

When fever and headache hide NMOSD: A 29-year-old woman with an atypical cerebral presentation: A case report

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Abstract. Cerebral involvement in neuromyelitis optica spectrum disorder (NMOSD) is rare. An initial presentation with an isolated severe headache and high fever is exceptionally uncommon, posing significant diagnostic challenges. Misdiagnosis is frequent even after cerebrospinal fluid (CSF) analysis and any delay in recognition or inappropriate treatment carries risks of clinical deterioration and mortality. A 29-year-old woman presented with recurrent fever (lasting >1 month) and severe headache (lasting >2 weeks) as the sole initial symptoms and was eventually diagnosed with NMOSD with cerebral syndrome. Initial empiric antimicrobial and antiviral therapy (ceftriaxone, acyclovir), along with symptomatic management, were unsuccessful. Meropenem was

also ineffective. A pivotal shift occurred with intravenous dexamethasone administration (5 mg), which rapidly reduced fever and inflammation. Treatment was subsequently escalated to high-dose intravenous methylprednisolone (0.5 g/day for 3 days), followed by a carefully tapered oral prednisone regimen. Acyclovir was gradually discontinued. Mannitol was administered concurrently to manage intracranial pressure. At the one-month follow-up, CSF analysis showed only mild pleocytosis and brain MRI revealed minimal residual punctate lesions. The patient achieved complete symptomatic resolution without neurological deficits. No recurrence occurred during the documented follow-up period. This case highlights a rare NMOSD cerebral presentation masked by intractable headache and fever. NMOSD should be considered in the differential diagnosis for unexplained fever and severe headache, even when initial CSF findings are inconclusive. In the present case, clinical improvement followed multiple therapeutic interventions. However, the marked response observed after glucocorticoid administration suggests it was a critical turning point in management, leading to rapid symptom control and excellent recovery. Timely initiation of glucocorticoid can result in full neurological recovery and prevent progression. This emphasizes the need for heightened awareness and timely steroid use in suspected cases.

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Abbreviations: NMOSD, neuromyelitis optica spectrum disorder; AQP4, aquaporin-4; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; WBC, white blood cells; OCB, oligoclonal bands; CRP, C-reactive protein; NGS, next-generation sequencing; ADA, adenosine deaminase; G test/GM test, (1,3)- β -D-glucan test/galactomannan test; CSF, cerebrospinal fluid; CNS, central nervous system; HSE, herpes simplex encephalitis; Anti-NMDAR, anti-N-methyl-D-aspartate receptor antibodies; Anti-GABAA, anti-gamma-aminobutyric acid A receptor antibodies; AE, autoimmune encephalitis; VE, viral encephalitis; MOG, myelin oligodendrocyte glycoprotein

Key words: neuromyelitis optica spectrum disorder, severe headache and fever, misdiagnosis, NGS, AQP4, hormone therapy

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a group of autoimmune-mediated inflammatory demyelinating diseases of the central nervous system (CNS), predominantly exhibiting optic nerve and spinal cord involvement. The pathogenesis of NMOSD is primarily associated with antibodies to aquaporin-4 (AQP4), which plays a central pathogenic role. Approximately 70-80% of patients with NMOSD test positive for AQP4-IgG (1). NMOSD can occur at any age, with a median onset ~39 years, preferably in young adults, with a marked female predominance. The female-to-male ratio in AQP4-IgG-positive patients is as high as 4.7-11:1. The incidence of NMOSD exhibits geographical variation, with

prevalence potentially higher among non-Caucasian populations, particularly in Asians (2). Approximately 20-30% of patients test negative for AQP4-IgG, with some of these individuals subsequently testing positive for myelin oligodendrocyte glycoprotein antibodies (MOG-IgG) (3). A subset of patients test negative for both AQP4-IgG and MOG-IgG, termed double-negative NMOSD (4). NMOSD is highly relapsing and disabling diseases. More than 90% of cases have a multitemporal course, with 40-60% experiencing a relapse within 1 year and ~90% within 3 years. About 50% of untreated patients develop severe residual visual or motor dysfunction within 5-10 years (5). Diagnosis relies on the integration of clinical presentation, laboratory testing for AQP4-IgG, and neuroimaging findings, with MRI playing a crucial role in revealing characteristic features such as longitudinally extensive spinal cord lesions and optic nerve involvement (6). NMOSD manifests through six principal clinical syndromes: Optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, acute diencephalic syndrome and cerebral syndrome (7). Clinically, NMOSD predominantly presents with severe optic neuritis and longitudinally extensive transverse myelitis as its hallmark features. By contrast, headache and high fever are a relatively rare complaint. It is noteworthy that the atypical presentation of NMOSD frequently leads to delayed diagnosis, thereby compromising the timing of treatment and affecting prognosis (8). This article reports on a patient with NMOSD presenting solely with severe headache and fever with an excellent outcome. The present case report may provide clinicians with decision support in similar situations, emphasizing the importance of early recognition and immediate administration of glucocorticoid.

Case report

Case presentation. A 29-year-old woman was transferred from a local hospital and admitted to the Department of Neurology of Nanjing Drum Tower Hospital (Nanjing, China) in August 2024 due to recurrent fever for >1 month and headache for ~2 weeks.

In July 2024, the patient developed an intermittent fever without any obvious trigger. The fever occurred intermittently every 5-6 days, with an interval usually lasting 2-3 days. The highest recorded temperature was 39.5°C. The patient reported no night sweats, dizziness, headache, cough, sputum production, abdominal pain, diarrhea, limb numbness, fatigue or slurred speech, and denied any issues with depression or attention. In mid-August 2024, the patient began experiencing a persistent headache involving the entire head, but most prominently in the frontal and occipital regions. The pain was described as a moderate to severe, dull, with occasional paroxysmal stabbing sensations. The headache's intensity fluctuated, notably worsening in the occipital region, which affected both work and sleep.

In August 2024, cranial MRI revealed multiple abnormal signals in the brain. The magnetic resonance angiography showed no significant abnormalities (data not shown). An incidental finding on cervical spine MRI showed only mild degenerative changes (disc bulges and osteophytes at C4-C6), with no evidence of cord compression or lesion. Then, an electroencephalogram (EEG) was performed 3 days after the

cranial MRI, and the results were normal. Blood tests showed a low leukocyte count of $3.3 \times 10^9/l$ (normal range, $3.5-9.5 \times 10^9/l$) and a low absolute lymphocyte count of $0.7 \times 10^9/l$ (normal range, $1.1-3.2 \times 10^9/l$). Tuberculosis antibodies, T-SPOT test and blood cultures were all negative. At the patient's local hospital, initial diagnostic considerations included intracranial infection or space-occupying lesions.

In late August 2024, the headache and fever worsened and the patient developed non-projectile vomiting, prompting transfer to another local hospital. MRI revealed multiple abnormal signals in the brain (data not shown). A lumbar puncture performed a day later showed elevated cerebrospinal fluid (CSF) pressure (220 mmH₂O; normal range, 70-200 mmH₂O), reduced glucose (2.13 mmol/l; normal range, 2.5-4.4 mmol/l) and elevated protein (732.6 mg/l; normal range, 150-450 mg/l), suggesting a CNS infection. Further testing revealed elevated anti-streptococcal hemolysin O levels (339.00 IU/l; normal: <200 IU/ml). The patient was started on acyclovir (0.5 g every 8 h) and ceftriaxone (2 g once daily), along with mannitol (20% 125 ml every 12 h) for dehydration and intracranial pressure reduction, yet the symptoms did not improve.

The patient was subsequently transferred to the emergency department of Nanjing Drum Tower Hospital (Nanjing, China) on the same day, where the antimicrobial therapy was continued. A tuberculosis test (T-SPOT) was negative. Following consultation with the neurology department, the patient was admitted (this is defined as hospital day 1). During examination, multiple dark-pigmented nevi were observed on the face, but there were no rashes, mucosal ulcerations or external ear canal herpes. Neurological examination was unremarkable, with preserved cognition, though there was a slight neck rigidity and a positive Babinski sign on the right lower limb. No significant abnormalities were noted in the remainder of the physical examination.

The patient's relevant medical history was pursued. The patient had a history of smallpox at age 6 and chemical fiber exposure in the work environment, but reported no similar cases among colleagues. There was no recent history of sepsis, trauma, surgery, tuberculosis, toxic or radioactive exposure, mosquito bites or travel to tropical regions, and the patient had no pets or poultry. A full blood workup upon admission revealed a low absolute lymphocyte count ($0.6 \times 10^9/l$; normal range, $1.1-3.2 \times 10^9/l$), elevated C-reactive peptide (9.7 mg/l; normal range, 0-6 mg/l) and increased interleukin-6 (27.38 pg/ml; normal range, 0-7 pg/ml). Complement C3 (0.59 g/l; normal range, 0.7-1.4 g/l), C4 (0.07 g/l; normal range, 0.1-0.4 g/l) and Clq (9.3 mg/dl; normal range, 15.7-23.7 mg/dl) levels were all reduced (Table I). Tests for tuberculosis antibodies, T-SPOT and blood cultures were normal (Table I). The TORCH panel [*Toxoplasma gondii*/other agents (such as *Treponema pallidum*, varicella zoster virus, etc.)/Rubella virus/cytomegalovirus (CMV)/herpes simplex virus (HSV)] (9) revealed elevated IgG antibodies for CMV, rubella and HSV. Sputum culture, stool bacterial flora, fungal smear, Epstein-Barr virus DNA and invasive fungal tests were all normal. Given the patient's multiple intracranial lesions, continued empirical antimicrobial therapy with ceftriaxone (2 g once daily) and acyclovir (0.5 g every 8 h) was maintained.

Two days after admission, the patient continued to experience recurrent fever, necessitating the administration

Table I. Core laboratory examination data.

Course of disease	Pre-hospitalization	First hospitalization	Second hospitalization	Normal range ^a
Peripheral blood				
White blood cells, x10 ⁹ /l	3.3	4.4	5.6	3.5-9.5
Lymphocytes, x10 ⁹ /l	0.7	0.5	1.2	1.1-3.2
CRP, mg/l	8.9	9.7	2.9	0-6
Complement C3, g/l	NA	0.59	NA	0.7-1.4
Complement C4, g/l	NA	0.07	NA	0.1-0.4
Complement C1q, mg/dl	NA	9.3	NA	15.7-23.7
Albumin, g/l	47.1	39.1	40.7	40-55
IgG, g/l	NA	20.2	NA	8.6-17.4
Invasive fungal G test/GM test	NA	-	NA	-
Epstein-Barr virus DNA	NA	<500	NA	<500
TORCH virus panel	NA	-	NA	-
T-SPOT	-	NA	-	-
Anti-tuberculosis antibodies	-	NA	NA	-
Culture	-	NA	NA	-
Autoantibodies	NA	NA	NA	-
Anti-AQP4 antibodies	NA	Serum (+1:32)	NA	-
Oligoclonal bands	NA	Monoclonal band positive (type 3: OCB count in cerebrospinal fluid greater than serum)	NA	-
Cerebrospinal fluid				
Pressure, mmH ₂ O	220	120	150	80-180
White blood cells, x10 ⁶ /l	NA	14.9	10	0-8
Lymphocytes, x10 ⁶ /l	NA	84.1	9	0-5
Protein, mg/l	732.6	800.1	315.3	150-450
IgG, mg/l	NA	155.0	24.5	≤34
IgG index	NA	0.78	NA	≤0.7
Glucose, mmol/l	2.13	2.13	3.86	2.5-4.5
Chloride, mmol/l	NA	122.7	127.6	120-132
Culture	NA	-	-	-
Pathology	NA	Moderate central nervous system inflammation, mixed cellularity, no cryptococcus or type cells found	Mild neurological inflammation	-
NGS	NA	-	-	-
Gamma interferon	NA	-	-	-
Ink staining	NA	-	-	-
Acid-fast smear	NA	-	-	-
ADA	NA	-	-	-
Anti-tuberculosis antibody	NA	-	-	-
Anti-AQP4 antibody	NA	Cerebrospinal fluid (+1:1)	NA	-
Oligoclonal band	NA	Monoclonal band positive (type 3: OCB count in cerebrospinal fluid greater than serum)	NA	-

^aNormal ranges of Nanjing Drum Tower Hospital. CRP, C-reactive protein; TORCH, *Toxoplasma gondii*/Other agents (such as *Treponema pallidum*, varicella zoster virus, etc.)/Rubella virus/cytomegalovirus/herpes simplex virus; NGS, next-generation sequencing; ADA, adenosine deaminase; AQP4, aquaporin-4; OCB, oligoclonal bands; G test/GM test, (1,3)-β-D-glucan test/galactomannan test; NA, result not available.

of acetaminophen for fever control. The severe headache prompted the administration of mannitol (125 ml q12h) to reduce intracranial pressure. Flurbiprofen Axetil (50 mg once)

was used for headache relief, along with potassium supplementation (potassium chloride sustained-release tablets 2 g every 12 h) and gastric protection (pantoprazole 40 mg once

daily). On hospital day 3, the antibiotic regimen was switched to meropenem (2 g q8 h). Despite ongoing fever, the patient's body temperature decreased after intravenous dexamethasone (5 mg), and mannitol treatment for intracranial pressure was continued. On hospital day 5, a second lumbar puncture showed a CSF pressure of 120 mmH₂O (normal range, 70-200 mmH₂O), decreased glucose (2.13 mmol/l; normal range, 2.5-4.4 mmol/l), elevated protein (800.1 mg/l; normal range, 150-450 mg/l) and increased white blood cells (WBC; 99x10⁶/l, normal range, 0-8x10⁶/l; with 84.9% lymphocytes, normal range, 40-80%). Cytopathology indicated moderate CNS inflammation. Tests for *Cryptococcus*, atypical cells and tuberculosis were negative, and next-generation sequencing showed no significant abnormalities. Demyelinating antibodies were tested, and anti-AQP4 antibodies were found positive in both serum and CSF. These findings, combined with an IgG index of 0.78 suggested a diagnosis of autoimmune encephalitis (AE).

On hospital day 6, a comprehensive cranial MRI was conducted, revealing multiple abnormal signals in the bilateral frontal-temporal lobes, right occipital lobe, left cingulate gyrus, left temporal lobe and punctate lesions in the brainstem (Fig. 1). Despite ongoing antimicrobial and symptomatic treatment, the patient still had intermittent fever and recurrent headaches. On hospital day 8, steroid therapy was initiated with methylprednisolone (0.5 g daily for 3 days, tapering thereafter). Acyclovir was reduced and oral prednisone was gradually tapered. Follow-up was planned for one month, with adjustments to the medication regimen.

The patient was discharged 10 days after steroid therapy; the patient was symptom-free, with no further headaches or fever, though occasional dizziness was noted upon sitting up. Neurological examination showed no Babinski sign on the right lower limb, and neck stiffness had resolved.

One month later, the patient returned for a follow-up examination. The patient's symptoms had completely disappeared. From the first day of admission, the patient had been taking prednisone 45 mg once daily. After completing laboratory tests and imaging studies, only a slightly elevated CSF WBC count of 10x10⁶/l (normal range, 0-5x10⁶/l) and isolated punctate lesions on MRI were observed, with enhancement (Fig. 1). The patient was advised to continue long-term oral prednisone 40 mg once daily, reducing the dose by one tablet (5 mg) every week. The patient refused to use immunosuppressive drugs due to financial reasons. Therefore, a plan for regular outpatient clinic follow-up with close clinical and radiological monitoring was implemented, and the importance of symptom awareness was emphasized. (laboratory test results are shown in Table I and imaging studies in Fig. 1).

Diagnoses. The final diagnosis was NMOSD with cerebral syndrome. The diagnostic basis was as follows: The patient is a woman with a subacute onset whose major symptoms were fever and headache. Neuroimaging revealed bilateral, multifocal lesions predominantly involving the cerebral lobes and white matter. These lesions exhibited a diffuse distribution with poorly defined margins. The MRI characteristics included a slightly hypointense signal on T1-weighted imaging, slightly hyperintense signal on T2-weighted imaging, hyperintense signal on fluid-attenuated inversion recovery sequences,

isointense signal on diffusion-weighted imaging and hyperintense signal on apparent diffusion coefficient maps. Patchy or punctate enhancement was observed.

According to the 2015 International Panel for NMO Diagnosis (IPND) criteria, the patient fulfilled three essential diagnostic criteria: i) Presence of at least one core clinical characteristic (cerebral syndrome accompanied by NMOSD-typical brain lesions); ii) positive anti-AQP4-IgG serostatus using a reliable detection method; iii) absence of red flags contraindicating NMOSD diagnosis, as defined by the Chinese Diagnostic and Therapeutic Guidelines for Neuromyelitis Optica Spectrum Disorders (2021 edition), and exclusion of alternative diagnoses.

A definitive diagnosis of NMOSD was consequently confirmed. All laboratory findings are presented in Table I. Representative neuroimaging features are displayed in Fig. 1.

Discussion

The present case report presents a rare initial manifestation of NMOSD. The patient's symptoms consisted solely of severe headache and high fever. Antibody testing revealed dual positivity for anti-AQP4 antibodies in both serum and CSF, with a stronger presence in the serum. Initially misdiagnosed as a CNS infection, the patient's symptoms resolved completely following a combination of steroid therapy and empirical anti-infective treatment. Follow-up imaging showed lesions were significantly reduced in both size and number, indicating a favorable prognosis. As reported in the literature (10-12), headache is recognized as an early presentation in several isolated case reports. Furthermore, reports exist describing NMOSD onset with headache combined with fever and other meningoencephalitis-like symptoms (13,14). Several of these reported cases share striking similarities in presentation and laboratory findings with the current patient, strongly suggesting that headache and fever can be rare initial manifestations of NMOSD that clinicians must not overlook.

The pathophysiology underlying headache and fever in NMOSD, though not fully elucidated, can be critically analyzed through several plausible mechanisms. Headache may arise from NMOSD-related inflammatory lesions affecting pain-sensitive intracranial structures. The presence of lesions in regions such as the periaqueductal gray matter, hypothalamus or areas adjacent to the ventricular system could disrupt normal pain modulation and central autonomic control (15). Furthermore, widespread inflammation leading to disruption of the blood-brain barrier and the release of pro-inflammatory cytokines (e.g., IL-6, which was elevated in this patient) may directly stimulate nociceptive pathways and trigger neurogenic inflammation, contributing to headache (16). The mechanism of fever is similarly linked to neuroinflammation. The detection of pro-inflammatory cytokines in the CSF can act on the preoptic area of the hypothalamus, the body's thermostat, leading to an elevated temperature set-point (17). Although no distinct hypothalamic lesion was identified in the present case, the diffuse inflammatory milieu itself could sufficiently perturb hypothalamic function to produce fever. This aseptic, inflammatory meningoencephalitis-like presentation may represent an atypical phenotypic presentation of an NMOSD attack, easily confused with specific infections

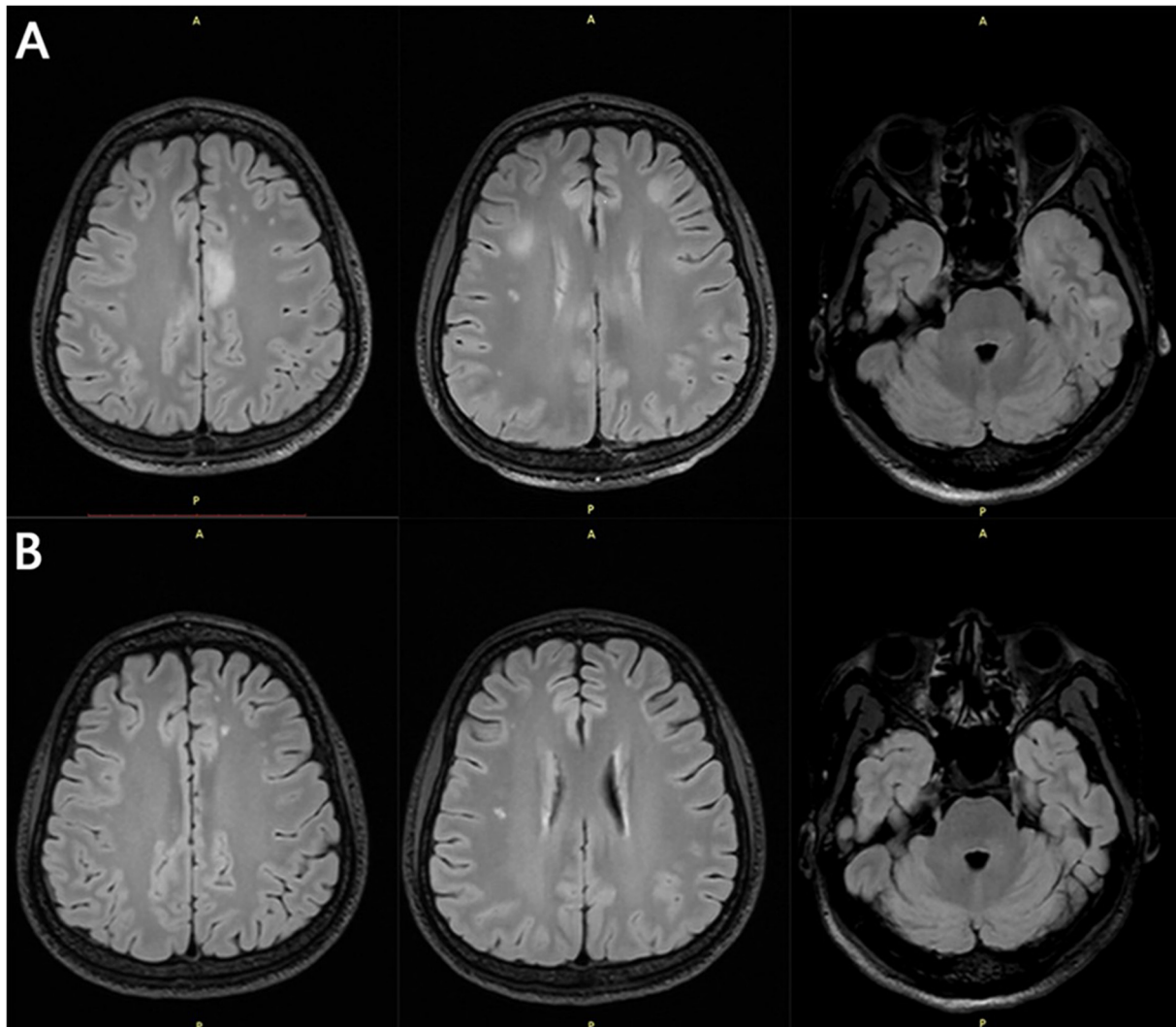


Figure 1. MRI of the head process. All sequences displayed are T2 FLAIR sequences. (A) First admission (September 2024). Cranial MRI without contrast + contrast-enhanced + perfusion + functional imaging: Multiple abnormal signals in the bilateral frontal insula and temporal lobes, and the right occipital lobe; punctate enhancement lesions in the left cingulate gyrus and left temporal lobe. The signals are uniform, with high signal intensity on FLAIR. The borders are poorly defined, with the largest lesion measuring 3.03x1.35 cm. The average signal intensity on FLAIR is 639. No edema or mass effect is observed. An infectious lesion is suspected. Chronic ischemic-hypoxic changes in the deep white matter of both cerebral hemispheres (Fezakas Grade 1). Multiple high signal intensity on FLAIR, appearing as punctate lesions. (B) Second admission for follow-up (October 2024). Multiple punctate lesions in the bilateral frontal and temporal lobes, with high signal intensity on FLAIR. Left cingulate gyrus and temporal lobe with punctate and strip-like enhancement lesions, with some lesions less distinct than previously (September 2024). Bilateral deep white matter hypoxic lesions in the cerebral hemispheres are unchanged from previous findings. FLAIR, fluid-attenuated inversion recovery; A, anterior; P, posterior.

or other conditions. A comprehensive evaluation to exclude other etiologies is crucial, enabling accurate diagnosis and timely initiation of immunotherapy, which is paramount for prognosis.

An important aspect of this case is the patient's reliance on glucocorticoid monotherapy due to financial constraints preventing the use of steroid-sparing immunosuppressants. While high-dose glucocorticoid are highly effective for acute NMOSD attacks, long-term monotherapy is suboptimal for relapse prevention (18). Maintenance immunosuppression with agents such as azathioprine, mycophenolate mofetil or rituximab is the standard of care to reduce the high relapse rate (19). Long-term glucocorticoid use carries significant risks, including osteoporosis, diabetes, hypertension and cataracts (20). More critically, reliance on monotherapy leaves patients vulnerable to breakthrough attacks, which can lead

to cumulative, irreversible neurological disability. This case underscores the socioeconomic barriers to optimal NMOSD care and highlights the need for strategies to improve access to effective, long-term preventive therapies.

In the present case, the detection of anti-AQP4 antibodies was pivotal to diagnosis. AQP4-IgG is a highly specific diagnostic biomarker for NMOSD, with specificity exceeding 90% and sensitivity of ~70%. Literature reports indicate that CSF in NMOSD typically demonstrates the following: Pressure: Mostly normal. WBC: Often elevated $>10 \times 10^6/l$ in the acute phase; approximately one-third of patients have $WBC >50 \times 10^6/l$; rare cases may reach $500 \times 10^6/l$. Neutrophils and eosinophils may be present. Protein: Frequently significantly elevated, potentially >1 g/l. Glucose and Chloride: Generally normal. Oligoclonal bands (OCB): Positive CSF-specific OCBs are found in about 20% of patients, accompanied by significantly elevated IgG

Table II. Differential diagnosis of the present patient.

Disease	Supportive criteria	Exclusion criteria
Acute disseminated encephalomyelitis	The clinical presentation is consistent with a first-ever acute or subacute onset of a demyelinating disease with multifocal involvement, with symptoms of fever and headache, preceded by a history of antecedent infections such as fever, and with encephalopathic symptoms that cannot be explained by fever. Cerebrospinal fluid cell counts and protein levels are high. Imaging shows diffuse, poorly defined, large (>1-2 cm) foci with predominantly white matter involvement, with accumulation of grey matter, especially in the basal ganglia and thalamus. The cerebrospinal fluid OCB positivity rate ranged from 12.5 to 20.0% (21). The patient of the present study responded well to hormone therapy and showed improvement in symptoms, and an MRI afterwards.	This patient was positive for AQP4 antibodies, and positive cerebrospinal fluid OCB did not turn negative quickly. Given that the symptoms of the patient did not match the initial presentation, a refined lumbar puncture was performed for further investigation.
Multiple sclerosis	Symptomatology consisted only of headache and fever and lacked other encephalopathic symptoms such as behavioural abnormalities and altered consciousness. CSF analysis suggested elevated protein, increased IgG index and positive oligoclonal bands for both type III (serum and CSF). Imaging suggested the presence of CNS white matter demyelinating lesions. Symptoms and MRI improved with hormone therapy.	This patient temporarily lacked temporal and spatial polymorphic features. Cerebrospinal fluid leukocytes rarely exceed 50, pressure is increased, glucose is decreased and AQP4 antibody is positive. Imaging non-parietal paraventricular typical lesion distribution, e.g., Dawson's sign.
CNS infections	This patient had fever, headache symptoms and neck resistance. The patient had a history of smallpox virus infection and tested IgG positive for multiple viruses. The cerebrospinal fluid had an increased cell count, increased protein count and decreased glucose. Imaging suggested diffuse, poorly defined lesions.	Routine blood leukocytes were not high and NGS was negative. The EEG was normal. Poor efficacy of anti-infective therapy. Complete lumbar puncture for further exclusion.
Double-peak encephalitis	The majority of post-VE AE cases show the clinical phenotype of double-peak encephalitis, while certain cases show a single-peak or pseudo-single-peak phenotype due to the mildly self-limiting AE phase or due to the lack of an inter-remission phase. The first peak is the VE stage with fever, headache, mental behavioural abnormalities, seizures and impaired consciousness, which resolves with antiviral treatment; the second peak is the AE stage with mental behavioural abnormalities as the most prominent manifestation, which also includes memory loss, autonomic dysfunction and movement disorders. In the AE stage, the CSF anti-neurological antibody changes from negative to positive, and a positive specific oligoclonal band can be seen. During the disease, the symptoms of 'second encephalitis' appear and MRI of the head suggests that the lesion is enlarged, and the CSF is positive for oligoclonal bands;	In 2012, Prüss <i>et al</i> (26) demonstrated a dynamic change from negative to positive anti-NMDAR antibodies in 30% of patients with HSE during the disease. A prospective study by Armangue <i>et al</i> (27) showed that 27% of patients with HSE can develop AE secondary to AE within 2-16 weeks (median, 32 d) of disease onset, 64% with anti-NMDAR encephalitis, and the remainder with anti-GABAA receptor antibodies and unknown antigens, among others. However, there was no antibody positivity in the present case, nor was there any antibody positivity during the follow-up after one month. Although the CSF leukocyte count ($99 \times 10^6/l$) and protein count (0.8 g/l) in the present case were at the range of VE CSF leukocyte count ($10-335 \times 10^6/l$) and protein (0.21-1.78 g/l), the NGS examination was negative for AE-related antibodies. In addition, double-peak encephalitis was positive for multiple oligoclonal bands (CSF). There were no new symptoms, nor peak and trough fluctuations in this patient.

Table II. Continued.

Disease	Supportive criteria	Exclusion criteria
	<p>the symptoms are relieved by immunotherapy and the lesion appears shrunk on MRI (27). The patient's symptoms were consistent with those reported, although in the present case, the AE antibody profile was negative and the symptomatology may have been atypical or self-limiting, or masked by the sequelae of VE. A report of so-called 'secondary encephalitis' after HSE was provided by Wang <i>et al</i> (28).</p>	

AQP4, aquaporin-4; CSF, cerebrospinal fluid; CNS, central nervous system; HSE, herpes simplex encephalitis; anti-NMDAR, anti-N-methyl-D-aspartate receptor antibodies; anti-GABAA, anti-gamma-aminobutyric acid A receptor antibodies; NGS, next-generation sequencing; AE, autoimmune encephalitis; VE, viral encephalitis.

levels (21). The CSF findings in this patient align well with these reported characteristics. Furthermore, other relevant NMOSD biomarkers include: i) myelin oligodendrocyte glycoprotein (MOG)-IgG: This is an established diagnostic biomarker for MOG antibody-associated disease. It is rarely simultaneously positive with AQP4-IgG and holds significant diagnostic and differential diagnostic value (22). Transient MOG-IgG positivity can occur during acute phases of other diseases, necessitating cautious clinical interpretation (23). ii) Other Autoantibodies: Approximately 50% of AQP4-IgG-positive NMOSD patients have coexisting positive autoantibodies, including serum antinuclear antibodies, anti-Sjögren syndrome A antibody, anti-Sjögren syndrome B antibody and anti-thyroid peroxidase antibodies (24). iii) Neurofilament light chain. Serial measurement is valuable for monitoring disease progression, assessing irreversible damage and evaluating treatment efficacy as an indicator of residual disability in NMOSD (25). Therefore, when evaluating similar cases, clinicians should maintain a heightened awareness regarding the importance of screening for specific antibodies, particularly when presenting symptoms are atypical. The differential diagnosis considered for this patient is detailed in Table II. Differential diagnosis includes: Acute disseminated encephalomyelitis, multiple sclerosis, CNS infections and double-peak encephalitis.

The diagnosis of NMOSD is still based on 'history + core clinical symptoms + imaging features + biomarkers', using AQP4-IgG for stratification, and referencing other subclinical and immunological evidence to make the diagnosis, in addition to the exclusion of other diseases according to the criteria of IPND 2015 (6). It is important to note that patients with NMOSD may test negative for AQP4-IgG either during the first episode or at some point in the course of the disease. In cases with early or atypical clinical and imaging features, laboratory and other relevant investigations should be fully refined, differential diagnoses carefully considered and patients followed up dynamically for relevant supporting or exclusionary evidence. However, this patient presented with suspiciously positive Babinski signs, which were evaluated by multiple neurologists, potentially leading to an easy misjudgment of the diagnosis and treatment. But during follow-up, the

patient's signs returned to normal, and it was surmised that the positive signs occurred in the context of a widespread lesion affecting the pyramidal system.

NMOSD with fever and headache, especially severe headache, as the first symptom is not typical, particularly when there are no other accompanying symptoms. If fever and headache symptoms persist, it is easy to misdiagnose the condition as a CNS infection, AE or other diseases. The patient was admitted with significant symptoms and extensive lesions. Since the patient's condition was severe and the etiology of the disease was not clearly defined, no high-dose hormone therapy was initiated at first. Through the appropriate auxiliary examinations, a relatively correct treatment plan was drawn up. This reflects the fact that, in clinical practice, the diversity and non-specificity of symptoms can complicate diagnosis and that early hormone intervention may be effective. However, it is necessary to take into account that the patient's infection was aggravated. This case underscores the importance of considering NMOSD in patients presenting with similar symptoms, particularly if they do not improve significantly after anti-infective and cranial pressure-lowering therapy. Emphasis should be placed on a comprehensive analysis of the history, signs, laboratory tests and imaging examinations to avoid diagnoses based solely on symptoms and to avoid misdiagnosis or missed diagnosis.

In conclusion, the present case study discussed the diagnostic and treatment process of a rare NMOSD presentation. It underscores the importance of eliminating infections and considering autoimmune etiologies in atypical cases, the critical role of specific antibody testing and the need for a balanced approach to acute and long-term management. This case report may provide guidance for the early diagnosis and comprehensive management of NMOSD in the future. In addition, the information contained therein will help to increase awareness of this disease among general medical practitioners, which is important for research on NMOSD.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

DA performed formal analysis. DA, LY and YX provided resources. DA and LY were responsible for the conceptualization of the study. DA, YZ and WZ performed data curation. DA, YZ and LY were involved in investigation. LY and YX confirmed the authenticity of the raw data during data validation. DA and YZ wrote the original draft. DA, LY and YX contributed to the interpretation of data. DA, LY and YX reviewed and edited the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent for publication of this case report and accompanying images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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