

**ANTI-MOG ANTIBODY
ASSOCIATED DISEASE
(MOGAD): ETIOLOGY,
EPIDEMIOLOGY,
CLINICAL FEATURES,
DIAGNOSIS AND
TREATMENT**

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MYELIN OLIGODENDROCYTE PROTEIN STRUCTURE AND FUNCTION

Oligodendrocytes are located in the gray matter and white matter of the central nervous system (CNS). In the gray matter, oligodendrocytes are close to the cell bodies of neurons. In the white matter, oligodendrocytes, through their extensions, involve segments of several axons (up to 60) (3).

The plasma membrane of the myelin sheath is made up of 70% lipids and 30% proteins. Lipids consist of phospholipids, glycolipids, and primarily cholesterol. Among the proteins, mention is made of myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated glycoprotein (MAG) and myelin oligodendrocyte glycoprotein (MOG) (3).

Myelin oligodendrocyte glycoprotein (MOG) is one of several proteins produced by oligodendrocytes, myelin-forming cells of the central nervous system (CNS)(1). MOG is an essential component of the membrane surface of oligodendrocytes, along with the other proteins mentioned above; these glycoproteins play key roles in the formation, maintenance, and integration of the myelin sheath (1).

Myelin oligodendrocyte glycoprotein (MOG) is a glycoprotein located on the surface of myelin and is found exclusively in the central nervous system (CNS). Although its exact role remains unclear, it is thought to act as a cell adhesion molecule, involved as a regulator of oligodendrocyte microtubule stability, and a mediator of the complement cascade (4).

MOG expression begins when myelination starts and is therefore a possible marker of differentiation to oligodendrocyte maturation. MOG is a protein expressed only in the outermost lamellae of the myelin sheath and on the surface of oligodendrocytes in the

central nervous system (CNS) and represents less than 0.05% of the total myelin proteins, but despite its sparse concentration, it is believed to be involved in important functions such as: regulation of oligodendrocyte microtubule stability, maintenance of myelin sheath structural integrity by its adhesion characteristics, and mediation of interactions between myelin and the immune system, being a surface marker of mature oligodendrocytes and participating in the interactions between myelin and its interactions (1, 2). However, its structure (extracellular domain) and the more superficial external location in myelin sheaths makes it easily accessible to potential antibodies and the involvement of the T-cell response (1).

HISTORICAL ASPECTS

For some time, MOG was thought to localize to the surface of myelin sheaths and oligodendrocyte processes only within the CNS. However, there are anecdotal data about its low expression in the peripheral nervous system (PNS), as well (1).

MOG was first identified in the late 1970's and has been extensively studied over the last 30 years, with some early experimental studies hypothesizing a pathogenic role in CNS inflammatory diseases (1, 4).

ANTI-MOG

A mature human MOG is a protein that contains a 29 amino acid signal peptide followed by the 218 amino acids of the mature protein. This glycoprotein is expressed only in mammals with a highly conserved amino acid sequence (>90%) among animal species, which suggests its important biological role. MOG belongs to the immunoglobulin superfamily, consisting of an extracellular immunoglobulin (IgV) variable domain, a hydrophobic transmembrane domain, a short cytoplasmic loop, a second hydrophobic region within the

membrane bilayer, followed by a cytoplasmic tail. Such a structure is unique because other members of this superfamily have a single transmembrane domain or are attached to the membrane surface by a glycolipid anchor (1).

The development of a more specific and sensitive laboratory methodology (cell-based assay (CBA) allowed revisiting the anti-MOG antibody in demyelinating diseases and establishing it as a new biomarker. So far, once the presence of the antibody in serum has been identified, it seems reasonable to include the following entities in the anti-MOG spectrum: recurrent optic neuritis or bilateral optic neuritis (NO), ADEM, anti-aquaporin-4 negative neuromyelitis optica spectrum disorders, and longitudinally extensive transverse myelitis (2).

So far, several research groups have detected serum anti-MOG antibodies with the above-mentioned optimized cell-based assays, mainly in patients with a phenotype of acute disseminated encephalomyelitis (ADEM), brainstem/cortical encephalitis, optic neuritis, (ON) (unilateral/bilateral), transverse myelitis (MT) and longitudinally extensive transverse myelitis (LETM). In other words, we can say that this unique clinical entity (different terms are used: anti-MOG disease, MOG-IgG-associated disorder, and – more commonly nowadays – MOG antibody disease (MOGAD) is an inflammatory demyelinating condition of the CNS characterized by a monophasic or multiphasic course of neurological deficits, that does not meet the criteria for typical MS or other known neuroinflammatory diseases (especially neuromyelitis optica spectrum disorders (1).

Therefore, MOG antibody disease (MOG-AD) is now recognized as a distinct nosological entity with specific management and therapeutic requirements (4).

EPIDEMIOLOGY

MOG-AD can occur in all decades of life, with a slight predominance in women and with a median age of onset between the early thirties. The most common presenting feature is optic neuritis (ON), occurring in 54-61% of patients, followed by myelitis, acute disseminated encephalomyelitis (ADEM), or an ADEM-like presentation (eg, brainstem attack) (4,7).

Although in most cases MOG antibody-associated demyelination occurs without any apparent inciting or predisposing event/disease, it has been associated with N-methyl-D-aspartate receptor demyelinating encephalitis, post-infectious demyelination following herpes simplex virus, *Borrelia* and Epstein-Barr virus infections and, more rarely, with typical relapsing MS. It remains unclear whether MOG antibodies play a pathogenic role in all of these conditions, or whether they represent a bystander effect or epiphenomenon (4).

PATHOGENESIS

A direct pathophysiological effect of MOG-IgG on the central nervous system (CNS) has yet to be elucidated [2]. It remains unclear whether MOG-IgG has a direct pathogenic role or whether it is a biomarker reflecting a disrupted myelin immune response in the spectrum of MOG-IgG-associated demyelinating disease. Growing clinical and pathological evidence now strongly indicates that MOGAD represents a distinct disease entity distinct from other neuroinflammatory and demyelinating diseases such as multiple sclerosis (MS) or aquaporin-4 (AQP4) IgG-positive neuromyelitis optica spectrum disorder (NMOSD) (9).

GENERAL CLINICAL FEATURES

MOG-AD is an inflammatory demyelinating condition of the CNS

characterized by a monophasic or relapsing course of neurologic dysfunction, which does not meet typical criteria for MS or other known neuroinflammatory conditions, and occurs in the presence of serum anti-MOG antibodies detected using specific assays (4).

Myelin oligodendrocyte glycoprotein-IgG (MOG-IgG)-associated disorder (MOGAD) is a newly defined neuroimmunologic disorder affecting the CNS, commonly presenting with acute disseminated encephalomyelitis in children and with optic neuritis and/or myelitis in adults (4,5).

In recent years, the role of serum immunoglobulin G antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) in patients with CNS inflammatory demyelination has been reviewed. While antibodies to MOG were originally thought to be involved in multiple sclerosis (MS), based on results from enzyme-linked immunosorbent assays employing linearized or denatured MOG peptides as the antigen, more recent studies using next-generation cell-based assays have demonstrated a strong association of antibodies to full-length, conformationally intact human MOG protein with optic neuritis (ON), myelitis, and brainstem encephalitis (mostly recurrent), as well as with acute disseminated encephalomyelitis (ADEM)-like presentations rather than classic MS (8).

Although some patients, especially children, may have a monophasic course, there are others who tend to have a highly recurrent course, potentially resulting in long-term neurologic disability, similar to those with neuromyelitis optica spectrum disorder (NMOSD). In fact, nearly half of NMOSD patients without aquaporin-4 (AQP4-IgG) harbor MOG-IgG. Furthermore, despite extensive testing for anti-aquaporin-4 antibodies, there remains a proportion of patients who phenotypically resemble those with NMOSD but are seronegative for AQP4-

IgG and MOG-IgG (5).

Based on evidence from immunological studies suggesting a direct pathogenic impact of MOG-IgG, neuropathological studies demonstrating discrete histopathological features, serological studies reporting a lack of aquaporin-4 (AQP4)-IgG in almost all MOG-IgG-positive patients, and cohort studies suggesting differences in clinical and paraclinical presentation, as well as treatment response and prognosis, MOG-IgG is now considered a clinical entity in its own right, distinct from classic MS and AQP4-IgG positive Neuromyelitis Optica Spectrum Disorders (NMOSD), which is now often referred to as MOG-IgG-associated encephalomyelitis (MOG-EM) (7).

It is important to emphasize, however, that MOG-EM and MS show a relevant clinical and radiological phenotypic overlap: like MS, MOG-EM follows a recurrent course in most cases, at least in adults, and 33 and 15% of adult patients with MOG-EM meet the McDonald's and Barkhof criteria for MS, respectively, at least once during the course of their illness. Thus, many MOG-EM patients were falsely classified as having MS in the past. However, screening large, unselected populations for rare biomarkers often decreases the positive predictive value of diagnostic tests, increasing the rate of false-positive results. Therefore, unselected screening of all patients with suspected or established MS for MOG-IgG should be discouraged and more specific criteria for testing for MOG-IgG are urgently needed. (7).

DIAGNOSIS

The clinical phenotype of MOGAD is broad and includes unilateral and bilateral anterior ON, long and short transverse myelitis (TM), ADEM, brainstem encephalitis, and cortical encephalitis with or without seizures. Furthermore, combinations of

these syndromes may occur, for example, as an NMOSD-like phenotype featuring ON and TM. Importantly, the clinical phenotype is strongly dependent on age, with a more ADEM-like phenotype in children and a more optic-spinal phenotype in adolescents and adults. In pediatric patients, the following four phenotypes account for 90% of MOGAD cases: 46% presenting with ADEM, 30% with ON, 11% with TM, and 4% with an NMOSD-like phenotype (ON + TM). Relapses in children and adults have been described in 40-80% of patients, especially in the form of ON (9).

Regarding MOG-IgG testing recommendations: these recommendations apply to all patients with suspected CNS demyelination attributed to autoimmune etiology and a monophasic or relapsing disease course. Given the very low pretest probability, we do not recommend general MOG-IgG testing in patients with a progressive disease course. These recommendations are primarily intended for use in adults and adolescents. Indications for MOG-IgG testing in young children need not be as stringent as in adults, as MOG-EM is believed to be significantly more frequent among young children with acquired demyelinating disease (up to 70%; frequency declining with age) than among their adult counterparts ($\leq 1\%$ in Western countries; probably $\leq 5\%$ in Japan and other Asian countries due to lower prevalence of MS), which reduces the risks associated with the previously described antibody screening. If costs play a role and disease is stable: test AQP4-IgG first, as it is more frequent in this condition than MOG-IgG. If disease is active, requiring quick decision-making, or if costs are not important: test AQP4-IgG and MOG-IgG in parallel (7).

These conditions apparently exhibit differential responses to immunotherapies, underscoring the need for accurate and

timely diagnostic procedures during which neuroimaging plays a key role. Due to the widespread involvement of the nervous system in MOGAD, magnetic resonance imaging (MRI) and optical coherence tomography (OCT) are important imaging tools to gain more knowledge about the disease and for the follow-up of patients with this rare set of disorders (9).

Magnetic resonance imaging abnormalities in MOGAD can be detected in the brain, optic nerve and/or spinal cord, depending on the clinically affected anatomical region of the nervous system. On brain magnetic resonance imaging, findings in children mainly reflect signs of ADEM with diffuse and disseminated white matter lesions on T2-weighted images, whereas in adults brain magnetic resonance imaging is normal or shows brainstem or cortical lesions. Acute ON can lead to optic nerve swelling and severe retinal neurodegeneration over time. Typical NO MRI findings in MOGAD are long lesions in the anterior part of the optic nerve with periorbital enhancement and often bilateral involvement. Spinal cord lesions in MOGAD can be visualized using MRI typically showing longitudinally extensive transverse myelitis (LETM) primarily affecting the gray matter, as seen as an 'H sign' in the axial plane (9).

Longitudinally extensive transverse myelitis (LETM) is common in both MOG-EM and AQP4-NMOSD, but rarely occurs in MS; as a caveat, however, non-contiguous lesions can mimic LETM in some patients with MS. However, short lesions do not by themselves exclude MOG-EM. Magnetic resonance imaging shows short lesions at least once throughout the disease course in about 44-52% of all patients with MOG-EM and about 15% of all patients with AQP4-NMOSD. Lesion length may also depend on MRI timing issues, with shorter lesions detected when MRI was performed early in the course

of acute myelitis or in clinical remission. Axial and sagittal plane images should be used to assess the extent of the lesion.

TREATMENT

This previously reported misclassification has potential therapeutic implications: (a) similar to what has been observed in AQP4-IgG positive NMOSD, some drugs approved for MS may be ineffective or even harmful in MOG-EM due to differences in immunopathogenesis; (b) MOG-EM is associated with a high risk of relapses after stopping steroid treatment for acute relapses and may therefore require close monitoring and careful steroid tapering; and (c) MOG-IgG positive patients may

be particularly responsive to antibody-depleting treatments for acute flares such as plasmapheresis or immunoadsorption, to long-term therapies targeting B cells such as rituximab, to intravenous immunoglobulin (IVIg) treatment (especially in children) and immunosuppressive treatments.

In an international retrospective review study of RTX-treated MOGAD patients from 29 centers in 13 countries, which included 121 patients and evaluated the effect of anti-CD20 B-cell depletion with rituximab (RTX) on rates of relapse in oligodendrocyte myelin glycoprotein (MOGAD), the primary endpoint was change in relapse rate after initiation of rituximab (8).

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