Original Research Article

A new addition to the demyelination club – MR imaging features of MOG antibody disease

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Abstract

Background: Myelin oligodendrocyte glycoprotein (MOG) antibody disease (MOG-AD) is an emerging entity to aid in early diagnosis with its specific clinical and imaging features. MOG-IgG helped to identify a subgroup with a clinical course distinct from NMOSD patients who shows seropositivity for aquaporin-4-IgG antibodies. Cases like optic neuritis (ON), encephalitis with brain demyelinating lesions, and/or myelitis (MONEM) suggest that MOG-IgG is associated with a wider clinical phenotype. Characteristic MRI features helps to differentiate MOG-AD from other neuroinflammatory disorders mainly multiple sclerosis and neuromyelitis optica. Due to its clinical and radiological features, most adult MOG ab+ cases were initially assigned to the loosely defined category of AQP-4– NMOSD. After taking MOG ab as the common denominator, these cases were re-evaluated. They showed additional characteristics which are different from AQP-4 ab+ NMO and other demyelinating disorders. These MOG ab were most commonly found in patients with isolated optic neuritis and combined optic neuritis/myelitis and only occasionally in isolated myelitis. MOG-IgG appears to be emerging as an potential biomarker of inflammatory disorders of the central nervous system. Growing body of evidence on MONEM is reviewed here, focusing mainly on its radiological aspects.

Keywords: Myelin oligodendrocyte glycoprotein (MOG), neuromyelitis optica spectrum disorder (NMOSD),

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INTRODUCTION

Myelin oligodendrocyte glycoprotein (MOG) is a glycoprotein located on the surface of myelin and found exclusively in central nervous system (CNS). Some cases of seronegative neuromyelitis optica spectrum disorder (NMOSD) showed antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG).[1,2] Neuromyelitis optica spectrum disorders as well as other demyelinating disorders basically associated with attacks on the optic nerves, spinal cord and brain[3]. However, wider clinical phenotype, (not limiting to NMOSD) is seen in MOG-IgG. Only a third or less of MOG-IgG seropositive patients fulfill the current diagnostic criteria for NMOSD.[4-7] Over the last 30 years, techniques such as enzyme-linked immunosorbent assay (ELISA) and Western blot have been used for MOG antibodies study[8-10]. After its identification, it has made it possible to categories a subset of patients presenting with internally homogenous clinical, radiological and immunological features which are distinct from neuromyelitis optica spectrum disorders (NMOSD), Multiple sclerosis (MS) [11]. Rapidly evolving with new terminology for Anti-MOG related diseases is- MOG-IgG-associated Optic Neuritis, Encephalitis, and Myelitis (MONEM). Majority of MOG-IgG-seropositive cases shown to have ON, optic neuritis plus myelitis, isolated myelitis or encephalitis with brain demyelinating lesions[12,13]

Historical aspects and diagnostic criteria

Until 2015, AQP4-IgG positive cases were diagnosed as NMO, although some of the patients with the classic NMO clinical features remained seronegative despite the use of sensitive serologic assays. These patients were studied for MOG ab+ with different cell-based assay to detect disease-associated MOG ab [14]. There is an unmet need for diagnostic criteria for MOG- EM. However, no specific clinical or radiological findings (except for the general

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requirement of a demyelinating CNS lesion) have yet been identified that are present in all MOG-IgG-positive patients and which would thus represent a diagnostic sine qua non. A lack of Dawson's finger lesions and ovoid/round lesions on brain MRI have been proposed to be typical for MOG-EM, but this awaits confirmation in independent and There is an unmet need for diagnostic criteria for MOG- EM. However, no specific clinical or radiological findings (except for the general requirement of a demyelinating CNS lesion) have yet been identified that are present in all MOG-IgG-positive patients and which would thus represent a diagnostic sine qua non. A lack of Dawson's finger lesions and ovoid/round lesions on brain MRI have been proposed to be typical for MOG-EM, but this awaits confirmation in independent and There is an unmet need for diagnostic criteria for MOG-EM. However, no specific clinical or radiological findings (except for the general requirement of a demyelinating CNS lesion) have yet been identified that are present in all MOG-IgG-positive patients and which would thus represent a diagnostic sine qua non. A lack of Dawson's finger lesions and ovoid/round lesions on brain MRI have been proposed to be typical for MOG-EM, but this awaits confirmation in independent and

Diagnostic criteria:

All MOG positive patients does not show any specific clinical or radiological findings. For time being MOG antibody disease should be diagnosed who me *et al.*

1. these three criteria- Monophasic or relapsing acute ON, myelitis, brainstem encephalitis, or encephalitis, or any combination of these syndromes
2. MRI or electrophysiological (visual evoked potentials in patients with isolated ON) findings compatible with CNS demyelination
3. Seropositivity for MOG-IgG as detected by means of a cell-based assay employing full-lengt

1. Monophasic or relapsing acute ON, myelitis, brainstem encephalitis, or encephalitis or any combinations of these symptoms.
2. MRI findings compactable with CNS demyelination.
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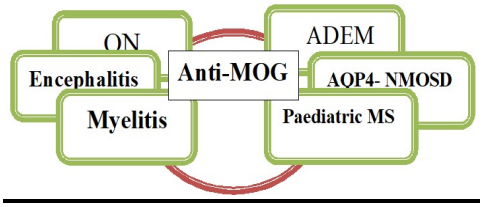
Pathophysiology

A glycoprotein of the immunoglobulin super family - MOG, is a component of the CNS myelin sheath, as are myelin basic protein (MBP) and proteolipid protein [15]. Subgroup of patients formerly diagnosed as having NMO by clinical and radiological criteria, in whom despite extensive testing no anti-AQP-4 ab could be found gave initiation for the MOG idnetitifacation[16]. MOG is a minor component of the CNS myelin sheath, accounting only for less than 0.5% of its composition. Many of its epitopes have been demonstrated to be highly immunogenic, both in rodents and humans [17-19]. Using different MOG mutants, the epitope specificity of MOG ab in the paediatric population has been analysed. In vitro, efficient activation of the complement cascade is seen by high-titre MOG-IgG in serum samples of humans. [20]. Striking pathological differences are seen between MOG-IgG and AQP4-IgG groups. Whereas the pathological hallmark of AQP4-IgG NMOSD is astrocytic damage, with secondary oligodendrocyte loss and demyelination, no evidence of astrocytopathy has been reported in MOG-IgG cases[21]. MOG-IgG-seropositive NMO phenotype in which cerebrospinal fluid (CSF) examination showed elevated MBP without elevation of glial fibrillary acidic protein (GFAP). These findings suggest inflammation and myelin destruction without astrocyte injury, which makes the CSF profile of MONEM clearly different from that of AQP4-IgG-associated NMOSD [22]. Clearly demyelinating lesions with marked infiltration of macrophages (often containing myelin degradation products) and T cells, and relative preservation of axons and astrocytes have been seen. In most cases, also B cell infiltration and IgG and complement deposition have been reported [23-25].

Clinical features:

The most common presentation –

1. Optic neuritis (ON), (54–61% of patients), 2. Long segment myelitis, 3. NMO, 4. Acute disseminated encephalomyelitis (ADEM) or 5. An ADEM-like presentation (e.g., brainstem attack) [26]. In the paediatric population, MOG ab were most commonly detected in monophasic ADEM [27]. Simultaneous occurrence of ON and TM is more common in MOG-IgG patients than among AQP4-IgG patients. Hallmark of MOG ab+ patients compared with NMO or MS, is seems to be simultaneous affection of bilateral optic nerves. Some MONEM cases shown brainstem involvement also. Cortical encephalitis has been described in MOG-IgG-positive patients [28].



Patients can be clinically diagnosed with NMOSD, acute demyelinating encephalomyelitis (ADEM), paediatric MS, or isolated myelitis or ON depending on the clinical assessment.

MR imaging

On orbital MRI, findings of optic nerve like optic nerve head swelling, retrobulbar involvement, and contrast-enhancing lesions with perineural enhancement were significantly more frequent in ON associated with MONEM than with AQP4-IgG NMOSD, whereas patients with AQP4-IgG more frequently shown chiasmal involvement. Another noticed feature is reduced calibres of optic nerves. [29,30.] In spinal cord MRI, long segment myelitis, lesions of the lower cord, (including the conus medullaris) seen in MOG-IgG patients, while patients with AQP4-IgG usually present with cervical and thoracic lesions [31]. On brain MRI, MOG-AD patients showed more common thalamic and pontine lesions as compared to AQP4-positive disease. Bilateral thalamic lesions are seen at onset frequently in children (about in 60% of patients). Compared to AQP4-positive patients, cerebellar peduncle lesions are only found in MOG-positive children. Imaging findings in paediatric patients could be confused with ADEM [28,32]. In our institute patients also came with features of sub clinical optic nerves atrophy, without any abnormal signal or enhancement in optic nerve. On evaluation they being positive for MOG ab. MOG myelitis mostly affect the lower spinal cord, mostly conus medullaris. But it can also cause long segment cervical and thoracic myelitis. In paediatric population, specifically in children with no history of prior vaccination; it can also mimics the imaging features of ADEM.

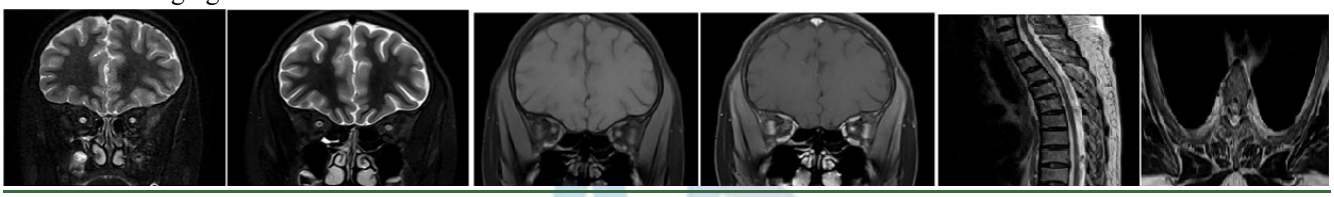


Figure 2

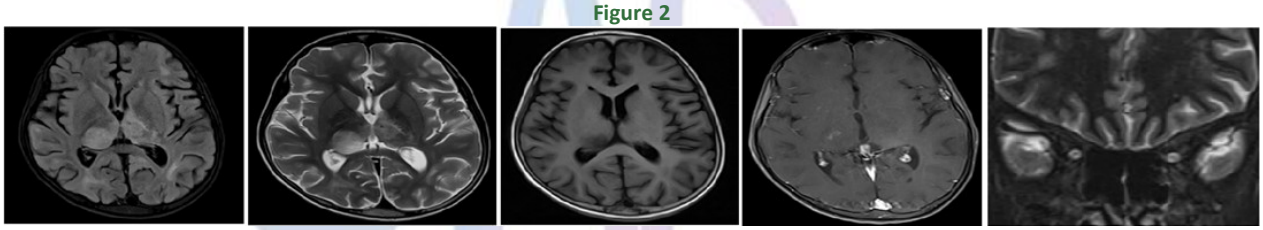


Figure 3

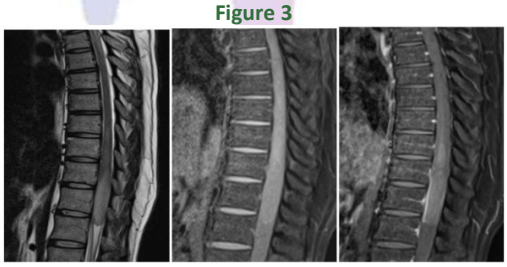


Figure 4

A: T2 STIR COR showing bilateral optic nerve atrophy (left> right) and hyperintense signal in left optic nerve.
B: T2 COR image of same patient shows findings consistent with T2 STIR COR.
C: T1WI FS COR
D: T1WIFS COR post contrast shows enhancement of left optic nerve suggestive of optic neuritis.
E: T2 SAG showing long segment (3 vertebrae) intramedullary hyperintense signal .
F: T2 AXIAL of same patient showing hyperintense signal involving centre of spinal cord suggestive of myelitis.
G: FLAIR image showing hyperintense signal in bilateral thalami and occipital lobes white matter.
H: T2WI AXIAL of same patient with findings consistent as FLAIR.
I: T1WI AXIAL showing isointense signal in bilateral thalami and occipital lobes white matter.
J: T1WIFS post contrast showing enhancement of lesion in right thalamus suggestive of active encephalitis.
K: T2 STIR COR showing hyperintense signal in left optic nerve.
L: T2 SAG shows long segment hyperintense intramedullary signal covering the entire cord diameter.
M: T1WIFS pre contrast image; **N:** T1WIFS post contrast showing heterogenous enhancement of the lesion suggestive of active myelitis.

Comparison with other demyelinating diseases

MOG AD	NMOSD[33]	MS[33]
Optic nerve: bilateral, long-length, and retro bulbar (mostly); perineural enhancement; optic disk swelling; optic chiasm is less involved. **Spinal cord**: mostly conus medularis; also thoracolumbar cord. **Brain lesions**: deep gray matter lesions (thalamus); ADEM-like lesions (large cerebral lesions); fluffy T2 hyperintense lesions in pons and cerebellar peduncles and adjacent to the fourth ventricle more common as compared to NMO; Dawson fingers rare.	**Optic nerve:** bilateral, long-length, and posterior involvement (intracranial), usually with involvement of optic chiasma. **Spinal cord**: LETM (>3 vertebral bodies); central/gray matter lesions; bright on T2WI, dark on T1WI. **Brain lesions**: periependymal and thin periventricular lesions with or without enhancement.	**Optic nerve:** mainly unilateral optic neuritis. **Spinal cord**: Lesions more commonly short segment of spinal cord (< 3 vertebral bodies). **Brain lesions**: Always abnormal; presence of Dawson's fingers, subcortical

T2WI: T2 weighted image; T1WI: T1 weighted image; STIR: Short Tau Inversion Recovery; FLAIR: Fluid attenuated inversion recovery; FS: Fat saturation; COR: Coronal.

CONCLUSION

MONEM shows different clinical and pathophysiological features from NMO and other demyelinating disorders. Also clinical spectrum of MONEM is extensive, like including ADEM and other demyelinating syndromes. MOG-IgG should be considered the biomarker of these demyelinating disorders which clinically mimics NMOSD but are negative for AQP4 ab. The location, distribution and morphology features of lesions could aid in diagnosis of MOGAD, particularly in association with clinical and biomarker information. Therefore, the definition of MOG-AD-specific diagnostic criteria, as well as identification of markers of disease status is crucial for management of patients.

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