

## Coexistence of NMDAR and CASPR2 Antibodies with HLA-B5 Positivity: A Puzzling Trilogy with Atypical Neuroimaging

Sir,

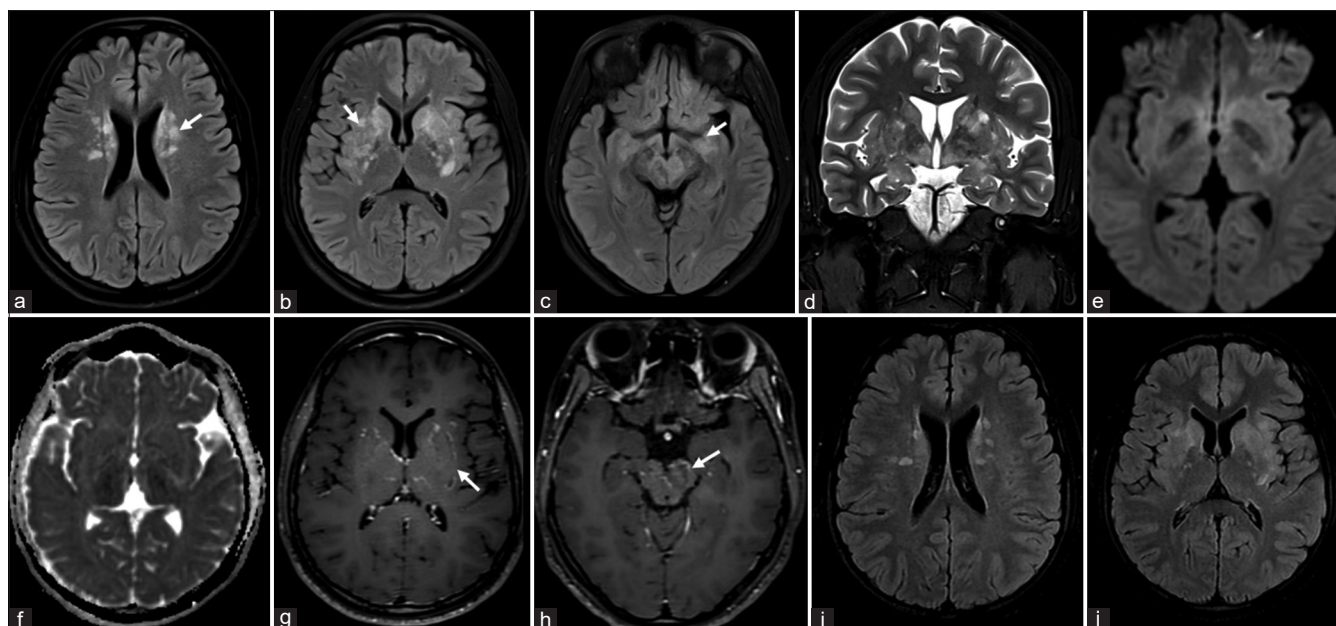
Autoimmune encephalitis has recently emerged as a major cause of neurologic morbidity, significantly mediated by anti-N-methyl-D-aspartate receptor (NMDAR) antibodies. Characteristic clinical features include a combination of neurologic manifestations like seizures, memory disturbances, behavioral abnormalities, and movement disorders.<sup>[1]</sup> Auto-antibodies against other proteins like contactin-associated protein-like 2 (CASPR2) are also associated with varied clinical presentations like limbic encephalitis, peripheral nerve hyperexcitability, cerebellar ataxia, seizures, and movement disorders.<sup>[2]</sup>

We describe the case of a 19-year-old girl who presented with progressive headache, insomnia, and emotional lability for the past year. She had an episode of subacute right hemiparesis with loss of speech output eight months before presentation, which showed near-complete resolution with the intravenous pulse of steroids. She had limb ataxia, dysarthria, intermittent vertical diplopia, and suicidal ideations. She also had recurrent skin pustules in childhood and recurrent oral ulcerations for which she was not formally evaluated or treated. On examination, she had bilateral vertical rotatory nystagmus, hypokinetic dysarthria, spasticity with exaggerated deep tendon reflexes and extensor plantar on the right side, ataxic gait, and incoordination of bilateral upper and lower limbs. She also had infrequent, involuntary, arrhythmic movements of the left upper limb, which were distractible and suppressible. Magnetic resonance imaging (MRI) of the brain showed T2-fluid-attenuated inversion recovery (FLAIR) hyperintensities involving bilateral corona radiata [Figure 1a], caudate, lentiform nuclei, internal and external capsules [Figure 1b], ventrolateral thalami, subthalamic nuclei, hypothalami [Figure 1d], and parahippocampal gyri with additional involvement of crus cerebri and tegmentum of the midbrain [Figure 1c]. There were no abnormal susceptibility or restricted diffusion areas on diffusion-weighted images (DWI) [Figure 1e] and the corresponding apparent diffusion coefficient (ADC) map [Figure 1f]. Corresponding abnormal T2/FLAIR hyperintense areas show patchy areas of punctate and nodular enhancement foci [Figure 1g and h] without any evidence of elevated perfusion parameters on T2 perfusion imaging. Her MRI brain done during the past episode of hemiparesis eight months ago was not available for review. Serum myelin oligodendrocyte glycoprotein (MOG) antibody, aquaporin-4, leucine-rich glioma-inactivated protein 1 (LGI1), alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA 1), AMPA 2, gamma-aminobutyric acid B (GABAB) receptor, antinuclear antibody (ANA) antibodies were negative. Cerebrospinal fluid (CSF) analysis showed

no cells and normal proteins. There was strong positivity noted for serum and CSF NMDAR and serum CASPR2 antibodies on indirect immunofluorescence assay. CSF also revealed oligoclonal bands. Because of mucocutaneous and neurological manifestations and atypical imaging findings, we considered the possibility of neuro-Behcet's sought human leukocyte antigen (HLA-B5), which returned positive. The pathergy test was negative. Evoked potentials and electroencephalography (EEG) were normal, and investigations did not reveal any malignancy. We initially treated her with a pulse dose of intravenous methylprednisolone. As the initial response to steroids was inadequate, she was treated with five cycles of large volume plasmapheresis followed by long-term immunomodulation with rituximab. There was a significant improvement in her ataxia, behavioral disturbances, and radiologic findings at follow-up [Figure 1i and j].

The patient had clinical features consistent with autoimmune anti-NMDAR encephalitis like headache, insomnia, and behavioral abnormalities.<sup>[1]</sup> The past episode of right hemiparesis was unusual for this diagnosis, although improvement with steroids favored immune-mediated pathophysiology. The classically described peripheral nerve hyperexcitability seen with CASPR2 antibody disease was conspicuously absent though she had neuropsychiatric features and cerebellar ataxia, which is reported to be the third most common manifestation of CASPR2 associated disease.<sup>[2]</sup>

The atypical neuroimaging findings seen in our patient deserve mention. T2 hyperintensities in medial temporal lobes on MRI are the most common abnormalities described in anti-NMDAR encephalitis, though it can be normal in up to half of the patients. Similarly, brain MRI in CASPR2 encephalitis can typically show bilateral medial temporal hyperintensities or remain normal. While bilateral T2 hyperintensities affecting hippocampi are common to both CASPR2 and anti-NMDAR encephalitis, involvement of other brain regions is rare. Involvement of the thalami, posterior limb of the internal capsule, brainstem, and cerebellar hemispheres is reported in CASPR2 antibody-associated neurological disease.<sup>[3]</sup> Isolated reports point to white matter changes in anti-NMDAR encephalitis during the dyskinetic stage of the disease, and early white matter changes may be evident on the first imaging.<sup>[4,5]</sup> Brainstem and white matter may also be affected in paraneoplastic encephalitis.<sup>[6]</sup> However, our case was unique in the extensive involvement of the white matter and deep gray matter at the mesencephalic and diencephalic region junction and brainstem, which had not been reported earlier to the best of our knowledge. Between 4% and 7.5% of patients with anti-NMDAR encephalitis have concurrent glial or neuronal surface antibodies, which might confer additional



**Figure 1:** MR imaging of the brain demonstrates T2-FLAIR hyperintensities involving bilateral corona radiata (a), caudate, lentiform nuclei, internal and external capsules (b), ventrolateral thalami, subthalamic nuclei, hypothalami (d), and parahippocampal gyri (c) with additional involvement of crus cerebri and tegmentum of the midbrain (c). DWI (e) and the corresponding ADC map (f) were normal. Abnormal T2/FLAIR hyperintense areas show patchy areas of punctate and nodular enhancement foci (g and h). Follow-up MRI scan at five months showing a reduction in FLAIR hyperintensities (i) and (j)

imaging features and influence prognosis.<sup>[7]</sup> This hypothesis might explain the extensive abnormalities and the atypical clinical features in this patient.

Another unique feature is the HLA-B5 positivity in this patient. HLA genotypes encode the major histocompatibility complex (MHC), especially MHC class II, which mediate antibody-mediated immune responses. Recent studies have revealed that specific HLA genotypes predispose toward the development of autoimmune encephalitis like anti-LGI1.<sup>[8]</sup> Though the patient had a history of oral ulcerations, she had no genital ulcers or skin manifestations/opthalmologic signs suggestive of Behcet's disease at the time of examination. The pathergy test was negative too, and the patient does not fulfill the International Study Group (ISG) criteria for Behcet's disease.<sup>[9]</sup> However, given the neuroimaging findings and brainstem involvement, probable neuro-Behcet's<sup>[9,10]</sup> disease cannot be ruled out. The possibility of the HLA genotype predisposing her to develop autoimmune encephalitis is an association that needs further exploration.

Cherian *et al.*<sup>[11]</sup> recently described triple positivity with MOG, NMDA, and CASPR. However, NMDA and CASPR dual positivity with atypical neuroimaging and an underlying HLA-B5 positivity is a novel finding. Atypical presentations should prompt a comprehensive serological workup as multiple antibodies can coexist.

### 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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Nil.

### Conflicts of interest

There are no conflicts of interest.

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