Wernicke's Encephalopathy Precipitated by Area Postrema Syndrome of NMO-SD

Respected Sir,

Neuromyelitis optica spectrum disorders (NMOSD) are autoimmune demyelinating diseases that have varied presentations as per the neuroaxis involved. Refractory vomiting, a feature of Area postrema syndrome can precipitate Wernicke's encephalopathy (WE) and mask NMO-SD. However, both disorders are altogether different, where one is caused due to a vitamin deficiency, and the other is caused by an autoimmune mechanism.

A 17-year previously healthy female with nausea and vomiting for 2 months. She was treated with anti-emetics and worked up for gastrointestinal causes but continued to worsen. On examination, she had ophthalmoparesis with normal pupillary reaction and fundus. She had a normal tone, power, and reflexes. She had mild ataxia but was able to walk unsupported. MRI brain revealed features of WE [Figure 1].

Thiamine level could not be done, and she was treated with high dose intravenous thiamine (500 mg thrice a day for 3 days followed by 5oo mg daily) based on high clinical suspicion and imaging. Her sensorium and general condition improved; she was discharged on oral thiamine. Three weeks later, she had a recurrence of symptoms and developed painless bilateral vision loss and itching all over the body. On examination, she had pyramidal signs. Her fundus examination was normal, color vision was impaired, and had RAPD in her right eye (retrobulbar optic neuritis). CSF examination revealed increased proteins with normal cell count. Imaging was repeated [Figure 2] and anti-AQP4 antibody was sent in view of NMOSD, which was positive. She was treated with IV steroids followed by plasma exchange with which there was significant improvement in her vision, gait, and general condition. She was started on rituximab maintenance therapy to prevent relapse.

There is significant clinical and radiological overlap between NMO-SD and Wernicke's encephalopathy. Both entities can present as encephalopathy, gait ataxia and vomiting, radiological changes around the ventricle (more commonly third and fourth), medial thalamus, and periaqueductal region. It is important to know the differences between the two for correct diagnosis [Table 1].

Our patient presented with intractable vomiting due to Area postrema syndrome, which is a core clinical criterion (revised 2015 NMOSD diagnostic guidelines) and can be an isolated manifestation of NMO-SD.[1] Thiamine has a short half-life of 14-18 days. It gets readily exhausted without intake, or if rapidly depleted.[2] Refractory vomiting and decreased intake in our patient precipitated thiamine deficiency leading to apathy, gait ataxia, and ocular findings. Her MRI features were notable for Wernicke's encephalopathy which masked

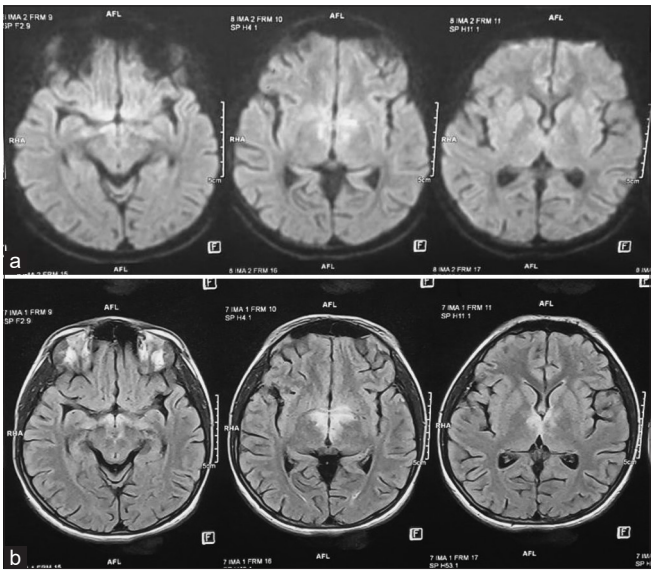

Figure 1: (a) Diffusion image showing restriction in bilateral mamillary body and ventromedial thalami. (b) Flair hyperintensity in bilateral mamillary body and ventromedial thalami

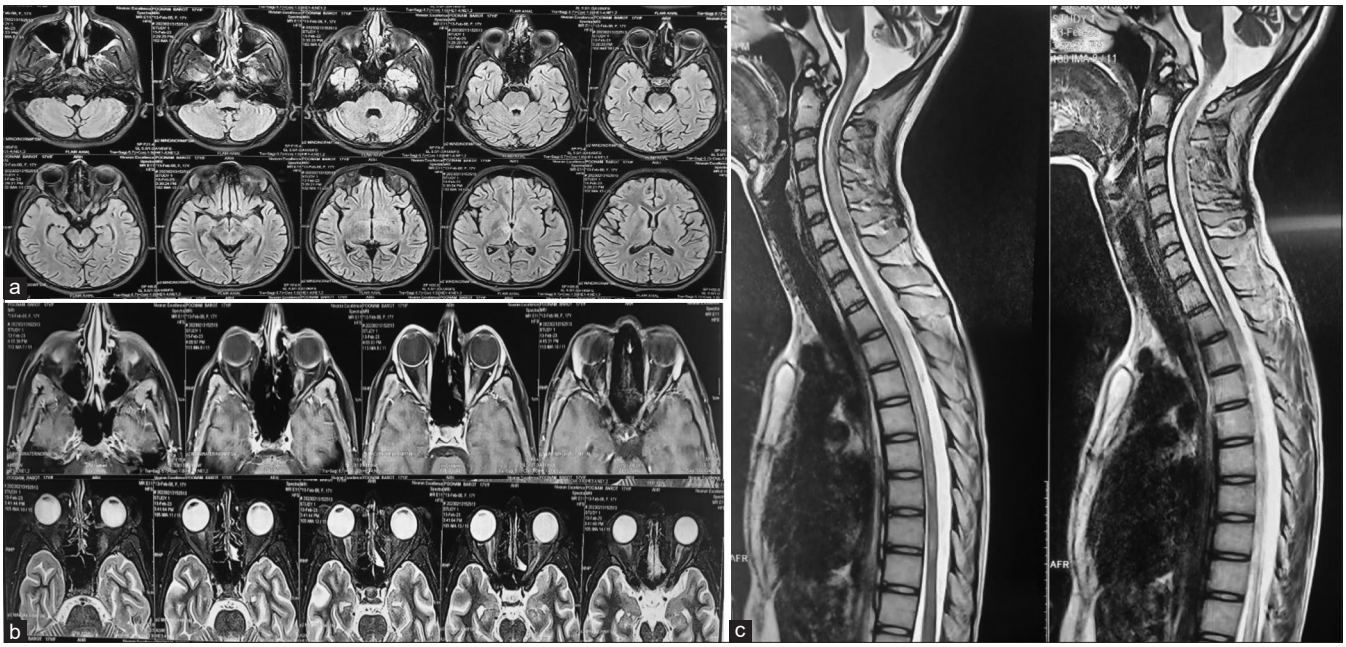

Figure 2: (a). Altered signal in bilateral thalami and posterior aspect of pons without contrast enhancement and diffusion restriction. (b). T2 hyperintense signal within the retrobulbar segments of bilateral optic nerve within the posterior aspect reaching the optic chiasma. (c). T2 hyperintense lesion extending from cervicomedullary junction to D8 vertebrae

Table 1: Clinical and Radiological differences in NMOSD and WE

	Neuromyelitis optica spectrum disorders	Wernicke's encephalopathy
1. Clinical features	Optic neuritis- bilateral simultaneous painful severe visual loss Intractable hiccups and vomiting Other cranial nerve palsies depending upon the location. Sensory disturbance, loss of bladder and bowel control Diencephalic features- narcolepsy Hemiparesis and seizures (rare)	Nystagmus, Ophthalmoplegia Ataxia and confusion
2. Radiology	Optic nerve- posterior and specifically chiasmal involvement Spinal cord- longitudinally extensive central or gray matter lesions Brain- typically high aquaporin-4 areas: third and fourth ventricle, periaqueductal, area postrema; corpus callosum; cloud like enhancing cerebral lesions.	Symmetrical lesions in periventricular, periaqueductal and tectum of dorsal midbrain, medial thalamic nuclei, hypothalamus, and cerebellar vermis.

NMO-SD. It was later that the patient developed optic neuritis and transverse myelitis which are features exclusive of NMO-SD. Most of the isolated symptoms (especially nausea, vomiting, and hiccups) are evaluated by primary physicians and gastroenterologists as was in our case. Thiamine is an important cofactor for the maintenance of energy metabolism in all cells.[3] The brain is the main site of damage due to its high energy requirement.[3] The classical triad of the syndrome may in fact be present in only 10% of cases, the most consistent characteristic being mental status changes.[3] The second most common characteristic is ophthalmoplegia. Complete ophthalmoplegia occurs rarely, whereas horizontal nystagmus is the most common ocular abnormality.[3] Gait ataxia can range from mild gait abnormality to a complete inability to stand. MRI can identify WE-related lesions in two-thirds of cases. MRI should be performed before thiamine administration as the lesions reverse quickly after initiation of treatment. Areas of increased T2 and FLAIR signals decreased T1 signal, and diffusion abnormality surrounding the aqueduct and third ventricle, medial thalamus, dorsal medulla, tectal plate, and mamillary bodies can be typically identified on the MRI.[4] Our patient had similar MRI findings which led to the diagnosis of Wernicke's encephalopathy. Thiamine levels can be measured in plasma; however, diagnostic confirmation is often difficult and delayed which can result in irreversible deficit.[5] Thus, a high degree of clinical suspicion should prompt the clinician to initiate treatment at the earliest opportunity. It should be noted that, in NMOSD, vomiting precedes the clinical syndrome while WE occur after vomiting.

AQP4 is the most widely expressed water channel in the brain, spinal cord, and optic nerves. It is specifically localized to the foot processes of astrocytes at the blood-brain barrier.[6] The AQP4 antibodies cause autoimmune astrocytopathy resulting in secondary demyelination.[7] The clinical presentation depends on the areas of CNS involvement. APS is the initial

presenting feature of NMOSD in approximately 10% of cases and can precede optic neuritis and myelitis in up to two-thirds of cases.[8] APS can present with nausea, vomiting, and hiccups. Typical MRI abnormalities are located at sites with high AQP4 expression areas- optic chiasma, peri-third and fourth ventricle, periaqueductal, area postrema, thalamus, hypothalamus, and sometimes cerebellum and corpus callosum.[9]

Though considered two different entities, astrocytes are the key players in the pathophysiology of NMOSD and WE. Thiamine deficiency is known to alter the astrocytic expression of glutamate transporters and levels of AQP4.[4] Recent evidence supports that lactic acidosis which develops due to thiamine deficiency may mediate increased AQP4 gene expression leading to swelling of astrocytes, inflammation, secondary edema, and white matter damage.[4] Thus, thiamine deficiency and immune-mediated neurological disorders can exacerbate each other. NMOSD and WE can have similar clinical presentations and radiological findings. It is important to distinguish NMOSD from WE by detecting AQP4 antibody.[10]

This case emphasizes the importance of considering APS in patients with intractable vomiting. It is important to know the clinical and radiological differences between the two and thoroughly evaluate patients of non-alcoholic WE to look for the etiology, including NMO-SD to expedite diagnosis and initiate timely treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Mahto Anuradha, Chheda Akash, Chaudhary Gaurav, Maniyar Aamna, Singh Rakesh, Shah Arjun

Department of Neurology, Grant Medical College and J. J. Hospital, Mumbai, Maharashtra, India

Address for correspondence: Dr. Chheda Akash, Associate Professor, Department of Neurology, Grant Medical College and J. J. Hospital, Mumbai, Maharashtra, India.
E-mail: akashchheda12@gmail.com

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