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Case reports in multiple sclerosis and neuroimaging, volume III - 2023

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Case report: Evolution of catatonic mutism and psychotic symptoms in an adolescent with Down syndrome: transition from Down syndrome disintegrative disorder to anti-N-methyl-D-aspartate receptor encephalitis

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During her first year of junior high school, a 12-year-old Japanese girl with Down syndrome experienced dizziness, gait disruption, paroxysmal weakness in her hands, and sluggish speaking. Regular blood tests and a brain MRI revealed no abnormalities, and she was tentatively diagnosed with adjustment disorder. Nine months later, the patient experienced a subacute sickness of chest pain, nausea, sleep problem with night terrors, and delusion of observation. Rapid deterioration then developed with simultaneous fever, akinetic mutism, loss of facial expression, and urine incontinence. These catatonic symptoms improved after a few weeks after admission and treatment with lorazepam, escitalopram, and aripiprazole. After discharge, nonetheless, daytime slumber, empty eyes, paradoxical laughter, and declined verbal communication persisted. Upon confirmation of the cerebrospinal N-methyl-D-aspartate (NMDA) receptor autoantibody, methylprednisolone pulse therapy was tried, but it had little effect. Visual hallucinations and cenesthopathy, as well as suicidal thoughts and delusions of death, have predominated in the following years. Cerebrospinal IL-1ra, IL-5, IL-15, CCL5, G-CSF, PDGFbb, and VFGF were raised in the early stage of initial medical attention with nonspecific complaints, but were less prominent in the later stages of catatonic mutism and psychotic symptoms. We suggest a disease concept of progression from Down syndrome disintegrative disorder to NMDA receptor encephalitis, based on this experience.

KEYWORDS

Down syndrome, Down syndrome disintegrative disorder, anti-NMDA receptor antibody encephalitis, cytokine, catatonia, Alzheimer's disease

1. Introduction

Acute or subacute regression in adolescents with Down syndrome (DS) has been increasingly recognized in the last decade and has been designated variously as Down syndrome disintegrative disorder (DSDD), Down syndrome regression disorder, or unexplained regression in Down syndrome (1–5). Although diagnostic criteria have not been established for DSDD, patients with this illness exhibit social disengagement and diminished interpersonal response, cognitive and linguistic loss, decreased independence in daily activities, and mental manifestations such as apathy, depression, stereotypies, hallucination, and catatonia (2, 3). The prevalence of DSDD seems relatively rare, with 30 cases being identified in a large cohort of 6,000 DS subjects (2). This condition differs from early-onset Alzheimer's dementia (AD) in DS, in that (1) DSDD mostly arise in 10–20 years of age, whereas AD typically affects DS subjects in their forties or later, gradually increasing in prevalence up to 50% by age 60 years; (2) onset is rapid in DSDD whereas insidious in AD; and (3) some proportion of DSDD subjects completely recover from the deterioration phase, which is not achieved in AD.

A multifactorial etiology has been proposed for DSDD, including prior psychosocial stressors, neuroinflammation, and incipient AD pathology and/or developmental neurotransmitter dysregulation (2–4). There has been increasing interest in autoimmune pathogenesis, owing to the higher prevalence of treated hypothyroidism and serum antithyroid peroxidase (TPO) antibodies than expected in the total DS community, as well as the effects of immunotherapies on DSDD to some extent (1, 4). This is substantiated by increased cell counts and protein levels in the cerebrospinal fluid (CSF) of some DSDD patients (4). However, most studies on CSF autoantibodies have produced null results, and the role of humoral immunity in this illness remains unknown (4).

Herein, we present a case of DSDD, with three separate phases: the first, nonspecific complaint and declining speech, the second, autistic regression with acute catatonia syndrome, and the third, psychosis with profuse hallucinations. CSF anti-N-methyl-D-aspartate (NMDA) receptor autoantibody was negative in the first and second phases of the cell-based assay but became positive in the third phase. Unexpectedly, some CSF inflammatory cytokines were elevated in the first phase but less prominent in the second and third phases. They included certain molecules whose involvement in the etiology of AD have been assumed. The relevance of CSF results, as well as the diagnostic boundary between DSDD and NMDA receptor encephalitis (NMDARE) in this instance, are discussed.

2. Case description

The girl with mosaic DS had a mild intellectual handicap and had been attending a special educational class since the age of 9, but she had no medical complications as a result of trisomy 21. Her premorbid demeanor was upbeat, and she enjoyed dancing and singing. She was somewhat obstinately diligent in academic works, and would cry with stress when she was called on in class but could not answer well to the questions. No autistic traits had been reported. Her intellectual quotient was assessed as 58 on the Wechsler Intelligence Scale for Children, 4th edition, at the age of 11 years.

Shortly after starting junior high school at the age of 12 years, the patient complained of fatiguability and paroxysmal weakening of fingers and acquired an unsteady gait over 3 months period. Slowness in the speech was also observed (Figure 1). Blood tests and brain MRI results were normal (Figure 2A), and the symptoms resolved spontaneously. But, following a summer holiday, the patient had weakness, insomnia, and severe gait disturbance, for which she was taken to the hospital for medical assessments. Brain and spinal cord MRI revealed no specific abnormalities, and routine blood, urine, and CSF samples, analyses, as well as nerve conduction velocity testing, were all unremarkable. She was tentatively diagnosed with adjustment disorder and was discharged. Thereafter nonspecific complaints waxed and waned.

Nine months later, a few weeks after the COVID-19 pandemic was settled down and the school activity restarted, the girl's linguistic communication and eye contact continued to deteriorate, as did her sleep maintenance insomnia, and night terrors. Within a week, she complained of chest pain, nausea, the delusion of observation, and the perception of how each piece of furniture was feeling. The next morning, she was discovered incontinent and unresponsive to her surroundings, her facial appearance being completely lost. When she arrived at our hospital, her body temperature was 38.1°C, which subsided soon after admission. Her awareness level fluctuated substantially, between E4V1M6 and E1V1M4 on the Glasgow Coma Scale. She demonstrated her intent by shaking or nodding her head. No focal neurological signs were noted on examination. However, she was akinetic and completely mute, stared into space, and held a fixed posture or showed waxy flexibility in her extremities. Drooling and retching, were common, as was oral dyskinesia. Blood and CSF tests, including herpes simplex virus DNA, came back within normal ranges. Brain MRI indicated several high-intensity spots in the frontal white matter, but no abnormalities in the hippocampus sections; sleep EEG revealed a widespread high voltage slow-wave activity, that progressed to irregular activity with a frequency range of 3–10 Hz upon awakening (Figures 2B, C, F). Lorazepam was prescribed to treat catatonic syndrome. The patient could talk in sentences the next morning, though as slow as uttering her name in 30 s or more. It was also established that she had experienced visual hallucinations of an unknown person. She could socially smile and laugh a few days later, but she had a prolonged appetite loss, that required tube feeding. The treatment regimen was supplemented with escitalopram, aripiprazole, and ramelteon. On day 14 of admission, she began playing card games, and the stomach tube was withdrawn. She was discharged, with some persistent behavioral and motor issues (Figure 1).

Soon thereafter, the patient came to manifest with a silly smile, paradoxical laughter, and monology. The patient claimed that there are many, invisible people or goods in her house, that dwarf and fairly are sitting on the air cleaner or her head/arms/clothing, that she was talking with someone in her ear and/or neck, that there are tubes in her ear/mouth/body, and that bad ideas come into her head prompting an urge to stab someone with a pair of scissors. A SPECT examination found hypoperfusion in the bilateral parietal and left occipital lobes (Figure 2E), contradicting

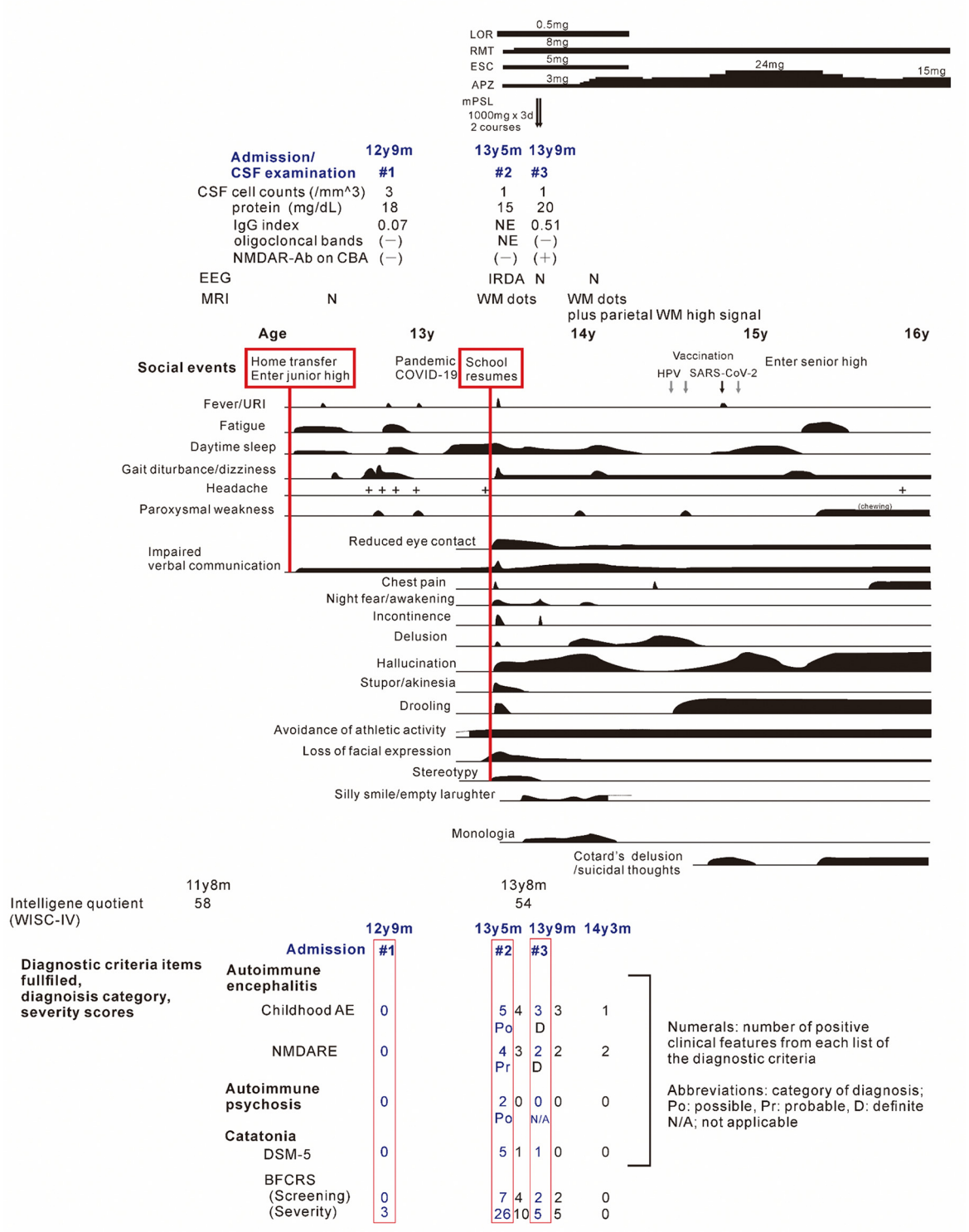

FIGURE 1
The clinical course of the patient. Periods of hospitalizations are shown at the top of the figure, below the charts of medication. **Bottom**: number of items satisfying the diagnostic criteria and/or scores on diagnostic scales for the childhood autoimmune encephalitis, autoimmune psychosis, and the NMDA receptor encephalitis, and for the catatonia, based on references (7, 8, 12–15). The patient's status was assessed at periods of (1) nonspecific complaints, reduced speech and unsteady gait, (2) on admission due to the catatonia syndrome, (3) on discharge after recovery from catatonic symptoms, (4) before administration of methylprednisolone, (5) after the third discharge, and (6) patient at age 14 years and 3 months. Psychosocial stressors preceding the first and second stage of illness are show in the red-flamed boxes. AE, autoimmune encephalitis; APZ, aripiprazole; BFCRS, Bush-Francis catatonia rating scale; ESC, escitalopram; IRDA, intermittent delta activity; mPSL, methylprednisolone; LOR, lorazepam; N, normal; NMDARE, anti-N-methyl-D-aspartate receptor encephalitis; RMT, ramelteon; WISC-V, Wechsler intelligence scores for children, fifth edition; WM, cerebral white matter.

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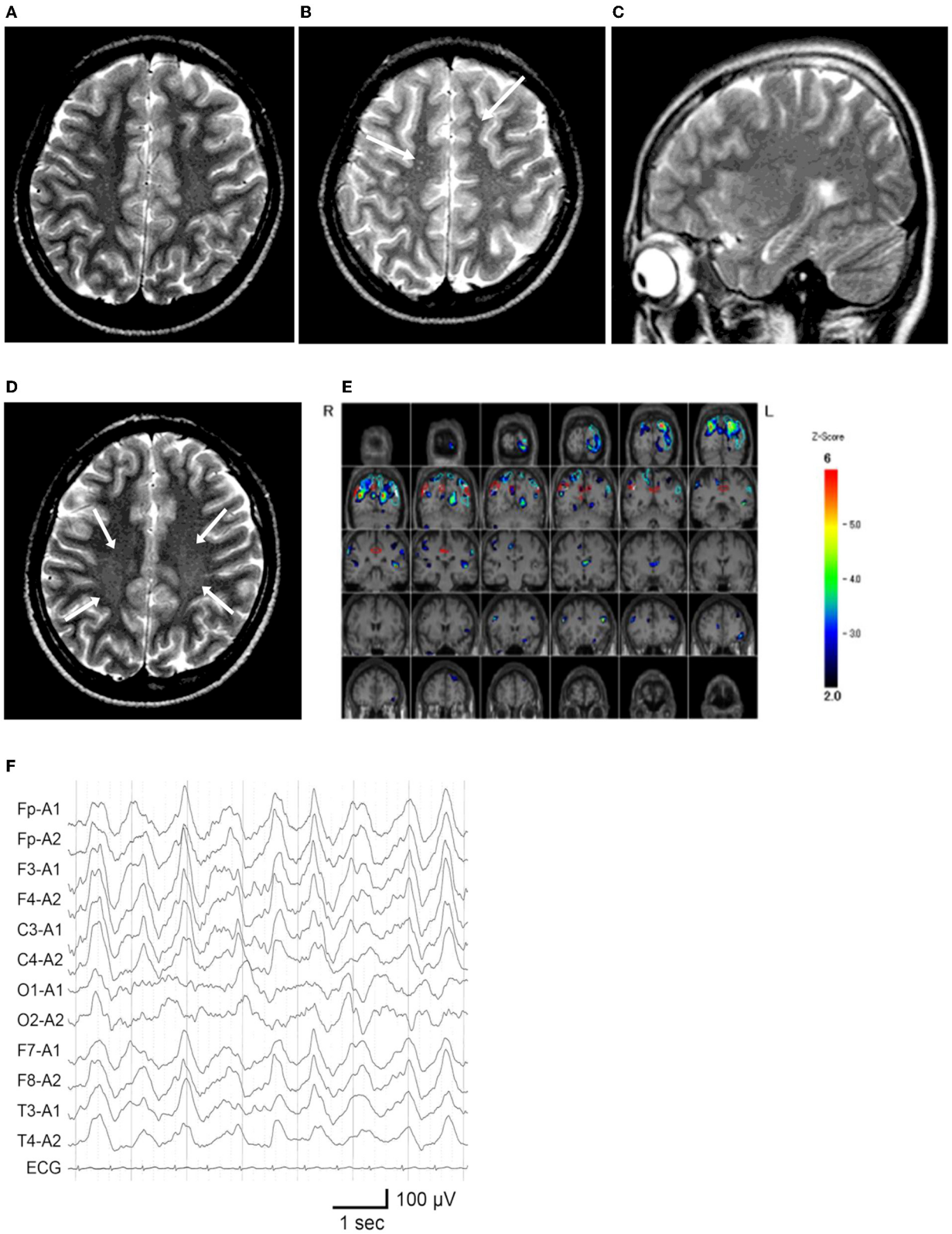

FIGURE 2
Neuroimaging and electroencephalography of the patient. **(A)** T2-weighted MR imaging at age 12 years and 5 months, during the first hospitalization. **(B, C)** MR images at age 13 years and 5 months, on the second admission owing to catatonic mutism. **(B)** Several high-intensity dots (arrows) are observed. **(C)** The hippocampus appears unremarkable on the para-midline sagittal slice. **(D)** MR image at age 14 years and 1 month, which demonstrated vague high signal areas (arrows) in the bilateral deep parietal white matter. **(E)** ^{99m} Tc-ECD SPECT at age 13 years and 6 months, colored by the easy Z-score imaging system. Hypoperfusion is observed in the bilateral parietal and left occipital areas. **(F)** Electroencephalogram on the first day of admission at 13 years and 5 months. Widespread high-amplitude slow-wave activity is detected.

A

	Hospitalization #1 12y9m		Hospitalization #2 13y5m		Hospitalization #3 13y9m		Controls (mean±SD)	
	CSF	blood	CSF	blood	CSF	Blood	CSF	blood
GluN2B-NT2 (EIA)	2.015	0.361	3	0.425	0.81	0.388	0.254 ± 0.075	0.3 ± 0.110
GluN2B-CT (EIA)	2.097	0.37	2.945	0.424	0.895	0.385	0.331 ± 0.110	0.371 ± 0151
GluN1-NT (EIA)	2.064	0.374	2.996	0.404	0.837	0.385	0.323 ± 0.091	0.337 ± 0.133
GluD2-NT (EIA)	3.003	0.4	2.162	0.434	0.952	0.387	0.378 ± 0.117	0.415 ± 0.180
Anti-NMDAR antibody (cell based assay)	negative		negative		positive			
IL-1β (pg/ml)	0.47		0.14		0.1		0.2 ± 0.2	
IL-1ra (pg/ml)	145.88		ND		ND		18.0 ± 23.8	
IL-2 (pg/ml)	1.68		0.77		1.41		1.2 ± 1.3	
IL-4 (pg/ml)	0.33		0.21		ND		0.3 ± 0.2	
IL-5 (pg/ml)	81.06		69.91		63.34		0.4 ± 0.5	
IL-6 (pg/ml)	5.45		2.16		4.48		3.6 ± 1.6	
IL-7 (pg/ml)	1.26		0.68		1.46		1.0 ± 1.2	
IL-8/CXCL8 (pg/ml)	51.85		19.82		25.09		38.0 ± 23.6	
IL-9 (pg/ml)	28.22		6.61		12.37		17.1 ± 5.8	
IL-10 (pg/ml)	8.87		3.3		4.99		2.3 ± 1.4	
IL-12 (pg/ml)	1.81		ND		0.92		2.0 ± 1.6	
IL-13 (pg/ml)	0.7		ND		0.26		2.8 ± 2.9	
IL-15 (pg/ml)	517.6		266.6		331.1		13.8 ± 7.2	
IL-17 (pg/ml)	11.86		5.29		6.15		14.4 ± 6.4	
Eotaxin/CCL11 (pg/ml)	1.77		0.04		0.47		2.3 ± 5.2	
IP-10/CXCL10 (pg/ml)	535.8		63.79		235.69		1116.2 ± 889.1	
MCP-1/CCL2 (pg/ml)	282.24		102.54		211.05		256.4 ± 73.5	
MIP-1a/CCL3 (pg/ml)	0.54		0.43		0.37		2.0 ± 1.6	
MIP-1b/CCL4 (pg/ml)	15.21		3.24		7.65		26.2 ± 16.2	
RANTES/CCL5 (pg/ml)	32.88		11.83		13.24		8.6 ± 7.5	
G-CSF (pg/ml)	65.29		14.1		30.1		6.3 ± 5.4	
GM-CSF (pg/ml)	1.31		0.88		0.78		111.4 ± 41.0	
IFN-γ (pg/ml)	12.02		3.13		2.95		10.3 ± 8.6	
PDGF-BB (pg/ml)	132.38		31.49		47.46		5.0 ± 4.6	
TNF-α (pg/ml)	3.45		1.31		2.47		38.5 ± 9.7	
VEGF (pg/ml)	444.4		301.97		303.38		12.0 ± 13.1	
Granzyme B (pg/ml)	NE		ND		ND		0.548 ± 0.18	
ND: not detectable, NE: not examined								

B C D

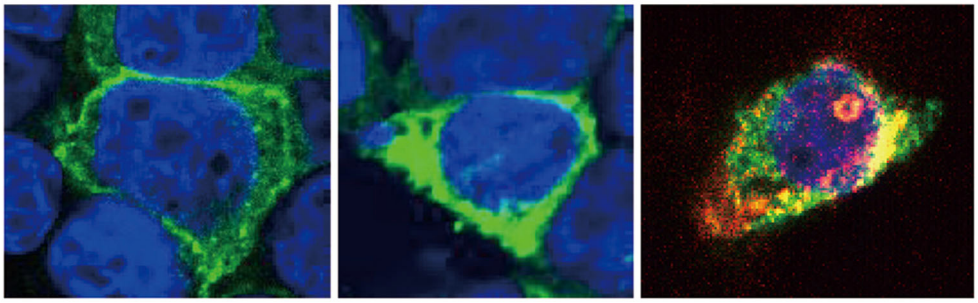

FIGURE 3
(A) Autoantibody to glutamate receptors and levels of cytokines, chemokines, and other factors in the cerebrospinal fluid (CSF) specimens, taken at three distinct phases of illness. Antibodies to GluN2B-NT2, GluN2B-CT, GluN1-NT, and GluD2-NT were measured by ELISA (6). Cytokines, chemokines, and other factors in CSF were measured by multiplex fluorescent immunoassays utilizing the Bio-Plex Pro Human Cytokine 27-plex Assay (Bio-Plex, Hercules, CA) (10). The panel comprises interleukin (IL)-1β, IL-1 receptor antagonist (IL-1ra), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8/CXCL8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17, eotaxin/CCL11, fibroblast growth factor-2 (FGF-2), granulocyte colony-stimulating factor (G-CSF),
(Continued)

FIGURE 3 (Continued)
granulocyte macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFN-γ), IFN-γ-induced protein 10 (IP-10)/CXCL10, monocyte chemotactic protein-1 (MCP-1)/CCL2, macrophage inflammatory protein-1α (MIP-1α)/CCL3, MIP-1β/CCL4, platelet-derived growth factor BB (PDGF-BB), regulated on activation, normal T cell expressed and secreted (RANTES)/CCL5, tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF). Levels of granzyme B in CSF were measured by the Human Granzyme B ELISA Kit (Cat. No. KT-078, Kamiya Biomedical Company, Seattle, WA, USA) (11). **(B–D)** Results on the cell-based assay (9) using CSF at age 12 y 9 m **(B)**, 13 y 5 m **(C)**, and 13 y 9 m **(D)**. **(B, C)** Cell bodies of cultured HEK cells, transfected with a cDNA coding GluN1/2B, are positively stained (green) by an antibody against the GuN1 epitope but are immunonegative by CSF staining. **(D)** Alongside the immunostaining of GluN1, the cell body is positively stained (red) by the CSF, taken just before the intravenous methylprednisolone therapy. Colocalization (yellow) of the immunostaining by the GluN1 antibody and the CSF is determined.

the pathophysiology of primary psychiatric illness to explain the catatonia and subsequent psychosis. CSF specimens from both admissions tested positive for anti-NMDA receptor antibodies by enzyme-linked immunosorbent assay (ELISA) (Figure 3) (6). Anti-TPO antibody was found to be positive; but, the patient was euthyroid. Clinical and paraclinical findings in this patient were compatible with DSDD, and at the same time fulfilled the criteria for probable NMDARE (7, 8). However, following points were rather atypical for NMDARE (Figure 1, Supplementary Tables S1, S2); (1) the presence of psychosocial stressors triggering each phase of illness, (2) the first phase of nonspecific complaints as long as 12 months, (3) the order of predominant movement disorder (catatonia) phase and late-evolving psychiatric phase, (4) negative CSF results, and (5) hypoperfusion on SPECT imaging not involving the limbic areas. With a diagnosis of DSDD, intravenous methylprednisolone was provided 3 months after the last admission, at age 13 years and 9 months. However, the effect of this treatment was minimal. Follow-up MRI revealed nonspecific high signal regions (arrows) in the bilateral deep parietal white matter (Figure 2D).

She then claimed to have delusions that her voices were recorded, that another person arose while she was fake, and that the present day was the dinosaur age. These psychotic symptoms were relieved by increasing the dosage of aripiprazole. During the period of preparation for high school admission, however, complaints of somatic symptoms or cenesthopathy predominated including throat discomfort, feeling like her face was slipping off, stubbed or dirty abdomen, dysesthesia in the distal extremities, and difficulty in chewing. Coupled with an auditory hallucination that someone was requesting and/or ordering her to die, the patient was influenced by thoughts over suicide and/or life expectancy, as well as the belief that she was already dead. She is currently a high school student, with persistent psychiatric issues. Such an extended course of hallucinations and delusions prompted us to examine the CSF specimen with cell based assay (CBA), which qualified a positive result of anti-NMDA receptor antibodies for the specimen taken just before the intravenous methylprednisolone (Figure 3) (9). The patient was diagnosed with definite NMDARE, for whom second-line immunotherapies are being planned. Ovarian tumor was not seen on an abdominal MRI.

CSF levels of IL-5, IL-15, CCL-5, granulocyte colony-stimulating factor, platelet-derived growth factor (PDGF)-bb, and vascular endothelial growth factor (VEGF) were raised throughout the course, highest at the first examination at the age of 12 years (Figure 3) (10, 11).

3. Discussion

Aside from autoantibody testing, cytokine study on CSF samples from DSDD patients, or even DS people without DSDD, has never been done. This is the first case of DS in which the CSF levels of cytokines and anti-NMDA receptor autoantibodies were measured before, during, and after the subacute catatonic regression. These three times corresponded clinically to the first phase with nonspecific complaints and declining speech, the second period of acute regression and catatonia, and the third phase of psychotic features.

The scores of catatonia symptoms peaked at the second admission (12, 13) (Figure 1), which finalized the syndromic diagnosis of catatonia at this stage. This was fair, however, given the negative CBA results, manifestations at this time also met the clinical symptoms of "possible" autoimmune encephalitis, "possible" autoimmune psychosis, as well as those of "probable" NMDARE (7, 8, 14, 15). Speech deterioration, catatonia, and other cognitive/behavioral difficulties are covered in both categories, indicating overlapping symptoms between DSDD and NMDARE (2, 4, 8). According to the published works (Supplementary Table S1), prior psychosocial stressors often trigger the onset of DSDD, which is not identified in NMDARE. In terms of clinical evolution, NMDARE present in an order of the prodromal phase with symptoms of infection up to 1 week, followed by the psychiatric phase of psychotic, cognitive, and mood disorders lasting weeks to months, and the subsequent neurological phase with movement disorders including catatonia. Auditory and/or visual hallucinations are common in NMDARE during the psychiatric phase, usually preceding catatonia. DSDD is characterized by the acute/subacute regression with depression and/or catatonia. Hallucinations can accompany this regression phase, i.e., not preceding catatonia, in relatively rare occasions. As for the paraclinical data of the patient, lack of pleocytosis, normal protein levels, absence of oligoclonal band, and IgG index in normal range, were not suggestive either of DSDD or NMDARE, some proportion (lower in NMDARE) of patients presenting these unremarkable data in each entity. Serum anti-TPO antibody is rather characteristic in DSDD, but can be detected in rare cases of NMDARE, although its role in the pathogenesis remains unclear in both entities. Extreme delta brush is specific to, but its absence does not reject, NMDARE. Rhythmic delta activity was a nonspecific finding, possibly accompany both. Hyperintensity punctate signals in the cerebral white matter on T2-weighted or fluid-attenuation inversion

recovery imaging were nonspecific findings, which can be seen in either NMDARE, DSDD, or even DS without regression. Notably, SPECT hypoperfusion in the parieto-occipital areas were common to DS subjects, whereas hyper-/hypoperfusion was predominant in the limbic systems including the medial temporal, the fronto-orbital, and the cingulate cortex in NMDARE (Supplementary Table S1).

Therefore, clinical features of the present patient until the third admission were typical for DSDD, rather not NMDARE. In the paraclinical data, normal CSF results and SPECT hypoperfusion in posterior areas were unusual for NMDARE. Through these multimodal diagnostics, we assumed that the diagnosis of DSDD was most appropriate for the patient. However, the patient began to experience profuse and extended hallucinations during and after the recovery from the catatonia and autistic regression. This evolution coincided with the positive CBA results of the cell-surface immunolabelling of cultured neurons expressing GluN1/GluN2B, when the criteria for "definite" NMDARE were fulfilled (7, 8). In other words, the formation of pathognomonic autoantibody was related to symptoms. Such a development has never been detected, with research on CSF autoantibodies from DSDD yielding negative results (4). Although this is an experience of single case, we speculate that the establishment of NMDARE may not be incidental, but may be linked to the neuroinflammatory aspects of DSDD. Catatonia in DS had an extremely high recurrence rate and required long-term medication and/or several courses of electroconvulsive therapy to maintain recovery, when compared to catatonia caused by other psychiatric and medical conditions (16). Persistent systemic and intracerebral inflammation has been seen in DS patients (17, 18), which may be causally linked to the development of DSDD, as well as to such a protracted psychiatric illness (4). The neuroinflammation innate to DS could have contributed to the formation of anti-NMDAR antibodies in the current patient. Having seen the sequential emergence of typical DSDD and definite NMDARE with ambiguous temporal boundary, we could consider this case to be post-DSDD NMDARE, similar to the concept of post-HSV encephalitis NMDARE (14). The current example may elicit repeated investigation of CSF antibodies in selected cases with prolonged and/or unique clinical courses.

Since different sets of CSF cytokines/chemokines have been examined in each study, the comparison of this aspect between NMDARE and DSDD was quite difficult (Supplementary Table S1). However, the elevation of some inflammatory molecules at the initial phase with nonspecific complaint, 1 year before catatonic regression began, supports their roles in the pathogenesis of DSDD. Overdosage of certain gene alleles on the 21 chromosomes may be involved in the inherent mechanisms for neuroinflammation in DS. The autoimmune regulator (*AIRE*) gene product alters the phenotypic of lymphocytes in the thymus, perhaps leading to the development of anti-TPO autoantibody. The positive results of the anti-TPO antibody in the current case, as well as the higher prevalence of this antibody in DSDD, support the hypothesis of autoimmunity in the pathogenesis of DSDD (3, 4). Another candidate is the amyloid precursor protein (*APP*) gene, which is thought to develop the amyloid plaques with the resultant provocation of inflammation in DS brains. Amyloid plaques in DS can be detected on neuropathology as early as 8–9 years of age when there are no signs of dementia. From this perspective, it is intriguing that IL-5, IL-15, PDGFbb, and VEGF were found to be raised in the CSF of the current patient, all of which are upregulated in AD brains, but not in NMDARE in general (19–22). These findings support the concept that pre-AD disease contributes to the evolution of DSDD (3). Additionally, the biphasic elevation of certain chemokines characterizes the post-HSV encephalitis NMDARE (23, 24). This trend could also be observed in the values of IP-10/CXCL10 and MCP-1/CCL2, though not significantly increased compared to the reference ranges (Figure 3A). This last issue necessitates investigations on further DSDD subjects.

In conclusion, the clinical course of the current patient was thought to denote a transition from DSDD to NMDARE. Positive results of anti-NMDA receptor antibodies on the CBA coincided with this transition. Cytokine profiles in the CSF implied a precedent Alzheimer's pathology as a part of causative factors for DSDD. Although the exact mechanism of transition remains uncertain, repeated CSF examination for autoantibodies may be necessary in selected cases of DSDD with protracted and recurrent clinical course and/or with unusual neurological phenotype for DSDD.

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. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

YM, MS, FT, HM, MO, YO, AY, and YW were in charge of the clinical management of the subject and decisions concerning the treatment. YT examined the anti-NMDA receptor antibody assays and measured the cerebrospinal cytokines, chemokines, and other molecules. YM and YS wrote the draft. MS, YW, ST, and YT critically reviewed the manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1200541/full#supplementary-material

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The use of intravenous immunoglobulin in the treatment of Hashimoto's encephalopathy: case based review

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Background: Hashimoto's encephalopathy (HE) is a controversial immunological neuropsychiatric disease, with a poorly understood pathogenesis. It is characterized by symptoms of acute or subacute encephalopathy which usually occur in the presence of elevated levels of antithyroid antibodies. Even though it is also known as steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT), some cases appear to be steroid-resistant. This review examined whether treatment of Hashimoto's encephalopathy with intravenous immunoglobulin (IVIG) is associated with better clinical outcomes than the standard therapy. Additionally, we presented a case of a 59-year-old man who presented with severe neurological manifestations and was successfully treated with intravenous immunoglobulin.

Methods: The online databases PubMed and EMBASE were searched.

Results: A total of 1,365 articles were identified. After the deletion of 112 duplicates, 1,253 studies were screened by evaluating the title and abstract, focusing on Hashimoto's encephalopathy cases where IVIG were used. 846 studies were excluded because they were not relevant to the topic or included pediatric population. Therefore, 407 full-text articles were assessed for eligibility. The final analysis included 14 eligible articles after 393 were excluded (irrelevant texts, not written in English, full-text not available). In the majority of the selected case-reports, IVIG was associated with a good outcome, sometimes even with dramatic improvements in patient's status.

Conclusion: In last years, intravenous immunoglobulin therapy proved its utility in Hashimoto's encephalopathy's treatment, being a well tolerated therapy associated with remarkable improvement in patient's status. Further research is still needed in order to define the optimal treatment protocol for Hashimoto's encephalopathy and to establish if intravenous immunoglobulin can also be used as a first-line therapy, alone or in combination with steroids.

KEYWORDS

Hashimoto's encephalopathy, autoimmune encephalopathy, anti-thyroid peroxidase, anti-thyroglobulin, intravenous immunoglobulin, alpha-enolase

1. Introduction

Hashimoto's encephalopathy (HE) is a rare autoimmune disease characterized by a variety of neurologic and/or psychiatric symptoms associated with an increase in anti-thyroid antibodies. HE presents a unique diagnostic challenge since the clinical manifestations are often insidious, with cognitive and behavioral disturbance that may associate with tremor, myoclonus or ataxia. Rarely, an acute onset can occur, with manifestations such as stroke-like episodes, epilepsy, or psychosis (1, 2). The term Hashimoto's encephalopathy was first used in 1966 by Lord Brain for the description of various neurological symptoms in association with Hashimoto's thyroiditis (3). The cause of HE has been proposed to be autoimmune because of its association with other autoimmune disorders, inflammatory findings in the cerebrospinal fluid (CSF) and response to treatment with steroids. For the severe steroid-resistant HE cases there are only a few reports suggesting that intravenous immunoglobulin (IVIG) might represent a solution.

1.1. Clinical case presentation

We report the case of a 59-year-old man, obese, with a history of stage 2 arterial hypertension and chronic venous insufficiency, without any known thyroid disease, who presented with fatigue, tremor, attention deficit, headaches and aphasia. Symptoms started 1 month before presentation, with gradual worsening until he became unable to perform his usual activities of daily living. He had no focal motor, sensory, cranial nerve, or cerebellar abnormalities on physical examination.

An extensive blood workup was performed, with normal results of coagulation tests, liver and kidney function tests, erythrocyte sedimentation rate, C-reactive protein, protein electrophoresis, lactate levels, ammonia levels, tumor markers and viral serology (human immunodeficiency virus, hepatitis B, hepatitis C). A macrocytic anemia associated with a decrease in vitamin B12 levels and presence of gastric parietal cell antibodies was identified.

Thyroid function tests revealed mild hypothyroidism: thyroid stimulating hormone (TSH) titer was 12.6 uIU/ml (normal: 0.4–4.0 uIU/ml); free T4 titer was 0.883 ng/dl (normal: 0.89–1.76 ng/dl) free T3 titer was 3.59 pg/ml (normal: 2.0–4.4 pg/ml). High levels of anti-thyroid antibodies were noted, with anti-thyroid peroxidase (anti-TPO) 657 IU/ml (normal: 0–35 IU/ml) and anti-thyroglobulin (anti-Tg) 629 IU/ml (normal 0–40 IU/ml).

Cranial computer tomography (CT) was negative for pathologies (Figure 1).

A diagnosis of Biermer anemia and autoimmune thyroiditis was made, with a high suspicion of HE. Intravenous treatment with methylprednisolone 1 g/day was started, associated with levothyroxine and vitamin B12.

After 5 days of therapy the patient experienced a rapidly progressive neurological and psychiatric deterioration, with cognitive dysfunction, confusion, disorientation, visual and auditory hallucinations and paraparesis. Brain magnetic resonance imaging (MRI) detected a moderate atrophy of the fronto-parietal cortex. The patient's general condition worsened even more, with generalized hypotonia, partial response to pain stimuli and ineffective ventilation, which led to his transfer to intensive care unit. A brain CT scan ruled out a subarachnoid hemorrhage or hematoma, an ischemic stroke or an expansive intracranial lesion. Lumbar puncture revealed elevated levels of proteins in the cerebrospinal fluid.

Because the patient was already on steroids, the response was considered to be unsatisfactory and intravenous immunoglobulin therapy (400 mg/kg daily, for 5 days) was started. Gradual improvement was noticed and a complete recovery developed over the following weeks.

During 1 year follow-up period, remission persisted and the patient was able to perform his usual social activities.

2. Materials and methods

In order to summarize the available information regarding the use of IVIG in HE, a literature research was performed in March 2023, using the PubMed and Embase databases, with "Hashimoto encephalopathy" and "intravenous immunoglobulin" as search terms, without any criteria based on the year or type of publication.

After rejecting duplicates, all articles were assessed independently by two authors to rate their quality based on the selection criteria,

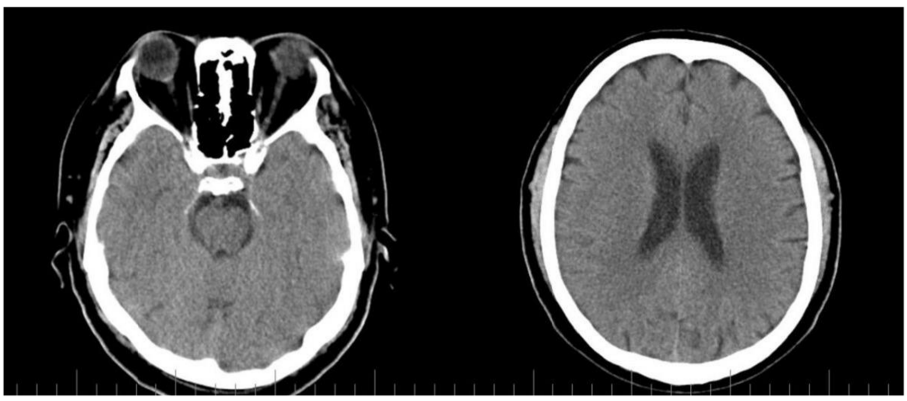

FIGURE 1
CT scan with no pathological findings.

which included cases where IVIG were used for the treatment of HE. The exclusion criteria were as follows: no relevant content to the purpose of the research; pediatric populations included; not written in English; full-text not available.

3. Results

The literature search identified a total of 1,365 articles (Figure 2). After the deletion of 112 duplicates, 1,253 studies were screened by evaluating the title and abstract, focusing on HE cases where IVIG were used. 846 studies were excluded because they were not relevant to the topic or included pediatric population. Therefore, 407 full-text articles were assessed for eligibility. The final analysis included 14 eligible articles after 393 were excluded (irrelevant texts, not written in English, full-text not available; Table 1).

4. Discussion

Hashimoto's encephalopathy is a rare and controversial neurological disease associated with autoimmune thyroiditis. It is characterized by unspecific neurological symptoms, such as altered mental status, confusion, cognitive decline, stroke-like episodes, seizures, acute delirium, memory loss, aphasia, myoclonus, ataxia, pyramidal and extrapyramidal signs, dementia, personality changes, hallucinations and delusional thinking. Even though the first case of HE was described in 1966, it still remains a poorly understood disorder (18, 19).

4.1. Epidemiology and pathogenesis

The prevalence of HE is estimated at 2.1/100,000 in the adult population but it might actually be higher than expected due to its

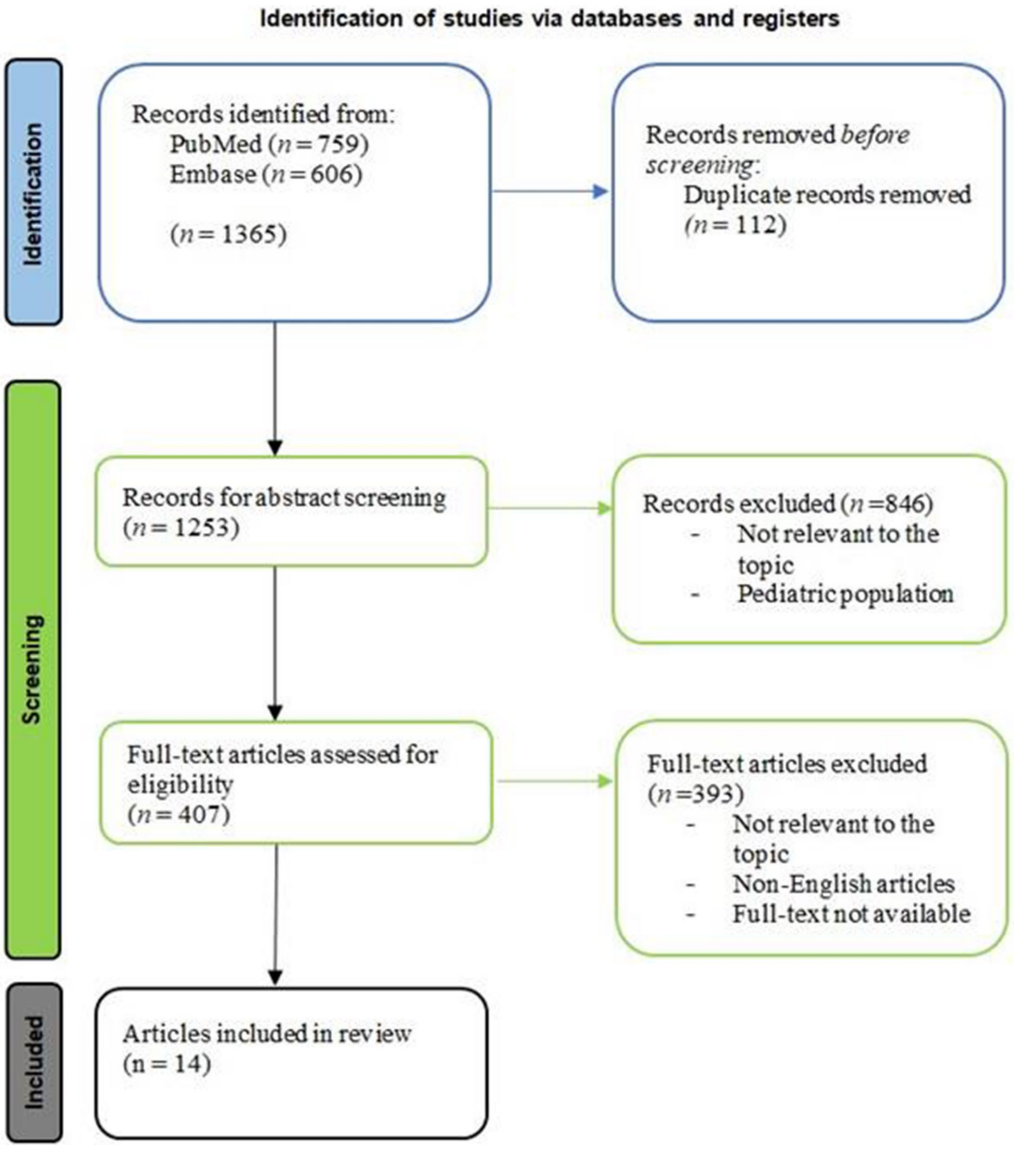

FIGURE 2
Article selection flowchart, according to PRISMA guideline.

TABLE 1 Schematic description of the selected cases.

Author Ref. # Case	Clinical manifestations	Initial treatment	Response	Secondary treatment	Follow-up
Aladdin et al. (4) 47-year-old ♀	- Progressive decline in recent memory, emotional lability, insomnia with agitation, generalized tonic–clonic seizures, post-ictal confusion. - Global rigidity, bradykinesia, masked face, anarthria, intermittent choreaoathetotic movements.	i.v. pulse steroid therapy (repeated twice).	Limited.	One course of IVIG.	No sensible changes.
Kondramashin et al. (5) 74-year-old ♂	- Progressive cognitive decline over the 6 months preceding presentation. - Waxing and waning. confusion which started 24 h prior to presentation.	i.v. solumedrol - 500 mg twice daily, 3 days + IVIG (0,4 mg/kg once daily for 5 days).	Fast improvement in mental status.		
Walia et al. (6) 43-year-old ♀	- Declining cognition, confusion, disorientation, inability to communicate or ambulate over the 3 months preceding presentation.	Oral prednisone + IVIG (400 mg/kg/day for 5 days)	Slight improvement of mentation.	IVIG 400 mg/kg/day for 3 days, every 4 weeks + tapering and discontinuation of oral prednisone.	Improvement in mental status and near-resolution of ataxia at 4-months follow-up. The final IVIG cycle was completed after 14 months of treatment. Complete clinical, serological and radiological remission after 7 years.
Ghosh et al. (7) 40-year-old ♀	- Progressive mood turnabouts, progressive decline in recent memory, executive dysfunction, dimness of vision over the 8 months preceding presentation. - Right-sided focal seizure with secondary generalization at presentation followed by alternating hemiparesis.	i.v. methylprednisolone (1 g/day for 5 days)	No clinical recovery.	IVIG 2 g/kg/day for 5 days.	Complete recovery of sensorium after 5 days of IVIG. Complete resolution of left hemiparesis after 2 weeks. Discharged with oral prednisolone + psychiatric treatment with tapering and discontinuation within the next 3 months.
Algahtani et al. (8) 25-year-old ♀	- Gradually progressive dizziness, imbalance, right-hand tremor, difficulty walking 2 months after delivery.	Pulse steroid therapy followed by oral prednisolone.	No significal improvement.	Plasma exchange for 5 days followed by IVIG.	Some improvement of the symptoms. Relapse after 6 months followed by a second round of immunomodulatory therapy.
Laycock et al. (9) 28-year-old ♀	- Lethargy, migraines, cognitive decline, poor concentration, generalized muscle aches over 1 year preceding presentation.	Pulsed IVIG therapy (high-dose steroids were avoided because of the concerns raised about the metabolic side effects).	Improvement in general intellectual functioning.		
Zhu et al. (10) 54-year-old ♀	- Memory loss and progressive cognitive decline over 5 days preceding presentation. - Coma after 4 days.	IVIG for 3 days followed by dexamethasone.	Recovery from coma.		Improvement in memory function at 3 months follow up.

(Continued)

TABLE 1 (Continued)

Author Ref. # Case	Clinical manifestations	Initial treatment	Response	Secondary treatment	Follow-up
Sapkota et al. (11) 49-year-old ♀	- Dizziness, gait imbalance, intermittent slurred speech. - Generalized tonic–clonic seizure followed by respiratory failure. - Concomittent pulmonary sarcoidosis.	Antiepileptic drug regime.	No clinical improvement.	5 days course of IVIG.	Improvement of cognition and overall encephalopathy after 2 days of IVIG.
He et al. (12) 61-year-old ♂	- Cognition dysfunction, slow reaction, impaired short-term memory, postural tremor. - One attack of generalized tonic–clonic seizure.	i.v. acyclovir for 7 days + methylprednisolone for 7 days (presumed diagnosis of viral encephalitis).	No important remission of symptoms.	i.v. methylprednisolone 500 mg/day+IVIG 0,4 g/kg/day for 5 days	Improvement of symptoms. Tapering of steroid therapy. Dramatic remission of symptoms at 2 months follow-up.
Drulović et al. (13) 38-year-old ♀	- Headache, gait impairment, personality changes, seizures over 6 months before presentation. - Known diagnosis of HE which responded well to steroid treatment.	Steroids.	Partial response.	IVIG 0,4 g/kg/day for 5 days.	Complete recovery over the following weeks. Persistence of remission during a 7-year follow-up period.
Cornejo et al. (14) 61-year-old ♀	- Malaise and bradypsychia for 2 months followed by a generalized seizure.	i.v methylprednisolone 1 g/day for 5 days followed by prednisone 2 mg/kg/day.	Initial response followed by comatose state.	IVIG 2 g/kg/day for 5 days + prednisone tapering	Resolution of neurological symptoms.
Yuceyar et al. (15) 34-year-old ♀	- Impaired attention, memory deficits, aggressive behavior, psychomotor restlessness, palpitations, weight loss, generalized tonic–clonic seizures. - Recurrent encephalopathy after each episode of hashitoxicosis.	i.v methylprednisolone 1 g/day for 7 days followed by 60 mg daily oral prednisolone.	Initial clinical improvement followed by seizure recurrence.	IVIG 2 g/kg/day for 3 days.	Improvement of confusional state but persistance of seizures. Multiple relapses in the next period. 3.5 months of 60 mg daily oral prednisolone. 2 months of 100 mg/day oral azathiopirine. 2 rounds of plasmapheresis in 2 months. Thyroidectomy+azathiopirine +levothyroxine-normal cognitive status.
Jacob et al. (16) 29-year-old ♀	- Neuro-psihiatric symptoms over a period of 14 years with multiple hospital admissions.	i.v dexamethasone 16 mg/day for 5 days.	Initial response followed by multiple relapses.	IVIG 400 mg/kg/day for 5 days.	Dramatic improvement within 24 h with a full recovery.
Wirkowscki et al. (17) 82 year-old ♀	- Changes in mental status, multifocal neurological deficits.	Oral prednisone and methotrexate.	No improvement.	Monthly courses of IVIG.	Clinical improvement.

i.v = intravenous.

underdiagnosis, taking into consideration that anti-thyroid antibody testing is not a routine investigation made in patients with neurological symptoms (20). It can affect people of all ages, but most commonly it occurs in the 4th-6th decades of life. It is considered to be a rare entity in the pediatric population. Similar to many autoimmune causes, the incidence is higher in females, with a female-to-male ratio of 4:1, which probably results from the fact that women suffer from Hashimoto's thyroiditis (HT) 10-20-times more often than men (21, 22).

HT has been reported to associate with other autoimmune diseases, such as vitiligo, alopecia, chronic autoimmune gastritis, celiac disease, type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, Sjogren disease, systemic lupus erythematosus, polymyalgia rheumatica, Addison's disease, hepatitis C virus related mixed

cryoglobulinemia (23). The most frequent associations reported are represented by autoimmune thyroiditis + vitiligo + chronic autoimmune gastritis and autoimmune thyroiditis + polymyalgia rheumatica + chronic autoimmune gastritis. Less commonly, HT is accompanied by additional autoimmune-origin endocrinopathies, thus forming what is known as autoimmune polyendocrine syndromes (APS) (24). Taking into consideration the mentioned potential associated pathologies in HT patients, it stands to reason that HE may also be encountered in the context of other autoimmune disorders.

The pathophysiology of HE remains poorly understood. An autoimmune background is suggested by the fluctuating course of the disease, by the presence of anti-thyroid autoantibodies and also by the good response to corticotherapy (25). The pathogenesis of HE has been attributed to three main mechanisms: immune complex deposition in the brain vessel wall, auto-antibody mediated mechanisms (including antibodies directed against thyroid and also extrathyroid antigens) as well as the toxic effects of some hormones produced as a response to hypothyroidism (26). An initial theory suggested that thyrotropin-releasing hormone (TRH) has toxic effects on the central nervous system. This theory was proposed in 1995 after Ishii et al. observed that a patient developed symptoms similar to those found in HE after intravenous administration of TRH (27). Taking into consideration that at the moment of diagnosis the majority of patients with HE are euthyroid, thyroid hormone dysregulation may not actually have a role in the pathogenesis of HE (28).

Despite the elevated titre of anti-thyroid antibodies, especially of anti-thyroid peroxidase antibodies, found in both serum and cerebrospinal fluid of the majority of patients with HE, a direct pathogenic effect on the central nervous system has still not been confirmed (29). The majority of authors agree with the fact that the levels of anti-thyroid antibodies do not correlate with the severity of the disease and that they should be treated only as a marker of an ongoing autoimmune process (30).

Most authors agree with the fact that HE might be the consequence of an autoimmune vasculitis or immune complex deposition with the subsequent disruption of the cerebral microvasculature (31, 32). This theory was confirmed by biopsy or autopsy. Al-Wafai et al. reported the first case of an angiographically proven vasculitis in a HE patient (33).

In recent years, antibodies against amino terminal domain of α-enolase (NH2-α-enolase Ab) have been identified in the serum and cerebrospinal fluid of patients with HE and they have been proposed as a more reliable marker of HE (34). α-enolase is a multifunctional glycolytic metalloenzyme playing multiple functions which is abundantly expressed in most cells, not only in the brain (35). Circulating antibodies against different epitopes of α-enolase have been identified in multiple patologies, such as rheumatoid arthiritis, systemic lupus erythematosus, membranous nephritis, Behcet's disease, systemic sclerosis, ulcerative colitis, infectious diseases, different forms of cancer (36). Fujii et al. in a proteomic analysis, concluded that in HE, autoantibodies against amino terminal of α-enolase might be an useful and a more specific diagnostic marker, neither carboxyl terminal nor the mid-region of α-enolase showing any specificity for HE (34). In contrast to their findings, in a more recent study, Mattozzi et al. observed that NH2-α-enolase Ab were found in just 1 patient from 24 patients with HE, which brings into question their utility as a specific marker for HE (37).

Gini et al. conducted a study to determine the target of IgG autoimmune response in HE. They examined the binding of IgG present in the serum and CSF of six HE patients and 15 controls to antigens found in the white matter of the human central nervous system (CNS). The results revealed that CSF IgG from HE patients specifically recognized three spots, identified as aldehyde reductase-I (AKRIAI) and dimethylargininase-I (DDAHI) which was present in 2 isoforms. Immunohistochemistry with anti-DDAHI antiserum showed endothelial cells in the normal human CNS. AKRIAI was found to be widely distributed in neurons and endothelial cells through immunohistochemistry. In the mouse CNS, IgG from HE CSF also immunostained both neuronal and endothelial cells. The presence of these specific autoantibodies in the CSF of HE patients could have significant diagnostic and pathogenetic implications, the autoimmune response against these enzymes leading to vascular and/or neuronal damage (38).

Later on, Benvenga et al. searched for amino acid sequence homologies between α-enolase, DDAHI, AKRIAI and the three classical thyroid autoantigens (TPO, Tg, TSH-receptor), which are also expressed in the CNS. They demonstrated the existance of multiple segments of homology between each CNS-protein and each thyroid antigen, suggesting that cross-reactivity between CNS autoantigens and thyroid autoantigens might contribute to the HE pathogenesis (39).

In another paper, Benvenga et al. wanted to extend their research, looking for additional CNS-expressed proteins homologous to thyroid autoantigens. Using bioinformatic methods to address this hypothesis, from a databank of 46.809 CNS-expressed proteins, they identified 46 proteins that shared homology with TSH-receptor, 27 proteins that shared homology with Tg, and 47 proteins that shared homology with TPO. Some proteins had a single segment of homology and other proteins had multiple segments of homology. The CNS areas where those proteins are expressed match CNS areas where pathological findings were detected at biopsy and/or by neuroimaging in patients in HE. They also mentioned the involvement in other autoimmune disorders of the proteins they found (40).

Endres et al. discussed the clinical considerations when dealing with patients in psychiatry who have schizophreniform or affective syndromes and elevated anti-thyroid antibodies. The primary concern was whether immunotherapy should be considered for patients who do not respond to guideline-based treatment to avoid overlooking HE. Out of the 530 patients analyzed, 91 individuals were identified to have elevated anti-thyroid antibodies. The study suggests that patients with anti-TPO and anti-Tg antibodies exhibited more frequent dysfunction in the blood-cerebrospinal fluid barrier, potentially facilitating the transfer of anti-neuronal antibodies from the bloodstream to the CNS. If these antibodies manage to access the CNS compartment, they may lead to neuronal damage (41). Zhu et al. presented a cases of HE with antibodies to α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor 2 (AMPAR2) both in serum and CSF, suggesting that AMPAR2 antibodies are not only met in limbic encephalitis and that high levels of thyroid antibodies can cause immune dysfunction, resulting in the production of anti-AMPAR2 antibodies that have harmful effects on neurons (10). Thus, anti-AMPAR2 antibodies could be considered non-specific antibodies which can occur in HE, but a rigorous differential diagnosis is necessary. Another study made by Takashi et al. aimed to investigate the role of anti-neuronal autoantibodies in HE. Two patients with

HE symptoms were studied. Autopsy and laboratory analyses were conducted on patient samples. The absence of CNS vasculitis was found in autopsy, but one patient's serum contained autoantibodies that reacted with a 36-kDa antigenic protein present in a soluble fraction obtained from human cerebral cortex. These findings suggest a potential association between anti-neuronal autoantibodies and HE pathogenesis (42). Current diagnostic criteria for HE require excluding alternative causes and the absence of anti-neuronal antibodies in CSF. Some published articles in literature show cases of autoimmune encephalitis diagnosed based on specific anti-neuronal antibodies, which also show an association with elevated levels of anti-TPO or anti-Tg antibodies. For example, in a case based literature review made by Matera et al., 6 cases of non-paraneoplastic anti-N methyl D-aspartate receptor encephalitis (anti-NMDArE) which also associated elevated levels of anti-thyroid antibodies were presented (43). Further studies are necessary to determine whether the presence of anti-thyroid antibodies is an incidental finding in autoimmune encephalitis or if they have the capacity to trigger other autoimmune processes, leading to the production of anti-neuronal antibodies.

Lately, there has been a surge of interest in a more aggressive form of Hashimoto's thyroiditis, accompanied by elevated serum IgG4 levels. IgG4-related disease (IgG4-RD) is a rare autoimmune condition characterized by the excessive production of IgG4 antibodies, leading to chronic inflammation and tissue damage in various organs. While the exact cause of IgG4-RD remains unclear, it is believed to result from an abnormal immune response (44). In IgG4-related thyroid disease, the abnormal immune response results in the infiltration of IgG4-secreting plasma cells into the thyroid tissue, leading to chronic inflammation. This immune attack targets the thyroid cells, causing damage and interfering with their normal function. Over time, this inflammation can lead to the development of Hashimoto's thyroiditis (45). IgG4-related thyroid disease showed correlations with a younger age group, a higher occurrence in males, higher levels of thyroid autoantibodies, diffuse low echogenicity, and a higher prevalence of subclinical hypothyroidism (46). The first reported case which suggested that the IgG4 fraction might account for the neurological manifestations observed in HE was a 60-year-old male who presented with severe symptoms of HE, exhibiting elevated IgG4 levels in both serum and CSF. The patient responded well to corticotherapy, with a subsequent decrease in serum IgG4 levels, while CSF levels of IgG4 were intermediate (47). The intricate and interconnected nature of autoimmune diseases makes possible the hypothesis that patients with IgG4-related thyroid disease and HE may also experience concurrent IgG4-related autoimmune disorders, such as pemphigus vulgaris and foliaceus, myasthenia gravis, thrombotic thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, autoimmune pancreatitis type 1, IgG4-related cholangiopathy, IgG4-related diseases in the head–neck area, IgG4-related kidney disease, etc. (48, 49).

4.2. Clinical manifestations

Hashimoto's encephalopathy manifests with a wide spectrum of symptoms that mimic a variety of neurological and psychiatric disorders. Presentation also varies considerably, with chronic, subacute, acute or fulminant patterns of an altered mental status (31, 50). Based on previous reports, HE has been classified in two subtypes: a vasculitic type and a diffuse progressive type. The vasculitic type is usually a relapsing form of HE characterized by episodic stroke-like symptoms suggesting a vascular background. The second one is characterized by an insidious onset of symptoms with a significant decline in cognitive functions and memory loss (51, 52).

Laurent et al. in a literature review which included 251 patients with HE, highlighted the variety of symptoms of this disease. At the initial clinical presentation, the following manifestations were found: convulsions (47%), confusion (46%), speech disorder (37%), memory impairment (43%), gait disturbance (27%), persecutory delusions (25%), myoclonus (22%), headaches (16%), coma (15%), depression (12%), isolated progressive memory impairment (11%), isolated psychiatric disorder (10%) (53).

As Laurent et al. did, the majority of case reports also prove that seizures are the most common symptom in patients with HE, many of them being the first manifestion of the disease (4). The type of epileptic presentation may include progressive focal or generalized onset seizures and even new-onset status epilepticus (54). Seizures usually occur more often in children with HE than in adult population. Alink et al. found that seizures were present in 80% of 25 children diagnosed with HE (55). For the majority of epileptic manifestations found in HE, common anticonvulsant therapy alone is usually ineffective. Immunotherapy is necessary for both initial and maintenance therapy of seizures (18).

Rare cases of HE with uncommon manifestations were described in isolated reports. Hwang et al. reported the case of a 56-year-old female who presented with orthostatic myoclonus, a manifestation characterized by multiple muscle fasciculations in the lower extremities that appear immediately upon standing (56). Another publication reported the case of a 32-year-old male who received a diagnosis of HE accompanying optic neuritis (57). Termsarasab et al., reported 2 cases of pure cerebellar ataxia without encephalopathy manifestations in 2 patients diagnosed with HE (58). Akathisia, a very rare occurrence of HE, was found in a patient with HE previously followed up for possible Alzheimer's disease plus Parkinson's disease (59). All of these neurological manifestations responded well to immunotherapy.

4.3. Diagnosis

Even though the first case of HE was described almost 60 years ago, diagnosis of HE still remains a diagnosis of exclusion. The most recent diagnostic criteria were proposed in 2016 by Graus et al. (60). All of the six criteria have to be met (Table 2).

The first diagnostic criteria were proposed by Pschen-Rosin et al. in 1999 (61). One of the criterias was the good response to steroid

TABLE 2 Diagnostic criteria of Hashimoto's encephalopathy.

1. Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes.
2. Thyroid disease (usually hypothyroidism) – subclinical or mild overt.
3. Normal brain MRI or with non-specific abnormalities.
4. Presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies – without a specific cut-off value.
5. Absence of well characterized neuronal antibodies in serum and CSF.
6. Reasonable exclusion of alternative causes.

treatment, but in the last years studies proved that there are many cases of steroid-resistant HE.

Due to the wide variety of conditions that can present with encephalopathy and the symptoms described above, HE can be difficult to diagnose. According to the majority of case reports of HE, one key finding leads to a corresponding diagnosis: abnormally elevated thyroid antibodies, namely thyroid peroxidase or thyroglobulin antibody, anti-TPO being the most common detected (62). The majority of cases occur in euthyroid or hypothyroid patients, even though HE can also occur in hyperthyroid patients (50, 63).

Abnormalities found in laboratory and imaging investigations are not pathognomonic but they may be useful in excluding other diagnoses (64). Even though cerebrospinal fluid analysis, electroencephalogram (EEG) and neuroimaging studies are not diagnostic, they may reveal some uncharacteristic changes (65). The most common abnormality identified in CSF analysis is elevated protein levels. In some cases, a mild lymphocytic pleocytosis can also be found (15, 66). Another helpful marker for the diagnosis of HE is the detection of anti-thyroid antibodies in CSF, which are present in the majority of cases (67). A literature review performed by Chong et al. proved that EEG is an useful tool in the diagnosis of HE, with abnormal EEG results being recorded in 98% of patients with HE (68). The main EEG finding consists in slow wave abnormalities, but epileptiform abnormalities, focal slowing, triphasic waves and photic stimulation induced discharges can also be found (69, 70). Brain MRI is usually normal, although in some cases, non-specific findings are observed, such as white matter changes, edema, atrophy, and ischemic lesions (71). Existing literature demonstrates that some of these abnormalities can be reversible after treatment (72). A recently published article reported the first description of conus medullaris involvement in HE, suggesting that the extension of MRI study to spinal cord may allow finding new pathological lesions useful in HE's diagnosis (73).

Taking into consideration the wide spectrum of symptoms met in HE and the non-specific laboratory and imaging investigations, a proper differential diagnosis should be made. Infectious, metabolic, vascular, neoplastic, paraneoplastic, neurodegenerative, psychiatric and other autoimmune etiologies should be ruled out (74–76).

4.4. Treatment

Despite the severe clinical manifestations which can occur in HE, once the diagnosis is made and the right treatment is initiated, HE becomes a treatable and easily reversible cause of acute encephalopathy, with a good prognosis.

Given the rarity of the disease, treatment guidelines are not clearly established. Corticosteroid therapy is the treatment of choice, HE being also called "steroid responsive encephalopathy associated with autoimmune thyroiditis" (SREAT) (77). Treatment is generally initiated with methylprednisolone 500–1,000 mg intravenous for 3–7 days followed by oral prednisone 1–2 mg/kg/day, with a gradual tapering of steroid dose after the desired result is achieved (78). Depending on the case, corticosteroid therapy duration can vary from months to years (79). There is typically an improvement or complete resolution of the symptoms within a few months (5). In the event of disease recurrence or occurrence of side effects associated with steroids, other immunotherapies can be added, such as mycophenolate, azathioprine, cyclophosphamide, methotrexate, rituximab (80, 81). It is important to note that long-term immunomodulatory therapy does not come without risks – serious side effects are possible and clinical and laboratory parameters must be closely monitored on a regular basis (82). Other effective immunotherapies associated with a shorter duration of therapy and less side effects are represented by IVIG and plasma exchange.

4.4.1. Intravenous immunoglobulin

Intravenous immunoglobulin is a concentrate of the pooled immunoglobulins obtained from at least 1,000 of healthy donors, prepared by using Cohn-Oncley procedure. Immunoglobulin is primarily composed of IgG, but it also contains various amounts of other proteins and auxiliary materials (83). The mechanisms by which IVIG has anti-inflammatory or immunomodulatory properties (Figure 3) have been difficult to define, but they were mainly attributed to blockade of the Fcγ receptor (FcγR) on immune cells, autoantibody neutralization by saturation of the neonatal Fc receptor (FcRn), inhibition of autoantibody production by stimulation of the Fc gamma receptor IIB (FcγRIIB), modulation of cytokine production and complement inhibition (84–89).

The use of intravenous immunoglobulin in the last 3 decades has revolutionized the treatment of previously untreatable conditions. The first time when IVIG were used for an autoimmune disease was in 1980 when Imbach et al. successfully used large intravenous doses of polyvalent Ig concentrate in children with acute, intermittent or chronic idiopathic thrombocytopenic purpura. A significant increase in platelet count was observed within 5 days in all patients, with variations in the subsequent course depending on the form of disease (90). This was just the first step in the success story of using IVIG preparations as an effective immunomodulatory therapy for a wide variety of conditions, including autoimmune or inflammatory diseases (91). The use of intravenous immunoglobulins in clinical neurology has been shown to be valuable in the treatment of new-onset or recurrent immune disorders as well as in chronic maintenance therapy (92). There is a strong evidence base for the use of IVIG therapy in Guillain-Barre syndrome, Chronic Inflammatory Demyelinating Polyneuropathy, multifocal motor neuropathy (93–95). In July 2021, based on the ProDERM study, U.S Food & Drug Administration (FDA) also approved a solution of IVIG for the treatment of adults with dermatomyositis (96). Additionally, based on controlled clinical trials, IVIG has shown to be effective in neurological conditions such as stiff-person syndrome, myasthenia gravis, inflammatory myopathies, multiple sclerosis, optic neuritis or autoimmune encephalitis (97, 98).

Intravenous immunoglobulin is generally considered a safe therapy, the majority of adverse effects associated to its administration being mild and transient. The occurrence of adverse effects depends on multiple factors, such as components of immunoglobulin products, rate of infusion and pacient-related risk factors (99). Depending on the time of occurrence, adverse effects can be immediate or delayed. The most frequent ones, representing more than 80% of intravenous immunoglobulin-induced adverse effects, are represented by flu-like symptoms, manifesting with fever, headache, chills, nausea, myalgia (100, 101). These symptoms

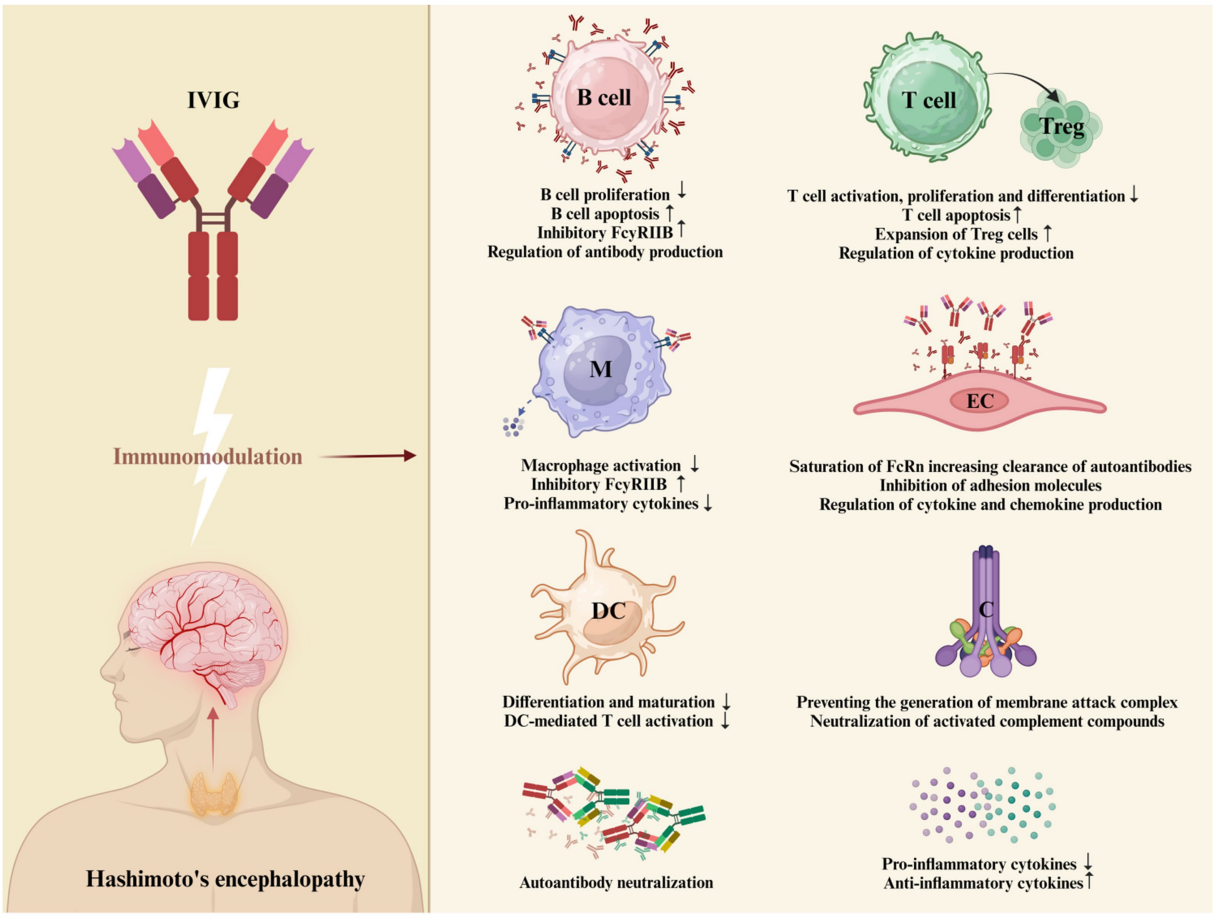

FIGURE 3
Proposed mechanism of action of IVIG in HE. IVIG employs multiple distinct mechanisms to exert its regulatory effects on various cellular and soluble constituents of the immune system. These mechanisms are not mutually exclusive and have the potential to collaboratively modulate the therapeutic outcomes. The proposed mechanism of action of IVIG in HE include: FcγR blockade leading to the potential inhibition of opsonized antigen binding, reduction in macrophage-secreted pro-inflammatory cytokines, and attenuation of granulocyte degranulation; stimulation of FcγRIIB to inhibit antibody production (84); intensified removal of pathogenic autoantibodies by saturating the FcRn or by IVIG binding to and neutralizing autoantibodies in serum (85); inhibition of T-cell proliferation and enhancing of the supressive properties of regulatory T (Treg) cells (86); prevention of membranolytic attack complex (MAC) generation and neutralization of C3a and C5a components; supressed production of pro-inflammatory cytokines, chemokines and adhesion molecules; stimulation of the production of anti-inflammatory cytokines (87); inhibition of differentiation and maturation of dendritic cells (84) (Created with BioRender.com). *B cell = B lymphocyte; M = macrophage; DC = dendritic cell; T cell = T lymphocyte; Treg = regulatory T cell; EC = endothelial cell; C = complement system.

are most often associated with rapid infusions and typically occur during the initial period of infusion. Other immediate adverse effects include dermatological reactions, chest tightness, dyspnea, vomiting, diarrhea, hypotension, tachycardia and anaphylactic reactions (102). Severe anaphylactic reactions are rare and they usually occur in IgA-deficient patients (103). The immediate adverse effects usually improve with the reduction of infusion rate or the temporary discontinuation of the infusion. Symptomatic therapy with analgesics, nonsteroidal anti-inflammatory drugs, antihistamines or glucocorticoids can also be used (102). Late adverse affects are rare but they can be severe or lethal. Thrombotic events, such as stroke, myocardial infarction and pulmonary embolism, can occur in patients being at high risk, due to the increased plasma viscosity induced by IVIG administration (104, 105). Renal impairment, another delayed side effect associated with intravenous immunoglobulin therapy, usually affects patients with preexisting renal dysfunction, diabetes, advanced age and dehydration. It can be avoided with a correct assessment of risk factors, proper pre-treatment hydration, urine output and kidney function monitoring and avoidance of sucro-stabilized immunoglobulin products which can induce renal failure by osmotic injury (106). Other delayed adverse affects are represented by pseuhohyponatremia, neutropenia, autoimmune hemolytic anemia, seizures, aseptic meningitis (107–111). Despite of all the possible adverse effects which can be associated with IVIG, it is still a well tolerated therapy with transient side effects, which changed the therapeutic approach in HE over the last decades.

The first case report of using IVIG for treating HE was published in 1998 by Wirkowski et al. They presented the case of a 82-year-old woman who developed neurological symptoms such as changes in mental status and multifocal neurological deficits in the presence of elevated titers of anti-thyroid antibodies. After an initial ineffective treatment with prednisone and methotrexate, an important clinical improvement was obtained with monthly courses of IVIG (17).

One interesting case reported by Jacob et al. in 2005 describes a 29-year-old woman who had multiple episodes of confusion and agitation over a period of 14 years, without a clear diagnosis. The initial hospital admission was in 1987 when cerebrospinal fluid examination identified pleocytosis and a presumed diagnosis of meningo-encephalitis was made. The patient had a good recovery with the antibiotic treatment but during the next years, the symptoms still persisted and she was also considered to have a psychiatric disorder. In 2003, another episode of confusion and drowsiness led to further investigations which identified an elevated thyroid peroxidase antibody titer. A remarkable response was obtained after a 5-day course of intravenous dexamethasone. In May 2004 the patient was re-admitted with the same symptoms but this time the confusion and agitation worsened even if another course of intravenous dexamethasone was administered. This was the moment when 400 mg/kg intravenous immunoglobulin was given, with a significant improvement within 12 h. The treatment had to be stopped because of a septicaemia resulted from an infected cannula site, but after a course of antibiotics the IVIG therapy was reinstated for 5 days with a complete recovery of the patient (16).

In the majority of cases (7, 8, 11–17), the initial treatment consisted in oral or intravenous corticotherapy, among with other immunosuppressive medication (e.g., methotrexate) or symptomatic medication (e.g., antiepileptic drugs). No improvement, partial improvement or full improvement but with the relapse of HE were identified. After intravenous immunoglobulin administration, a remarkable clinical response was obtained, either consisting in a full recovery in a short period of time without the need of using more medication, or a partial recovery with the need of administration of another rounds of IVIG among tapering of steroid therapy.

In some cases, IVIG was used as the first-line therapy, either alone or in combination with steroid therapy (5, 6, 9, 10). These cases were published in the last 7 years, so the initial use of IVIG may be the result of the data found in literature which sustains the beneficial effects of IVIG in the treatment of HE.

Based on our literature research, the first case-report about the use of IVIG as a first-line treatment was published in 2017 by Zhu et al. They presented the case of a 54-year-old woman who suffered from progressive cognitive decline and was initially treated with acyclovir for a suspicion of viral encephalitis. Four days later the patient went into a coma and 3 days of IVIG therapy was initiated, followed by dexamethasone. The outcome was remarkable, with a fully recovery from coma. However, at 3 months follow-up, the patient's memory deficits did not completely recover. What was also interesting about this case, beside the IVIG ability to wake up a patient out of a coma, was the identification of antibodies against α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) both in serum and cerebrospinal fluid. This was also the first case report on the detection of anti-AMPAR antibodies in HE (10). AMPAR is a subtype of glutamate receptor which mediates fast excitatory synaptic transmission in the central nervous system, being involved in synaptic plasticity, learning and memory (112). They were initially described by Lai et al. in 10 patients with limbic encephalitis (113) and multiple studies concluded that anti-AMPAR can be associated with a coexisting neoplasia (114), which was ruled out in Zhu et al.'s case. Zhu et al. speculated that in HE, the production of anti-AMPAR can be the result of immune dysfunction in the brain induced by the elevated levels of anti-thyroid antibodies (10).

Laycock et al. described the case of a 28-year-old woman who received a diagnosis of autoimmune thyroiditis at 20 years old. In the last years she was suffering of chronic fatigue, poor concentration, cognitive decline, symptoms which made her unable to sustain employment. Blood tests showed an adequate thyroxin replacement. After the diagnosis of HE was made, based on elevated levels of anti-TPO both in blood and cerebrospinal fluid, they had to choose the adequate treatment. Her BMI was 35.7 kg/m^2 so there were some concerns raised about the metabolic adverse effects of steroid therapy. As a result, IVIG was used as the first-line treatment, with significant improvement in general intellectual functioning (9). This case shows the importance of tailoring the treatment to the patient.

A case reported by Alladin et al. in 2022 focused on a rare presentation of HE, characterized by rapidly progressive dementia with irreversible cerebral damage which rendered steroid therapy and intravenous immunoglobulin ineffective. It was the case of a 47-year-old woman who had a 2-year history of progressive decline in memory, emotional lability, insomnia, agitation, generalized tonic–clonic seizures, global rigidity with declined mobility which made her bedbound. Brain imaging investigations identified vascular abnormalities consistent with vasculitis of the large and medium arteries, among severe atrophy of the caudate and temporal lobes which were probably the result of a chronic cerebral inflammation caused by a long-lasting occult form of HE. The patient received two courses of steroid therapy (1 g methylprednisolone) with limited response, followed by a course of intravenous immunoglobulin, which also did not lead to a sensible change in the clinical condition (4). The current case shows the importance of HE early diagnosis, despite the versatile clinical presentations, and of timely management with immunosuppressive therapy in order to prevent permanent damage of the central nervous system.

In the majority of the selected case-reports, IVIG was associated with a good outcome, sometimes even with dramatic improvements in patient's status. It was generally used as a second-line therapy, but the 3 cases when IVIG was used as a first-line therapy may offer new perspectives about the initial treatment approach in HE.

5. Conclusion

Hashimoto's encephalopathy still remains a challenging disease, due to the variety of clinical manifestations, poorly understood pathogenesis, non-specific laboratory and imaging abnormalities and lack of treatment guidelines. Early diagnosis and treatment are essential for avoiding irreversible damage.

Steroids represent the current standard treatment of HE but steroid-resistant HE cases have also been reported. The non-responsive cases to the corticosteroid treatment, or those suffering from severe adverse effects, can receive other immunomodulatory therapies, such as mycophenolate, azathioprine, cyclophosphamide, methotrexate or rituximab. These therapies can also have serious side effects, so there is a need for a safer alternative treatment option.

In last years, IVIG therapy proved its utility in HE's treatment, being a well tolerated treatment associated with remarkable improvement in patient's status. Further research is still needed in order to define the optimal treatment protocol for HE and to establish if IVIG can also be used as a first-line therapy, alone or in combination with steroids.

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.

Author contributions

VŞ: data curation, methodology, supervision, and conceptualization. MC: methodology, writing – original draft, supervision, and conceptualization. AA: data curation, investigation, and writing – original draft. CL: writing – review and editing, methodology, and supervision. AC: investigation and writing – review and editing. OS: data curation and writing – original draft. RH: data curation, writing-review and editing. LŞ: investigation, methodology, supervision, and conceptualization. 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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Glossary

HE	Hashimoto's Encephalopathy
SREAT	Steroid responsive encephalopathy associated with autoimmune thyroiditis
CSF	Cerebrospinal fluid
IVIG	Intravenous immunoglobulin
TSH	Thyroid stimulating hormone
anti-TPO	Anti-thyroid peroxidase
anti-Tg	Anti-thyroglobulin
CT	Computer tomography
MRI	Magnetic resonance imaging
HT	Hashimoto's thyroiditis
APS	Autoimmune polyendocrine syndromes
i.v	Intravenous
TRH	Thyrotropin-releasing hormone
NH2-α-enolase Ab	Antibodies against amino terminal domain of α-enolase
AKRIAI	Aldehyde reductase-I;
DDAHI	Dimethylargininase-I
anti-NMDArE	Anti-N methyl D-aspartate receptor encephalitis
IgG4-RD	IgG4-related disease
EEG	Electroencephalogram
Fc	Fragment crystallizable region
Ig	Immunoglobulin
FcγR	Fc gamma receptor
FcRn	Neonatal Fc receptor
FcγRIIB	Fc gamma receptor IIB
AMPAR	α-Amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor

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A case report of neurosyphilis coexisting with a positive MOG antibody manifested as optic neuritis

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Background: Neurosyphilis refers to an infection of the central nervous system by *Treponema pallidum*. The clinical manifestations of neurosyphilis are diverse, making it easy to miss or misdiagnose. Anti-myelin oligodendrocyte glycoprotein antibody-associated disease is a recently defined immune-mediated inflammatory demyelinating central nervous system disease. Few studies have reported the coexistence of the two diseases.

Case presentation: This case report presents a 37years-old male patient with neurosyphilis manifested as optic neuritis with a positive myelin oligodendrocyte glycoprotein (MOG) antibody. This patient received intravenous administration of 3.2 million units of procaine penicillin every 4h for 2weeks, followed by a two-week intramuscular injection of benzathine penicillin. Additionally, methylprednisolone sodium succinate was administered intravenously at 1,000mg/day, gradually reduced to 500mg/day and 240mg/day every 3days. Subsequently, prednisone tablets at a dosage of 60mg/day were orally administered, with a gradual reduction of 5mg/day every 3days until reaching a dosage of 30mg/day. The patient's visual acuity was improved after 26days of hospitalization. However, the visual field and color vision did not. At 3months of follow-up, the symptoms remained unchanged despite the patient continued taking oral prednisone tablets at a dosage of 30mg/day.

Conclusion: Neurosyphilis could be a potential triggering factor for MOGAD. In patients with neurosyphilis, it is strongly recommended to perform testing for MOG antibody along with other brain disease antibodies.

KEYWORDS

neurosyphilis, MOG, MOGAD, optic neuritis, *Treponema pallidum*

Introduction

Neurosyphilis is an infection of the central nervous system (CNS) by syphilis spirochete, and its clinical manifestations are diverse. Ocular symptoms are specific manifestations of neurosyphilis (1), which can occur at any stage of the disease and damage multiple eye structures (2, 3). Anti-myelin oligodendrocyte glycoprotein immunoglobulin G (IgG) antibody-associated disease (MOGAD) is an immune-mediated inflammatory demyelinating disease of the CNS. Optic neuritis is one of the main symptoms of MOGAD (4). Few studies have reported

the coexistence of neurosyphilis and positive myelin oligodendrocyte glycoprotein (MOG) antibodies. It remains unknown whether the clinical manifestations, treatments, and prognosis of patients with neurosyphilis or positive MOG antibody alone differ from those of patients with both diseases.

In this case report, we presented a male patient with neurosyphilis manifested as optic neuritis and positive MOG antibody. He tested positive for both serum *Treponema pallidum*-specific antibody and MOG antibody. The visual acuity was successfully restored after 26 days treatment with penicillin and corticosteroids, while the visual field and color vision impairments were not ameliorated.

Case presentation

A 37 years-old male patient was admitted to our hospital with blurred vision in both eyes for over a year and an aggravation of the symptoms for a month. He had experienced decreased visual acuity and color vision disorder in both eyes with unknown cause for over a year. The patient stated that he could not see the traffic light clearly when crossing the street. He was diagnosed with chorioretinopathy in both eyes at a local hospital but did not receive standard treatment. Since then, the patient has visited different hospitals successively and taken methylcobalamin supplements, but without significant response. This patient reported no history of chronic or genetic diseases. He visited sex workers twice before admission. One occurred 1 year ago, and the other occurred 2 months ago.

The examination results in other hospitals are as follows: (1) Fundus angiography (3 months after onset): the circulation time was roughly normal. Optic disc fluorescence was fair in both eyes. Dotted translucent fluorescence was observed in the retina of the right eye. Subretinal fluorescence was stained in the late circulation of both eyes. The diagnosis was chorioretinopathy in both eyes. (2) Visual evoked potential (VEP) (7 months after onset): the VEP was abnormal in both eyes. Conduction disorder of the visual pathway was detected, especially in the right eye. (3) Optical coherence tomography (7 months after onset): the mean thickness of RNFL: OD, 66 μm; OS, 70 μm. The symptoms at admission were blurred vision in both eyes with color vision disorder but no optical rotation, double vision, dizziness, headache, or other discomforts.

The results of physical examination at admission in our hospital are as follows: Body temperature, 36.8°C; heart rate, 84 beats/min; respiratory rate, 20 breath/min; blood pressure, 118/74 mmHg. The patient had no rash on the skin, mucous membranes of the whole body, or enlargement of superficial lymph nodes. He exhibited Argyll Robertson pupils: bilateral pupils significantly constricted with a diameter of approximately 2 mm; weak direct and consensual light reflex; normal near reflex. The visual acuity was determined by examining whether the patient could recognize hand movement in front of the right eye and count fingers 50 cm from the left eye. This patient also presented significant color vision changes.

The urine routine, stool routine, coagulation, liver and kidney function, electrolyte, and levels of C-reactive protein, blood lipid, blood glucose, and myocardial enzyme at admission were normal. This patient tested positive for serum *Treponema pallidum*-specific antibody, with a 1:32 (Trust test) titer on the third day of admission. The fluorescent treponemal antibody absorption (FTA-ABS) test showed that the FTA-ABS-IgG and FTA-ABS-IgM antibodies were positive. The result of the human immunodeficiency virus infection (HIV) test was negative. The results of the cerebrospinal fluid (CSF) test were as follows: (1) pressure: 190 mmH_2O; (2) white blood cells WBC: 59.0×10^6/L, (3) neutrophil percentage: 3%; (4) lymphocyte percentage: 30%; (5) monocyte percentage: 67%; (6) Cl levels: 121.8 mmol/L; (7) glucose levels: 3.24 mmol/L; (8) protein levels: 1142 mg/L; (9) CSF IgG concentration: 34.3 mg/dL (Supplementary Table S1). The antibody was tested by flow cytometry using the EUROIMMUN kit (Germany) and the CBA-IF method of the Neurological Research Laboratory of Medical Innsbruck. The patient tested positive for the MOG antibody IgG (1:200) in both serum and CSF samples on the fifth day of admission. The serum and CSF samples also tested negative for anti-flotillin-1/2 antibody IgG, anti-MBP antibody IgG, and anti-AQP4 antibody IgG. The CSF was reexamined 1 week after treatment: (1) pressure: 135 mmH_2O; (2) WBC: 44×10^6/L; (3) Cl levels: 128.1 mmol/L; (4) glucose levels: 4.0 mmol/L; (5) protein levels: 881 mg/L; (6) CSF IgG concentration: 25.5 mg/dL (Supplementary Table S1). The patient tested positive for CSF anti-*treponema pallidum* antibody IgG, with a titer of 1:26 (FTA-ABS test).

The visual acuity examination showed a visual acuity of 0.2 in the right eye and 0.15 in the left eye. The color vision test indicated red-green color weakness. The fundus examination revealed significant optic disc edema and blurred disc margins in the left eye (Figure 1).

The visual field examination showed an insular visual field, referring to severe concentric narrowing with only a remaining visual field within a range of 5 to 10 degrees around the center, in the

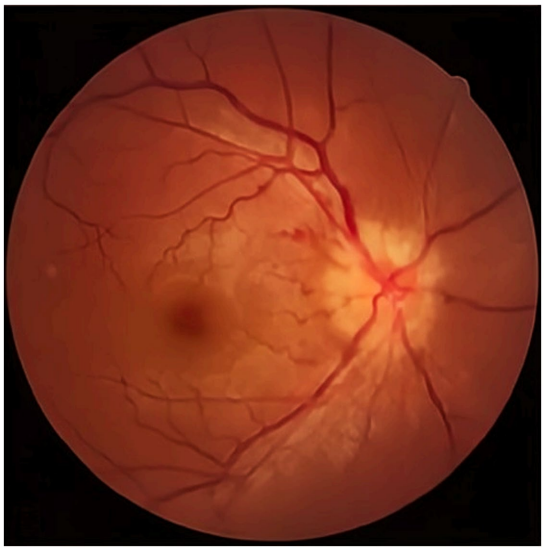

FIGURE 1
The fundus examination.

Abbreviations: CNS, central nervous system; IgG, immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; VEP, visual evoked potential; FTA, fluorescent treponemal antibody; HIV, human immunodeficiency virus; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; ADEM, acute disseminated encephalomyelitis.

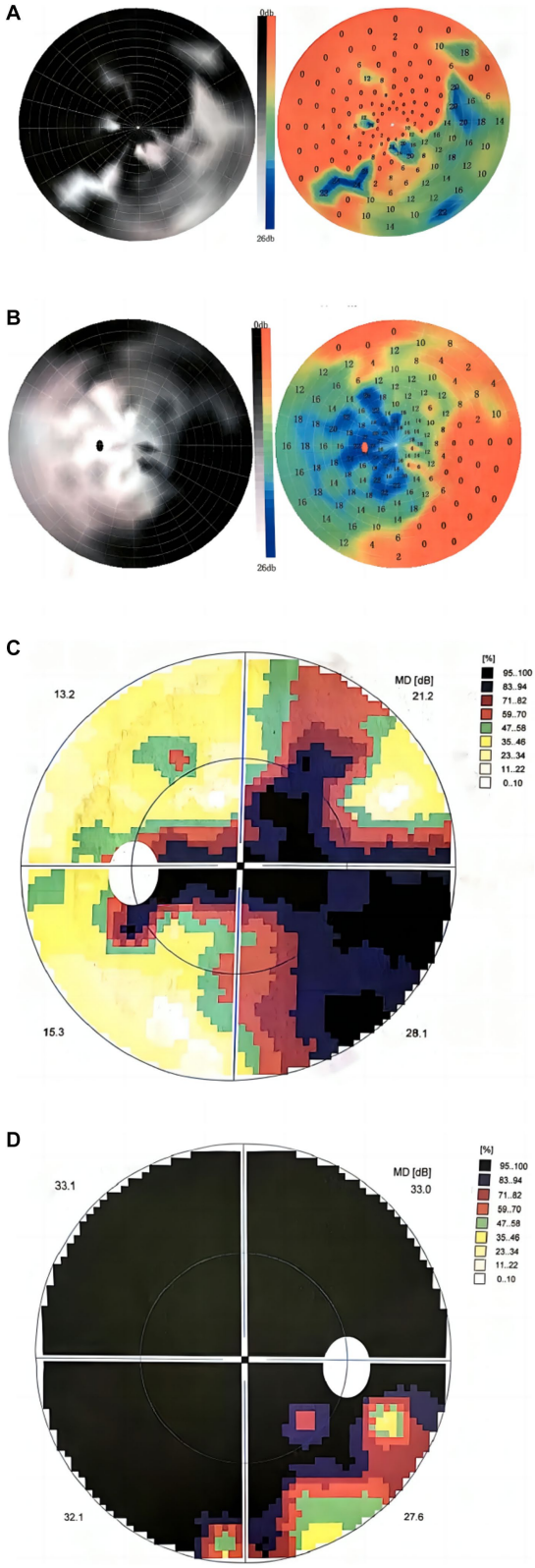

FIGURE 2
Visual field maps at 3 and 16 months after onset. **(A,B)** The visual field map 3 months after onset showed **(A)** an infratemporal insular visual field in the right eye, **(B)** central scotoma connected to the physiological scotoma in the left eye, and arcuate scotoma on the nasal side. **(C,D)** The visual field map at 16 months after onset showed **(D)** a smaller insular visual field in the inferotemporal region of the right eye, **(C)** central scotoma connected to the physiological scotoma in the left eye, and arcuate scotoma on the nasal side.

inferotemporal region of the right eye (Figures 2A,D), a central scotoma connected to the physiological scotoma in the left eye (Figures 2B,C), and an arcuate scotoma on the nasal side. The brain magnetic resonance imaging (MRI) and enhanced scan detected a few small microvascular lesions in the bilateral frontal lobe, parietal lobe, and right insular lobe. No abnormal signal was observed in the cerebellum or brainstem. No abnormal enhanced lesion was observed in the enhanced scan of the brain (Figures 3A,C–F). The cervical spine MRI and the enhanced scan revealed mild posterior median protrusion of the cervical intervertebral disc 3–4, 4–5, 5–6, and 6–7, cervical intervertebral disc degeneration, and mild hyperosteogeny of the cervical vertebral body 3–7 (Figure 3B). No abnormal enhanced lesion in the enhanced scan or abnormal signal in the cervical spinal cord was detected. No abnormality was observed in the orbital MRI.

The VEP showed poor bilateral P100 differentiation and delayed latency, suggesting abnormal bilateral visual pathway conduction. Based on the medical history and results of the auxiliary examination (Supplementary Table S2), the diagnosis of neurosyphilis combined with MOGAD was made. This patient received intravenous administration of 3.2 million units of procaine penicillin every 4 h for 2 weeks, followed by intramuscular injection of benzathine penicillin for an additional 2 weeks. The examination results showed serum *Treponema pallidum* (+) with a titer of 1:8 (TRUST test) and cerebrospinal fluid *Treponema pallidum* (+) with a titer of 1:5. Penicillin sodium at 3.2 million U (q4h) was administered for 2 weeks. Then, methylprednisolone sodium succinate at 1,000 mg/day was given via intravenous infusion. The dosage was successively reduced to 500 and 240 mg/day every 3 days. Next, prednisone tablets (60 mg/day) were orally administered, and the dosage was reduced by 5 mg/day every 3 days until it was 30 mg/day. When corticosteroid treatment started, penicillin sodium treatment was replaced by intramuscular administration of benzathine penicillin, which lasted for 2 weeks (Figure 4). The patient's visual acuity (0.8 in the right eye, 0.6 in the left eye) were improved after 26 days of hospitalization. However, the visual field and color vision did not. Then, the patient and his family requested discharge and refused lumbar puncture. The CSF examination was not performed before discharge. The patient was advised to take prednisone tablets (30 mg/day) orally and continue the treatment after discharge. The symptoms were not significantly improved at 3 months of follow-up. This patient exhibited no meningeal irritation signs during the disease.

Discussion and conclusions

Neurosyphilis can occur at any stage of syphilis infection with four common clinical subtypes: asymptomatic neurosyphilis, meningeal neurosyphilis, meningovascular syphilis, and paralytic dementia (5). Approximately 5% of untreated syphilis patients develop neurosyphilis (6), and the incidence of neurosyphilis of various manifestations is around 0.47–2.1 per 100,000 population (7, 8). Ocular syphilis is a subtype of neurosyphilis, accounting for 2–10% of all syphilis cases (9). Syphilis is a bacterial infection that can damage any structure of the eye (2), and approximately 20% of the cases with damage involve the optic nerve (10). Anti-myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an inflammatory demyelinating disease of the CNS, with the most common manifestation being optic neuritis, followed by myelitis, acute disseminated encephalomyelitis (ADEM), and ADEM-like manifestations (11).

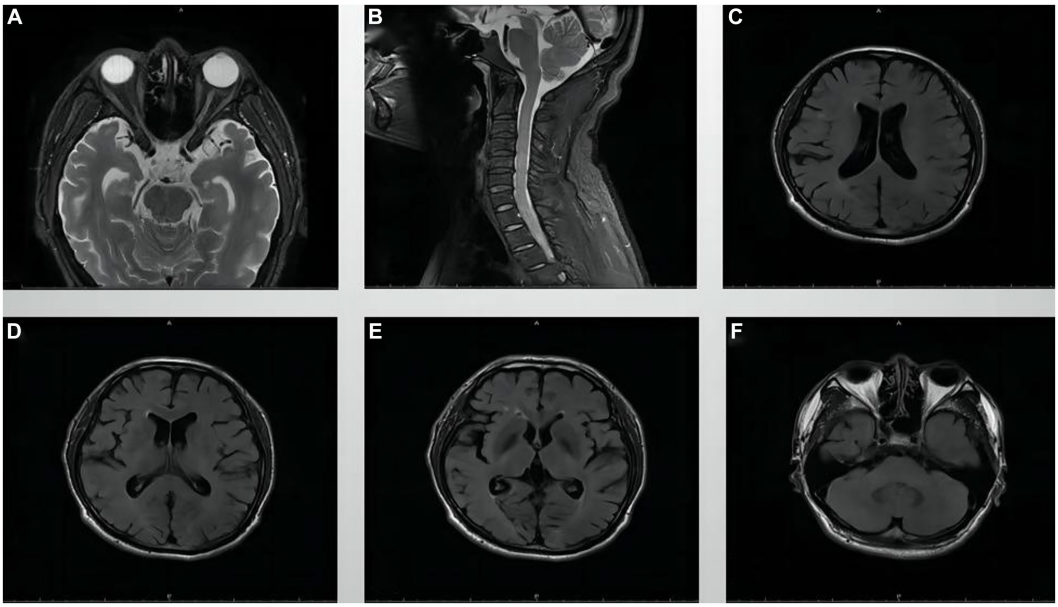

FIGURE 3
MRI images of the orbit, cervical spine, and brain. **(A)** Orbital MRI, **(B)** Cervical spine MRI, and **(C–F)** Brain MRI.

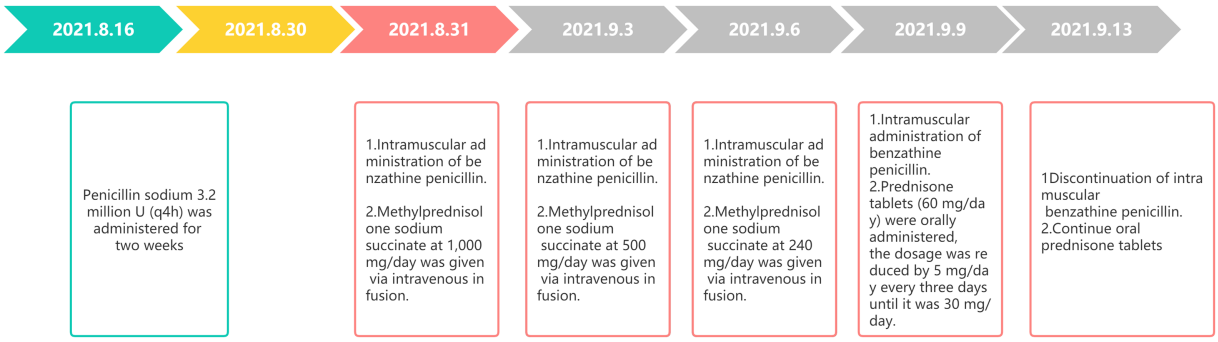

FIGURE 4
Treatment course.

Previous studies have reported cases of CNS infectious diseases combined with immune-mediated diseases, such as neurosyphilis combined with AQP4 antibody-positive neuromyelitis optica spectrum disorders (12), neurosyphilis combined with anti-N-methyl-D-aspartate receptor encephalitis (13), herpes simplex encephalitis combined with autoimmune encephalitis (14), and SARS-CoV-2 combined with MOGAD (15, 16). These findings suggest that viral infection may be related to initiating and developing immune-mediated diseases. Whether producing virus-induced autoimmune antibodies may induce immune responses warrants further investigation.

In this case report, we presented a patient with both neurosyphilis and MOGAD. *Treponema pallidum* can invade the CNS via the blood or lymphatic system, inducing inflammatory reactions and disrupting the blood–brain barrier. However, the underlying mechanisms remain unclear. Considering the medical history, physical examination, and imaging of this patient, as well as his two visits to sex workers (one occurred 1 year ago and the other occurred 2 months ago before admission), we speculated that this patient might have developed chorioretinopathy caused by neurosyphilis, and the disease had a slow progression. He had blurred vision in both eyes for over a year and an aggravation of the symptoms for a month. The rapid onset was different from that of neurosyphilis-induced oculocutaneous syphilis. The symptoms, including acute loss of binocular vision, visual field defects, color vision changes, etc., suggested that it might be an acute phase of MOGAD-ON. Therefore, we considered that the etiology of optic neuritis as a combination of neurosyphilis and MOGAD, and neurosyphilis could be a potential triggering factor for MOGAD. The combination treatment of corticosteroids and penicillin successfully restored the patient's visual acuity but did not ameliorate the visual field and color vision impairments. Considering that high-dose corticosteroid is not recommended in treating neurosyphilis (17, 18), we initially treated this patient with standard antisyphilitic treatment, followed by high-dose corticosteroid. Further serum and cerebrospinal fluid antibody tests were not performed because this patient requested discharge. While the patient's visual acuity improved, there were no significant changes in visual field and color vision. Subsequent telephone follow-ups indicated a relatively stable condition.

A recent report by Gudenkauf et al. (19) described a case of meningoencephalomyelitis associated with MOG-IgG seropositivity in a patient with syphilis. While both their case and ours involved syphilis infection and MOG-IgG seropositivity, our case involves the coexistence of two distinct etiologies and had a more precise diagnosis, offering a more clinically valuable and standardized therapeutic regimen. Firstly, in our case, a series of optic neuritis episodes occurred, starting with neurosyphilis-related optic neuritis and followed by MOGAD-related optic neuritis. The unique disease progression appeared to be closely linked to the patient's visits to sex workers. In contrast, the case reported by Gudenkauf et al. only presented symptoms related to MOGAD-associated meningoencephalomyelitis. Moreover, this patient experienced additional symptoms, including fever, nausea, vomiting, diarrhea, body aches, and headache between the second and third doses of penicillin therapy, raising the possibility of influenza infection. Therefore, it cannot be asserted that syphilis infection mediated the development of MOGAD-associated meningoencephalomyelitis. Secondly, the diagnosis in our case was based on positive anti-*treponema pallidum* antibody IgG in both blood and CSF samples. Additionally, clinical symptoms and signs, as well as funduscopic examination findings supported the diagnosis. However, in their case, neither syphilis nor MOG antibody in CSF were tested. Thirdly, the treatment regimen in our case was carefully considered, taking into account potential conflicts in treating optic neuritis due to syphilis and MOGAD-associated optic neuritis. Therefore, we opted for a comprehensive approach, beginning with antisyphilitic therapy, followed by corticosteroid treatment. The treatment for syphilis was consistently maintained throughout the process. The outcomes of this treatment regimen were highly favorable, resulting in a significant improvement in the visual acuity of this patient. This treatment regimen could serve as a valuable guideline for patients with similar presentations.

In conclusion, neurosyphilis may be a triggering factor for MOGAD. We recommend testing the MOG antibody and other brain disease antibodies, such as AQP4 and NMDAR antibodies, in patients with neurosyphilis. Treatment with penicillin and corticosteroids is recommended, but attention should be given to the sequences of their administration.

Patient perspective

This study was approved by the Ethical Review Committee of the Hospital of Chengdu University of Traditional Chinese Medicine (Chengdu, China) (Approval no. 2019KL-061). All procedures were per the Journal of International Medical Research, the ethical standards of the institutional and/or national research committee, and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent to participate in this study was provided by the patient. Written informed consent was also obtained for publishing any potentially identifiable images or data included in this article.

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

The studies involving human participants were reviewed and approved by the Ethical Review Committee of the Hospital of Chengdu University of Traditional Chinese Medicine (Chengdu, 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

MS: Conceptualization, Data curation, Writing – original draft. DL: Data curation, Writing – original draft. ZL: Data curation, Writing – original draft. ML: Data curation, Writing – review & editing. SJ: Investigation, Writing – review & editing. DY: Investigation, Writing – review & editing. JG: Conceptualization, Supervision, Writing – review & editing. GC: Conceptualization, Supervision, Writing – review & editing.

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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.2023.1258043/full#supplementary-material

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Case report: Seropositive myasthenia gravis complicated by limbic encephalitis positive for antibodies to AMPAR and Lgi1

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Objectives: Autoantibodies to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and leucine-rich glioma-inactivated 1 (Lgi1) are associated with autoimmune encephalitis. We described an acetylcholine receptor (AChR)-positive patient with myasthenia gravis who developed limbic encephalitis with antibodies to AMPAR and Lgi1.

Methods: A single-case report with detailed, prospective clinical and biomarker data including serial laboratory testing and histopathology.

Results: A 49-year-old woman was diagnosed with anti-AChR antibody-positive generalized myasthenia gravis in 1983. After 9 months of the removal of thymoma in 1984, she developed influenza-like symptoms and then symptoms of limbic encephalitis. Retrospective analysis of serum showed high concentrations of anti-AMPAR and lower concentrations of anti-Lgi1 antibodies. Cerebral CT was normal, EEG showed bifrontal dysrhythmia, and CSF showed mild pleocytosis. Immuno-histochemical examination of the thymoma confirmed staining for Glur2, a subunit of AMPAR. The patient recovered with mild sequelae, but low levels of anti-AMPAR and anti-Lgi1 antibodies were detectable for over 25 years subsequently.

Discussion: This case confirms earlier reports of AMPAR-associated autoimmune encephalitis co-occurring with thymoma and myasthenia gravis and is unique in its observational length. It shows, moreover, that antibodies to AMPAR and Lgi1 can persist despite clinical recovery.

KEYWORDS

myasthenia gravis, autoimmune encephalitis, neuroimmunology, immunology, thymoma

1. Introduction

Generalized myasthenia gravis is commonly associated with autoantibodies targeting the acetylcholine receptor (AChR) and, in some patients, it is associated with either thymus hyperplasia or the presence of a thymoma. The latter can also be associated with a broad array of neuroglial antibodies linked to autoimmune encephalitis (1).

We present a retrospective, single-case report of generalized myasthenia gravis with thymoma complicated by limbic encephalitis several months following the initial treatment of myasthenia. Retrospective serum testing showed high levels of autoantibodies targeting the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and lower levels of antibodies to the leucine-rich glioma-inactivated 1 (Lgi1). Despite recovery, this patient continued to have low levels of neuroglial autoantibodies that did not appear to be associated with a higher risk of relapse.

2. Case report

A previously healthy 49-year-old woman was diagnosed with myasthenia gravis with elevated levels of antibodies to the AChR in 1983. Investigation revealed a thymoma, and she underwent a thymectomy in 1984 with a complete macroscopic removal of the thymus and thymoma. Histological examination showed a focal lymphoepithelioma in an otherwise normal thymic gland. She was treated with a combination of oral prednisolone and azathioprine as well as pyridostigmine. She also received a single series of plasma exchanges following the thymectomy to prevent disease relapse.

After 9 months of thymectomy, she experienced influenza-like symptoms and within days, she developed cognitive decline with amnesia that progressed over the course of a few days. On hospital admission, she was fully alert and cooperative but had both anterograde and retrograde amnesia. Neurological examination was otherwise normal. Neuropsychological assessment demonstrated marked defects in information retention, learning, and spatial orientation. Cerebral CT was normal, but EEG showed episodes of bilateral rhythmic frontal and temporal 2–5 Hz activity. The cerebrospinal fluid showed slight pleocytosis (11 mononuclear cells/mm^3, normal <5/mm^3), normal IgG concentration, and no oligoclonal IgG bands. On the presumptive diagnosis of autoimmune encephalitis, she was treated with plasma exchange. Her cognitive symptoms improved dramatically although her antegrade affection persisted for approximately 6 months. The following year she had a recurrence of amnesia affecting short-time memory that improved markedly with plasma exchange. Subsequently, she remained well and was able to live independently despite mild memory difficulties.

Her myasthenic symptoms remained well controlled apart from minor fluctuations. In 2002, her weakness worsened, and the serum levels of AChR antibodies increased following a period of poor medical compliance. Her symptoms remained stable following the reintroduction of azathioprine. Cerebral MRI in 2005 was suggestive of bilateral hippocampal sclerosis (Figure 1A).

We retrospectively tested the patient's serum samples using immunoblots from Ravo Diagnostica GmbH[1] and cell-based assays from Euroimmune AG[2] for comparison. Samples collected during the first encephalitis episode in 1984 showed high levels of AMPAR antibodies and lower concentrations of antibodies to Lgi1. The AMPAR antibody level increased sharply during the recurrence of limbic encephalitis in 1985 and declined following plasma exchange. Both anti-AMPAR and anti-Lgi1 antibodies persisted in low concentrations for the next 25 years (Figure 1B).

Immunohistochemical analysis of the thymoma showed strong positive staining for the GluR2-subunit of the AMPAR (Anti-GluR2 Mouse Monoclonal Antibody, Invitrogen, #32–0300) and moderate staining for Lgi1 (Anti-LGI1 Rabbit Antibody, Sigma Aldrich, #PRS4489) (Figure 2). Lymphoepitheliomas from three patients with myasthenia gravis with no encephalitic serum antibodies and not suffering from encephalitis were tested with the same antibodies, and all showed similar staining.

3. Discussion

This case was first reported in 1989 (2) and re-studied recently with testing of neuroglial antibodies targeting an AMPAR subunit and Lgi1. The clinical onset of limbic encephalitis occurred 9 months after the removal of the thymoma and was directly preceded by symptoms of a viral infection. Based on the serological levels of the two antibodies and a clinical picture dominated by symptoms of limbic encephalitis without faciobrachial dystonic seizures, we suspect the probable causative antibody to be against AMPAR.

While earlier case reports have described the co-occurrence of thymomas, myasthenia gravis with AChR-antibodies, and autoimmune encephalitis associated with both AMPAR and Lgi1 antibodies (3–5), the pathological mechanisms underlying this association remain unknown. A recent study found an increased risk of autoimmune disease following thymectomy (6), and some patients with thymoma-related myasthenia gravis can experience symptom worsening and an increase in anti-AChR antibody titers following thymectomy (7, 8). This was not, however, found in our case.

Retrospective analysis showed that our patient had high titers of anti-AMPAR and anti-Lgi1 antibodies when she first presented with limbic encephalitis in 1985, but low concentrations (1:10) of the AMPAR antibody were also present the preceding year when she was hospitalized for myasthenia gravis. Low concentrations of such antibodies do not occur frequently in the normal population. This suggests that the increased levels of these antibodies were not a result of the thymectomy but rather that the removal of the thymus and thymoma together with an infection activated an already established pathological immune response.

The patient's thymoma stained strongly for the AMPAR-subunit GluR2 and to a lesser degree for Lgi1. We found a similar staining pattern in three thymomas from patients with no encephalitic serum antibodies suggesting that AMPAR and GluR2 represent self-antigens in the thymoma as part of negative T cell selection. Whether the AMPAR and GluR2 antigens in thymomas associated with autoimmune encephalitis differ from those present in subjects without autoimmunity is unknown, we know that patients with paraneoplastic cerebellar degeneration have genetic alterations in Yo-antigens in their ovarian tumors (9). We know, moreover, that HLA predisposition for autoimmunity is important as this has been linked to abnormal T cell autoreactivity (10).

Our analysis of patient samples collected over a 25-year period represents the longest longitudinal observation of AMPAR and Lgi1 antibodies documented. Our findings highlight the potential risk of

1 www.ravo.de

2 www.euroimmun.com

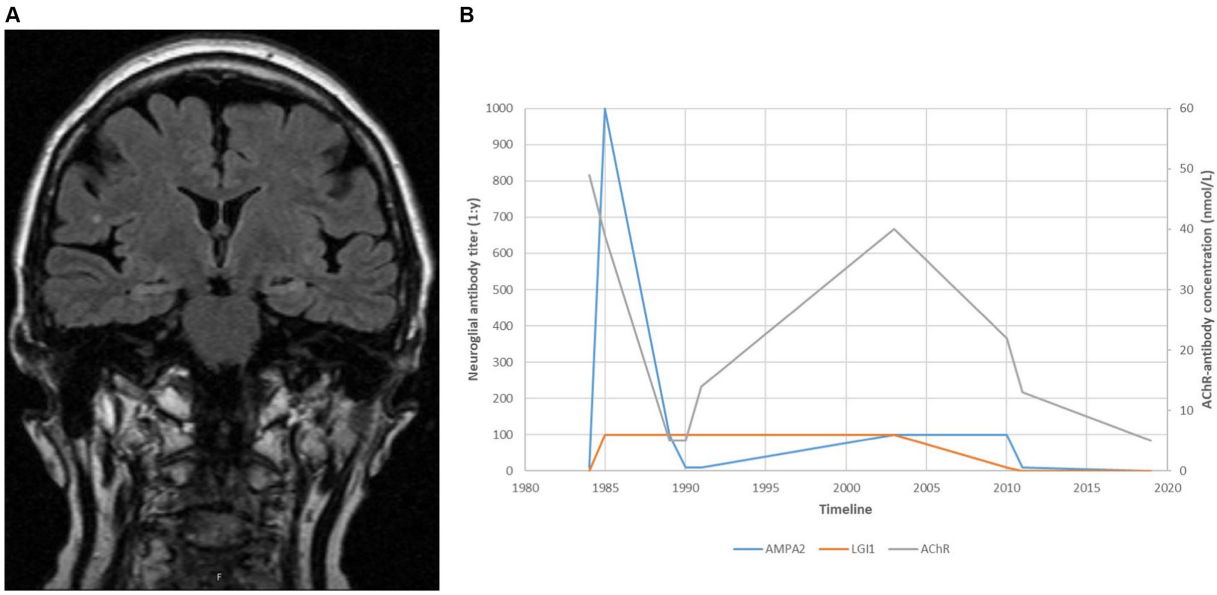

FIGURE 1
(A) A cerebral MRI taken in 2005, suggestive of medial temporal sclerosis approximately 20 years after recovery from distinct amnesia and both ante- and retrograde affection. **(B)** Antibody titres over time.

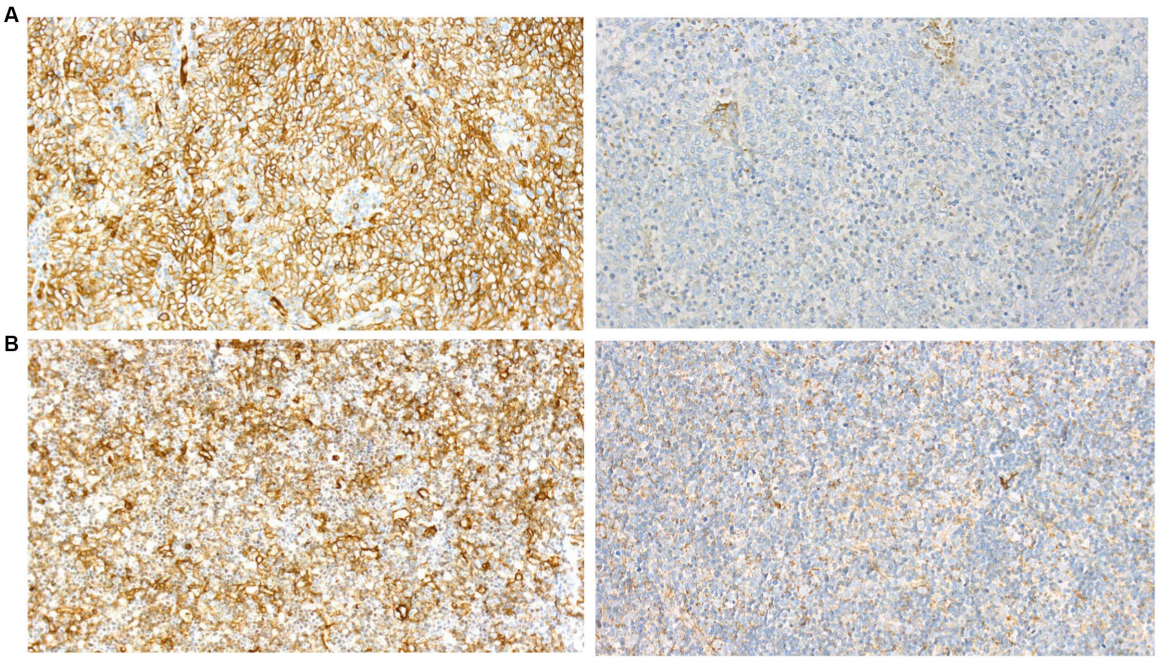

FIGURE 2
Immunohistochemical examination of thymoma from **(A)**, our patient and **(B)**, a control for GluR2 (left) and Lgi1 (right) showing similar staining pattern.

multiple autoantibody associations, including that between limbic encephalitis and thymoma. In our patient, anti-AMPAR antibody levels increased after thymectomy, and a viral infection could have been a precipitating factor for limbic encephalitis. Following recovery, low levels of autoantibodies could be detected for 25 years without any signs of clinical progression. This suggests that low levels of these antibodies are not an indication of ongoing autoimmune encephalitis, but rather a marker of a previous episode. This contrasts with recent findings where persisting autoantibodies to the N-methyl-D-aspartate receptor (NMDAR) in patients with NMDAR-encephalitis were associated with a higher risk of relapse (9).

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 from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. 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

MN, CV, and NG contributed to the conception and design of the study. MH organized the database. HH contributed to histopathological data. All authors contributed to the manuscript revision, and read and approved the submitted version.

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In memoriam

In memorial of Prof. Johan Arild Aarli (1936–2023) who initially took care of the patient. Prof. Aarli was a close friend, colleague, mentor, and president of the World Federation of Neurology 2005–2009.

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: Successful autologous hematopoietic stem cell transplantation in a patient with GAD antibody-spectrum disorder with rapidly progressive dementia

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The prevalence of neurological syndromes associated with antibodies to glutamic acid decarboxylase is increasing. While cognitive impairment is a common feature of this condition, it seldom emerges as the primary symptom. In this study, we discuss a case of refractory dementia associated with the glutamic acid decarboxylase spectrum disorder. Interestingly, this case showed a favorable outcome following autologous hematopoietic stem cell transplantation. We also provide an in-depth review of the current literature on the use of this therapeutic approach for the treatment of this disease.

KEYWORDS

autoimmune diseases of the nervous system, dementia, encephalitis, glutamic acid decarboxylase, neurocognitive disorders

Introduction

The range of neurological syndromes associated with antibodies to glutamic acid decarboxylase (GAD) continues to expand. Documented syndromes encompass stiff-person syndrome (SPS), ataxia, limbic encephalitis, epilepsy, nystagmus, and myoclonus (1). Cognitive impairment frequently appears in association with these syndromes (2), and isolated, rapidly progressive dementia has been observed (3). Collectively, these syndromes are now designated as GAD antibody-spectrum disorders (GAD-SDs) (1).

Treatment of GAD-SDs primarily involves pharmacological interventions to alleviate symptoms, complemented by immunotherapy. The majority of clinical evidence supporting immunotherapy is drawn from studies focused on patients with stiff-person syndrome, as SPS remains the most commonly diagnosed manifestation of GAD-SD. Thus, therapeutic strategies for other GAD-SDs are often derived from these data. The primary immunotherapy employed is intravenous immunoglobulin (IVIg) because of its proven efficacy in SPS. Other immunotherapeutic modalities with variable success include plasmapheresis, corticosteroids,

TABLE 1 Comparative table of formal neuropsychological assessments (pre- and post-HSCT).

Test	A* April 2015	B* August 2015	C* March 2023	Comparison* C x A or C x B
	Values in Z score			Difference ≥ 0,5 DP
RAVLT – A1-A5[1]	−0.3	−1.25	−0.7	**Improvement** (C > B)
RAVLT – A6[2]	0	−0.29	−0.2	No change (C = A; C=B)
RAVLT – A7[3]	0	−0.58	−0.5	No change (C = A; C=B)
WMS – LM I[4]	0	−0.3	0.3	**Improvement** (C > B)
WMS – LM II[5]	−0.3	0	0.7	**Improvement** (C > A; C > B)
CFT – Copy[6]	2.5	2.5	2.5	No change (C = A; C=B)
CFT – Immediate[7]	−0.5	0.1	-0.1	No change (C = A; C=B)
CFT[7] – Delay[8]	0.4	−0.05	-0.05	No change (C = A; C=B)
WAIS-R[9] – Digit Span	−0.3	−2	−0.6	**Improvement** (C > B)
WAIS-R[6] – Information	0	0.3	0.3	No change (C = A; C=B)
WAIS-R[6] - Vocabulary	−0.6	−0.3	−0.3	No change (C = A; C=B)
WAIS-R[6] - Similarities	0	0.7	0.7	**Improvement** (C > A)
WAIS-R[6] - Arithmetic	0	−0.3	0.3	**Improvement** (C > A)
WAIS-R[6] – Pict. Comp.[10]	−1.7	–	0.7	**Improvement** (C > A)
WAIS-R[6] – Block Design	–	−0.6	−0.3	**Improvement** (C > A)
WAIS-R[6] – L-N[11]	−0.3	–	1	**Improvement** (C > A)
WAIS-R – Digit Symbol-Coding	−0.3	−2	−0.6	**Improvement** (C > B)
Five-point Test	−1.5	−2	−0.3	**Improvement** (C > A; C > B)

No 2023 test scores decreased in comparison with scores from previous assessments.
[1]RAVLT – A1–A5: Rey Auditory Verbal Learning Test – Learning curve: tests A1 to A5. [2]RAVLT – A6: immediate recall (after distraction list B1, not presented here). [3]RAVLT – A7: delayed recall (after 20 min). [4]WMS-LM I- Wechsler Memory Scale – Logical Memory I subtest: immediate recall. [5]WMS-LM II: delayed recall. [6]CFT: Rey-Osterieth Complex Figure Copy: immediate copy for posterior reproduction. [7]CFT: immediate reproduction (3′ after copying). [8]CFT: delayed reproduction (30′ after copying). [9]WAIS-R: Weschsler Adult Intelligence Scale – Revised. [10]Pict. Comp.: WAIS-R Picture Completion subtest. 11 L-N: WAIS-R Letter-Number subtest.

and immunosuppressants. For patients who are resistant to these therapies, hematopoietic stem cell transplantation (HSCT) may be promising (1, 4).

In this paper, we discuss a patient who presented with rapidly progressive dementia and later manifested other GAD-SD symptoms. Despite being resistant to multiple immunotherapies, the patient responded positively to HSCT. Additionally, we provide a review of GAD-SD cases in the literature that have undergone HSCT treatment.

Case description

A 50-year-old woman, who had been a bank branch manager, sought medical attention in February 2015 due to a recent onset of forgetfulness. Over a period of weeks, she struggled with memorizing passwords and phone numbers, recognizing familiar clients, and performing work tasks. Within 2 months, she was experiencing frequent feelings of déjà vu. These symptoms, although fluctuating, progressively worsened, culminating in spatial disorientation that prevented her from leaving her home without assistance.

The patient's medical history included regular smoking, hypertension, ischemic heart disease, obstructive sleep apnea, and hypothyroidism. Neurological examinations revealed pronounced memory impairment, executive dysfunction, and visuospatial deficits. Comprehensive neuropsychological evaluations between April and August 2015 confirmed this deterioration (Table 1, assessments A* and B*).

Initial blood work showed elevated glycated hemoglobin (HbA1c of 8.0%) but a standard metabolic panel, including thyroid function, vitamin B12, homocysteine, and folate levels. Serological tests for HIV, syphilis, and hepatitis were negative, and inflammatory markers were unremarkable. Although brain MRI and 18F FDG-PET scans were normal, EEG detected epileptiform discharges from the left temporal lobe. Investigations for autoimmune encephalopathies revealed significantly raised serum levels of anti-GAD (>2,000 IU/mL) and anti-ZnT8 (>500 IU/mL) antibodies, the latter being linked to type 1 diabetes. CSF analysis was typical, but anti-GAD antibodies were present. Other anti-neuronal antibody tests, both surface and intraneuronal, were negative. Neoplastic screening was unremarkable.

The patient was initially treated with methylprednisolone (1 g daily for 3 days) without improvement. Rituximab was then administered and adjusted based on the CD19 count. Despite a partial response and reduced serum anti-GAD levels, over the next 2 years, the patient developed left temporal lobe epilepsy, diabetes, ataxia, and stiff limb syndrome symptoms in her right leg. Intravenous immunoglobulin (IVIg) treatment was considered but was unavailable due to the COVID-19 pandemic. Azathioprine was tried unsuccessfully.

Recurrent episodes of isolated cognitive decline persisted. They were managed with high-dose corticosteroids, although symptom

relief seemed to stem mainly from the adjustment of symptomatic treatments. Three years into azathioprine treatment, the patient suffered a subacute decline in all GAD-SD symptoms that correlated with high serum anti-GAD levels. Azathioprine was halted, and although monthly low-dose IVIg was attempted, higher doses were denied by her health insurance. At this point, autologous hematopoietic stem cell transplantation (HSCT) was proposed.

Seven years after her initial symptoms (April 2022), the patient underwent HSCT. Despite post-transplant complications, such as treatment-resistant diarrhea due to pseudomembranous colitis, she displayed improvements in both physical and cognitive function (Figure 1, patient timeline). A follow-up neuropsychological assessment 10 months post-HSCT showed enhanced cognitive performance across various domains (Table 1, assessment C*). Subsequent brain MRIs and EEGs were standard. The patient regained many higher-level functions, managed her banking independently, and achieved better glycemic control, even discontinuing insulin use. Currently, her Modified Rankin Scale (mRs) score is 0, indicating no symptoms.

Discussion

"Dementia" refers to an acquired cognitive impairment in one or more cognitive domains. This decline from a previous level of functioning interferes with daily life activities and with an individual's independence (5, 6). While neurodegenerative etiologies account for the majority of dementia cases (7), it is essential to identify potentially treatable causes (8, 9). Autoimmune etiologies should be considered, especially in instances with a rapidly progressive course, fluctuating symptoms, and the presence of seizures (9). It should be noted that these features are not exclusive. For example, rapidly progressive dementia can manifest in various diseases (10). Conditions like Lewy body disease, Parkinson's disease, and vascular cognitive impairment can exhibit fluctuating symptoms (11). Furthermore, seizures are commonly associated with dementia (12).

Rapidly Progressive Dementia (RPD) constitutes a small fraction of all dementias (3–4%). It is characterized by cognitive and functional impairments that manifest within 1–2 years, often within just weeks or months, as seen in our patient's initial presentation (13). RPD can have different etiologies, with the most common being prion (a prototypical RPD), autoimmune, infectious, vascular, metabolic, neoplastic, and atypical manifestations of traditional degenerative diseases such as Alzheimer's disease. Prompt evaluation is vital to identify potential treatable causes, such as autoimmune and inflammatory etiologies (10, 13).

The 1960s saw the first suspected descriptions of cognitive impairment due to autoimmune encephalitis. In 1966, Lord Brain chronicled a patient's cognitive decline not associated with cancer (14). By 1968, Corsellis and colleagues had defined paraneoplastic limbic encephalitis as a distinct clinicopathological entity (15). Since then, our understanding of autoimmune encephalitis has grown exponentially, leading to the identification of numerous antineuronal antibodies (16), some of which cause dementia. Such cases are occasionally referred to as "autoimmune dementias" or "autoimmune encephalopathies" (9, 17). A study of 75 RPD cases over three years at a tertiary center identified 15 instances of an autoimmune nature, one of which was linked to anti-GAD antibodies (18). In the literature, we identified eight cases of anti-GAD dementia (refer to Table 2).

Glutamic acid decarboxylase (GAD) is an enzyme predominantly found in the central nervous system (CNS) and pancreatic beta cells. The first identification of autoantibodies targeting GAD dates back to 1988. In subsequent years, GAD antibodies have been linked to other clinical manifestations such as cerebellar ataxia, limbic encephalitis, myoclonus, and nystagmus. These varied clinical syndromes associated with GAD antibodies have been collectively categorized as "GAD antibody-spectrum disorders" (1).

Treatment strategies for GAD-SDs, excluding SPS, have not been universally agreed upon. However, intravenous

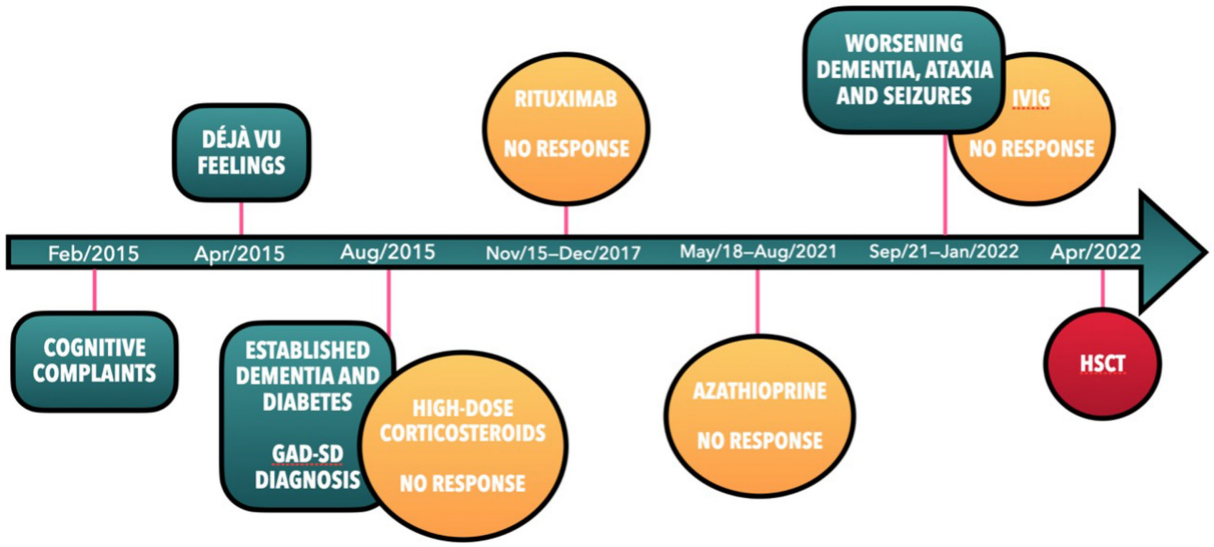

FIGURE 1
Timeline of key events.

TABLE 2 Anti-GAD dementia cases.

Author	Year	*n*	Pre-treatment antibody titers	Treatment	Outcomes
Akkari et al. (19)	2021	1		IVIg	Improvement
Mirabelli-Badener et al. (20)	2012	1	Anti-GAD 641 U/mL (serum) Anti-Abs 154 pmol/L	Methylprednisolone + IVIg + Mycophenolate+ Rituximab	No improvement in symptoms. Only reduction in anti-GAD levels (<69 U/mL)
Markakis et al. (21)	2014	1	Anti-GAD 37,550 UI/mL (serum) 15,400UI/mL (liquor)	Methylprednisolone + PLEX+ Prednisolone	Symptom improvement and decrease in anti-GAD serum levels (9,600UI/mL)
Alencar et al. (22)	2017	1	Anti-GAD >100 U/mL (serum)	Methylprednisolone + IVIg + Glatiramer	Symptom improvement
Takagi et al. (23)	2011	1	Anti-GAD 2,865.2 U/mL (serum) (67.8 U/mL)	IVIg	No improvement in symptoms or reduction of antibody levels
Ren et al. (24)	2021	3	Anti-GAD 19,610UI/ml (serum) 3,325UI/mL (CSF) _____ >300UI/mL (serum) >300 UI/ml (CSF) _____ 3,400UI/mL (serum) 13UI/mL (CSF)	Methylprednisolone + IVIg + PLEX _____ Methylprednisolone + IVIg _____ Methylprednisolone + IVIg, Mycofenolato, Rituximabe, PLEX	Symptom improvement _____ No improvement in symptoms _____ Symptom improvement

GAD, gamma-aminobutyric acid decarboxylase; *N*, number; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; MP, methylprednisolone; Anti-GAD serum levels, normal, <1 UI/mL – positive, >5 UI/mL – high, > = 2,000 UI/mL; Anti-GAD CSF levels, normal:<1 UI/mL- high:> 100 UI/mL.

TABLE 3 Autologous HSCT for anti-GAD spectrum disorders.

Author	Year	Condition (*n*)	Antibody titers (serum)	Previous treatment	Outcomes
Sanders et al. (26)	2014	SPS (2)	Anti-GAD: 5.6 and 127 Ui/mL	IVIg + Azathioprine + PLEX	Long-term remission
Kass-Iliyya et al. (27)	2021	SPS (3) PERM (1)	SPS pts.: Anti-GAD >2000 Ui/mL PERM pt.: Anti-GAD 372 Ui/mL + Anti-Gliadin positive + Anti- Glycine positive	IVIg +/− PLEX +/− Rituximab	All patients improved mobility and ambulation
Burt et al. (28)	2021	SPS (23)	Anti-GAD: 2,5 to >250 Ui/mL	IVIg +/− Rituximab or Azathioprine	17 responders (11 in remission for 3.5 years) – improvement in stiffness, spasms, mobility, and quality of life 6 non-responders

HSTC, hematopoietic stem cell transplantation; GAD, gamma-aminobutyric acid decarboxylase; (*n*), number of cases. SPS, stiff person syndrome; PERM, progressive encephalomyelitis with rigidity and myoclonus; EMG, electromyography; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; ATG, anti-thymocyte globulin; Anti-GAD 65, immunoprecipitation assay (IPA) / < ou igual a 0.02 nmol/L liquor; Anti-GAD -ELISA- serum level, POSITIVE > 10 UI/ML AND HIGH LEVEL > 100.000.

immunoglobulin (IVIg) is a prominently recognized modality, especially given its demonstrated efficacy in SPS patients (1, 25). The applicability of treatments across the range of GAD-SD manifestations remains an area of uncertainty, but current approaches seem plausible.

Recent literature has highlighted the potential for treating SPS using autologous hematopoietic stem cell transplantation (HSCT) (26–28). Cumulatively, these studies examined 29 patients who underwent HSCT (Table 3). While IVIg is a costly and long-term immunomodulatory strategy, autologous HSCT, despite its inherent risks, holds promise for

inducing prolonged remissions not only in GAD-SD but also in other neurological autoimmune disorders (29). Extensive consultations were held with our patient and her family regarding the potential benefits and risks of HSCT. The patient had expressed feelings of disappointment and depression stemming from the relentless progression of her disease and numerous unsuccessful treatments with conventional immunomodulatory and immunosuppressive strategies.

Autologous HSCT, as previously mentioned, is not without risks. Patients undergoing this procedure face potential threats from opportunistic infections and adverse reactions related to the drugs used (30). Notably, there is a documented case of a patient who developed severe anti-GAD encephalitis following an HSCT procedure (31). Additionally, other autoimmune conditions may emerge post-procedure (32). It is imperative that these considerations be meticulously weighed when recommending autologous HSCT to any patient diagnosed with GAD-SD. Nevertheless, our patient, fully aware of these risks, expressed that she would opt for the same course of treatment if faced with the decision again.

Conclusion

There is a broad spectrum of neurological conditions that can manifest as rapidly progressive dementia. Among these, autoimmune dementias, such as those presenting as GAD-SD, should always be on the differential list. Accurate diagnosis is pivotal, as it can guide appropriate treatment. In instances where patients are unresponsive to initial immunotherapies, consideration of HSCT as a treatment option becomes crucial.

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. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. 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

CD: Conceptualization, Writing – original draft, Writing – review & editing. DK: Conceptualization, Writing – original draft, Writing – review & editing. SN: Conceptualization, Writing – review & editing. HT: Conceptualization, Writing – review & editing. PK: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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Relapsing polychondritis-associated meningoencephalitis initially presenting as seizure: a case report and literature review

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Background and purpose: Relapsing polychondritis (RP) is a rare rheumatologic disorder that may affect the neurological system with various presentations. In this study, we present a case and summarize the clinical characteristics of RP-associated meningoencephalitis.

Case presentation: A 48-year-old man presented with first-ever seizures that were well controlled by valproate. Physical examination results were unremarkable, except for binaural deformation. The initial brain magnetic resonance imaging (MRI) without contrast and electroencephalogram (EEG) findings were normal. However, the patient subsequently developed recurrent fever, scleritis, headache, lethargy, and left arm paresis. Repeated brain MRI with contrast demonstrated increased enhancement of the pia mater and abnormal diffusion-weighted imaging (DWI) signals in the bilateral auricles. The cerebrospinal fluid (CSF) analysis showed 2 leukocytes/μL, 736.5 mg/L of protein, and no evidence of infectious disease or autoimmune encephalitis. Meningoencephalitis secondary to RP was considered. The patient's condition improved significantly and quickly with the administration of dexamethasone (10 mg per day). Oral methylprednisolone was continued, and the patient remained well without relapse during the 9-month follow-up period.

Conclusion: RP-associated meningoencephalitis is rare but fatal. Although symptoms vary, red or deformed ears remain the most common and suggestive features. Non-specific parenchymal changes and/or meningeal enhancement can be observed on brain MRI scans. CSF lymphocytic pleocytosis with mild protein elevation was observed in most patients.

KEYWORDS

relapsing polychondritis, inflammatory meningoencephalitis, seizure, neuroimmune disease, immunosuppressants

Introduction

Relapsing polychondritis (RP) is a rare rheumatological disorder characterized by recurrent inflammation and destruction of cartilage throughout the body (1). Patients can present with multiple sets of complaints, including ear pain, nasal pain, hoarseness, throat pain, arthritis, episcleritis, scleritis, and less frequently, cardiac, neurological,

and renal diseases (2). Neurological involvement is rare but fatal in RP (3) and is difficult to diagnose due to its rare frequency and variable presentation. Encephalitis, meningitis, meningoencephalitis, myelitis, polyneuritis, seizures, stroke, cerebral aneurysm, and headache have also been reported (2, 3). In this study, we report a case, review the literature, and summarize the clinical characteristics of meningoencephalitis associated with RP.

Methods

We report a case of meningoencephalitis associated with RP from the Sir Run Run Shaw Hospital. In addition, we performed a literature search of the online database PubMed in July 2023 using Endnote with the terms "relapsing polychondritis" combined with "meningoencephalitis," without time frame restrictions. The reference lists of the selected articles were screened for additional relevant articles. Owing to confusion and overlap in the diagnoses of encephalitis, meningitis, and meningoencephalitis, only articles that explicitly stated the diagnosis of meningoencephalitis were included in this study. Articles without full text, those written in languages other than English, and those without sufficient clinical data were excluded. The adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is shown in Figure 1.

The full texts of potentially relevant literature were reviewed by two authors (DZ and JMS) independently. Disagreements were resolved through discussion and consultation with a third author (YQS or JW). Clinical information, including age, sex, neurological symptoms, neuroimaging findings, cerebrospinal fluid (CSF) analysis, electroencephalogram (EEG) findings, treatment, and prognosis, was extracted from each article (Table 1).

Results

Case presentation

A 48-year-old man presented to the emergency department with cluster seizures. Following intravenous injections of diazepam and valproate, the patient gradually became fully oriented, alert, and afebrile. Cranial computed tomography (CT) and CT angiography performed in the emergency department were normal. The patient was admitted to the neurology department to evaluate the etiology of the first-ever seizures.

Neurological examination was unremarkable on admission; however, binaural deformation was present (Figure 2). In the past year, the patient experienced recurrent auricular pustules, which improved after treatment at another hospital, but auricular hypertrophy and deformation remained. Laboratory examination results were as follows: 6,900/μl of white blood cell count (neutrophils 75.2%), 26.8 mg/L of C-reactive protein (reference value < 6.0 mg/L), 315.8 IU/mL of thyroglobulin antibody (TGAb) (reference value 0.0–4.1 IU/mL), and 245.20 IU/mL of thyroid peroxidase antibody (TPOAb) (reference value 0.0–5.6 IU/mL). Thyroid-stimulating hormone (TSH), T3, T4, tumor markers, and hepatic and renal functions were normal. The antinuclear antibody series, antiphospholipid antibodies, vasculitis series, serum human immunodeficiency virus (HIV) serology, and rapid plasma reagin (RPR) tests were negative. Brain magnetic resonance imaging (MRI) without contrast and EEG were unremarkable. On the fourth day of hospitalization, the patient developed a transient low fever with spontaneous remission the next day. Lumbar puncture was suggested but refused by the patient, who was then discharged with oral valproate therapy.

After 18 days of initial discharge, the patient was readmitted because of fever, headache, and left arm paresis. During the past half a month, the patient had recurrent mild fever, with a body temperature fluctuating between 37 and 38°C, accompanied by headache. The patient reported no cough, expectoration, frequent urination, urgency, abdominal pain, diarrhea, or seizure recurrence. The white blood cell count was 12,100/μL (neutrophils 83.1%), and the C-reactive protein was 18.3 mg/L, as tested in another hospital. Ceftriaxone was intravenously administered for more than 4 days without any relief. On the day before admission, left arm numbness and weakness occurred, which lasted for half an hour, followed by slurred speech and difficulty in expression. Considering that stroke could not be ruled out, aspirin and clopidogrel were administered along with ceftriaxone, acyclovir, and valproate.

Upon admission, vital signs were as follows: body temperature 38.9°C, pulse 83 bpm, respiratory rate 19/min, and blood pressure 123/72 mmHg. The patient was somnolent but arousable and responded slowly. The cranial nerve examination was normal, except for red eyes. Motor system examinations revealed left arm paresis graded 4+ on the Medical Research Council (MRC) scale. Kernig's signs were positive, with no neck resistance. There were no abnormalities in the reflex, sensory, or coordination systems. Laboratory tests showed a white blood cell count of 14,300/μL (neutrophils 88.6%), C-reactive protein of 17.6 mg/L, erythrocyte sedimentation rate of 60 mm/h, and procalcitonin within the normal range. Aspirin and clopidogrel were discontinued upon admission to the hospital ward. Ceftriaxone and acyclovir were continued. Lumbar puncture was performed the day after admission, with an opening pressure of 175 mmH_2O. CSF analysis showed 2 leukocytes/μL, 736.5 mg/L of protein, and 50.0 mg/dL of glucose (103 mg/dL of simultaneous blood glucose). CSF adenosine deaminase, occult blood, Gram stain, acid-fast staining, ink staining, tuberculosis, and herpes virus antibodies were all negative. CSF cytology revealed a mixed-cell inflammatory response. CSF metagenomic next-generation sequencing revealed the presence of streptococcus. Contrast-enhanced brain MRI demonstrated an increased enhancement of the pia mater (Figure 3), with no abnormal signals in the brain parenchyma. Abnormal DWI signals were observed in the bilateral auricles (Figure 3). EEG revealed a moderate slow-wave change, which was more pronounced on the right side. Both peripheral blood and CSF autoimmune encephalitis antibody spectrum tests, including anti-N-methyl-D-aspartate receptor (anti-NMDAR), anti-leucine-rich glioma-inactivated 1 (anti-LGI1), anti-contactin-associated protein-like 2 (CASPR2), anti-gamma aminobutyric acid-B receptor ($GABA_BR$), anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1 (anti-AMPAR1), anti-AMPR2, anti-immunoglobulin-like cell adhesion molecule 5 (anti-IgLON5), anti-dipeptidyl-peptidase-like

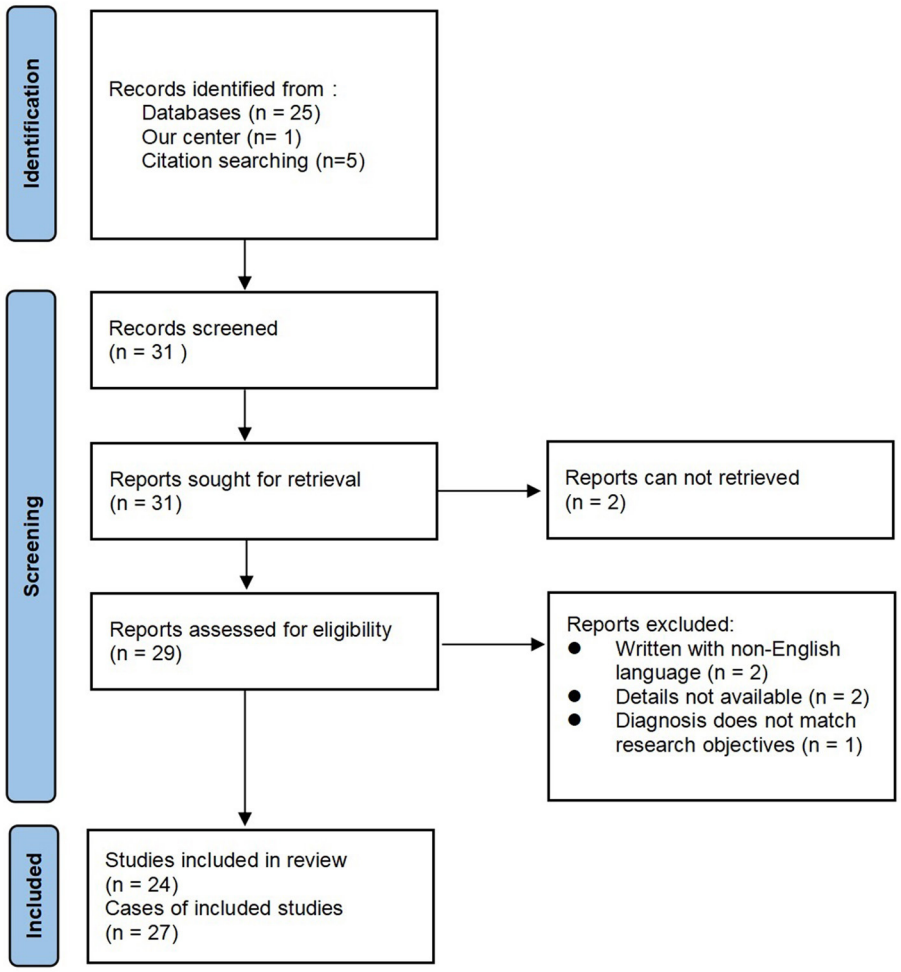

FIGURE 1
Adapted PRISMA 2020 flow diagram.

protein 6 (anti-DPPX), anti-glutamic acid decarboxylase 65 (anti-GAD65), anti-metabotropic glutamate receptor 5 (anti-mGluR5), anti-glycine receptor (GlyR), and anti-R2R, were all negative. The T-SPOT.TB test and IgG4 were also negative.

Although ceftriaxone was administered before admission, consultation with the Infectious Disease Department suggested that bacterial meningitis was not considered. Therefore, meningoencephalitis secondary to RP was suspected. Consultation with the Rheumatology Department yielded a similar opinion as ours.

The patient gradually became drowsy during hospitalization. The paresis of the left arm became severe. His son, who was taking care of him, also developed fever. The coronavirus disease 2019 (COVID-19) nucleic acid test results were positive. Considering the COVID-19 infection, dexamethasone (10 mg/day) was administered intravenously, along with symptomatic treatment for COVID-19. After 2 days of steroid therapy, there was a significant improvement in drowsiness and paresis, with no seizure recurrence. Dexamethasone (10 mg/day) was given for 2 weeks, followed by methylprednisolone at 56 mg/day, which was gradually tapered during follow-up. A follow-up EEG performed 6 months after disease onset was normal, and valproate was therefore discontinued. During the 9-month follow-up, the patient remained well without neurological disorders while continuing with methylprednisolone (current dose, 12 mg/day).

Literature search result

The literature review yielded an additional 26 cases of meningoencephalitis associated with RP from 24 articles (Table 1). There were 22 men and 4 women, and 1 patient did not state the sex. The mean patient age was 53 (range, 25–76) years (Table 2). Only 26% (7/27) of the patients had been diagnosed with RP before the reported neurological event. Most patients (95%, 26/27) had red or deformed ears, while fever was reported in 52% (13/25) of the cases. Various symptoms were reported, including headaches (56%, 15/27), psychiatric symptoms (44%, 12/27), memory or cognitive disturbance (41%, 11/27), cranial nerve symptoms (37%, 10/27), confusion (33%, 9/27), and weakness (19%, 5/27). Brain MRI revealed the presence of parenchymal lesions in 81% (22/27) of the patients, while only nine cases indicated meningeal enhancement.

TABLE 1 Reports of patients with relapsing polychondritis and meningoencephalitis.

References	Age-Sex	RP history	Ear sign	Fever	Neurological symptoms	Seizure (type)	Meningeal	Parenchyma*	CSF Pleocytosis	CSF protein (mg/L)	EEG	Immunotherapy#	Prognosis
Ohta et al. (4)	57 M	N	+	+	Vertigo, hearing loss, headache, memory loss, anxiety, depression	-	-	T	119 (L85%)	860	Diffuse slow wave	mPSL-P, PSL	Improved
Fujiki et al. (5)	45 M	N	+	+	Headache, confusion, euphoria, disorientation forgetfulness	-	-	T	800 (L94%)	860	NA	**PSL**	Improved
	62 M	N	+	-	Memory loss, confusion, euphoria, hearing loss, amnesic	-	-	T	2,400 (L83%)	46,000	NA	mPSL-P, **PSL**	Not improved
Ota et al. (6)	57 M	1 year	+	+	Vertigo, hearing loss, weakness, seizure, delirium, personality change	GTCS	+	-	1,056 (L15%)	690	NA	PSL, mPSL-P, **PSL**	Not improved
Kao et al. (2)	40 M	N	+	+	Headache, confusion	-	-	T, basal	1,500 (L17%)	850	Intermittent slow in the left	mPSL-P, PSL	Improved
Erten-Lyons et al. (7)	51 M	1 year	+	-	Progressive dementia, anxiety, depression, insomnia	Myoclonus	-	Peri-V, DWM	39 (L65%)	890	Normal	PSL, CTX	Declined, died
Imamura et al. (8)	76 F	N	+	+	Decreased speech and voluntary behavior, impaired consciousness, hearing loss	-	-	WM	+	↑	NA	mPSL-P, MTX, CTX	Declined, died
Wang et al. (9)	54 M	N	+	+	Bipolar disorder, headache, memory loss, hallucination, hearing loss	-	-	WM	800 (L95%)	600	Background slow wave	DXM, CTX + mPSL, mPSL-P, **PSL + Aza**	Improved

(Continued)

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TABLE 1 (Continued)

References	Age-Sex	RP history	Ear sign	Fever	Neurological symptoms	Seizure (type)	Meningeal	Parenchyma*	CSF Pleocytosis	CSF protein (mg/L)	EEG	Immunotherapy#	Prognosis
	44 M	N	+	-	Memory loss, anxiety	-	-	T	190 (L90%)	570	NA	mPSL-P, **PSL + Aza**	Improved
	52 M	N	+	+	Headache, memory loss, difficulty in communicating, deafness, gait disorders, urinary incontinence	-	-	-	230 (L29%)	510	NA	DXM, mPSL-P + IVIG, **PSL**, mPSL-P	Improved-recur-improved
Choi and Lee (10)	68 F	2 months	+	-	Dysarthria, impaired language function	-	+	WM	100 (L67%)	416	Moderate (slow wave)	PSL + MTX, mPSL-P, PSL + MTX, **PSL**	Improved
Garcia-Egido et al. (11)	57 M	N	+	+	Headache, seizure, confusion	GTCS	-	Peri-V	700 (L98%)	750	NA	PSL, PSL + CTX/MTX, **PSL + Infliximab**	Recur-improved
Fujiwara et al. (12)	60 M	N	+	NA	Headache, speech impediment, acalculia, agraphia, right-left disorientation, mild right hemiparesis	Focal	+	-	Normal	Normal	NA	**PSL**	Improved
Prinz et al. (13)	63 ?	NA	+	NA	Headache, neuropsychological retardation	-	-	+	Lymphocytic	NA	NA	NA	NA
Nara et al. (14)	39 M	N	+	-	Headache, psychiatric symptoms	-	-	DWM	19 (L100%)	710	NA	PSL, mPSL-P, **PSL**	Improved
Baba et al. (15)	72 M	2 years	+	+	Somnolent, dysarthria, cognitive, hemi spatial neglect	-	-	WM	781 (L13%)	5,820	NA	DXM, PSL, **CTX**	Improved
Jeon (16)	48 F	2 months	+	-	Headache	-	-	C, basal	71 (L58%)	866	NA	mPSL-P	Declined, died
Tsai et al. (17)	44 M	N	+	-	Headache, seizure, confusion, hallucination	+	-	WM	Lymphocytic	NA	NA	mPSL-P + CTX, PSL + CTX, **Aza**	Improved

(Continued)

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TABLE 1 (Continued)

References	Age-Sex	RP history	Ear sign	Fever	Neurological symptoms	Seizure (type)	Meningeal	Parenchyma*	CSF Pleocytosis	CSF protein (mg/L)	EEG	Immunotherapy#	Prognosis
Ducci et al. (18)	69 M	N	+	-	Ataxia, paraparesis, tinnitus, vertigo, confusion, tremor	-	+	-	71 (L97%)	697	NA	PSL, **MTX**	Improved
AI-Tabbaa and Habal (19)	25 M	N	+	-	Hallucination, anxiety, depression	-	+	Peri-V, WM	21 (L81%)	NA	NA	mPSL-P, CTX, PSL, rituximab, **PSL + MTX**	Declined
Cao and Zhang (20)	64 M	N	+	+	Headache, dull response, unsteady gait, paralysis, cognitive decline	-	+	Peri-V	520 (L40%)	770	NA	PSL, mPSL-P + MTX, **MTX**	Improved
Anada et al. (21)	65 M	N	-	+	Drowsy, urinary retention	-	-	Basal	NA	NA	NA	mPSL-P, **PSL**	Improved
Lin et al. (22)	38 M	2 years	+	-	Abnormal behavior, slurred speech, memory loss/aphasia, weakness, impaired vision, diplopia, insaneness	-	-	T, basal	15	533	NA	PSL, mPSL-P, mPSL-P + IVIG, **PSL + MMF**	Improved
Matsumoto et al. (23)	61 M	N	+	+	Headache, confusion, delirium, unable to communicate	Myoclonus	+	basal	189 (L52.6%)	1,990	Poorly organized	DXM, mPSL, **PSL + MTX**	Improved
Lokken and Wang (24)	36 M	N	+	-	Headache, vision loss	-	+	T	NA	NA	NA	Adalimumab + PSL	Died
Yokota et al. (25)	49 M	4 years	+	-	Hearing loss, cognitive impairment	-	-	T, DWM	Normal	540	Diffuse slow wave	PSL, mPSL-P, PSL + CTX, **PSL + MTX**	Improved
Our case	46 M	N	+	+	Seizure, headache, somnolent, slow response, left arm weakness	Focal	+	-	Normal	737	Diffuse slow wave	DXM, **mPSL**	Improved

The cases above are listed according to the published date. Aza, azathioprine; CSF, cerebrospinal fluid; CTX, cyclophosphamide; DXM, dexamethasone; EEG, electroencephalogram; GTCS, generalized tonic-clonic seizure; IVIG, intravenous immunoglobulin; L, lymphocytic; mPLS, methylprednisolone; mPLS-P, methylprednisolone pulse; MMF, Mycophenolate mofetil; MTX, methotrexate; N, no; NA, not available; PLS, prednisolone; RP, relapsing polychondritis. *Basal, basal ganglia area; C, cerebellum; DWM, deep white matter; Peri-V, periventricle region; T, temporal lobe; WM, white matter. #The bold font shows the treatment that the patient was still receiving at the time of the literature report. +Means positive for this item, while − means negative. ?Means sex was stated for this patient. ↑Means protein elevated in this patient, but exact numerical value was not available.

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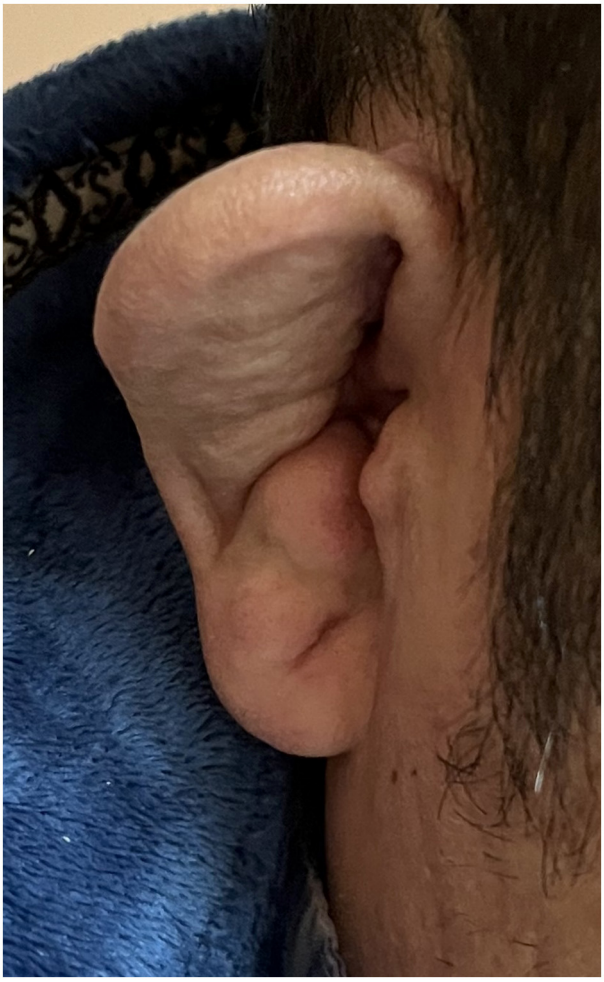

FIGURE 2
Deformed ear.

In CSF analysis, pleocytosis was observed in 88% (22/25) of the patients, with lymphocyte predominance in 75% (15/20). CSF protein elevation was observed in 95% (21/22) of the patients, of whom 85% (17/20) had protein levels between 450 and 1,000 mg/L. Slow-wave changes were the most common EEG result (75%, 6/8), although very few cases have been reported. Steroids were the mainstay of treatment, with 52% (14/27) of the patients receiving immunosuppressive therapy combined with steroids. Improvement was achieved in 73% (19/26) of the patients, with a mortality rate of ∼15% (4/26).

Discussion

Currently, the diagnosis of RP is established clinically by excluding differential diagnoses. There are three diagnostic criteria for RP. Rose et al. evaluated the sensitivities of these different criteria and modified the Michet criteria in 2018 (Table 3). Based on recurrent auricularis, scleritis, and response to steroids, our case fulfilled the Damiani and Levine criteria and the Modified Michet criteria for RP.

Neurological involvement in RP is rare and affects ∼3% of patients; however, it is an important cause of death (3). The pathogenesis of central nervous system (CNS) involvement in RP is still unknown but appears to be related to autoimmunity. Cerebral and meningeal vasculitis have been reported in autopsy cases of RP with meningitis or meningoencephalitis (2, 4, 9). The diagnosis of CNS complications in RP is mainly clinical and challenging because of the varied clinical features.

The onset of meningoencephalitis can precede the diagnosis of RP or occur during a relapse of RP. In our study, we found that only 26% of patients had been previously diagnosed with RP. The diagnosis of RP was first confirmed because of the reported neurological events in most patients. In this situation, the diagnosis of RP is even more challenging owing to its complicated manifestations and the need for additional differential diagnoses. Our study summarizes the clinical characteristics of meningoencephalitis in RP to facilitate its recognition, prompt diagnosis, and treatment.

Previous studies have revealed that the peak age of onset of RP is in the fifth decade of life (2, 9). The mean age of patients with meningoencephalitis in our study was 53 years, which is in line with the age characteristics of RP onset. RP affects both men and women with an equal distribution (2). However, in our study, we found that RP-associated meningoencephalitis predominantly affected men, which is consistent with a previous study (25). It is reported that RP-associated myelodysplastic syndromes are mostly seen in men >60 years of age (1). Another study found that male patients had a higher prevalence of hearing loss, vestibular disorders, and uveitis events (30). However, since the etiology and pathophysiology of RP remain unclear, there is currently insufficient evidence to explain the reasons for this sex distribution difference.

A red or deformed ear is one of the most common and suggestive features of RP and is present in up to 90% of patients during the course of the disease (1). In our study, this sign was present in 96% of the included patients. For the patient in our center, recognition of the deformed ear ultimately led to the diagnosis. The mean delay in RP diagnosis is 2.9 years (9). Our patient had recurrent auricular pustules for more than 1 year before this event without a clear diagnosis. However, the patient may not have met the diagnostic criteria because of the limited involvement of anatomical locations at that point. However, it is crucial to recognize this special and suggestive sign and delve deeply into the diagnosis.

Neurological symptoms are diverse in this group of patients, with headaches, psychiatric symptoms, memory disturbance, hearing loss, and confusion being relatively common. Seizures were reported in only 26% of the patients and were mainly of focal origin. In our case, focal seizures were the initial neurological symptom, which appeared 1 week earlier than the other symptoms. Seizures have also been reported as an initial symptom of RP in a limited number of cases (31). Although seizures are more common in other connective tissue diseases, such as systemic lupus erythematosus, RP should also be included in the differential diagnosis of new-onset seizures, especially those with suggestive signs such as cauliflower ear and/or red eyes.

Brain MRI findings in patients with RP-associated meningoencephalitis include non-specific white matter changes and preferential involvement of the medial temporal lobes (9).

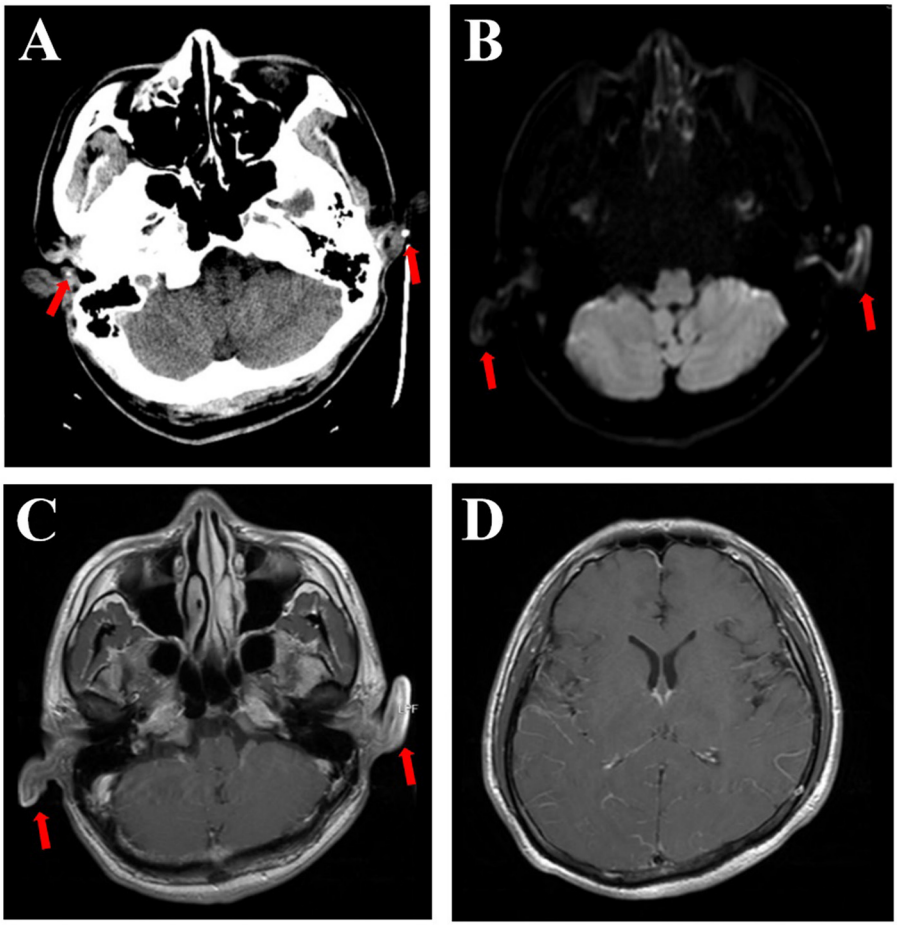

FIGURE 3
Brain CT scan showing calcification (arrows), which can be seen in the polychondritic ears **(A)**. DWI shows abnormal signals in the bilateral auricles (**B**, arrows). T1-weighted MRI with contrast showed abnormal signals and thickening of both ears (**C**, arrows) and increased enhancement of the pia mater **(D)**.

Nine patients have been reported with meningeal enhancement on contrast-enhanced T1-weighted MRI, including those from our center. However, because some cases did not state whether brain MRI was performed with or without contrast, the prevalence of meningeal enhancement was unclear. Calcification and thickening in the ears on CT scans (2, 9) and abnormal DWI and T1-weighted signals in the auricles on MRI scans (9) could also clarify the diagnosis but may easily be neglected.

A CSF analysis is required to rule out infectious diseases and steroid contraindications. In line with a previous study, pleocytosis was common in CSF tests, with a predominance of mononuclear cells (9). A predominance of polymorphonuclear cells was also observed in some cases of marked peripheral inflammation (9). In the cases included in our study, eight patients had a CSF white blood cell count of $>500/\mu L$. Among them, four patients showed pleocytosis with a predominance of polymorphonuclear cells. In this scenario, it is more crucial to fully rule out infectious diseases. An increase in CSF protein levels is also very common, and most patients show a mild elevation. The patient from our center demonstrated a normal CSF cell count and mild protein elevation; however, CSF metagenomic next-generation sequencing revealed streptococcus infection. Given that sufficient intravenous ceftriaxone had been administered for more than 1 week before this CSF study, streptococcus or other bacterial meningitis was not considered.

The treatment of RP is largely empirical owing to its rarity, diversity of symptoms, unpredictable recurrence, and potential CNS involvement (9). High-dose or pulse-range steroids are the mainstays of treatment. High-dose steroids should be started immediately when RP is complicated by meningoencephalitis (4). For patients who did not respond to steroids or experienced recurrence during steroid tapering, immunosuppressants such as cyclophosphamide, methotrexate, azathioprine, and mycophenolate mofetil were added. Biologics, such as infliximab (11), rituximab (19), and adalimumab (25), have also been used in a few severe cases with various prognoses. Some studies have suggested that the combined use of methylprednisolone pulse therapy and immunosuppressants is effective in improving prognosis (25). The reported mortality rate of RP-associated meningitis was 12% (3/25) and that of patients with RP-associated encephalitis was 36.4% (4/11) (11). For patients with RP-associated meningoencephalitis in our study, the reported mortality rate

TABLE 2 Clinical characteristics of patients with meningoencephalitis complicated in relapsing polychondritis.

	n/N (%)
Mean age, y (SD)	53 (12)
Sex	
Male	22/26 (85%)
Female	4/26 (15%)
Previously diagnosed with RP	7/27 (26%)
Symptoms and signs	
Cauliflower ear	26/27 (96%)
Fever	13/25 (52%)
Seizure	7/27 (26%)
Headache	15/27 (56%)
Psychiatric symptoms	12/27 (44%)
Memory/cognition disturbance	11/27 (41%)
Cranial nerve symptoms	10/27 (37%)
Confusion	9/27 (33%)
Weakness	5/27 (19%)
Brian MRI	
Meningeal enhancement	9*
Parenchymal lesion	22/27 (81%)
CSF pleocytosis	22/25 (88%)
>500/μL	8/25 (32%)
Lymphocyte predominant	15/20 (75%)
CSF protein elevation	21/22 (95%)
450~1,000 mg/L	17/20 (85%)
EEG	
Slow wave change	6/8 (75%)
Prognosis	
Improved	19/26 (73%)
Not improved or declined	7/26 (27%)
Mortality	4/26 (15%)

*Percentage was not calculated as many case reports did not state whether brain MRI was performed with or without contrast. For patients with multiple CSF study results, the one performed during the reported neurological event, or the latest one before steroid use, was included in the analysis. Psychiatric symptoms included anxiety, depression, bipolar disorder, hallucination, euphoria, and delirium. CSF, cerebrospinal fluid; EEG, electroencephalogram; MRI, magnetic resonance imaging; RP, relapsing polychondritis; SD, standard deviation.

TABLE 3 Diagnostic criteria of relapsing polychondritis.

McAdam et al. (26) (three out of six)	1) Recurrent bilateral auricular chondritis 2) Non-erosive seronegative inflammatory polyarthritis 3) Nasal chondritis 4) Ocular inflammation 5) Respiratory tract chondritis 6) Cochlear and/or vestibular damage
Damiani and Levine (27) (any of these)	1) Three out of six McAdam's criteria 2) One out of six McAdam's criteria + positive histology 3) Two out of six McAdam's criteria + response to corticosteroid or dapsone
Michet et al. (28) (any of these)	1) Inflammation in two out of three cartilages: auricular, nasal, and laryngotracheal 2) Inflammation in one of the above + meeting two other signs of ocular inflammation, hearing loss, vestibular dysfunction, or seronegative inflammatory arthritis
Modified Michet's criteria (any of these) (29)	1) Inflammation in two out of four sites: auricular, nasal, laryngotracheal, and ocular inflammation 2) Inflammation in one of the above + meeting two other signs hearing loss, vestibular dysfunction, seronegative inflammatory arthritis, or dermatologic and cardiovascular manifestation

was 15% (4/26), with an improvement in 75% (19/26) of the patients. Relapse of RP is common, and therefore, close follow-up is essential for the timely adjustment of the treatment plan. Considering that the patient in our center had COVID-19, steroid pulse therapy was not initiated. Dexamethasone (10 mg/day), which is the recommended steroid regimen for COVID-19, was administered. We were initially very concerned that our immunosuppressive regimen was not strong enough because the patient was gradually declining and very lethargic before the steroid treatment. Fortunately, the patient showed immediate improvement. However, considering the normal CSF cell count and the absence of abnormal parenchymal signals, CNS inflammation in our patient may not have been severe. Therefore, clarifying factors such as peripheral blood inflammation indicators, results of CSF analysis, or neuroimaging findings that may help predict prognosis and guide immunosuppressant selection is an important factor that deserves further research.

This study has several limitations. First, the diagnoses of encephalitis, meningitis, and meningoencephalitis may overlap and be easily confused. Therefore, in our study, we only included cases that were clearly diagnosed with meningoencephalitis. Second, only studies published in English were included, and the sample size was relatively small. Third, a biopsy was not performed on our patient; therefore, we were unable to make a histopathological diagnosis.

Conclusion

Meningoencephalitis associated with RP is rare but fatal. Our study found that it predominantly affects men, with red or deformed ears being the most common and suggestive feature, although the symptoms can vary. Abnormal parenchymal signals and/or meningeal enhancement can be observed on brain MRI. CSF lymphocytic pleocytosis with mild protein elevation was observed in most of the patients. Recognition of disease characteristics is important because immunosuppressive therapy

is effective and should be initiated without delay to achieve a satisfactory prognosis.

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.

Author contributions

DZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Visualization, Writing – original draft, Writing – review & editing, Investigation. JS: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. XZ: Data curation, Investigation, Methodology, Writing – review & editing. JW: Project administration, Resources, Supervision, Writing – review & editing. YS: Formal analysis, Project administration, Supervision, Writing – review & editing.

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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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Treating seronegative neuromyelitis optica spectrum disorder with inebilizumab: a case report

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Background: Neuromyelitis optica spectrum disorder (NMOSD) is a devastating inflammatory disease of the central nervous system that is often severely disabling from the outset. The lack of pathognomonic aquaporin 4 (AQP4) antibodies in seronegative NMOSD not only hinders early diagnosis, but also limits therapeutic options, in contrast to AQP4 antibody-positive NMOSD, where the therapeutic landscape has recently evolved massively.

Case presentation: We report a 56-year-old woman with bilateral optic neuritis and longitudinally extensive myelitis as the index events of a seronegative NMOSD, who was successfully treated with inebilizumab.

Conclusion: Treatment with inebilizumab may be considered in aggressive seronegative NMOSD. Whether broader CD19-directed B cell depletion is more effective than treatment with rituximab remains elusive.

KEYWORDS

NMOSD, inebilizumab, AQP4, longitudinally extensive transverse myelitis, optic neuritis, case report, CD19, seronegative

Introduction

Neuromyelitis optica spectrum disorder (NMOSD), characterised by acute optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM), is a rare autoimmune disease of the central nervous system. Compared with patients with multiple sclerosis, NMOSD patients tend to be older at onset, have more severe relapses, and remission is often incomplete, resulting in rapid progression of disability, highlighting the need for effective therapies. Relapse-independent accumulation of disability is rare. In most patients, a pathognomonic antibody against the water channel aquaporin 4 (AQP4) can be detected. Notably, myelin oligodendrocyte glycoprotein (MOG) antibodies can be detected in a subset of patients who are AQP4 antibody negative, suggesting a separate and well-defined disease entity that shares the clinical phenotype known as MOG antibody disease (1).

AQP4 is highly expressed on astrocytic end feet lining the abluminal cerebral vasculature. Binding of AQP4 antibodies (Ab) triggers an inflammatory response involving immune cell infiltration and activation of the classical complement pathway, culminating in the formation of a membrane attack complex and demyelinating lesions (2). Regions of high AQP4 expression (grey matter of the spinal cord, optic nerve) are clinically most

affected. With the recent development of targeted monoclonal antibodies, including terminal complement inhibition (3), interleukin-6 pathway blockade (4, 5) and CD19-directed B cell depletion (6), the therapeutic landscape has certainly changed. While these drugs are approved for AQP4-positive NMOSD, none of the trials were designed to test efficacy in seronegative patients, who represent 20% of NMOSD patients.

Inebilizumab (INE) is an afucosylated IgG1 antibody directed against CD19. This modification of the Fc region results in optimised affinity for the Fc gamma receptor IIIA on leukocytes, significantly enhancing B-cell depletion due to increased antibody dependent cellular cytotoxicity (7). INE is given intravenously (induction with two infusions of 300 mg at day 1 and 15, maintenance therapy 300 mg every 6 months) and therefore has a high bioavailability. Given its size, INE is unlikely to penetrate the parenchyma as long as the endothelial barrier is intact. In contrast to CD20, CD19 is additionally expressed on pro-B cells, plasma blasts and plasma cells. By targeting a broader range of B cell subsets, INE is thought to cause more complete and rapid B cell depletion than traditional CD20 antibodies such as rituximab and ocrelizumab.

Interestingly, a post-hoc analysis of the double-blind, randomised, placebo-controlled phase 2/3 N-MOmentum trial suggests a treatment effect of INE in seronegative NMOSD. In this subgroup analysis by Marignier et al. 6 double seronegative patients showed a reduction in relapses at the individual level, although this was limited by the small sample size and did not withstand statistical testing (8).

To our knowledge, we are the first to report the successful treatment of a patient with seronegative NMOSD with the CD19 antibody INE in a real-world setting.

Case description

A 56-year-old female patient was initially admitted to a secondary care centre. Her medical history included arterial hypertension, type 2 diabetes mellitus and breast cancer undergone full remission following treatment more than 15 years ago. The patient had just returned from a pilgrimage when she noticed a subacute sensorimotor deficit in her left hand. Initially physicians suspected a stroke, but the brain magnetic resonance imaging (MRI) showed no signs of acute or subacute ischemia or inflammation. She was admitted for further diagnostic evaluation. The next day she complained of blurred vision with no reported loss of visual acuity at that time. Over the next 3 days there was a marked clinical deterioration: The patient developed a vesiculopapular rash with secondary clustered crustation on her neck, ear and décolletage (Figure 1A) and became increasingly agitated and confused. Cerebrospinal fluid (CSF) examination revealed a mild pleocytosis of 10 [0–4] /µl. Empirical antiviral treatment with aciclovir was started on suspicion of herpes zoster encephalitis. However, subsequent polymerase chain reaction testing of the CSF was negative for varicella-zoster, herpes simplex and other neurotropic viruses. A follow-up cerebral MRI revealed a right parahippocampal T2 lesion that was not evident on the initial MRI (Figures 1B,C). In addition, there were T2 hyperintense lesions in both optic nerves, which were consistent with optic neuritis (Figure 1D). At this point the patient was referred to our tertiary care facility.

Here the patient was diagnosed with blindness in the right eye, severe reduction of visual acuity in the left eye (<0.1) and a marked ataxic tetraparesis. The rash, misdiagnosed as herpes zoster, turned out to be self-induced excoriation caused by the patient's own fingers in an attempt to relieve a perceived severe burning and itching over the skin, which we attributed to a central pain syndrome, probably the cause of the agitation.

MRI of the spinal cord revealed spinal cord T2 hyperintense lesion locations and extension compatible with transverse myelitis (Figures 1E,F). A follow-up spinal tap was negative for oligoclonal bands. Chest/lung computed tomography scan revealed no evidence of pulmonary sarcoidosis. Initial testing for anti-AQP4 and anti-MOG antibodies was performed 12 days after clinical onset and prior to immunotherapy. Sera were analysed by cell-based indirect immunofluorescence at EUROIMMUN (Lübeck, Germany); staining at serum dilutions ≥1:10 was considered positive. Assays were negative at that time and at follow-up (Table 1). In contrast to AQP4-Ab-positive NMOSD, the diagnostic criteria for seronegative NMOSD are far more complex and require the presence of ≥2 core criteria, at least one of which must be ON, LETM or area postrema syndrome. Additional MR criteria must also be met. In our case, the patient had two core clinical features (bilateral ON and LETM) with brain MRI showing extensive (>1/2 optic nerve length) T2 hyperintense lesions of both optic nerves, a white matter lesion not suggestive of MS and acute myelitis involving more than 3 contiguous segments. In addition, differential diagnoses were ruled out as far as possible by repeated serological and CSF analysis. Thus, we diagnosed seronegative NMOSD according to the 2015 revised criteria of the International Panel for NMO Diagnosis (9). We started treatment with high-dose intravenous methylprednisolone at 1 g per day for 5 consecutive days. Due to lack of improvement, 7 sessions of plasma exchange were performed every other day with concomitant oral prednisolone therapy (60 mg/d) and prolonged tapering. The concomitant medications at that time were pantoprazole, L-thyroxine, liraglutide, basal insulin, naloxegol, pregabalin and mirtazapine.

Given the recently approved therapies for AQP4-positive NMOSD and the fulminant onset of the disease, we decided to start INE as an off-label use. Administration of 300 mg on days 1 and 15 was well tolerated with no immediate or subacute adverse events. Prior to discharge to a rehabilitation clinic, the patient could recognise the basic shapes of most everyday objects with her left eye and was able to stand with much assistance.

At a follow-up visit 3 months later, the patient reported being able to walk up to 500 m with a walker. The right eye remained blind, colour vision had returned to the left eye, but she was still unable to read a newspaper. A brain MRI showed a new inflammatory T2 lesion in the left frontal white matter, possibly representing paraclinical disease activity before the immunotherapy could take full effect. Prednisolone was reduced from 20 mg to 5 mg/d. When we administered the second cycle of INE at the six-month follow-up, there were no new cerebral lesions and the inflammatory cervical myelopathy decreased in volume (Figures 1G,H). Walking was unrestricted; unfortunately, the visual impairment remained unchanged. Clinical stability was maintained after 12 months of treatment. A synopsis of the clinical course is shown in Figure 2.

Discussion

First, our case illustrates that the potpourri of symptoms in NMOSD can be misleading, especially at the onset of the disease and for physicians unfamiliar with inflammatory disorders of the central

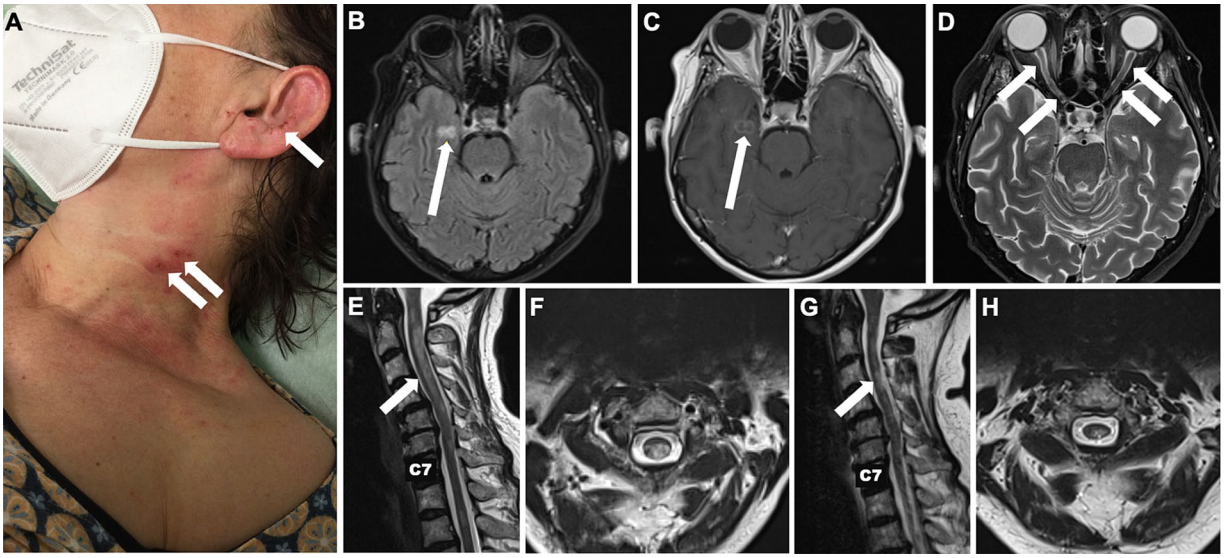

FIGURE 1
Skin changes and longitudinal MRI of brain and spinal cord. Localised painful rash with crusts on the neck and lateral face initially due to *repetitive scratching* in central neuropathic pain syndrome initially misdiagnosed as herpes zoster reactivation **(A)**. Cerebral T2-weighted FLAIR MRI showing a new hyperintense parahippocampal lesion that evolved within 6 days from symptom onset **(B)** and presented gadolinium enhancement **(C)**. T2 hyperintense lesions in both optic nerves consistent with optic neuritis **(D)**. Hyperintense spinal cord lesions compatible with cervical longitudinally extensive transverse myelitis reaching from the atlas to the 6th vertebra upon admission to our tertiary care centre **(E,F)** and after 6 months **(G,H)**.

TABLE 1 Dynamics of the laboratory findings at our tertiary care centre before and during INE therapy.

	Before high dose GC	Before induction of INE	3-month FU	6-month FU/second administration of INE	12-month FU/third administration of INE
Anti-AQP-4-Ab	Negative	Negative	Negative	–	–
Anti-MOG-Ab	Negative	–	Negative	–	–
IgG (mg/dl)	872	549	–	587	615
B cells (CD 19+)	–	22%	0.2%	0.0%	0.0%
T cells (CD3+)	–	72%	68%	75%	87%
Leukocytes *10^1000 γl	7.6	8.2	14.5	12.3	11.7
Neutrophils *10^1000 γl	5.06	5.26	12.39	10.06	9.01
Lymphocytes *10^1000 γl	1.80	2.27	0.70	1.02	1.30
Monocytes *10^1000 γl	0.61	0.47	0.71	0.97	1.07
CSF cells/mm^3	13	3	–	–	–
CSF OCB	Negative	Negative	–	–	–

AQP-4-Ab, aquaporin-4 antibody; CSF, cerebrospinal fluid; FU, follow-up; GC, glucocorticoids; IgG, immunoglobulin G; INE, inebilizumab; MOG-Ab, myelin oligodentrocyte glycoprotein antibody; OCB, oligoclonal bands.

nervous system. This is problematic because of the aggressive nature of the disease, where disabling clinical events require immediate and equally aggressive treatment (10). In this case, diagnosis was delayed by the lack of availability of an immediate MRI and neurological expertise in the secondary care clinic.

Besides diagnostic uncertainty due to lack of AQP4 antibodies, the case highlights the unmet need for tailored on-label therapies for patients with seronegative NMOSD.

Due to the severe first relapse, we hypothesised that this patient might benefit from the broader and rapid B cell depletion induced by INE: its effect can be seen within a week of administration. Although INE has only a half-life of about 18 days as it is eliminated by the reticuloendothelial system the effect of B cell depletion lasts for months (11, 12). By targeting CD19, INE also covers plasma blasts and plasma cells, as well as pro-B cells that do not express CD20 and would therefore be spared by rituximab. In fact, with regards to seropositive NMOSD, AQP4 antibodies have been shown to be secreted by a subpopulation of CD19-positive, CD20-negative plasma blasts that are increased during relapses in NMOSD patients (13).

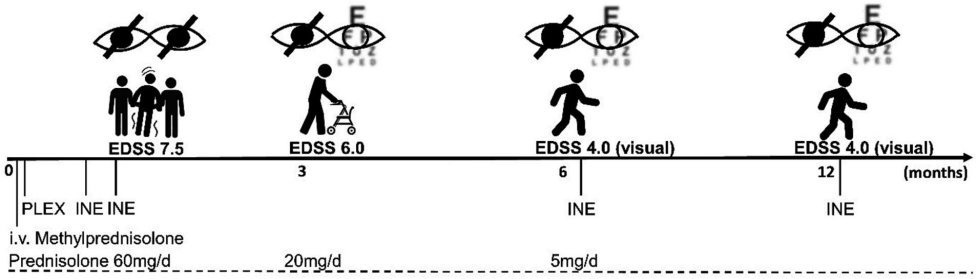

FIGURE 2
Timeline of the disease course. After initial high-dose i.v. methylprednisolone therapy, seven plasma exchange sessions (PLEX) were performed, and concomitant prednisolone was tapered to a dose of 5 mg/d over 6 months. The first cycle of INE infusions was administered a few days after PLEX, with a 14-day interval. The overall EDSS improved from 7.5 to 4.0 at 6 months and remained stable over the 12-month follow-up period, with persistent deficits mainly representing visual impairment.

In addition to antibody production, B cells can promote inflammation through cytokine secretion and as antigen-presenting cells, so broader depletion of autoreactive B cell populations by INE may also be more effective in seronegative NMOSD. Such superiority may be suggested by data from a further subgroup analysis of the N-MOmentum trial showing a reduction in relapse rate in patients with disease activity on rituximab after switching to INE. However, although including seronegative cases these patients were predominantly AQP4 Ab-positive (14). A comprehensive role for B cells in pathophysiology of NMOSD besides antibody production is supported by results of studies investigating interleukin-6 signalling pathways on NMOSD putting the relevance of plasma blasts in perspective: While Tocilizumab reduced relapse risk in seronegative and seropositive patients (15), Satralizumab was not beneficial in seronegative subgroup analysis (4). This suggests the relevance of additional pro-inflammatory pathways affecting disease activity as discussed above.

Conclusion

To our knowledge, this is the first report of successful treatment with INE in a patient with double seronegative NMOSD outside of clinical trials. Although our experience with INE is encouraging, larger case series are clearly needed to show whether the presumed superiority of broader B cell depletion over earlier agents such as rituximab outweighs the additional cost. Randomised therapy trials focusing on seronegative NMOSD are tempting but are unlikely to yield reliable conclusions due to the inherent heterogeneity of the disease. Given the central role of B cells in the pathophysiology of NMOSD, it may be a reasonable option for physicians to consider (off-label) use of INE in patients with seronegative NMOSD, especially those with severe inflammation.

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

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

DL: Writing – original draft, Writing – review & editing. NZ: Writing – original draft, Writing – review & editing. MP: Writing – original draft, Writing – review & editing. MKS: Writing – original draft, Writing – review & editing. AH: Writing – original draft, Writing – review & editing.

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Conflict of interest

AH received speaker fees and travel grants from and served on advisory boards for Alexion Pharmaceuticals, Argenx, Horizon Therapeutics and UCB.

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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Case report: A case of primary angiitis of the central nervous system: misdiagnosed for 3.5 years

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Introduction: Primary angiitis of the central nervous system (PACNS) is an uncommon inflammatory condition that exclusively affects blood vessels within the brain parenchyma, leptomeninges, and spinal cord. Due to its infrequency and the variability in its clinical presentation and imaging findings, diagnosing PACNS can be challenging.

Case description: In this study, we present the case of a teenager who initially presented with headaches and epilepsy. Comprehensive laboratory tests yield normal results. A series of brain magnetic resonance imaging (MRI) revealed a progression of changes, starting from localized cerebral atrophy and culminating in the development of a contrast-enhanced mass with vasogenic edema. Immune-associated encephalitis and mitochondrial encephalopathy were suspected, but immunologic investigations, mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) sequencing using biopsied muscle, and muscle pathologies were all negative. Ultimately, a diagnosis of PACNS was confirmed through a stereotactic brain biopsy, which took place 3.5 years after the onset of symptoms. The patient responded favorably to treatment with glucocorticoids and cyclophosphamide.

Conclusion: In summary, we have described a case of PACNS characterized by localized cerebral atrophy and tumor-like MRI findings, who was misdiagnosed as immune-associated encephalitis or mitochondrial encephalopathy for 3.5 years. We emphasize the importance of dynamic observation of MRI changes, as well as brain biopsy.

KEYWORDS

PACNS, serial MRIs, tumor-like presentation, brain biopsy, mitochondrial encephalomyopathy, misdiagnosis

Introduction

Primary angiitis of the central nervous system (PACNS) is a rare condition associated with high levels of disability and mortality. Its clinical presentation varies significantly depending on the size of the affected blood vessels in the brain and spinal cord, encompassing symptoms such as headaches, altered cognition, focal deficits, seizures, and visual disturbances, among others. In the United States, the estimated average incidence rate stands at 2.4 cases per 1,000,000 person-years (1). People of all ages can be susceptible to PACNS. Notably, PACNS may manifest distinctive imaging features, which can include normal findings, multiple infarctions, hemorrhages, microbleeding, demyelination, unique or multiple contrast-enhanced masses, and meningeal thickening (2). These imaging findings may resemble cerebrovascular diseases,

Rasmussen encephalitis, mitochondrial encephalomyopathy, neoplasms, and more. Due to its low incidence, wide range of clinical presentations, and significant variations in neuroimaging, identifying PACNS can be challenging. Biopsy remains a critical diagnostic tool; however, many clinicians are apprehensive about its invasive nature and the possibility of not sampling affected tissue, particularly in pediatric patients.

In this context, we present the case of a 16-year-old girl with a 3.5-year history of recurring headaches and epilepsy. Due to atypical clinical manifestations and nonspecific MRI findings, she was misdiagnosed for a very long time. Final diagnosis of PACNS was confirmed through histological analysis, which revealed lymphocytic vasculitis. In summary, we underscore the importance of considering PACNS as a potential diagnosis in teenagers with epilepsy who exhibit brain lesions on magnetic resonance imaging (MRI) scans.

Case description

A 16-year-old girl, without any significant family medical history, presented with a three-and-a-half-year history of headaches and epilepsy. The initial manifestation was a tic in her left eyelid, which subsequently spread to her left oral region, left upper limb, and left lower limb, eventually affecting both limbs. Alongside these motor symptoms, she also experienced episodes of altered consciousness. No family history or significant medical history were reported, except her motor skills are poorer compared to her peers. Her neurological examination yielded normal results. Comprehensive laboratory tests, including blood gas analysis, routine blood counts, chemistry panel, liver function tests, kidney function assessment, and ammonia levels, all returned unremarkable results. Lactate acid in blood at rest was normal (0.91 mmol/L, normal: 0.7–2.2 mmol/L). Notably, her serum homocysteine levels were slightly elevated at 21.05 μmol/L (normal range: 5–15.0 μmol/L), though this finding had limited clinical significance. Extensive infectious evaluations, including cerebrospinal fluid analysis, HIV, and treponema pallidum testing, along with an autoimmune encephalitis panel, revealed no abnormalities. Additionally, autoimmune serologic tests, such as antinuclear, anticardiolipin, ANCA, rheumatoid factor, and antineuronal antibodies, were all negative. Her endocrine evaluations yielded normal results. Electroencephalography demonstrated asymmetric slow waves on the right side, interspersed with sharp waves, particularly in the frontotemporal region. A T2-weighted MRI obtained 1 year after the onset of symptoms displayed hyperintensity in the frontoparietal lobes, along with localized cerebral atrophy. This lesion exhibited hypointensity on diffusion-weighted imaging (DWI) and hyperintensity on the apparent diffusion coefficient (ADC) map (Figures 1A1–E1).

Immune diseases were actively sought but no evidence found. However, doctors cannot definitively exclude this possibility. A brain biopsy was considered. However, due to its invasive nature, her parents declined the brain biopsy in favor of diagnostic immunotherapy. Then, the girl underwent treatments with immunoglobulin (0.4 g/Kg per day for 5 days) and rituximab (0.6 g per 6 months) successively. Her symptoms were initially controlled, but soon relapsed. Mitochondrial encephalomyopathy was considered at another hospital due to the clinical presentation and findings on brain MRI. Consequently, a muscle biopsy was conducted. However, no specific changes indicative of mitochondrial encephalopathy, such as damaged red blood cells, were observed under a light microscope. Furthermore, both mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) sequencing using biopsied muscle failed to reveal any pathogenic variants associated with mitochondrial encephalopathy, effectively ruling out this possibility.

Serial MRI assessments were performed every 6 months. A subsequent MRI, conducted 3.5 years after symptom onset, revealed a right frontal lesion that exhibited hypointensity on T1-weighted imaging (T1 WI), hyperintensity on T2-weighted imaging (T2 WI) and FLAIR, along with enhancement on contrast-enhanced MRI (Figures 1A2–E2). Magnetic resonance spectroscopy (MRS) indicated an increased choline/creatinine ratio within the lesion (Figure 1G). MR angiography (MRA) did not reveal any involvement of large-or medium-sized blood vessels (Figure 1H). FDG-PET scans revealed atrophy in the right frontal lobe, right temporo-insula, right parietal, and right occipital cortex, along with multiple calcifications and reduced glucose metabolism, predominantly in the right frontal lobe and right temporo-insula (Figures 1I,J). To make a definite diagnosis, stereotactic brain biopsy was performed. Histological analysis revealed lymphocytic vasculitis (Figure 2). Previous extensive diagnostic work-up has ruled out secondary causes of CNS vasculitis, such as systemic vasculitis, infections, neoplasms. So, PACNS was confirmed. Subsequently, the patient received treatment with intravenous methylprednisolone pulses, starting at 500 mg per day and reducing the dose by half every three days. This was followed by a three-month course of gradually tapered oral glucocorticoids, combined with monthly intravenous cyclophosphamide at a dose of 0.4 g. At the six-month follow-up, there was no evidence of relapse. A time course of events can be found in Figure 3.

Discussion

PACNS is an uncommon inflammatory condition primarily affecting various sizes of blood vessels within the central nervous system (CNS), and it manifests with a wide range of clinical symptoms, including seizures, cognitive impairment, altered consciousness levels, and focal neurological deficits. The specific features of the disease can vary depending on the predominant size of the affected brain vessels. In a study conducted in 2016, Boysson et al. compared the characteristics of PACNS patients with isolated small-vessel involvement to those with large/medium-vessel involvement. They discovered that patients with isolated small-vessel PACNS tended to be younger and presented with a higher frequency of seizures, cognitive impairment, altered consciousness, and dyskinesias, although they experienced fewer strokes at the time of diagnosis (3, 4). Our current case, involving a teenager presenting with headache and epilepsy, aligns with the findings mentioned above.

MRI imaging in PACNS can display a variety of patterns, including normal findings, multiple infarctions, hemorrhages, microbleeds, areas of demyelination, solitary or multiple contrast-enhanced masses accompanied by perilesional edema and mass effect, as well as meningeal thickening, among others (2). Cortical atrophy was identified in some patients (5). But the pathogenesis of atrophic changes is poorly understood. We speculate that the cerebral atrophy may be attributed to secondary ischemic and hypoxic changes in neuronal cells and demyelination of nerve fibers, both consequent to

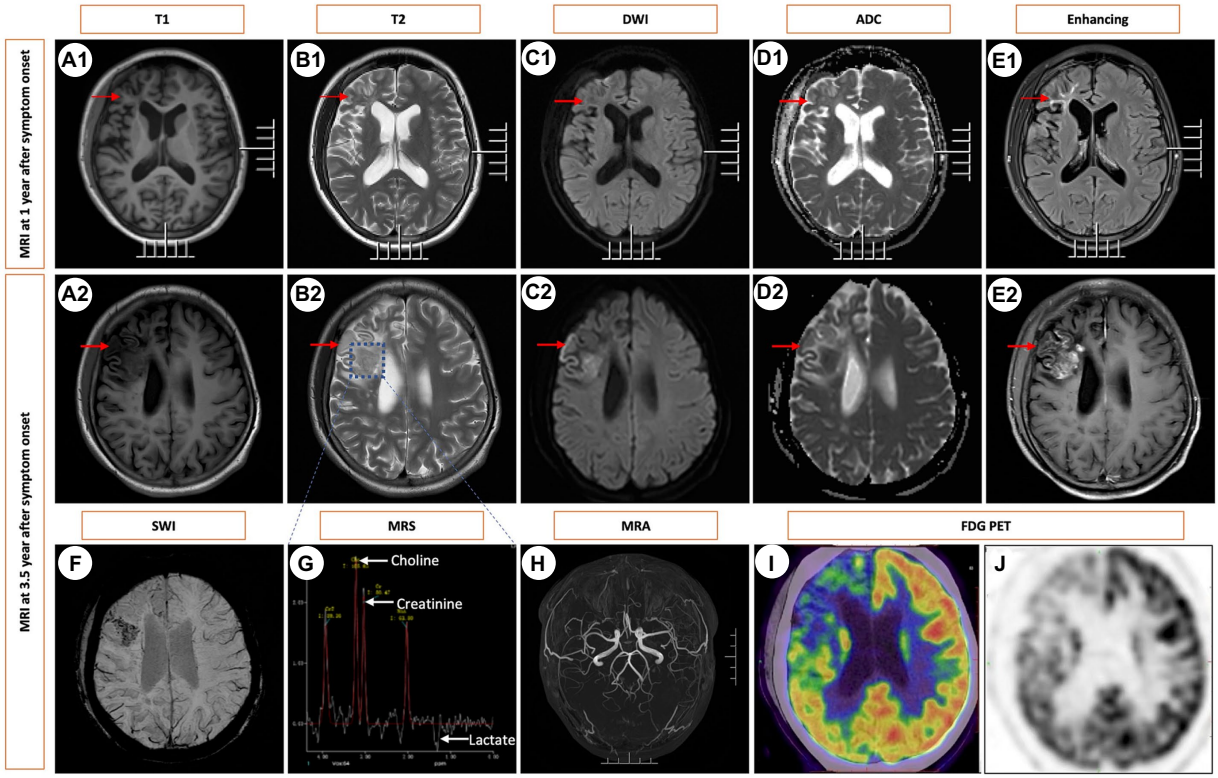

FIGURE 1
Sequential Brain MRIs Following Symptom Onset. Brain images obtained at 1 year **(A1–E1)** and 3.5 years after the onset of symptoms **(A2–E2)** and **(F–J)**. T1-weighted MRI revealed hypointense white matter lesions in the frontoparietal lobes (indicated by arrowheads) along with localized cerebral atrophy **(A1)**. This lesion exhibited hyperintensity on T2 WI **(B1)**, hypointensity on DWI **(C1)**, and hyperintensity on the ADC **(D1)**, along with enhancement on contrast-enhanced MRI **(E1)**. At the 3.5-year mark from symptom onset, a solitary mass was identified in the right frontal lobe, exhibiting hyperintensity on T2 WI and contrast enhancement following gadolinium injection, accompanied by edema but without any mass effect. The corresponding images are shown in A2-E2. SWI showed microbleeds within the mass **(F)**. MRS indicated an increased choline/creatinine ratio within the lesion **(G)**. MRA did not reveal any vascular abnormalities **(H)**. FDG-PET scans revealed atrophy in the right frontal lobe, right temporo-insula, right parietal, and right occipital cortex, along with multiple calcifications and reduced glucose metabolism, predominantly in the right frontal lobe and right temporo-insula **(I,J)**. T1, T1-weighted imaging. T2, T2-weighted imaging. DWI, diffusion-weighted imaging. ADC, apparent diffusion coefficient. SWI, susceptibility weighted imaging. MRS, magnetic resonance spectroscopy. MRA, magnetic resonance angiography. FDG PET-CT, ^{18}F-fluorodeoxyglucose PET-computed tomography.

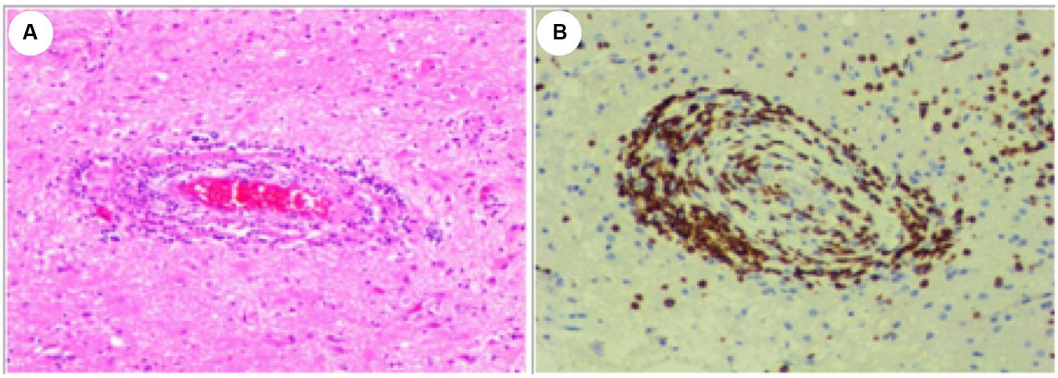

FIGURE 2
Histological Examination of the Lesion. **(A)** Hematoxylin and eosin (HE) stain. **(B)** CD3 positive. The examination revealed dense perivascular chronic inflammation characterized by the presence of lymphocytes. Lymphocytes predominantly infiltrated and disrupted the walls of small blood vessels. Original magnification×100.

vasculitis. Further investigation is warranted to elucidate the pathogenetic mechanisms. MRI manifestations can often resemble conditions such as cerebrovascular diseases, Rasmussen encephalitis, mitochondrial encephalomyopathy, neoplasms, and more. Therefore, it's very easy to misdiagnose this condition in clinical practice. In the early stages of our patient's illness, MRI showed infiltrative white

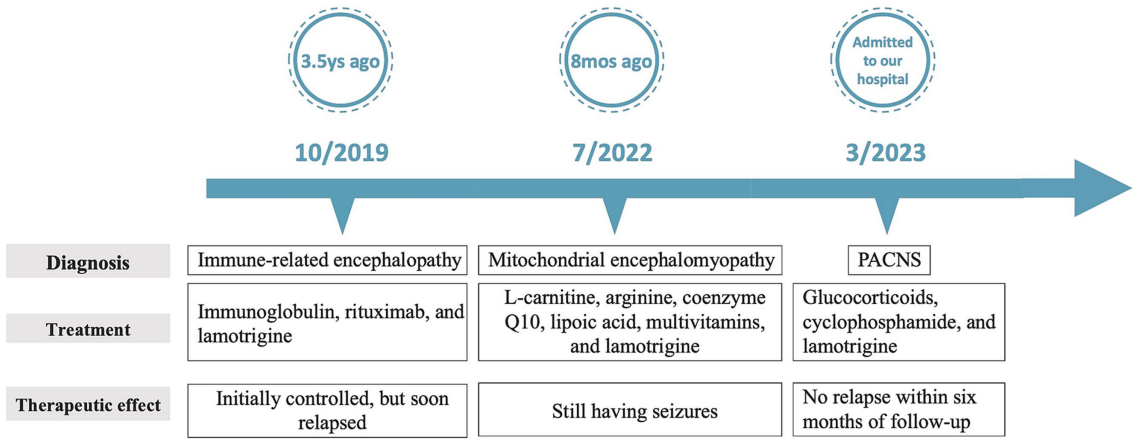

FIGURE 3
A time course of events.

matter lesions, coupled with localized cerebral atrophy. However, at the 3.5-year mark from symptom onset, the MRI indicated a solitary contrast-enhanced mass with vasogenic edema. It indicates the importance of dynamic observation of MRI changes.

A tumor-like presentation is a rare occurrence in PACNS, accounting for approximately 11.76% of cases as reported previously (4). This specific presentation of PACNS is primarily associated with involvement of small-sized blood vessels. Consequently, the clinical profile of patients with a tumor-like presentation of PACNS closely resembles that of PACNS patients with isolated small-vessel involvement. Previous research findings have indicated that patients with a tumor-like presentation of PACNS typically exhibit predominant involvement of small-sized blood vessels. This aspect often necessitates pathological confirmation because conventional vascular imaging techniques, such as MRA and computed tomography angiography (CTA), typically yield negative results (4). Digital subtraction angiography (DSA) is a helpful study in the imaging of PACNS, especially in PACNS with the medium and smaller arteries involvement. However, vasculopathy shown in DSA cannot be differentiated from noninflammatory etiologies. High resolution vessel wall MRI (VW-MRI) is emerging as a valuable tool for distinguishing between causes of intracranial arterial narrowing. In PACNS, VW-MRI typically reveals uniform, smooth enhancement and thickening of the affected arteries. Beyond differentiating PACNS from conditions like atherosclerosis or Reversible Cerebral Vasoconstriction Syndrome, VW-MRI can also guide the selection of the most affected vessels for tissue biopsy, potentially improving diagnostic accuracy (5–7). Histological studies have shown that a lymphocytic vasculitis pattern is more commonly observed in these cases. This indicates that the clinical presentation, MRI findings, and pathological features of PACNS correspond to each other and largely depend on the size of the affected blood vessels.

The diagnosis of PACNS is established by considering isolated neurological symptoms, evidence of brain vessel involvement on neurovascular imaging, or a CNS biopsy, and by ruling out all conditions that may mimic or contribute to CNS vasculitis (8). Biopsy remains the gold-standard method for achieving a definitive diagnosis, as it provides direct evidence of vascular involvement. In this case report, this adolescent presented with a combination of symptoms, including headaches, epilepsy, and focal hemispheric lesions displaying unilateral asymmetry. Initially, although lactate acid in blood at rest was normal, mitochondrial encephalomyopathy was still considered due to the clinical presentation and findings on brain MRI. However, muscle pathologies of the patient did not show specific changes indicative of mitochondrial encephalopathy, such as damaged red blood cells. In addition, both mtDNA and nDNA sequencing failed to reveal any pathogenic variants associated with mitochondrial encephalopathy, effectively ruling out this possibility. Additionally, the MRI's tumor-like presentation and an increased choline/creatinine ratio observed in the lesion on MRS raised suspicion of neoplastic involvement. Given the challenges in distinguishing between malignant neoplasms and tumor-like PACNS before biopsy, histological confirmation became imperative. A stereotactic brain biopsy of the right frontal region was performed, revealing a dense perivascular chronic inflammation characterized by lymphocytic infiltration. This infiltration was accompanied by local brain tissue necrosis, strongly indicative of PACNS. An extensive diagnostic work-up was completed to rule out secondary causes of CNS vasculitis, such as systemic vasculitis, infections, neoplasms. Consequently, a definitive diagnosis of PACNS was established. Subsequently, the patient was treated with glucocorticoids in combination with cyclophosphamide. There was no evidence of relapse at the six-month follow-up. However, the long-term prognosis remains uncertain.

In summary, we have presented a case of unilateral hemispheric PACNS, which was conclusively diagnosed through a brain biopsy. The evolving changes in serial brain MRI scans as the disease progressed were also illustrated to underlines the importance of dynamic observation of MRI changes. When young individuals present with seizures, exhibit negative neurovascular imaging results, and display unilateral abnormalities on MRI, it is prudent to consider the possibility of isolated small-vessel PACNS. In such cases, a biopsy becomes essential to definitively exclude other potential diagnoses.

Patient perspective

"In 2019, when I was just 13 years old, I experienced my first seizure. Before the seizure occurred, I felt dizzy and had chest congestion. It began with my left eyelid twitching, followed by twitching in my left mouth, and then it gradually spread to my left upper limb, left lower limb, and eventually affected both of my limbs. I lost consciousness during this episode, as my classmates later recounted. Approximately 5 min later, I regained consciousness. Following this incident, I underwent a thorough medical evaluation. Doctors identified a lesion in my brain, but its nature remained a mystery. Despite being prescribed lamotrigine, I continued to experience seizures, occurring approximately twice a year, much to the concern of my parents. In 2023, both my parents and I decided to follow the doctor's recommendation to undergo a biopsy to establish a definitive diagnosis. Following the biopsy, I received treatment that yielded positive results. I've since returned to school and have remained seizure-free. I make regular visits to my doctor every 3 months, hoping to remain seizure-free in the future."

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

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 from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. 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

LQ: Writing – original draft, Writing – review & editing. MH: Writing – review & editing. WL: Writing – review & editing.

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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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Case report: Orthostatic leg tremor as the initial manifestation in a patient with metabotropic glutamate receptor-5 encephalitis without cortical dysfunction: complexities in identification and treatment

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Objective: Metabotropic glutamate receptor 5 (mGluR5) encephalitis is such a rare type of autoimmune encephalitis that its diagnosis remains a challenge.

Case report: A 19-year-old female patient initially presented with anxiety and orthostatic leg tremors without cortical dysfunction. We found that this patient was positive for mGluR5 antibodies in both serum (1:1,000) and cerebrospinal fluid (1:32). After comprehensive intervention, the patient showed complete recovery at the 18-month follow-up.

Discussion: This report expands our knowledge of the possible presentations of mGluR5 encephalitis for early diagnosis, which makes it possible to prevent serious consequences and improve the prognosis.

KEYWORDS

mGluR5, autoimmune encephalitis, orthostatic leg tremor, prednisone, motor disorder

Introduction

Autoimmune encephalitis (AE) is a group of novel neurological disorders associated with antibodies against neuronal cell-surface or synaptic proteins that can develop with abnormal symptoms in neurological and psychiatric manifestations (1). A recent epidemiological study estimated the prevalence rate of AE to be ~13.7/100,000, resulting in a heavy burden of disease with expensive costs (2). Since the discovery of the many common subtypes such as N-Methyl-D-Aspartate (NMDA), leucine-rich glioma inactivated (LGI1) (3, 4) and anti-Hu (3, 5) receptor encephalitis, an astonishing amount of novel AE antibodies have been described. Among the various novel AEs, metabotropic glutamate receptor (mGluR) encephalitis is so rare that it can present with a series of neuropsychiatric symptoms, particularly cortical dysfunction, but lacks specific symptoms and signs (all cases are summarized in Supplementary Table 1). Because reported cases are rare, clinicians cannot know about all the symptoms of mGluR5 encephalitis, let alone reach the same consensus

on a diagnosis. For early diagnosis and treatment, clinicians, especially psychiatrists, should consider this disease while performing differential diagnoses. Here we report the case of a patient with anti-mGluR5 encephalitis who was initially admitted to a psychiatric ward for orthostatic leg tremor after being diagnosed with dissociative conversion disorder 2 months earlier.

Case presentation

A 19-year-old female patient (168 cm/77 kg), Han Chinese, a sophomore student, with a surgical history of left oophorectomy for teratoma 8 years earlier and a stressful event of failing an exam, was admitted to our hospital with anxiety, orthostatic leg tremor, sweating, and weight loss of 4 kg in 2 months. The outpatient doctor misdiagnosed her as having disjunctive-conversion disorder, and she received escitalopram oxalate 10 mg/d at the first treatment and was recommended to be hospitalized. The patient still had the above symptoms, and she could not complete Romberg's test or Straight-Line-Walking test when she was hospitalized for the disease course of 11 weeks. Repeat cranial MRIs showed no lesion in the brain (Figures 1A–I). Cancer biomarkers and immune indices in serum, electroencephalogram, and electromyography were negative (Supplementary material). The patient had a high level of IgG in the cerebrospinal fluid (CSF; 0.0749 g/L; normal range, 0.005–0.041 g/L). The cell count in the CSF was normal, and antibodies were detected against proteins related to autoimmune mGluR5 encephalitis (1:1,000 in serum and 1:32 in CSF; Figures 1J, K). Also, the oligoclonal band antibody was positive only in the CSF.

This patient was diagnosed with mGluR5 encephalitis and started on 5 days of high-dose intravenous methylprednisolone (1,000 mg/day) and intravenous immunoglobulins (0.4 g/kg/day). Subsequently, she received oral prednisone (45–55 mg/d) and anti-anxiety drugs (escitalopram oxalate, 10–20 mg/d) for 2 weeks. At 2 weeks after discharge (namely, a 2-week follow-up), the anxiety and orthostatic leg tremor were mildly alleviated (prednisone 35 mg/d and escitalopram oxalate 5 mg/d). Finally, the patient recovered completely at the 6-week follow-up (20 mg prednisone and 5 mg escitalopram oxalate), and her mGluR5-antibody titer in the serum was reduced to 1:32. Specific drug use is shown in the Supplementary Figure 2. The patient maintained recovery without any recurrence at the 18-month follow-up.

Discussion

Given the finding of specific mGluR5 antibodies in both CSF and serum and the resolution of orthostatic leg tremors after immunotherapy therapy (immunoglobulin and steroids) and anti-anxiety drugs (escitalopram oxalate) in this patient, the diagnosis of mGluR5 encephalitis can be confirmed. Looking back at the course of the disease, this patient seemed to start with anxiety (psychiatric symptom) and gradually develop into orthostatic tremors, sweating, and weight loss. Psychiatric symptoms may be one of the potential and nonspecific early symptoms of mGluR5 encephalitis, but comorbidities with cognitive and motor disorders may have been more helpful in early identification. The following findings indicate that cognitive impairment may be more prevalent than motor disturbances in mGluR5 encephalitis. Based on a previous study in which 14 cases of mGluR5 encephalitis were enrolled, the clinical manifestations included mental and psychiatric disorders (13), cognitive disorders (11), sleep dysfunctions (9), seizures (8), and disorders of consciousness (6), but only four patients appeared to have motor disorders (6). Meanwhile, reviewing previous literature on motor disorders in mGluR5 encephalitis, we found that only one case reported postural hand tremor, and others showed orofacial dyskinesia, akinetic mutism, and psychomotor slowness, respectively (6, 7). In conclusion, although common symptoms of mGluR5 encephalitis may include psychotic symptoms, dysmnesia, or disorders of consciousness, clinicians should also pay attention to rare symptoms, for instance, motor symptoms (orthostatic leg tremor). Abnormal mGluR5 antibodies in the central nervous system may disrupt glutamate homeostasis and trigger the release of neurotoxic factors, which in turn may result in neurodegeneration in selective regions, including the cerebellum and amygdala (8–10). Some studies considered orthostatic tremor as the initial presenting feature in cerebellar and pontine lesions or autoimmune diseases (11, 12). In addition, sweating and weight loss could be prodromal symptoms in this case, which is consistent with previous research results (6).

In our case, the patient mainly manifested orthostatic leg tremors rather than mental and psychiatric symptoms or cognitive dysfunction. The possible reasons for the above phenomena may be that the patient was in the early stages of mGluR5 encephalitis or that there are some potential mechanisms of overlapping effects in the special trigger threshold of mGluR antibodies. Previous basic studies indicated that mGluR5 encephalitis classically presents with memory deficits and psychosis (7), and mGluR1 encephalitis may be mainly associated with cerebellar ataxia (13–15). However, mGluR1 and mGluR5 assemble into a homodimer with 85% similar amino acid sequence homologs in structure to activate subsequent receptors (14). We speculate that symptom presentation may overlap between mGluR1 and mGluR5 encephalitis at a specific threshold of triggering, for example, when the mGluR5-antibody titer in the serum and CSF is high.

A notable limitation is that in this case report, we were unable to perform bone marrow aspiration to exclude the possibility of cancer in the blood system. During the 18-month follow-up, we did not test the concentrations of mGluR5 antibodies in the CSF and only tracked the prognosis after 18 months.

Conclusion

Although the motor complications of mGluR5 encephalitis may be rare, clinicians should recognize them as soon as possible, which will be helpful for early diagnosis and intervention.

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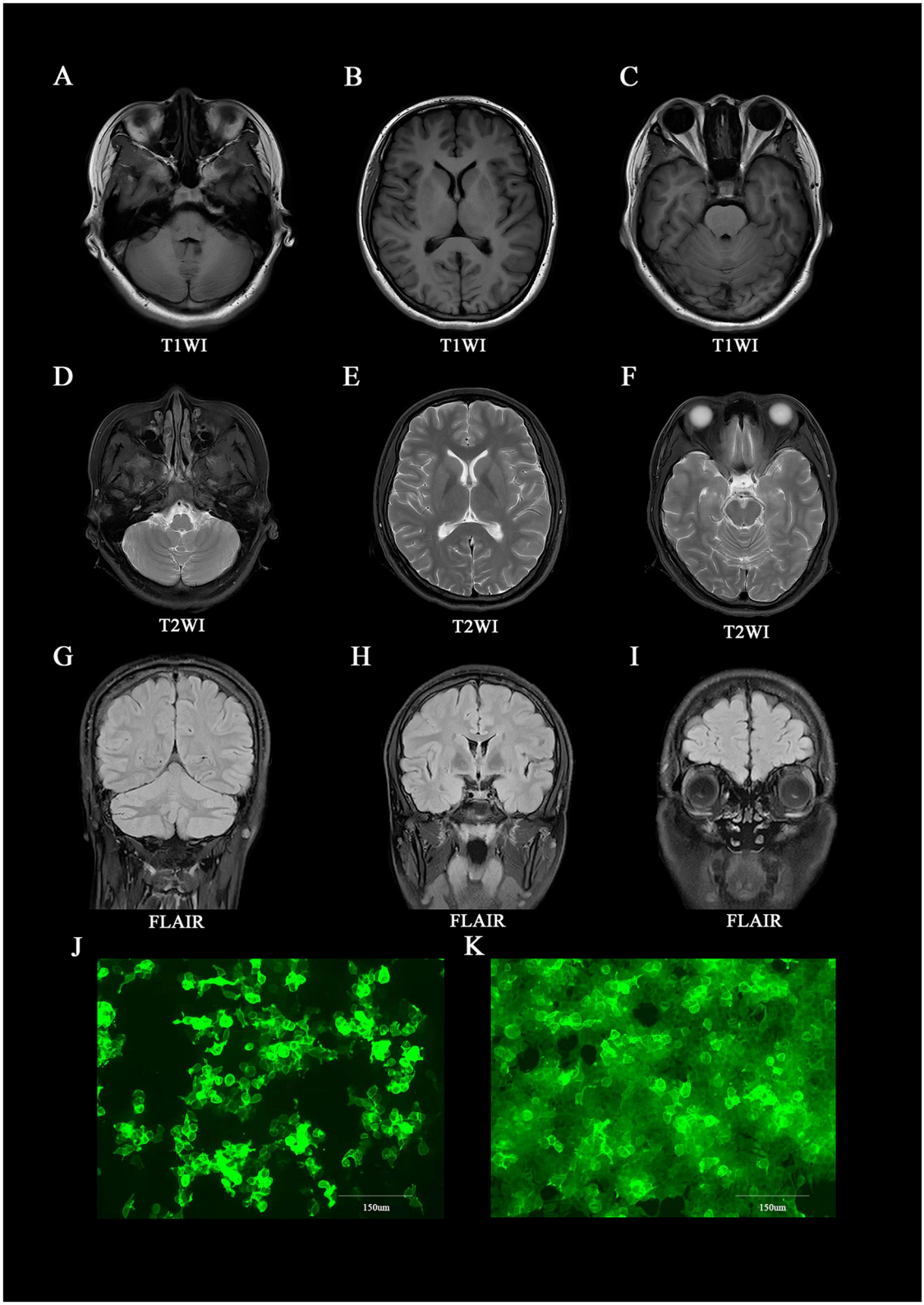

FIGURE 1
Brain MRI and immunofluorescence of anti-mGluR5 antibodies in the patient. **(A–I)** Brain MRI at the time of initial presentation, showing lesions on the whole of the brain. **(J, K)** Immunofluorescence against mGluR5 in **(J)** cerebrospinal fluid (1:32) and **(K)** serum (1:1,000).

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

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: Writing – original draft. QL: Investigation, Writing – original draft. M-fL: Investigation, Writing – review & editing. X-hM: Writing – review & editing, Methodology. X-tH: Writing – review & editing, Conceptualization. J-jX: Writing – review & editing. W-jG: Conceptualization, Writing – review & editing.

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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.2023.1288075/full#supplementary-material

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Case report: Diagnostic challenge: a new multiple sclerosis "relapse" leading to the diagnosis of anaplastic astrocytoma

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Cerebral tumors and multiple sclerosis (MS) can show overlapping clinical and magnetic resonance imaging (MRI) features and even occur concurrently. Due to the emergence of new symptoms, not usually MS related, an MRI was conducted in a 29-year-old woman with relapsing-remitting MS and showed a significant size progression of a parieto-occipital lesion, with mild clinical correlates, such as blurred vision, difficulty in speaking, and headache. Contrast-enhanced MRI and fluorothymidine positron-emission tomography (PET) did not point toward neoplasm, a lesion biopsy, however, showed astrocytoma, which was confirmed as grade III astrocytoma after the radical resection of the tumor. In the case of an atypical lesion, a tumor should be considered in patients with MS. A small fraction of high-grade gliomas show no enhancement on MRI and no hypermetabolism on PET. Biopsy proved to be the essential step in a successful diagnostic workup. To the best of our knowledge, this is the first case of anaplastic astrocytoma with these radiological features reported in a patient with MS.

KEYWORDS

astrocytoma, multiple sclerosis, magnetic resonance imaging, positron-emission tomography, case report

1 Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (1). MS lesions can vary in size from millimeters to one or two centimeters in diameter (2). Lesions are only larger than 2 cm in a rare tumefactive variant of MS. This variant may radiographically closely resemble a brain tumor and present itself clinically with symptoms generally associated more frequently with tumors (3).

Primary brain tumors are a rare type of cancer in adults. Two thirds of these come from astrocytic cell lineage. Tumors can present in patients as headaches, focal deficits—cognitive, motor, sensory or linguistic, seizures or visual problems (4), all depending on the location of the lesion. The incidence of primary brain tumors in the MS patient population

is estimated at 0.27% (5). The risk of metastatic tumorous lesions in the brain can differ in some cases in the MS population compared to the general population. However, the reports stating higher or lower incidences of specific tumor types are not completely consistent. Lung, breast and kidney cancer and melanoma are most commonly associated with brain metastases (6). Of these types, urinary system cancer was repeatedly found to be increased in the MS population, however, surveillance bias cannot be excluded (5). The incidence of brain metastases in the general population ranges from 7 to 14/100,000 people per year (7).

MRI constitutes a standard in neuroimaging of brain tumors (8). In cases where MRI is not decisive and suspicion of neoplasm is high, we may consider applying other modalities, such as PET.

Case reports of gliomas coexisting with multiple sclerosis (MS) have been described in the literature since 1973 (9). Due to the complex clinical and radiological traits inherent to both entities, this concurrent phenomenon remains challenging to diagnose.

We present a case report of a female MS patient with anaplastic astrocytoma, that had an appearance of tumefactive lesion on MRI. Adequate clinical correlation was missing. Fluorothymidine-PET showed no accumulation of the radiopharmaceutical. The case report below is written with respect to the CARE checklist.

2 Case report

The patient experienced the initial symptoms of MS (optic neuritis on the left eye followed by paresthesias of the right hand) at the age of 17. She fulfilled the diagnostic criteria of MS (10) (juxtacortical and periventricular demyelination lesions hyperintense in T2-weighted and Fluid Inversion Recovery sequences (a small lesion was also visible in the location of the future tumor), spinal cord lesions hyperintense in T2/Turbo Inversion Recovery Magnitude sequence, and 12 oligoclonal bands in the cerebrospinal fluid; the results of cerebrospinal fluid analysis were otherwise unremarkable: the protein level was 0.37 g/L and there were no cells found in the analysis performed at the time of initial diagnosis). Therefore, the patient was treated with high-dose steroids (3 g of intravenous methylprednisolone). Her clinical symptoms and signs completely resolved in 2 weeks, and subsequently, the long-term treatment with glatiramer acetate (40 mg/three times a week) as disease-modifying therapy (DMT) was started. At the age of 26, the DMT escalation to the dimethyl fumarate (240 mg/twice a day) was performed because of clinical progression.

The details of particular symptoms/signs, brain magnetic resonance imaging (MRI) changes, DMT as well as the treatment of particular attacks and the Expanded Disability Status Scale (EDSS) at the most important time points of the patient's clinical course are described in Table 1.

At the age of 29, clinical symptoms of blurred vision mainly in the right half of the visual field, mild anomic aphasia, extreme fatigue, and dull headache bilaterally in the occipital region occurred. The patient reported that the pain was a little more intense early in the morning after waking up. These symptoms developed slowly over 2 months. MRI of the brain revealed size progression of the left parieto-occipital cortico-subcortical lesion (42 × 42 × 34 mm vs. 32 × 30 × 25 mm in the previous MRI), which had an expansive character and showed no gadolinium enhancement (Figure 1). Moreover, the lesion was described by the radiologist as heterogenous, hyperintense in T2-weighted and Fluid Attenuated Inversion Recovery sequences, hypointense in T1-weighted sequence and there was no restriction of diffusion observed. With regard to the size and character of the lesion, the anomic aphasia could be explained by edema spreading to the angular gyrus. The patient reported blurred vision bilaterally (predominantly in the right visual field) and this symptom, according to the ophthalmologist, was most probably associated with Uhthoff's phenomenon.

In the context of MRI progression and newly developed clinical symptoms, the patient was treated with 5 g of methylprednisolone. The follow-up MRI showed no progression of the lesion; however, the symptoms showed no significant improvement after steroid treatment with the exception of a transitory reduction of the headache intensity. The non-MS etiology of the lesion was thus considered. ^{18}F-fluorothymidine PET-MRI did not demonstrate an increased accumulation of radiopharmaceutical within the lesion and there was no post-contrast enhancement of the lesion (Figure 2). A tumefactive lesion was still considered probable on the basis of this examination. This finding, however, cannot definitely exclude the tumor diagnosis for several reasons mentioned in the discussion below.

Because of the clinical progression, DMT escalation was considered. The biopsy of the lesion was performed to definitely exclude the tumor as the etiology of the patient's clinical status before the DMT escalation. The histological examination of the biopsy sample revealed anaplastic astrocytoma.

The craniectomy and radical extirpation of the tumor was performed. The histological examination confirmed the diagnosis of anaplastic astrocytoma grade III with mutation in isocitrate dehydrogenase.

The prognosis of this type of tumor is rather poor, with a mean 5-year survival of 28.6% (11), which increases to 41.8% if the patient receives adjuvant chemo- and radiotherapy (12). For overall survival, positive prognostic factors have been described: age (<41), isocitrate dehydrogenase mutation, radical resection and Karnofsky performance status of at least 90% (13), however, another source states a positive effect of Karnofsky performance status of at least 70% (14). In the latter case (Karnofsky performance status of 70%), our patient would have all of the positive factors mentioned above.

A neuropsychological examination was performed pre- and postoperatively and this included a battery of tests (Wechsler Adult Intelligence Test—Symbol Encoding Test and Digit Span Forward and Backward Test, Trail Making Test A/B, Stroop Task, Verbal Fluency Test, Rey-Osterrieth complex figure and Montreal Cognitive Assessment). The patient showed improvement in several tests (tests of attention and psychomotor processing speed, working memory, visual-constructive abilities and Montreal Cognitive Assessment) after surgery. Tests for executive function remained unchanged.

The patient started fractionated radiotherapy with a total dose of 59.4 Gy (33 × 1.8 Gy), followed by chemotherapy (temozolomide, 12 cycles in total/28-day cycle: 150 mg/m^2 of body surface (i.e., 220 mg) once a day for five consecutive days). This therapy follows the guidelines for this type of tumor (15). She also discontinued the dimethyl fumarate medication because

TABLE 1 Clinical course, treatment and brain MRI changes at the most important time points of the patient's disease.

	Patient's age	Newly developed clinical symptoms/signs	Treatment of acute relapse (intravenous methylprednisolone)	Brain MRI	EDSS at the maximum of clinical symptoms	Resolution of symptoms	DMT
2009	17	Optic neuritis on the left eye and positive sensory symptoms of upper limb	1 g daily for 3 days	Demyelinating lesions in supra- and infratentorial region, hyperintense in T2-weighted and Fluid Attenuated Inversion Recovery sequences	1.5	Complete	GA
2015	23	Mild paraparesis, negative sensory symptoms of the right upper limb and right lower limb	1 g daily for 3 days	Radiological activity—postcontrast (gadolinium) enhancement in three supratentorial lesions, and progression in lesion number	2.0	Complete	GA*
2016	24	Vertigo and mild urinary retention	1 g daily for 3 days	No significant changes	3.0	Incomplete	GA*
2018	26	Mild spastic paraparesis, more expressed on the right lower limb	1 g daily for 3 days	No significant changes	3.5	Complete	GA*
2019	27	Progression of vertigo, very mild dysarthria	1 g daily for 3 days	No significant changes	2.0	Incomplete	DMF**
2021	29	Dull occipital headache, blurred vision in the right half of the visual field, mild anomic aphasia, fatigue	1 g daily for 5 days	Size progression of the left parieto-occipital corticosubcortical lesion, which had an expansive character and was hyperintense in T2-weighted sequence and hypointense in T1-weighted sequence and showed no contrast enhancement	3.5	Incomplete	DMF

GA, glatiramer acetate; DMF, dimethyl fumarate; EDSS, expanded disability status scale.

*Despite mild clinical and radiological progression, the patient did not fulfill the local criteria for DMT escalation (at the appropriate time point, the escalation to 2nd line treatments was approved only in patients with two relapses in 1 year with parallel progression on the MRI).

**Due to the change of reimbursement criteria of the local health insurance companies, the patient's medication was escalated to DMF.

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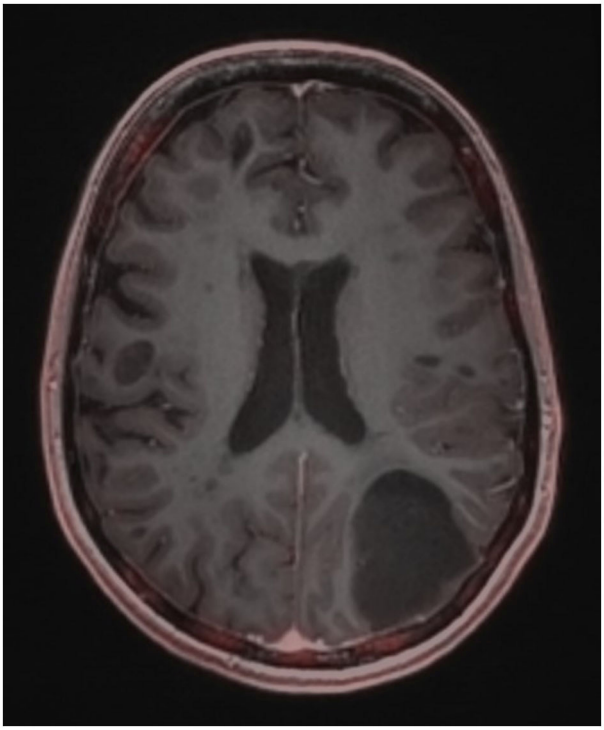

FIGURE 1
Brain MRI using contrast agents.

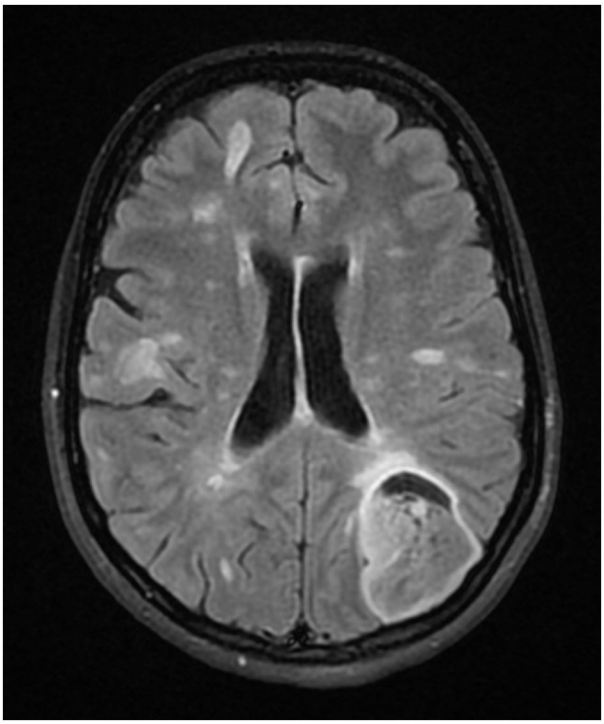

FIGURE 2
18F-fluorothymidine PET-MRI of the brain.

of the cumulative risk of leukopenia, to which the patient was prone (last leukocyte count before chemotherapy was below the lower limit of normal range: 3.080 × 109/l), and started with the administration of glatiramer acetate (40 mg/three times a week), which is allowed for patients with MS and active oncological disease with anti-cancer treatment.

Currently (at the age of 30), the patient has been clinically and radiologically stable for 18 months and presents with several persisting symptoms, including combined speech deficit with mild dysarthria and very mild anomic aphasia, and blurred vision emerging after physical activity (which was attributed to Uhthoff's phenomenon). The Karnofsky performance status is 70 due to inability to work (16), current EDSS score is 3 (functional systems: ambulation 0, pyramidal 2, cerebellar 0, brainstem 2, sensory 1, visual 1, cerebral 2, bowel and bladder 0).

The episodes of care are summarized in Table 2.

3 Discussion

To the authors' knowledge, this is the first published report of anaplastic astrocytoma non-accumulating on fluorothymidine PET imaging and non-enhancing on MRI in an MS patient.

In the case of atypical MS plaques, the issue of possible concurrence of MS and brain tumor may arise. Several clinical and radiological aspects should be considered in this situation and the biopsy of the lesion may in some cases be needed for final resolution. Clinically, any uncommon neurological symptoms and signs in MS patients should suggest more extensive investigations to exclude overlapping pathologies (17). The same applies for slowly developing symptoms with no spontaneous remission and no improvement following acute relapse medication. All these atypical features suggested non-MS etiology of the lesion in our patient.

Neuroimaging mostly helps to resolve the situation. Tumefactive demyelinating lesions are generally defined as acute, large (>2 cm) lesions. On imaging, they usually present with relatively little mass effect or surrounding edema, contrast enhancement in an open-ring pattern, high ADC values, and low relative cerebral blood volume (18–20). While the great majority of tumefactive demyelinating lesions and brain tumors enhance with gadolinium contrast, some of the lesions of both types may show no gadolinium enhancement, which was the case with our patient.

The use of conventional fluorodeoxyglucose PET in the detection of brain tumors is limited as it constitutes a high background signal (21). If the primary brain tumor, especially grade IV glioma, is considered, fluorothymidine PET imaging provides higher detection sensitivity. However, the detection rate decreases with the lower grade gliomas (22). Moreover, a correlation between fluorothymidine uptake and contrast enhancement on MRI in high-grade gliomas has been reported (23) since the fluorothymidine concentration in the tissue depends strongly on the disruption of the blood-brain barrier (24).

The stereotactic biopsy of the lesion and its histologic examination represents the final diagnostic approach in equivocal cases (25). It is safe and reliable, especially if specimens from multiple sites within the lesion are targeted. According to published data, the diagnostic accuracy of the stereotactic biopsy reaches 82%−99% (26).

TABLE 2 Timeline of the episodes of care.

Month/year	New clinical symptoms/examination/ intervention	Test or treatment results	Notes
03/2021	Blurred vision, headache, anomic aphasia, fatigue	Clinical progression (aphasia, blurred vision, new type of headache) leading to MRI examination and treatment of the presumed relapse (see next two lines)	
03/2021	MRI	Size progression of the left parieto-occipital corticosubcortical lesion	Tumefactive appearance
03/2021	Treatment of presumed acute relapse of MS: methylprednisolone IV, 1 g daily for 5 days	Only a minimal effect on headache and no impact on other clinical symptoms	
04/2021	Follow-up MRI	No significant change in the lesion	
06/2021	PET/MRI	No accumulation of the radiopharmaceutical within the lesion	Tumefactive appearance of the lesion
07/2021	Planned DMT escalation (blood tests, chest X-ray, exclusion of focus of infection)	No contraindication found	Given the remaining uncertainties regarding the tumefactive lesion, lesion biopsy was planned prior to DMT escalation
09/2021	Stereotactic biopsy	Anaplastic astrocytoma	A tumor resection was planned
10/2021	Radical resection of the tumor	Anaplastic astrocytoma grade III confirmed	Based on the results of histological examination of the tissue taken during resection, chemo- and radiotherapy was planned
11/2021	Fractionated radiotherapy	59.4 Gy (33 × 1.8 Gy)	
03/2022	Adjuvant chemotherapy: temozolomide: 12 cycles in total/28-day cycle: 150 mg/m^2 of body surface daily for five consecutive days	Clinically stable with very mild headache, blurred vision following physical activity; MRI with no residual tumor detected	

MRI, magnetic resonance imaging; MS, multiple sclerosis; IV, intravenously; PET/MRI, positron emission tomography/magnetic resonance imaging; DMT, disease-modifying treatment.

However, as in every case report, the ability to generalize particular findings mentioned in our case report to the broader patient population is limited.

4 Patient perspective

The interdisciplinary team consisting of neurology, neurosurgery, oncology and psychiatry specialists provides the patient with consistent support. Subjectively, the patient experiences only subtle neurological disability. Ongoing fatigue does, however, preclude her from keeping up with her occupation. Her mood is stabilized and motivation to continue with the therapy is high.

"Radiotherapy and chemotherapy were manageable. The only thing that bothers me is the daily headache, although it is mostly mild. And fatigue, which makes me unable to do everything as before. But I'm glad I'm self-sufficient."

5 Conclusion

Tumefactive lesions with atypical clinical symptoms not responding to the acute corticosteroid medication should raise a "red flag" of non-MS etiology. [18]Fluorothymidine PET is frequently used to confirm or exclude the tumor, but its sensitivity in lower-grade gliomas might be limited. The stereotactic biopsy of the lesion represents the most important method in cases without clinical-radiological correlation. The possibility of dual pathology must always be kept in mind.

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

MP: Conceptualization, Writing—original draft. IŠ: Conceptualization, Methodology, Supervision, Writing—review & editing. JK: Supervision, Writing—review & editing. PŠ: Supervision, Writing—review & editing. LH: Supervision, Writing—review & editing. MK: Supervision, Writing—review & editing. HP: Supervision, Writing—review & editing. EN: Supervision, Writing—review & editing. LK: Supervision, Writing—review & editing. EV: Supervision, Writing—review & editing.

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Conflict of interest

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Cerebellar encephalitis associated with anti-mGluR1 antibodies: a case report and comprehensive literature review

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Anti-metabotropic glutamate receptor 1 encephalitis is an uncommon autoimmune condition characterized by a subacute onset of cerebellar syndrome. Frequently, it also manifests as sleep disorders and cognitive or behavioral changes. While immunotherapy is the primary treatment approach, the disease remains poorly understood. Herein, we present a case of anti-metabotropic glutamate receptor 1 encephalitis, highlighting its primary cerebellar syndrome manifestation. The first magnetic resonance imaging scan showed no obvious abnormality. Lumbar puncture showed increased cerebrospinal fluid pressure, increased white blood cell count and protein level. The next-generation sequencing of cerebrospinal fluid showed Epstein–Barr virus infection, and the patient was diagnosed with viral cerebellar encephalitis. However, antiviral therapy was ineffective. Finally, anti-metabotropic glutamate receptor 1 was measured at 1:1,000, and the patient was definitely diagnosed with anti-metabotropic glutamate receptor 1 encephalitis. Therefore, clinicians should pay attention to such diseases to avoid misdiagnosis.

KEYWORDS

cerebellar encephalitis, anti-mGluR1 antibodies, case report, EBV, literature review

Introduction

Anti-metabotropic glutamate receptor 1 (mGluR1) encephalitis is a seldom-encountered autoimmune disorder impacting both the central and the peripheral nervous system. It primarily instigates an acute or subacute cerebellar syndrome with varying severity. mGluRs are G-protein-coupled receptors situated both pre-and post-synaptically across the central and peripheral nervous systems, predominantly expressed in Purkinje cells. Their roles span cerebellar development, synaptic transmission modulation, synaptic plasticity, pain perception, memory, learning, and anxiety management (1). mGluR1 activation fosters long-term depression in parallel fiber-Purkinje cell synapses, a pivotal process for cerebellar motor learning (2). In this report, we present a case of cerebellar encephalitis associated with anti-mGluR1.

Case presentation

A 50-year old male laborer with a 15-year history of hypertension was admitted to our facility on 25 March 2020, presenting with symptoms of fever, dizziness, slurred speech, and

unsteady gait persisting for 20 days. About 20 days before admission, he had shown a peak temperature of 37.5°C accompanied by the same neurological symptoms. An initial cranial MR scan did not indicate any anomalies (Figure 1A). Further, the head and neck CTA revealed a stenosed right middle cerebral artery and a barely discernible constriction at the ostium of the left vertebral artery. Lumbar puncture indicated a pressure of 230 mmH_2O. The cerebrospinal fluid had leukocytes at 190×10^6/L (reference range: 0–8×10^6/L) and protein levels at 0.54 g/L (reference range: 0.2–0.4 g/L). CSF mNGS identified 4 sequences of Epstein–Barr virus (EBV). Viral cerebellar encephalitis was suspected, but despite antiviral therapy, there was no symptomatic improvement, prompting his visit to our hospital.

Upon examination, his vitals were recorded as: temperature 36.6°C, pulse rate 70 bpm, respiratory rate 19 breaths per minute, and blood pressure at 141/92 mmHg. Cardio-respiratory and abdominal assessments were unremarkable. Neurological evaluation indicated clear consciousness, coherent speech, horizontal nystagmus in both eyes, imprecise bilateral finger-nose and heel-shin tests, positive Romberg sign, and no other evident abnormalities. A preliminary diagnosis suggested cerebellar encephalitis, and a treatment regimen of Acyclovir combined with Dexamethasone (10 mg) was initiated.

Post-admission, standard blood tests, biochemistry, coagulation profile, D-dimer, myocardial enzymes, BNP, thyroid function and antibodies, PCT, ESR, CRP, tumor markers, and TORCH were all found to be within normal limits. A repeat lumbar puncture yielded a pressure of 210 mmH_2O, white blood cells at 50×10^6/L, protein at 0.50 g/L, with cerebrospinal fluid cytology predominantly indicating a lymphocytic response. Both the cerebrospinal fluid and serum tested negative for a series of autoimmune encephalitis antibodies (anti-NMDAR, AMPAR1, AMPAR2, LGI1, CASPR2, GABABR, GAD65), paraneoplastic neurological syndrome antibodies (Hu, Yo, Ri, Amphiphysin、Ma2, CV2/CRMP5), and ganglioside antibodies (GM1-IgG, GD1b-IgG, GQ1b-IgG, GM1-IgM, GD1b-IgM, GQ1b-IgM).

During hospitalization, the patient's condition deteriorated, exhibiting sleep disturbances and altered mental behavior. A treatment regimen comprising Olanzapine, Eszopiclone, intravenous human immunoglobulin (0.4 g/kg for 5 days), and methylprednisolone sodium succinate (500 mg for 3 days) was administered. The patient was discharged after showing improvement. However, on 1 May 2020, he experienced exacerbation of dizziness and unsteady walking, with a new symptom of coughing when drinking water. A subsequent head MRI did not reveal any discernible abnormalities. Both serum autoimmune encephalitis antibody and serum AQP-4 tests were negative. Further examination of cerebellar encephalitis antibody profile at Peking Union Medical College Hospital revealed the presence of serum anti-mGluR1 with an end-point titer of 1:1,000 (Figure 2), leading to a definitive diagnosis of Anti-mGluR1 encephalitis. The patient was readmitted to our facility, receiving Human Immunoglobulin (0.4 g/kg for 5 days), Methylprednisolone (500 mg for 3 days followed by a tapering regimen), Mycophenolate Mofetil (0.5 g twice daily), and Olanzapine (5 mg nightly). Although the patient's psychiatric symptoms improved, there was negligible enhancement in cerebellar ataxia. Post-discharge, he continued rehabilitation exercises with periodic follow-ups. A subsequent review on 14 April 2023, revealed an mRS score of 3, and a cranial MRI indicated cerebellar atrophy (Figure 1B).

Discussion

In the presented case, the patient's initial symptoms, characterized by clumsiness in speech and unstable gait, were accompanied by a prodromal infection. Physical examination confirmed the presence of cerebellar syndrome. The progression of the illness saw the patient manifesting psycho-behavioral disturbances and cognitive impairments. An initial MRI scan did not reveal notable abnormalities. Lumbar puncture indicated elevated cerebrospinal fluid pressure, increased white blood cell count, and elevated protein levels. The next-generation sequencing of cerebrospinal fluid revealed a viral infection, leading to a presumptive diagnosis of viral cerebellar encephalitis. However, given the ineffectiveness of the antiviral therapy, the differential diagnosis was refined to consider immune-related cerebellar encephalitis. This led to an extended immune-related

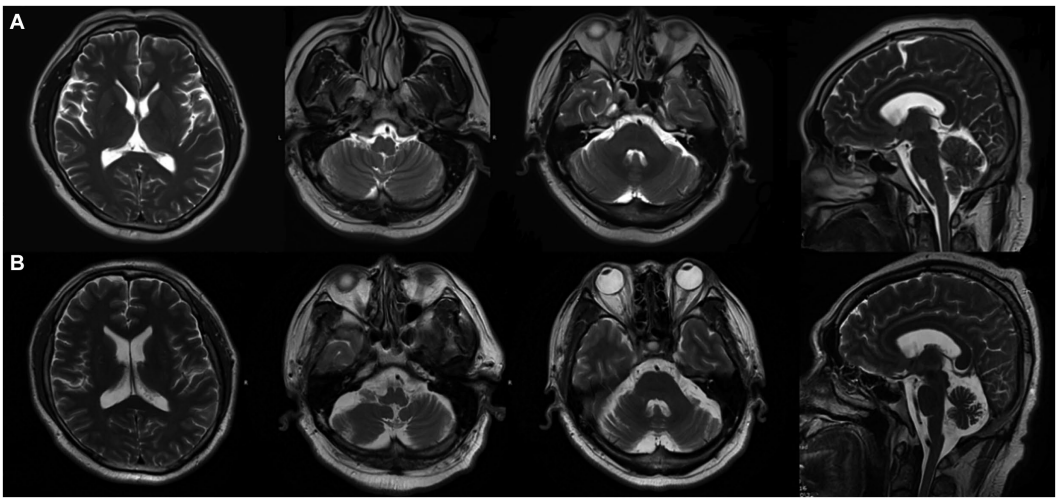

FIGURE 1
On 25 March 2020 **(A)**, cranial MRI showed no abnormality, and on 20 April 2023 **(B)**, cranial MRI showed cerebellar atrophy.

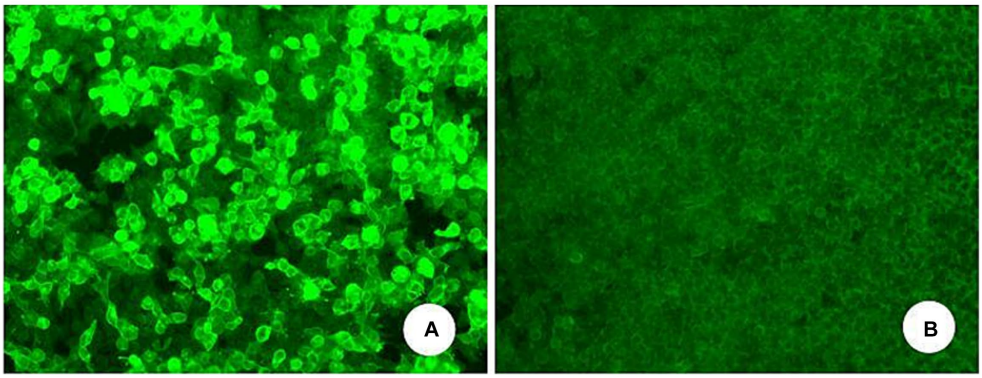

FIGURE 2
Serum anti-mGluR1-IgG positive **(A)** and negative control **(B)** of another serum individuals sample (transfected cell method).

antibody profile test, confirming the presence of anti-mGluR1 with an end-point titer of 1:1,000, and culminating in a definitive diagnosis of anti-mGluR1 encephalitis.

Smitt et al. (3) first documented two anti-mGluR1 encephalitis cases, where both individuals exhibited cerebellar ataxia and had a prior history of Hodgkin lymphoma. To date, literature has recorded 36 such cases globally. Research by Khojah et al. (4) highlighted that 25% of patients experienced one or more prodromal symptoms—ranging from fever, headache, and fatigue to weight loss, nausea, vomiting, night sweats, and flu-like manifestations—with a median interval of 30 days leading up to neurological symptom onset. In a literature review, three patients reported prior infections, including a trigeminal herpes zoster infection a month before onset (5), a streptococcal pharyngitis 2 months prior (6), and a dengue virus infection (7). The link between such infections and anti-mGluR1 encephalitis remains ambiguous. These findings hint at potential post-infectious factors contributing to the development of anti-mGluR1 encephalitis, or the possibility that infections could catalyze its pathogenesis (4). EBV was detected in the cerebrospinal fluid of patients. As the first discovered human oncovirus, EBV infects more than 90% of the world's people, and once infected, most will remain latent in B lymphocytes in an asymptomatic form of infection and cannot be cleared (8). Infection leads to a spectrum of EBV-associated diseases when the balance between the virus and the host is disrupted (9). The relationship between viral infection and cerebellar encephalitis in this patient needs further investigation.

Over the recent years, it's been reported that 27% of patients with herpes simplex virus encephalitis (HSE) subsequently develop secondary autoimmune encephalitis (AE), which includes predominant cases of anti-NMDAR encephalitis (64%) and other variations such as GABAbR encephalitis, LGI1 encephalitis, and AMPAR encephalitis (10). Notably, 30% of patients without neurological symptoms post-HSE infection demonstrated autoantibodies, including NMDAR (27%) and other antibodies (73%) in serum and/or cerebrospinal fluid. This case study postulates that the emergence of anti-mGluR1 encephalitis in the presented patient might be associated with preceding viral infection. Several hypotheses abound regarding the etiology of autoimmune encephalitis post-HSV (herpes simplex virus) infection (11): (1) Molecular mimicry, where exogenous pathogen antigens structurally resemble the host's own antigens, resulting in specific antibodies or effector T cells produced against these exogenous antigens inadvertently cross-reacting with the host's analogous antigens, leading to autoimmune repercussions. (2) The release of autoantigens from disintegrated neurons post-viral infection, which disrupts central immune tolerance (12). (3) Autoinflammatory responses against the herpes virus infection, where HSV triggers T and B cell activation, producing a cascade of inflammatory cytokines. These might infiltrate the blood-cerebrospinal fluid barrier, instigating immune responses in the CNS and subsequently recognizing CNS autoantigens (13). (4) Genetic predispositions (14). (5) Secondary immunodeficiencies. For instance, HIV infections might induce an immune response dysregulation to NMDAR, culminating in the emergence of AEs (15). However, the nexus between anti-mGluR1 encephalitis, its prodromal infections, and its specific mechanisms remains nebulous and warrants further in-depth research.

In a retrospective analysis encompassing 36 cases of anti-mGluR1 encephalitis (4), 16.7% of patients had diagnoses of unrelated autoimmune diseases to mGluR1 antibodies, including conditions like multiple sclerosis, Hashimoto's thyroiditis, Sjögren's syndrome, and pernicious anemia. Furthermore, 22.2% had associated malignancies, with six cases being lymphomas. Notably, 50% of these malignancy cases manifested autoimmune cerebellar or encephalitis within 5 years of onset. Iorio et al. (16) reported a unique case of anti-mGluR1 encephalitis associated with prostate cancer. Immunohistochemistry of the patient's prostate adenocarcinoma revealed significant mGluR1 expression in the tumor's luminal acinar epithelial cells. Additionally, patient IgG was observed binding to tumor mGluR1. Intriguingly, mGluR1 receptor expression has been substantiated in prostate cancer, with its expression correlating with the progression of the malignancy (17). Additionally, mGluR1 expression is evident in human cutaneous T-cell lymphoma cell lines (18). While it's uncertain if malignancies play a direct role in instigating anti-mGluR1 encephalitis, it's paramount for physicians to undertake tumor-related assessments, including tumor markers and PET-CT scans in such patients. As of now, this patient has not demonstrated autoimmune diseases unrelated to mGluR1 antibodies or malignant tumors. Continuous observation and regular follow-ups are crucial.

The clinical presentation of this patient centered on cerebellar syndrome. In the literature, anti-mGluR1 encephalitis manifests a spectrum of symptoms, including gait instability, cerebellar dysarthria, abnormal eye movements, and limb ataxia (Table 1). As the disease unfolds, the majority of patients exhibit behavioral changes, cognitive impairments, taste dysfunction, autonomic dysregulation, seizures,

and sleep disorders. Rarer clinical manifestations encompass visual disturbances and limb weakness (19). Dyskinesias, when manifested, present as myoclonus or dystonia in adults, while children predominantly exhibit athetosis (20).

For the anti-mGluR1, detection rates in serum and cerebrospinal fluid stood at 97% and 95%, respectively (19). In some cases, the antibody was detected solely either in serum or cerebrospinal fluid. For our particular patient, only the serum was tested, as he opted against a repeated lumbar puncture. Notably, NMDA-R, LGI1 and CASPR2 encaphalitis, typically present with CSF cell numbers in the range of 0–20 leukocytes/μL. Our patient had 190 leukocytes/μL in CFS, which was significantly higher than other typical autoimmune encephalitis. We reviewed the literature and found that the number of CSF cells in patients with mGLuR1 encephalitis, which has been reported so far, ranges from 0 to 214 leukocytes/μL. And nearly half of such patients demonstrated leukocytosis in the cerebrospinal fluid, accompanied by specific oligoclonal bands or an increased IgG index.

TABLE 1 Basic information, clinical symptoms and laboratory tests of 36 patients diagnosed with anti-mGluR1 encephalitis in the literature.

Demographic features	Number of patients
Median age	52.5 (3,81)
Gender	
Male	19
Female	17
Clinical manifestations	
Cerebellar symptoms	**34**
Ataxia	31
Dysarthria	19
Nystagmus	10
Titubation	7
Dysmetria	7
Vertigo	6
Diplopia	4
Intention tremor	4
Oscillopsia	2
Behavioral symptoms	10
Cognitive symptoms	10
Sleep difficulties	10
CSF features	
Leukocytes/μL	30
Normal (0–5)	15
Pleocytosis (>5)	15
Median	5.5 (0,214)
Oligoclonal Bands	22
Negative	10
Positive	12
Brain MRI	**33**
Normal	9
Cerebellar atrophy	15
Cerebellar hyperintensity	7
Spinal cord lesions	2
Other lesions	5

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

Electroencephalography (EEG) can reveal bilateral focal frontotemporal slow waves, potentially associated with epileptiform discharges (6). Though early imaging displayed abnormalities in merely one-third of the patients, encompassing findings like brain atrophy, variable brain and spinal cord lesions, and cerebellar abnormalities such as cerebellar hyperintensity, leptomeningeal enhancement, atrophy, or edema, these typically were concentrated in the medial cerebellar hemisphere and vermis (4). Intriguingly, as time progressed, positive MRI results were observed in three-quarters of these patients. Such deviations in MRI results, transitioning from normal to abnormal, are attributed to the degeneration of Purkinje cells due to prolonged antibody exposure (21)—a shift highlighting the imperative of timely intervention. PET scans are instrumental in excluding hidden malignancies. In line with the guidelines from the European Federation of Neurological Societies, a PET-CT follow-up is strongly advised in instances with heightened suspicion of a paraneoplastic syndrome (22). In the context of our patient, the initial cranial MRI did not present any abnormalities. Despite this, post-initiation of the immunomodulatory therapy, while the patient's clinical symptoms remained stable over the span of 3 years, subsequent MRI scans indicated cerebellar atrophy. This evokes concerns about the long-term prognosis for patients with anti-mGluR1 encephalitis.

For most individuals diagnosed with anti-mGluR1 antibody-associated encephalitis, first-line immunotherapy treatments such as steroids, plasma exchange, and intravenous immunoglobulins are prescribed. According to a study by Khojah et al. (4), 41.7% of these patients progressed to second-line therapy, including agents such as rituximab, azathioprine, cyclophosphamide, mycophenolate mofetil, tacrolimus, and hydroxychloroquine. Among these, 93.3% did not achieve full remission with the second-line treatment, and 36.1% utilized more than three distinct treatment modalities. Even then, merely 15.4% managed to attain complete remission. Comparatively, patients with anti-mGluR1 encephalitis tend to have a grimmer prognosis than those with other autoimmune encephalitides, such as anti-mGluR5 encephalitis, anti-NMDAR encephalitis, or anti-LGI1 encephalitis (6, 23, 24). Independent of the underlying cause of anti-mGluR1 encephalitis, commencing treatment at an early stage remains pivotal.

Conclusion

In summation, when encountering patients with acute or subacute onset prominently manifesting cerebellar syndromes—and where common autoimmune and paraneoplastic antibody profiles return negative—screening for the rarer anti-mGluR1 becomes imperative. A minority of these patients might harbor tumors. Acute-phase cerebrospinal fluid evaluations might display mildly elevated leukocyte counts. A definitive diagnosis necessitates the detection of anti-mGluR1-IgG in serum and/or cerebrospinal fluid. It's evident that this disease exhibits a limited response to immunotherapy, underscoring the importance of early therapeutic interventions. Upcoming research endeavors should aim to elucidate the intricate relationship between anti-mGluR1 antibody-associated encephalitis, prodromal infections,

and tumors. Additionally, we must embark on the quest to uncover more effective treatment regimens.

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

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 from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. 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

XC: Conceptualization, Data curation, Investigation, Writing – original draft. YaC: Conceptualization, Funding acquisition, Investigation, Methodology, Writing – original draft. LD: Investigation, Methodology, Writing – original draft. NL: Methodology, Project administration, Writing – review & editing. TL: Formal analysis, Methodology, Writing – review & editing. YuC: Resources, Supervision, Validation, Writing – review & editing. WD: Funding acquisition, Methodology, Supervision, Validation, Writing – review & editing.

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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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Successful switch to ofatumumab after liver injury associated with ocrelizumab treatment in multiple sclerosis: a case report

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Drug-induced liver injury (DILI) is a potential adverse event of disease-modifying therapies (DMTs) for the treatment of multiple sclerosis (MS), as well as of methylprednisolone pulsed therapy used in case of MS relapse. DILI may be induced by different mechanisms, including idiosyncratic reaction, autoimmune hepatitis or viral reactivation. In patients receiving the humanized anti-CD20 monoclonal antibody (mAb) ocrelizumab, DILI has been rarely reported and was mostly associated with hepatitis B virus (HBV) reactivation. Here we present the case of a woman with highly active relapsing–remitting MS who had experienced two episodes of DILI while receiving different DMTs, and was successfully switched to ofatumumab, a fully human anti-CD20 mAb, after a further event associated with ocrelizumab treatment and unrelated to HBV reactivation. Despite sharing the mechanism of action, differences in structure, pharmacokinetic/pharmacodynamic profile, and use of ancillary drugs (only needed for ocrelizumab) may have accounted for the successful switch. To our knowledge, this is the first report of a successful switch from ocrelizumab to ofatumumab due to DILI. Ofatumumab may therefore represent a valid therapeutic option for patients experiencing DMTs- and ocrelizumab-induced liver injury, providing that HBV reactivation has been ruled out.

KEYWORDS

case report, liver injury, ocrelizumab, ofatumumab, multiple sclerosis, monoclonal antibody, B-cell depletion

1 Introduction

Drug-induced liver injury (DILI) is a potential adverse event of disease-modifying therapies (DMTs) for the treatment of multiple sclerosis (MS), an autoimmune demyelinating and degenerative disease of the central nervous system (1, 2). In this context, severe hepatic failure is a rare event, and drug discontinuation rate due to hepatic injury is generally <1% (1). Nonetheless, a signal of disproportionate reporting of DILI events was observed for several DMTs in a pharmacovigilance study based on the Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS) (3). Of note, DILI has been associated also with pulsed intravenous methylprednisolone (IVMP) therapy used for the treatment of MS relapse (4).

Anti-CD20 monoclonal antibodies (mAb) are increasingly used for the treatment of MS (5). The humanized mAb ocrelizumab, approved in 2017–2018 by the FDA and European Medicines Agency (EMA) for the treatment of relapsing MS and primary progressive MS (6), has been rarely associated with alterations of the hepatic profile. More recently (2020–2021), ofatumumab, a fully human anti-CD20 mAb, was approved by the Agencies for relapsing MS (7). These two mAbs have the same mechanism of action but are administered via different routes (intravenous [IV] for ocrelizumab and subcutaneous [SC] for ofatumumab) and exhibit different pharmacokinetic/pharmacodynamic profiles (8), summarized in Table 1.

Therapeutic management of patients who have experienced DILI may be challenging. We report the case of a woman with highly active relapsing–remitting (RR) MS who was successfully switched to ofatumumab after having experienced multiple episodes of DILI, the latest occurring during ocrelizumab treatment, and unrelated to hepatitis B virus (HBV) reactivation. To our knowledge, this is the first report of a successful switch from ocrelizumab to ofatumumab due to liver toxicity.

2 Case presentation

A 57-year-old woman was diagnosed with RRMS when she was 29 years old. At that time, she experienced an episode of numbness in her left upper limb. Her past medical history was unremarkable except for vitiligo. No familiar history of MS or other autoimmune disorders was reported. Magnetic resonance imaging (MRI) showed multiple brain hyperintense T2 lesions involving areas typical for MS, and one spinal cord lesion. Oligoclonal bands were detected in the cerebrospinal fluid, and the diagnostic work-up did not show any red-flags of better explanation. Clinically definite MS was diagnosed a few months later after the occurrence of optic neuritis and increased lesion load at MRI. Starting from 1999, she was sequentially treated with interferon beta-1a (IFN), azathioprine, glatiramer-acetate, and then switched in 2013 to IFN 44 mcg thrice a week. The treatment with IFN 44 was uneventful until February 2016, when the patient complained of marked fatigue and jaundice. Blood chemistries showed a marked elevation of serum aspartate aminotransferase (AST, 819 UI/L; upper limit of normal [ULN] 41 UI/L), serum alanine aminotransferase (ALT, 498 UI/L; ULN 50 UI/L), and gamma-glutamyl transpeptidase (GGT, 302 UI/L; ULN 38 UI/L), with mild elevation of serum alkaline phosphatase (ALP, 157 UI/L; ULN 126 UI/L) and serum total bilirubin (2.5 mg/dL; ULN 1.2 mg/dL) with prevalent increase of the conjugated fraction. IFN was discontinued and two months later, after normalization of liver enzymes, she was switched to fingolimod. Unfortunately, nine months later (February 2017) fingolimod was discontinued due to a diagnosis of breast cancer, which was successfully treated with surgery, followed by tamoxifen treatment for the subsequent 5 years. In August 2017, the patient was started on glatiramer-acetate, but this was discontinued a few months later due to recurrent allergic reactions to the drug and a grade 2 increase in serum aminotransferases. Liver enzymes normalized spontaneously within one month from DMT discontinuation, and the event was attributed to the possible combined hepatic toxicity of glatiramer-acetate and tamoxifen. A transient, mild elevation in serum aminotransferase was again observed a few weeks later, shortly after a course of IVMP for MS relapse (balance issues and lower limbs hypoesthesia with T5 level). She was then switched to dimethyl-fumarate and in June 2020, after a further course of IVMP for MS relapse (dizziness and left-sided facial numbness), she experienced a remarkable elevation in liver enzymes requiring hospital admission. The patient was discharged with a diagnosis of probable DILI associated with treatment with dimethyl-fumarate/high-dose IVMP.

Due to recurrence of MS activity, the patient was started on natalizumab in October 2020. She received 18 administrations of natalizumab with clinical and MRI stabilization, in the absence of any elevations in serum liver enzymes, which were tested monthly. In May 2022, the drug was discontinued due to JCV positivity (index 3.56), and in July 2022 the patient was switched to ocrelizumab, after having received an abdominal ultrasound which did not show any abnormal liver findings. Six days after the first IV infusion of ocrelizumab 300 mg, a mild elevation in AST (within twofold ULN) and ALT (within threefold ULN) was observed, while ALP, GGT and bilirubin were all within normal ranges (Figure 1). One week after the second administration of ocrelizumab 300 mg IV, the patient complained of nausea, increasing fatigue and anorexia. Blood tests showed a marked increase in liver enzymes with a clear hepatocellular pattern (AST 1234 U/L, ALT 1198 U/L, ALP 236 U/L, GGT 224 U/L, bilirubin 4.5 mg/dL with 2.8 mg/dL conjugated; Figure 1). Anti-mitochondrial, anti-nuclear and anti-smooth muscle autoantibodies were all negative, as well as cytomegalovirus (CMV) and Epstein–Barr virus (EBV) DNA, anti-toxoplasma antibodies, HBsAg, anti-HBV antibodies and

TABLE 1 Pharmacodynamic and pharmacokinetic profiles of ocrelizumab and ofatumumab.

	Ocrelizumab	Ofatumumab
Structure	Recombinant humanized monoclonal anti-CD20 IgG1 antibody (molecular mass of approximately 145 kD)	Fully human anti-CD20 monoclonal IgG1 antibody (theoretical average molecular weight of 145 kDa).
Administration route	Intravenous	Subcutaneous
Dosing	600 mg IV every six months[a]	20 mg SC every four weeks[b]
Ancillary drugs	100 mg methylprednisolone (or equivalent) Antihistamines	Not required
Half-life	26 days	16 days
Elimination	not directly studied, as antibodies are cleared principally by catabolism (i.e., breakdown into peptides and amino acids).	target-mediated route (related to binding to B cells) and target-independent route (non-specific endocytosis followed by intracellular catabolism)
Time to $CD20^+$ cells depletion	By 14 days	By 14 days
Median time to $CD20^+$ B cells recovery	72 weeks	24.6 weeks

Data derived from refs. (6, 7). [a]First dose administered as two 300 mg IV doses two weeks apart. [b]Maintenance after a loading dose consisting of three 20 mg SC weekly administration.

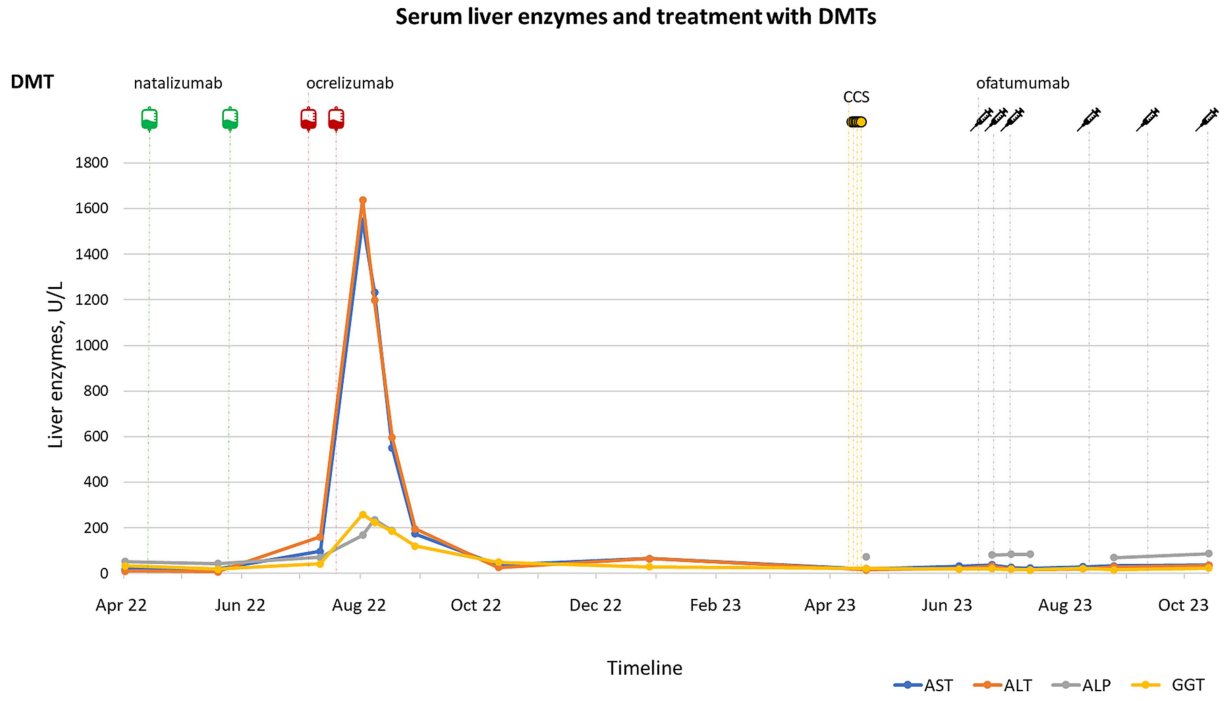

FIGURE 1
Timeline of disease-modifying treatments (DMTs) and dexamethasone (CCS) administration (upper panel) and serum liver tests (lower panel) during the latest episode of DILI experienced by the patient. A mild elevation in serum transaminase [serum alanine aminotransferase (ALT), and serum aspartate aminotransferase (AST)] was observed shortly after the first administration of ocrelizumab 300 mg IV, followed by a severe elevation in transaminase, gamma-glutamyl transpeptidase (GGT) and serum alkaline phosphatase (ALP) detected two weeks after the second dose. The levels of liver enzymes returned below the upper limit of normal (ULN) within two months, without the administration of any corticosteroid treatment. No further elevations were observed during the follow-up, including after ofatumumab start.

HBV DNA, which had tested negative also before ocrelizumab start. She only received IV hydration and liver enzymes gradually decreased, reaching values within the normal range in two months.

An abdominal ultrasound performed in December 2022 showed patchy echogenicity of the liver, suggestive of marked inhomogeneity of its parenchymal architecture, consistent with chronic liver disease. After consultation with her treating hepatologist, the prosecution of treatment with ocrelizumab was not recommended and the second dose scheduled for February 2023 was not administered. MS was clinically and radiologically stable up to April 2023 (brain MRI performed in June 2022, i.e., before starting ocrelizumab, and 3 months after the first dose of ocrelizumab were both unchanged compared to the previous examination taken in November 2021).

In April 2023, when B cells were still depleted, she experienced a spinal cord relapse (severe balance issues preventing her from walking unaided); at that time, the patient was no more taking tamoxifen (discontinued in April 2022). As, in the past, the administration of IVMP was followed by derangement of liver enzymes, intramuscular dexamethasone was chosen over IVMP to treat the relapse. After dexamethasone treatment, a good recovery from MS relapse was observed, and no elevation in serum liver enzymes was detected. A further abdomen ultrasound (May 2023) showed the persistence of an inhomogeneous liver structure with a pseudonodular pattern, and normal stiffness at elastography. Further investigation with a dedicated MRI was suggested, which did not show any abnormalities, nor pathological areas of diffusion restriction.

After further consultation with the Hospital hepatologist, ofatumumab was started in June 2023, with three weekly SC doses of 20 mg over the first month (loading dose), followed by a monthly dose of 20 mg, with close monitoring of liver enzymes. At the time of writing, the patient has been treated with ofatumumab for five months, and no elevation in liver enzymes has been observed. No further relapses were reported, and a brain MRI performed in October 2023 showed no new lesions compared to the previous scan taken in September 2022. Adherence to ofatumumab treatment was confirmed by persistent B cell depletion at monitoring blood tests, starting from July 2023. At month 3 after ofatumumab start, the patient's satisfaction with ofatumumab treatment was explored using the treatment satisfaction questionnaire of medication (TSQM) v1.4 (9), showing an 81% satisfaction rate.

3 Discussion

Pathogenetic mechanisms of DILI may be heterogeneous and include idiosyncratic reactions, trigger of autoimmune hepatitis (AIH) and viral reactivation (10). Differential diagnosis between DILI and AIH may be challenging, especially in patients with a pre-existing autoimmune disorder like MS, and both DILI and AIH have been described in association with DMTs and IVMP pulsed therapy (10). In our patient, liver injury was characterized by a hepatocellular pattern, autoantibodies were negative, and it resolved spontaneously

after drug withdrawal. In our opinion, these findings overall suggest that its pathogenesis was plausibly idiosyncratic (11), although we lack histopathological assessment as liver biopsy was not performed due to the spontaneous resolution of injury after each episode.

A peculiarity of this case is that three distinct episodes of DILI (12) were observed over 7 years, occurring while receiving three different DMTs (IFN, dimethyl-fumarate and ocrelizumab), and showing a temporal association with IVMP in at least one occasion, when the patient was under tamoxifen treatment. IVMP pulsed therapy is known to be associated with liver injury. In a prospective observational study including 175 MS patients receiving IVMP (1,000 mg/day for 5 days) for disease activity, a 8.6% prevalence of liver injury was observed, being the injury severe (according to Hy's law) in 2.5% of the cases (4).

In our patient, the association of IVMP with other drugs (IFN, tamoxifen or dimethyl-fumarate) may have increased the odds for DILI, as the use of IVMP alone was not followed by remarkable serum aminotransferase elevation. The potential hepatotoxicity of both IFN and dimethyl-fumarate is well established. In the LiverTox® database, which classifies drugs based on the number of published reports of convincingly documented idiosyncratic liver injury, IFN is assigned a likelihood score A (i.e., well-known cause of clinically apparent liver injury), whereas dimethyl-fumarate a score C (i.e., probable rare cause of clinically apparent liver injury) (13). Furthermore, IFN was associated with a signal of disproportionate reporting in a pharmacovigilance-based study (3). The use of concomitant therapies, including tamoxifen, may have contributed to the liver injury observed in our patient; accordingly, the use of concomitant drugs was reported in 47% of DILI cases from the FARES study (3).

Ocrelizumab is considered to be associated with a low likelihood of liver injury (category D, i.e., rare cause of clinically apparent liver injury), and this is probably related to HBV reactivation (13). With few exceptions (14–16), all the ocrelizumab-associated DILI events reported in the literature were indeed associated with HBV reactivation (1). B-cell depleting therapies may cause reactivation of hepatitis B through their immunosuppressive action, and HBV reactivation may, in turn, induce acute hepatocellular injury, potentially leading to acute liver failure (17). In our patient, serological markers of HBV infection were repeatedly negative, as it was HBV DNA, thus allowing us to rule out that the latest episode of DILI was associated with HBV reactivation. As low-dose IVMP (100 mg) is administered as an ancillary drug before ocrelizumab infusion, we cannot exclude that this might have contributed to the DILI event associated with ocrelizumab, also considering the previous history of IVMP-associated DILI (mostly observed in association with other treatments) (18).

The choice of switching the patient to ofatumumab was based mainly on the following reasons: (i) evidence of MS activity requiring treatment with a high-efficacy DMT; (ii) serum aminotransferase elevations are uncommon during ofatumumab therapy, and clinically apparent liver injury associated with this DMT has not been reported to date in the Livertox® database (13); (iii) differences in structure, pharmacokinetic and pharmacodynamic between ocrelizumab and ofatumumab, including a different route of administration; and (iv) the lack of requirement for any ancillary drugs with ofatumumab. Treatment with alternative high-efficacy DMTs was also discussed. PML risk (index 3.54 plus previous exposure to immunosuppressive treatment) and patient's convenience (she needs to travel for almost 3 h to get to the hospital) led to the exclusion of natalizumab, as it was deemed to have a detrimental impact on her quality of life, even if adopting an extended interval dosing. Sphingosine 1-phosphate modulators were also discussed, but their efficacy/safety profile was considered less favorable compared to that of CD20-depleting mAbs (18–20).

In our patient, the switch to ofatumumab was safe so far, as no further elevations in liver enzymes were observed over five months of treatment, and effective, without any new signs of MS activity.

The main limit of this case report is the short period of observation after ofatumumab start, and further follow-up is needed to confirm ofatumumab safety profile over long term, especially in case of concomitant administration of drugs with potential hepatotoxicity. Another limitation is the lack of histopathological liver assessment, as biopsy was not performed due to the spontaneous resolution of liver injury.

In conclusion, the present case report indicates that ofatumumab may be safely administered in patients who had experienced DILI associated with DMTs and specifically during ocrelizumab treatment, providing that HBV reactivation has been ruled out.

4 Patient perspective

The patient manifested a high rate of satisfaction with ofatumumab treatment, despite a tighter schedule of administration of ofatumumab compared to ocrelizumab and the SC route. The satisfaction was mainly driven by an optimal tolerability to the drug, including the lack of liver adverse events.

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

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 from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. 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

AM: Conceptualization, Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing. AB: Data curation, Writing – review & editing. AL: Data curation, Writing

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Conflict of interest

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Probable secondary hemophagocytic lymphohistiocytosis manifesting as central nervous system lesions after COVID-19 vaccination: a case report

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare systemic inflammatory disease commonly characterized by histiocyte infiltration in multiple organs, such as the liver, spleen, lymph nodes, bone marrow, and central nervous system. The clinical features of HLH include fever, splenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, and elevated blood ferritin levels. HLH is categorized as either primary or secondary. Coronavirus disease 2019 (COVID-19) vaccines may occasionally trigger secondary HLH, which is related to hyperinflammatory syndrome.

Case presentation: A 58-year-old woman, previously diagnosed with Graves' disease, presented with cognitive decline 2 weeks after receiving the first dose of the ChAdOx1 nCoV-19 vaccine. Brain MRI revealed a hyperintense lesion on T2-weighted and fluid-attenuated inversion recovery images in the bilateral subcortical white matter and right periventricular area. Vaccination-associated acute disseminated encephalomyelitis was suspected and methylprednisolone and intravenous immunoglobulin (IVIg) were administered. From the 5th day of IVIg administration, the patient developed fever and pancytopenia. In the findings of bone marrow biopsy, hemophagocytosis was not observed; however, six of the eight diagnostic criteria for HLH-2004 were met, raising the possibility of HLH. Although there was no definitive method to confirm causality, considering the temporal sequence, suspicion arose regarding vaccine-induced HLH. Splenectomy was considered for therapeutic and diagnostic purposes; however, the patient died on the 28th day of hospitalization owing to multiple organ failure.

Conclusion: To date, 23 cases of COVID-19 vaccine-related HLH have been reported. Additionally, HLH in COVID-19 patients has been reported in various case reports. To the best of our knowledge, this is the first reported case of central nervous system involvement in HLH related to any type of COVID-19 vaccine. This case suggests that even when there are no systemic symptoms after COVID-19 vaccination, HLH should be considered as a differential diagnosis if brain lesions are suggestive of CNS demyelinating disease.

KEYWORDS

hemophagocytic lymphohistiocytosis, COVID-19 vaccines, ChAdOx1 nCoV-19, natural killer cell, acute disseminated encephalomyelitis

1 Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare immune disorder resulting from histiocyte infiltration into multiple organs, such as the liver, spleen, lymph nodes, bone marrow, and central nervous system (CNS). HLH is characterized by fever, cytopenia, splenomegaly, hypertriglyceridemia, hypofibrinogenemia, and elevated blood ferritin levels (1). HLH can be classified as primary or secondary. CNS involvement is less common among patients with secondary HLH compared with those with primary HLH. HLH can be difficult to differentiate from other disorders because infiltration of the CNS may manifest as an array of nonspecific neurological symptoms, including cranial nerve palsy, elevated intracranial pressure, and an altered level of consciousness (2). Brain magnetic resonance imaging (MRI) findings may also vary (2). As a result, delayed diagnosis of HLH with neurological manifestations is common, resulting in a poor prognosis. In this case report, we described a woman with secondary HLH with neurological manifestations following Coronavirus disease 2019 (COVID-19) vaccination with the Oxford Astra-Zeneca® ChAdOx1 nCoV-19 vaccine.

2 Case presentation

A 58-year-old female patient presented to the hospital with the chief complaints of aphasia and cognitive decline that began 2 weeks prior to presentation (Figure 1). Four weeks prior to the hospital visit, the patient had received the first dose of the COVID-19 vaccine (ChAdOx1 nCoV-19, Oxford Astra-Zeneca®). The patient did not experience any adverse events during the vaccination. In terms of medical history, she had been diagnosed with Graves' disease 20 years prior and had received medical treatment at that time. Subsequently, the patient achieved complete remission and has not been taking any medications since then.

Upon admission, the patient showed stable vital signs and was alert. Neurological examination revealed no limb weakness, sensory deficits, or cranial nerve deficits. Language assessment revealed transcortical aphasia and agraphia, with dyscalculia and finger agnosia. Blood test results were unremarkable, except for a decrease in hemoglobin level (Hb; 9.4 g/dL; normal range, 12–16 g/dL). Brain MRI revealed hyperintensity in the bilateral subcortical white matter and right periventricular area on both T2-weighted and fluid-attenuated inversion recovery images. Susceptibility-weighted imaging (SWI) revealed hypointensity in the same lesion area, and diffusion restriction was also observed on diffusion-weighted imaging, although without contrast enhancement (Figure 2). Analysis of a cerebrospinal fluid (CSF) sample showed a white blood cell count of 4/mm^3, protein of 43.6 mg/dL, and glucose level of 66 mg/dL (serum glucose, 154 mg/dL). The finding of a CSF to serum glucose ratio of 0.5 or less was not considered a significant finding, as it is likely attributed to a time delay in the lumbar puncture procedure. Considering the current test results, post-vaccination acute disseminated encephalomyelitis (ADEM) was suspected, and 1 g of methylprednisolone was administered intravenously daily for 5 days. Spinal cord MRI was performed to differentiate it from other demyelinating disorders of the CNS; however, the findings were unremarkable. The IgG index was 0.49, and CSF oligoclonal bands, serum anti-aquaporin 4 antibodies, and serum anti-myelin oligodendrocyte glycoprotein antibodies were negative. Following high-dose steroids therapy, the patient scored 21 on the Korean mini-mental state examination, showing a 3-point improvement in the "attention and calculation" domain compared to before steroid therapy. Aphasia also improved, and the patient was able to speak words and simple sentences. Moreover, the patient was able to perform one-digit addition and subtraction. However, cognitive decline persisted. Hence, intravenous immunoglobulin (IVIg) therapy was initiated at 400 mg/kg/day on day 13, lasting for 5 days. Agraphia and cognitive function improved slightly during IVIg therapy, but her platelet level dropped to 10.8 K on day 3 of IVIg administration (admission day 15), and a fever of ≥38°C persisted from day 5 of IVIg administration (admission day 17). Blood tests indicated pancytopenia (white blood cell count, 3,920/mm^3; Hb, 6.8 g/dL; and platelet count, 44,000/mm^3). The C-reactive protein level was 8.5 mg/dL (normal range 0.0–0.3 mg/dL), and procalcitonin was 0.54 ng/mL (normal range 0–0.5 ng/mL). Blood, sputum, and urine cultures were performed to identify the cause of fever, but findings were unremarkable. The serum viral antibody test results were negative. CSF samples were tested using polymerase chain reaction and were negative for herpes simplex virus, varicella-zoster virus, and Epstein–Barr virus. Chest and abdominal computed tomography did not indicate infection, but showed hepatomegaly and splenomegaly.

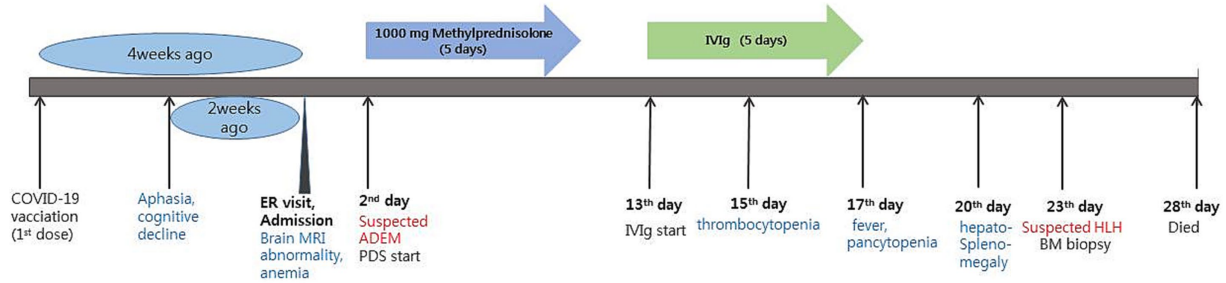

FIGURE 1
Timeline of the patient's disease and treatment course. ER, emergency room; ADEM, acute disseminated encephalomyelitis; PDS, prednisolone; IVIg, intravenous immunoglobulin; HLH, hemophagocytic lymphohistiocytosis.

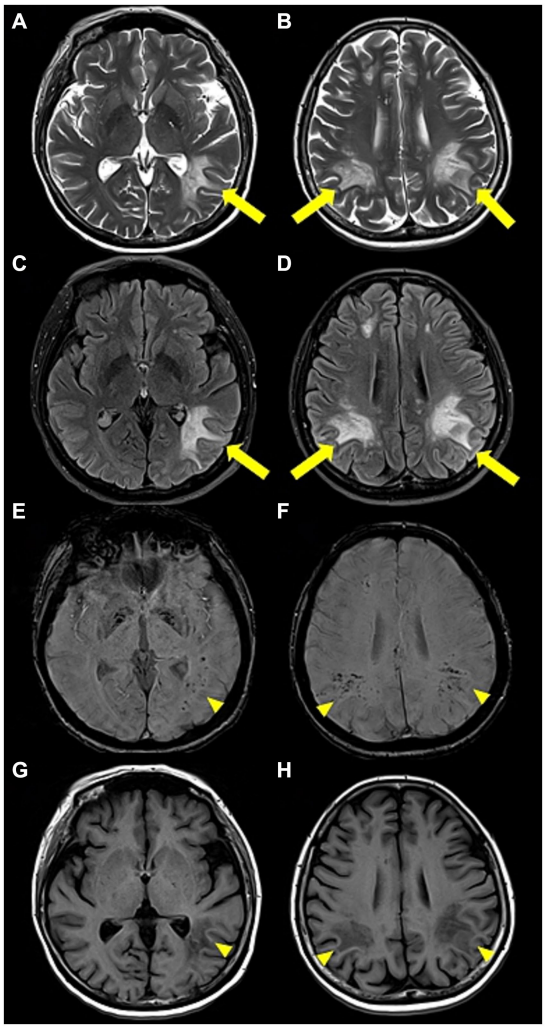

FIGURE 2
Brain magnetic resonance images. **(A,B)** Axial T2-weighted and **(C,D)** axial fluid-attenuated inversion recovery images revealed high-signal intensity lesions (yellow arrow) in the bilateral subcortical white matter and the right periventricular area. **(E,F)** Axial susceptibility-weighted images and **(G,H)** axial T1-weighted images showed low-signal intensity lesions (yellow arrowhead) in the same area.

Subsequently, the patient was referred to the hemato-oncology department for fever of unknown cause, and pancytopenia that lasted more than a week. HLH was suspected. Additional blood tests and bone marrow biopsies were also performed. Bone marrow biopsy did not indicate hemophagocytosis. However, six out of the eight HLH-2004 diagnostic criteria were met including fever, splenomegaly, cytopenia (Hb 6.8 g/dL and platelets 44,000/mm^3), hypertriglyceridemia (triglycerides 268 mg/dL), increased ferritin (>1,675 mcg/L), and reduced natural killer cell (NK cell) activity (<40.0 pg./mL). As a results, the patient was diagnosed with probable HLH following COVID-19 vaccination, based on the temporal sequence, although it was not definitively proven. Splenectomy was planned to assess the preexisting causes of HLH (other than vaccination) and treatment. Unfortunately, the patient died on day 28 owing to sudden hypotension and multiple organ failure.

3 Discussion

Our patient presented with acute aphasia and cognitive decline 2 weeks after receiving the first dose of the COVID-19 vaccine. Subsequent brain MRI findings suggested ADEM, which led to the administration of high-dose steroids and IVIg. However, during the course of treatment, the patient developed systemic symptoms including fever and pancytopenia, eventually resulting in a diagnosis of HLH.

HLH is classified as either primary HLH (pHLH) or secondary HLH (sHLH) (3). pHLH predominantly affects children and is caused by genetic mutations that influence immune inactivation signaling pathways. In contrast, sHLH is triggered by infections, autoimmune disorders, and malignant tumors. Both pHLH and sHLH can involve the CNS, although CNS involvement is more common in pHLH (4). Neurological involvement may manifest as an array of nonspecific symptoms, including cranial nerve palsy, elevated intracranial pressure, and an altered level of consciousness. Moreover, brain MRI findings are not specific, so it is often difficult to differentiate HLH from CNS demyelinating disorders, such as ADEM or vasculitis of the CNS (2). Diagnosis of HLH may be delayed if only CNS symptoms manifest initially, or systemic symptoms develop a considerable time following the initial CNS symptom onset (1). CNS involvement indicates poor prognosis (5). In our case, the patient initially experienced CNS symptoms without systemic symptoms following a recent COVID-19 vaccination, leading to a provisional diagnosis of ADEM. However, approximately 4 weeks after the initial CNS symptoms, systemic symptoms presented, raising the suspicion of HLH. With a delay in diagnosis, multi-organ failure occurs, resulting in death.

A previous study was conducted to classify the differences in MRI findings among patients with pediatric pHLH, pediatric sHLH, and ADEM (4). In this study, comparison of the brain MRI scans of patients with pHLH and sHLH revealed that hypointense but clear lesions were observed on T1-weighted images more frequently in sHLH than in pHLH. Other distinct patterns emerged in the comparative analyses of the pHLH, sHLH, and ADEM groups. Compared to pHLH, ADEM cases exhibited more prominent lesions in the periventricle, brainstem, hypothalamus, and basal ganglia, displaying a higher frequency of hypointense signal intensity on T1-weighted images and an asymmetric distribution. In contrast, patients with pHLH manifested larger lesions than those with ADEM. The juxtacortical lesions were more distinctly visible in the ADEM group than in the sHLH group (4). Furthermore, a previous report showed that hemorrhagic brain lesions can sometimes be observed in HLH, possibly due to ischemic injury and necrosis from perivascular infiltration in systemic inflammation (6). In our patient, hypointense lesions on T1-weighted imaging and hypointense hemorrhagic lesions on SWI strongly suggested sHLH, rather than pHLH or ADEM. In cases showing lesions suspicious for CNS demyelinating and hemorrhagic lesions, even in the absence of typical systemic symptoms, HLH should be considered as a potential differential diagnosis.

To date, several cases of HLH following COVID-19 vaccination have been reported. mRNA-based COVID vaccines such as BNT162b2mRNA (Pfizer-BioNTech®) or mRNA-1273 (Moderna Therapeutics) have shown potential to trigger hyper-inflammatory

TABLE 1 Clinical characteristics and treatment outcomes of patients with HLH after COVID-19 vaccination.

Case (ref.)	Age/sex	Vaccine	1st/2nd	Symptoms onset after vaccination	Underlying disease	HLH-2004 diagnostic criteria[a] (number of criteria to be satisfied)	Hscore	Treatment	Outcomes
Case 1 (10)	68/M	ChAdOx1nCov-19	1st	10 days	Hypertension Gout Bowen's disease	1,2,3,4,6	250	No therapy	Spontaneous improvement
Case 2 (12)	36/F	ChAdOx1nCov-19	1st	9 days	None	1,2,4	200	Methylprednisolone, IVIg	Improvement within 72 h, 2nd episode after 6 days, improved after IVIg
Case 3 (21)	71/F	ChAdOx1nCov-19	1st	7 days	Hypertension	1,2,3,4,5,6,8	293	Dexamethasone Etoposide	Discharged after 8 weeks in good condition
Case 4 (20)	60s/M	ChAdOx1nCov-19	1st	5 days	Hypertension	1,4,5,6,8,	259	Methylprednisolone IVIg Anakinra	Alive
Case 5 (20)	70s/F	ChAdOx1nCov-19	1st	7 days	Essential thrombocythemia Breast cancer in remission	1,4,5,6,8	220	Methylprednisolone IVIg Anakinra	Death
Case 6 (20)	30s/M	ChAdOx1nCov-19	1st	8 days	Ankylosing spondylitis	1,2,4,5,6,8	219	Methylprednisolone	Alive
Case 7 (21)	20/M	BNT162b2 mRNA	1st	2 days	None	1,2,3,4,5,6,7,8	229	Dexamethasone	Alive
Case 8 (13)	85/M	BNT162b2 mRNA	1st	Shortly	None	5,6	N/A	N/A	N/A
Case 9 (14)	52/M	BNT162b2 mRNA	1st	1 day	T-cell lymphoma	1,2,4,5,6,8	239	Dexamethasone Etoposide	Death (neutropenic fever and Bacteroides bacteremia)
Case 10 (14)	53/M	BNT162b2 mRNA	1st	4 days	Interstitial lung disease	1,4,6,8	213	Dexamethasone IVIg Anakinra	Alive
Case 11 (14)	55/F	BNT162b2 mRNA	1st	3 days	MAC, MDS pulmonary aspergillosis	1,2,3,4,8	208	Anakinra	Slowly recovered
Case 12 (7)	24/F	BNT162b2 mRNA	1st	10 days	None	1,2,3,5	259	Dexamethasone IVIg Anakinra	Discharged 14 days after treatment initiation in good condition

(Continued)

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TABLE 1 (Continued)

Case (ref.)	Age/sex	Vaccine	1st/2nd	Symptoms onset after vaccination	Underlying disease	HLH-2004 diagnostic criteria[a] (number of criteria to be satisfied)	Hscore	Treatment	Outcomes
Case 13 (16)	60/M	BNT162b2 mRNA	1st	6 days	Barrett's esophagus	1,2,3,4,6,8	198	Prednisone Etoposide	Partial remission
Case 14 (18)	14/F	BNT162b2 mRNA	1st	15 days	None	1,2,3,4,5,6	N/A	IVIg Methylprednisolone	Alive
Case 15 (17)	85/F	BNT162b2 mRNA	1st	12 days	Hypertension, Nephrosclerosis	1,3,4,6	N/A	Methylprednisolone	Alive
Case 16 (15)	38/F	BNT162b2 mRNA	2nd	21 days	None	1,4,6,7,8	147	Methylprednisolone	Discharged after 1 week after recovered within weeks
Case 17 (9)	21/M	BNT162b2 mRNA	2nd	14 days	None	1,2,3,4,5,6	319	Methylprednisolone Dexamethasone	Discharged 23 days after treatment initiation with good condition
Case 18 (16)	32/F	BNT162b2 mRNA	2nd	52 days	None	1,2,3,4,5,6,7	271	Dexamethasone Etoposide	Slowly recovered
Case 19 (19)	33/M	BNT162b2 mRNA	2nd	3 days	Hyperlipidemia allergies	1,2,3,4,6	274	Prednisone Methylprednisolone Anakinra IVIg	Death (acute liver failure)
Case 20 (14)	48/F	mRNA-1273	1st	8 days	HIV disseminated MAC and IRIS	1	130	Prednisone Infliximab	Improvement within 72 h
Case 21 (14)	57/M	mRNA-1273	1st	12 days	Controlled HIV	3,4,8	185	Methylprednisolone	Death
Case 22 (11)	43/F	Chinese inactivated SARS-CoV-2 vaccine	1st	Shortly	EBV	1,3,4,5,6,7	261	Dexamethasone	Discharged 17 days after start of dexamethasone
Case 23 (8)	61/unknown	Ad26.COV2.S	1st	10 days	Hypertension, Warthin's right parotid gland tumor	1,2,3,4,5,6	186	Dexamethasone IVIg	Death (acute respiratory insufficiency, cardiorespiratory arrest- 46 days after vaccination)

IVIg, intravenous immunoglobulin; MAC, Mycobacterium avium complex; MDS, myelodysplastic syndrome; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome; EBV, Epstein-Varr virus; mRNA, messenger RNA; N/A, not applicable.[a]HLH 2004 diagnostic critereia: 1—Fever (≥ 38.3°C); 2—splenomegaly; 3—cytopenia in ≥ 2 lines (Hb < 9 g/dL, plt < 100/nL, neutrophils < 1.0/nL); 4—ferritin ≥ 500 μg/L; 5—hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥ 265 mg/dL, fibrinogen < 1.5 g/L); 6—hemophagocytosis in bone marrow or spleen or lymph nodes; 7—low or absent Natural killer cell activity; 8—soluble CD25 (soluble IL-2 receptor) ≥ 2,400 U/mL.

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syndrome due to an excessive secretion of interleukin-1-beta by dendritic cells in response to the spike protein encoded by the mRNA vaccine (7). Furthermore, adenovirus vector-based COVID vaccines, such as ChAdOx1 nCov-19 (AstraZeneca-Oxford) and Ad24.COV2.S (Janssen-Johnson & Johnson), may also potentially induce hyper-inflammatory syndrome, either as a reaction to the COVID-19 spike protein similar to mRNA vaccines or due to an exaggerated host immune response to the adenoviral component of the vaccine (8). To date, 23 cases of COVID-19 vaccine-related HLH have been reported (7–21) (Table 1). Of these, six patients developed HLH following ChAdOx1 nCov-19 vaccination, similar to our patient. Moreover, all six patients, including ours, developed HLH after the first dose of the vaccine. Thirteen of 23 patients developed HLH following BNT162b2mRNA vaccination (nine after the first dose and four after the second dose). Two patients developed HLH following the first dose of mRNA-1273 vaccination, one after Ad24.COV2.S vaccination, and the other after the first dose of inactivated severe acute respiratory syndrome coronavirus 2 vaccine. Among the 23 patients, twenty initially presented with fever, while one presented with appetite loss, lethargy, and rash without fever. In contrast, one patient with pre-existing well-controlled human immunodeficiency virus infection showed hypothermia (30.2°C) at the time of presentation (14). Another patient had an altered level of consciousness and dysarthria without fever, and was diagnosed with a transient ischemic attack. However, this patient developed fever 1 month later, and was eventually diagnosed with HLH (16). Similarly, our case showed no fever upon admission, but fever occurred during hospitalization for treatment of brain lesions. However, one important difference from previous reports was the presence of brain lesions, indicating CNS involvement in HLH, as observed in our patient.

Treatment for HLH primarily begins with immunosuppressive agents like cyclosporine and dexamethasone to manage immune system hyperactivity. If this approach proves insufficient, cytotoxic chemotherapy agents are administered to target excessive T cells and NK cells. Options include etoposide-based regimens or cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) therapy, commonly used in lymphoma. In cases of CNS involvement, intrathecal methotrexate injections may be considered. However, if patients do not respond to initial therapy, experience reactivation, or are diagnosed with primary HLH, allogeneic hematopoietic stem cell transplantation (HSCT) becomes necessary (22). The long-term survival rate after allogeneic HSCT is approximately 22–59% (23). In our case, initially misdiagnosed as ADEM, immunotherapies such as high-dose steroids and IVIg were administered, resembling initial immunotherapy for HLH; however, these treatments proved ineffective. Therefore, prompt diagnosis of HLH is crucial for timely initiation of aggressive treatment, including cytotoxic agents. Unfortunately, our study of the present case had several limitations. Firstly, we were unable to perform a splenectomy for therapeutic and diagnostic purposes to confirm hemophagocytosis in the spleen. Additionally, we could not perform an autopsy or brain histopathology examination to exclude other causes and definitively confirm sHLH with CNS involvement. To the best of our knowledge, this is the first report of sHLH with CNS involvement following vaccination with all types of COVID-19 vaccines, including the ChAdOx1 nCov-19.

In conclusion, sHLH should be considered as a differential diagnosis in cases that present with neurological symptoms without systemic symptoms, such as fever, following COVID-19 vaccination. This is important because these neurological symptoms could indicate CNS involvement related to HLH.

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 study involving humans was approved by Chosun University Hospital IRB/2023-10-007. The study was conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the patient's legal guardian for the publication of this case report.

Author contributions

JK: Writing – original draft. JC: Writing – review & editing. JB: Writing – original draft, Writing – review & editing.

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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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Gait instability, ophthalmoplegia, and chorea with orofacial dyskinesia in a man with anti-Ri antibodies: a case report

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A 79-year-old man was admitted for 2 weeks of dizziness, followed by diplopia, involuntary movement and progressive gait disturbances. Neurologic examination revealed horizontal and vertical gaze paresis, bilateral choreiform movement with orofacial dyskinesia, and limb/truncal ataxia. MRI revealed fluid-attenuated inversion recovery image-hyperintense signal abnormalities in the dorsal midbrain, pontine and medulla. Within another few days, the patient developed type II acute respiratory failure requiring artificial invasive ventilation. Because autoimmune encephalitis was suspected, he received intravenous immunoglobulin therapy followed by intravenous methylprednisolone, but only his ophthalmoplegia improved minimally. Serological tests were positive for anti-Ri onconeural antibodies. CT-guided mediastinal lymph node biopsy was performed and revealed small cell lung carcinoma. We report the rare manifestation of anti-Ri antibody-associated paraneoplastic neurological syndrome (PNS), and this case can alert us to the importance of respiratory management in this diverse neurologic disease. Furthermore, PNSs positive for anti-Ri antibodies should be added to the list of differential diagnoses of chorea with orofacial dyskinesia.

KEYWORDS

paraneoplastic neurological syndrome, anti-Ri antibody, chorea with orofacial dyskinesia, respiratory failure, case report

Introduction

Paraneoplastic neurological syndrome (PNS) can be caused by altered immune reactions mediated by distant tumors. These reactions can be described as conditions that result from the indirect effects of cancer secondary to antigen–antibody interactions incited by the underlying malignancy. Onconeural antibodies are antibodies against intracellular antigens and are considered high-specific markers of a paraneoplastic etiology. Anti-Ri antibody-associated PNSs are known to exhibit characteristic symptoms such as opsoclonus-myoclonus syndrome (OMS) and ataxia, but heterogeneous clinical manifestations have been reported (1). This rare PNS is more common in women with breast cancer and in men with bladder cancer, lung cancer or seminoma (2). We herein report a patient with anti-Ri antibody-positive PNS who presented with characteristic clinical manifestations followed by acute respiratory failure.

Case description

A 79-year-old man presented with a two-week history of dizziness, which was followed by diplopia, involuntary hyperkinetic movements of both the arms and face, and an unsteady gait. His medical history included type II diabetes and hypertension, which were well controlled with oral medications. He did not take any psychiatric agents. He repeatedly fell and felt dyspnea upon exertion. On admission, he was afebrile and had an oxygen saturation of 98% with 3 L of inhaled oxygen. He remained oriented but was not clearly conscious and seemed agitated. Neurologic examination revealed horizontal and vertical gaze palsy in both eyes without opsoclonus. Normal direct and indirect pupillary responses were observed. There was no facial muscle weakness or sensory deficits. Prominent bilateral choreiform movements were observed (see Supplementary Video S1), and these movements appeared during the day and disappeared during sleep. Repeated involuntary movements of his face, such as frowning and sticking out his tongue, were observed (see Supplementary Video S2), resulting in hyperkinetic dysarthria. No signs of meningeal irritation were noted. He had full motor power and no sensory deficits. His reflexes were decreased in the lower extremities. He had bilateral ataxia on finger-to-nose testing, dysdiadochokinesia, and heel-to-shin dysmetria. Due to severe truncal ataxia, he had difficulty holding an end-sitting or standing position.

The blood cell counts were normal with normal erythrocyte morphology on the blood smear. Basic serum biochemistry tests showed only nonspecific findings, with elevated C-reactive protein and creatine kinase and reduced sodium results. The aquaporin-4 antibody, antinuclear antibody, interferon-gamma release assay, and angiotensin converting enzyme results were negative or within the normal range. Anti-thyroid peroxidase (24 IU/mL, normal range < 16) and anti-thyroglobulin antibodies (51.2 IU/mL, normal range < 28) were positive, but the patient had normal thyroid hormone levels. His glutamic acid decarboxylase antibody level was mildly elevated (35 U/L, normal range < 5). He had a normal glucose level with a glycated hemoglobin level of 6.9% (National Glycohemoglobin Standardization Program). A screening test for tumor markers revealed elevated pro-gastrin-releasing peptide (121 pg./mL, normal range < 81), squamous cell carcinoma antigen (3.3 ng/mL, normal range < 1.5), and neuron-specific enolase (25.7 ng/mL, normal range < 16.3%). A cerebrospinal fluid examination revealed mild lymphocyte pleocytosis (24 cells/mm^3, normal range < 5), mild elevation in protein (53.6 mg/dL) with a high IgG index (0.81), and negativity for cytology and viral markers. A brain MRI revealed fluid-attenuated inversion recovery image-hyperintense lesions in the dorsal medulla, pons, and midbrain with no associated enhancement or restricted diffusion (Figure 1). There was no abnormal signal or atrophy in the basal ganglia. An electroencephalogram did not reveal epileptiform discharges.

Figure 2 shows the clinical course and treatment of the patient. On day 3 of admission, he further deteriorated with hypercapnic hypoxic respiratory failure (pH, 7.299; $PaCO_2$, 77.9 mmHg; PaO_2, 68.8 mmHg) requiring artificial invasive ventilation. Because autoimmune encephalitis, such as Bickerstaff brainstem encephalitis, was suspected, he received intravenous immunoglobulin (0.4 g/kg/day for 5 days) followed by two courses of intravenous methylprednisolone each for three days, with partial recovery of the ophthalmoplegia; however, the treatment had no effect on his hyperkinetic movement or respiratory failure. Subsequently, he was found to be negative for the anti-GQ1b antibody. Serological tests were positive for anti-Ri onconeural antibodies but negative for anti-Yo, anti-Hu, anti-Ma1, anti-Ma2, anti-amphiphysin, and anti-CV2/collapsin response mediator protein 5 (CRMP5). The antibodies against N-methyl-D-aspartate receptor (NMDAR), leucine-rich glioma-inactivated protein 1 (LGI1), contactin-associated protein 2, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, γ-amino butyric acid B receptor, dipeptidyl aminopeptidase-like protein 6 and myelin oligodendrocyte glycoprotein in the serum and cerebrospinal fluid were all negative.

Chest contrast-enhanced computed tomography (CT) revealed no mass in the pulmonary field, but pleural effusion and mediastinal lymphadenopathy, including in the para-aortic lymph nodes, were noted (Supplementary Figure S1). CT-guided mediastinal lymph node biopsy was performed and revealed small cell lung carcinoma (Supplementary Figure S2). This patient was diagnosed with anti-Ri antibody-associated paraneoplastic brainstem encephalitis with small cell lung cancer. He and his family refused any treatment for his lung cancer, and he was then transferred to another facility.

Discussion

The present case showed a characterized and rare presentation of PNS with positivity for anti-Ri antibodies, such as ophthalmoplegia, chorea with orofacial dyskinesia and gait disturbance, and these symptoms were followed by acute respiratory failure. The anti-Ri antibody is a marker of $CD8^+$ T-cell-mediated PNS and is strongly associated with cancer. The clinical manifestations result from a central nervous system injury to neuroanatomic regions that express neuro-oncological ventral antigen (NOVA)-1 and NOVA-2, which are RNA-binding proteins that regulate neuronal pre-mRNAs that are mainly expressed in the dorsal brainstem and cerebellum (3). Autopsies of anti-Ri PNS patients revealed neuronal cell loss with astrogliosis in the brainstem and Purkinje cell loss with Bergmann gliosis in the cerebellum. Immunohistochemistry has shown a predominance of B cells and $CD4^+$ T cells in perivascular spaces and cytotoxic $CD8^+$ T cells in parenchymal infiltrates (4). The production of anti-Ri antibodies results from an immune-mediated response against processed onconeural polypeptides presented to CD4+ T helper cells on major histocompatibility complex (MHC) class I. Among parenchymal inflammatory cells, Ri-specific cytotoxic $CD8^+$ T lymphocytes conceivably target neurons that express Nova-derived peptides in the context of upregulated MHC class 1 (4).

Although OMS was previously thought to be the classical manifestation of anti-Ri PNS (5), Simard et al. (2) claimed that only 25% of patients in their French cohort presented with OMS. Recently, the clinical phenotype of PNSs positive for the anti-Ri antibody has been considered more divergent. Basically, patients with anti-Ri antibodies present with neurologic syndromes involving the brainstem or cerebellum, such as limb and truncal ataxia resulting in gait disturbances and ophthalmoplegia with and without OMS (1). Atypical symptoms and signs, such as isolated confusion, syndrome of inappropriate antidiuretic hormone secretion, and dysautonomia with central hypoventilation, were also detected in a minority of the patients (2). In a retrospective case series of 28 patients with anti-Ri antibodies (1), the most common initial symptom was gait instability (86%). Horizontal gaze palsy (21%) and jaw opening dystonia (14%) were also common accompanying symptoms. Similarly, a retrospective French cohort of 36 patients with anti-Ri (2) showed four main symptoms at disease onset, and these included cerebellar syndrome (39%), which presented with gait instability/ataxia

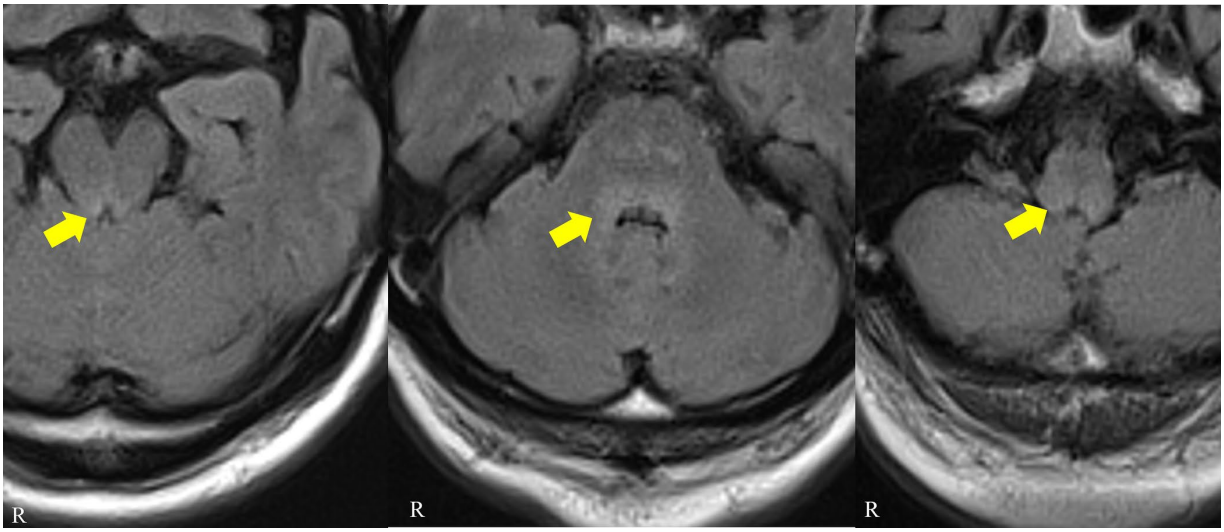

FIGURE 1
Patient brain MRI. Axial fluid-attenuated inversion recovery images showing hyperintense signals in the dorsal midbrain, pons and medulla (arrows).

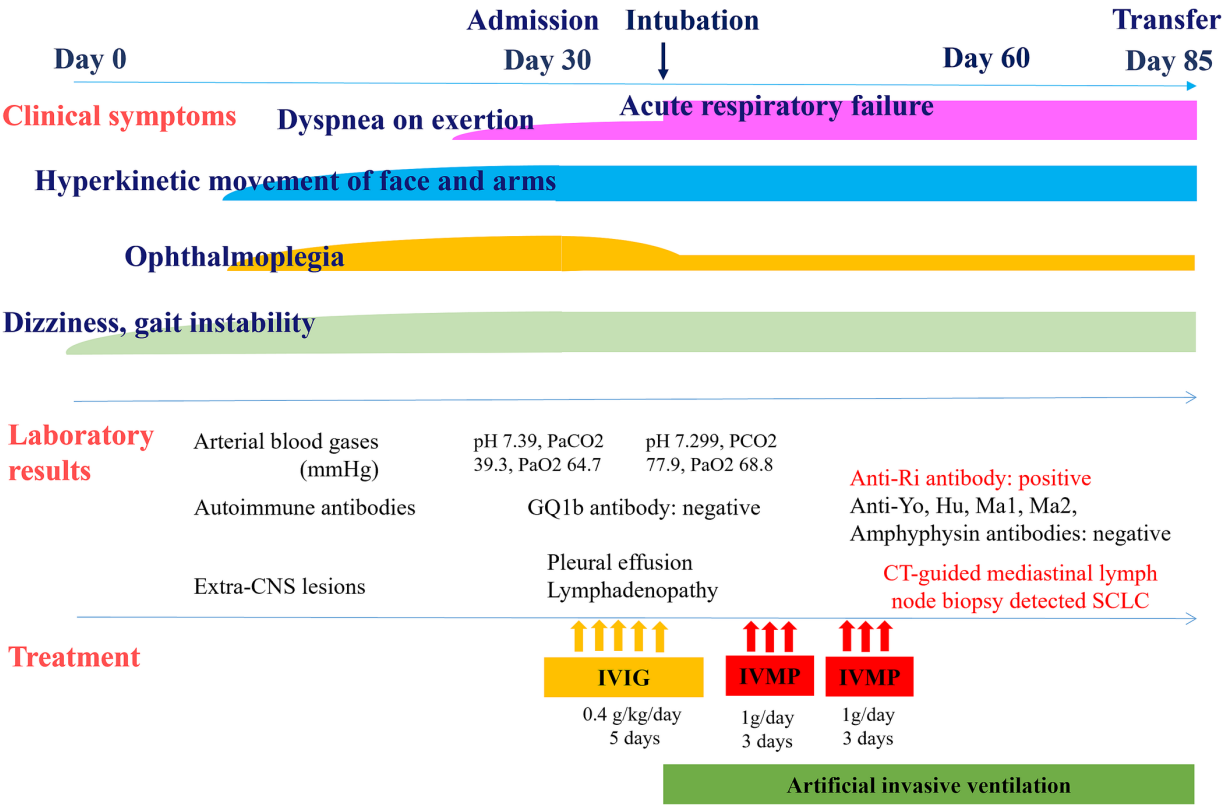

FIGURE 2
Clinical course and treatment of the patient.

and an action tremor; an isolated tremor (25%); oculomotor disturbances (17%); and other symptoms (19%). Our patient also initially suffered from diplopia and gait disturbances because of truncal ataxia, and these symptoms are considered common clinical manifestations of anti-Ri PNS.

Chorea with orofacial dyskinesia was the most striking manifestation in our patient. The most common antibody identified in paraneoplastic chorea is CRMP-5/CV2, followed by anti-Hu and NMDAR antibodies (6). Patients with paraneoplastic chorea can be normal on brain MRI or can exhibit extensive T2 hyperintense

TABLE 1 Patients positive for anti-Ri antibody presenting as paraneoplastic chorea

Author	Patients (age, y/sex)	Tumor	Other sings	Chorea characteristic	Immunotherapy/ chorea outcome	Oncologic therapy/ chorea outcome	Brain MRI	Concomitant antibodies
Pittock et al. 2003 (in review) (1)	50, female	Chest lesion (details not described)	Cerebellar symptoms, peripheral neuropathy, dysphagia	Not described	Not described	Not described	Not described	Anti-Hu
O'Toole et al. 2013 (in review) (9)	63, male	SCLC	Sensory ganglionopathy, myelopathy	Initially, focally occurring in the limbs, then generalized	PLEX, CTX, IVMP/Improved from bedbound to ability to mobilize with a walker	Chemotherapy/ gradual improvement over time	Not described	Anti-Hu, CRMP-5/ CV2
Martinková et al. 2009 (8)	60, female	Breast cancer (ductal carcinoma in situ)	Schizoaffective psychosis	Initially, hemichorea, then generalized	Amantadine sulfate, IVMP/ no improvement	Mastectomy, chemotherapy, anastrozole/no improvement	Atrophy in the caudate, putamen, para-hippocampal gyrus, hippocampus	Anti-Hu
Our case	79, male	SCLC	Gait disturbance, ophthalmoplegia, orofacial dyskinesia, respiratory failure	Bilateral chorea with orofacial dyskinesia	IVIg, IVMP/no improvement	Not applicable	FLIAR-hyperintensity in the dorsal brainstem without basal ganglia involvement	GAD 65 (low titer)

CRMP-5, collapsin response-mediator protein 5; SCLC, small cell lung carcinoma; IVIg, intravenous immunoglobulins; IVMP, intravenous methylprednisolone; PLEX 5, plasma exchange; CTX, cyclophosphamide; FLAIR, fluid-attenuated inversion recovery; GAD, glutamic acid decarboxylase.

signals in the bilateral basal ganglia (7). To our knowledge, only one case of anti-Ri antibody-positive paraneoplastic chorea has been reported in the literature (8). That report presented the disease course of a 60-year-old woman who initially developed acute schizoaffective psychosis. Two weeks later, her choreiform movements gradually occurred predominantly on her left side. After two months, she was diagnosed with ductal carcinoma *in situ* in the left breast. She underwent mastectomy, which was followed by the administration of chemotherapy and anastrozole. Although her breast cancer was treated effectively, her choreiform movements were persistent and generalized. Positive results for anti-Hu and anti-Ri antibodies were obtained. Brain MRI revealed bilateral atrophy in the caudate, putamen, parahippocampal gyrus and hippocampus. The patient received amantadine sulfate and intravenous methylprednisolone, but neither had any effect on her chorea. In the literature, there have been no other case reports of paraneoplastic chorea with positivity for anti-Ri antibodies; there was only one of 14 patients with paraneoplastic chorea in the 2013 review (9) and one of 28 patients with anti-Ri antibodies in the 2003 review (1). In all three of these patients, anti-Hu antibodies were simultaneously positive (Table 1). The detected tumors were SCLC (one case was not described in detail) and breast cancer. In the review by O'Toole, a favorable response to chemotherapy and immunotherapy was obtained in one of the patients, with regard to the patient's chorea, but the patient in the case reported by Martinková and our patient did not show any improvement in their chorea with treatment. Furthermore, jaw dystonia is a common involuntary movement of the face in anti-Ri PNS patients (10). Orofacial dyskinesia, including grimacing, forceful jaw opening and closing, and masticatory-like movements, is often observed in patients with paraneoplastic chorea with positivity for anti-CRMP5/ CV2, anti-Hu and anti-NMDAR antibodies (5) but has also been reported in patients with anti-LGI 1 (11) or anti-voltage-gated potassium channel complex antibodies (12). To our knowledge, this is the first case of anti-Ri PNS without concomitant anti-CRMP5/ CV2 or anti-Hu antibodies in which choreiform movements with orofacial dyskinesia was a striking clinical feature.

Central hypoventilation, especially during sleep (known as Ondine syndrome), may occur in a minority of Ri-PNS patients (2, 13). The condition was considered to affect the dorsal pontine, causing horizontal gaze palsy, and the pathology then extended downward to the medulla oblongata, causing Ondine's curse. Acquired central hypoventilation may result from pathologic involvement of the brainstem respiratory nuclei, as has been observed in other autoimmune diseases, such as anti-Hu brainstem syndrome and anti-NMDAR encephalitis (14, 15). Tay et al. (16) reported a case similar to our patient who presented with confusion, horizontal gaze palsy, gait disturbance, hemiataxia and SIADH, subsequent bulbar involvement and type II respiratory failure. Positive results for anti-Ri antibody and negative results for anti-Yo, anti-Hu and anti-Ma antibodies were obtained. Postmortem findings revealed $CD8^+$ T-cell-centered lymphocytic infiltration, particularly in the pons, medulla and circulatory and respiratory centers. Vigliani et al. (17) reported a man with brainstem encephalitis who was positive for both anti-Hu and anti-Ri antibodies and who subsequently developed acute respiratory failure. The postmortem findings included diffuse neuronal loss and reactive gliosis throughout the whole brain stem. Velazquez et al. (18) reported a 64-year-old man who presented

progressive muscle weakness, hypersomnia, tongue myoclonus, horizontal gaze palsy, ptosis and ventilator-dependent respiratory failure. He was positive for anti-Ri antibodies, and a peripancreatic lymph node biopsy showed poorly differentiated carcinoma from a pancreaticobiliary or pulmonary origin. His brain MRI was normal, and his brain pathology was not described. Stewart et al. (19) reported a rare case of nasopharyngeal carcinoma that was positive for anti-Ri antibodies and presented with opsoclonus, facial and limb myoclonus, truncal ataxia and type II respiratory failure. Brain MRI revealed abnormal signals in the left posterior medulla oblongata that extended into the left cerebellar peduncle. In our case, horizontal gaze palsy indicated lesions in the dorsal pontine, and vertical gaze palsy and hypoventilation suggested extension of the lesion to the mesencephalon and medulla, which was supported by the MRI findings. Although no other reports of hypoventilation in anti-Ri-PNS patients were found in our search, hypoventilation may cause sudden death, indicating the importance of cardiopulmonary monitoring in patients with anti-Ri-PNS.

Conclusion

We report a case of anti-Ri antibody-associated paraneoplastic brainstem encephalitis with small cell lung cancer that presented as gait instability, ophthalmoplegia, cerebellar symptoms, chorea with orofacial dyskinesia and acute hypoventilation. This report expands the body of knowledge on the clinical manifestations associated with anti-Ri antibodies and alerts us to the importance of respiratory management in these patients. Furthermore, PNSs positive for anti-Ri antibodies should be added to the list of differential diagnoses for patients with choreiform movement and orofacial dyskinesia.

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 humans were approved by the Institutional Ethical Committee of Dokkyo Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The patient provided their written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

MS: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. HF: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. HO: Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. HS: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. MH: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration. KS: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration.

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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.2024.1359781/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Chest contrast-enhanced computed tomography Pleural effusion and para-aortic lymphadenopathy were noted (arrow).

SUPPLEMENTARY FIGURE S2
The cytological finding of the lymph node biopsy sample revealed small cell lung carcinoma with small-sized neoplastic cells, high nuclear/cytoplasmic ratio, scant cytoplasm, fine granular chromatin and molding (Papanicolaou stain; original magnification, x1000).

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Stiff-person syndrome in association with Hashimoto's thyroiditis: a case report

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Stiff-person syndrome (SPS) is a rare neurological disorder characterized by chronic and progressive axial muscle rigidity and paroxysmal painful muscle spasms. The present case study described an SPS patient (increased anti-GAD65 antibody in serum and cerebrospinal fluid) with co-occurring Hashimoto's thyroiditis and decreased C3 complement levels. The clinical presentation, diagnostic approach, and treatment employed for this unique case were comprehensively described in detail. In this case, we comprehensively presented a case of SPS with co-occurring Hashimoto's thyroiditis and an associated decrease in serum C3 complement, as well as a discussion on the current data on this topic.

KEYWORDS

stiff-person syndrome, Hashimoto's thyroiditis, anti-GAD antibodies, autoimmune diseases, paraneoplastic syndromes

Introduction

Stiff-person syndrome (SPS) was initially described as "stiff-man syndrome" by Moersch (1) and subsequently renamed by Blum and Jankovic (2). SPS is a rare autoimmune disorder characterized by chronic and progressive stiffness of the axial muscle or limbs, along with paroxysmal painful muscle spasms. The primary manifestation of SPS is the involvement of the nervous system, resulting in stiffness, weakness, and spasms in the trunk and limb muscles. Subsequently, an abnormal gait and impaired movement are observed in affected patients. Furthermore, laryngeal and respiratory muscle spasms can lead to breathing difficulties and esophageal obstruction, which may pose serious or even life-threatening consequences. Typical results of electromyography (EMG) include continuous motor unit activity (CMUA) in muscles at rest. Additionally, co-contraction of agonist and antagonist muscles is another sign observed on EMG. The onset of SPS typically occurs between the ages of 20 and 50 (3) and is frequently accompanied by some other autoimmune diseases, such as type 1 diabetes mellitus (T1DM) (4). Given the low incidence of SPS and limited reports on its concurrent occurrence with Hashimoto's thyroiditis, along with decreased serum C3 complement levels, there may be a gap in the clinical understanding of SPS. In this case, we comprehensively presented a case of SPS with co-occurring Hashimoto's thyroiditis and an associated decrease in serum C3 complement levels as well as a discussion on the current data on this topic.

Case presentation

General case information

The patient is a 36-year-old right-handed Chinese married woman. The patient presented with initial symptoms of bilateral leg fatigue, difficulty initiating steps, and a loss of lower limb control. Subsequently, the patient's symptoms gradually progressed to limb rigidity, limited knee joint mobility, and intermittent difficulty initiating movements. Eventually, both walking and standing functions were affected. At an early stage of the illness, the patient was diagnosed with a "somatic symptom disorder" at a major medical center according to the physical symptoms at the time. Subsequently, the patient's condition evolved and progressed, with the manifestations of mental and psychological symptoms, such as anxiety, depression, paranoia, and obsessive-compulsive disorders. Accordingly, the patient was examined at a local neurology specialist hospital. Considering increased autoimmune thyroid antibody levels and the physical clinical symptoms, the patient was diagnosed with "Hashimoto's thyroiditis and Hashimoto's encephalopathy." The patient's symptoms improved with steroid treatment; however, discontinuation of steroids led to the recurrence of gait disturbance.

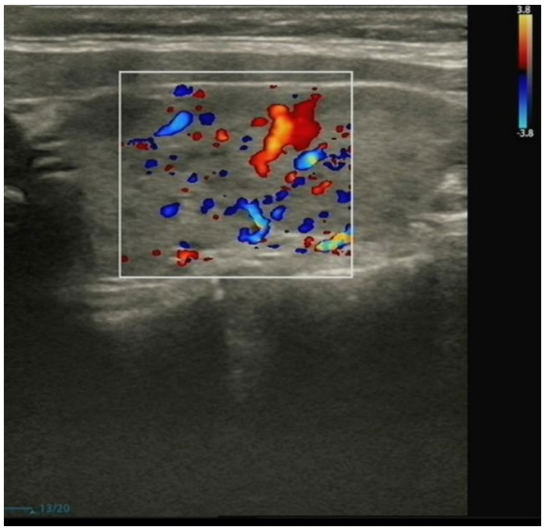

FIGURE 1
The representative ultrasonographic image of the thyroid of the patient.

Auxiliary examinations and investigations

The patient mainly received routine blood tests, other serologic tests, and cerebrospinal fluid (CSF) tests, inducing creatine kinase, paraneoplastic autoimmune antibodies, antineutrophil cytoplasmic antibodies (ANCA), complement proteins, erythrocyte sedimentation rate, ceruloplasmin, folate, vitamin B12 (VitB12), tumor markers, rheumatoid factors, glycated hemoglobin (HbA1c), and thyroid function during the hospitalization (Supplementary Table 1). The elevated thyroid peroxidase and thyroglobulin antibodies indicated a thyroid-associated autoimmune disorder (Supplementary Table 2). Furthermore, within the spectrum of paraneoplastic antibodies, the presence of anti-glutamic acid decarboxylase 65 (anti-GAD65) antibody was positive, with serum titer of 100 AU and a CSF titer of 25 AU, which may have diagnostic implications (Supplementary Tables 3, 4). It was noted that there was a slight decrease in serum C3 complement levels but no change in C4 complement levels (Supplementary Table 5). Other parameters were within normal reference ranges. Additionally, the ultrasonography of the abdomen and pelvis revealed a slightly rough wall of the gallbladder and a cystic hypoechoic lesion in the left adnexal region in the patient. There were no obvious abnormalities or space-occupying lesions in the liver, pancreas, spleen, bilateral kidneys, bilateral ureteric ducts, bladder, or uterus. The ultrasonography of the thyroid showed heterogeneous changes in both thyroid glands (Figure 1). The chest computed tomography (CT) and brain magnetic resonance imaging (MRI) showed no significant abnormalities (Figures 2, 3).

Abbreviations: SPS, Stiff-person syndrome; EMG, Electromyography; CMUA, Continuous motor unit activity; T1DM, Type 1 diabetes mellitus; ANCA, Antineutrophil cytoplasmic antibody; VitB12, Vitamin B12; HbA1c, Hemoglobin A1c; GAD65, Glutamic acid decarboxylase 65; CT, Computed tomography; MRI, Brain magnetic resonance imaging; CSF, Cerebrospinal fluid; γ-GABA, Gamma-aminobutyric acid; GD, Graves' disease; SLE, Systemic lupus erythematosus.

The diagnostic significance of EMG in the patient is markedly evident (Figure 4). Prior to the intravenous administration of 10 mg diazepam, extensive motor unit-like activity was observed in the muscles of both lower limbs, specifically the bilateral tibialis anterior and right vastus medialis (Figure 4A). Then, EMG recordings were taken at 1-, 3-, 5-, and 10-min intervals after diazepam administration, revealing that the right tibialis anterior muscle entered electrical quiescence during the relaxation phase without any signs of fibrillation potentials or positive sharp waves (Figure 4B). These findings strongly suggested a neuromuscular inhibitory effect induced by diazepam.

Diagnosis process

The patient primarily presented with stiffness of the lower limbs and trunk, which could be triggered by tactile stimulation, such as mild contact with another individual. The serum and CSF testing yielded positive results for the anti-GAD65 antibody, and the treatment with clonazepam (a benzodiazepine) was proven to be efficacious. The EMG findings indicated significant motor unit potentials in the relaxed state of muscles in the lower limbs (bilateral tibialis anterior and right adductor magnus). However, these changes disappeared following the intravenous administration of diazepam. This case met the diagnostic criteria for SPS as published by Chia et al. (5).

Case resolution

The patient initially received intravenous methylprednisolone at a dosage of 0.5 g per day for 5 days, followed by oral prednisone at a dosage of 40 mg per day, with a weekly reduction of 10 mg until 10 mg per day. Additionally, the patient was administered supplemental mycophenolate mofetil at a dosage of 0.25 g (bid), with an increment

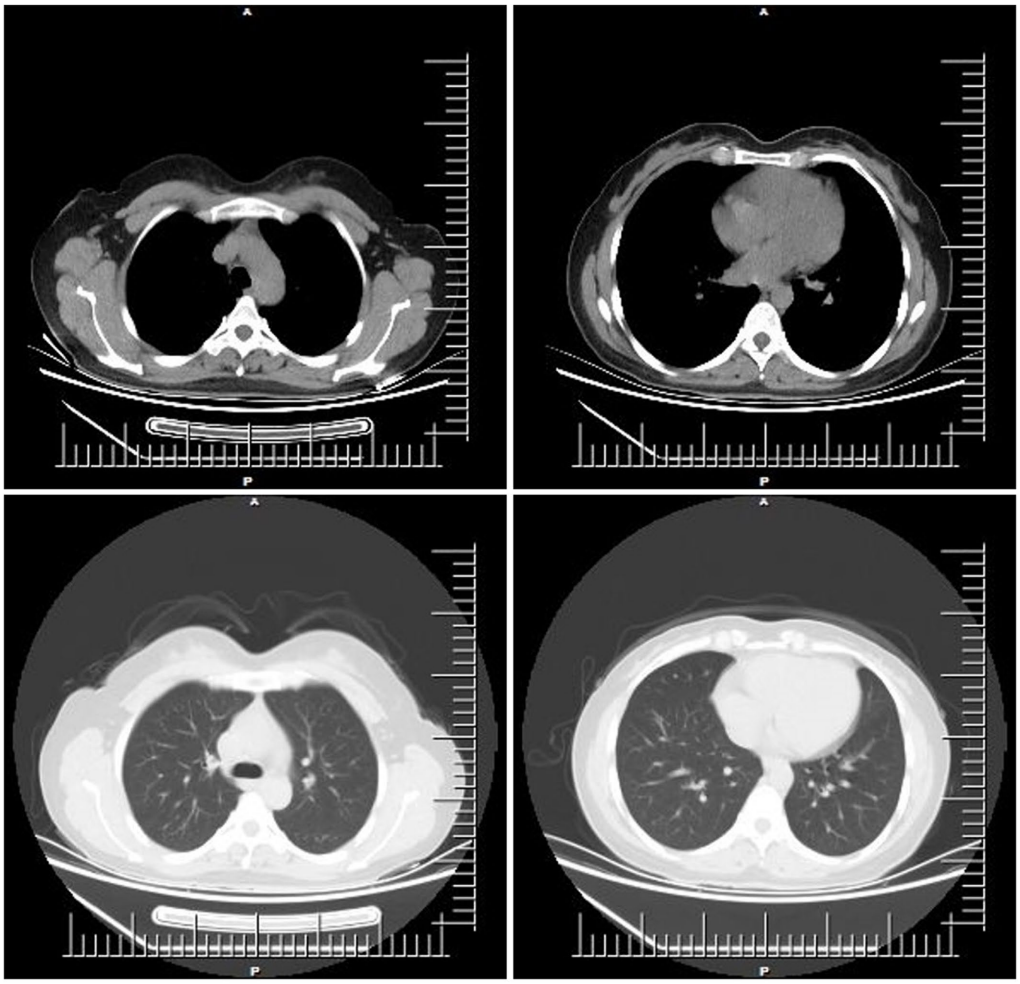

FIGURE 2
The representative chest computed tomography (CT) images of the patient.

of 0.25 g per week until 0.5 g (bid) of mycophenolate mofetil. Furthermore, clonazepam (a daily dosage of 0.5 mg) and tizanidine were orally administered to the patient. Following this protocol, the patient experienced a significant improvement in limb stiffness and pain, along with increased ease in movement and the ability to climb stairs. Moreover, serum C3 complement levels returned to normal levels, while C4 complement levels remained unchanged (Supplementary Table 6).

Discussion

The etiology and pathogenic mechanisms of SPS remain unclear. GAD65 is mainly localized in the gray matter of the spinal cord, basal ganglia, and brainstem nuclei. GAD65 antibody levels in the serum and cerebrospinal fluid of SPS patients are significantly elevated compared to healthy individuals (6). The potential mechanism underlying SPS involves an autoimmune response targeting the GAD65 protein within neurons, leading to a decrease in the synthesis and release of gamma-aminobutyric acid (γ-GABA) from inhibitory neurons. Decreased levels of γ-GABA may impede the formation of inhibitory signals in postsynaptic neurons, leading to a state of relative disinhibition among innervating nerves (7). This high excitability of lower motor neurons promotes continuous firing pulses that innervate skeletal muscles, ultimately causing muscle stiffness. Anti-GAD65 antibodies sometimes manifest in different clinical ways. The clinical manifestations of anti-GAD65 antibody-associated neuroimmune diseases are associated with the distribution of GAD65, with SPS, cerebellar ataxia, or limbic encephalitis as primary manifestations (8). Limbic encephalitis is the most common primary manifestation and frequently manifests as epileptic seizures, which is considered to be related to the inhibition of GABA function in hippocampal neurons and the excitability of the limbic cortex (9). Some patients exhibit stiff-person syndrome, which might be attributed to the hyperexcitability of α-motor neurons resulting from the inhibition of GABAergic cholinergic neurons in the notochord. This leads to the persistent synchronous contraction of antagonistic and non-antagonistic muscles (7). Additionally, the presence of cerebellar ataxia in some patients may be attributed to the inhibition of GABA release from cholinergic neurons in cerebellar Purkinje cells, leading to their excessive excitation (10).

SPS is an autoimmune disorder that may have co-occurring autoimmune disorders such as GAD-related T1DM, Hashimoto's

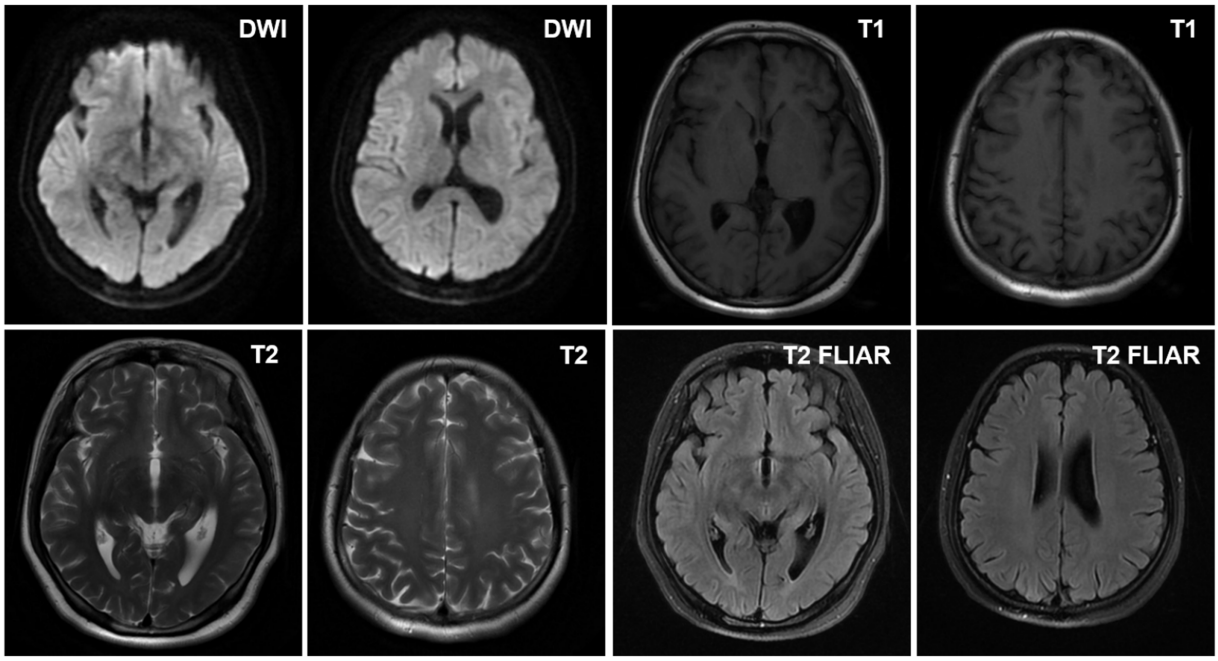

FIGURE 3
The representative images of brain magnetic resonance imaging (MRI) of the patient.

thyroiditis, Graves' disease (GD), minimal change nephrotic syndrome, and myasthenia gravis (11) (Supplementary Table 7). Solimena et al. (12) initially identified the presence of GAD antibodies in the serum of a patient with SPS and T1DM, suggesting a potential intimate relationship between SPS and T1DM. We reported a case of SPS with Hashimoto's thyroiditis. However, we observed a concurrent decrease in C3 complement levels in this case. The C3 complement is an active protein synthesized primarily by hepatocytes and macrophages within the complement system. It actively participates in both classical and alternative pathways of complement activation through its processes of activation and cleavage, thereby orchestrating the complement cascade and generating membrane attack complexes that ultimately result in cellular lysis. The activation of the complement system leads to decreased serum C3 complement levels. In systemic lupus erythematosus (SLE), lupus nephritis, and other related diseases, there is a consensus that C3 plays a crucial role in disease onset and progression. Some existing studies suggest that decreased C3 complement levels in patients with SLE are significantly related to disease activity, increased susceptibility to infection, and disease recurrence (13). Patients with lupus nephritis also exhibit decreased serum C3 complement levels, which can return to normal after remission. Studies also report that changes in C3 complement are associated with the development and progression of autoimmune diseases of the nervous system. A mouse model has demonstrated that selective inhibition of the C3a receptor can alleviate the degeneration of neurons in the brain of SLE mice. This may imply that the C3a receptor is a potential target of treatment for lupus encephalopathy (14). Previous studies have reported that activation of the complement system is associated with the pathogenesis of multiple sclerosis, and complement C3 may play a crucial pathogenic role in multiple sclerosis (15). Quantitative assessment of C3 uptake revealed that, in comparison to serum from healthy controls, serum from patients with Guillain–Barre syndrome exhibited a higher deposition of C3 fragments at sensitized targets (16). The findings of another study indicated the presence of C3d deposits in myelinated fibers within skin biopsies obtained from patients with paraproteinemic neuropathy (17). Furthermore, C3 complement deposits are also present in the neuromuscular junction of patients with myasthenia gravis, and exacerbation of myasthenia gravis is accompanied by increased complement consumption (18). These studies have indicated the association of C3 complement with autoimmune neurological diseases. In this case, we report a patient with SPS and Hashimoto's thyroiditis who exhibited a reduction in complement C3 levels without any underlying etiologies accounting for such a decrease. Currently, there is a paucity of research on the immunological mechanism of SPS, and the role of C3 complement in SPS remains unknown. Studies have shown that the abnormal expression and activation of C3 complement can aggravate the damage to neurons in the brain. C3 complement binds to ligand-gated non-selective cation channels (such as transient receptor potential vanilloid type 1 (19)) on the cell membrane of neurons, triggering Ca^{2+} influx and inducing neuronal damage. A large number of C3 complement depletions cause a decline in the serum content of C3 complement. We detected decreased C3 complement levels in this SPS patient and observed a return to normal C3 complement levels 6 months after the treatment. Although there may be insufficient evidence to establish a definitive correlation between reduced C3 complement levels and SPS in the patient, this could present a possible opportunity to explore potential biomarkers for SPS. Additionally, it is important to note that complement activation plays a role in the pathogenesis of Hashimoto's thyroiditis (20); therefore, we cannot definitively

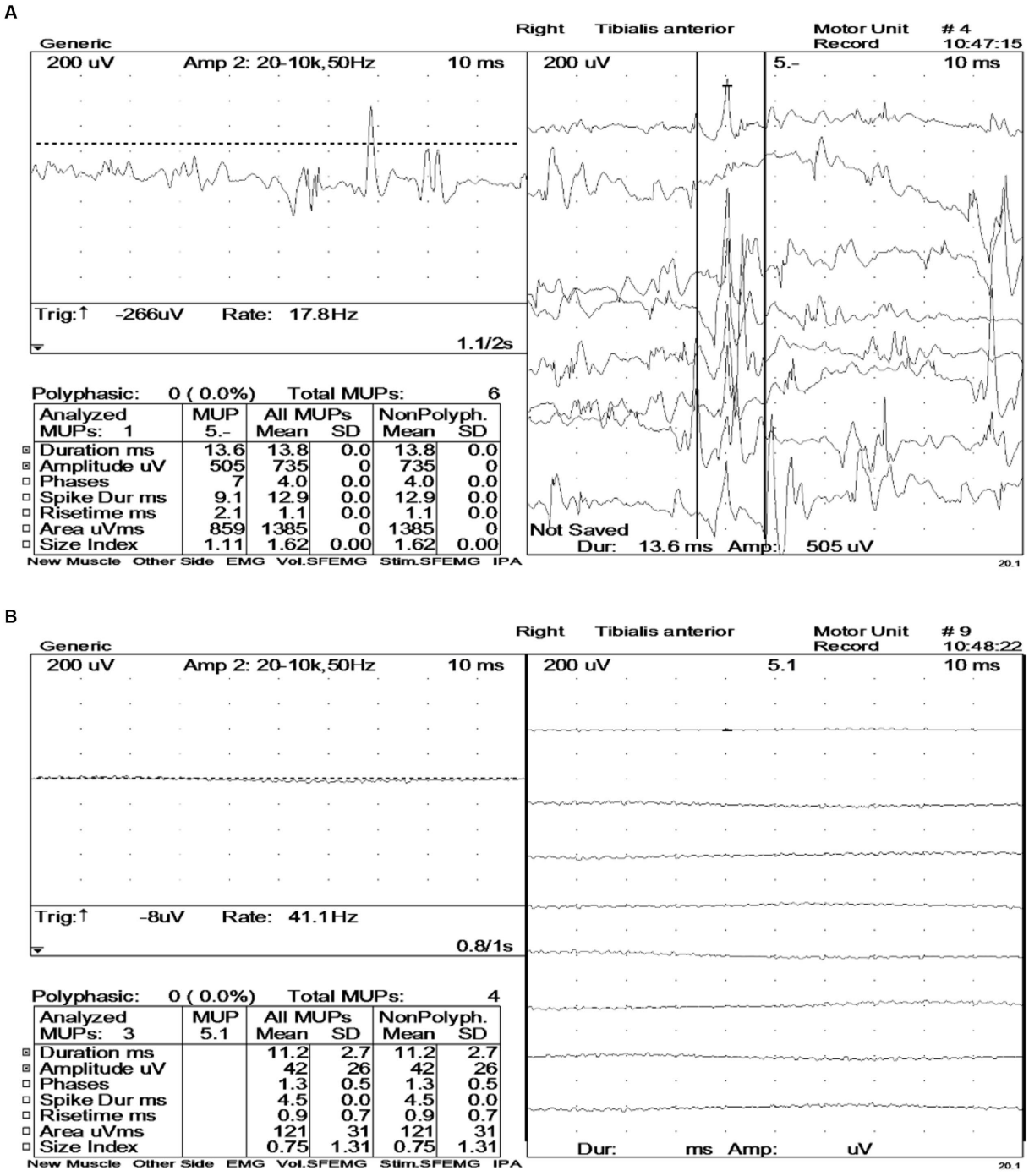

FIGURE 4
Electromyography (EMG) before and after intravenous administration of diazepam (10 mg). **(A)** Large numbers of motor unit-like units were seen in both the tibialis anterior muscles and the right vastus medialis muscle. During voluntary contractions, the duration and amplitude of the motor units in the examined muscles were all within the normal range. **(B)** During the relaxation phase, the right tibialis anterior muscle exhibited electrical silence, with no evidence of fibrillation potentials or positive sharp waves.

conclude that C3 complement alone contributes to the development of SPS. In other words, the decrease in C3 complement levels may also be a concurrent manifestation of Hashimoto's thyroiditis. This limitation should be acknowledged in our report. In future studies, we will deeply focus on the alterations in C3 complement levels, particularly during immunotherapy, SPS disease recurrence, and Hashimoto's thyroiditis remission or relapse.

The treatment options for SPS are diverse, with immunomodulatory therapy being the foremost and pivotal approach (21). High-dose corticosteroid pulse therapy is considered a potentially effective treatment for SPS. The patient exhibited significant symptom improvement following the administration of high-dose corticosteroid pulse therapy, thereby further substantiating the autoimmune etiology of SPS.

Conclusion

The incidence of SPS in the population is relatively low, yet it poses significant health risks to patients. SPS is closely associated with autoimmunity, and the presence of anti-GAD65 antibodies is frequently detected in serum and cerebrospinal fluid. The present case study described a patient with SPS (increased anti-GAD65 antibody in serum and cerebrospinal fluid) co-occurring Hashimoto's thyroiditis, accompanied by a decrease in C3 complement levels. The association between complement C3 and SPS, as well as its potential as a biomarker, requires further longitudinal observation in the future.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

The study involving a human was approved by the Ethics Review Committee of Yancheng Third People's Hospital (Review-2023-59). The study was conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by-product of routine care or industry. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

MC: Writing – original draft, Data curation, Investigation, Validation. ZH: Data curation, Formal analysis, Writing – review & editing. HS: Data curation, Supervision, Writing – review & editing. CW: Data curation, Supervision, Writing – review & editing. YS: Conceptualization, Project administration, Writing – review & editing.

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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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1360222/full#supplementary-material

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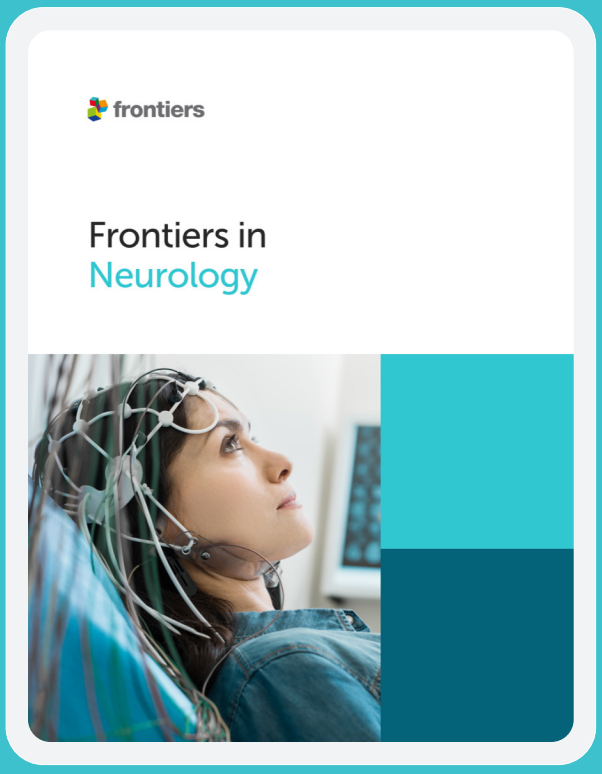

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