INTERNAL MEDICINE

□ CASE REPORT □

# Ophthalmoplegia and Flaccid Paraplegia in a Patient with Anti-NMDA Receptor Encephalitis: A Case Report and Literature Review

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## Abstract

We herein report the case of a 26-year-old woman with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis presenting with ophthalmoplegia and flaccid paraplegia. She developed disorientation and hallucination after fever and vomiting. Hypothermia, hypoventilation, hypertension, paralytic ileus and hyponatremia were present. Neurological examination showed mild consciousness disturbance and bilateral ophthalmoplegia on admission, flaccid paraplegia with leg areflexia on Day 4. Anti-NMDAR antibodies were detected in the serum and cerebrospinal fluid samples. Motor nerve conduction velocity was decreased in the tibial and peroneal nerves. F-wave amplitudes were reduced in the tibial nerve. MRI disclosed lesions in the callosal splenium, hippocampus and cerebral subarachnoid regions. In addition to various encephalitic symptoms, physicians should pay more attention to peripheral nerve damage in patients with anti-NMDAR encephalitis.

**Key words:** anti-NMDA receptor encephalitis, Guillain-Barré syndrome, Miller Fisher syndrome, transient splenial lesion, hyponatremia, SIADH

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## Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis typically occurs in young women with neuropsychiatric symptoms followed by seizures, consciousness disturbance, language dysfunction and involuntary movements. Patients frequently develop central hypoventilation and dysautonomia (1-6). Ovarian teratoma is also an underlying pathogenesis in young women with this encephalitis (1-6).

Recently, anti-NMDAR encephalitis has been reported in several patients with other autoimmune disorders in the central nervous system, including multiple sclerosis, neuromyelitis optica and similar conditions (7-10). The full clinical spectrum associated with anti-NMDAR antibodies is likely to widen with increasing recognition. However, little is known about the peripheral nerve involvement, including Guillain-Barré syndrome (GBS) and Miller Fisher syndrome (MFS) (11, 12). We herein report a patient with ophthalmoplegia and flaccid paraplegia with leg areflexia during the course of anti-NMDAR encephalitis.

## Case Report

A 26-year-old woman experienced a fever, anorexia and vomiting, and was diagnosed with acute gastroenteritis at a neighboring clinic. Three days later, disorientation and abnormal speech were observed, and the patient was admitted to our department. Physical examination showed hypothermia (34.3℃), a high blood pressure of 144/94 mm Hg and the loss of bowel sounds. Her consciousness state was slightly drowsy with visual hallucination. Ocular movements

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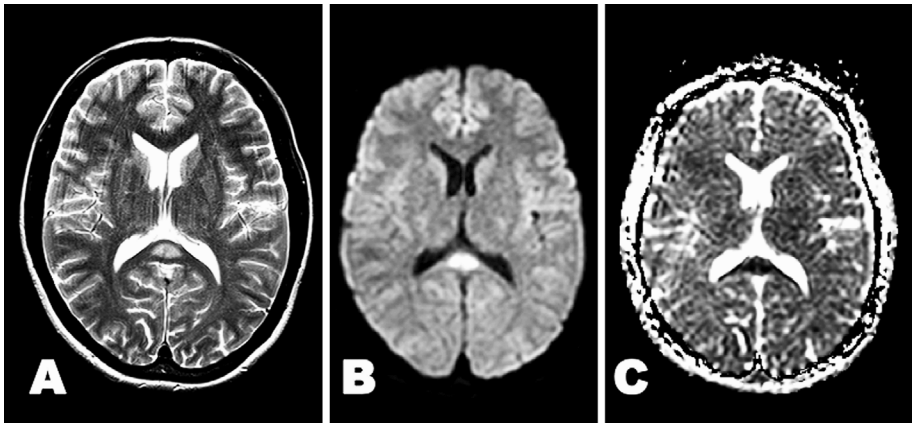


**Figure 1. A transient splenial lesion on MRI. A) T2-weighted imaging. B) DWI. A hyperintense lesion was found in the callosal splenium. C) The ADC map showed a hypointense splenial lesion.**

were impaired in all directions of both eyes. The pupillary size was equal (2.0 mm), and light reflexes were normal on both sides. Other cranial nerves were normal. Muscle stretch reflexes were normal and plantar responses were flexor. The remaining function was normal, including the motor, the sensory and the cerebellar system. Routine laboratory studies showed serum sodium levels of 124 mEq/L and plasma antidiuretic hormone (ADH) levels were 2.5 pg/mL (normal ranges of 0.3-3.5 at normal serum sodium levels). Plasma ADH levels were not suppressed by marked hyponatremia. Urine volumes were 0.9-1.2 L/day, and urine sodium levels were more than 20 mEq/L. Central venous pressures (CVP) was 10-13 cm $H_2O$. Serum and cerebrospinal fluid (CSF) samples were analyzed for anti-NMDAR antibodies using an enzyme-linked immunosorbent assay (13-15) and cell-based assay (2). Serum and CSF levels of antibodies to GluRε2-NT2, GluRε2-CT1, GluR ζ1-NT and GluRδ2-NT were increased respectively at 2-10 folds compared to controls. Both serum (1:40) and CSF (1:2) reacted with human embryonic kidney (HEK293) cells transfected complementary DNA encoding NR1 and NR2B subunits of NMDAR. Serum levels of antibodies to gangliosides GM1, GD1a, GD1b, GQ1b and GT1a were not detected. Serological tests of antinuclear and voltage-gated potassium channel antibodies were negative. Pathogen tests for *Campylobacter jejuni*, *Mycoplasma pneumoniae*, cytomegalovirus, Epstein-Barr virus, rubella virus, herpes simplex virus and other viruses were negative. Chest X-ray, electrocardiography and carotid ultrasonography were normal. Abdomen X-ray disclosed marked retention of gastrointestinal gas. At 4 days after neurological onset (Day 4), hypoventilation and flaccid paraplegia were present. Muscle stretch reflexes were reduced in the upper extremities and absent in the lower extremities. A CSF study exhibited protein of 139 mg/dL, 246 mononuclear cells/$mm^3$ and normal cytology. Myelin basic protein was increased to 787 μg/mL (normal ≤102). Oligoclonal immunoglobulin G band was not detected. Motor and sensory nerve conduction studies were performed on Day 6. Motor nerve conduction velocity (MNCV) was decreased in the peroneal (37.1 m/s) and the tibial nerve (38.9 m/s). That of the median and the ulnar nerve was 58.0 m/s and 48.1 m/s, respectively. Amplitudes of compound muscle action potentials were within the normal ranges in these nerves. Sensory nerve conduction velocity and amplitudes of sensory nerve action potentials were within the normal ranges in the median, the ulnar, the peroneal and the sural nerve. F-waves were elicited in the median (94%), the ulnar (100%) and the tibial nerve (94%). Amplitudes of F-wave were decreased in the tibial nerve. Electroencephalogram showed slow waves, predominantly in the frontal region. Auditory brainstem response and short-latency somatosensory evoked potentials using the stimulation in the median nerve were normal. Brain magnetic resonance imaging (MRI) was performed on Day 2. T2-weighted imaging and diffusion-weighted imaging (DWI) disclosed a hyperintense lesion in the central splenium of the corpus callosum. The apparent diffusion coefficient (ADC) map showed a hypointense lesion in the callosal splenium (Fig. 1). Fluid-attenuated inversion recovery (FLAIR) imaging displayed hyperintense lesions in the medial temporal lobes and the cerebral subarachnoid regions (Fig. 2). Second brain MRI revealed no splenial lesion on Day 9. Spinal cord MRI was unremarkable. Pelvic MRI exhibited a small massive lesion in the left ovary (Fig. 3). Gynecological examination and the radiological finding strongly suggested a diagnosis of ovarian teratoma.

*Clinical course and treatment*: mechanical ventilator was used from Day 4. The patient was treated with intravenous immunoglobulin (0.4 g/kg/day for five days) twice on Day 5 and Day 17. Her consciousness disturbance, hypothermia, respiratory failure, dysautonomia and hyponatremia were gradually ameliorated. When external ophthalmoplegia became severe on Day 14, the pupillary size was 3.5-4.0 mm and light reflexes were mildly sluggish on both sides. There were no brainstem lesions on conventional and gadolinium-enhanced follow-up MRI. Intravenous methylprednisolone (1,000 mg/day for three days) was administered on Day 35, followed by prednisolone (50 mg/day, per os). The patient was removed from mechanical ventilation on Day 40. Oph-

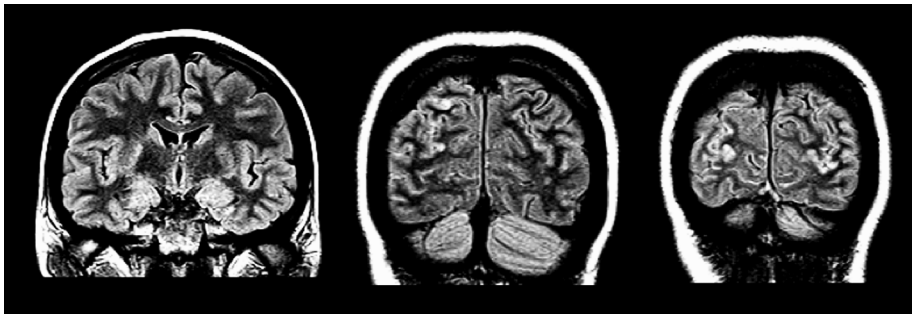

**Figure 2.** **Hippocampal and cerebral subarachnoid lesions on MRI. FLAIR imaging showed hyperintense lesions in the medial temporal lobes and the cerebral subarachnoid region.**

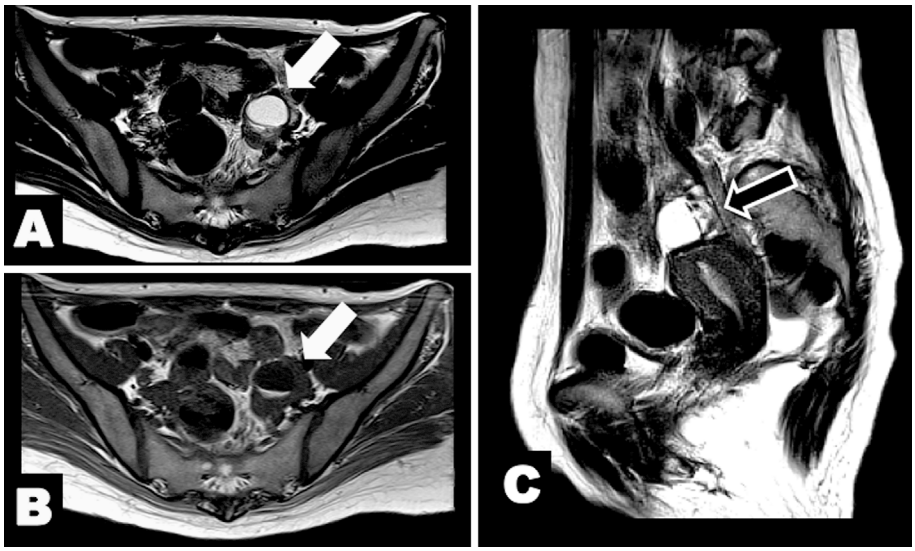


**Figure 3.** **An ovarian lesion on pelvic MRI. A) Axial T2-weighted imaging. B) Axial T1-weighted imaging. C) Sagittal T2-weighted imaging. A small mass (26 mm in long diameter) was found in the left ovary (arrows).**

thalmoplegia and lower limb muscle weakness were attenuated concurrently. Three months after admission, ocular movements, muscle strength and muscle stretch reflexes in the lower extremities were normalized. MNCV was normal in the peroneal (45.5 m/s) and the tibial nerve (46.9 m/s) on Day 177. Amplitudes of F-wave were also normal in the tibial nerve. The electrophysiological alternations from the early stage to the recovery stage suggested a mild degree of demyelinating neuropathy in the lower limbs. Neurological deficits were ameliorated completely. She refused surgical resection of the left ovarian tumor. We have investigated the patient carefully at the outpatient departments of neurology and gynecology.

## Discussion

We reported a distinct patient with GBS-like condition of ophthalmoplegia and lower limb muscle weakness during the course of anti-NMDAR encephalitis. In addition, the present patient had marked hyponatremia and a transient splenial MRI lesion.

In general, NMDARs are ligand-gated cation channels and can play a crucial role in synaptic transmission and plasticity. The receptors are heteromers of NR1 subunits binding glycine and NR2 (A, B, C or D) subunits binding glutamate (16). NR1 and NR2 combine to express receptor subtypes with distinct pharmacological properties, localization and the ability to interact with intracellular messengers. Overactivity of NMDARs causing excitotoxicity is an underlying mechanism of epilepsy, dementia and stroke whereas these hypoactivity induces neuropsychiatric symptoms of schizophrenia (17-19). In 100 cases reported by Dalmau et al. (3) and 44 cases reported by Irani et al. (6), the common early clinical features included seizures, confusion, amnesia, behavioral changes and psychosis. The later distinctive aspects revealed conscious disturbance, involuntary movements and dysautonomia. The present patient experienced no involuntary movements and epileptic seizures during her entire clinical course, although hypothermia and hyponatremia were present. Hypothermia was described in only three (3%) of 100 patients with anti-NMDAR encephalitis (3). On the other hand, as a possible etiology of hyponatremia, syndrome of inappropriate secretion of ADH (SIADH) or cerebral sodium wasting syndrome (CSWS) was suspected in

**Table. Previous and Present Cases of Anti-NMDAR Encephalitis and Peripheral Nerve Involvement**

| Reference Number (Reported years) | Age/sex | Tumor | Interval between anti-NMDAR encephalitis and peripheral nerve diseases | Anti-NMDAR antibodies | Serum antibodies to gangliosides | Treatment | Prognosis |
|---|---|---|---|---|---|---|---|
| 11 (2011) | 19 years/man | Absence | Anti-NMDAR encephalitis on Day 37 of GBS | Anti-NR1/NR2B antibodies | Negative | IVIg, mPSL | Sequelae |
| 12 (2011) | 23 years/woman | Absence | Anti-NMDAR encephalitis on Day 2 of MFS | Anti-GluRε 2, anti-NR1/NR2B antibodies | Anti-GQ1b IgG, anti-GT1a IgG | IVIg, mPSL | Good |
| Present case | 26 years/woman | Ovarian teratoma | Ophthalmoplegia on admission and flaccid paraplegia on Day 7 of anti-NMDAR encephalitis | Anti-GluRε 2-NT2, anti-GluR ε 2-CT1, anti-GluR ζ 1-NT, anti-GluRδ 2-NT , anti-NR1/NR2B antibodies | Negative | IVIg, mPSL | Good |

GBS: Guillain-Barré Syndrome, IVIg: intravenous immunoglobulin, MFS: Miller Fisher syndrome, mPSL: methylprednisolone, ND: not described, NMDAR: N-methyl-D-aspartate receptor

the present patient. The volemic state has been pointed out as the most crucial factor for the differential diagnosis of both syndromes. The plasma volume is normal or increased in SIADH patients whereas that is decreased in CSWS patients. The urine volume is normal or decreased in SIADH patients. CSWS patients have polyuria and dehydration symptoms (20). The present patient had normal CVP and urine volume without dehydration signs. These laboratory findings supported the diagnosis of SIADH rather than CSWS. Dilutional hyponatremia due to SIADH was not mentioned in previous review and case series reports of anti-NMDAR encephalitis (1-6). Interestingly, SIADH is uncommon in GBS patients. A previous study suggested that a mild to severe degree of SIADH occurred in 24 of 50 patients (48%) at some stages of GBS (21). The peripheral nervous system is rarely affected in patients with anti-NMDAR encephalitis (11, 12). The previous cases are summarized in Table.

In a case reported by Tojo et al. (11), a 19-year-old man developed limb muscle weakness and dysesthesia at 2 weeks after flu-like symptoms of cough and rhinorrhea. MNCV was decreased in the median and the tibial nerve with conduction block. No sensory nerve action potentials and F-waves were elicited. The patient was diagnosed with GBS. Psychomotor agitation was present on the 37th hospital day. Immunoreactivity against heteromers of NR1/NR2B subunits was positive in the serum and CSF samples. No serum IgG antibodies to GM1 or GQ1b were detected. In another case, a 23-year-old woman had an antecedent respiratory infection. One week later, she developed diplopia and unsteady gait. On the 2nd hospital day, mental and behavioral changes were noted. MNCV and compound muscle action potentials were normal. F-wave amplitudes were decreased in the median and the tibial nerve. Serum levels of IgG antibodies to GQ1b and GT1a were increased. IgM and IgG antibodies to GluRε2 and NR1/NR2B were detected in serum and CSF samples. The coexistence of MFS and anti-NMDAR encephalitis was considered. In the present case, the distinct neurological profile revealed extraocular and leg muscle paralysis with lower limb areflexia. The present and two previous patients experienced prodromes of respiratory or gastrointestinal infection. High frequency of preceding infection has been reported in patients with GBS and anti-NMDAR encephalitis. Whether there is the similar pathogenesis or incidental co-morbidity between these diseases remains unclear. Parainfectious common autoimmune reactions can trigger the development of anti-NMDAR encephalitis and acute demyelinating neuropathy.

With respect to the radiological hallmarks of anti-NMDAR encephalitis, the brain MRI findings were unremarkable in 45 of 100 patients described by Dalmau et al. (3). The remaining 55 patients had T2- or FLAIR-hyperintense lesions in the hippocampus, the cerebellum, the cerebral cortex, the frontobasal and insular regions, the basal ganglia and the brainstem. The most common lesion was found in the medial temporal lobes. The lesion of the corpus callosum was reported in 4 patients. Follow-up MRI was normal in most of patients (3). Otherwise, transient splenial lesion (TSL) was described in a variety of diseases or conditions, including encephalopathy, epileptic seizure and antiepileptic medication (22-24). However, there are no literatures of the diffusion-restricted TSL in patients with anti-NMDAR encephalitis. Brain DWI and ADC map findings have not been noted in patients with this type of encephalitis. In the present patient, the nonspecific encephalitic condition and SIADH may have contributed to the transient restriction of water diffusivity in the callosal splenium.

In conclusion, we highlighted GBS-like deficits, SIADH and TSL in a patient with anti-NMDAR encephalitis. Physicians should pay more attention to the cranial and the peripheral motor nerve involvement. Further clinico-immunological examination is needed to elucidate the full spectrum of anti-NMDAR encephalitis or its partial overlapping with other neurological autoimmune diseases.

**The authors state that they have no Conflict of Interest (COI).**

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