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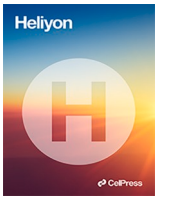

Case report

Neuromyelitis optica spectrum disorder with ultra-longitudinally extensive transverse myelitis: A case report and literature review

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ABSTRACT

Background: Neuromyelitis optica spectrum disorders (NMOSD) is characterized by inflammatory demyelinating events in the central nervous system (CNS), primarily affecting the spinal cord and optic nerve, with a significant influence of astrocytes. Longitudinal extensive transverse myelitis (LETM) is a distinct and relatively rare spinal cord syndrome, commonly associated with NMOSD.
Case presentation: This report describes a unique case of myelitis in a patient diagnosed with NMOSD. The patient exhibited an uncommon manifestation of ultra- LETM (u-LETM), coexisting with connective tissue disorders including Sjögren's syndrome and autoimmune hepatitis-primary cholestatic cirrhosis. In the acute phase, high-dose methylprednisolone pulse therapy was administered in combination with intravenous human immunoglobulin, while prednisone was gradually tapered and discontinued upon stabilization of the patient's condition. Simultaneously, sequential disease-modifying therapy was initiated, starting with long-term oral administration of mycophenolate mofetil, followed by cyclophosphamide, telitacicept, and Inebilizumab. During follow-up visits conducted every three months, the patient showed gradual improvement, eventually achieving the ability to stand and walk independently.
Conclusions: Early and comprehensive evaluation of autoimmune diseases is crucial in patients with NMOSD presenting with u-LETM as the initial symptom. Prompt treatment initiation, followed by disease-modifying therapy, is essential for improving patient prognosis.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD), formerly known as neuromyelitis optica (NMO), encompasses a cluster of inflammatory demyelinating conditions of the central nervous system (CNS) primarily mediated by autoantibodies (NMO-IgG) targeting the aquaporin 4 (AQP4) protein. These disorders predominantly affect astrocytes, in both the spinal cord and the optic nerve [1,2], but can also manifest as postrema, diencephalic, brainstem, and cerebral syndromes. Epidemiological studies have demonstrated that ADs such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), and autoimmune thyroid disease (AITD) can all coexist with NMOSD [3].

The prevalence of NMOSD varies between 0.5- 10 cases per 100,000 individuals [4], and typically presents sporadically, with only

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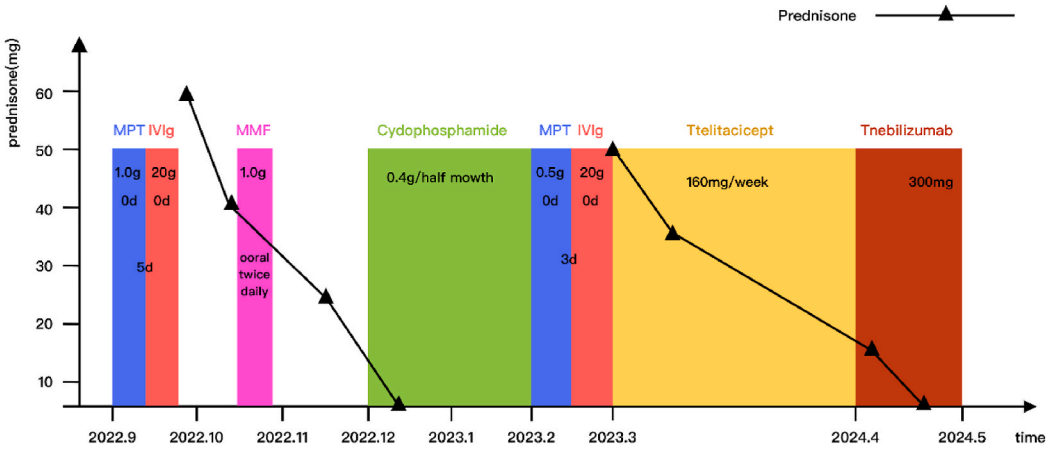
a few reported familial cases [2]. NMOSD primarily affects middle-aged women with,a female-to-male ratio of 4.7:1 in the Chinese population [5]. Its primary clinical manifestations include severe optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM), both of which are associated with high recurrence and disability rates [2,6]. Weihe et al. [7]previously described a case series of transverse myelitis with complete spinal cord transection (lesions exceeding tenvertebral segments on MRI), indicating of a poor prognosis, resulting in the designation of sever cases as 'ultra-longitudinally extensive transverse myelitis (u-LETM)'. A subsequent retrospective study on u-LETM patients showed that over two-thirds of patients were diagnosed with NMOSD, while approximately



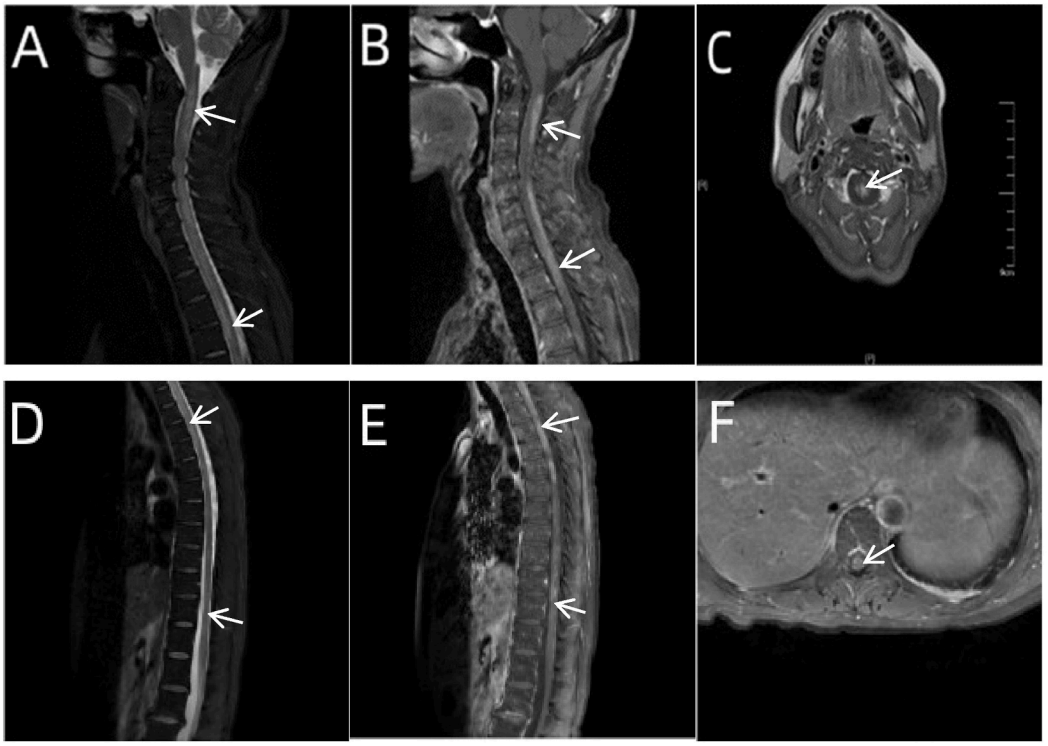


Fig. 1. Cervicothoracic MRI(First episode of NMOSD). Sagittal T2-weighted imaging of the cervical spinal cord (A) showed diffuse multiple patches with slightly increased signal intensity; sagittal post-Gd T1-weighted imaging of the cervical spinal cord (B) showed diffuse mild-to-moderate enhancement; axial post-Gd T1-weighted imaging of the cervical spinal cord (C) showed central involvement. Sagittal T2-weighted imaging of the thoracic spinal cord (D) showed diffusely scattered multiple patches and strips with, slightly increased signal intensity; sagittal post-Gd T1-weighted imaging of the thoracic spinal cord (E) showed diffuse mild-to-moderate enhancement; axial post-Gd T1-weighted imaging of the thoracic spinal cord(F) showed central involvement.

one third exhibited comorbidity with one or more systemic autoimmune diseases [8].

This report presents a rare case of NMOSD with u-LETM. While u-LETM is typically associated with SLE and paraneoplastic LETM in the literature [9]. Herein, we present the case of a patient with coexisting connective tissue disorders (CTDs), including SS and autoimmune hepatitis with-primary cholestatic cirrhosis. The findings of this case broaden our understanding and provide valuable clinical into the improvement of patient prognosis.

2. Case description

2.1. Initial symptoms

A 57-year-old female was admitted to the Neurology Department of our hospital on September 20, 2022, with a two-week history of defecation difficulties following an infection, and a one-week history of numbness in both hands and weakness in both lower limbs. At symptom onset, the patient exhibited symptoms of an upper respiratory tract infection, followed by difficulties in defecation and urination after 4–5 days. One week prior to admission, the patient further developed numbness in the fingertips of both hands, weakness and numbness below the knees, and difficulties walking. Four days prior to admission, her symptoms progressed, with weakness and numbness in both lower limbs progressing up to the chest. This worsening of symptoms prompted her to visit our hospital. The patient's medical history was largely unremarkable. She had previously experienced xerostomia and xerophthalmia, but refrained from seeking medical attention. She hada healthy lifestyle, regular menstrual cycles, was the mother of one woman, and had no known family history of genetic disorders. Upon physical examination at admission, her blood pressure was 118/84 mmHg. She exhibited clear consciousness and normal speech, with no cranial nerve abnormalities. Muscle strength assessment revealed grades of 5 in the proximal upper limbs, 4+ in the distal upper limbs, 1 in the left lower limb, and 0 in the right lower limb. Decreased muscle tone was observed in both lower limbs. She demonstrated hypersensitivity to pinprick sensation below both wrists, extending to the hands, and a significantly decreased pinprick sensation below the 5th thoracic spinal segment. Additionally, she presented with bilateral loss of motion and vibration below the hips, and a positive bilateral Babinski sign. The patient's EDSS score was recorded as 8.5.

2.2. Diagnostic workup

Biochemical examination revealed elevated levels of liver enzymes, including alanine aminotransferase (ALT) at 122 U/L, aspartate aminotransferase (AST) at 70 U/L, and markedly high gamma-glutamyltransferase (GGT) at 701 U/L. Alkaline phosphatase (ALP) was elevated to299 U/L. The albumin levels were low at 29.6 g/L. Direct bilirubin was 7.8 μmol/L, and total bile acids were 30.3 μmol/L. Fasting blood glucose, electrolytes, thyroid function, muscle enzymes, and renal function tests were all within the normal limits. Tests for hepatitis virus antibodies yielded negative results. The autoantibody spectrum notably showed high-titer antinuclear antibodies (ANA) with cytoplasmic granular type karyotype 1 ANA at a titer of 1:1,000 and nuclear membrane type karyotype 2 ANA at a titer of 1:320–1,000. Quantitative antinuclear antibody testing revealed significantly elevated levels of anti-Ro-52 antibodies >400.00 RU/mL and anti-mitochondrial M2 antibodies >400.00 RU/mL, consistent with autoimmune liver disease. Urinary light chain quantification was normal, and blood and urine immunofixation electrophoresis revealed no evidence of monoclonal proteins.

Type II, Detection of CNS demyelinating disease antibodies based on cell-based assays (CBA) showed that both the serum and cerebrospinal fluid (CSF) were positive for the AQP4 antibody, with a serum titer of 100++, and a cerebrospinal fluid titer of 1:10+. Oligoclonal banding (OCB) by isoelectric focusing electrophoresis indicated type II, suggesting IgG synthesis only in the cerebrospinal fluid and no blood-brain barrier impairment. Ganglioside antibodies detected by western blotting suggested no abnormalities in the serum; however, CSF testing identified positive anti-sulfatide antibody IgM, suggesting the presence of specific immune responses. OCB, Western Blot and CBA were performed by Jiangsu Simcere Diagnostics Co. Ltd. (Nanjing 210002,China). Electrocardiography (ECG) demonstrated sinus rhythm with no axis deviation or changes in T waves.

Ultrasound examination of the liver indicated diffuse liver injury. Submandibular and parotid gland ultrasonography revealed no significant abnormalities. Magnetic resonance imaging (MRI)revealed no enhancement of the optic nerve; however, multiple small ischemic and demyelinating changes were identified in the brain. MRIof the cervical spine further revealed multiple diffuse abnormal signals within the cervical spinal cord, including a prominent lesion in the medulla oblongata, indicative of an inflammatory or demyelinating pathology (Fig. 1A and B,C). MRI of the thoracic spine further revealed extensive abnormal diffuse signals extending from the thoracic spinal cord to the conus medullaris, consistent with characteristics typical of inflammatory or demyelinating lesions (Fig. 1D and E,F).

Visual evoked potentials (VEP) indicate prolonged latency of the bilateral P100 peaks, suggesting impaired conduction in the bilateral visual pathways. Ophthalmological examination, including optical coherence tomography (OCT) of the optic nerve, revealed a subtle reduction in the thickness of the retinal nerve fiber layer in the right eye.

2.3. Diagnosis, treatment and outcomes

According to the diagnostic criteria of NMOSD (IPND, 2015) [10], AQP4 - IgG positive NMOSD diagnostic criteria: (1) at least one core clinical characteristics; (2) Detection of AQP4-IgG positive by reliable method (CBA method is recommended); (3) Other diagnoses were excluded. The core clinical features：(1) ON; (2) acute myelitis; (3) area postrema syndrome, characterized by episodic hiccups, nausea and vomiting without other explanation; (4) other brainstem syndromes; (5) Symptomatic narcolepsy、diencephalic syndrome, the brain MRI have NMOSD diencephalon lesions characteristic; (6) Cerebral syndrome with characteristic cerebral lesions

of NMOSD.

Blood testing for AQP4-IgG was positive. Combined with the core symptom of myelitis, other diseases were excluded allowing a diagnosis of NMOSD, with CTD found at the same time. The patient was treated with high-dose methylprednisolone pulse therapy (MPT), starting with 1,000 mg daily for three days, followed by 500 mg daily for two days, 250 mg daily for two more days, finally transferring to a maintenance dose of 60 mg daily. This steroid regimen was supplemented with a five-day course of intravenous human immunoglobulin (IVIg), and twice-daily administration of 250 mg ursodeoxycholic acid capsules. Upon discharge, notable improvements were observed: the patient's defecation normalized, and the sensory level decreased to below the 10th thoracic spinal segment. Muscle strength in the left and right lower limbs improved to grades 2 and 1 respectively.

Following discharge, the patient continued rehabilitation therapy while tapering the prednisone dose by 5 mg/week until complete discontinuation. Concurrently, owing to the presence of autoimmune hepatitis-primary cholestatic cirrhosis, and SS, she began long-term oral treatment with MMF (1.0 g twice daily).

After three months, the patient returned for consultation with a rheumatologist, who recommended the addition of intravenous cyclophosphamide (0.4 g/half month), in conjunction with oral MMF to enhance CTD therapy. Gastrointestinal symptoms, including nausea and vomiting, were more pronounced following the administration of intravenous cyclophosphamide. After five doses of intravenous cyclophosphamide, the patient experienced decreased vision in the right eye upon waking in the morning, and returned to our hospital for follow-up examination. Neurological examination revealed decreased vision in the right eye, with no other new positive neurological signs. Enhanced MRI of the optic nerve revealed abnormal signal changes near the orbital apex of the right retrobulbar optic nerve, indicating optic neuritis (Fig. 2A and B,C). Plain MRI of the cervical and thoracic spine revealed a significant reduction in the extent of lesions in the cervical and thoracic spinal cord compared to. Serum testing revealed markedly elevated AQP4 antibodies at a level of 10+ (CBA method; Jiangsu Simcere Diagnostics Co. Ltd. Nanjing 210002,China) . Considering the possibility of NMOSD relapse, the patient was treated with intravenous MPT (500mg once daily for 3 days), combined with IVIg (0.4 g/kg once daily for 3 days), followed by oral prednisone (50 mg/day, orally once daily) with a gradual tapering regimen until discontinuation. Owing to the patient's intolerance to cyclophosphamide and the unavailability of inebilizumab in China that time the treatment was substituted with a weekly subcutaneous injection of telitacicepts (160 mg). After nearly 14 months of telitacicept treatment, the patient's condition gradually stabilized, allowing independent walking. Once inebilizumab became available in China, the patient's treatment was re-evaluated and changed to inebilizumab (300 mg, administered intravenously on days 1 and 15). The patient has since been consistently monitored with regular follow-up assessments every three months, during which her condition has remained stable without further relapses. During follow-up the patient has maintained an EDSS score of 5.5, and a retest for serum AQP4 antibodies was negative.

3. Discussion

In the present, the patient exhibited LETM that affected the entire spinal cord, including the medulla oblongata and the cervical, thoracic, and conus medullae. NMOSDwas confirmed based on a positive AQP4-IgG test and u-LETM, after excluding other potential etiologies. Notably, the presence of u-LETM in NMOSD is more likely to be associated with systemic autoimmune diseases, while screening for ADs can aid in the diagnosis of NMOSD. Further investigations revealed elevated titers of antinuclear antibodies (ANA), karyotype 1 and 2 ANA, and anti-Ro-52 antibodies. The patient's history of xerostomia and xerophthalmia contributed to a definitive diagnosis of a CTD, strongly suggestive of SS. Additionally, the presence of anti-mitochondrial and anti-mitochondrial M2 antibodies, along with liver function tests and abdominal ultrasound findings, supported the diagnosis of autoimmune hepatitis-primary cholestatic cirrhosis. A significant proportion of u-LETM cases are diagnosed as NMOSD, which commonly coexists with other ADs, such as SLE, SS, and AITD [3]. However, comorbidities such as autoimmune hepatitis and primary cholestatic cirrhosis are infrequently reported in the literature. As a case report, this study has certain limitations. However, this case report nevertheless improves our

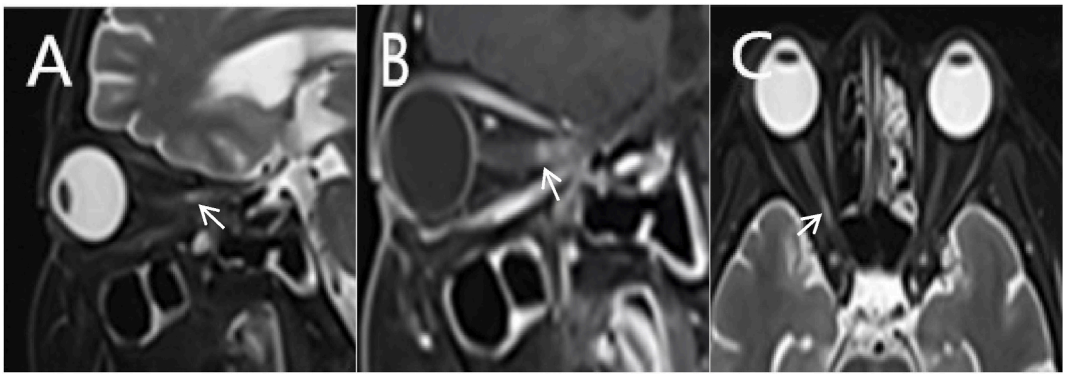


Fig. 2. Optic nerve MRI following the second recurrence of NMOSD. Sagittal T2-weighted imaging (A) showed hyperintensity of the right optic nerve; sagittal post-Gd T1-weighted imaging (B) showed hyperintensity of the right optic nerve; axial T2-weighted imaging (C) showed hyperintensity of the right optic nerve.

understanding of NMOSD with u-LETM as the initial symptom, highlighting its frequent comorbidities with autoimmune diseases, which will aid in promoting diagnosis, allowing early treatment to improve patient prognosis.

Although ADs often coexist with NMOSD, there is no recognized sequence in which these conditions manifest. Cases have been reported where one condition may precede or follow the other, or both may exist simultaneously [11]. In this patient, symptoms of xerostomia and xerophthalmia indicated a potential preexistence of SS prior to the onset of NMOSD. However, it was not feasible to ascertain the precise temporal relationship with autoimmune hepatitis-primary cholestatic cirrhosis.

Management of NMOSD involves acute-phase treatment and disease-modifying therapy (DMT) during remission. Acute-phase interventions include glucocorticoid pulse therapy, plasma exchange, and IVIg to alleviate symptoms, shorten the disease duration, enhance disability outcomes, and prevent complications. DMT involves the use of immunosuppressive agents, monoclonal antibodies, and stem cells. Immunosuppressive agents such as azathioprine and MMF are also commonly employed. Monoclonal antibodies targeting B cells include rituximab (RTX), inebilizumab and ofatumumab, while eculizumab, and ravulizumab target the complement system. Monoclonal antibodies against IL-6 receptors such as tocilizumab and satralizumab, are commonly prescribed to prevent disease recurrence. The patient in the present case was prescribed high-dose intravenous MPT in combination with IVIg during the acute stage.

Once the patient's condition stabilized, the prednisone dose was gradually tapered and eventually discontinued. Given the patient's coexisting ADs, long-term oral treatment with MMF, and the risk of NMOSD recurrence, intravenous inebilizumab was introduced. Prior to inebilizumab treatment, the patient was treated with telitacicept, a novel drug targeting upstream signaling for B cell activation and the subsequent production of autoimmune antibodies. In a single-center, single-arm, open-label study conducted by Guan et al., which enrolled eight patients with recurrent NMOSD in China, telitacicept administration following plasma exchange showed significant potential as a safe treatment for recurrent NMOSD. This study suggests that telitacicept may prolong the recurrence interval and reduce the annual number of recurrences. During the treatment period with telitacicept as a DMT, the patient's condition remained stable, without any relapses or adverse reactions. After nearly 4 months of follow-up after inebilizumab treatment, the patient showed further improvement without any recurrence.

The patient further underwent ganglioside antibody testing to assess potential peripheral nerve involvement, as she had experienced bilateral hand numbness in the early stages of the disease. Sulfatide, an acidic sugar ester, is primarily found in the myelin sheath of the central and peripheral nerves and plays a role in neurilemmal formation [12]. The association between elevated anti-sulfatide antibody levels and specific types of peripheral neuropathy has been debated in previous studies. Most researchers agree that high-titer anti-sulfatide antibodies are commonly associated with sensory axonal peripheral neuropathy. Anti-sulfatide antibodies include both IgM and IgG types, with IgG showing a lower specificity than IgM and potentially being positive in other peripheral neuropathies, various nervous system diseases, and even in healthy individuals [13,14]. In the present case, the CSF was positive for the anti-sulfatide antibody IgM, but blood and urine immunofixation electrophoresis did not support the presence of an IgM monoclonal gammopathy. Moreover, the electrophysiological findings did not indicate definitive neuromyelin or axonal neuropathy. As such, the significance of the CSF-positive anti-sulfatide IgM antibody in this patient warrants long-term follow-up.

In conclusion, this case of NMOSD featuring u-LETM and an unusual comorbidity with primary cholestatic cirrhosis highlights the diagnostic and therapeutic challenges in managing complex autoimmune disorders. The presence of u-LETM further underscores the need for meticulous neuroimaging and comprehensive immunological profiling to diagnose and effectively treat NMOSD accurately. This case emphasizes the importance of personalized medical strategies to achieve optimal outcomes, particularly when faced with rare manifestations and comorbidities in autoimmune diseases.

CRediT authorship contribution statement

Furong Li: Writing – original draft. **Xiaowen Sui:** Resources, Formal analysis. **Xin Pan:** Resources, Investigation. **Chang Liu:** Validation, Supervision. **Lili Xie:** Supervision, Data curation. **Hongling Zhao:** Validation, Supervision. **Shubei Ma:** Writing – review & editing.

Ethics declarations

The case report complies with all ethics regulations.

This case report was reviewed and approved by the Central Hospital of Dalian University of Technology with the approval number: YN2024-120-01.

Consent for publication

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

Availability of data and materials

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

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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