Neuromyelitis Optica Spectrum Disorder with Vertical Gaze Palsy and Hypersomnolence

Sir,

A 45-year-old female presented to us with complaints of blurred vision and double vision for 2 weeks. She had holocranial throbbing headaches and increased somnolence for 1 week. There were reduced taste and smell perception for 3 days. There was no fever, facial asymmetry, or numbness and weakness of limbs. Two years back, she had developed acute-onset giddiness and unsteadiness of gait associated with multiple episodes of vomiting and recurrent hiccups. There was impaired taste and olfaction then also. Her evaluation had revealed a lesion in the dorsal medulla possibly demyelination. She had responded to methylprednisolone pulse therapy at another hospital and remained symptom-free since then.

Physical examination revealed a conscious-oriented but lethargic patient with 6/6 visual acuity in both eyes. The pupils were normal size bilaterally, reacting to light and accommodation. Fundus examination was normal. There was bilateral conjugate vertical gaze palsy (upgaze and downgaze) with mild restriction of abduction bilaterally and horizontal binocular diplopia. There was no involvement of 5^{th}, 7^{th}, 8^{th}, 9^{th}, 10^{th}, 11^{th}, and 12^{th} cranial nerves. Motor and sensory examination was normal. There was no incoordination or meningeal signs. The clinical localization was the rostral midbrain and thalamic region. In view of the history of a possible demyelinating illness, a similar pathology was invoked in the current illness. Other possibilities considered were Wernicke's encephalopathy (WE), stroke (artery of Percheron infarct), straight sinus thrombosis, neoplasm, etc.

WE occurs due to thiamine deficiency usually in the setting of excessive alcohol abuse, but it has also been described in severe malnutrition associated with postoperative states, hyperemesis gravidarum, etc., It is characterized by

ophthalmoparesis, ataxia, and encephalopathy with magnetic resonance imaging (MRI) showing T2/FAIR hyperintensities in periaqueductal gray (PAG) matter, mammillary bodies, and medial thalami.[1] The condition promptly responds to parenteral thiamine administration. Our patient had no predisposing factors which could lead to thiamine depletion. Acute ischemic stroke involving the branches of the distal basilar artery or straight sinus thrombosis causing infarction of rostral midbrain and thalamus can present with sudden-onset confusion, somnolence, oculomotor disturbances, hemiparesis, hemisensory loss, and ataxia.[2,3] The artery of Percheron occlusion can cause bilateral medial thalamic and rostral midbrain infarction producing a similar clinical and radiological picture. However, our patient had subacute onset of complaints with no evidence of long tract signs or disturbance of consciousness, and the risk factors for atherosclerosis or venous thrombosis were lacking. The history of a steroid-responsive brainstem lesion also pointed toward an alternate etiology. The absence of long tract signs and the lack of papilledema argue against the possibility of neoplastic lesion.

Investigations revealed normal hematological and biochemical parameters in the blood. MRI showed symmetrical diffusion restriction in the PAG matter and bilateral medial thalami with no contrast enhancement. Similar finding was noted in the dorsal medulla [Figure 1]. MRI spine was normal. Cerebrospinal fluid examination showed 10 cells/mm^3, 30% polymorphs, and 70% lymphocytes. Protein and sugars were normal. Serum anti-aquaporin 4 (AQP-4) antibody was positive by immunofluorescence assay. Serum angiotensin-converting enzyme levels were not elevated. cANCA and pANCA antibodies were negative. She was treated with methylprednisone pulse therapy followed by oral steroids which resulted in complete resolution of the symptoms. Azathioprine was added in view of seropositivity for neuromyelitis optica (NMO). She is on follow-up to monitor the further course of the illness.

NMO is a rare demyelinating illness of the central nervous system (CNS) characterized by relapses and occurrence of optic neuritis and longitudinally extensive transverse myelitis (LETM).[4] This patient presented to us with a relapsing demyelinating illness, but the presenting features were neither optic neuritis nor myelitis. NMO spectrum disorder (NMOSD) was diagnosed in our patient based on AQP-4 antibody positivity and the latest diagnostic criteria. The diagnostic criteria for NMO have undergone dynamic changes over the past two decades so much so that the latest consensus criteria allows the diagnosis even without myelitis or optic neuritis.[5]

The discovery of AQP-4 antibody in NMO patients and its role in immunopathogenesis have changed the understanding of the disease dramatically.[6,7] The spectrum of the disease presentation was expanded with the identification of the antibody association with intracranial lesions. It is present in about 70%–80% patients with NMO-like illness. The target for the antibody is the aquaporin-4 or the "water channel" protein involved in the regulation of transport of water molecules across the cell membranes. It is found in high concentration in the astrocyte foot processes at its interface with the capillary endothelial cell basement membrane. It is also present in ependymal cells and the osmosensitive regions of the brain-like area postrema but is absent in neurons.

According to the revised diagnostic criteria by the international panel for NMO diagnosis criteria in 2015, lesions located in area postrema, diencephalon, brainstem, and cerebrum in addition to spinal cord and optic nerve are considered.[4] The detection of AQP-4 antibody and a core clinical characteristic involving any of the above six regions with the exclusion of other diseases is sufficient to make the diagnosis of NMOSD. Diagnosis can be made even without antibody positivity if two of the above six sites are involved with one of them at least being optic neuritis, LETM, or area postrema syndrome. Our patient was a middle-aged female whose symptoms localized to mesencephalon and diencephalon. She had a relapsing illness with her initial episode being the "area postrema" syndrome. She lacked the classical features of NMO, namely optic neuritis and LETM, although it was biphasic illness. There was temporal dissemination of lesions in space and time and the detection of NMO antibody helped in definitive diagnosis of the illness. Our patient meets the criteria for the new terminology of NMOSD. It is debatable if the term NMOSD is still relevant as the disease can manifest without myelitis or optic neuritis, and the involvement of the optic nerves or spinal cord is no longer essential for diagnosis.

NMO presenting with vertical gaze palsy and hypersomnolence is very rare with only isolated case reports. Lee *et al*. have described a patient presenting as dorsal midbrain syndrome with upward gaze palsy, light near dissociation, eyelid retraction, and convergence–retraction nystagmus.[8] Vertical gaze palsy occurs due to involvement of rostral interstitial

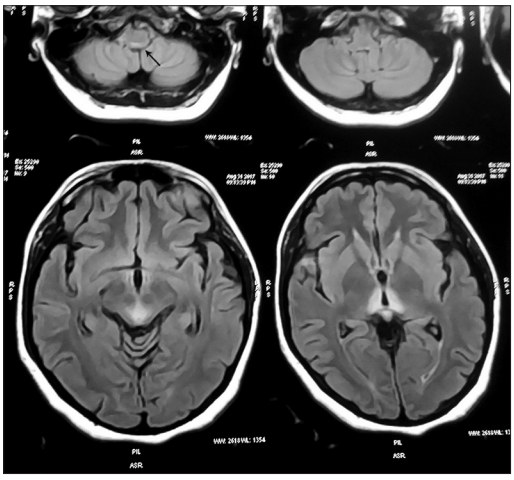

Figure 1: FLAIR magnetic resonance imaging brain showing bilateral symmetrical hyperintensity involving medial thalami and periacqueductal midbrain. Hyperintense lesion noted in dorsal medulla also (black arrow)

nucleus of medial longitudinal fasciculus (riMLF) which contains the burst neurons for generating vertical saccades and is located in the PAG matter of midbrain. Our patient had bilateral conjugate paralysis of both upward and downward components of vertical gaze which are controlled by separate pathways of synapses originating in riMLF.[9] She had bilateral mild abduction limitation causing horizontal binocular diplopia. This is likely a pseudoabducens palsy resulting from bilateral paramedian thalamic lesions which disrupt the descending inhibitory pathways of convergence.[10] Other oculomotor manifestations described in NMOSD include wall-eyed bilateral internuclear ophthalmoplegia syndrome, horizontal gaze palsy, oscillopsia, vertical diplopia (trochlear palsy), gaze-evoked nystagmus, and lateral rectus palsy.[11-14] These are related to lesions involving caudal midbrain, pons, and medulla.

Normal alertness is mediated by an intact intralaminar, reticular and ventral anterior nuclei of thalamus along with the reticular activating system in the brainstem.[15] The patient in this case had excessive somnolence but retained consciousness. Headache (migraine-like) could be attributed to PAG matter inflammation and its dysfunction which is a major component of the descending antinociceptive pathways in the brainstem.[16]

The patient complained of significant impairment of taste and smell during the illness in both the initial and the current episodes. Aquaporin 4 is present in the olfactory nerve terminals and the olfactory epithelium which may explain the hyposmia.[17] The involvement of the central taste pathways in the brainstem, and the gustatory relay stations of thalamus might be responsible for the hypogeusia.

The case is highlighted for the unique presentation of NMOSD as bilateral supranuclear vertical gaze palsy which is hitherto is not reported. The presentation of NMOSD as a relapsing illness with neither myelitis nor optic neuritis is also quite uncommon. Early recognition of nonopticospinal presentations of NMO and screening for AQP-4 antibody in patients with atypical demyelinating lesions of the CNS becomes important to prevent relapses and consequent disability.

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.

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