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Original Research Article

INTRACTABLE VOMITING AS THE INITIAL PRESENTATION OF NEUROMYELITIS OPTICA SPECTRUM DISORDER: A CASE REPORT

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Abstract
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 therapeutics plasma exchange, intravenous methylprednisolone and oral prednisolone and follow up tb azathioprine 50 mg. 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

Introduction

Neuromyelitis optica (NMO, also known as Devic's disease) is an idiopathic inflammatory syndrome of the central nervous system (CNS) that is characterized by severe attacks of optic neuritis (ON) and myelitis.[1]

Intractable nausea and vomiting are often encountered in gastroenterology medical clinics, and common diagnoses associated with these symptoms include gastroenteritis and pyelonephritis. These 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.[2,3] 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.[4]

NMO had been considered as a subtype of multiple sclerosis (MS); however, after the identification of a disease-specific autoantibody, NMO-IgG, in the serum of patients with NMO, a dramatic conceptual change occurred. NMO-IgG binds selectively to aquaporin-4 (AQP4).[5,6] AQP4 is a waterchannel protein that assembles as homotetramers in cell membranes and plays a major role in fluid homeostasis of the CNS. AQP4

is found throughout the brain but is particularly abundant in the optic nerves and spinal cord.[7]

NMO has occasionally been associated with other autoimmune diseases, including hypothyroidism, Sjogren's ¨ syndrome (SS), systemic lupus erythematosus (SLE), pernicious anemia, ulcerative colitis, primary sclerosing cholangitis, rheumatoid arthritis, mixed connective tissue disorders, and idiopathic thrombocytopenic purpura.[1]

Early diagnosis is extremely important to allow the prompt initiation of immunosuppressive therapy which can reduce the significant morbidity associated with this disorder. All patients with suspected NMOSD should be treated for acute attacks as soon as possible with high-dose intravenous methylprednisolone -1 gram daily for three to five consecutive days and in some cases, plasma exchange should be used. It is recommended that every patient with NMOSD be started on an immunosuppressive agent, such as, azathioprine, methotrexate, or mycophenolate and in some cases, rituximab, soon after the acute attack and usually be treated for about 5 years after the attack. These advances have helped improve the prognosis and outcome in these disorders.

Case presentation:

55 years old female , non smoker, non alcoholic presented with chief complaints of vomitting last 1 month, sudden in onset, non projectile in nature, 7-8 episode per day, 20-30ml, non billus vomitus per episode, not improved by taking medications. She had multiple admission in private hospital but did not respond to treatment. After 1 month, she had complaint of weakness in right lower limb which was also sudden in onset and progressive in nature, starting from right foot to whole of the right lower limb over1 -2 days. No weakness in left lower limb, associated with numbness in bilaterally lower limb which was also sudden in onset and progressive in nature, starting from right foot to whole of the right lower limb , left lower limb and trunk just below nipple over1 -2 days, associated with urinary retention and also associated with blurred vision which was bilateral, sudden in onset, painless and progressive in nature.

On General Physical Examination Patient was conscious oriented to time place person, Moderately built and well nourished and hemodynamical stable. **Cranial Nerves** –optic nerve examination-Corneal reflex-b/l present, Fundus –disc and macula –wnl. **Vision-**Right eye-finger counting close to face, Left eye-finger counting at 2 metre, b/l Pupil-normal size reactive to light. Rest cranial nerves examination –WNL. Right lower limb muscle tone decreased and power 0/5. B/l ankle jerk and knee jerk diminished (1+).B /l plantar- extenser and b/l abdominal reflex-absent. **Pain –**Decrease pain sensation in b/l lower limb ,trunk just below bilaterally nipple compared with upper limbs. **Touch- –**Decrease touch sensation also in b/l lower limb , trunk just below bilaterally nipple compared with upper limbs. **Temperature**- Decrease hot sensation also in b/l lower limb , trunk just below bilaterally nipple compared with upper limbs. **Vibration** –b/l impaired in lower limb and normal in upper limb, **Position**- b/l imparied in lower limb and normal in upper limb. Respiratory system, cardiovascular system and abdominal systemic examination were normal.

Complete blood count, renal function test, liver function test and lipid profile were with in normal limit. Urine complete examination was normal. Viral marker-non reactive. ECG and chest x-ray were normal. CEMRI brain-cervico-medullary junction involved suggestive area postrema syndrome(Image 1), CEMRI orbit suggestive optic neuritis (Image 2) and MRI whole spine suggestive transverse myelitis (Image 3). CSF- TLC - 100-120 cells/cu.mm, DLC - N-70% ,L-30%, Protein – 55.50 mg/dl(15-50),Sugar - 83mg/dl(50-80), ADA - 1.8, Oligoclonal bands- Absent, Anti neuromyelitis optica antibody/ aquaporin 4 – positive(1:10). **Visual evoked potential**-b/l normal latency and reduced amplitude suggestive optic neuritis. ANA by IFA –negative, anti ro and la –negtive, thyroid profile- normal and ANCA profile – normal and serum vitamin b12 and folic acid level normal. Points favor to neuromyelitis optica spectrum syndrome- Optic neuritis, Acute myelitis, Area postrema syndrome, Anti aquaporin 4 positive, CSF TLC 100-120, DLC-N70%, L30%, OLIGOCLONAL BANDS ABSENT.

History, physical examination and investigation were suggestive Neuromyelitis optica spectrum disorder. Patient was treated with 5 cycle of therapeutic plasma exchange every alternate day and also treated with inj methyl prednisolone 1gram i/v od for 5 days followed by tb prednisolone 60mg od ABF and planned for tapering and add tab azathioprine 50mg bd. Progress report during treatment- Around 4-5 days after treatment urinary retention, blurred vision, vibration and position sense improved, b/l planter extensor and abdominal reflex present and right lower limb power was improved to 4/5 . vomiting was completely improved. Now patient is on azathioprine 50mg bd in medicine opd follow up.

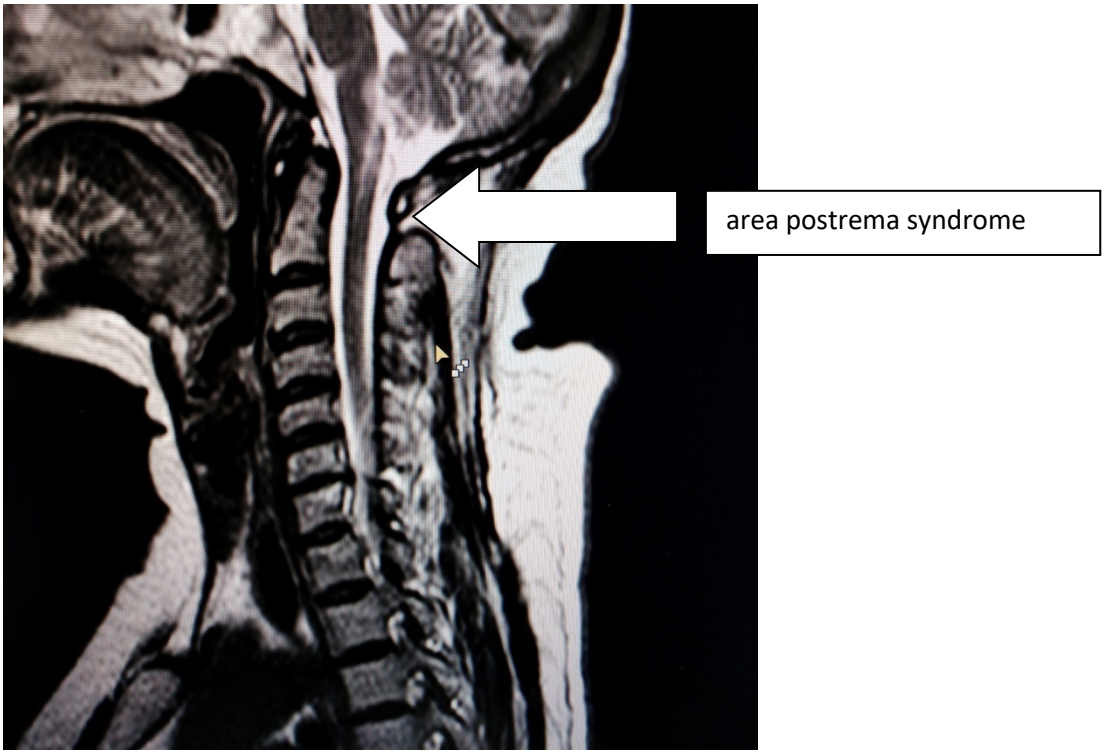

Image:1. CEMRI Brain- suggests hyperintensities in area postrema

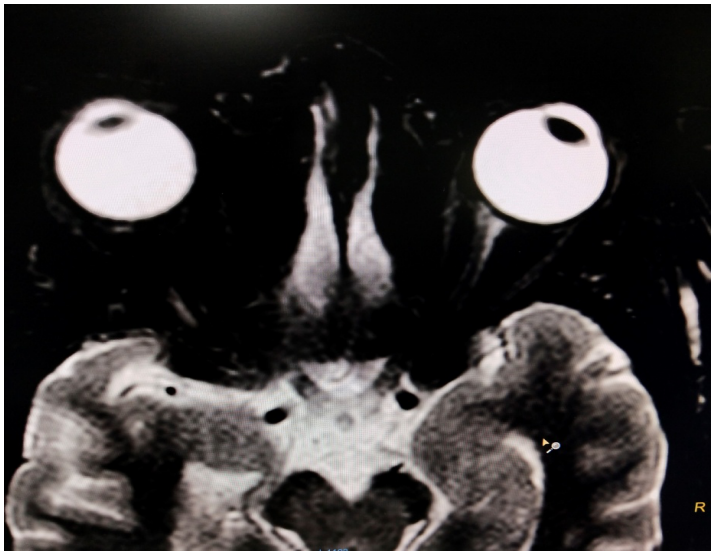

Image 2: CEMRI Orbit-CEMRI orbit suggests optic neuritis

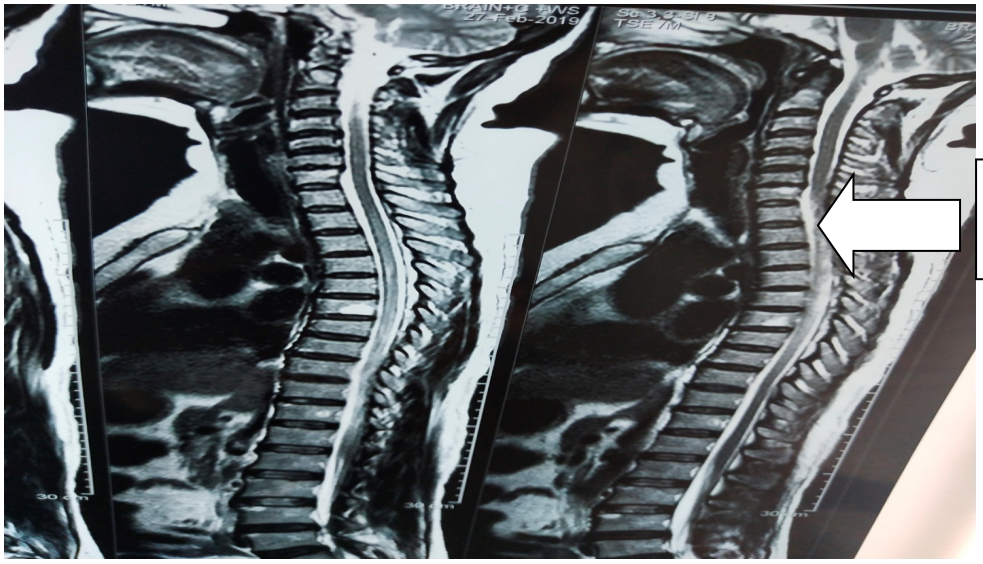

Image 3: MRI screening of spine – suggests longitudinally extensive transverse myelitis.

Discussion:

Neuromyelitis optica (NMO) is a rare autoimmune disorder in which the patient's immune system attacks the optic nerves and spinal cord.[8,9] 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.[10] 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. 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.[11]

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 antiAQP4-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.[12] Takahashi et al. reported that intractable nausea, vomiting, and hiccups was the starting symptom in 15 of the 35 NMO patients (43%) in their study.[13] 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.[14] Additionally, Sato et al. found that 30 of 144 NMOSD patients (21%) had hiccups and 24 (17%) had nausea.[15] Misu et al. documented INH symptoms in eight of the 47 patients (17%) with recurrent NMO in their study.[16] In our case, optic neuritis developed about 4 weeks after the onset of intractable nausea and vomiting, which is consistent with previous case reports. Our patient had complain of intractable hiccups, which were also present other studies.[13-15]

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. 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.[17] Our patient was negative for ANA and SS-A antibodies and also negative for other coexisting antibodies.

Hyperintense signals on T2WI in the area postrema were previously reported in NMOSD patients.[18] 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.[19] 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.[20,21] 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.[12] 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.[14] 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. Brain abnormalities in NMOSD are more common than previously thought, and some patients even manifest brain symptoms as their first presentation. Although many of the brain lesions in NMOSD are nonspecific, their characteristic locations and configurations are helpful in the diagnosis of NMO or NMOSD. The underlying pathomechanisms of various brain lesions in NMOSD are still unknown, and further studies are needed. An understanding of diverse brain manifestations is now crucial for early and correct diagnosis of NMOSD.

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