Myelin Oligodendrocyte Glycoprotein Antibody Syndrome and Seizures: A Diagnostic Clue

Sir,

Myelin oligodendrocyte glycoprotein (MOG) antibodies are highly conserved proteins expressed on the oligodendrocytes of mammals, including human beings.[1] They have been detected in various demyelinating disorders like optic neuritis, transverse myelitis, and acute disseminated encephalomyelitis (ADEM) and the term MOG-encephalomyelitis (MOG-EM) has been proposed to unify these heterogenous presentations.[2] There is growing evidence of seizures as a manifestation of MOG-EM. We present three teenagers who presented with seizures in association with focal neurological deficits and were eventually diagnosed as MOG-EM, emphasizing that this initial history of seizures might help clinch this diagnosis, over other demyelinating disorders.

Case 1: A 12-year-old girl presented with acute onset unsteadiness and imbalance while walking and diminution of vision from both eyes, over a few days. On evaluation, magnetic resonance imaging (MRI) brain revealed multiple confluent and discrete contrast enhancing lesions in the brain parenchyma with bilateral optic neuritis [Figure 1]. She was treated empirically with intravenous methylprednisolone (IVMP) with complete symptomatic improvement, following which she came to us for detailed evaluation. Examination revealed no focal deficits and repeat imaging [Figure 2] revealed decrease in lesion size and resolution of enhancement, without any additional lesion. She had a history of recurrent seizures (right focal to bilateral tonic clonic) at 6 years of age for which she was evaluated and found to have normal brain imaging and was treated with sodium valproate. Subsequently, she was seizure-free and the drug was discontinued 1 year ago. However, she had seizure recurrence (left focal to bilateral tonic clonic), 1 month prior to symptom onset and was controlled with oxcarbazepine. Her cerebrospinal fluid (CSF) examination was acellular, with a protein and glucose content of 20.9 mg/dl and 56.9 mg/dl (corresponding random blood sugar-91 mg/dl), respectively. CSF oligoclonal bands, Venereal Disease Research Laboratory (VDRL), gene Xpert for tuberculosis, India Ink staining, and Cryptococcal antigen testing were all negative. Serum aquaporin-4 antibody was negative but serum MOG antibody by cell-based assay was positive. She was continued on oral steroids and azathioprine followed by gradual taper with no relapses.

Case 2: A 13-year-old boy presented with recurrent episodes of focal neurological deficits associated with fever since the past 7 years. He had two episodes of pure motor paraparesis with stiffness of limbs, and one episode of horizontal binocular diplopia, all of which were exquisitely responsive to corticosteroids. He also had history of febrile seizures (semiology: generalized tonic clonic) at the age of 5 years (imaging: Not done) and one episode of febrile status epilepticus 6 months later, which required ventilator assistance and treatment in the hospital for 10 days. His current complaints were acute onset progressive difficulty in walking associated with difficulty gripping objects. Examination revealed grade 1 + spasticity in all 4 limbs (modified Ashworth scale), power of bilateral 4/5 and 5/5 in the lower and upper limbs (modified research council) respectively, and a handgrip of 80%. Sensory examination was normal and deep tendon reflexes were brisk with bilateral extensor plantar. His previous and follow up MRI brain and

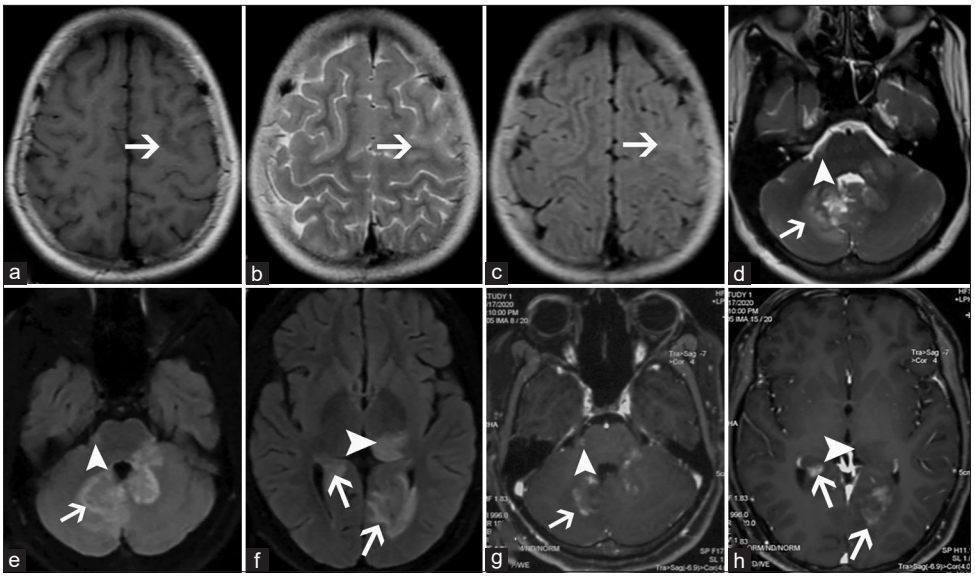

Figure 1: Axial T1-WI (a) shows focal area of hypointensity (arrow in A) in left precentral cortical region, which is hyperintense (arrows in b and c) on T2-WI (b) and FLAIR images (c). On follow-up imaging, axial T2-WI (d) and FLAIR (e, f) images show multifocal hyperintense lesions in bilateral dentate nuclei and adjacent white matter (Right side > left, arrows in d, e, and g), left middle cerebellar peduncles, right anterolateral pons (arrowheads in d, e, and g), left posterior thalamus (arrowhead in f and h), and both occipital lobes (arrows in f and H). On contrast administration, axial T1-WIs (g and h) shows patchy enhancement within these lesions

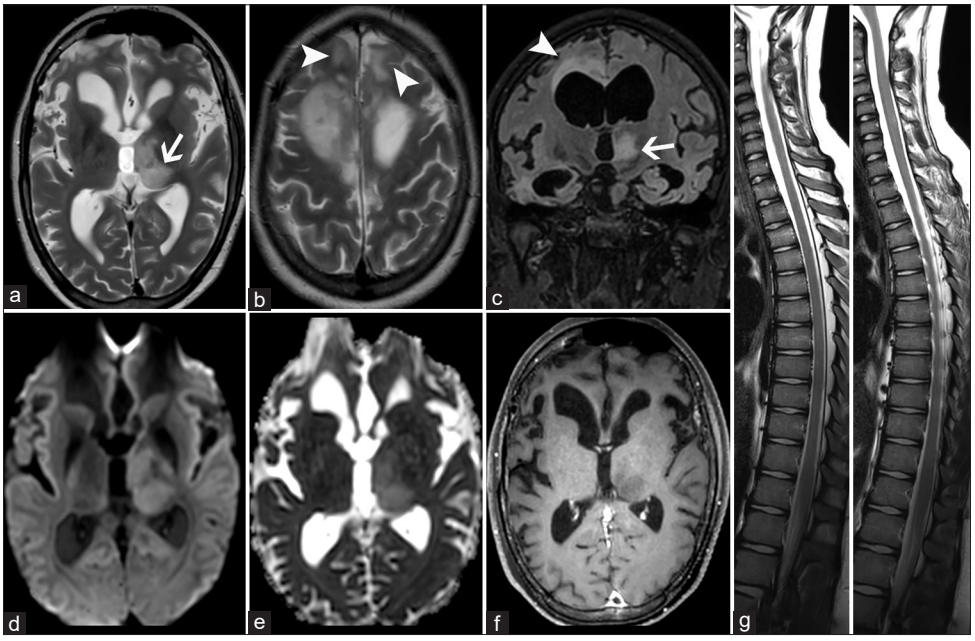

Figure 2: Axial T2-W (a and b) and coronal FLAIR (c) images show areas of hyperintensities in bilateral frontal lobes (arrowheads in b and c) and left thalamus (arrow in b and c). No diffusion restriction is seen in diffusion trace images (c) and ADC maps (d). No enhancement is seen following gadolinium administration in T1-WI (g). Sagittal T2 (g) images show no focal lesions in the spinal cord

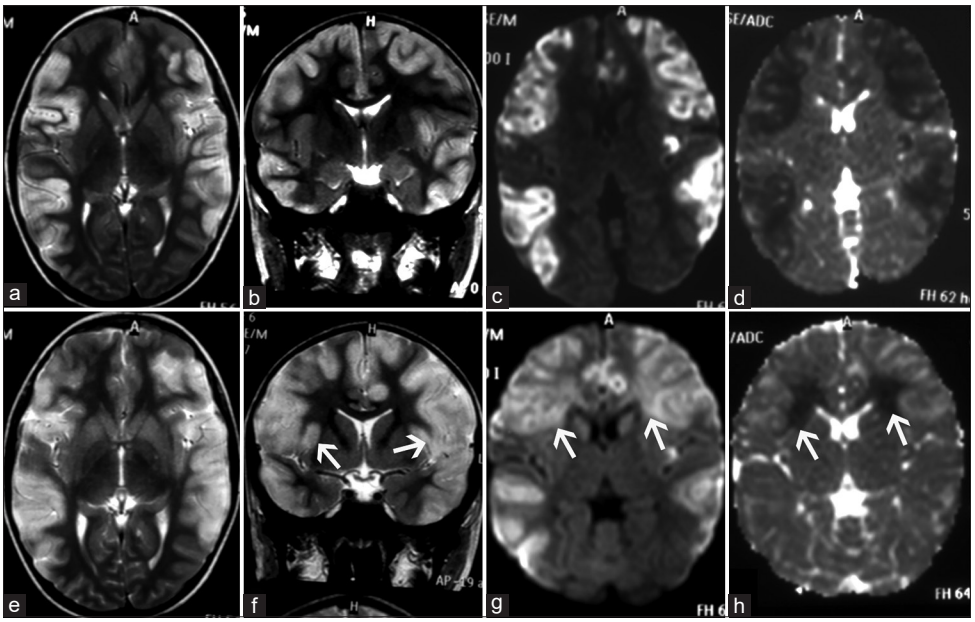

Figure 3: Axial T2-WIs (a and b) shows bilateral almost symmetrical areas of cortical hyperintensities in frontal and temporal lobes. The lesions are bright in diffusion trace images (c) and dark on ADC maps suggesting diffusion restriction. No enhancement is seen following gadolinium administration in T1-WI (not shown). Follow-up MRI done after 9 days shows progression of T2 hyperintensities to involve bilateral inferior frontal gyri (arrows in f) in axial T2-WI (e and f). Diffusion trace image (g) and ADC maps (h) show fresh areas of diffusion restriction in bilateral periventricular white matter (arrow in g and h)

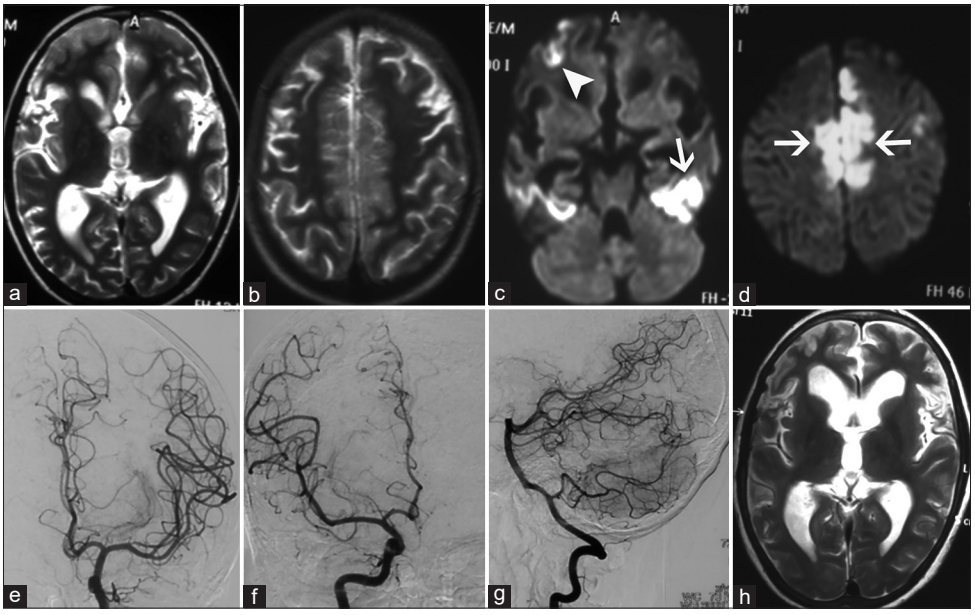

Figure 4: FU MRI after 13 months. Axial T2-WIs (a and b) shows prominent Sylvian fissures and loss of white matter in both frontal lobes suggestive of atrophy. Diffusion trace images (c and d) show bright areas of diffusion restriction in left posterior temporal lobes (arrow in c), right frontal lobe (arrowhead in c), and bilateral medial frontal regions (arrows in d). No enhancement is seen following gadolinium administration in T1-Wi (not shown). IADSA of left ICA (e), right ICA (f), and right VA (g) were unremarkable without any evidence of vasculitis. FU MRI done after another 14 months shows regression of lesions with atrophy

the last MRI spine images are provided in Figures 3, 4, and 5, respectively. Possibilities of primary demyelination versus secondary (vasculitis, sarcoidosis, Behcet's, mitochondrial) were considered and he was evaluated for the same. CSF examination, vasculitic panel, serum angiotensin converting enzyme (ACE) levels, HLA-B51, and CPK levels were normal. His VEP was bilaterally prolonged and although aquaporin-4 antibody was negative, his serum MOG antibody was strongly positive. Considering his background of multiple relapses, he was treated with rituximab with good symptomatic improvement.

Case 3: A 14-year-old boy presented with acute onset vision loss from the right eye, over a few days, which completely

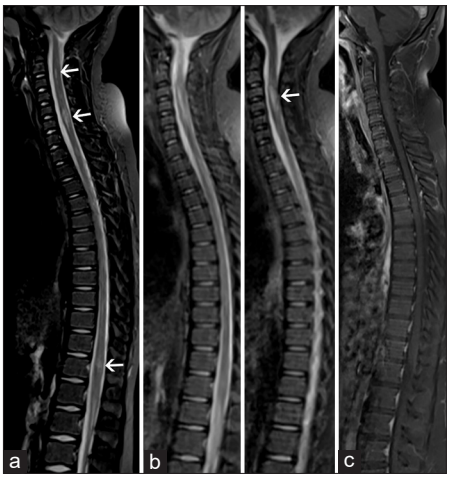

Figure 5: Sagittal T2 (a) and STIR (b) images show multiple short segment hyperintense lesions (arrows) scattered throughout the cord. No enhancement is seen following gadolinium administration in T1-WI (c)

resolved with a 3-day course of IVMP. He developed similar complaints in his left eye 6 months later, which also recovered with the same treatment. Three months later, he developed complaints of right focal seizures with secondary generalization, following which he was started on levetiracetam with no seizure recurrence. MRI brain done at this time was found to be normal. He developed acute onset urinary hesitancy 1 month back without any incontinence, which again was treated with IVMP. His MRI spine revealed a central demyelinating lesion at D12-L1 level while his MRI brain was normal. Serum aquaporin-4 antibody and serum ACE levels were negative but serum MOG antibody by cell-based assay was positive. CSF examination was denied.

The coexistence between MOG and seizures is evolving into a relevant and challenging association with important prognostic and therapeutic implications. It has increasingly been recognized that seizures are an important clinical manifestation of MOG-EM and occur more frequently in the same when compared to neuromyelitis optica spectrum disorder (NMOSD) or multiple sclerosis.[3,4] In addition, seizure clustering has also been described as an isolated presentation of MOG-EM, which can precede the typical demyelination episode by months to years.[5] However, seizures have also been reported in individuals who are serum MOG antibody positive without parenchymal lesions on MRI brain contradicting the hypothesis that seizures occur secondary to cortical involvement in an encephalitic illness. This could entail that in some cases, MOG antibodies target oligodendrocytes in higher density at the subcortical gray matter level (compared to cortical gray matter), directly leading to epileptogenesis.[6] However, the fact that some patients with high MOG antibody titers never develop seizures makes a causal relationship extremely difficult to establish and is still debated. Experimental murine data has not been able to solve this conundrum since the purified human IgG MOG antibodies used on them had the ability to recognize the human isoform in approximately 70% of cases only.[7] Thereby exploring their pathogenicity in another species is questionable and bound to produce false negative results.

Foiadelli *et al.*[6] in their review have identified 106 patients with seizures and MOG spectrum disorders, some of which presented before, after, or concomitant with the demyelinating episode. They also identified that seizures were commoner in the pediatric population and with a cortical encephalitis presentation.

All our patients were teenagers and were negative for other aquaporin-4 antibodies and had dramatic improvement with treatment. Our observations seek to strengthen the body of evidence in support of co-existence of isolated seizures and serum MOG antibodies, adding to the ever-expanding spectrum of MOG-EM.

Testing for serum MOG antibodies should strongly be considered in teenage patients with isolated seizures (especially when clustering is present) and unexplained encephalitis. They can be even considered in patients who present with focal seizures but have normal brain imaging or who do not respond adequately to anti-epileptic therapy. Their relevance in prognosticating the risk for developing a future demyelinating event needs to be investigated through well-designed trials.

Highlights

- Serum MOG antibodies have been detected in various demyelinating disorders: optic neuritis, transverse myelitis, and acute disseminated encephalomyelitis (ADEM).
- MOG-encephalomyelitis (MOG-EM) has been proposed to unify these heterogenous presentations.
- There is growing evidence of seizures as a manifestation of MOG-EM.
- Testing for serum MOG antibodies should strongly be considered in patients with isolated seizures (especially when clustering is present) and unexplained encephalitis, especially in teenagers.
- Testing for serum MOG antibodies can be considered in patients who present with focal seizures but have normal brain imaging or who do not respond adequately to anti-epileptic therapy.

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Conflicts of interest
There are no conflicts of interest.

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