Review Article

Evolution in anti-myelin oligodendrocyte glycoprotein antibody detection and its clinical significance: a narrative review

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Abstract: Myelin oligodendrocyte glycoprotein (MOG) is a protein exclusively expressing on the surface of myelin sheaths and oligodendrocyte plasma membrane in the central nervous system of mammals, and it has a highly conserved nucleotide and amino acid structure between species. Evidence from animal research support that anti-MOG antibodies (MOG-Abs) are pathogenic antibodies rather than a bystander secondary to myelin destruction. Similarly, immunoglobulin-G against myelin oligodendrocyte glycoprotein (MOG-IgG) is considered a demyelinating disease-associated autoantibody in human beings. In clinical studies, several detection methods, including ELISA, immunoblot, radio immunoprecipitation assays and Cell-based assays (CBAs), have been applied in identifying MOG-Abs in idiopathic inflammatory demyelinating diseases (IIDDs) of human beings. CBAs method is recommended by many proposed diagnostic criterions for MOG-Abs-associated disorders (MOGAD). This method involves transfection of mammalian cells with MOG antigen, binding of MOG-Abs to MOG antigen, binding of secondary antibodies to MOG-Abs and quantification method. However, the reliability for CBAs systems of MOG-Abs detection can be influenced by numerous factors, such as length of MOG antigen, expression vectors, cell lines, secondary antibodies, and read-out systems. In addition, there are controversial results on the studies of IIDDs with MOG-IgG positive. Nowadays, more and more evidence suggests that patients positive for MOG-IgG share common features, but further clinical and laboratory researches are needed to clarify if MOGAD is an independent disease entity. In this review, we intend to summarize the detection methods of MOG-Abs and their sensitivity and specificity to MOGAD in human.

Keywords: Myelin oligodendrocyte glycoprotein (MOG); anti-MOG antibodies; immunoglobulin-G against myelin oligodendrocyte glycoprotein (MOG-IgG); MOG-IgG associated disorders

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Introduction

Myelin oligodendrocyte glycoprotein (MOG) is a protein exclusively expressing on the surface of myelin sheaths and oligodendrocyte plasma membrane in the central nervous system (CNS) of mammals (1,2), and it has a highly conserved nucleotide and amino acid structure between species, including humans, rats, mice, and bovine animals (2,3).

In animal studies, MOG is the antigen for experimental

autoimmune encephalomyelitis (EAE), which is the typical animal model of multiple sclerosis (MS). Also, inflammatory and demyelinating changes of EAE are enhanced by some of the anti-MOG antibodies (MOG-Abs) (3). Similarly, immunoglobulin-G against myelin oligodendrocyte glycoprotein (MOG-IgG) is considered a demyelinating disease-associated autoantibody in human beings. However, there are controversial results on the studies of humans.

Many factors increase the possibility for MOG to become an antigen that triggers immune response in the CNS. On one hand, as MOG is not expressed in the peripheral organs, immunological tolerance targeting it may be not fully established. On the other hand, this protein is easily accessible by both humoral immune reactions and cell-mediated immune responses (4). MOG is mainly on the plasma membranes of oligodendrocytes and the external surface of myelin, with its highest antigen density in the outermost lamellae of myelin sheaths, therefore giving it a chance to be an accessible antigen for the immune reaction (2). In addition, up to 15 different alternatively spliced isoforms of MOG have been detected in humans, with some of them can be found in a secretory form. These secretory MOG proteins have potential to trigger autoimmunity when they enter the cerebrospinal fluid (CSF) and subsequently flow to the peripheral circulation (3).

In this review, we intend to summarize the detection methods of MOG-Abs and their sensitivity and specificity to MOG-Abs-associated disorders (MOGAD) in human. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-20-4547/rc).

Pathogenicity of MOG-Abs and its initiation

Pathogenic and non-pathogenic MOG-Abs

Evidence from animal research support that MOG-Abs are pathogenic antibodies rather than a bystander secondary to myelin destruction. Some initial research has demonstrated that human MOG-Abs can also mediate demyelination *in vitro* and *vivo*. In one study, human MOG-Abs leaded to complement-dependent pathogenic effects in a murine *ex vivo* animal model (5). In another study, MOG-Abs purified from patients with idiopathic inflammatory demyelinating diseases (IIDDs) induced pathological changes in two different rat models upon co-transfer with cognate MOG-specific T cells (6). Utilizing IgG purified from sera or plasma of MOG-IgG seropositive patients, Fang and colleagues found that MOG-IgG is pathogenic both in vitro and *in vivo*, leading to pathological manifestations different from that of neuromyelitis optica spectrum disorder (NMOSD) (7). Pathology research on human beings have provided further direct evidence about pathogenicity of MOG-Abs in MOGAD patients. In a study by Shu and colleagues, brain biopsies of MOGAD patients shown unique pathological features with T cells, macrophages, and complement-mediated demyelination (8).

According to the present studies, anti-MOG responses are typically related to $CD4^+$ T cells and complement-fixing IgG1 antibodies. These cellular immune responses contain T cells specific for several different T cell epitopes, while humoral immune responses also include various effects (3,9). However, certain subtypes of the MOG-specific T cells are not encephalitogenic. Similarly, although different kinds of MOG-specific autoantibodies exist, only those recognizing conformational epitopes on the extracellular domain of MOG are pathogenic. In fact, low titers of MOG-Abs were detected in some MS patients, other neurological diseases patients and healthy individuals even using the most advanced cell-based assays (CBAs) method (10,11). Explanation for this finding is that nonspecific MOG-Abs in low-titer may belong to natural antibodies that are relatively common and non-pathogenic; or some factors in the serum bind to MOG and produce a nonspecific positive signal; or current detection methods cannot promise an absolute specificity (1,3).

Initiation of MOG-Abs production

One most studied mechanism of triggering MOG-Abs is molecular mimicry. Exogenous antigen sharing the same epitope with MOG may cause sensitization of encephalitogenic T cells and can later activate the native MOG-specific B cells, which generate MOG-Abs production. Some candidate exogenous antigens have been found. For example, MOG-Abs repertoire can cross-react with Epstein-Barr virus (EBV) nuclear antigen (12) and a bovine milk protein butyrophilin (13). However, it is worth noting that some of these results come from non-specific MOG-Abs detection methods.

Another popular explanation of MOG-Abs initiation is autoantigen exposure. It is possible that a direct CNS infection or a peripheral initiator can cause a breakdown of blood-brain barrier (BBB), allowing MOG leaking into peripheral circulation, or allowing circulating lymphocytes

entering CNS. And then MOG that is used to be exclusively confined to the CNS may be recognized as a non-self-antigen when meet with peripheral lymphocytes (9), which starts an MOG-specific immune response, including MOG-Abs secretion.

MOG-Abs may either be produced within the CNS or pass through the BBB from the periphery (14). There are some hypotheses that MOG-Abs are likely to be generated in peripheral circulation, because the fact that MOG-Abs are more easily detected in serum compared with CSF. However, the place of origin is not the only factor affecting the concentration of MOG-Abs in CNS and peripheral circulation. Other factors can also explain the low titer of MOG-Abs in CNS. One such example is that antibodies can be consumed in immune response and experience concentration decrease.

MOG-Abs detection

Several detection methods, including ELISA, immunoblot, radio immunoprecipitation assays and CBAs, have been applied in identifying MOG-Abs in IIDDs of CNS.

ELISA or immunoblot

As target antigenic region of MOG-Abs and its affinity to MOG protein is diverse in different patients (15), MOG-Abs detection by ELISA or immunoblot utilizing linear, refolded, or denatured MOG proteins, which may alter antigen conformation and immunodominant epitopes that affect the tertiary structure of the folded proteins, may cause the inaccessibility of MOG-Abs to these antigens (4). Therefore, detecting MOG-Abs by ELISA or immunoblot has generated inconsistent results in MS patients. Similarly, some non-pathogenic nonspecific MOG-Abs at low-titer in healthy population and patients with other disease were also detected by these methods (1). Data from 16 studies (immunoblotting, 7 studies and ELISA, 9 studies) show that MOG-Abs were detected in 20% MS patients, while the parentage in healthy individuals and people with headache, back pain, neurodegenerative diseases, infections and other inflammatory diseases was 13% (1). More recent study has confirmed that ELISA showed no concordance with CBAs for detection of human MOG-IgG (16).

Radio immunoprecipitation assays

Accordingly, a detection technology maintaining native conformational human MOG is quite necessary. In later studies, self-assembling radiolabeled tetramers with folded MOG and unfolded MOG were both created. Then serum from different origin was utilized to test the system. As expected, MOG-Abs from human selectively bound the folded MOG tetramers, whereas sera from EAE induced with MOG peptide immunoprecipitated only the unfolded tetramers. Thus, a more-specific radio immunoprecipitation assays (RIAs) for clinical detection utilizing natively-folded MOG was established (17-19). Studies on MOG-Abs RIAs for IIDDs have revealed that MOG-Abs detection could be clinically significant. In O'Connor's study, 19% of people with acute disseminated encephalomyelitis (ADEM), while only 2% of MS patients and only 1% of healthy or neurological controls were positive for MOG-Abs, demonstrating that non-MS demyelinating diseases are more related to MOG-Abs than MS, and specific pathogenic MOG-Abs are rarely found in healthy individuals (18). This shows that, compared to ELISA and immunoblot, RIAs have better sensitivity, with higher MOG-Abs detection ratio in demyelinating diseases, and better specificity, with low MOG-Abs positivity in healthy controls. However, application of this method is limited due to its complicated process and high cost.

Cell-based assays

Detection methods with reliable results, and higher sensitivity and specificity have been invented. One of them is CBAs, which involves transfection of mammalian cells with MOG antigen, binding of MOG-Abs to MOG antigen, binding of secondary antibodies to MOG-Abs and quantification method. The reliability for CBAs systems of MOG-Abs detection can be influenced by numerous factors, such as length of MOG antigen, expression vectors, cell lines, secondary antibodies, and read-out systems.

The importance of natural conformation of MOG protein in MOG-Abs detection has been proved in the previous methods, and it has also been confirmed in CBAs (1). Therefore, in majority of established CBAs, full length MOG antigen is presented on the cells in its native state, making the identified antibodies with higher disease relevance (20).

Some articles have mentioned that glycosylation of MOG protein in CBAs might affect its sensitivity and specificity. For example, Marti Fernandez's study discovered that sensitivity of MOG-Abs detection might be improved by a neutral glycosylation-deficient mutant of MOG (21).

But relevant studies are still limited, and more research are need.

CBAs established by different secondary antibodies, such as human IgG (heavy and light chain), IgG-Fc (constant chain) or IgG1, have been tested. Secondary antibodies restricting to human IgG-Fc and human IgG1 may improve CBAs (22). In a study, anti-human IgG1 substantially enhances specificity of MOG-Abs detection by removing two-thirds of false positives cases compared to anti-human IgG. However, other studies have shown that anti-human IgG was comparable to IgG1-Fc antibody (15,23). Furthermore, secondary antibodies targeting human IgG1 might fail to identify patients with IgG2, IgG3, or IgG4 subclasses (11).

Flow cytometry (CBA-flow cytometry, CBA-FACS) and immunofluorescence (CBA-immunofluorescence, CBA-IF) are two main read-out technologies, and both have high sensitivity and specificity. In Brilot's study utilizing CBA-FACS, MOG-IgG were detected in 40% of children with clinically isolated syndrome (CIS)/ADEM but none of the control children affected by other neurological diseases and healthy children (24). In another study conducted by Di Pauli, 44% ADEM patients were seropositive for MOG-IgG while only rarely in CIS, MS, other neurological diseases, and none of the healthy controls were seropositive (10).

General speaking, over 70% of CBAs have specificity at 100% with seronegative in all the healthy or neurological control. And its sensitivity seems to be higher than the previous methods. In non-MS idiopathic inflammatory demyelinating syndromes, about 28% patients were MOG-Ab-positive. These patients are usually diagnosed as ADEM, AQP4-Ab-negative NMOSD, optic neuritis, myelitis, encephalitis and other unclassified syndromes, indicating that MOG-Abs is a biomarker for non-MS demyelinating disease rather than clinically definite MS (1).

Recommendations for MOG-Abs detection

In 2018, two independent research groups have described the relative standard MOG-Abs detection methods and have given a proposed diagnostic criterion for MOG-Abs-associated demyelination in human, respectively. In summary, these recommendations are the use of CBAs with only full-length MOG, use of IgG1-specific or IgG-Fc secondary antibodies, use of a second method as confirmation, and measurement of levels only in the serum (25,26). Recently, a study compared the reproducibility of 11 antibody assays for MOG-IgG and MOG-IgM from 5 international centers and its result indicated excellent agreement of MOG-IgG CBAs for high positive and negative samples (16).

It is worth noting that, the titer of MOG-Abs can be changed according to multiple factors. Take CBAs itself as example, although as the recommend detection method, various CBAs can also be heterogeneous (27,28). Therefore, a second methodologically different CBAs should be used to confirm positive result when a borderline positive sample is tested. Other factors including disease severity and treatment strategy. Titer of MOG-Abs is dynamic during the disease course and can suggest the prognosis for disease. Some clinical observational research with long term follow-up indicates that patients that become MOG-IgG seronegative soon may have no or rare relapses, while patients with clinical relapses often have persistent positive serological status (29). Titer of MOG-Abs can also be altered after treatment. Zhou and colleagues reported a MOGAD patient experienced MOG-IgG seroconversion after treated with azathioprine plus oral methylprednisolone (30). Thus, repeating MOG-Abs detection ought to be taken in follow up to identify patients in different clinical subtypes (9).

MOG-Abs in human demyelinating diseases

Early ELISA and immunoblot studies established the clinical relevance of MOG-Abs with MS (31) and ADEM (32), but MOG-Abs were also detected in some health controls and some patients with non-demyelinating disease. More recent studies utilizing CBAs have shown a more closed association between MOG-IgG and NMOSD with aquaporin-4 autoantibody seronegative and optic neuritis (ON) (33-35), and MOG-IgG is rarely found in healthy controls, or other inflammatory and non-inflammatory neurological diseases using this method (19,24,36-38), which reveals that MOG-IgG has a high specificity to demyelinating diseases.

MOG-Abs in multiple sclerosis

Using ELISA or immunoblot, the positive rate of MOG-Abs is around 20% among the MS patients. The proportion of MS patients with MOG-Abs positive is substantially higher than that of patients with non-inflammatory CNS diseases, infections, and other inflammatory diseases. However, the presence of antibodies in more than 10% of the healthy control individuals has posed challenges to the reliability of these methodologies (1,4).

In 2001, CBAs were first used for MOG-Abs detection in a subset of MS people (20) and then in numerous studies in patients with MS of different ages, sexes, and races. However, these studies yielded inconsistent results at the very beginning. After specificity of CBAs was improved by methodological advance, studies have proclaimed that patients with relapsing-remitting or primary progressive MS are predominantly MOG-Abs negative (11). In one study, only 2 of 685 MS patient were positive for MOG-Abs, suggesting that MOG-Ab are exceptional in MS phenotype (39). Similarly, a few researches did find positive rate in serum MOG-Abs in MS patients was higher compared to healthy volunteers (37), but the majority of studies confirmed that a lack of disease specificity was revealed by low titers of MOG-Abs that were considered to be equivocal in a large number of MS patients; while MS patients who were clearly seropositive for MOG-Abs usually showed atypical MS that experienced clinical features commonly being observed in MOGAD, such as optic neuritis, transverse myelitis and demyelinating lesions in brainstem and brain. Moreover, there was no prognostic value for MOG-Abs in MS patients (40). From the opposite perspective, CSF-restricted oligoclonal IgG bands, a hallmark of MS, were absent in almost 90% of MOGAD patients, further indicating distinct clinical features of the two diseases (41,42).

MOG-Abs in neuromyelitis optica spectrum disorder

Using CBAs, MOG-Abs were first identified by Mader (43) as being presented in a subgroup of patients with AQP4 antibody-negative NMOSD, and the subsequent studies also supported this finding (44-46). Overall, MOG-Abs have a prevalence of about 25% among NMOSD with AQP4-antibody negative (3,4). A strong relationship between MOG-Abs and bilateral optic neuritis was found, which is relatively rare seen in MS (35,47,48). Furthermore, ON in patients with MOG-Abs has manifested as significantly optic disk swelling, distinguishing this new disease entity from AQP4 antibody-positive ON (47,49). Compared to patients with other IIDDs, MOG-Abs positive patients with longitudinally extensive transverse myelitis as initial symptoms are more likely to be suffered from further episodes of ON but have better outcome (50). In addition, patients seropositive for both AQP4 and MOG antibodies have been reported when detecting MOG-Abs by ELISA, while double seropositivity is not common when utilizing CBAs (41).

Moreover, whether MOG antigen or MOG-Abs participate in NMOSD pathogenesis is needed to be further clarified, as one recent research has found that a role of AQP4-specific, but not MOG-specific T-cells, in NMOSD (51).

MOG-Abs in acute disseminated encephalomyelitis

Identification of the association of MOG-Abs and ADEM was first conducted with MOG tetramers (19). Subsequent research has revealed that around 40% patients diagnosed as ADEM are positive for MOG-Abs (22,23). MRIs manifestation in ADEM patients with high MOG-Abs titers is characterized by large hazy bilateral cerebral lesions and/or longitudinally extensive transverse myelitis, which is consisted to the clinical feature of MOGAD (32). Although part of these MOG-Abs-positive ADEM may mimic MS, they are distinguished from the typical MS by optic neuritis and longitudinally extensive transverse myelitis (2).

MOG-Abs-associated diseases

Clinically, although some cases of MOG-IgG positive patients fulfill the diagnostic criteria of MS, NMOSD, ADEM, or other IIDDs, there are no distinct types of these diseases that can explain all presentations of MOG-Abs positive patients.

Some symptoms that are common in other IIDDs can also be seen in MOGAD but with different features. Take ON as an example. In a study, ON of MOGAD underwent a severe vision loss at onset but had relatively better visual recovery than that of NMOSD (52). Another research found that ON of MOGAD usually caused longitudinally extensive optic nerve lesion with anterior enhancement and perineural soft tissue enhancement (53).

MOGAD patients also have unique symptoms that are rare in other IIDDs. For instance, 20.7–40% MOGAD patients had typical presentations of encephalitis, manifested as seizure, encephalopathy, meningeal irritation, fever, headache, nausea, vomiting, intracranial hypertension, cerebrospinal fluid pleocytosis and cortical lesions (54,55). Another example is the age dependence of clinical manifestations in MOGAD. Differences in clinical manifestations (56,57) and initial diagnosis (58) have been noticed between pediatric-onset and adult-onset patients in some research. And the genetic background for this age dependence phenomenon has been discovered (59).

Furthermore, patients with MOGAD share similar

features, including optic neuritis, transverse myelitis, brainstem encephalitis, encephalopathy and epilepsy. These findings may be evidences for considering MOG-Abs as a characteristic antibody of an independent disease entity. In 2018, two independent teams have proposed preliminary diagnostic criteria for MOGAD, naming the syndrome with "MOG encephalomyelitis" (24) and "MOG-IgG related diseases" (25) respectively. Both diagnostic criteria emphasis that MOG-IgG positive in serum is necessary for the diagnosis for MOGAD. Jarius's criteria also suggested that "MOG encephalomyelitis" often manifested as ON, transverse myelitis, brainstem encephalitis or encephalitis (or combination of these syndromes), and the patients should have MRI or electrophysiological examination results consistent with CNS demyelinating disease (24). Lopez-Chiriboga's criteria suggested that symptoms such as ADEM, ON, chronic relapsing inflammatory optic neuropathy, transverse myelitis, demyelinating encephalopathy, or brainstem syndrome (or any combination of these manifestations) are common seen in "MOG-IgG related diseases", but other differential diagnoses ought to be excluded (25).

However, whether MOGAD is independent is still controversial. On one hand, some studies show evidence of important pathogenic role of MOG-Abs in MOGAD. For example, a recent study has found that higher titers of MOG-Abs were observed in MOGAD patients with more severe phenotypes and during their active disease. On the other hand, some opposite evidence is observed (15). MOG-Abs can also be detected in some autoimmune diseases or conditions of nervous system damage. For instance, patients with antibodies against MOG and N-methyl-d-aspartate receptor (NMDAR) simultaneously were reported sometimes. A study has observed that MOGAD (11.9%) may more commonly co-exist with antibodies to NMDAR (NMDAR-Abs) compared to AQP4-IgG-positive NMOSD (0.6%) (60). And patients with double positive for MOG-Abs and NMDAR-Abs may have double-syndrome, encephalitis and demyelinating, or have various clinical symptoms which are typical for MOGAD (61) or anti-NMDAR encephalitis (62) respectively. The titers of antibodies and the relationship between antibodies and clinical symptoms are required to be clarified by longer follow-up. MOG-Abs detected following infection is another example of MOG-Abs as a concomitant antibody. In a case report, a patient who suffered from infectious mononucleosis due to Epstein-Barr virus infection developed MOG-Abs-positive ADEM with a titer of 1:1024, but his symptoms quickly improved after steroid pulse therapy followed by oral betamethasone. MOG-Abs at the 6-month follow-up were negative (63).

Conclusions

In the present review, we searched English articles involving clinical MOG-Abs detection mainly published after 2000 in PubMed and included those closely relate to IIDDs for discussion. It shows that MOG protein is a potential antigen in the CNS, which is easily accessible by mainly humoral immune responses. MOG-Abs are pathogenic antibody of MOGAD. Though the exactly pathogenic mechanism of MOG and MOG-Abs has not been fully understood, we have made great progress in the MOG-Abs detection. More and more evidence suggests that patients with MOGAD share common features, but further clinical and laboratory researches are needed to clarify if MOGAD is an independent disease entity.

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