Myelin oligodendrocyte glycoprotein antibody-associated disease

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List of Abbreviations

ADCC- antibody-dependent cellular cytotoxicity
ADEM- acute disseminated encephalomyelitis
AFM- acute flaccid myelitis
APC-antigen presenting cells
AQP4-4-aquaporin 4
AZA-azathioprine
CBC- complete blood count
CIDP-Chronic inflammatory demyelinating peripheral neuropathy
CNS- central nervous system
CRION-chronic relapsing inflammatory optic neuropathy
EDSS-expanded disability status scale
FLAIR- fluid-attenuated inversion recovery
FLAMES- FLAIR-hyperintense lesions in anti-MOG associated encephalitis with seizures.
HEK293- human embryonic kidney cells
HNK-1- human natural killer-1
IPMSSG-international pediatric multiple sclerosis study group
IVG-immunoglobulin variable
IVIG-intravenous immunoglobulin
IVMP-intravenous methylprednisone
LETM-longitudinal extensive transverse myelitis
MAG-myelin associated glycoprotein
MBP-myelin basic protein
mGCPIL- macular ganglion cell layer and inner plexiform layers
MHC-major histocompatibility complex
MOGAD-myelin oligodendrocyte glycoprotein antibody-associated disease
MOG-myelin oligodendrocyte glycoprotein
MS-multiple sclerosis
NBD-Neuro Bechet disease
NMDAR-N-methyl-D-aspartate receptor encephalitis
NMO-neuromyelitis optica
NMOSD-neuromyelitis optica spectrum disorder
OCS-oral corticosteroids
OCT-optical coherence tomography
ON- optic neuritis
PF-prolonged fever

PLP-proteolipid protein

PNS- peripheral nervous system

pRNFL- peripapillary retinal nerve fiber layer

RTX-rituximab

SPECT-single photon emission computed tomography

TM-transverse myelitis

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Summary

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Myelin oligodendrocyte glycoprotein (MOG) associated disease (MOGAD) is a rare antibody-mediated inflammatory demyelinating disorder of the central nervous system (CNS) characterized by a spectrum of phenotypes including optic neuritis (ON), acute demyelinating encephalomyelitis (ADEM), transverse myelitis (TM), and cortical encephalitis. Even though the clinical manifestations of MOGAD are similar to those of neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS), the widespread use of novel cell-based assays has enabled experts to recognize MOGAD as a distinct entity with different immunological pathogenesis. MOG is primarily expressed in the CNS and is located on the outer membrane of myelin sheaths. This glycoprotein's function is not fully understood; however, it may serve as a regulator of microtubular stability, cell surface receptor, or mediator of myelin fiber adhesion. Its position on the outermost surface of oligodendrocytes makes it an accessible target for autoantibodies that cause pathological alterations. Optic neuritis appears to be the most common initial manifestation in adults, whereas ADEM is most prevalent in children. The disease can either be monophasic or relapsing, the latter associated with ON as the initial assault, older age at onset, or persistence of MOG-Immunoglobulin-G (IgG) seropositivity. Despite this, demyelinating lesions on T2 MRI frequently remit, with secondary progression rarely linked to MOGAD, in contrast to MS, which typically has clinically silent residual, relapsing-remitting, and progressive lesions on MRI. Observational open-label experience indicates a need for high-dose intravenous (IV) steroids, (IV) immunoglobulins (IVIG), and plasma exchange in conjunction or alone in treating severe acute attacks. For maintenance therapy, chronic immunosuppressive medications, including oral steroids, oral immunosuppressants, and rituximab, are appropriate. Interestingly, MOGAD patients have more favorable outcomes than those with multiple sclerosis or aquaporin-4-IgG-NMOSD (AQP4-IgG-NMOSD), yet additional incident case studies are required to optimize treatments for relapse prevention.

Keywords: MOGAD, MOG, myelin oligodendrocyte glycoprotein antibody, encephalitis, optic neuritis, multiple sclerosis.

Sažetak

Bolest povezana s mijelinskim oligodendrocitnim glikoproteinom (MOG) (MOGAD) je rijedak upalni demijelinizirajući poremećaj središnjeg živčanog sustava (SŽS) posredovan antitijelima koji je karakteriziran spektrom fenotipova uključujući optički neuritis (ON), akutni demijelinizirajući encefalomijelitis (ADEM), transverzalni mijelitis (TM), i kortikalni encefalitis. Iako su kliničke manifestacije MOGAD-a slične onima neuromijelitisa optičkog spektra (NMOSD) i multiple skleroze (MS), široko rasprostranjena uporaba novih staničnih testova omogućila je stručnjacima da prepoznaju MOGAD kao poseban entitet s različitom imunološkom patogenezom. MOG se prvenstveno izražava u CNS-u i nalazi se na vanjskoj membrani mijelinskih ovojnica. Funkcija ovog glikoproteina nije u potpunosti shvaćena; međutim, može poslužiti kao regulator stabilnosti mikrotubula, receptor na staničnoj površini ili posrednik adhezije mijelinskih vlakana. Njegov položaj na krajnjoj vanjskoj površini oligodendrocita čini ga dostupnim ciljem za autoantitijela koja uzrokuju patološke promjene. Čini se da je optički neuritis najčešća početna manifestacija u odraslih, dok je ADEM najčešći u djece. Bolest može biti monofazna ili relapsirajuća, pri čemu je potonja povezana s ON kao početnim napadom, starijom dobi na početku ili postojanošću seropozitivnosti na MOG-Imunoglobulin-G (IgG). Unatoč tome, demijelinizirajuće lezije na T2 MRI često se povuku, sa sekundarnom progresijom rijetko povezanom s MOGAD-om, za razliku od MS-a, koja obično ima klinički tihe rezidualne, relapsno-remitentne i progresivne lezije na MRI. Opservacijsko otvoreno iskustvo ukazuje na potrebu za visokom dozom intravenskih (IV) steroida, (IV) imunoglobulina (IVIG) i/ili izmjenom plazme u liječenju teških akutnih napada. Za terapiju održavanja prikladni su kronični imunosupresivni lijekovi, uključujući oralne steroide, oralne imunosupresive i rituksimab. Zanimljivo je da pacijenti s MOGAD-om imaju povoljnije ishode od onih s multiplom sklerozom ili akvaporin-4-IgG-NMOSD (AQP4-IgG-NMOSD), no potrebne su dodatne studije slučaja kako bi se optimizirali tretmani za prevenciju recidiva.

Ključne riječi: MOGAD, MOG, mijelinsko oligodendrocitno glikoproteinsko protutijelo, encefalitis, optički neuritis, multipla skleroza.

1. Introduction

Myelin oligodendrocyte glycoprotein (MOG), a surface protein on oligodendrocytes, was initially thought to be a possible antibody target in MS(1); however, early investigations were equivocal. Using immunoblot and enzyme-linked immunosorbent assay, anti-MOG-antibodies were identified in a subset of patients with ADEM but only rarely in adult patients with multiple sclerosis(2). Later, newer generation of cell-based assays were developed and further identified MOG-Abs in adults and in children with ADEM, anti- aquaporin-4-antibody (AQP4-Ab)-seronegative NMOSD, optic neuritis, transverse myelitis, and other associated conditions. Thus, myelin oligodendrocyte-associated disease has been confirmed as a separate demyelinating disease of the central nervous system(3). This article examines MOGAD's epidemiology, pathogenesis, clinical signs and symptoms, diagnosis, therapy, and prognosis.

2. Pathogenesis

2.1. MOG structure and function

The myelin sheath surrounds large axons in the central nervous system and the peripheral nervous system (PNS) to allow rapid conduction of action potential. In the CNS, the myelin-forming cells are the oligodendrocytes, and the extension of their plasma membrane (oligodendrocyte processes) serves as the insulator sheath(4). The myelin oligodendrocyte glycoprotein is located on the outermost layer of the oligodendrocyte processes. Other proteins expressed by oligodendrocytes include the myelin basic protein (MBP), proteolipid protein (PLP), and myelin-associated glycoprotein (MAG). The interaction between these glycoproteins serves a role in forming and maintaining the myelin's structural integrity. (5,6)

MOG is a minor component of the myelin sheath and yet is thought to have several important functions, such as regulating oligodendrocyte microtubule stability and maintaining the myelin sheath's structural integrity via adhesion features, and mediating interactions between myelin and the immune system (7). In several experimental studies, significant loss of MBP was noted in the presence of anti-MOG antibodies, whereas antibodies to other myelin components, such as MBP and MAG, were ineffective in causing such MBP degradation. MOG and MAG are glycosylated with Human Natural Killer-1 (HNK-1) epitopes in oligodendrocytes(8). These epitopes on nerve cells play an essential role in myelin's structure and function as they are linked to cell migration, neuron-to-glial cell contact, and astrocytic process outgrowth (9). Therefore, the idea that MOG is involved in adhesion between adjacent myelin fibers becomes more acceptable.

Expressed only in mammals, MOG is composed of a signal peptide of 29 amino acids followed by 218 amino acids of the mature protein(10). As an Immunoglobulin superfamily member, it is highly immunogenic(7). It consists of an extracellular immunoglobulin variable (IgV) domain, transmembrane hydrophobic domain, cytoplasmic loop, and a second hydrophobic domain near the membrane, followed by a cytoplasmic end. The outermost location on the myelin sheath and the extracellular component makes MOG an accessible target for potential antibodies, resulting in demyelination (11).

MOG's role in the pathogenesis of demyelinating disorders can be supported because the MOG gene is located on the major histocompatibility complex (MHC) locus. This region encodes molecules expressed on cells involved in antigen presentation, inflammation activation, and innate and adaptive immunity initiation(10). Moreover, the gene shares structural similarities with the B7-CD28 superfamily, which encodes for proteins found on the surface of professional antigen-presenting cells (APC). This further supports that MOG has an immunogenic role in demyelinating processes(12).

2.2. MOG antibody

Human's MOG-IgG potential pathogenic activity was supported before by in vitro experiments: antibodies to MOG are typically of IgG1 isotypes, proven to promote complement-mediated cellular death(13,14). Notably, circulating MOG antibodies alone do not promote inflammation and neurodegeneration in normal animals(15). However, in animal models, antibodies obtained from anti-MOG NMO may elicit inflammatory demyelination in vivo or in vitro after direct injection into the cerebrospinal fluid (CSF) or brain tissue of mice with T-cell mediated autoimmune encephalomyelitis(16,17). In vivo, MOG antibodies reach the central nervous system (CNS) in the setting of inflammation, as the blood-brain barrier breaks down, allowing their passage to the CNS.(15,18,19).

2.3. Pathology

The pathogenesis of MOGAD has been illuminated by autopsies and biopsies obtained from confirmed disease cases(20,21). According to these studies, MOGAD pathology is characterized by the coexistence of perivenous and confluent demyelination in the white and grey matter, with a higher incidence of intracortical demyelinating lesions. Inflammation is characterized by CD4-positive T cells and granulocytic infiltration, unlike MS, which predominantly consists of CD8-positive T cell inflammation.

A perivascular pattern of complement deposition is also noted in MOGAD cases, which differs from AQP4-IgG-NMOSD, where complement deposits colonize astrocytes of the glia limitans where AQP4 is expressed(20). The astrocytic damage is a distinctive feature

of AQP4-IgG-NMOSD, as AQP4 expression is mainly preserved in MOGAD patients. Although the selective loss of MOG is expected, only one case to date demonstrated such findings(21). Therefore, it is hypothesized that upon anti-MOG antibody binding to the MOG epitope, the whole myelin is destroyed either by complement or antibody-dependent cellular cytotoxicity (ADCC) phagocytosis. For selective loss of MOG antigen to occur, binding of MOG antibody would have to induce endocytic internalization of MOG antigen into the cell(20). In seropositive NMOSD, AQP4-IgG targets the AQP4-antigen primarily by this mechanism(22).

3. Epidemiology

MOGAD has only recently been recognized as a distinct clinical entity from other autoimmune demyelinating disorders, so epidemiological data are limited.

According to a study in the Netherlands, with collected samples between 2014 and 2017, MOGAD incidence was 1.6 per million person-years(23). In the UK, a study concluded an incidence of 3.4 per million person-years(24). When compared to AQP4-IgG NMOSD, the frequency of MOGAD varies by region. MOGAD is more common in Sri Lanka and the United Kingdom(23–25), whereas AQP4-IgG NMOSD appears more prevalent in Korea (26). Additionally, compared to higher cases reported among East Asians and Africans and a strong association with HLA observed in AQP4-IgG-NMOSD(27), MOGAD showed no ethnic tendency or HLA association(28).

Female predominance is typical in autoimmune diseases. Indeed in both MS and NMOSD, the ratio between females and males is 1.4:1 to 2.3:1 and 9:1, respectively (27,29). However, no significant sex differences were noted with anti-MOG-positive patients (24).

MOGAD has a variable onset age between 20 and 30, with the highest prevalence among children. A study in Israel examined how the age of onset affects the disease's course. They reported that early-onset MOGAD (<18 years) and late-onset MOGAD (>50 years) both had a monophasic course (14/20 and 3/3, respectively), while most young adults (64 % of patients aged 30–40 years) had a recurrent disease (30).

4. Clinical features

The autoimmune response to MOG results in nonspecific clinical features that overlap with those seen in MS and NMOSD. The most commonly observed are acute attacks of optic neuritis, acute disseminated encephalomyelitis, and transverse myelitis (30–32). The

attacks can be preceded by an infectious illness or vaccination and usually develop over days with varying recovery times(33,34) and subsequently can be either monophasic or relapsing, depending on the symptom and the onset of age(30). As we delve deeper into each clinical sign and symptom, distinct entities that are MOGAD-related emerge.

4.1. Optic neuritis

Inflammation of the optic nerve and its covering (ON) is the most common presenting symptom in adults with anti-MOG antibodies(32). The acute attack typically manifests bilaterally with significant visual impairment and eye pain, especially with movement(35). Caution is advised when examining a child because the inflammation is usually unilateral and can be misinterpreted as a nonspecific headache(36). Optic neuritis manifests similarly in other demyelinating disorders; however, apparent differences remain from MS and AQP4-IgG-NMOSD, suggesting MOGAD is a separate diagnosis. Using the expanded disability status scale (EDSS) score, one study demonstrates that visual impairment is more severe than MS or NMOSD but has favourable outcomes when revaluated after a follow-up period. Compared to AQP4-antibody-positive patients, the EDSS scores of MOGAD patients decreased significantly(37).

Fundoscopy may detect more prevalent unilateral or bilateral optic disc edema than in MS but similarly to bilateral involvement as seen in AQP4-IgG NMOSD . When bilateral, it may be confused with papilledema caused by increased intracranial pressure (35). Despite this, an MRI is sufficient for exclusion and will typically reveal anterior and longitudinal inflammation of the optic nerve(37,38). According to some studies, those with optic neuritis as their initial symptom are more likely to develop a relapsing form of the disease with a higher recurrence rate(16,32). As the primary treatment, an inadequate corticosteroid treatment cycle(≤3 months) can also increase the likelihood of relapse(32). As the patient develops recurrent episodes of optic neuritis, chronic relapsing inflammatory optic neuropathy (CRION) is diagnosed(39,40).

4.2. ADEM

Acute disseminated encephalomyelitis is an immune-mediated demyelinating disease that predominantly affects children and young adults. In ADEM-diagnosed children, up to 68% develop antibodies to MOG, making it the most common initial presentation (41). Ataxia, dysarthria, seizures, altered sensorium, and behavioural abnormalities, including confusion and agitation, are just a few of the symptoms that can appear suddenly, corresponding to the affected area of the central nervous system. According to the International Paediatric Multiple Sclerosis Study Group (IPMSSG), ADEM is diagnosed if the following criteria are met: first clinical CNS event with the suspected demyelinating

origin, encephalopathy that cannot be explained by fever or systemic illness, and abnormal brain MRI during the acute phase that is compatible with ADEM but not indicative of any other CNS disease (42). In ADEM, lesions are large, poorly demarcated, and bilaterally distributed which differ from MS, where lesions are typically smaller, well-demarcated, and predominantly localized periventricularly in the white matter supra and infratentorial but also cortically and subcortically especially in the corpus callosum (43,44). While most develop a monophasic course of the disease, a small group of patients experience repeated ADEM attacks and are diagnosed with multiphasic ADEM. López-Chiriboga et al. investigated the relationship between such relapse and persistent MOG-IgG. Recurrence was observed in 88% of patients with constant MOG-IgG positivity, whereas only one of eight patients with transiently positive antibodies had the same outcome (44).

Another study compared paediatric patients' clinical presentation and prognosis of acquired demyelinating syndromes associated with MOG antibodies to those without anti-MOG antibodies. Results demonstrated no clinical symptoms, gender ratio, or age changes, except for a greater white blood cell count in cerebrospinal fluid (CSF) and behavioural issues at initial presentation in anti-MOG-positive patients (45).
When evaluating the MRI data, both groups of patients exhibited large bilateral lesions; however, the spinal cord was more commonly affected in children with MOG antibodies, with lesions extending longitudinally in more than three segments, a condition known as longitudinal extensive transverse myelitis (LETM) (45). Cobo-Calvo's study produced similar results, demonstrating that thalamic and brainstem involvement are distinct signs of MOGAD (46). Worthy of note is that, in most children with MOGAD, the MRI alterations disappeared during a follow-up MRI examinations, and patients included in treatment protocol for MOGAD experienced improved clinical outcomes(37,47). Resolution and rapid recovery typical for MOGAD are related to the fact that MOG is expressed on mature oligodendrocytes rather than on progenitor cells; hence rapid recruitment of new oligodendrocytes ensues. Nonetheless, several studies indicate that the resolution of a lesion on an MRI does not necessarily mean a favourable prognosis, as up to forty percent of patients demonstrated long-term cognitive impairment (32). Additionally, one study revealed that children who tested positive for MOG-IgG were more likely than their non-MOG-IgG counterparts to develop post-disease epilepsy(48).

4.3. Transverse myelitis

Transverse myelitis is an acute inflammation of the spinal cord parenchyma that causes motor, sensory, and autonomic impairment(49). TM is a common presenting sign in adult

MOGAD patients, and it can occur alone or in conjunction with ADEM or optic neuritis(50–52). The inflammatory condition is characterized by extensive longitudinal demyelination located centrally and encompassing more than three contiguous segments, with the most frequently affected cervical and thoracic spinal cords(53). MS, on the other hand, affects fewer than three segments, with lesions typically located posteriorly. Classic symptoms are partial or complete lower extremity paralysis with hypoesthesia below the lesion site and across the sensory level of the torso(54). In most cases, involvement of the medullary conus occurs, which causes urinary, bowel, and erectile dysfunction. In some instances, demyelination affecting the posterior part of the medulla and cervical cord is suspected if flexion of the neck elicits an electrical sensation spreading to the extremities, a phenomenon known as the Lhermitte(50,51).

4.4. AQP4 seronegative NMOSD

The clinical criteria for NMOSD include an episode of optic neuritis, transverse myelitis, or area postrema syndrome; and a second episode of one of the conditions mentioned or a brainstem, diencephalic, or other cerebral syndromes (55). Even with the most sensitive assays, AQP4-IgG is not detected in about 25% of patients who met the criteria for NMOSD. Given that neuromyelitis optica spectrum disorder is rarely associated with false negatives, it is likely that a different disease with overlapping clinical symptoms is the cause of such findings(56). In fact, 15 to 40 percent of AQP4-IgG-NMOSD-seronegative patients had MOG-IgG(57–60). These represent only about a third of the entire MOGAD population, underlining the need for MOGAD-specific diagnostic criteria.

4.5. Cerebral cortical encephalitis

Ogawa first reported a new anti-MOG phenotype known as cerebral cortical encephalitis in 2017(61). Since then, 21 cases have been reported, manifesting with cortical inflammation and seizure attacks. According to Wang's review, most affected patients were males (72.6%) with an onset of age averaging 26.8 years. Symptoms include fever, headache, hemiparesis, hemianopsia, aphasia, memory deficits, and psychiatric problems. Cortical inflammation was primarily unilateral and associated with swelling and hyperintense lesions on the MRI FLAIR sequence without white matter involvement. Some have referred to these occurrences as "unilateral cortical fluid-attenuated inversion recovery (FLAIR)-hyperintense lesions in anti-MOG-associated encephalitis with seizures" with the abbreviation FLAMES(62). Following treatment with corticosteroids, all patients fully recovered, and no unprovoked seizure attacks were observed (63).

4.6. Brainstem and cerebellar lesions

One-third of MOGAD patients exhibit brainstem and cerebellar demyelination(34,64). Unlike MS, single brainstem attacks are uncommon in MOGAD and typically manifest with transverse myelitis, ADEM, or optic neuritis demyelinating lesions. While some patients can have no symptoms, most develop ataxia and diplopia, occasionally preceded by viral prodromes. It is essential to distinguish between lesions occurring in MS, AQP4-IgG-NMOSD, and MOGAD since treatment and prognosis differ significantly. Compared to MOGAD, AQP4-IgG-NMOSD typically manifests with nausea, vomiting, and hiccups due to the involvement of area postrema (34).

4.7. Other clinical features

Given the likelihood of false-positive MOG-IgG results, particularly at low titers, it is prudent not to attribute unexpected clinical characteristics to MOGAD. However, specific MOG detection cell-based assays have expanded the clinical spectrum and include many atypical presentations. The following conditions were related to sufficiently high titers of MOG-IgG and occurring with the previously described manifestations:

- **Prolonged fever** – Although fever is not an uncommon sign in MOGAD patients, it is usually short-lived and precedes ADEM diagnosis by a few days. A recent study suggests that even prolonged fever lasting over two weeks can be an initial presentation of anti-MOG disease (65). The study included 12 cases, subdivided according to initial diagnosis as prolonged fever (PF) of unknown origin, aseptic meningitis, and PF in already diagnosed patients. Several cases developed ON or ADEM, and MOGAD diagnoses were established. Other papers report cases of aseptic meningitis with brain imaging revealing aberrant lesions in several locations. In the majority, headache, fever, and optic neuritis were among the most common early symptoms, with some preceding influenza-like clinical picture. A further investigation detected elevated MOG-IgG serum levels(66–68).
- **Peripheral nervous system involvement-** One study has demonstrated the association between MOGAD and peripheral neuropathy:19 of 271 MOGAD patients had PNS lesions, most frequently paresthesia and radicular pain, as well as polyneuropathy,myeloradiculitis, multifocal motor neuropathy, brachial neuritis and migrant sensory neuritis(69). Another study described an anti-MOG-positive patient who presented with peripheral neuropathy and numerous spinal and cerebral lesions (70). However, even after treatment, the patient experienced recurrence on multiple occasions, identical to chronic inflammatory demyelinating peripheral neuropathy (CIDP), and showed consistent positivity for

MOG-IgG on follow-up (70). Nonetheless, before assigning MOGAD a PNS phenotype, careful consideration is needed as further research should be conducted to determine whether this clinical manifestation is directly linked to MOG-IgG or another inflammatory etiology.

- **Anti-N-methyl-D-aspartate-receptor encephalitis**- anti-NMDAR-encephalitis is a frequent clinical manifestation in MOGAD patients. Several cases of anti-NMDAR encephalitis coexisting with anti-MOG antibodies have surfaced recently (71–75). Patients initially presented with headaches, fever, seizures, and cognitive impairment in two instances and tested positive for MOG-IgG(73,75). Those who showed double positivity for MOG-IgG and anti-NMDAR antibodies had an increased risk of developing leptomeningeal enhancement in addition to seizures and encephalopathy (71,74).
- **'Leukodystrophy-like' phenotype-** In a retrospective analysis of data collected from 31 pediatric patients, seven patients exhibited confluent and bilateral white matter abnormalities on MRI, resembling the demyelinating pattern of leukodystrophy diseases. Although all seven patients responded well to steroid treatment, four had a relapsing disease. The overall outcome was worse with this 'leukodystrophy-like' phenotype compared to children with other phenotypes, as demonstrated on follow-up examination, revealing persistent cognitive and behavioral issues and ongoing seizures(76). In a separate study, two patients presented with a progressive disease course, an unusual occurrence for MOGAD. MRI results revealed 'leukodystrophy-like' lesions with bilateral white matter involvement (77).

4.8. Overlapping syndromes

The discovery of MOG-IgG in other syndromes has raised the question of whether MOG also plays a role in non-demyelinating diseases. Unlike AQP4-IgG-NMOSD, for which a link with malignancies such as breast and lung cancer has been established (78), the incidence of MOGAD as a paraneoplastic disease is less well understood. One incidence of ovarian teratoma followed by MOG-IgG-positive optic neuritis has been described (79). The patient, identified with a right cystic mature teratoma, had the entire tumor excised. With high levels of MOG-IgG, optic neuritis of the left eye manifested eleven months after tumor resection and was preceded by viral infection. The relationship between the teratoma and the positive MOG-IgG has been substantiated because the teratoma expressed MOG-positive neuroectodermal tissue, and the MOG-IgG level fell considerably after excision and corticosteroid

therapy(79). Separate cohort studies found two other cases of ovarian teratomas with increased anti-MOG antibodies (64,80,81).

According to other research, two Japanese patients were diagnosed with the anti-MOG antibody-associated disease, meeting the criteria for Neuro- Behcet-Disease (NBD). Both cases presented with recurrent oral ulceration, with one patient developing acneiform nodules and the other with superficial thrombophlebitis (82). Additionally, the coexistence of MOGAD with other autoimmune disorders, such as systemic lupus erythematosus and, more recently, ankylosing spondylitis, have been reported(83,84). A possible connection between TNFα inhibitors and initiation of the demyelinating process is suggested; however, further studies are required to support this relationship (84).

4.9. Association with COVID-19

Since the beginning of the COVID-19 pandemic, multiple cases of neurological complications following SARS-CoV2 infection have been recorded. One patient was diagnosed with bilateral optic neuritis two weeks after a confirmed COVID-19 infection. The patient presented with bilateral eye pain and visual loss, and additional assessment revealed that his serum contained elevated levels of MOG-IgG. Methylprednisolone was administered, and consequently, the symptoms improved (85). A different patient with persistent headaches was eventually confirmed with MOG-positive encephalitis developing after COVID-19 infection(86). These data suggest a relationship between COVID-19-induced inflammation and a short-lived secondary autoimmune reaction characterized by transient MOG antibodies.

5. Evaluation and diagnosis

5.1. When to screen for MOGAD

The overlap in clinical and radiological manifestations between MOGAD, MS, and AQP4-IgG-NMOSD necessitates the presence of a MOG antibody for diagnosis. However, examining every patient with optic neuritis will increase the likelihood of false-positive results and overdiagnosis. Considering the diversity in treatment options and the fact that some can be harmful if not appropriate for the disease, this becomes a problem rather than a solution. Therefore, guidelines and recommendations for testing MOG-IgG were established by several studies and are summarized as follows(54,87):

- Acute disseminated encephalomyelitis (ADEM) or Multiphasic ADEM (MDEM) with brain MRI findings of significant, extensive T2 hyperintense lesions.

- Optic neuritis that is bilateral, recurrent with severe vision loss at attack or after, affecting the anterior optic pathway and presenting with optic disc swelling.
- Involvement of the conus medullaris at onset, with urinary, bowel, and erectile dysfunction symptoms persisting after therapy.
- Cortical encephalitis that is unilateral or bilateral with T2 hyperintense demyelination and swelling.

5.2. Diagnostic criteria

The following diagnostic criteria for MOG antibody-associated disease were suggested by mayo clinic, Department of Neurology (44):

- Seropositivity for MOG-IgG by cell-based-assay
- Any of the following clinical manifestations:
  1. ADEM
  2. Optic neuritis or CRION
  3. Transverse myelitis
  4. Brain or brainstem involvement associated with MRI finding of demyelination.
  5. Any combination of the above
- Exclusion of alternative diagnosis

5.3. Investigation methods

Once MOGAD is considered, the following investigation methods are applied to determine the full clinical and radiological status of the patients:

- Cell-based assay for MOG autoantibody detection
- Cerebrospinal fluid evaluation
- MRI of the orbits, brain, and spinal cord, with or without gadolinium enhancement.
- Optic coherence tomography

5.3.1 Cell-based assay

The gold standard for diagnosing MOGAD is testing for MOG-IgG using a cell-based assay(88). The use of full-length human MOG expressed on human embryonic kidney cells (HEK293) as the target antigen improves the accuracy of test results(2). Sampling for patients' serum instead of CSF is favourable as MOG-IgG levels are low in the latter. Samples are then diluted to determine the titer of positivity, and the most significant dilution achieved is recorded. For most tests, the threshold for a positive result is a titer of 1:20 (89); however, this threshold is associated with a greater likelihood of false-positive results(89). The sampling timing is also crucial, as the highest levels are detected during

acute attacks, and the lowest are observed during remission, chronic phase, or following treatment(34). Therefore, repeated testing during acute episodes and treatment-free phases are reasonable and advisable when a patient's MOG-IgG result is negative, but clinical and radiological presentation strongly implies MOGAD as the diagnosis (87). MOG-IgG can also be detected by immunohistochemistry, ELISA, or western blotting, but these procedures aren't recommended due to their limited specificity for detecting the antibody(90). A cell-based assay's specificity ranges between 97.8 and 100 percent(89,91). The positive predictive value seems more variable and depends on disease prevalence in the population, and the titers considered. It can range from 72% to 94%; hence testing for this rare disease in low-likelihood settings should be avoided to prevent misdiagnosis(89).

5.3.2 Cerebrospinal fluid analysis

Approximately fifty percent of MOGAD patients exhibit CSF pleocytosis dominated by lymphocytes and monocytes. Pleocytosis is more prevalent in acute attacks than between bouts(92,93). Additionally, the location and clinical presentation influence the degree of pleocytosis; in ADEM-anti MOG patients, pleocytosis can reach 75 percent, whereas, in MOGAD patients presenting with ON, pleocytosis is lower, reaching about 25 percent(46).

Moreover, the presence of oligoclonal bands should be examined when the clinical presentation is ambiguous. This CSF result is most consistent with a diagnosis of MS, as 88 percent of MS patients express it (94). Compared to MOGAD patients, oligoclonal bands are seen in 5 percent to 20 percent and are infrequent in those with an ON phenotype(92,93,95).

Also, up to fifty percent of patients may have high CSF protein levels, indicating a viral infection as an alternate diagnosis(95).

5.3.3 MRI findings

- **MRI of the orbits**-Optic neuritis is the most common presentation of MOGAD in adults; hence, a focused orbital examination is more valuable than a generalized brain MRI for ON diagnosis. On MRI T2 weighted image, the extensive and swollen optic nerve is observed (96). The nerve enhancement is extensive and longitudinal, encompassing more than fifty percent of the nerve's length (97). It predominantly affects the anterior optic pathway and can extend to the fundus, which results in optic disc edema (97). Chiasmatic or retro-chiasmatic involvement is infrequent compared to AQP4-IgG-NMOSD, where it is a common

feature (96,97). Interestingly, isolated optic nerve sheath enhancement can be detected and may extend to the surrounding fatty tissue, which is rare in MS and AQP4-IgG-NMOSD (35,98). Compared to MS, where lesions are unilateral and limited in extent (97,99), optic neuritis in MOGAD shows bilateral enhancement in 25 to 50 percent of cases (32,38,97,100,101).

- **MRI of the brain-** Magnetic resonance imaging of MOGAD patients reveals both supratentorial and infratentorial abnormalities on T2 weighted images. Patients with ADEM phenotype display large and poorly demarcated ('fluffy') cortical or subcortical T2 hyperintense lesions of the white matter (44). Grey matter involvement is also known, particularly in the thalamus and basal ganglia, which overlaps with AQP4-IgG-NMOSD but is unusual in MS(43,44,102). As indicated on single-photon emission computed tomography (SPECT) scans, those with a cerebral cortical encephalitis phenotype had unilateral or bilateral cortical swelling and hyper-perfusion, as shown on single-photon emission computed tomography (SPECT) scans(61,103). When using gadolinium contrast, leptomeningeal enhancement appears to be a unique feature in individuals with MOGAD and is more common in children than adults (46,104). Other lesions tend to be patchy and more significant in enhancement than MS, with well-defined smaller lesions. In addition, lesions in the peduncles of the cerebellum are a common infratentorial abnormality seen in both MOGAD and MS patients (34,64,105). The small, well-defined lesions seen in MS patients, on the other hand, serve to distinguish them from MOGAD lesions, which are more extensive with hazy borders. Diffuse T2 hyperintense lesions in the brainstem are another noteworthy result, accounting for 20% of infratentorial abnormalities. They can affect the medulla, pons, or midbrain and, predictably, manifest as a pattern of large, poorly defined lesions similar to those seen in other parts of the brain(34). However, after treatment, lesions resolved in most patients, regardless of the affected area (37,47,97).
- **MRI of the spinal cord-** On sagittal MRI, a common finding in MOGAD patients is T2 hyperintense lesions of three or more vertebral segments, also known as longitudinally extensive transverse myelitis (LETM). Short lesions involving two vertebral segments or fewer are reported less frequently and may imply MS as the cause (51,52,81,106). Whether short or longitudinal, lesions are typically central, involving grey and white matter, and may be accompanied by cord swelling (37,51). Yet, some patients demonstrate sagittal linear hyperintensity and "H"-shaped hyperintensity on axial sequences, reflecting isolated grey matter involvement (106). This unique MRI feature can be helpful, as the same study

reports occurrence in 28% of MOGAD patients, 8% in AQP4-IgG-NMOSD, and an absence in MS patients (106). Interestingly, involvement of the lumbosacral area is more common in MOGAD patients than in MS or AQP4-IgG-NMOSD patients and is more frequently associated with persistent bladder dysfunction among MOGAD patients (37,51,106). Of particular importance, when leptomeningeal enhancement spreads to the nerve roots of the cauda equina and is associated with lower motor neuron signs, acute flaccid myelitis must be ruled out (69).

5.3.4 Optical coherence tomography (OCT)

OCT is a noninvasive imaging technology that creates retinal cross-sectional images using low-coherent light (107). It is imperative when evaluating optic neuritis in individuals with MOGAD, as the condition often affects the anterior optic pathway. The thickness of the combined macular ganglion cell layer and inner plexiform layers (mGCPIL), as well as the peripapillary retinal nerve fiber layer (pRNFL), are used to quantify the extent of retinal loss (108). OCT reveals pRNFL thickening at presentation, consisting of the common bilateral optic disc edema (109,110). In months to follow, both pRNFL and mGCPIL become thinner, although thinning of the latter is already prominent in the first few weeks (107,111). The single attacks in MOGAD patients do not result in severe damage but rather the cumulative changes that subsequently result in optical atrophy (109–111); therefore, MOGAD patients who experience recurring episodes should be evaluated and treated promptly to minimize the damage. Of important note, when comparing the visual outcomes, MOGAD patients show better visual acuity results than those with AQP4-IgG-NMOSD but are otherwise comparable to MS patients(109,110,112).

6. Differential diagnosis

In adults and children, an event of CNS demyelination can represent one of many neuroinflammatory disorders, including AQP4-IgG-NMOSD, multiple sclerosis, and MOGAD. Distinguishing MOGAD from AQP4-IgG-NMOSD is relatively easy since both have reliable antibody biomarkers, and concurrent positivity is rare (57,87). However, it is more challenging to identify MOGAD from MS, mainly due to high false positives in low titers with MOGAD and the lack of distinctive antibody biomarkers in multiple sclerosis. Nevertheless, some clinical and radiological findings may help identify MOGAD from MS; for example, the absence of oligoclonal bands is predictable with anti-MOG positives but unlikely in MS patients as this is a common CSF finding (92,113). Additionally, abnormal residual T2 findings on MRI are more suggestive of MS since most lesions tend to

resolve over time in MOGAD patients (38,114), and rarely do MOGAD patients exhibit secondary progressive disease (115). Finally, as several MS therapeutic approaches are ineffective against MOGAD, these findings are especially noteworthy for patients with the recurring disease.

Jarius recognizes other findings that should encourage clinicians to reassess the diagnosis of MOGAD (87). They include sudden onset of symptoms that reaches maximum deficit in less than 4 hours (consider ischemic event) or symptoms worsening over weeks (consider progressive MS, tumor, sarcoidosis); lesion that is round and adjacent to lateral ventricle (Dawson finger-like periventricular lesion on MRI); dual positivity for AQP4 and MOG-IgG (rare occurrence and should indicate re-testing of both); And predominant involvement of peripheral nervous system (as MOG is mostly in CNS).

As MOGAD can affect many regions of the CNS, the clinical picture is typically diverse, with optic nerves, brain, and spinal cord involved solely or in combination. Thus, the list of possible alternative diagnoses extends to neuroborreliosis, neurotuberculosis, neurosyphilis; systemic lupus erythematosus; Behcet disease; anti-n methyl-D-aspartate encephalitis (can coexist with MOGAD); gliomatosis cerebri; posterior reversible encephalopathy syndrome and others (75,87). Notably, acute flaccid myelitis (AFM) should be considered in children with motor weakness and rapidly worsening myelitis (116). Typically, MRI reveals prominent T2 hyperintensity in the grey matter, which coincides with lower motor signs at presentation. Other characteristics comparable to MOGAD include LETM on MRI with a history of viral infection preceding the onset of neurological symptoms. Specifically, a history of prior CNS inflammation and a clinical course of more than ten days is more indicative of MOGAD than AFM (116).

7. Treatment

MOGAD is a relatively new syndrome with heterogeneous clinical manifestations and low population prevalence. Due to these restrictions, no large multicentre treatment trials have been performed to date, and therapeutic regimens tend to resemble those of AQP4-IgG-NMOSD. Thus, the primary objective is to initiate treatment as soon as possible and identify those with a higher risk of relapse so that preventative measures can be taken.

7.1. Acute attacks

initial treatment with high-dose intravenous methylprednisolone (IVMP) is recommended as most patients show excellent response with rapid resolution of symptoms (117). IVMP

is dosed at 1000 mg in adults or 20-30mg/kg/day in children for five consecutive days (118). Alternatively, oral prednisone at 1250 mg once daily can be considered in adults (118). Some studies report nearly complete recovery in over 50% of patients after administration of IVMP (81), and even more specifically in patients presenting with brainstem and cereal cortical encephalitis as their initial attack (74). However, rapid reduction in glucocorticoid treatment is associated with an increased relapse rate, and slow tapering is advised (100,117).

Plasma exchange is suggested in patients with more severe attacks or if unresponsive to initial IVMP. It is administered as one exchange every other day for up to seven cycles in total. In children, intravenous immunoglobulin (IVIG) is the treatment of choice as second-line, given at a dose of 2 grams per kilogram over 2 to 5 days (119).

7.2. Attack prevention

Unlike multiple sclerosis, attack-related disability in MOGAD patients is relapse-dependent (117), stressing the need for effective preventive intervention in patients at risk of relapse. Some experts agree that persistent MOG-IgG positivity is a reliable predictor of relapse risk (46), while others contend that such a judgment should be based on a comprehensive clinical picture (117). Standard immunomodulating medications or immunosuppressants, such as oral corticosteroids (OCS), repeated rounds of intravenous immunoglobulin (IVIG), azathioprine (AZA), rituximab (RTX), mycophenolate mofetil (MMF) and tocilizumab, are available as therapeutic options (100,117,118). Once again, there are no randomized controlled trials for preventive therapy in MOGAD, and therapeutic strategies are established from knowledge of treatment efficacy in other CNS autoimmune diseases.

- **Oral immunosuppressants**- AZA and MMF are commonly used oral immunosuppressants for MOGAD patients. They suppress immune system activity by interfering with B and T cell proliferation through different mechanisms (120,121). In retrospective observational data, relapse rates were reduced in patients treated with either AZA or MMF, but still, up to 50% of patients relapsed (64,100,122–125). In addition, the use of azathioprine or mycophenolate mofetil was proven to decrease the dosage of corticosteroids and their side effects, as demonstrated in studies of other autoimmune diseases (126). Also, when combined with prednisone, better results were achieved, as they can prevent early relapse until immunosuppressants take effect (118).
- **Azathioprine**- AZA is a prodrug that belongs to the thiopurines drug class. Nonenzymatically, it is transformed into 6-mercaptopurine, which is then

metabolized into active and non-active compounds by different enzymes. Incorporating the active metabolites (thioguanine nucleotides) in the DNA of lymphocytes interfere with their proliferation and subsequently results in immunosuppression. Thiopurine-s- methyltransferase enzyme activity generates inactive metabolites, and its deficit can push the reaction towards the HPRT pathway, resulting in adverse side effects. Thus, testing for TPMT enzyme levels is required in all patients before starting treatment to adjust dosing or switch to an alternative drug (120,127).

In patients with regular TPMT activity, the typical dose is between 2 and 2.5 mg per kg given orally as a single or divided dose (127). Regular monitoring of complete blood count (CBC) and liver and kidney function is recommended before and after therapy as toxicity is associated with elevated liver enzymes and kidney damage (118). Other adverse effects include rashes, infections, cytopenia, and hypersensitivity and rarely can increase the risk for malignancies (skin or lymphoma) (120,127).

- **Mycophenolate mofetil-** MMF is a prodrug of mycophenolic acid with a potent immunosuppressive effect. It is classified as a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH)**,** an enzyme involved in the de novo synthesis of guanine nucleotides. It thus interferes with B and T cell proliferation (121,128). In the first two weeks, the dose in adults is 500 mg per oral, twice daily, and subsequently reaches a maintenance dose of 1000 mg twice daily. In children, the dose is 650 mg per body surface area (118).

  Like azathioprine, regular CBC and liver and kidney monitoring are recommended before and after therapy. Adverse effects are primarily associated with gastrointestinal disorders ranging from mild diarrhea and abdominal pain to more severe conditions like gastrointestinal bleeding and perforation (129).

- **Prednisone-** Prednisone is a synthetic glucocorticoid that mediates anti-inflammatory and immunosuppressive effects (130). Initial doses of up to 1mg/kg per day (118), followed by a slow taper, are a common and convenient strategy for acute attack prevention in MOGAD patients. However, its prolonged use as maintenance therapy is restricted due to the vast adverse effects (100,122,123). Examples include increased risk of infections, delayed wound healing, skin fragility, mood changes, cushingoid appearance, edema, adrenal suppression, and osteoporosis (131). Vitamin D and calcium supplements are advised to decrease the risk for osteoporosis, together with antibiotics as prophylaxis for infections (118).

- **Intravenous immunoglobulin therapy**- the effectiveness of IVIG infusions as maintenance therapy in MOGAD patients was promising by multiple studies (100,122,132). Recent research compared relapse rates of IVIG with other medications and demonstrated favorable treatment response among this group with the lowest relapse rates of 20%. On the contrary, annualized relapse rates with RTX, AZA, and MMF exceeded 50% (123). The lack of immunosuppressive effect associated with increased risk of infection is another advantage IVIG has over the other medications (133). However, limitations on usage arise partly due to its high cost and other side effects that can harm a subset of patients. The risk of renal failure is particularly concerning as IVIG increases the risk for thromboembolic events (133). Also, an allergic response could rise in IgA deficient patients if IgA levels are not checked before administration and adjusted to IgA depleted infusions.

  Cycles of IVIG are administered over one to five days, once a month, with a dose ranging between 1 to 2 g/kg (118). Subcutaneous application of immunoglobulin therapy is feasible and enables treatment maintenance at home. They are particularly beneficial in children due to the difficulty of IV access, however, its usage in MOGAD patients has not been thoroughly investigated (134,135).

- **Rituximab-** RTX is a monoclonal antibody that depletes B cells by targeting CD20 on B cells (136). The effectiveness of rituximab as preventive therapy is inconsistent. Several studies suggest a reduction in the annualized risk of relapse, while others report comparable results to AQP4-IgG-NMOSD patients, namely the occurrence of new attacks within a few weeks of the initial infusion (41,100,122–124,137,138). Nonetheless, due to the risk of secondary hypogammaglobulinemia after treatment, CBC and specifically IgA, IgG levels should be monitored as well as CD19 and CD20 due to RTX-induced depletion of both (139–141).

- **Tocilizumab-** tocilizumab is a monoclonal antibody that targets interleukin 6, which is necessary for B-cell maturation and antibody production (142). Effectiveness in lowering relapse rates is somewhat less than that observed for RTX (143). Adverse effects such as cytopenia and risk for infections necessitate regular monitoring of complete blood counts, with attention to the liver function test (118).

8. Prognosis

MOGAD has a variable clinical presentation, with either a monophasic or multiphasic pattern. More recent data indicate that recurrent attacks are common among MOGAD patients, especially if presenting with optic neuritis as their initial episode(16,32). Other investigations revealed that MOG-IgG positivity's persistence could predict relapsing disease compared to patients with transient positivity (44,122,144). However, it is still controversial whether serial testing for MOG antibodies should be utilized in practice to support such a claim. Generally, monophasic disease is more likely among pediatric MOGAD patients, notably if ADEM manifested as their first episode. On the contrary, children with optic neuritis as the first sign or with attack onset at an older age had a greater probability of recurrence (145).

The attack severity in MOGAD is comparable to AQP4-IgG-NMOSD and initially appears disproportionate, with blindness, gait problems, and bladder dysfunction commonly present in the acute phase (32,146). Disability at first and subsequent attacks is measured by the extended disability status scale (EDSS). The score ranges between 0 and 10; 6 or more designate the need for walking aid and 10 as death resulting from the attack (147). In one retrospective cohort of 61 MOGAD patients with a median follow-up of nearly 15 years, more than 60% of patients had EDSS scores <3 at their last visit, pointing to favourable outcomes (148). Another study of 29 patients, with a median follow-up of 14 years, demonstrated an EDSS score of six or greater in only 7 percent of patients (149). Similarly, in studies with a shorter follow-up time, bowel and bladder sphincters and erectile dysfunction were more common than visual, motor, or cognitive impairments (32). However, secondary progression like MS is uncommon in MOGAD patients (115), in which MRI findings after multiple relapses demonstrate full recovery, while patients with MS had persistent lesions on MRI scan even after symptoms resolve (38,114).

Although attacks in MOGAD can be detrimental, they rarely result in death. In the same cohort of 29 patients, one patient died after multiple CNS attacks, despite proper treatment initiation (149). Another study reported death due to brain herniation despite the appropriate treatment with corticosteroids. A subsequent autopsy revealed several cortical and subcortical demyelinating lesions in the frontal, parietal and temporal lobes, with histopathological testing confirming MOG-IgG presence (20). One study analyzing causes of death among AQP4-IgG NMOSD patients identified the infection as the leading cause, presumably due to prolonged immunosuppressive therapy (150). As immunosuppression was proved to be successful for relapse prevention in MOGAD

patients, comparing the benefits of such achievement to the risk of infection underlines the need for incident cohort studies on MOGAD patients to acquire a better knowledge of the disease prognosis.

9. Conclusion

MOGAD was previously thought to be a variant of NMOSD; however, pathohistological investigations have demonstrated a different inflammatory mechanism that in some aspects resembles that of MS or AQP4-IgG-NMOSD but still carries distinctive features, making it a separate diagnosis. In addition, the recent advances in MOGAD research have revealed the disease's heterogeneous clinical presentation, as it can affect multiple brain regions, the optic nerves, and the spinal cord. Nonetheless, as a novel inflammatory demyelinating disorder of the CNS, further research is required to determine its incidence worldwide, what other diagnostic approaches could be applied, and how the current diagnostic tools could be improved. Ultimately, randomized controlled trials should be conducted to establish the most effective treatment strategies to minimize the side effects and decrease the relapse likelihood.

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12. Biography

Aya Younes was born on August 7^{Th,} 1996, in Beer Sheva, Israel. In 2014, Aya graduated with honors from high school. The following year, she worked as a school assistant and a tutor for a teenager diagnosed with neurofibromatosis type 1. During 2016-2022, Aya studied general medicine at the University of Zagreb, School of medicine, Croatia. During her studies, she attended clinical rotations in The Department of Gynecology, Pediatric Neurology, and Family medicine.