

Intractable nausea and vomiting as an uncommon presentation in an anti-aquaporin 4-positive patient

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Abstract

Autoantibodies targeting aquaporin 4 (AQP4) water channels are a sensitive and specific biomarker for neuromyelitis optica spectrum disorder (NMOSD). Presence of AQP4 antibodies distinguishes NMOSD from multiple sclerosis. We present our experience with an anti-AQP4 antibody-positive patient diagnosed with NMOSD who complained of intractable nausea and vomiting, not restricted to optic neuritis or acute myelitis during the first attack. Her symptoms partially resolved after appropriate therapy with intravenous methylprednisolone and oral prednisolone. Through this case, we hope to draw attention to an unusual neurological presentation of NMOSD which should be included in the differential diagnosis of intractable nausea and vomiting.

Keywords

Intractable nausea, vomiting, neuromyelitis optica spectrum disorder, aquaporin 4, gastroenterology, methylprednisolone

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Introduction

Intractable nausea and vomiting are often encountered in gastroenterology medical clinics, and common diagnoses associated with these symptoms include gastroenteritis and pyelonephritis. Undeniably, these

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symptoms are not usually considered as the possible initial presentation of neuromyelitis optica spectrum disorder (NMOSD). NMOSD is an immune-mediated disorder of the central nervous system which is characterized by severe relapsing episodes of optic neuritis and transverse myelitis.

The presence of antibodies against aquaporin 4 (AQP4) in the serum or spinal fluid distinguishes NMOSD from multiple sclerosis.^{1,2} Certain symptoms, including uncontrollable nausea and vomiting, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome, and symptomatic cerebral syndrome, are now recognized as relatively specific indicators of NMOSD that are caused by brainstem involvement, specifically the area postrema.³ Early diagnosis is extremely important to allow the prompt initiation of immunosuppressive therapy which can reduce the significant morbidity associated with this disorder.

Case report

An otherwise previously healthy 43-year-old Chinese woman presented with a 2-month history of intractable nausea and vomiting. She had suffered loss of appetite and had lost 4.5 kg of body weight. Upper gastrointestinal tract endoscopy, abdominal ultrasound, and a computed tomography scan of her abdomen and pelvis were evaluated by a gastroenterologist at another hospital, and all found to be normal. Routine laboratory test results showed that she had normal liver, thyroid, and kidney functions, a normal complete blood count, and normal levels of urea, coagulation factors, creatinine, electrolytes, fasting blood glucose, and serum lipids. She was prescribed various antiemetics, but nausea and vomiting continued five to six times daily. She subsequently experienced optic neuritis involving the right eye,

which partially improved after 60 mg/day oral prednisone treatment for 5 days.

Two weeks later, the patient complained of lower limb weakness and paresthesia, which gradually ascended to the torso; urinary retention followed. At this point, she was admitted to our neurology ward. Physical examination showed right papillitis with early optic atrophy, weakness of the lower limbs, and increased muscle stretch reflexes with a bilateral Babinski sign. The finger-to-nose test was unstable on the right side. Levels of serum folic acid, vitamin B12, and paraneoplastic biomarkers were within normal ranges. Valid evoking wave of the right eye was absent on examination of the visual evoked potential pattern. Magnetic resonance imaging (MRI) of the brain and the cervical spine revealed hyperintense lesions on T2-weighted images (T2WI) of the medulla and cervical cord, with a diagnosis of longitudinally extensive transverse myelitis (Figures 1–3). Antibodies to AQP4 were positive both in the serum and in the cerebrospinal fluid (CSF). The CSF was colorless with a normal pressure, and contained 20/mm³ leukocytes. Total protein levels in the CSF were 228 mg/L, the IgG index was 0.6, and CSF oligoclonal bands were negative. Other autoantibody tests were negative for anti-Sjögren's syndrome (SS)-B and anti-Ro52 antibodies, but positive for antinuclear (ANA) and anti-SS-A antibodies. A diagnosis of NMOSD with medullary involvement, optic neuritis, and transverse myelitis was made. The patient was treated intravenously with methylprednisolone at 1 g/day for 5 days and oral prednisolone at 60 mg once a day after the course of intravenous methylprednisolone. After 2 weeks, intractable nausea and vomiting subsided, and paresthesias and weakness of the lower limbs improved greatly.

The patient gave written informed consent for the dissemination of images and other personal information for educational



Figure 1. T2-weighted magnetic resonance images of the cervical spine showing longitudinally hyperintensity signal in the cervical cord (red arrows)

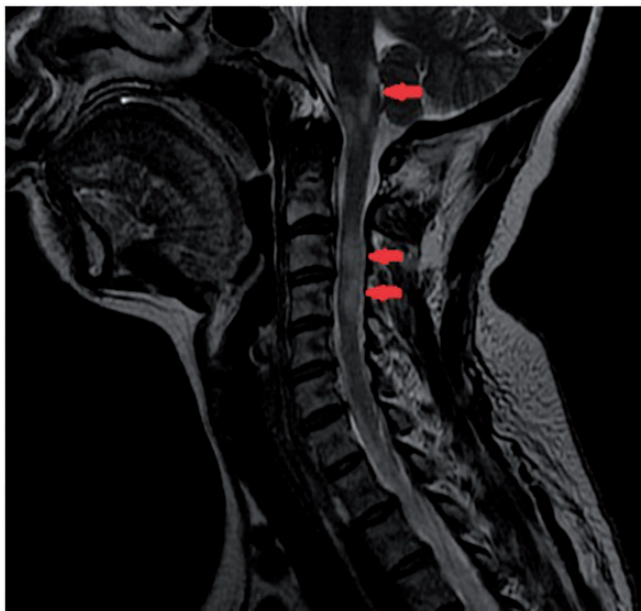


Figure 2. T2-weighted magnetic resonance images of the brain showing hyperintense signal in the medulla and cervical cord (red arrows)

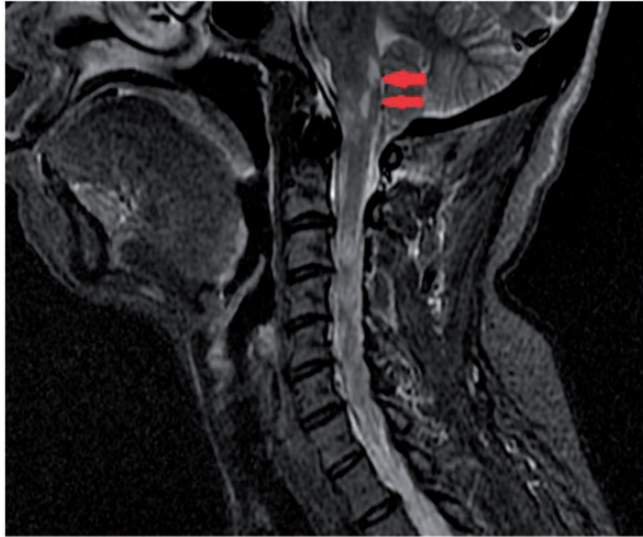


Figure 3. T2-weighted magnetic resonance images of the brain showing hyperintensity in the dorsal medulla (red arrows)

and research purposes. The study was approved by the Ethics Review Committee of Tianjin Baodi Hospital.

Discussion

Neuromyelitis optica (NMO) is a rare autoimmune disorder in which the patient's immune system attacks the optic nerves and spinal cord.^{4,5} Previously, loss of vision and spinal cord dysfunction were considered necessary symptoms for a diagnosis of NMO. However, notable advances in our understanding of NMO have been made with the development of autoantibodies against AQP4 protein found in cell membranes.⁶ AQP4 is expressed on optic nerves, the hypothalamus, subpial and subependymal layers, the immediate periventricular regions, gray matter of the spinal cord, and the area postrema. The diagnostic criteria for NMO were developed in 2006 for the related clinical syndrome NMOSD.⁷ Recently, the core features of NMOSD have been further revised, and currently include: optic neuritis, myelitis,

area postrema syndrome, diencephalic syndrome, and other brainstem and cerebral syndromes.⁸ Patients with one of these six core clinical characteristics and who are positive for antibodies against AQP4 can be diagnosed with NMOSD. In the present case, we diagnosed our patient with anti-AQP4-positive NMOSD after the onset of area postrema syndrome, optic neuritis, and transverse myelitis.

Nausea and vomiting are non-specific symptoms that are not usually appreciated as a possible initial manifestation of NMOSD. Indeed, the Mayo Clinic (Rochester, MN, USA) reported a 12% prevalence rate of nausea and vomiting as the heralding symptom of anti-AQP4-positive NMOSD.⁹ Takahashi et al.¹⁰ reported that intractable nausea, vomiting, and hiccups (INH) was the starting symptom in 15 of the 35 NMO patients (43%) in their study, while 12 of 119 NMO patients (10%) in another study initially displayed INH symptoms, and the median interval time was ~20 days (range: 7–60 days) from the initial INH signs to the occurrence

of other neurological symptoms.¹¹ Additionally, Sato et al.¹² found that 30 of 144 NMOSD patients (21%) had hiccups and 24 (17%) had nausea, and Misu et al.¹³ documented INH symptoms in eight of the 47 patients (17%) with recurrent NMO in their study. In our case, optic neuritis developed about 8 weeks after the onset of intractable nausea and vomiting, which is consistent with previous case reports. However, our patient did not complain of intractable hiccups, which conflicts with other studies. After the course of intravenous methylprednisolone pulse therapy in our patient, the symptoms of nausea and vomiting subsided and did not recur.

Pittock et al.¹⁴ reported that coexisting antibodies, including ANA (43%), extractable nuclear antigen (15%), SS-A (10%), and SS-B (3%), were observed in up to 50% of patients with NMOSD. Our patient was positive for the presence of ANA and SS-A antibodies, but negative for other coexisting antibodies. Hyperintense signals on T2WI in the area postrema were previously reported in NMOSD patients,¹⁵ and this symptomatology is associated with discrete lesions. In keeping with this, the brain MRI of our patient revealed T2WI hyperintense lesions in the area postrema as well as the cervical spine.

AQP4 is the main marker for blood–brain barrier function. Histopathological findings have shown that the area postrema is the first point of attack in NMOSD patients because of the selective loss of AQP4 in the medullary floor of the fourth ventricle and area postrema. This can also be accompanied by tissue rarefaction, the variable deposition of terminally activated complement components, inflammation, and nonlytic alterations in reactive astrocytes.¹⁶ Therefore, the AQP4 antibody can easily attack the AQP4 of astrocytes in this area and trigger the onset of inflammatory demyelination. It has been experimentally

shown that ablation of the area postrema and an increase in the firing of area postrema neurons are associated with intractable vomiting.^{17,18} The lack of AQP4 immunoreactivity in the affected area postrema and the resulting disruption of water or neurotransmitter homeostasis may activate area postrema neurons and induce vomiting.⁹ The lower centers of hiccup are controlled by a region of the medulla. Efferent nerves are vagus nerves and central fibers of the phrenic nerve, whereas afferent nerves are phrenic nerves and intercostal nerves that can reach the diaphragm nerve of the diaphragm, glottis, and other respiratory muscles. Irritant lesions of efferent or afferent nerves can give rise to nausea and vomiting.¹¹

Currently, there is no curative treatment for NMOSD. The recommended treatment for acute attacks is methylprednisone (1 g/kg) for 5 days. If no improvement is observed then a trial of plasma exchange or intravenous immunoglobulins can be considered. Azathioprine, mycophenolate mofetil, or rituximab can also be used to achieve immunosuppression. Additionally, there are several novel immunotherapies, such as complement inhibition, blockade of AQP4-IgG binding to AQP4, granulocyte-targeted therapies, and eosinophil-targeted therapies. Fortunately, the symptoms of our patient partially resolved after treatment with intravenous methylprednisolone and oral prednisone.

Conclusion

NMOSD should be diagnosed promptly so that appropriate treatment can be started as soon as possible to reduce associated morbidity. Furthermore, NMOSD should be taken into consideration when encountering patients with intractable nausea and vomiting.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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