

## MOG Antibodies in Acquired Demyelinating Diseases in Children

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## ABSTRACT

Myelin Oligodendrocyte Glycoprotein antibodies (MOG-ab) have been identified in a range of acquired demyelinating syndromes in the pediatric population. Numerous studies have aimed to establish the role of MOG-ab in these disease processes as well as describe the features of MOG-ab-associated pediatric demyelinating syndromes. This review intends to provide an overview of the literature on MOG-ab in acquired demyelinating diseases in children with an emphasis on the clinical course, laboratory and neuroimaging findings, treatment, and prognosis of these disease entities.

## INTRODUCTION

Pediatric demyelinating diseases encompass a spectrum of entities that vary in their course and severity. They range from acute onset monophasic diseases – such as Clinically Isolated Syndromes (CIS), Acute Disseminated Encephalomyelitis (ADEM), Optic Neuritis (ON), and Transverse Myelitis (TM) – to chronic multifocal polyphasic conditions – such as Multiple Sclerosis (MS) and relapsing Neuro Myelitis Optica (NMO). The individual prognosis for each condition is highly variable with regards to functional recovery and risk for future episodes of Central Nervous System (CNS) inflammation, demyelination, and dysfunction. Discriminating between demyelinating disorders and establishing reliable biomarkers for diagnosis, prognosis and risk of progression to a polyphasic demyelinating condition has been the focus of intense investigation. In this context, the role of disease-associated antibodies continues to be explored. Among these, Myelin Oligodendrocyte Glycoprotein antibodies (MOG-ab) have been identified in a range of acquired demyelinating syndromes in the pediatric population [1-4].

## MOG ANTIBODIES

MOG is a CNS myelin-specific glycoprotein. Its molecular function is not yet fully understood, however proposed functions include participation in cell adhesion, regulation of microtubule stability, and activation of complement [5]. While MOG is quantitatively a minor component of myelin (0.05%), its location on the outermost surface of the myelin sheath and in the membrane of oligodendrocytes [5,6] makes it accessible to antibodies and a target for auto-antibody mediated diseases.

MOG was first identified as a target of demyelinating antibodies in animal models and in Experimental Autoimmune Encephalomyelitis (EAE) [7,8]. Several subsequent studies have demonstrated the role of MOG as an autoantigen for T and B cell responses in EAE [9]. MOG-ab, predominantly from the IgG1 subtype, have been

shown to be capable of inducing complement mediated cytotoxicity and augmenting demyelination in animal models [2,4]. In children, the anti-MOG humoral immune response has been shown to be specific for demyelinating CNS diseases and can differentiate them from viral encephalitis [10]. While it remains unclear if MOG-ab have demyelinating activity, the data suggests MOG-ab do not merely reflect myelin destruction [11].

Recently, the development of Cell-Based Assays (CBA) using transfected cells has impacted how MOG antibodies are measured and has facilitated the identification of clinically relevant MOG-IgG. Prior detection methods, based on western blotting or ELISA, were less accurate due to their inability to distinguish specific antibodies against conformational MOG epitopes, specifically those that have been shown to be biologically significant [12]. CBA offers an advantage in this sense but still poses the issue of technical heterogeneity leading to sometimes variable results [13].

In a recent study by Thulasirajah, serum MOG Abs were identified via a live cell staining immunofluorescence assay with HEK-293A cells transfected with MOG and were deemed “positive” if the titer was  $> 1:160$  [14]. A titer of  $\geq 1:160$  has been used to indicate MOG-ab-positivity in several other studies [1,15,16].

## CLINICAL PRESENTATION

The initial clinical presentation in MOG-ab seropositive patients is quite variable. MOG-ab have been identified in a range of pediatric acquired demyelinating syndromes, including ADEM, ON, NMO, and TM. To encompass the demyelinating syndromes associated with positive MOG- IgG antibodies, Dos Pasos et al recently proposed the term “MONEM” (MOG-IgG-associated ON, encephalitis, and myelitis) [13].

While there is no single clinical presentation associated with MOG-ab seropositivity, studies have suggested age-dependent phenotypes. A retrospective study by Fernandez-Carbonell et al demonstrated a bimodal distribution in MOG seropositive patients, with encephalopathy being more common in younger patients (3-8 years) and ON in older patients (13-18 years) [17]. Hacohen et al also observed an age-dependent phenotype with brain manifestations (clinical and radiographic) in younger children (9 years and younger) and

optic neuritis (with normal brain imaging) findings in older children (older than 9 years) [18].

**CSF Findings:** Several authors agree on pleocytosis and rare Oligoclonal Bands (OCB) being classic findings in the CSF of children with MOG-ab associated demyelinating disease [14,16,18,19].

**MRI Findings:** Thulasirajah et al observed that the MRI burden of lesions in the brain and spine is extensive in patients with MOG-ab-positive pediatric demyelinating diseases. They noted confluent and asymmetrical subcortical and deep white matter lesions. The spinal cord lesions were longitudinally extensive [14]. Similarly, Bauman et al found that the brain MRI of children with ADEM and MOG-ab was characterized by large, hazy, bilateral widespread lesions without clear boundaries. They also observed an increased frequency of LETM [19].

The presence of Corpus Callosum (CC) lesions has been described to be a statistically significant difference between MOG seropositive and seronegative patients. In a retrospective study, CC lesions were present in 52% of seronegative patients and 0% of the seropositive patients [17].

**Disease Course:** MOG-ab have been identified in both monophasic and polyphasic forms of demyelinating CNS diseases. Although initially associated with MS, recent studies have suggested that MOG-ab are in fact almost exclusively associated with non-MS disease courses [1,11,16]. MOG-ab are positive in 33-66% of pediatric ADEM cases [16,19,20]. In the subtype of ADEM that develops recurrent optic neuritis, called ADEMOM, 100% of patients appear to be MOG-ab positive [21] suggesting that ADEMOM may actually be a distinct disease entity from ADEM.

Transient MOG-ab have been associated with a monophasic disease course, whereas persisting MOG-ab have been associated with a recurrent (non-MS) disease course [3,19,22,23]. Recently, Hennes et al found that among 210 children with acquired demyelinating syndromes, 22/65 (33.8%) of MOG-ab-positive children experienced clinical relapse. These children tended to have persisting high MOG-ab titers (after 24 months). These children were additionally characterized by higher age at onset (median age 8 vs 4.5 years), female sex predominance, and optic nerve involvement [16].

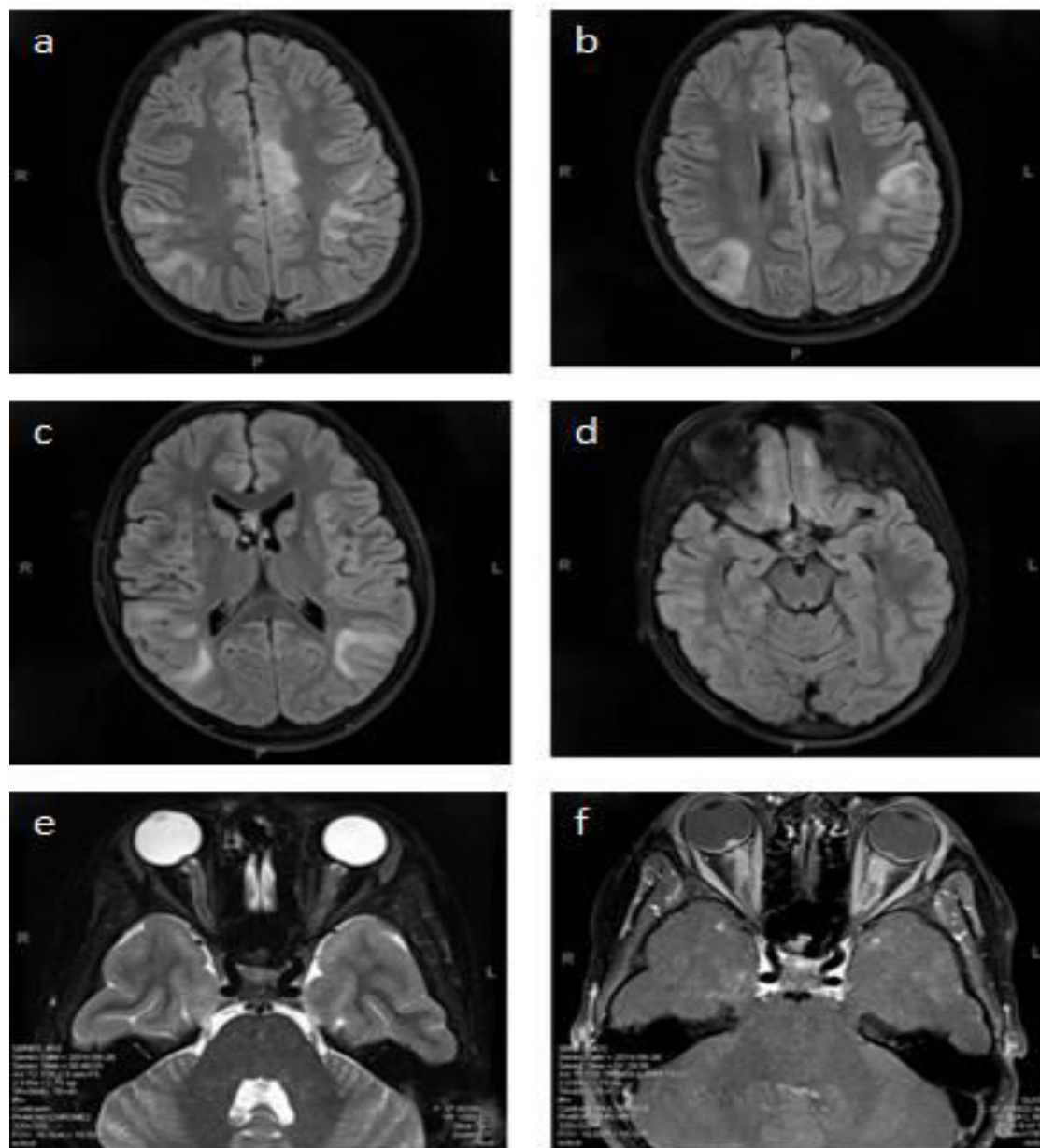
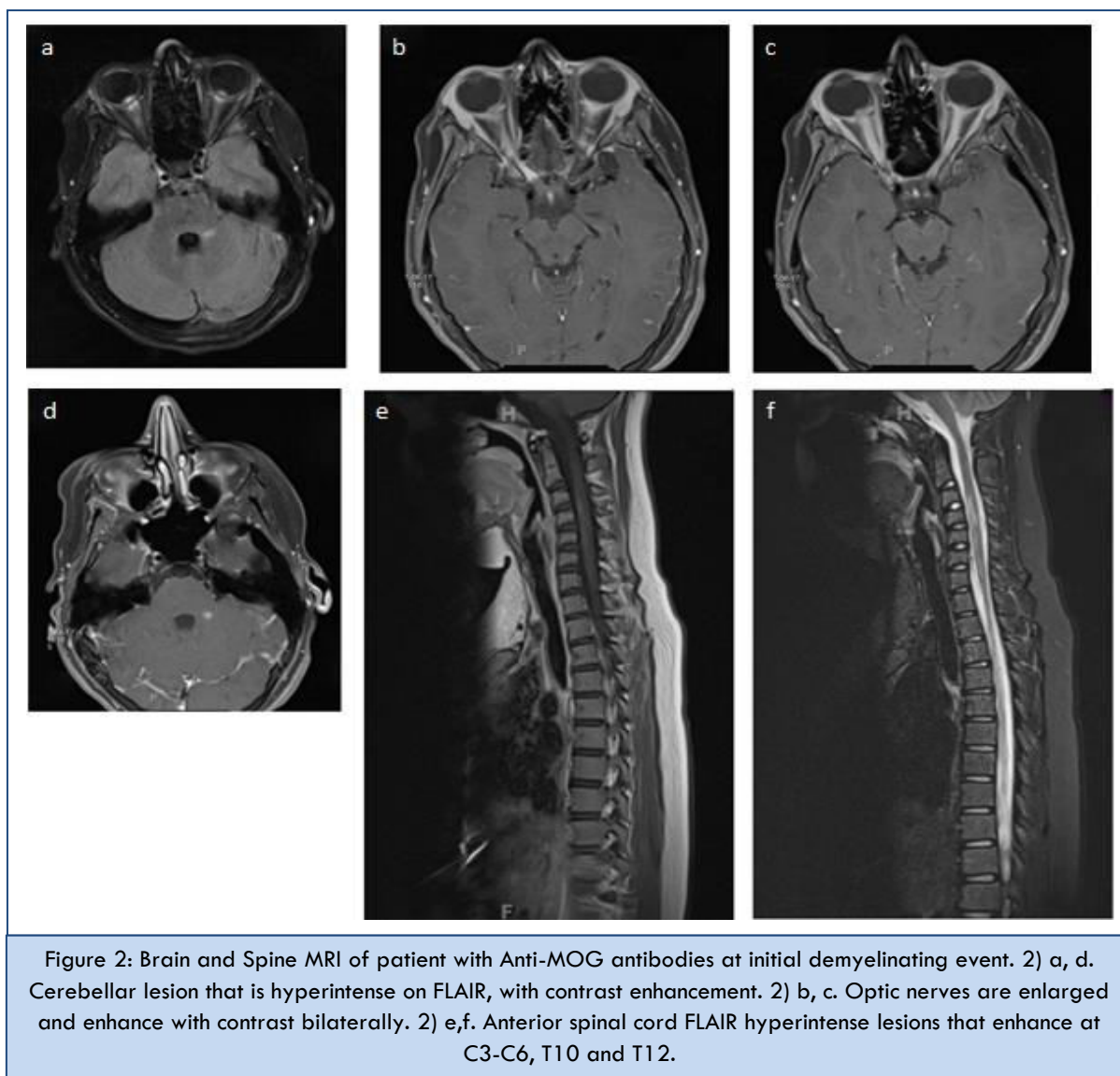


Figure 1: Brain MRI of patient with Anti-MOG antibodies at initial demyelinating event. 1) a-d. Multiple areas of large diffuse cortical and juxta cortical T2/FLAIR hyperintensities involving bilateral frontal, temporal, parietal and occipital areas. 1) e-f. Thickening of the optic nerves with abnormal T2 signal of the bilateral intraorbital, canalicular and prechiasmatic optic nerves with evidence of bulging of the optic disc and flattening of the posterior sclera, with contrast enhancement.



## TREATMENT AND PROGNOSIS

Children with NMO and anti-MOG-IgG antibodies may have a more benign disease course (than those with anti-AQP4 antibodies) that is responsive to milder forms of immunomodulation [23]. It appears that children with anti-MOG-ab demyelinating syndromes have rapid resolution of both clinical and imaging findings following steroid and IVIG therapy [14]. Although disease modifying drugs are extensively used in the treatment of patients with MS, a recent prospective study showed that they are not associated with clinical improvement in patients with relapsing MOG-ab associated disease. Rather, intravenous immunoglobulins (IVIG), rituximab, mycophenolate mofetil, and azathioprine (in descending order of efficacy) have been associated with a reduction in relapse frequency [18].

## CONCLUSION

MOG-ab have been identified in a range of non-MS, acquired demyelinating syndromes. While there is no single clinical presentation associated with MOG-ab seropositivity, studies suggest unique patterns in initial presentation, clinical course, and response to treatment. Further large, longitudinal prospective investigations will be essential in further elucidating the pathophysiology of MOG-ab-positive demyelinating syndromes and guiding future diagnostic and management strategies for these patients.

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