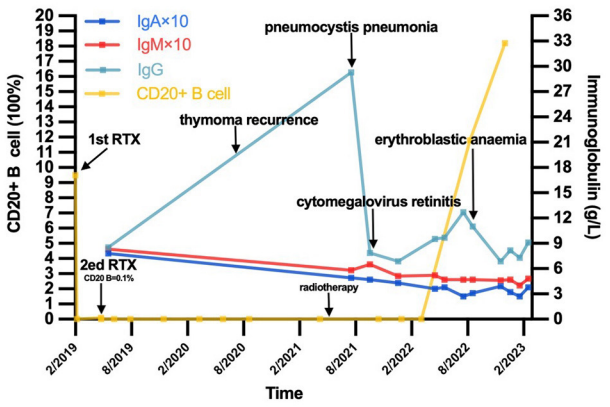

FIGURE 1
The timeline of this patient's course and the trend of CD20+ B cell as well as immunoglobulin level. IgA, immunoglobulin A; IgM, immunoglobulin M; IgG, immunoglobulin M.

multiple opportunistic infections. Both RTX and thymoma can induce hypogammaglobulinemia.

The incidence of hypogammaglobulinemia following RTX treatment ranges from 13 to 56% in patients with non-Hodgkin lymphoma and autoimmune diseases, which is more common and severe than neutropenia (4, 5). Most studies believe that persistent IgG deficiency is linked to an increased risk of serious infections after RTX and that decreased IgM and IgA are less clinically significant (5–8). At present, the etiology of hypogammaglobulinemia after RTX has not been fully clarified, and many studies believe that it is the result of the interaction of multiple factors (9). RTX mainly acts on the surface antigen of CD20, which is mainly expressed in peripheral blood circulation B cells but not bone marrow stem cells and CD20-negative plasma cells (10). Therefore, RTX will not completely inhibit humoral immunity. However, in patients with haematologic diseases, combined chemotherapy may lead to persistent hypogammaglobulinemia related to the stagnation of B-cell reconstruction (11). It is unclear whether the differences in dosage and interval of RTX will have a variable impact on the degree and duration of B-cell depletion (12, 13).

Theoretically, with the regeneration of peripheral blood CD20+B cells, the immunoglobulin level should return to the normal level. After two doses of rituximab 100 mg, the level of B lymphocytes in this patient remained at 0 for 3 years. As the level of IgG returned to normal, the levels of IgA and IgM in peripheral blood continued to be lower than the normal limit, even after CD20+ B cells returned to the normal level. There might be other factors influencing immunological function.

Immunological disturbances such as Good's Syndrome may occur in patients with thymoma, including a reduction in circulating B lymphocytes, hypogammaglobulinemia and decreased T lymphocytes (14), presenting with a variable phenotype of immunodeficiency. The current patient had persistent hypogammaglobulinemia, B-cell deficiency and thymoma, Good's syndrome should be considered. Decreased T lymphocytes, inversion of the CD4+/CD8+ ratio also occurred in this patient (11). Comparing with the treatment of RTX, Good's syndrome is more accountable for the subsequent immunodeficiency.

At present, there are no proven diagnoses or treatments. Immunoglobulin replacement reduces the risk of infection with primary and secondary immunodeficiency associated with hypogammaglobulinemia. Some studies believe that the clinical manifestations of severe infection are more reliable as indicators of alternative treatment than laboratory indicators (15). The B-cell phenotype of patients receiving immunoglobulin replacement therapy after rituximab is mainly naive B cells, and the switching memory B cells are reduced (16).

Conclusion

In MG patient under B cell depletion therapy had thymoma relapse, Good's syndrome may induce prolonged B cell depletion, persistent hypogammaglobulinemia and opportunistic infections.

Data availability statement

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

Ethics statement

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

Author contributions

JR and RL analyzed data and wrote the main manuscript text. JW and JL followed up patients and collected data. JG and YY examined immunoglobulin and lymphocyte level in serum. HH helped interpret relevant indicators. FG provided ideas and guidance for this article. All the authors read and approve the final revision of the manuscript.

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Conflict of interest

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

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Treatment of IgG4-related disease-associated hypertrophic pachymeningitis with intrathecal rituximab: a case report

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IgG4-related disease-associated hypertrophic pachymeningitis (IgG4RD-HP) is a fibroinflammatory autoimmune disorder in which diagnosis is difficult without biopsy. Guidance on management of disease refractory to glucocorticoids and intravenous rituximab is limited. We present the case of a 68-year-old woman with IgG4RD-HP who developed sensorineural hearing loss with associated bulky basilar pachymeningeal enhancement. Her cerebrospinal fluid was inflammatory and had an elevated IgG4 concentration, strongly suggestive of IgG4RD-HP. Biopsy of involved meninges was not possible due to surgical risk. Over years she developed bilateral optic neuropathies and hydrocephalus, requiring intravenous rituximab and ventriculoperitoneal shunt. Her disease was refractory to glucocorticoids. Despite maintenance intravenous rituximab, she developed slowly progressive symptoms of intracranial hypertension and hydrocephalus with persistently inflammatory spinal fluid. Switching to intrathecal rituximab therapy led to dramatic improvement in gait and headache and reduced pachymeningeal bulk and metabolic activity. In patients with IgG4RD-HP refractory to glucocorticoids and intravenous rituximab, intrathecal rituximab may be an efficacious therapy.

KEYWORDS

IgG4-related disease, pachymeningitis, hydrocephalus, intrathecal rituximab, CSF IgG4, optic neuropathy

1. Introduction

IgG4-related disease-associated hypertrophic pachymeningitis (IgG4RD-HP) is a fibroinflammatory disorder in which a combination of peripheral and intrathecal inflammation may play a role (1). The first-line treatment for IgG4-RD is glucocorticoids. Intravenous rituximab is a second-line therapy but has limited ability to penetrate the blood-brain barrier. Intrathecal rituximab has been reported to lead to clinical improvement in IgG4-RD-HP (2, 3). We report a patient with IgG4RD-HP who developed hearing loss, optic neuropathy, and hydrocephalus and experienced clinicoradiographic improvement on intrathecal rituximab after failure of intravenous rituximab.

2. Case history

In March 2012, a 68-year-old woman developed left-sided sensorineural hearing loss confirmed by audiogram. Brain MRI showed dural-based enhancing nodules involving the prepontine and perimesencephalic cisterns (Figures 1A, B). The lesion encased the basilar artery and internal carotid arteries and also involved the left internal auditory canal, suprasellar cistern abutting the optic chiasm, orbital apices, and bilateral cavernous sinuses. Other than left-sided hearing loss, cranial nerves, strength, reflexes, sensation, and gait were normal. Initial serum, CSF, and systemic imaging studies excluded infectious, autoimmune, and neoplastic mimics (Table 1). She had no oral or genital ulcers. Serum IgG4 was elevated at 128 mg/dL (normal range 3.9–86.4). A CSF examination from September 2012 demonstrated 79 nucleated cells/mcL (97% lymphocytes), an elevated protein concentration of 148 mg/dL (normal 5–55 mg/dL), and a CSF glucose of 49 mg/dL (normal 50–75 mg/dL). Oral prednisone 60 mg daily and methotrexate 15 mg weekly were begun to treat inflammatory pachymeningitis suspicious for IgG4RD-HP.

Following her prednisone taper, in October 2014 she developed right afferent pupillary defect and worsening pinhole corrected visual acuity (20/30 OD, 20/40 OS) and was diagnosed with an optic neuropathy. January 2015 CSF showed 107 nucleated cells/mcL (98% lymphocytes), protein 181 mg/dL, glucose 56 mg/dL. The CSF IgG4 was 5.06 mg/dL and the serum IgG4 was 111.2 mg/dL. A diagnosis of IgG4RD-HP was made based on clinicoradiographic presentation and elevated CSF IgG4 based on previously published diagnostic cutoff of 2.27 mg/dL (4).

Vision deteriorated to count fingers OD over months. Rituximab 1,000 mg IV every 2 weeks for the first two doses replaced methotrexate in March 2015. In July 2015 she developed obstructive hydrocephalus resulting in unsteady gait with magnetic quality and subsequent fall. Ventriculoperitoneal shunt placement in August 2015 improved her gait. During shunt placement, biopsy of brain and dura uninvolved by pachymeningitis showed non-specific reactive gliosis. She continued intravenous rituximab every 4 months. Pinhole corrected visual acuity improved to 20/60 OD with inferior altitudinal defect and 20/25 OS with temporal hemianopsia. In February 2020, she developed morning headaches

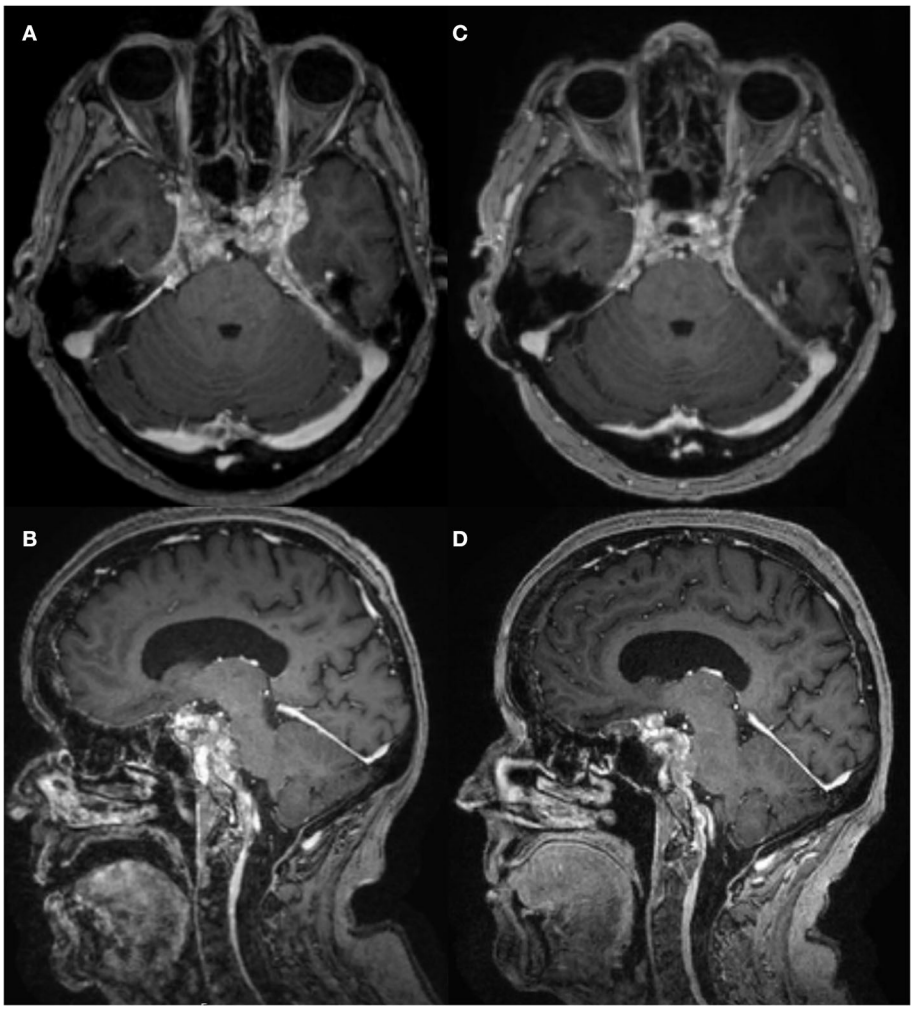

FIGURE 1
Brain MRI T1 post-contrast, pre- and post-intrathecal rituximab. **(A, B)** January 2021, before intrathecal rituximab. **(C, D)** March 2022, after two cycles of intrathecal rituximab. There was mild improvement in enhancement and pachymeningeal bulk after cycle 1, but not after cycle 2.

TABLE 1 Diagnostic testing investigating for infectious and inflammatory mimics of IgG4-related disease.

Serum test	Value	CSF test
Antinuclear antibody	1:80, nucleolar pattern (normal <1:40)	Cytology without malignant cells
C3	125 (normal 86–184 mg/dL)	VDRL negative
C4	22 (normal 16–38 mg/dL)	Cryptococcal antigen negative
Erythrocyte sedimentation rate	13 mm/h	Mycobacterial culture without growth
ANCA	Negative	
SS-A, SS-B	Negative	Imaging
Anti-Smith	2.53 (normal 0–19.99)	CT chest/abdomen/pelvis showed no lesions suggestive of sarcoidosis or malignancy.
Anti-RNP	0.46 (normal 0–19.99)	
Anti-dsDNA	Negative	
Anti-Scl70	1.13 (normal 0–19.99)	
Rheumatoid factor	<30	
Interferon gamma release assay	Negative	
Tuberculin skin test	No induration	
Anti-mitochondrial	Negative	
Anti-tTG IgA	2.3 (normal 0–15 U/mL)	

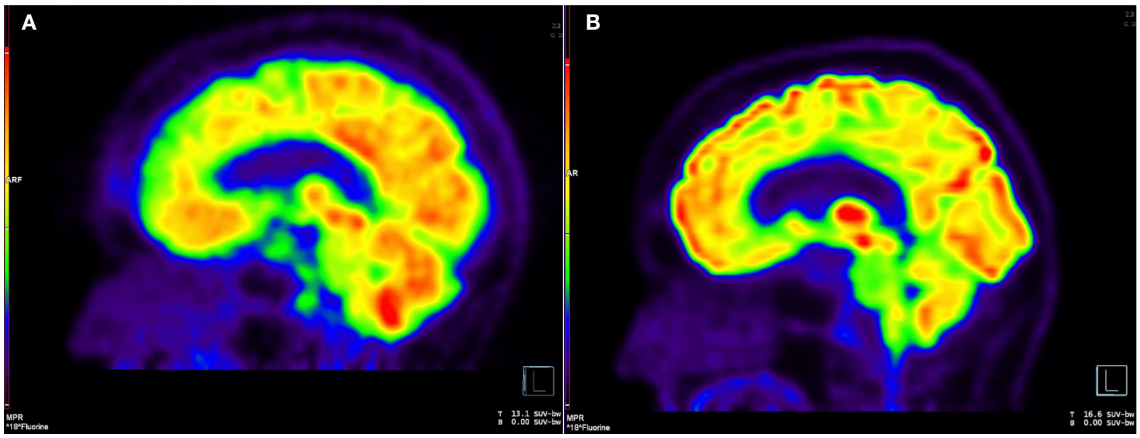

FIGURE 2
Brain FDG-PET, pre- and post-intrathecal rituximab. **(A)** Sagittal image from 18F-FDG PET before intrathecal rituximab demonstrates diffuse, patchy cerebral cortical hypometabolism and intense nodular uptake along the retroclival region, corresponding to areas of pachymeningeal disease. **(B)** Follow-up imaging after intrathecal rituximab demonstrates interval resolution of previously seen cortical hypometabolism and abnormal retroclival uptake.

worsened by supine position. Lumbar puncture June 2020 showed opening pressure 18 cm H2O, 23 nucleated cells/mcL, protein 727 mg/dL, and elevated IgG4 17.4 mg/dL with serum IgG4 74 mg/dL. X-rays showed intact shunt. Shunt was reprogrammed with symptomatic relief, but symptoms recurred in December 2020. Brain FDG-PET showed hypermetabolism in areas of pachymeningitis (Figure 2A).

The patient's gait grew more unsteady, such that she had to walk with a walker at all times. Due to her persistent headache, gait worsening, pachymeningitis, and intrathecal inflammation, a decision to escalate therapy to intrathecal ritixumab was made. She underwent shunt revision in January 2021 with addition of on/off valve to prevent CSF drainage to peritoneal cavity in preparation for intrathecal rituximab administration via the shunt.

In March 2021, 2 days prior to receiving intrathecal rituximab, visual acuity with pinhole correction was 20/30−2 OD with inferior altitudinal defect and 20/25−2 OS with temporal hemianopsia. Intrathecal rituximab was administered according to the following protocol: the shunt valve was turned off for 30 min to allow for spinal fluid to accumulate, after which 15 mL of CSF was drained, 10 mg of rituximab was

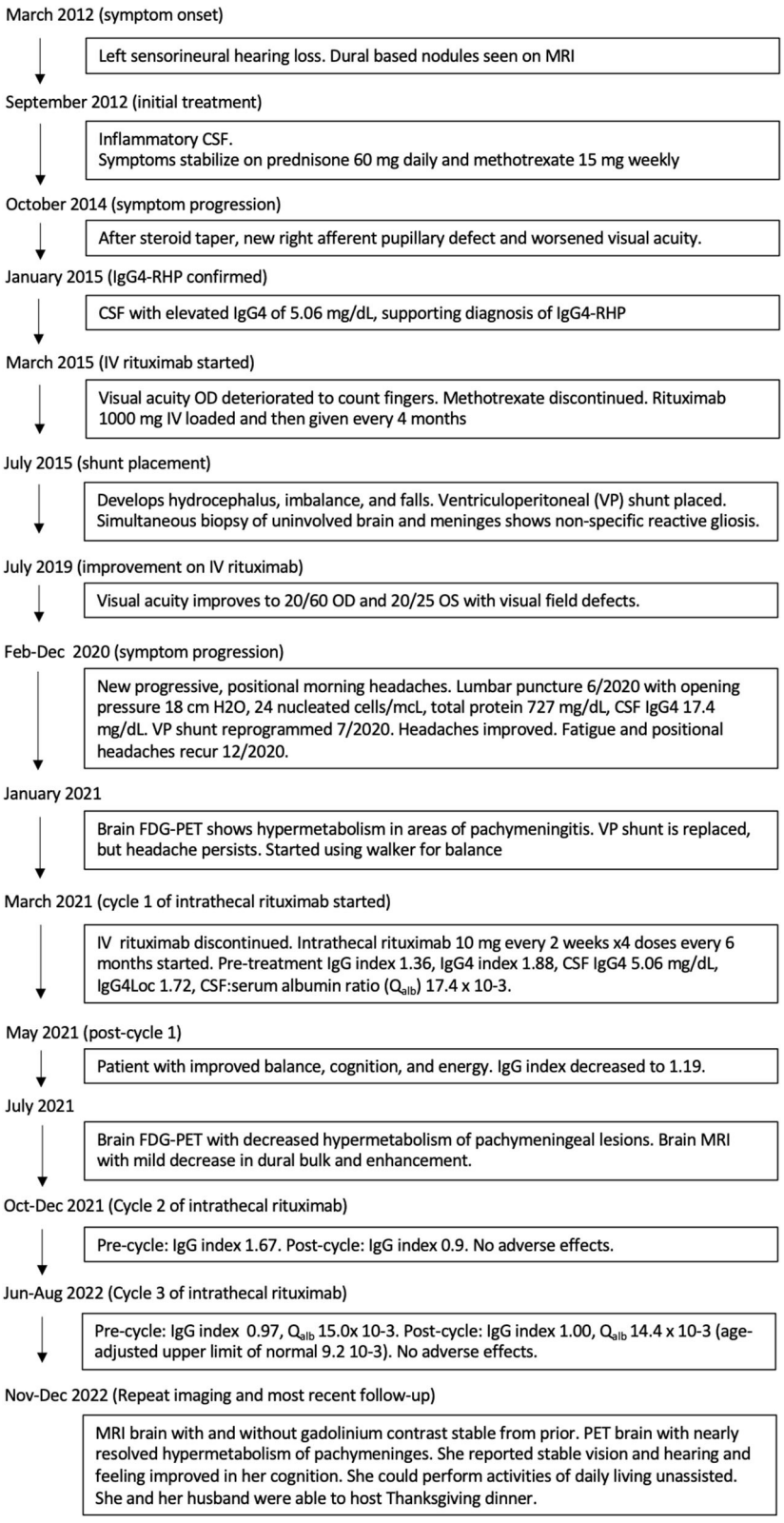

FIGURE 3
Flowchart of the patient's clinical course of treatment.

administered via the shunt, and 6 mL of CSF administered to flush the tubing. After 1 h, the shunt valve was turned back on to allow for normal drainage. This protocol was repeated every 2 weeks for total of four sessions, occurring every 6 months.

CSF drawn before the first treatment showed elevated CSF IgG index 1.36, IgG4 index 1.88, IgG4 2.7 mg/dL, IgG4Loc 1.72, and CSF:serum albumin ratio 17.4 x 10-3. She tolerated intrathecal rituximab well with facial (Q_{alb}) flushing as the only side-effect. She felt remarkable improvement in her ability to think clearly, an increase in her energy level, and vastly improved steadiness of gait and turning ability. IgG index in May 2021 decreased to 1.19. Brain PET July 2021 showed mild decreased hypermetabolism of the pachymeninges. Brain MRI showed mild decrease in dural bulk and enhancement with less encasement of the basilar and internal carotid arteries. In October 2021, her visual acuity with pinhole correction improved to 20/30 +1 OD and 20/25 +1 OS with persistent visual field defects as before. IgG index at beginning of second cycle in October 2021 was 1.67, which reduced to 0.9 in December 2021. Brain MRI in March 2022 showed no decrease in pachymeningeal bulk. At January 2022 follow-up, she reported no headaches nor falls saying, "I feel like I am enjoying life the way I am supposed to." November 2022 brain MRI was stable (Figures 1C, D). Brain PET showed nearly resolved hypermetabolism of the pachymeninges (Figure 2B). She has continued to improve, and at last follow-up in December 2022 she had a normal gait and was able to walk down a long hallway without a cane. Figure 3 provides a summary of the patient's history, testing and treatment over time.

3. Discussion

This case report describes the protocol used for intrathecal rituximab administration in a case of refractory IgG4RD-HP, a treatment that led to an excellent outcome and was remarkably well tolerated. IgG4RD is a multisystemic fibroinflammatory disorder. Diagnosis is the assimilation of information from the clinical examination, serological evaluation, radiologic evidence, and pathology findings (5). It is also important to exclude potential mimickers. Diagnosis of the disease involving the pachymeninges and CNS is frequently challenging, particularly if the sites of disease pose challenges to biopsy, as seen in our case. Standard treatment of IgG4-RD includes glucocorticoids (5, 6). Therapies targeting B-lymphocytes, particularly the intravenous administration of rituximab, have also demonstrated good success in a high percentage of IgG4-RD patients (7).

In IgG4RD-HP, disease is often isolated to the meninges and inflammation can be restricted to the intrathecal compartment, making measurement of CSF IgG4 markers a useful diagnostic adjunct (4, 8). Cutoffs for such markers have been suggested as alternatives to biopsy when it is contraindicated or uninformative, like in our patient (4). Our patient's values for CSF IgG4 (5.06 mg/dL >2.27 mg/dL) and IgG4Loc (1.72 >0.47) were above these cutoffs, which helped rule in IgG4RD-HP after other disorders were excluded (4, 9).

Despite initial improvement and stabilization with ventriculoperitoneal shunt and intravenous rituximab, her symptoms ultimately progressed. One possible explanation for this is the failure of intravenous rituximab to target intrathecal inflammation. Intravenous rituximab achieves 0.1–0.5% CSF concentration as compared to that of serum (3, 10). Thus, in some IgG4RD-HP patients who respond to intravenous rituximab, it is possible this small amount of penetrance may be enough to control disease. However, patients refractory to intravenous rituximab may have greater response to the higher effective dose that intrathecal rituximab provides.

Two reports in the literature describe successful treatment of IgG4RD-HP with intrathecal rituximab after failure of intravenous rituximab (2, 3). In both cases, the patients had frontal pachymeningitis, a location that affords lower surgical risk, allowing for biopsy confirmation. Both received intrathecal rituximab <3 years after diagnosis and demonstrated marked improvement in pachymeningeal enhancement and associated parenchymal T2 hyperintensities. One of the cases also described normalization of CSF:serum albumin ratio (QQ_{alb}), a measure of CSF flow rate and blood-CSF barrier dysfunction (2, 9). Neither measured CSF IgG4 markers or described adverse effects from intrathecal rituximab.

Our report differs in that the patient carried the diagnosis for 9 years before intrathecal rituximab administration, had bulkier pachymeningeal disease, and did not have associated T2 hyperintensities. Though our patient had mild improvement in pachymeningeal enhancement and thickening on MRI and metabolic activity on FDG-PET with intrathecal rituximab, she had less robust response than the other two cases. This is likely because of the greater fibrous changes that accumulated in her pachymeninges. In principally fibrotic manifestations of IgG4RD, such as thyroiditis or pachymeningitis, delayed treatment may not be able to reverse fibrotic bulk despite adequate inflammatory control due to the accumulation of non-inflammatory fibrosis over time (5, 11). She had improvement, but not normalization, in Q_{alb} and IgG index with intrathecal rituximab, likely also due to persistent pachymeningeal fibrous changes leading to impaired CSF flow. As in the previous reports, intrathecal rituximab was well-tolerated in our patient.

In conclusion, our report provides a longitudinal description of IgG4RD-HP disease progression in a patient who became refractory to intravenous rituximab and demonstrated clinical, immunologic, and radiographic improvement with intrathecal rituximab. Intrathecal rituximab should be considered as a treatment option in cases of refractory IgG4RD-HP.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

DB: acquired, analyzed, and interpreted data, drafted and critically revised the manuscript, and designed figures. SH and BC: acquired data and critically revised the manuscript. BP: acquired and interpreted MRI and PET images. AO'S: acquired and interpreted PET images. AV and PJ: critically revised the manuscript. JS and NV: conceived the study, acquired, analyzed, and interpreted data, and critically revised the manuscript. All authors approved the final manuscript.

Conflict of interest

DB receives funding from Biogen as part of a Translational Neuroscience Research Fellowship.

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1189778/full#supplementary-material

SUPPLEMENTARY VIDEO 1
Video of the patient's gait after receiving several cycles of intrathecal rituximab. Prior to intrathecal rituximab therapy, the patient required a cane for ambulation. After intrathecal rituximab, she can walk independently.

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Case Report: Paroxysmal weakness of unilateral limb as an initial symptom in anti-LGI1 encephalitis: a report of five cases

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Anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis is the second most common kind of autoimmune encephalitis following anti-N-methyl-d-aspartate receptor (NMDAR) encephalitis. Anti-LGI1 encephalitis is characterized by cognitive impairment or rapid progressive dementia, psychiatric disorders, epileptic seizures, faciobrachial dystonic seizures (FBDS), and refractory hyponatremia. Recently, we found an atypical manifestation of anti-LGI1 encephalitis, in which paroxysmal limb weakness was the initial symptom. In this report, we describe five cases of anti-LGI1 encephalitis with paroxysmal limb weakness. Patients had similar presentations, where a sudden weakness involving a unilateral limb was observed, which lasted several seconds and occurred dozens of times each day, with the anti-LGI1 antibody being positive in both serum and cerebrospinal fluid (CSF). FBDS occurred after a mean of 12 days following paroxysmal limb weakness in three of five patients (Cases 1, 4, and 5). All patients were given high-dose steroid therapy, which had a good effect on their condition. Based on this report, we suggest that paroxysmal unilateral weakness may be a kind of epilepsy and be connected to FBDS. As an unusual neurological presentation, paroxysmal weakness can be included in the clinical manifestations of anti-LGI1 encephalitis, helping to raise awareness of the recognition of anti-LGI1 encephalitis in patients with this symptom and leading to early diagnosis and early treatment, which would contribute to improved clinical outcomes.

KEYWORDS

case report, Anti-LGI1 encephalitis, autoimmune encephalitis, paroxysmal, limb weakness

Introduction

First proposed in 2010 (1), anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis is the second most common type of autoimmune encephalitis (2), accounting for about 12.8% in China (3). It is characterized by rapid progressive dementia, psychiatric disorders, epileptic seizures, and faciobrachial dystonic seizures (FBDS) (4).

At the beginning of the disease, some prodromal symptoms can be found in patients with anti-LGI1 encephalitis, such as paroxysmal dizziness spells, seizures, fatigue, or drowsiness (5, 6). Qiao reported a patient who suffered paroxysmal hyperhidrosis as an initial symptom (7). These non-specific or uncommon manifestations prevent patients from early diagnosis and early treatment. The paroxysmal weakness of the unilateral limb reported in our patients has never been seen in anti-LGI1 encephalitis, and this is the only case report documented on record.

Herein, we describe five cases of anti-LGI1 encephalitis with paroxysmal limb weakness as an initial symptom.

Patients and methods

A total of five patients with anti-LGI1 encephalitis, treated at the First Affiliated Hospital of China Medical University (Shenyang, China) between 2019 and 2022 (58 cases of LGI-1 encephalitis were treated in total during the same period) were investigated. This is a retrospective study of the patient characteristics and treatment outcomes, and ethical committee approval was not required for this study, but written informed consent of all patients was obtained. The clinical features of the five cases are included in Table 1. In all five patients, the diagnosis of anti-LGI1 encephalitis was not only dependent on their clinical characteristics and magnetic resonance imaging (MRI) of brain, but also positive anti-LGI1 antibodies in serum and CSF (8).

The anti-LGI1 antibody was detected by cell based assay (CBA) and tissue based assay (TBA), where the principle was to transfect the gene of the anti-LGI1 encephalitis antigen into mammalian cells by plasmid pcDNA3.1. The corresponding antigen was specifically expressed in mammalian cells, and green fluorescent protein was expressed during transfection as an internal reference for detection. Then, the transfected cells were fixed on a 96-well microplate, and the semi-quantitative detection of specific antibodies in human serum and cerebrospinal fluid samples was carried out using the principle of indirect immunofluorescence. Then, observed under a fluorescence microscope for result judgment, the cells were first observed through the green channel to check for successful transfection. If the plasmid transfection was successful, green fluorescence could be observed in the cells. Then, the cells were

TABLE 1 Patient's clinical features.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years), sex	60, male	33, female	61, male	59. male	55, male
Involved limb	Left arm and leg	Left leg	Right arm	Left arm	Left arm
FBDS	Yes	No	No	Yes	Yes
Days from weakness to FBDS onset	20	–	–	13	5
Short-term memory deterioration	Yes	No	Yes	Yes	No
Psychiatric disorder	No	No	Yes	Yes	No
EEG	Normal	Normal	Normal	Normal	Normal
Cranial MRI	T2-weighted and FLAIR hyper- intensity in the right hippocampus	Normal	T2-weighted and FLAIR hyper-intensity in the left hippocampus	Normal	Normal
CSF analysis	Normal	Normal	Normal	Normal	Normal
Anti-LGI1 positivity and titer	Serum 1:100 CSF 1:3.2	Serum 1:30 CSF1:10	Serum 1:30 CSF1:30	Serum 1:30 CSF1:10	Serum 1:100 CSF1:10
Immunotherapy	Methylprednisolone 500mg for 5 days, half decrement every 3 days, subsequent oral steroid tapering	Methylprednisolone 1000mg for 3 days, half decrement every 3 days, subsequent oral steroid tapering	Methylprednisolone 500mg for 5 days, half decrement every 3 days, subsequent oral steroid tapering	Methylprednisolone 500mg for 5 days, half decrement every 3 days, subsequent oral steroid tapering	Methylprednisolone 500mg for 7 days, half decrement every 3 days, subsequent oral steroid tapering
Outcome (follow-up)	Occasional paroxysmal limb weakness and FBDS (3 months). recurrence (20 months), FBDS reduced after methylprednisolone 500mg, weakness and FBDS disappeared (28 months)	Paroxysmal limb weakness disappeared (3 months)	Paroxysmal limb weakness disappeared (2 months) Short-term memory deterioration (4 months)	Occasional paroxysmal limb weakness and FBDS, normal mental status (2 months)	Paroxysmal limb weakness and FBDS disappeared, normal mental status (3 months)

observed through the red channel, and if there was a clear red fluorescence in the transfected cell membrane of the sample well, it was considered a positive sample. If there was no clear red fluorescence in the transfected cell membrane of the sample well or if untransfected cells also showed red fluorescence, it was considered a negative sample. The results could be further confirmed by overlapping the green and red channels. Samples with positive results were selected 3 to 5 fields of view under a microscope, comparing the red fluorescence with the control sample. The positive titer value was given by comparing the intensity of the red fluorescence with that of the control sample.

Different sample types had different starting dilutions for the CBA method. The starting dilution for serum samples was 1:10, while the starting dilution for cerebrospinal fluid samples was 1:1. Usually, when the titer of anti-LGI1 encephalitis antibody reaches 1:10 in serum and 1:1 in cerebrospinal fluid at the same time, a positive diagnosis can be made.

Result

Case 1

A 60-year-old man was admitted to hospital due to paroxysmal weakness in his left limbs. At first, these episodes occurred once every few days and lasted for several seconds. However, over time, the frequency of weakness increased to 3-4 times an hour, and he also experienced a sensation of ants crawling on his left arm and leg. About 20 days after the onset of weakness, he started experiencing involuntary movements in his left limbs and face, which lasted for several seconds and occurred multiple times a day. These events were classified as FBDS. A cranial MRI showed hyper-intensity in the right hippocampus on T2 and fluid attenuated inversion recovery (FLAIR) sequences (Figure 1). Lab tests revealed the positivity of anti-LGI1 antibody in both serum (1:100) and CSF (1:3.2). The patient was diagnosed with anti-LGI1 encephalitis and was treated with methylprednisolone at 500mg for 5 days, with a gradual tapering every 3 days, followed by oral prednisone. During his hospitalization, the frequency of the repetitive weakness and FBDS reduced to once every few days. Three months after the initial testing, anti-LGI1 antibody in serum was negative; however it increased to 1:1000 in the 20th month after disease onset. At this point, the patient again developed paroxysmal weakness in his left limbs and FBDS, which occurred multiple times a day, and was readmitted to the neurological department. However, a follow-up cranial MRI showed a significant reduction of right hippocampus hyper-intensity on T2 weighted and FLAIR sequences (Figure 1). Another round of corticosteroid impulse therapy was also effective, and the symptoms was progressively improved. Over the course of the 28-month follow-up period, paroxysmal left limb weakness and FBDS disappeared, and anti-LGI1 antibody in serum was negative.

Case 2

A 33-year-old woman complained of paroxysmal weakness in her left leg. She first noticed the symptoms when she wanted to rise from a chair but failed because of the powerless state of her left leg, which returned to normal after 5 seconds. Then she found the episodes of repetitive weakness occurred more than 10 times each day without any apparent triggers. She couldn't walk during the onset of weakness and sometimes even fell down. Cranial MRI and EEGs did not reveal any abnormalities. Low-dose carbamazepine was administered as an experimental treatment but did nothing to relieve the weakness. Lab tests revealed the positivity of anti-LGI1 antibody in both serum (1:30) and CSF (1:10). Based on this information, the patient was diagnosed with anti-LGI1 encephalitis and treated with methylprednisolone of 1000mg for 3 days, with a decrement by half every 3 days, By the 4th day of immunotherapy, the weakness had disappeared and only reoccurred seven times during her hospitalization. After discharge from hospital, she continued taking prednisone orally. During the 3 months of follow-up, she did not experience any recurrence of the weakness (Supplementary Video 1).

Case 3

A 61-year-old man was admitted to hospital because of a 2-month history of repetitive weakness with short-term memory deterioration and psychiatric disorders. During an episode, he would yell at people and seemed to be out of control, and it was noticed that he couldn't raise his right arm. Additionally, he displayed irritability and visual hallucinations, such as watching somebody else taking a tumble. These symptoms lasted for about 2 minutes each time and occurred more than 10 times a day. The patient also had impaired memory, as evidenced by forgetting what he ate for breakfast, and he scored 20/30 on the Montreal Cognitive Assessment (MoCA) and 16/30 on the Mini-Mental State Examination (MMSE). Cranial MRI showed hyper-intensity on T2 and FLAIR sequence in the left hippocampus (Figure 2). Lab tests revealed the presence of anti-LGI1 antibody in both serum (1:30) and CSF (1:30). Based on these findings, he was diagnosed with anti-LGI1 encephalitis and was treated with methylprednisolone of 500mg for 5 days, with a decrement by half every 3 days, followed by oral prednisone. During his treatment, his repetitive weakness disappeared, and his memory improved (with a score of 21/30 on MoCA and 26/30 on MMSE). After 4 months of follow-up, the patient had no recurrence of his symptoms.

Case 4

A 59-year-old man was admitted to hospital because of repetitive weakness and numbness in his left arm, which was initially diagnosed as cerebral infarction. However, despite treatment, his condition did not improve and instead worsened over time. The frequency of his weakness increased from less than 10 times a day to dozens of times each day. He also developed dementia and exhibited abnormal behavior, which made it difficult for him to communicate with people around him. About 13 days after weakness onset, he began experiencing paroxysmal convulsions in his left arm, leg, and face. These convulsions,

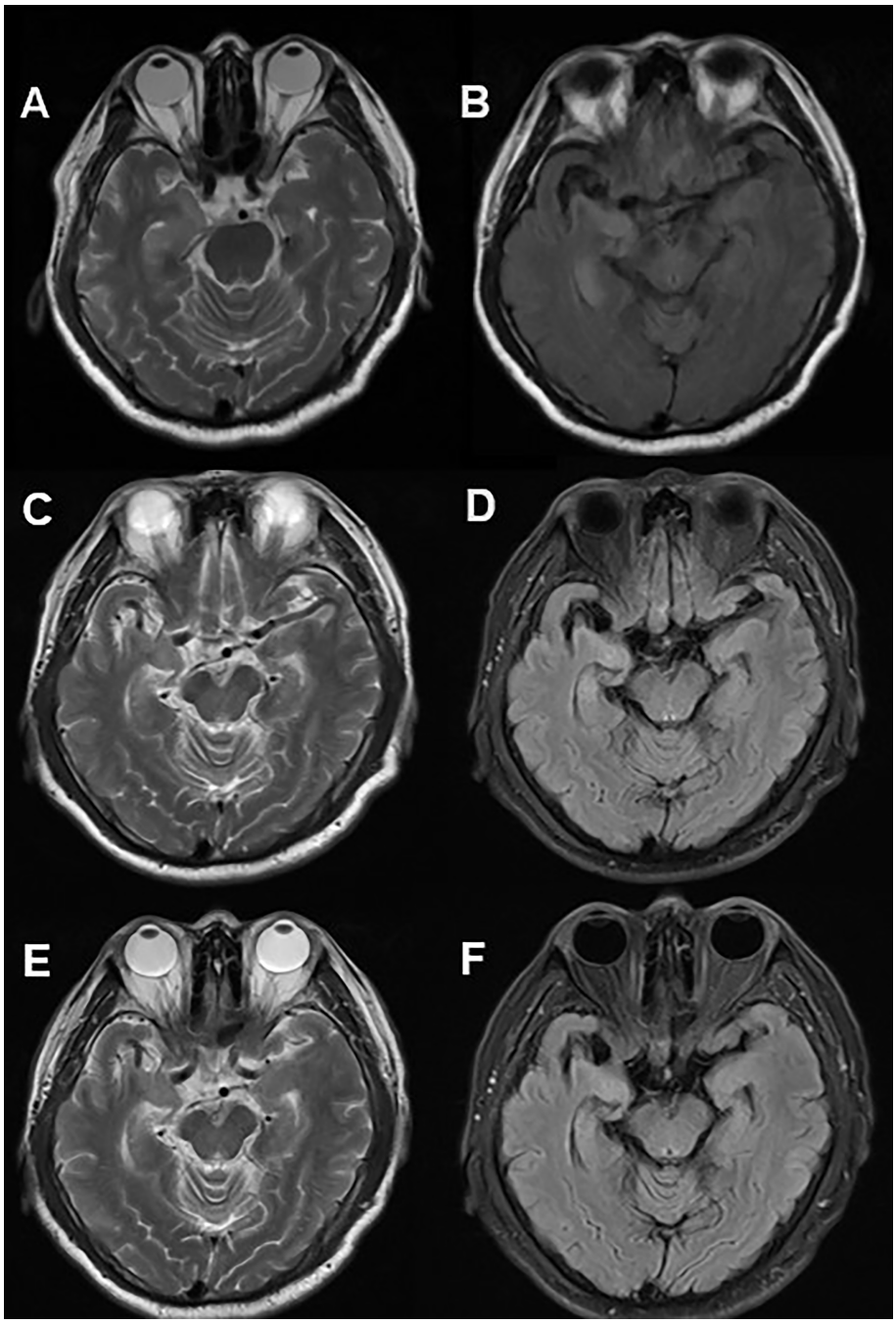

FIGURE 1
Cranial MRI in Case 1. Axial T2 weighted **(A)** and FLAIR **(B)** sequences showed hyper-intensity in the right hippocampus. 20 months after immunotherapy, a control cranial MRI showed a significant reduction of right hippocampus hyper-intensity in T2 **(C)** weighted and FLAIR **(D)** sequences. 28 months after immunotherapy, no significant changes contrasted **(E, F)** with **(C, D)**.

known as FBDS, lasted for 2 seconds and occurred 10 times every hour, leading to him falling. However, his cranial MRI and EEGs revealed no abnormalities. However, lab tests revealed the presence of anti-LGI1 antibody in both serum (1:30) and CSF (1:10). Based on these findings, he was diagnosed with anti-LGI1 encephalitis and was treated with methylprednisolone of 500mg for 5 days, with a half-dose reduction every 3 days, followed by oral prednisone. Before being discharged from hospital, the frequency of FBDS decreased sharply to about 20 times a day, and his overall mental state improved, although he still had some memory impairment. Over the following 3 months of follow-up, he recovered, and paroxysmal weakness and FBDS occurred occasionally.

Case 5

A 55-year-old male complained of paroxysmal weakness in his left arm, manifested in him not being able to fully clench his fist for

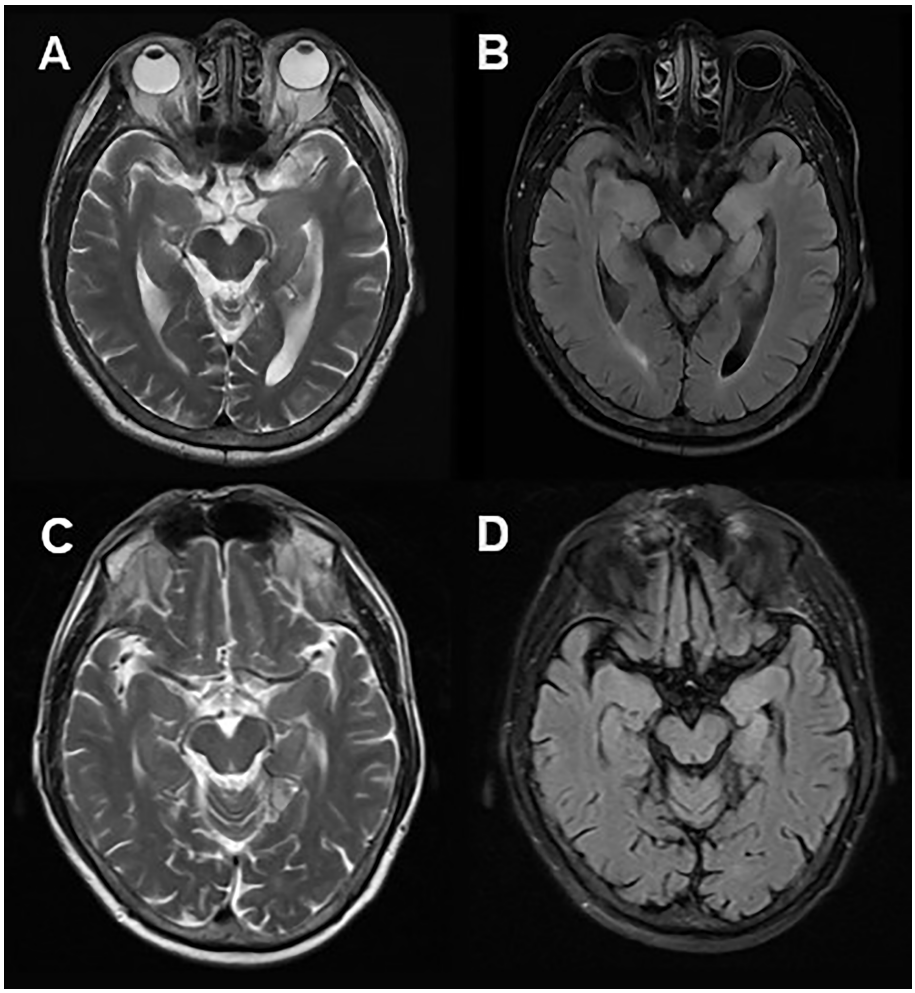

FIGURE 2
Cranial MRI in Case 3. Axial T2 weighted **(A)** and FLAIR **(B)** sequences showed hyper-intensity in the left hippocampus. 2 months after immunotherapy, a control cranial MRI showed a significant reduction of right hippocampus hyper-intensity in T2 weighted **(C)** and FLAIR **(D)** sequences.

10 seconds, and occurred 2 or 3 times daily. Five days later, he suffered paroxysmal convulsions affecting his left arm and face, accompanied by more frequent episodes of weakness occurring more than 10 times per day. Despite undergoing cranial MRI and EEGs tests, no abnormalities were found. However, lab tests revealed the presence of anti-LGI1 antibody in both serum (1:100) and CSF (1:10). He was diagnosed with anti-LGI1 encephalitis and treated with methylprednisolone of 500mg for 7 days, with a half-dose reduction every 3 days, followed by oral prednisone. At the 7th day of treatment, repetitive weakness and FBDS had disappeared. During the 3 months of follow-up, he did not experience any recurrence of symptoms (Supplementary Video 2).

Treatment and outcome

All five patients received high doses of steroid therapy at an initial dose of 500 or 1000 mg a day. Their conditions rapidly improved, with the frequency of paroxysmal weakness and FBDS decreasing, and their mental states became better.

At the last follow-up, there were no relapses in four patients (Cases 2–5). Case 1 suffered a relapse in the 20th month, and a new round of corticosteroid impulse therapy was still effective.

Some studies suggest that when the antibody titer in the cerebrospinal fluid is less than 1:10, it may be falsely positive and anti-LGI1 encephalitis cannot be diagnosed. At this time, a patient's clinical symptoms and imaging results should be considered to diagnosis encephalitis. In these cases, although there were low titers of antibodies in the cerebrospinal fluid, the diagnosis of encephalitis was confirmed based on the serum antibody titer, as well as the patient's clinical symptoms and imaging results, and the effectiveness of immunotherapy.

Discussion

This report describes five patients with anti-LGI1 encephalitis who had paroxysmal unilateral weakness as an initial symptom, accompanied by other clinical manifestations, such as FBDS, memory deficits, and psychiatric disorder.

As the most common limbic encephalitis, anti-LGI1 encephalitis is an acute or subacute disorder, and mainly affects adults between the ages of 30 to 80 with a higher incidence in men (9). In our report, 4(80%) of five patients were men, and the average age was 53.6 years (median, 59 years; range, 33–61 years), which agreed with the results of previous studies. LGI1, a secreted neuronal protein, forms a trans-synaptic complex with the presynaptic disintegrin and metalloproteinase domain-containing protein 22 (ADAM22), which interacts with AMPA receptors, and the postsynaptic ADAM23, which interacts with voltage-gated potassium channels Kv1.1 (10, 11). In addition, IgG secreted in patients with anti-LGI1 encephalitis disrupts the LGI1 signal of presynaptic and postsynaptic neurons, causing neuronal hyperexcitability and reversible memory deficits (12).

FBDS are characteristic symptoms of anti-LGI1 encephalitis and are considered pathognomonic, with brief inflexible posturing events typically lasting several seconds, usually less than 3 seconds, and occurring dozens of times during the day. FBDS involve the face and the ipsilateral arm, and sometimes the ipsilateral leg. The origin of FBDS is still a topic of heated discussion with no definitive conclusions. Because of epileptiform EEG changes, some researchers considered that FBDS are atypical epileptic phenomena (13), and that FBDS arises from network dysfunction between cortical and subcortical regions. Imaging abnormalities in basal ganglia have also been discovered in patients who experience FBDS (14, 15). Immunotherapy has been found to be effective in treating FBDS and can lead to their cessation (6, 16).

This abnormal pattern of weakness in the patients with anti-LGI1 encephalitis lasted for several seconds every time and occurred hundreds of times per day. This weakness involved a unilateral limb without any apparent inducement and did not respond to antiepileptic drugs. However, it showed a favorable response to high-dose steroid therapy. Following with the weakness, involuntary movements of the affected limbs and ipsilateral face, which are clinically recognized as FBDS, appeared gradually at the same time in three (Cases 1, 4, and 5) of the five cases. The mean duration from weakness to FBDS onset was about 12 days.

Paroxysmal limb weakness can be seen in patients with paroxysmal kinesigenic dyskinesia (PKD), but this type of weakness typically occurs after sudden motion state changes and usually manifests in the teen years. Furthermore, the relief of weakness in PKD patients is associated with immunotherapy but not carbamazepine (17). Therefore, in our patients, the weakness was considered a symptom of encephalitis.

The clinical manifestations of paroxysmal limb weakness in the cases we reported are similar to FBDS. In addition, immunotherapy has been found to be highly effective in preventing weakness and FBDS. Therefore, considering the temporal relationship between paroxysmal limb weakness and FBDS, we hypothesize that weakness may be a prodromal manifestation of FBDS and the mechanism of the paroxysmal limb weakness is similar to that of FBDS, suggesting that it is a form of epilepsy. However, we were unable to confirm this hypothesis, as we did not find any abnormalities in EEGs. Additionally, due to timely treatment or short-term follow-up, we did not find the appearance of FBDS in Case 2 and Case 3. As our report only analyzed five cases, it remains unclear whether the relationship between paroxysmal limb weakness and FBDS is coincidental or causal. To our knowledge, paroxysmal limb weakness has not been previously reported as an initial symptom of anti-LGI1 encephalitis or associated with FBDS.

Various paroxysmal and repetitive manifestations have been reported in the literature. Paroxysmal dizziness spells (PDS) were first proposed by Gadoth; these are partial seizures or aura phenomena which cannot be detected by EEGs (6). Another study by Beimer et al. identified a patient with anti-LGI1 encephalitis who suffered from ictal speech and manual automatisms, and video EEGs confirmed that the abnormal symptoms were a special seizure type (18). Qiao et al. also suggested that paroxysmal hyperhidrosis could be a possible form of epilepsy, which is different from an autonomic symptom (6). Furthermore, video EEGs observed epileptic waves during recurrent chest discomfort for the patient reported by Lee (19). These paroxysmal or ictal symptoms could be categorized as a specific type of seizure.

This article reports on the characteristics of paroxysmal limb weakness and analyzed its features, which are easily misdiagnosed as TIA or epilepsy in clinical practice. Finally, it was confirmed as a diagnosis of anti-LGI1 encephalitis. This recurrent type of symptom has not been reported internationally. Due to the limitations of sample size and time, this article cannot yet determine the overall incidence and long-term prognosis of this paroxysmal symptom and requires further observation with larger sample sizes.

While the association of weakness with FBDS remains unclear, paroxysmal unilateral limb weakness has been identified as an initial symptom of anti-LGI1 encephalitis. When paroxysmal unilateral symptoms, such as weakness of limbs, convulsions, and hyperhidrosis, are noticed, it is essential for patients to undergo LGI1 antibody testing for accurate diagnosis and treatment of this unusual disease.

Based on this report, we demonstrate an unusual neurological presentation that is included in the clinical manifestations of anti-LGI1 encephalitis, helping to recognize anti-LGI1 encephalitis in patients with this symptom and leading to early diagnosis and early treatment, which would contribute to improved clinical outcomes.

Data availability statement

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

Ethics statement

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

publication of any potentially identifiable images or data included in this article.

Author contributions

SW wrote the manuscript; SW and XS revised the manuscript; all authors contributed to follow-up, information collection, and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1191823/full#supplementary-material

SUPPLEMENTARY VIDEO 1
The patient of case 2 couldn't move with her powerless left leg.

SUPPLEMENTARY VIDEO 2
The patient of case 5 couldn't fully clench his fist with his powerless left arm.

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Case report: Reversible brain atrophy with low titer anti-amphiphysin antibodies related to gastric adenocarcinoma

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Amphiphysin (AMPH) autoimmunity is associated with a variety of neurological complications, including encephalitis, peripheral neuropathy, myelopathy, and cerebellar syndrome. Its diagnosis is based on clinical neurological deficits and the presence of serum anti-AMPH antibodies. Active immunotherapy, such as intravenous immunoglobulins, steroids, and other immunosuppressive therapies, has been reported to be effective in most patients. However, the extent of recovery varies depending on the case. Herein, we report the case of a 75-year-old woman with semi-rapidly progressive systemic tremors, visual hallucinations, and irritability. Upon hospitalization, she developed a mild fever and cognitive impairment. Brain magnetic resonance imaging (MRI) showed semi-rapidly progressive diffuse cerebral atrophy (DCA) over 3 months, while no clear abnormal intensities were observed. The nerve conduction study revealed sensory and motor neuropathy in the limbs. The fixed tissue-based assay (TBA) failed to detect antineuronal antibodies; however, based on commercial immunoblots, the presence of anti-AMPH antibodies was suspected. Therefore, serum immunoprecipitation was performed, which confirmed the presence of anti-AMPH antibodies. The patient also had gastric adenocarcinoma. High-dose methylprednisolone, and intravenous immunoglobulin were administered and tumor resection was performed, resulting in resolution of the cognitive impairment and improvement in the DCA on the post-treatment MRI. After immunotherapy and tumor resection, the patient's serum was analyzed using immunoprecipitation, which showed a decrease in the level of anti-AMPH antibodies. This case is noteworthy because the DCA showed improvement after immunotherapy and tumor resection. Additionally, this case demonstrates that negative TBA with positive commercial immunoblots do not necessarily indicate false positive results.

KEYWORDS

anti-amphiphysin syndrome, paraneoplastic neurological syndrome, brain atrophy, immunoprecipitation, neuropathy, encephalopathy

1. Introduction

Paraneoplastic neurological syndrome (PNS) is an immune-mediated neurological disorder caused by antibodies against intracellular, neuronal surface or synaptic proteins expressed by cancer cells. The detection of these antibodies is useful for PNS diagnosis and recent studies report the presence of a variety of onconeural antibodies (1).

Amphiphysin (AMPH), an intracellular synaptic vesicle protein, plays a critical role in regulating clathrin-coated synaptic vesicles (2). Anti-AMPH antibodies were initially reported in three women with paraneoplastic stiff-person syndrome (SPS) by De Camilli et al. (3). However, several reports and studies have demonstrated that AMPH autoimmunity is related to a broad spectrum of neurological manifestations, such as limbic encephalitis, peripheral neuropathy, myelopathy, brainstem encephalitis, and cerebellar dysfunction (4–9). Two case series studies have reported that the most common neurological manifestations are limbic encephalitis and neuropathy (7, 9). Furthermore, only <10% of anti-AMPH antibody-positive patients fulfill the diagnostic criteria for SPS (9).

Herein, we report a case of anti-AMPH syndrome in a patient with gastric adenocarcinoma who presented with semi-rapidly progressive systemic tremors and rigidities followed by encephalopathy and peripheral neuropathy. Despite the negative results of fixed tissue-based assay (TBA) in detecting antineuronal antibodies, the presence of anti-AMPH antibodies was suspected in commercial immunoblots, which was subsequently confirmed by immunoprecipitation assay. The patient's symptoms were effectively treated with a combination of high-dose methylprednisolone, intravenous immunoglobulin (IVIg), and tumor resection, resulting in significant improvement in cognitive impairment and surprising recovery of the diffuse cerebral atrophy (DCA).

2. Methods

A range of surface and intracellular antineuronal antibodies were analyzed using TBA, as previously reported (10, 11). Briefly, adult female Wistar rats were sacrificed without perfusion and their brains were removed and fixed in 4% paraformaldehyde for 1 h at 4°C. The brains were cryoprotected in 40% sucrose for 48 h, embedded in freezing compound media, and snap-frozen in isopentane chilled with liquid nitrogen. Subsequently, 6-μm-thick tissue sections were incubated with 0.3% hydrogen peroxide for 15 min, 5% goat serum for 1 h, and patient and control sera (1:200) at 4°C overnight. After incubating with biotinylated secondary antibodies against human IgG (1:2,000, BA-3000, Vector), immunoreactivity was developed using the avidin–biotin–peroxidase method. Two experts (M.H. and H.N.) who are familiar with the immunohistochemical technique independently evaluated the assay results.

Immunoprecipitation was performed using an extract from HEK293T cells expressing FLAG-tagged human AMPH. The cells were lysed in the lysis buffer (TNET: 1M Tris-HCl pH 7.5, 450 mM NaCl, 0.5 M EDTA, 10% Triton X-100, protease inhibitors). The extract was pre-cleared with 20 μL of protein G Sepharose beads (GE Healthcare, Chicago, Illinois, IL, U.S.A.) for 30 min at 4°C to avoid non-specific binding. Similarly, the same amount of IgG in the serum from a healthy control or the patient was immobilized in 15 μL of protein G Sepharose for 30 min at 4°C. After a brief washing, the pre-cleared extracts were incubated with the immobilized IgG for 30 min at 4°C, and then extensively washed with TNET buffer. The bound IgG and protein complex was eluted from the beads by boiling in 30 μL of a sodium dodecyl sulfate-polyacrylamide gel electrophoresis sample buffer. The eluents were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis and detected with anti-DDDDK-tag (FLAG) antibodies (MBL, Tokyo, Japan) or anti-human IgG-HRP antibodies (Proteintech, Rosemont, Illinois, IL, USA).

Statistical significance was evaluated using one-way analysis of variance and the *post hoc* Tukey's test, and statistical significance was set at $p < 0.05$.

3. Case description

A 75-year-old woman with a history of hypertension and dyslipidemia presented to our hospital with oral and bilateral upper limb tremors that had been worsening over the last 3 months. Her first clinical presentation was intractable oral tremor, which had appeared 8 months prior to her first visit.

At the first visit, she exhibited oral tremor, asymmetric tremor, cogwheel rigidity, brachybasia, postural reflex disorder, and constipation, which were not contradictory to Parkinson's disease (PD). Levodopa/decarboxylase inhibitors were prescribed, which resulted in a slight improvement in her parkinsonism-like syndrome (tremors and rigidities), but not significantly. Two months later, she complained of visual hallucinations. Brain magnetic resonance imaging (MRI) did not show clear abnormal intensities or specific atrophy (Figures 1A–D, M–P). Therefore, we suspect rapidly progressive PD and subsequent dementia with Lewy bodies (DLB), and prescribed donepezil; however, the hallucinations did not improve. The following month, her systemic tremor and visual hallucinations worsened, and irritability increased despite medication use. She was admitted to our hospital for careful examination 3 months after her first visit.

On admission, her vital signs were as follows: body temperature, 37.5°C; heart rate, 80 bpm; and blood pressure, 151/98 mmHg. Her oxygen saturation level was 97% at ambient air.

Neurological examination confirmed disturbance of consciousness (Glasgow Coma Scale score of 13 [E4V4M5]) with severe restlessness, visual hallucination, irritability, cognitive impairment [Hasegawa's Dementia Scale-Revised (HDS-R) score of 6 out of 30], decreased deep tendon reflexes in the lower limbs, severe systemic tremor mainly in the limbs, and asymmetric cog-wheel rigidity in the upper and lower limbs. Due to the irritability and severe tremor, we could not evaluate her neurological symptoms related to ataxia. Moreover, sensory disturbance and limb numbness could not be confirmed. She was unable to stand on admission.

Initial laboratory tests did not reveal any specific abnormalities. Complete blood count, liver function, and renal function test results were assessed to be within reference range (RR) despite the mildly

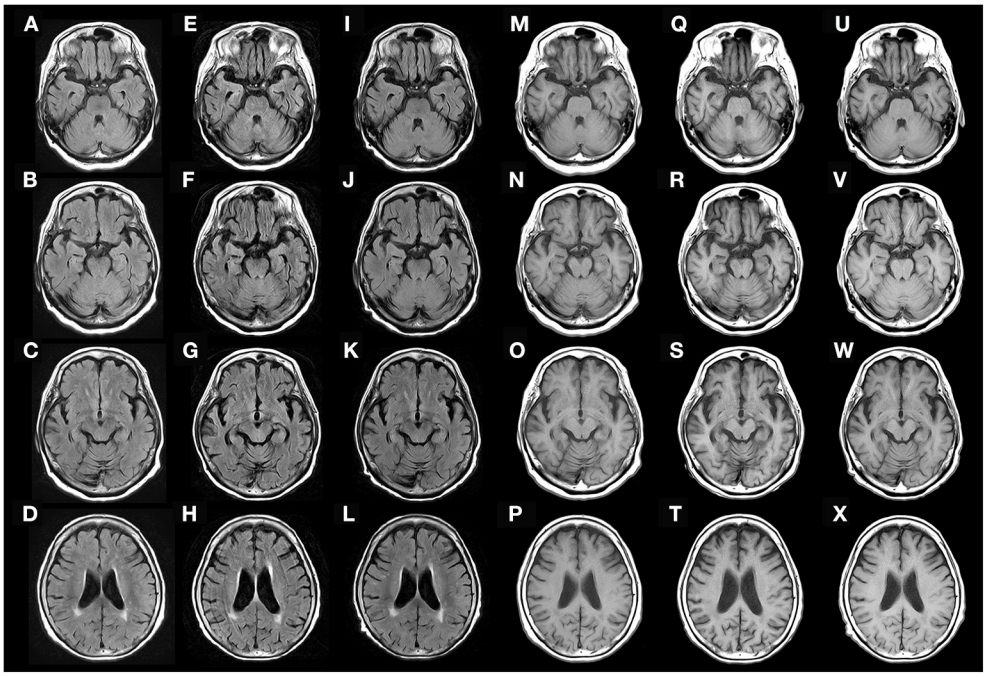

FIGURE 1
Fluid-attenuated inversion recovery (FLAIR) **(A–L)** and T1-weighted **(M–X)** brain MRI obtained 3 months before admission **(A–D, M–P)**, on admission **(E–H, Q–T)**, and 9 weeks after the initial treatment **(I–L, U–X)**. Diffuse cerebral atrophy was observed on admission **(E–H, Q–T)**, but rapidly recovered after immunotherapy **(I–L, U–X)**.

increased C-reactive protein level (2.97 mg/dL; RR: <0.30 mg/dL). Tumor-specific laboratory tests revealed high serum levels of tumor markers (carcinoembryonic antigen, 6.06 ng/mL; cancer antigen 125, 132.5 ng/mL). The RR of CEA is <5.0 ng/mL, and CA125 is <35 ng/mL, respectively. Cerebrospinal fluid analyses showed elevated levels of lactate dehydrogenase (LDH) (42 IU/L; RR: <25 IU/L) and interleukin-6 (IL-6) (11.3 pg/mL; RR: <4.0 pg/mL) with normal cell counts (two leucocytes/μL) and total protein levels (43 mg/dL; RR: 10–50 mg/dL). Oligoclonal bands were negative. Serum paraneoplastic screening by fixed TBA did not show any significances (Supplementary Figure 1); however, EUROLINE PNS 12 Ag (Euroimmun) showed a weak positive 6 and 10, suggesting a low titer of anti-AMPH antibodies.

Brain MRI revealed semi-rapidly progressive DCA over a period of 3 months without clear abnormal intensities (Figures 1E–H, Q–T). Contrast-enhanced brain MRI was also performed, but no clear abnormal gadolinium enhancement was observed (data not shown). Contrast-enhanced whole-body computed tomography (CT) did not reveal any tumors, and no epileptic discharges were observed on electroencephalography. A nerve conduction study was not performed before treatment, and radionucleotide testing, such as positron emission tomography-CT, single-photon emission CT, dopamine transporter scan, and ^{123}I-metaiodobenzylguanidine myocardial scintigraphy, could not be performed because it was not available in our hospital.

Based on her symptoms, which did not contradict encephalopathy, and the possible detection of anti-AMPH antibodies, we suspected that she had anti-AMPH syndrome. She received two courses of high-dose methylprednisolone over 2 weeks (1,000 mg/day × 3 days intravenously as one course per week). After treatment, her fever and visual hallucinations resolved completely, and her systemic tremor slightly improved, but remained moderate. At that time, she could stand using an assisting device, but could not walk. However, after initiating intravenous immunoglobulin (IVIg) treatment (4 weeks after the initial high-dose methylprednisolone therapy), she could walk without the use of any assisting devices, and her cognitive impairment partially recovered (HDS-R score of 22). At that time, the abnormal increase in LDH and IL-6 in the cerebrospinal fluid had decreased (LDH, 22 IU/L; IL-6, 2.6 pg/mL). Over the next 5 weeks (9 weeks after initial treatment), her cognitive impairment had almost fully resolved (HDS-R score of 28) and DCA had partially recovered (Figures 1I–L, U–X). To determine the presence of peripheral neuropathy, we performed a nerve conduction study after the IVIg treatment, which showed low-amplitude compound muscle action potential and sensory nerve action potential, suggesting axon loss rather than demyelination (data not shown).

Because the anti-AMPH antibody is known as a paraneoplastic antineuronal antibody, we performed various tests to detect malignancy. Although colonoscopy and random skin biopsy showed normal findings, gastroscopy revealed type 0-IIa gastric tumors, and histological results suggested gastric adenocarcinomas with no evidence of metastasis (Figure 2A). After IVIg treatment (6 weeks after the initial high-dose methylprednisolone therapy), endoscopic submucosal dissection was performed and the tumors were completely removed. The pathological diagnosis was two well-differentiated adenocarcinoma lesions (Figures 2B, C).

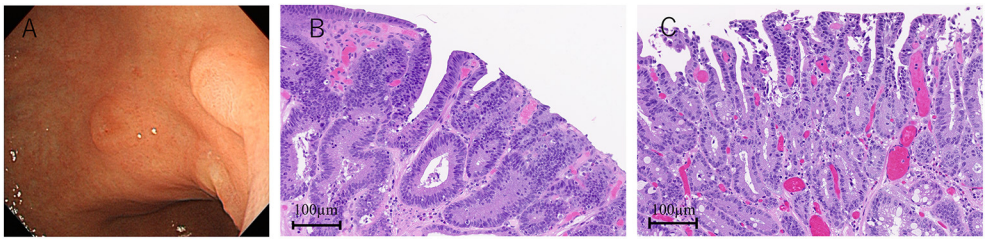

FIGURE 2
Gastroscopy and pathological findings. Two lesions of type 0-IIa gastric tumor **(A)**. Hematoxylin-eosin staining shows two adenocarcinomas **(B, C)**.

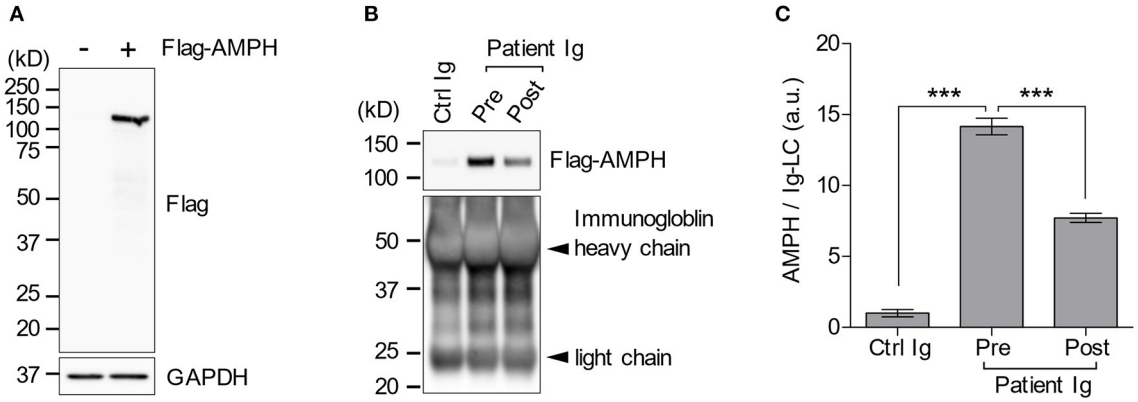

FIGURE 3
Immunoprecipitation assay. Flag-AMPH combined protein was successfully expressed in HEK-293T cells. However, the anti-FLAG antibody did not show any non-specific bands **(A)**. The patient's serum contained anti-AMPH antibodies, which decreased after immunotherapy **(B, C)**. AMPH, amphiphysin; FLAG, anti-DDDDK-tag; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; Ig, immunoglobulin. ***$p < 0.0001$.

Despite active immunotherapy and tumor resection, her oral tremor persisted at a moderate degree. Although, the oral intake of baclofen slightly improved it, she did not experience a full recovery. Nonetheless, she could walk independently without difficulty. The patient was discharged 74 days after admission. We also performed an immunoprecipitation assay since TBA failed to detect anti-AMPH antibodies in the patient's serum. A subsequent western blotting analysis revealed the presence of anti-AMPH antibodies and their continuous decrease 10 months after immunotherapy (Figures 3A–C). The clinical timeline is shown in Supplementary Figure 2.

4. Discussion

In this report, we presented a rare case of reversible brain atrophy in anti-AMPH syndrome in a patient with gastric adenocarcinoma who presented with semi-rapidly progressive systemic tremors, rigidities, encephalopathy, peripheral neuropathy, and DCA. The symptoms were markedly reduced by active immunotherapy and tumor resection. As all treatments were applied within a relatively short time period of each other and were effective, it was difficult to determine which was the most effective treatment.

In the early stage, the diagnostic criteria advocated by the Internal Parkinson and Movement Disorder Society in 2015 (12), this patient's symptoms were consistent with "clinically probable PD" because we could not find any "absolute exclusion criteria" or "red flags." In addition, the manifestation of visual hallucinations suggested co-occurrence of DLB. However, on admission, the patient showed rapidly progressive gait impairment requiring regular use of a wheelchair within 1 year of onset. This was a "red flag" for PD. Finally, the detection of anti-AMPH antibodies ruled out the diagnosis of PD/DLB. Moreover, the possibility of progressive supranuclear palsy or multiple system atrophy had also been ruled out.

The latest diagnostic criteria of paraneoplastic neurological syndrome (PNS) were published in 2021 (13). To meet the criteria for "definite PNS," confirmation of the cancer typically associated with the detected antibody is necessary. In the case of anti-AMPH antibodies, breast or small cell lung cancer is usually associated. If the cancer is not typical for the detected antibody, the diagnosis of "definite PNS" requires demonstrating antigen expression by the tumor. Our patient met only the diagnostic criterion of "probable PNS" because gastric adenocarcinoma is not typical in anti-AMPH syndrome and the expression of antigen on the cancer was not tested. Moreover, the clinical findings in our patient were atypical of autoimmune encephalitis due to long-term progression (>3 months), the absence of cerebrospinal

fluid pleocytosis, and MRI features suggestive of encephalitis (14); however, the patient exhibited cognitive impairment, visual hallucinations, and irritability. Therefore, we diagnosed the patient with encephalopathy related to anti-AMPH antibodies.

Although the reason why fixed TBA failed to detect serum antibodies is not clear, it is widely recognized not all antibodies that work in immunoprecipitation are equally adaptable for use in immunohistochemistry. Several factors, such as antibody titer, antigen-specificity, and epitope masking during fixation, can influence the outcome of immunohistochemistry experiments. One possible reason could be that the concentration of anti-AMPH antibodies was very low to be detected by fixed TBA. Moreover, in this study, we used rat brain for fixed TBA, which may possess different epitopes compared to human AMPH. Furthermore, the low sensitivity of fixed TBA has already been reported in the other autoimmune diseases (15, 16). In a recent study, commercial immunoblots have been reported to show high rates of false positivity, and none of the weak-positive sera in EUROLINE PNS 12 Ag were confirmed by other techniques (17). However, serum antibody purification was not performed, and false negatives could not be completely ruled out, particularly in low-titer anti-AMPH antibody cases. Nonetheless, further studies are needed to determine the sensitivity and specificity of immunoprecipitation for PNS-related autoantibodies, because this is the first report of detecting these autoantibodies by immunoprecipitation.

AMPH is classified as an intracellular synaptic antigen, which distinguishes it from typical intracellular antigens found in the nucleus and cytoplasm (18, 19). Unlike typical antibodies against intracellular antigens, anti-AMPH antibody may be directly pathogenic, as demonstrated by the passive transfer of purified anti-AMPH antibodies from patients to a rat, which resulted in SPS-like symptoms (tremors and rigidities). These antibodies may also induce synaptic dysfunction (gamma-aminobutyric acid release) and internalization of complexes into the cytoplasm (2, 20), suggesting a potential mechanism for their pathogenicity. In addition to SPS, AMPH autoimmunity has been associated with various neurological manifestations, including encephalitis and peripheral neuropathy, and various types of malignancies, including breast cancer, small-cell lung carcinoma, and gastric cancer (7, 9). Moon et al. (7) initially introduced the term "anti-AMPH syndrome" in 2014 to describe 20 anti-AMPH antibody-positive patients who did not meet the criteria for SPS, and found that IVIg and steroid treatments were effective in improving their symptoms (7). As described in the case presentation, our patient exhibited both encephalopathy and peripheral neuropathy, as well as tremors and rigidities.

Some patients were reported to be resistant to IVIg or steroid treatments; in those cases, second-line treatments, including rituximab or cyclophosphamide, would be considered (7, 21). To the best of our knowledge, no previous reports have described reversible brain atrophy in anti-AMPH syndrome. However, a few toxic, metabolic, and endocrine disorders have been reported to cause reversible brain atrophy (22–24). Among autoimmune encephalitis cases, only those with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis have been reported to show reversible DCA (25–28). Iizuka et al. initially reported two young women who presented with reversible DCA and anti-NMDAR encephalitis (25). They also reported that DCA might occur in about 33% of anti-NMDAR encephalitis cases, but was not associated with poor outcomes unless cerebellar atrophy coexisted (29). Regarding the mechanisms of DCA, they speculated the following risk factors: systemic complications (heart failure and septic shock), status epilepticus, malnutrition, prolonged use of corticosteroids, long-term exposure to various antiepileptic agents, and prolonged use of propofol (29). However, at the time DCA was observed, our patient was not treated with corticosteroids, antiepileptic agents, or propofol. Systemic complications (heart failure or septic shock) and malnutrition were not observed. In addition, electroencephalography did not detect epileptic discharges. Thus, the postulated mechanisms were not applicable to our patient. Still, one possible mechanism of DCA is explained by NMDAR internalization and its dysfunction without neuronal death (29). Although the mechanism underlying the recovery from brain atrophy in our case remains unclear, our findings suggest that early active immunotherapies, combined with tumor resection and low antibody titers, can contribute to favorable outcomes in the recovery of brain atrophy.

5. Conclusion

In conclusion, we reported a case of anti-AMPH syndrome in a patient with gastric adenocarcinoma who presented with semi-rapidly progressive systemic tremors followed by encephalopathy and peripheral neuropathy. The patient showed a significant reduction in symptoms following active immunotherapies and tumor resection. Early diagnosis and treatment may lead to improved clinical outcomes in patients with anti-AMPH syndrome. Furthermore, it should be noted that negative TBA results with positive commercial immunoblots do not necessarily indicate a false positive, particularly in case with low-titer antineuronal antibodies.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Review Board of Fujimi Kogen Hospital (Reference Number 126). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

RA was the attending physician, decided on the treatment policy, collected patient data, and performed immunoprecipitation. Y-JK prepared the recombinant plasmid, transfected cells, and performed western blotting analysis. TY and MY examined the patient and provided a critical opinion regarding encephalopathy. MH and HN performed and evaluated the TBA. RA played a major role in study conception and drafted the manuscript. TO revised the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

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Conflict of interest

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Supplementary material

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Case report: Anti septin-5-encephalitis as a treatable cause of cerebellar ataxia and psychiatric symptoms

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Objectives: Anti-septin-5 encephalitis is a rare disease with only few published cases, mainly based on retrospective CSF and serum analyses. Predominant symptoms are cerebellar ataxia and oculomotor abnormalities. Due to the rareness of the disease, treatment recommendations are scarce. Herein, we prospectively describe the clinical course of a female patient with anti-septin-5 encephalitis.

Methods: We describe diagnostic workup, treatment and follow-up of a 54-year-old patient presenting with vertigo, unsteady gait, lack of drive and behavioral changes.

Results: Clinical examination revealed severe cerebellar ataxia, saccadic smooth pursuit, upbeat-nystagmus, and dysarthria. Additionally, the patient presented with a depressive syndrome. MRI of the brain and spinal cord were normal. CSF analysis showed lymphocytic pleocytosis (11 cells/μl). Extensive antibody testing revealed anti septin-5 IgG in both CSF and serum without coexisting anti-neuronal antibodies. PET/CT detected no signs of malignancy. Corticosteroids, plasma exchange, and rituximab led to transient clinical improvement followed by relapse. Re-applied treatment with plasma exchange followed by bortezomib resulted in moderate but sustained clinical improvement.

Discussion: Anti septin-5 encephalitis represents a rare but treatable and therefore relevant differential diagnosis in patients with cerebellar ataxia. Psychiatric symptoms can be observed in anti septin-5 encephalitis. Immunosuppressive treatment including bortezomib is moderately effective.

KEYWORDS

case report, septin-5, autoimmune encephalitis, bortezomib, cerebellar syndrome

Introduction

Anti-septin-5 encephalitis is an extremely rare antibody-associated autoimmune disorder, with only few reported cases so far. Most cases have been retrospectively diagnosed from archived sera and cerebrospinal fluid (CSF) of patients with initial diagnosis of encephalitis of unknown origin (1–3). The clinical manifestations of the disease can vary, but progressive cerebellar

ataxia and ocular movement abnormalities are consistently reported, with onset at a median age of 59 years (4). In some cases, psychiatric symptoms were reported in patients with septin-5-IgG and coexisting septin-7-IgG (3). MRI and CSF findings were heterogeneous in reported cases varying from normal CSF findings to elevated leukocyte count and/or protein levels. Response to immunotherapy was variable in reported cases with a rather limited overall benefit; however, spontaneous remission was also observed (1, 2). The detailed pathomechanism behind autoimmune septin-IgG related encephalitis remains unclear.

Case report

A 54-year-old woman presented to our hospital with progressive vertigo, oscillopsia, and severe gait and limb ataxia developing over 3 months. She also experienced behavioral changes and severe depressive symptoms, including a lack of drive and passive suicidal thoughts, several months before the onset of her cerebellar symptoms. Her medical history included arterial hypertension, rheumatoid arthritis, and Graves' disease. She had no pertinent family history, and there was no record of alcohol or drug abuse in her personal history. At the time of admission, she was on treatment with antihypertensive drugs, L-thyroxine, quetiapine, and sertraline. On neurological examination, she presented severe left-sided cerebellar limb as well as trunk ataxia, dysarthria, upbeat nystagmus, and a saccadic smooth pursuit. Her initial Scale for the assessment and rating of ataxia (SARA) score was 14 (range 0–40; higher values indicate more severe ataxia). Extended laboratory blood examinations yielded no pathological results. Magnetic resonance imaging (MRI) of the brain and spinal cord showed no abnormalities (Figure 1A). Cerebrospinal fluid (CSF) analysis revealed a lymphocytic pleocytosis (11 cells/μl; reference-value: ≤5/μl), with normal protein, normal CSF/serum-quotient of albumin and without CSF- and/or serum-specific oligoclonal bands. Extensive testing of anti-neuronal antibodies, assessed by BIOCHIP mosaic cell-based immunofluorescence assays (Supplementary Table 1), revealed serum (1:10.000; reference value: <1:100) and CSF (1:320; reference-value: negative) anti-septin-5 IgG (Figure 2); no other auto-antibodies were detected. Tests for thyroid function and antibodies, including TSH (Thyroid-Stimulating Hormone), T_3 (Triiodothyronine), T_4 (thyroxine), auto-antibodies against TPO (Thyroid peroxidase), thyroglobulin and TSH-receptor, were normal. Whole-body FDG-positron emission tomography/computed tomography (PET/CT) scan without dedicated brain imaging showed no signs of malignancy.

The patient was initially treated with intravenous methylprednisolone over 5 days (1 g per day), followed by oral tapering starting with 80 mg prednisone per day, but this treatment did not produce any significant clinical effect (Figure 1C). Subsequent CSF analysis during prednisone taper showed no signs of inflammation anymore. Furthermore, anti-septin-5 antibodies decreased in the CSF (1:1), while serum levels remained high (1:10.000). Subsequently, the patient received seven cycles of plasma exchange, which led to moderate clinical improvement, with her SARA score decreasing to 11.5 points. Plasma exchange was followed by B-cell depleting therapy with the monoclonal anti-CD20-antibody rituximab (2 × 1 g with an interval of 2 weeks). After 5 months, the patient showed clinical improvement, with a SARA score of 10.5 points. Psychiatric symptoms also showed significant remission, and she was able to discontinue medication with quetiapine and sertraline.

Although B cells remained undetectable in serum and anti-septin IgG remained low both in CSF (1:3.2) and serum (1:32), 5 months after initiation of rituximab treatment the patient was re-admitted to our hospital with a severe deterioration of both her neurological and psychiatric symptoms. Her SARA score had increased to 22, and we also found increased anti-septin IgG titer in serum (1:100), while MRI still showed no signs of inflammation or degeneration (Figure 1B). No lumbar puncture was performed at this or any further timepoints. Five cycles of plasma exchange was ineffective this time. Therefore, we initiated treatment with the proteasome inhibitor bortezomib (1.3 mg/m² body surface per cycle). Three cycles were applied over 5 months without any adverse effects, which led to an overall moderate improvement of both her neurological and psychiatric symptoms. In a follow-up examination 2 months after the last cycle of bortezomib, her SARA score was 11, but the anti-septin IgG titer in serum remained at 1:100.

Discussion

Anti-septin-5 encephalitis is a newly described disease with a limited number of reported cases. In this study, we present a prospectively diagnosed and monitored case of anti-septin-5 cerebellitis with distinctive symptoms, including behavioral changes and a severe depressive syndrome. Our patient's treatment with steroids, plasma exchange, rituximab, and bortezomib resulted in a moderate clinical effect of both her neurological and psychiatric symptoms.

In line with previously reported cases, our patient displayed progressive cerebellar ataxia and oculomotor abnormalities. However, we observed additional behavioral changes and a severe depressive syndrome, which has been described before in association with coexisting septin-7 IgG but not with septin-5 (3). We did not detect any other anti-neuronal antibodies, such as anti-glutamic acid decarboxylase (GAD) or N-type calcium channel antibody (CCN), which were described in other cases (1). Cognitive and behavioral alterations have already been described as being associated with cerebellar lesions, termed as Cerebellar Cognitive and Affective Syndrome (CCAS) (5). Although a secondary adjustment disorder cannot be excluded, the rapid reduction in psycho-behavioral symptoms following immunotherapy supports a causal link to septin-5 IgG.

Although detailed pathophysiology of anti septin-5 IgG is unclear, septines play a crucial role in the CNS, organizing neuronal cytoskeletal development and regulating endo- and exocytosis at synaptic terminals, so it is feasible that disrupting their function may lead to neurological deficits (6–8). Apart from septin-5, septin-3 and septin-7 are also associated with autoimmune CNS diseases (3, 9). Whether there is direct pathogenic effect of anti-septin-5 IgG or other components such as T-cell mediated cytotoxicity also play a role is unclear. However, there are hints pointing toward a direct pathogenicity, although this needs further confirmation (3).

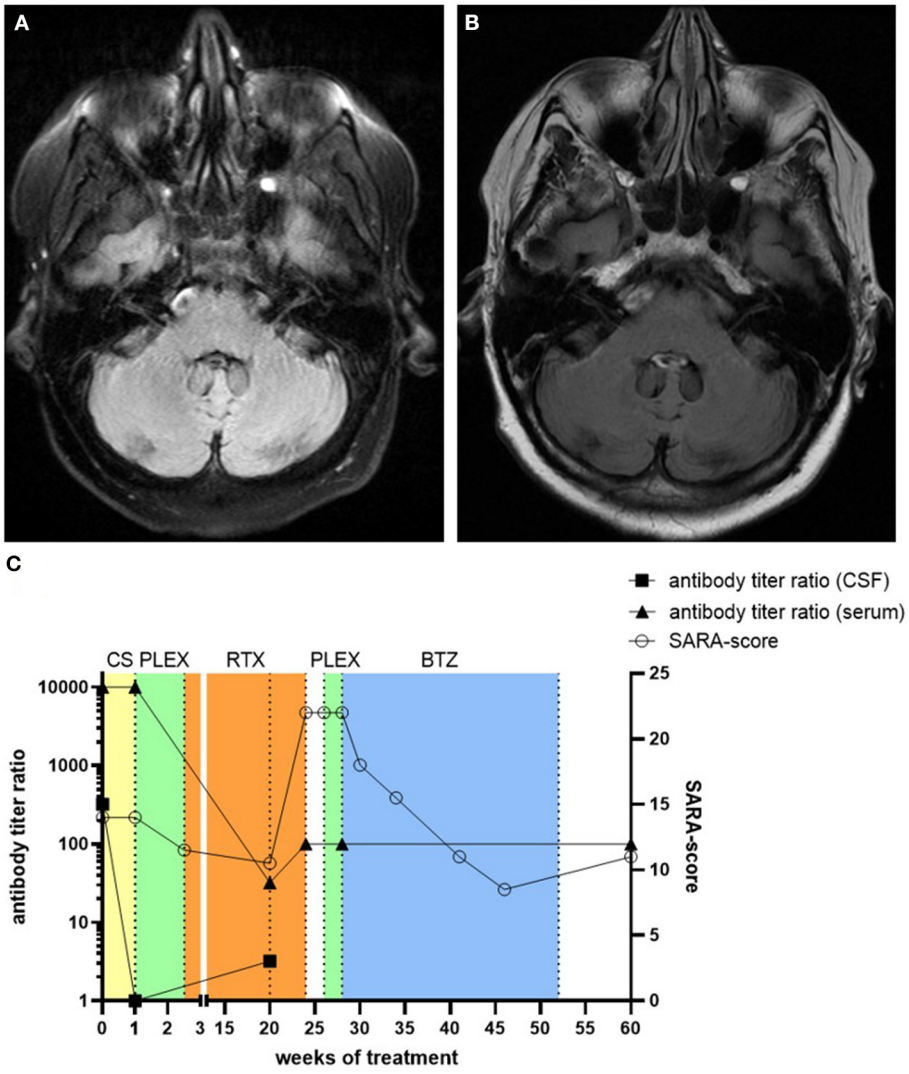

FIGURE 1
Native axial FLAIR MR-images of the patient 4 months after symptom onset **(A)** and after clinical deterioration 5 months after treatment with rituximab **(B)**. No cerebellar atrophy or inflammatory lesions were detected. The clinical course of the patient at different time-points with corresponding treatment regimens, SARA-score values, and antibody titer ratio in both CSF and serum is depicted **(C)**. CS, corticosteroids; RTX, rituximab; PLEX, plasma exchange; BTZ, bortezomib.

Similar to most published cases, repeated MRI-scans showed no evidence of neuroinflammation, a disturbed blood-brain barrier, or atrophy. In line with previously reported cases, initial CSF analysis revealed a lymphocytic pleocytosis (1). Subsequent lumbar puncture after treatment with intravenous methylprednisone and oral prednisone taper yielded normal results, which may be interpreted as a paraclinical response to cortisone. The detected anti-septin-5 IgG titers in serum (1:10.000) was comparable to previously described serologic findings and antibody titers (1). We observed no evidence of malignancy in our patient as was the case in the other published cases. However, we did not perform any follow-up screening for malignancies. Still, the number of described cases is still too low to exclude a paraneoplastic etiology of anti-septin-5 encephalitis (10).

In our patient, corticosteroids, plasma exchange, and rituximab showed a significant therapeutic effect, as it was described in previous studies, which however was only temporary. Unfortunately, the patient remained clinically stable for only 5 months, before relapsing with a more severe syndrome than initially. One prodromal indication of the clinical deterioration could be the slight increase in CSF anti-septin-5 IgG titers (1:1 → 1:3.2) 1 month before. However, no further lumbar punctures were performed subsequently to support this. Since anti-septin-antibodies remained detectable in serum and CSF at the time of clinical deterioration despite ongoing B-cell depletion, we opted for a treatment with the proteasome inhibitor bortezomib, which is known to promote apoptosis of plasma cells that cannot be depleted with rituximab (11). Bortezomib led to a moderate but sustained improvement of the neurological symptoms for

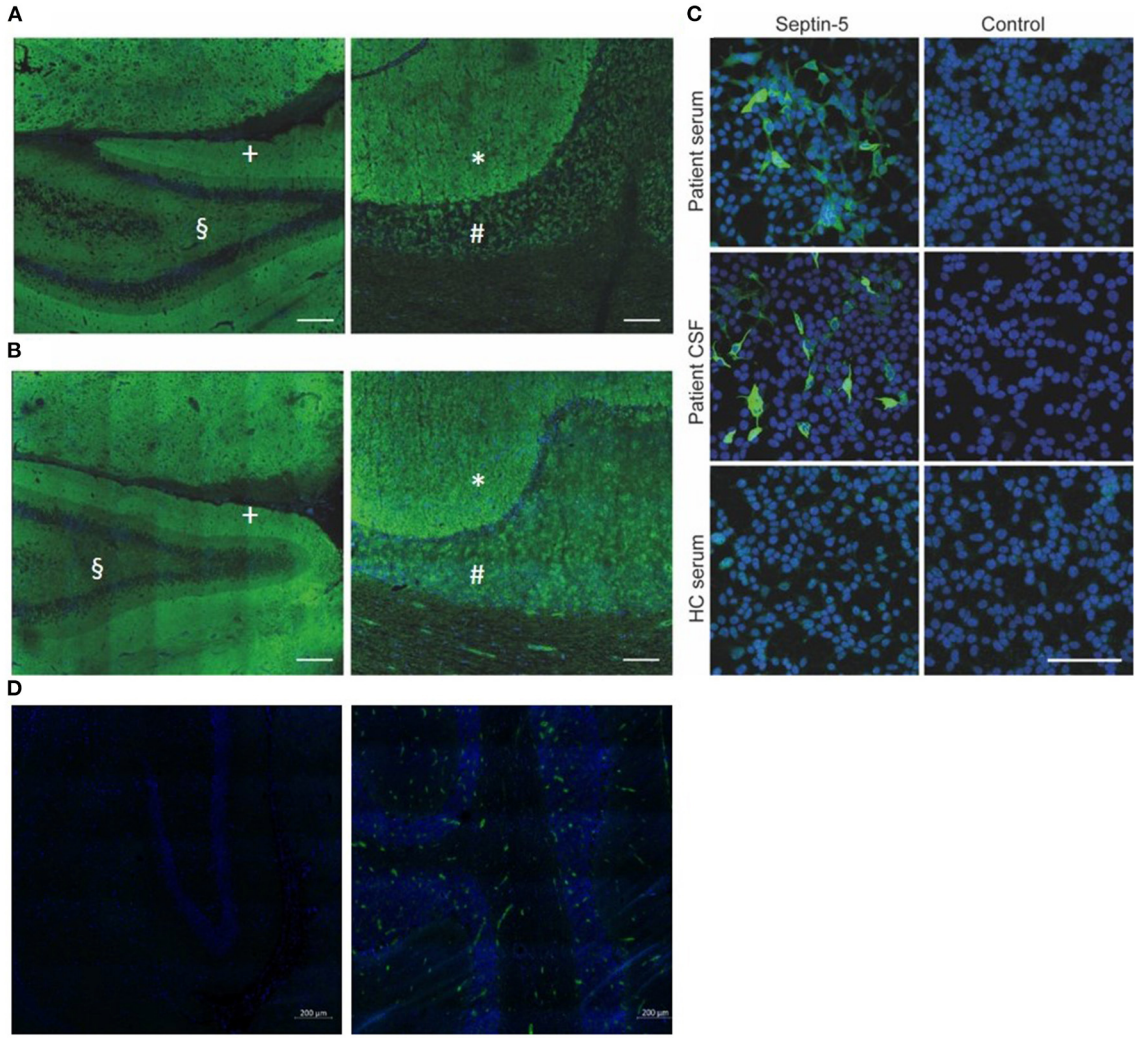

FIGURE 2
(A, B) Strong neuropil staining of rat hippocampus (**A** left, **B** left; scale bar: 200 μm) and primate cerebellum (**A** right, **B** right; scale bar: 100 μm) after incubation with patient CSF **(A)** and serum **(B)**, both from the time of diagnosis. The inner molecular layer (§) of the hippocampus exhibits a weaker immune-reactivity, compared to the outer layer (+). The molecular layer of the cerebellum (*) exhibits a stronger immune-reactivity as compared to the granular layer (#). **(C)** Cell-based assay with human Septin-5 transfected HEK-293 T cells confirms the presence of antibodies against Septin-5 in both patient CSF and serum (dilutions: Serum 1:100, CSF 1:10; scale bar: 100 μm). **(D)** Negative controls of rat hippocampus **(left)** and primate cerebellum **(right)**. Weak immune-reactivity is due to secondary antibodies within the vessels. Green: Alexa-488 Anti-human IgG, blue: DAPI. CSF, cerebrospinal fluid; HC, healthy control.

8 months up to now. The use of bortezomib, which has been described before in refractory autoimmune encephalitis, especially in N-methyl-d-aspartate receptor (NMDAR) encephalitis, may be an option in autoimmune septin-5 encephalitis (12).

In conclusion, anti-septin-5 cerebellar ataxia should be considered as differential diagnosis in patients presenting with a global cerebellar syndrome. Psychiatric symptoms represent a possible additional manifestation of anti-septin-5 encephalitis. Immunotherapy including plasma exchange, rituximab, and bortezomib are potentially effective treatment options. However, further studies with larger cohorts are required to provide specific therapeutic recommendations.

Data availability statement

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

Ethics statement

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

publication of any potentially identifiable images or data included in this article.

Author contributions

JW and IM designed the study, collected the clinical data, and wrote the first draft of the manuscript. JW, IM, JH, FT, TW, TJ, and AS treated the patient. KB provided the histopathological images. JW, IM, JH, FT, and AS interpreted the clinical data. JH, FT, and AS co-wrote the manuscript. All authors discussed the results reviewed and commented the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

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Supplementary material

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Case report: A case of neuro-Behçet's syndrome presenting as brain stem mass lesions

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Neuro-Behçet's syndrome, a severe and rare manifestation of Behçet's disease (BD), can be misdiagnosed due to its challenging clinical presentation. This article presents the case of a 20-year-old cis-gender male with intermittent fever, bilateral uveitis, and neurological symptoms who was found to have multiple brain stem mass lesions on brain imaging. A careful medical history elicited recurrent painful oral and genital ulcerations which were important in making the correct diagnosis. As there are no validated criteria or definite set of tests available to confirm neuro-Behçet's disease, the diagnosis is often established by exclusion after ruling out other potential etiologies. In our case, after an extensive negative workup for infectious, neuro-degenerative and malignant etiologies combined with the patient's medical history, a diagnosis of Behçet's disease with neurological involvement (neuro-Behçet's syndrome) was made. High doses of steroids were given, and the patient had a favorable outcome. Repeated magnetic resonance imaging of the brain 2 years later showed no new brain lesions. Neuro-Behçet's disease should be included as a differential diagnosis of unexplained brain stem lesions in the right clinical context. In these situations, providers should obtain medical histories related to genital and oral ulcers and eye problems as these may help to narrow down the diagnosis. The clinical presentation and challenges of this uncommon presentation of BD including a brief literature review of neuro-Behçet's disease with brain stem mass lesions are discussed in this case study.

KEYWORDS

neuro-Behçet's, brain stem, uveitis, genital ulcer, immunoglobulin

Introduction

Neuro-Behçet's syndrome or disease (NBD) is characterized by neurological symptoms in a patient who has suffered or is suffering from other systemic symptoms of Behçet's disease (BD) (1). NBD is relatively rare and has a mean duration of development, of approximately 5 years from the onset of BD (2).

NBD is typically classified into parenchymal or non-parenchymal, based on the area of the brain involved. Parenchymal disease is the most common and includes cerebral, brain stem, or spinal cord disease, while non-parenchymal disease involves the cerebral vasculature, including thrombosis and other stroke syndromes, intracranial hypertension, and meningeal syndromes (2).

Unfortunately, no specific test can isolate the disease, thus making the diagnosis challenging and primarily clinical. Although specific NBD diagnostic criteria have been suggested in the literature, none has been validated (3). The diagnosis of NBD can pose further challenges since it is sometimes difficult to differentiate NBD itself from secondary neurologic symptoms related to BD treatment (2). NBD can cause long-term morbidity and mortality, making early recognition and treatment essential (2).

In this report, we discuss the case of a young immunocompetent male who presented with neurological deficits and ring-enhancing brain stem lesions; a careful medical history revealed oral and genital ulcers and uveitis, leading to the diagnosis of parenchymal NBD. A brief literature review of NBD presenting as a brain mass lesion is also included.

Case report

A 20-year-old, non-Hispanic Black, cis-gender male with a history of iron deficiency anemia presented with several weeks of intermittent headache and mild fever. While the fever resolved, the headache became constant, and over the following month, he developed a worsened peripheral vision with mild photophobia, left upper extremity weakness, expressive aphasia, and difficulty in walking due to the loss of balance. Since the age of 15, he had experienced recurrent, painful oral and scrotal ulcers that would last for several days at a time. He was sexually active but had not been tested for sexually transmitted infections.

Vital signs were unremarkable. On physical examination, he had left lower facial droop, weakness of his left wrist and fingers, and hyperreflexia of the left lower extremity. A scrotal ulcer was present. On ophthalmologic exam, he had decreased vision in the left homonymous inferior quadrantanopia, bilateral posterior uveitis, chorioretinal scarring, and a single white retinal lesion suspicious for infectious or metastatic disease. On admission, he was found to have CD4 lymphocytopenia (163,000 cells/mcL).

Computerized tomography (CT) of the brain was obtained which showed a heterogenous region with surrounding vasogenic edema centered in the right thalamus and gangliocapsular region (involving the entire right basal ganglia, including the putamen, globus pallidus, and caudate, as well as the posterior aspects of the internal and external capsule). There was a 3-mm leftward midline shift; a mass effect on the Foramen of Monro, right lateral ventricle, and third ventricle; and dilation of the bilateral lateral ventricles. The CT scan also demonstrated a partial effacement of the basal cisterns.

Given the concern for an infectious or neoplastic process or central venous infarct sequelae, contrast-enhanced magnetic resonance imaging (MRI) of the brain was obtained. On MRI, abnormalities were also found involving the right midbrain, with further extension into the pons with mixed regions of T1 isointense and hypointense dense regions and with predominantly T2 and fluid-attenuated inversion recovery (FLAIR) hyperintense lesions. Additionally, there were multiple ring-enhancing lesions in the right thalamic region (with the largest measurement of 9 mm) and midbrain (with the largest measurement of 7 mm), with a surrounding T2 hyperintense region attributable to edema (Figure 1). At this point, additional differential diagnoses were considered, including neurocysticercosis, autoimmune encephalitis, vasculitis, and multiple sclerosis among others.

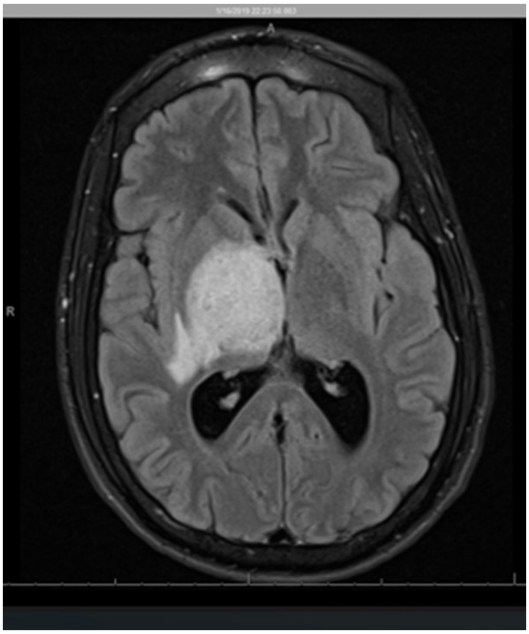

FIGURE 1
Axial view MR imaging (T2 FLAIR). The image shows a heterogeneous region centered in the right thalamus/gangliocapsular region, involving the entire right basal ganglia, including the putamen, globus pallidus, caudate, and the posterior limb of the internal capsule as well as the posterior aspect of the external capsule. There is a 1-cm right-to-left midline shift and compression of the lateral ventricles and the third ventricle with subsequent mild dilatation of the lateral ventricles concerning obstructive hydrocephalus.

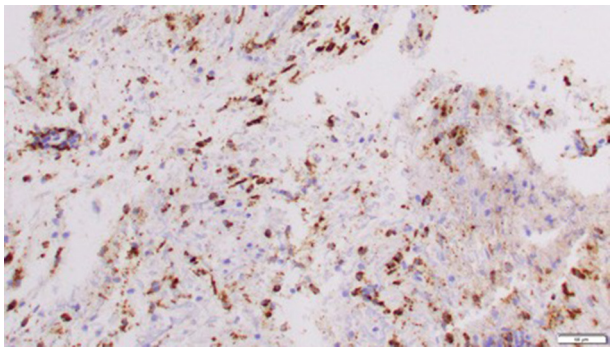

FIGURE 2
Immunohistochemistry of brain tissue revealed numerous CD68+ histiocytes (Mag. X 20).

CT angiography (CTA) of the head and neck with and without contrast showed no large branch arterial occlusion, high-grade stenosis, arteriovenous malformation, or aneurysm.

Due to concerns for autoimmune etiologies, edema, and mass effects, the patient was started on dexamethasone, while the workup was ongoing. Given concerns for an infectious process (brain mass

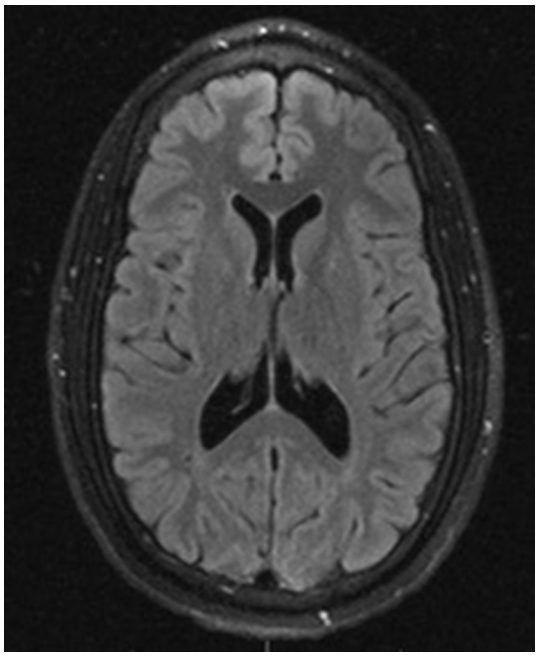

FIGURE 3
Axial view T2 FLAIR MRI imaging 2 years after initial presentation showed complete resolution of brain lesions.

suspicious for brain abscess, in a sexually active person with CD4 lymphopenia), he was also started on broad-spectrum antibiotics.

Right-sided stereotactic needle biopsy with stealth navigation was performed, and a representative brain tissue sample showed only polymorphonuclear cells on the frozen specimen; therefore, no further neurosurgical intervention was performed. The brain tissue sample histopathology showed parenchymal and perivascular mixed inflammation and reactive gliosis with no evidence of malignancy or inflammation. Infectious studies of the brain tissue biopsy, including cultures (bacterial, fungal, and mycobacterial) and stains (Grocott's methenamine silver, periodic acid—Schiff, and gram stains), were all negative. Most parenchymal and vascular lymphocytes stained positive for CD3, with a subset of these positive for CD8 as well. Immunohistochemistry of the brain tissue also revealed rare CD20+ perivascular cells, numerous CD68+ histiocytes (some of which are microglia), and a Ki67 nuclear proliferation index of 2–3% (Figure 2).

Given the concern for malignancy, a CT scan of the chest, abdomen, and pelvis was completed, but the results were completely unremarkable for any disease process. Other infectious workups included blood cultures and fungal (histoplasmosis and cryptococcus), parasitic (toxoplasmosis and echinococcosis), bacterial (syphilis and tuberculosis), and viral (human immunodeficiency virus, cytomegalovirus, herpes simplex virus, hepatitis B, and hepatitis C) studies, which were all negative.

Further studies revealed that he had mildly elevated antinucleotide antibody titers (1:40—speckled), an erythrocyte sedimentation rate (ESR) of 69 mm/hr (normal range, 0–10), and C-reactive protein (CRP) of 1.3 mg/dl (normal range: <1). He had an elevated total serum protein of 8.3 gm/dL (normal range, 6.3–8.2), a normal serum albumin of 4 gm/dL, an elevated serum globulin of 4.3 gm/dl (normal range, 2–3.5), elevated immunoglobulin (Ig) G of 1830 mg/dl (normal range, 700–1600), and IgA of 534 mg/dl (normal range: 70–400). IgM was within normal limits.

An MRI of the brain after 5 days of high-dose methylprednisolone (1 g daily) and antibiotics showed an improvement in ring-enhancing lesions of the right thalamus, midbrain, and pons with a less mass effect. His neurological symptoms also improved significantly after several days of treatment. Given the negative infectious workup, antibiotics were discontinued after day 7 of admission. Neuro-Behçet's syndrome was diagnosed, given the patient's history, workup, clinical, and radiographic improvement after steroids and absence of alternate diagnostic etiologies. The pathergy test was negative. Genetic testing for HLA-B51 was collected but not resulted. The patient responded well to high-dose steroids and continued on an oral prednisone taper and azathioprine therapy after discharge. A 2-year follow-up brain MRI later showed no new or enhancing lesions (Figure 3) although the patient continued to have minimal residual deficits in mobility and vision.

Discussion

Behçet's syndrome (or disease) is a chronic multisystemic inflammatory disorder characterized by systemic vasculitis with perivascular inflammatory infiltrates. The disease is associated with recurrent and relapsing oral ulcers, genital ulcers, skin lesions, eye lesions (notably uveitis), and broader systemic manifestations, such as arthritis and gastrointestinal or central nervous system involvement (4, 5). Behçet's disease (BD) is unique among systemic vasculitides given its ability to affect both arterial and venous circulation and all blood vessel sizes—large, medium, and small.

Approximately 10% of Behçet's syndrome patients have neurologic involvement, which is referred to as neuro-Behçet's disease (NBD). This presentation of the disease is considered a serious manifestation of BD due to the possibility of severe and permanent neurological deficits and associated poor quality of life (6). NBD is more common and severe in men than women, as seen in our study.

In our patient, the clinical presentation of headache, subjective fevers, visual complaints, focal neurological deficit, aphasia, and loss of balance led to initial differential diagnoses that included neurologic malignancy, autoimmune process, and infection. Cerebral CTA did not show any obvious vascular anomalies. Evaluation for the presence of vascular anomalies including cerebral venous thrombosis (CVT) is an integral part of neuro-Behçet's disease (NBD) workup as CVT is considered a major form of presentation of vascular NBD. Lumbar puncture was not obtained in our patient given the mass effect, midline shift, and early decision to pursue stereotactic brain biopsy.

Although the pathergy test was negative, this is not required for diagnosis. A pathergy test is an important diagnostic adjunct for BD or NBD with a specificity of 92% and a sensitivity of 47% in a large series (7). A positive reaction is typically indicated by a papular reaction of ≥2 mm in diameter surrounded by erythema or a pustular reaction of 24–48 h after an obliquely inserted needle

TABLE 1 Summary of neuro-Behçet's disease with brain stem mass lesions.

Age/ Gender	Brain stem area affected	Main clinical presentation	HLA-B51 status	Pathergy	Ig status	Histopathology main findings	Outcome	References
20* Male	Thalamus, midbrain pons	Headache, photophobia, focal weakness, aphasia	NA	Negative	Elevated IgG and IgA	Perivascular inflammation and reactive gliosis	Resolution of the lesion but minimal deficits in mobility and vision.	Current case
46 Male	Mesencephalon	Left lower limb hemiparesis	NA	Negative	NA	ND	Resolution of symptoms after 10 days	(13)
39 Male	Thalamus	Hemiparesis, hyperreflexia, and ataxic gait	NA	NA	NA	ND	Clinical improvement	(19)
33 Male	Midbrain	Headache, nausea, vomiting	Negative	Positive	WNL	Reactive gliosis without inflammatory cell infiltration	Clinical improvement and shrinkage of lesions	(20)
34 Male	Midbrain and pons	Forgetfulness, irritability, unsteady gait, dysarthria, lower extremity weakness	Positive	Positive	ND	ND	Initial improvement to steroids but died 1 month later due to aspiration	(16)
43 Female	Thalamus, cerebral peduncle	Throbbing headache, photophobia, facial paresis, and ptosis	NA	NA	ND	Extensive gliosis and perivascular cuffing by foamy macrophages	Marked improvement, with complete remission of paresis and ptosis	(21)
47 Male	Pons	Ataxia, dysarthria, hyperreflexia, neurogenic bladder	Positive	ND	ND	ND	Died	(22)
41 Male	Pons	Dysarthria, truncal and limb ataxia, hyperreflexia	Positive	Negative	IgD WNL	ND	Improvement in symptoms and brain lesions	(22)

*Index case; BG, basal ganglia; Ig, immunoglobulin; WNL, within normal limits; ND, not done; NA, not available.

prick (7). The brain biopsy performed on the 4th hospital day was negative for malignancy, while all infectious etiology workups, including cultures of brain tissue, were also negative.

Our patient met diagnostic criteria established by the International Study Group for Behçet's disease with a history of recurrent oral and scrotal ulcers over the previous 5 years, self-reported frequent "skin abscesses," and ocular lesions in the absence of other accountable etiologies (7).

Brain imaging revealed a right basal ganglia/thalamus lesion that was likely causing the patient's left upper extremity weakness. The location of the diencephalon lesion also supported the parenchymal neuro Behçet's diagnosis (8).

The genetic testing result for HLA-B51 was unfortunately not available. HLA-B51 is considered a hallmark of Behçet's syndrome even though its role in pathogenicity is unclear. HLA-B51 may be important in the genetic clustering of Behçet's syndrome (given disease prevalence in eastern Asia and Mediterranean regions) and could play a role in determining clinical phenotypes in this heterogeneous condition (9, 10). On the other hand, the prevalence of HLA-B51 is low in many patients who live in non-endemic regions, suggesting other factors unrelated to HLA-B51 are likely contributing to the pathogenesis of Behçet's disease (4).

Headache is the commonest neurological symptom of neuro-Behçet's disease (NBD). As typified by our case, intermittent headache is commonly reported, up to 82% of BD, with migraine being the commonest type of primary headache (11, 12). Intermittent headache in young patients (40 years or younger) with unexplained brain lesions should prompt further consideration for NBD including a history of oral and genital ulcers and ocular symptoms (13).

The brain stem is the most commonly involved area of the brain. At the same time, 20% of individuals with neurologic symptoms were asymptomatic in one series (6, 14). The varied presentations of neuro-Behçet's disease may mimic other disease processes (3, 6, 8). Coupled with the rarity of the disorder, this often makes obtaining an accurate diagnosis a drawn-out process. In our case, the MRI findings on admission, showing thalamic and midbrain ring-enhancing lesions, in conjunction with the patient's history of recurrent oral/genital lesions and ocular lesions make NBD a possible differential diagnosis (15). Many patients with

NBD do not often discuss their recurrent genital and oral ulcers when they present for evaluation, and providers may have to specifically elicit this history to make the correct diagnosis (16). Increased awareness about NBD among providers, especially when unique associations exist, in the absence of alternative diagnoses, could reduce the burden of unnecessary diagnostic testing and treatments (17).

In addition to CD4 lymphocytopenia, our patient's parenchymal and vascular lymphocytes from the biopsied brain tissue mostly expressed CD3, with a subset of these positive for CD8 and rare CD20 cells. The significance of these findings is not entirely clear, but CD3+ CD20+ cells may have a role in autoimmune disease and CD20+ malignancy. A similar abnormal immunophenotypic profile of peripheral lymphocytes has been described in Behçet's disease, including increased absolute numbers of $CD4^{-}$CD8 bright and $CD4^{+}CD8^{+}$ cells, reflecting an immune dysregulation as underlying disease pathogenicity (18).

In our patient, in addition to T and B cells, there were numerous microglia/histiocytes and some macrophages. There were no eosinophils, Langerhans cells, or large histiocytic cell infiltrates to suggest histiocytosis such as Rosai–Dorfman disease, Langerhans cell histiocytosis, or Erdheim–Chester disease. The microglia/histiocytes in our case are considered to be reactive and responding to a pathological insult related to BD and not necessarily related to histiocytosis. More studies are needed to understand the association of T-lymphocyte subsets with the pathogenesis of Behçet's disease.

Even though our patient had elevated ESR and CRP, these are very non-specific markers of inflammation that may be evident at presentation but are of limited value in the differential diagnosis of NBD (1).

Our case shared some similarities and a few notable differences when compared to other cases of Neuro-Behçet's disease with brain mass lesions previously published in the literature. A summary of our literature review as of the time of submitting this article is summarized in Table 1.

All the cases except the two cases described by Hirose et al. had an association with oral or genital ulcers (22). As a group, effective treatment involved the use of high-dose or pulsed steroids.

The role of hyperglobulinemia and hyperimmunoglobulinemia in the pathogenesis of Behçet's disease (BD) is not clear but has been an area of some interest (23, 24). Our patient had elevated serum globulin and immunoglobulins including IgG and IgA. A Mediterranean study comparing 70 BD patients and 35 healthy controls demonstrated a significant elevation in the level of serum globulin (g/dl) in the BD group compared with healthy controls ($p < 0.001$) (23). This hyperproteinemia was explained by an increase in the concentration of specific polyclonal immunoglobulins related to B-cell activation (23). More studies are needed in this area to determine if serum globulin and immunoglobulin could be included as part of a screening tool to determine who may be at additional risk for BD and by extension, NBD when epidemiological and clinical history suggests.

A management option for acute NBD is based on expert opinions as good controlled or comparative trials are lacking (1, 25). Moderate- to high-dose steroids are typically recommended which can be followed by tapering doses of steroids or a prolonged course of colchicine for maintenance (25). If high-dose steroids are ineffective, pulsed steroids or infliximab should be considered. In addition to infliximab, other immunosuppressants and disease-modifying therapies (DMTs) such as azathioprine, methotrexate, mycophenolate, and cyclophosphamide may also be employed in management. These DMTs offer the advantage of providing a steroid-sparing option, reducing the frequency of further neurological relapse, and maintaining prolonged anti-inflammatory effects (1). In our case, we provided an oral prednisone taper and azathioprine therapy after a course of high-dose steroids. In those with CVT, the use of anticoagulation is controversial but still advocated by many experts in addition to immunosuppressants (1).

The limitations of our case include (i) unavailability of HLA-B51 with potential utility in diagnosis as alluded to above and (ii) no CSF analysis done as a spinal tap was avoided due to concern for increased intracranial pressure at presentation. CSF studies have a supportive role in the diagnosis of NBD and are recommended if there are no contraindications (1). Apart from helping to rule out CNS infections, CSF studies may show CSF pleocytosis, elevated CSF protein, and interleukin-6 which are often present in parenchymal, and to a lesser extent, in brain stem NBD (1). CSF pleocytosis has been shown to portend a poor prognosis in NBD (6). Normal CSF parameters do not, however, rule out a diagnosis of NBD and IL-6, which in particular may not always correlate with disease activity (26).

In conclusion, providers should consider neuro-Behçet's disease as a possible differential diagnosis in brain stem lesions, especially in young adults with genital or oral lesions. The role of T-lymphocyte subsets, hyperglobulinemia, and hyperimmunoglobulinemia in Behçet's disease should be better defined.

Data availability statement

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

Ethics statement

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

Author contributions

FA contributed to the conception and original draft of the manuscript. FA and SH contributed to the discussion section. NM contributed to writing the introduction and abstract sections. TQ contributed to preparing the radiographic images. KD-E contributed to the generation of the histopathological slide. CS contributed to editing the whole manuscript. CS and FA were involved in the critical revision of the manuscript. FA and TQ were involved in the direct patient care of the subject described in the

case report. All authors contributed to the manuscript revision and read and approved the submitted version.

Conflict of interest

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

Publisher's note

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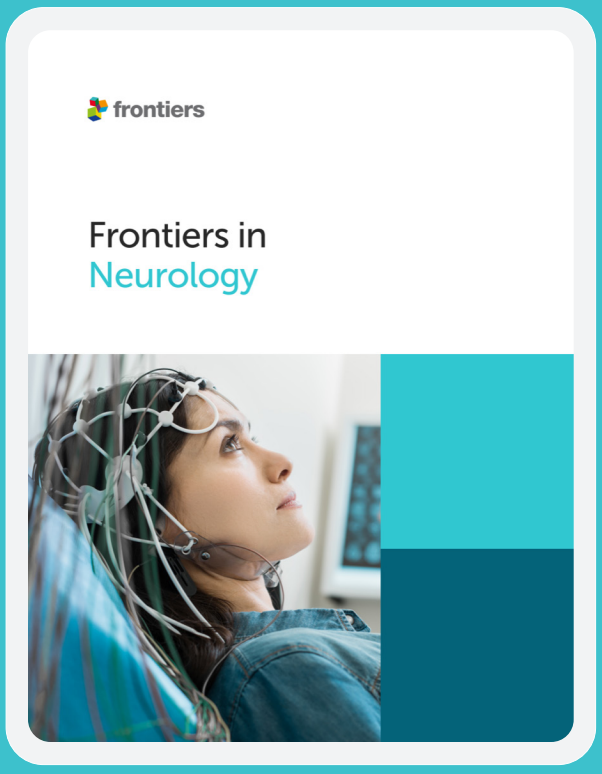

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