Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease (MOGAD)

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List of Abbreviations

ADEM - acute disseminated encephalomyelitis

AFM - acute flaccid myelitis

AQP4 - aquaporin 4

AQP4-IgG+ NMOSD - AQP4 Immunoglobulin G positive NMOSD

AQP4-IgG- NMOSD - AQP4 Immunoglobulin G negative NMOSD

AQP4 IgG - aquaporin 4 antibodies

CCE - cerebral cortical encephalitis

CBA - cell-based assay

CNS - central nervous system

CRION - chronic relapsing inflammatory optic neuropathy

CSF - cerebral spinal fluid

EBV - Epstein Barr virus

ELISA - enzyme-linked immunosorbent assay

FACS - fluorescence activated cell sorting

FLAIR - fluid attenuated inversion recovery

GFAP - glial fibrillary acidic protein

HLA - human leukocyte antigen

Ig - immunoglobulin

IgV - immunoglobulin variable

IL-6 - interleukin-6

IPMSSG - International Pediatric Multiple Sclerosis Study Group

IV - intravenous

IVIG - intravenous immunoglobulin

LEON - longitudinally extensive optic neuritis

LETM - longitudinally extensive transverse myelitis

MAG - myelin-associated glycoprotein

mGCIPL - macular ganglion cell and inner plexiform layer

MHC - major histocompatibility complex

MOGAD - myelin oligodendrocyte glycoprotein antibody-associated disease

MOG - myelin oligodendrocyte glycoprotein

MOG-Abs - MOG-antibodies

MS - multiple sclerosis

NMOSD - neuromyelitis optica spectrum disorder

OCB - oligoclonal bands

OCT - optical coherence tomography

ON - optic neuritis

PLEX - plasma exchange

pRNFL - peripapillary retinal nerve fiber layer

TCR - T-cell receptor

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Summary

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Myelin Oligodendrocyte Glycoprotein (MOG) is a component of myelin found in the mammalian Central Nervous System (CNS) and is present on both myelin sheaths and oligodendrocyte plasma membranes. In 2007, MOG became popular since anti-MOG antibodies were found in patients with neuroinflammatory conditions like optic neuritis, myelitis, and neuromyelitis optica spectrum disorder (NMOSD) lacking aquaporin 4 (AQP4) antibodies, along with brainstem and cerebral cortical encephalitis. This discovery has led to the classification of Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD), a clinical condition distinct from multiple sclerosis (MS) and traditional NMOSD. Diagnosing MOGAD poses a unique challenge due to varying interpretations of clinical symptoms, imaging, and serological findings among researchers and its similarity with MS and AQP4 IgG+ NMOSD.

Treatment strategies for MOGAD attacks include intravenous steroids or plasma exchange, while long-term management approaches are still being studied. Current treatments draw heavily from NMOSD protocols, such as immunosuppressants like azathioprine and mycophenolate mofetil. However, the fact that there is moderate effectiveness of drugs like Rituximab in MOGAD, a key player in NMOSD treatment, proves that more than one size fits treatment plan will be needed on MOGAD. Research on therapies targeting interleukin 6 (IL 6), a cytokine involved in the immune response, and other innovative methods such as T cell modulation, is ongoing to keep up with the changing landscape of MOGAD treatment.

The ongoing research on MOGAD is a beacon of hope, underscoring the need for implementation of global diagnostic criteria and deeper insights into its causes. This research is instrumental in supporting tailored treatments and understanding the disease's prevalence and genetic influences. The collaborative efforts across countries, focused on personalized treatment plans, are essential for improving outcomes and minimizing complications in individuals with MOGAD.

Sažetak

Mijelinski oligodendrocitni glikoprotein (MOG) sastavni je dio mijelina koji se nalazi u središnjem živčanom sustavu (CNS) sisavaca i prisutan je i na mijelinskim ovojnicama i na plazma membranama oligodendrocita. Godine 2007. MOG je postao popularan jer su anti-MOG antitijela pronađena kod pacijenata s neuroupalnim stanjima kao što su optički neuritis, mijelitis i poremećaj optičkog spektra neuromijelitisa (NMOSD) kojima nedostaju antitijela na akvaporin 4 (AQP4), zajedno s zahvaćanjem moždanog debla i cerebralnim kortikalnim encefalitisom. Ovo otkriće dovelo je do klasifikacije bolesti povezane s mijelinskim oligodendrocitnim glikoprotein antitijelima (MOGAD), kliničkog stanja koje se razlikuje od multiple skleroze (MS) i tradicionalnog NMOSD-a. Dijagnosticiranje MOGAD-a predstavlja jedinstveni izazov zbog različitih tumačenja kliničkih simptoma, neuroradioloških slika i seroloških nalaza među istraživačima te njegove sličnosti s MS-om i AQP4 IgG+ NMOSD-om.

Strategije liječenja za MOGAD relapse uključuju intravenske steroide ili izmjenu plazme, dok se dugoročni pristupi liječenju još proučavaju. Trenutačni tretmani uvelike se oslanjaju na NMOSD protokole, te uključuju imunosupresive kao što su azatioprin i mikofenolat mofetil. Međutim, činjenica da postoji umjerena učinkovitost lijekova poput rituximaba u MOGAD-u, ključnom lijeku u liječenju NMOSD-a, dokazuje da će za MOGAD biti potreban drugačiji plana liječenja. Istraživanje terapija usmjerenih na interleukin 6 (IL 6), citokin uključen u imunološki odgovor, i druge inovativne metode kao što su imodulacija T stanica, nastavljaju se kako bi se išlo u korak s promjenjivim krajolikom MOGAD liječenja.

Istraživanje MOGAD-a koje je u tijeku je svjetionik nade, naglašavajući potrebu za implementacijom globalnih dijagnostičkih kriterija i dubljim uvidom u njegovu etiologiju. Ovo istraživanje je ključno u podržavanju prilagođenih tretmana i razumijevanju prevalencije bolesti i genetskih utjecaja. Zajednički napori među zemljama, usmjereni na personalizirane planove liječenja, ključni su za poboljšanje ishoda i minimiziranje komplikacija kod pojedinaca s MOGAD-om.

1. Introduction

Myelin Oligodendrocyte Glycoprotein (MOG) is a component of myelin found in the mammalian Central Nervous System (CNS), expressed on the surface of myelin sheaths and oligodendrocyte plasma membranes and is highly conserved within mammalian species (1). Its role is theorized to be a cellular adhesive, regulator of oligodendrocyte micro-stability, and a mediator of the complement cascade (2, 3). Recent interest in it is due to MOG-antibodies found in patients with optic neuritis, myelitis, neuromyelitis optica spectrum disorder (NMOSD) without aquaporin 4 (AQP4) antibodies, and brainstem and cerebral cortical encephalitis (4). Because of the specific clinical course, management, and predictors of the inflammatory demyelinating disease associated with MOG antibodies, it is now considered a clinical entity separate from MS and NMOSD: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). This thesis aims to complete a literature review of the pathophysiology, clinical manifestations, diagnostic criteria, treatment, and management of MOGAD.

2. Pathophysiology

2.1. Role of Myelin Oligodendrocyte Glycoprotein

MOG is a transmembrane protein expressed on the outermost lamellae of the myelin sheath as well as the cell body and processes of oligodendrocytes, the myelin-forming cells of the CNS (2). Proteolipid proteins (PLP and DM20) and myelin basic proteins comprise the bulk of oligodendrocytes, physically and in research (5). Glycoproteins, such as MOG, comprise a much smaller percentage of oligodendrocytes and are essential in glial-glial and glial neuronal interactions (6). For example, myelin-associated glycoprotein (MAG), a much more thoroughly researched glycoprotein than MOG, is hypothesized to mediate the axon glial adhesion that precedes myelination. Currently, MOG, however, is only known as a marker of mature oligodendrocytes (7, 8) and its exact role still needs to be elucidated. Possible functions of MOG include cellular adhesive, an oligodendrocyte micro-stability regulator, and a complement cascade mediator (2, 3).

2.2. Structure of Myelin Oligodendrocyte Glycoprotein

MOG is expressed solely in mammals and is highly conserved. It contains a signal peptide of 29 amino acids followed by 218 amino acids of the mature protein (9). Its high conservation within mammals infers an essential biological role.

MOG is also a member of the immunoglobulin superfamily and is characterized by a distinctive structure: an extracellular immunoglobulin variable (IgV) domain, a hydrophobic transmembrane segment, a brief cytoplasmic loop and another hydrophobic section within the membrane bilayer, leading to a cytoplasmic tail (Fig. 1) (10). This structure sets MOG apart from other superfamily members, which typically possess either a single transmembrane domain or are connected to the membrane surface through a glycolipid anchor.

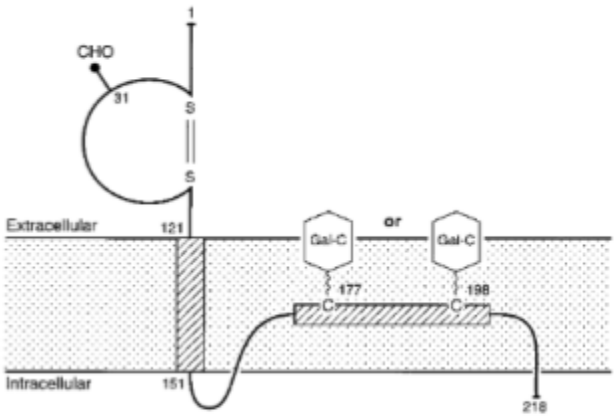

Fig. 1. Topology of MOG as proposed by Kroepfl et al. (10)

2.3. Immune Response in Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease

2.3.1. Central and Peripheral Tolerance as Sites of Autoreactivity

Although multiple sclerosis (MS), NMOSD, and MOGAD share similar clinical features, the specific autoimmune response mechanisms in each condition require further investigation, which is crucial for comprehending the distinct nature of each disorder. The general pathway of MOGAD is as follows: the immune system produces antibodies against the MOG protein on the myelin sheath of nerve fibers, initiating a targeted autoimmune response. The autoimmune response includes activating complement pathways and recruiting inflammatory cells, ultimately demyelinating nerve fibers and disrupting neural conduction (11). Thus, the clinical manifestations of MOGAD, such as optic neuritis, transverse myelitis, and other neurological

symptoms, are direct consequences of this immune-mediated demyelination and the secondary axonal damage that may ensue.

There is debate over where the initial pathogenic event triggering demyelination occurs. In the literature, there are two models of demyelination: the outside-in and the inside-out model. In the outside-in model, the disease processes begin in the periphery. Autoreactive immune cells migrate into the CNS and initiate an immune response. The inside-out model states that the disease process is due to pre-existing damage to the CNS, which then initiates an immune response to the injury site, resulting in an inflammatory response (12). The outside-in model is the agreed-upon model for the disease process of MOGAD (2,13).

The immune system has multiple checkpoints where ineffective or potentially harmful cells are removed. These checkpoints may be ineffective in MOGAD. Central tolerance, otherwise known as negative selection, where autoreactive immune cells are removed, occurs in the primary lymphoid organs, specifically the thymus for T-cells and the bone marrow for B-cells. In the thymus, immature T-cells express T-cell receptors (TCR). These receptors interact with peptides bound to self-major histocompatibility complex (MHC) on stromal and bone-marrow-derived cells. T-cells with TCRs that engage with self-peptide-MHC with low-affinity, meaning they are not auto-reactive, will be spared from clonal deletion (14). Thus, autoimmunity may stem from an undeveloped central tolerance toward MOG where self-reactive T cells are not removed (15). This hypothesis is both corroborated and not. In one study by Bruno et al. (2002), authors found no chance that MOG was found outside the CNS; thus, there was no chance that central tolerance was the reason for MOGAD activation (16). However, Gotter et al. (17) found intrathymic MOG mRNA, which they state is most likely due to using a more sensitive method using purified cells as opposed to whole thymus or laser capture areas.

If there is an error within central tolerance, peripheral tolerance is the next step in the immune system to prevent autoreactivity. Peripheral tolerance occurs in the secondary lymphoid organs, such as the spleen and lymph nodes. It is performed through the processes of anergy, apoptosis of

the self-reactive T cells through the absence of costimulatory molecules or the presence of inhibitory molecules (e.g., PD1 or CTLA), and with the help of Tregs (18). Thus, peripheral tolerance against MOG could also be a point of error.

2.3.2. B Cells Role in Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease

In MOGAD, B cells are vital players, producing autoantibodies against MOG, known as MOG-antibodies (MOG-Abs), leading to demyelination and neurological symptoms. Knowing how the B cells and the antibodies they make contribute to MOGAD may lead to further elucidation of the disease treatment. For example, Winklemeier et al. (19) discovered that MOG-specific B cells were not linked to levels of MOG-Abs in serum, thus suggesting different sources of MOG-Abs. They suggest two other sources, both corroborated by other studies (20-22): long-lived plasma cells, which are negative for CD20, and CD20+ memory B cells that are readily differentiated into anti–MOG secreting cells.

Besides antibody production, other functions of B cells have been examined as reasons for auto-immunity. For example, B cells produce proinflammatory cytokines such as GM-CSF (23); thus, therapies targeted at B cell reduction may reduce antibodies and pro-inflammatory cytokines. Molnarfi et al. (24) found that in animal models, MOG-specific B cells were essential as antigen-presenting cells to activate MOG specific T cells and encephalitis. Although antibodies are a distinct feature of MOGAD, treatment using anti-CD20 therapy with CD20 being a general marker of B cells, has shown limited effectiveness in many patients. A thorough investigation revealed that the application of rituximab led to a 37% decrease in relapse rates, with only a third of patients experiencing no relapse within two years (25). The moderate efficacy of B cell depletion treatment could indicate diverse disease mechanisms in these individuals, possibly involving processes that trigger T cell activation and the production of MOG antibodies.

2.3.3. T Cells Role in Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease

T cells also play an essential role in MOGAD pathogenesis, as exemplified by the following findings: First, since MOG antibodies are IgG1, class switching must have occurred, thus implying the help of follicular T helper cells (26). Second, MOG antibodies are not pathogenic unless they are coupled with MOG-specific or encephalitogenic T cells, as exemplified by Spadaro et al. (27), who found that MOG antibodies caused pathological changes in vivo after co-transfer with myelin-reactive T cells. Upon 22 brain biopsies of patients diagnosed with CNS demyelinating disease who were positive for MOG antibodies, Hoftberger et al. (28) found CD4+ T-cell dominated inflammatory reaction with granulocytic infiltration predominates, thus disrupting BBB and creating a pro-inflammatory environment.

2.3.4. Environment and Genetic Factors Contributing to Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease

The interplay between genetic and environmental influences is crucial in comprehending MOGAD development. For example, individuals with certain genetic predispositions might be more vulnerable to triggers such as viral infections, which could increase their chances of developing MOGAD. Moreover, gene-environment interactions may impact the course of the disease; genetic variations can influence how individuals respond to factors like vitamin D levels, leading to differences in disease severity and progression.

The genetic susceptibility to MOGAD most likely involves some candidate genes linked to immune system regulation. However, findings have been mixed. Sun et al. (29) demonstrated a possible association between specific human leukocyte antigen (HLA) class II alleles and pediatric-onset MOGAD in Chinese pediatric patients, thus hinting at a foundation for the abnormal immune response seen in MOGAD patients (29). However, studies in the EU, specifically the Netherlands and the UK, have found no such association (30, 31).

Various research studies have also pointed out differences in complement system activation between NMOSD and MOGAD, with Lin et al. (32) finding that there seems to be more plasma C3 and C4 consumption in the NMOSD compared to MOGAD (32).

Additionally, environmental factors could be significant in understanding the development of MOGAD. Approximately 20-40% of MOGAD cases have been associated with preceding infections. A study in Japan (4) showed that this precedent was more frequent in the pediatric-onset group (39% for those <10 years old) than in the adult-onset group (13.5%). This may be due to factors such as molecular mimicry or bystander activation (4).

Similarly to the genetic susceptibility in patients with MOGAD, studies have shown mixed connections between infections, especially Epstein-Barr virus (EBV) and MOGAD. Some studies point towards a possible connection, and others say there is none (33, 34). COVID-19 has also been hypothesized as a potential trigger of MOGAD, however, again, results are mixed (35). The diversity of findings is most likely due to a combination of factors, mainly that autoimmune conditions, even heavily researched ones such as MS, have a notoriously complicated and usually unknown etiology. Furthermore, the small sample sizes in most studies and the relatively new dedication in research to MOGAD as a separate disease entity lends itself to irregular and diverse results.

Vitamin D is also being researched as a potential treatment option for MOGAD since its deficiency has been hypothesized to be an environmental factor contributing to it (36).

Some innovative research is also investigating how the gut microbiome may contribute to MOGAD. This research indicates that gut microbiome population changes impact system activity and autoimmune responses. This avenue of research offers insights into the influences on MOGAD and underscores the potential for innovative treatment approaches focused on the microbiome (37).

3. Epidemiology

Hor et al. (4) completed a review of MOGAD and compiled the data of the seven population-based studies completed worldwide as of June 2023. The cities and countries included Oxfordshire (UK), Verona (Italy), a Dutch nationwide incidence study, Japan, a nationwide audit in Singapore, and a survey in Chumphon (Thailand), Olmsted County (Minnesota, USA), and Martinique Island. The findings from this review give insight into MOGAD worldwide and include the following (specific numbers from individual countries can be viewed in Fig. 2):

The authors (4) calculated a MOGAD prevalence of approximately 1.3-2.5 per 100,000 people and an annual incidence rate of about 3.4-4.8 per million. Interestingly, in Caucasian populations, the prevalence of MOGAD is reported to be slightly higher than that of AQP4-Immunoglobulin G positive NMOSD (AQP4-IgG+NMOSD). No significant latitude gradient was identified in a comprehensive Japanese survey, nor were there evident racial predispositions or strong associations with HLA observed in MOGAD cases.

Unlike AQP4-IgG+NMOSD, which has a very high female-to-male ratio (up to 9:1), they (4) did not find an apparent female preponderance in MOGAD (around 1.2:1). MOGAD can onset in all age groups, with a mean/median age at onset of approximately 28–30 years. Roughly 30% of MOGAD cases are in the pediatric age group, and MOGAD comprises approximately 35–40% of cases of acquired CNS demyelinating syndrome in the pediatric population. Approximately 35–50% of MOGAD cases have a relapsing course, with the relapse risk being slightly higher (~60%) in the young adult-onset group. Optic neuritis is the most common presenting phenotype (~40%). Age-related onset phenotype is a feature of MOGAD, where acute disseminated encephalomyelitis (ADEM) is more common in pediatric patients <10 years old, while myelitis and brainstem encephalitis are more common in adult patients.

4. Clinical Features

4.1. Overview

While there isn't a sign that can definitively pinpoint MOGAD, there are several symptoms that strongly suggest the condition, such as vision loss due to optic neuritis affecting one or both eyes, neurological changes characteristic of ADEM along with signs of transverse myelitis such as weakness in limbs, sensory loss and disruptions in bowel, bladder or sexual functions.

Children tend to have ADEM as the first symptom, whereas adults present more commonly with optic neuritis. Symptoms usually worsen over days before peaking, with recovery times varying from weeks to months. Infections or vaccinations may trigger these episodes (38).

In some cases, MOGAD may affect parts of the CNS and resemble AQP4-IgG seronegative NMOSD. This can lead to a combination of myelitis and optic neuritis, sometimes involving separated CNS regions. Additionally, individuals with MOGAD may experience symptoms like cerebral encephalitis, resulting in seizures, headaches, and localized neurological issues. It is more common for the brainstem to be impacted in connection with symptoms of ADEM than on its own (38).

In contrast to MS and AQP4-IgG negative NMOSD, a significant portion of individuals with MOGAD (40 to 50%) experience a monophasic course without subsequent relapses. However, there is no way to predict which course a patient will take. Some research has found there to be an age-related shift in the rate of relapse across age groups. Adults tend to have higher relapse rates and worse long-term recovery outcomes (38). In one study, children with monophasic disease course became MOG-Ab negative earlier than relapsing children, but this was not found in adults (38).

4.2. Optic Neuritis

Optic neuritis is the most common symptom of MOGAD in adults and becomes increasingly more severe during each subsequent MOGAD relapse (39, 40). Optic neuritis is generally characterized by nerve inflammation and can result from inflammatory conditions or have an

unknown cause. While the features of optic neuritis in MOGAD resemble those seen in multiple sclerosis (MS) and NMOSD associated with aquaporin-4 antibodies, some specific symptoms are more indicative of MOGAD. Eye pain upon movement is a symptom of optic neuritis common to all causes; however, in MOGAD, it typically precedes vision loss (41). Up to 50% of patients complain of a new-onset, often severe periorbital and frontotemporal headache a few days before the visual deficit (41). It is important to remember that the sensation of eye pain might be interpreted as a headache in children, thus leading to challenges in making a diagnosis and potentially, therefore, being underreported (42). Vision impairment is typically central and often more pronounced than in MS but less pronounced in severity to that observed in AQP4-IgG+NMOSD cases, with many patients reaching a point where they can only perceive hand movements (39).

In cases of acute optic neuritis linked to MOGAD, clinical examinations reveal swelling of the optic disc in up to 86% of cases, which is more prevalent than in MS or AQP4-IgG+NMOSD (39). This swelling can be severe enough to lead to bleeding around the disc. In up to 50% of cases, the optic neuritis is bilateral, and in such cases, the swelling might be mistaken for papilledema (39, 43). In such cases, when a diagnosis is unclear, MRI can exclude papilledema and reveal anterior and longitudinal inflammation of the optic nerve (44).

Generally, recovery from optic neuritis in MOGAD patients is positive, with a small percentage, 6-14%, ending up with visual acuity of 20/200 or worse compared to the higher proportion seen in AQP4+NMOSD cases (39). However, optic disc pallor has a lingering effect in MOGAD cases. Despite the recovery outlook, more than half of individuals may encounter relapses and some may rely on glucocorticoids, even meeting the criteria, for chronic relapsing inflammatory optic neuropathy (CRION) (43).

4.3. Acute Disseminated Encephalomyelitis

ADEM is the most common initial presentation of MOGAD in children, noted in 68% of all MOG-positive pediatric cases (45). It is a condition where the immune system attacks the

covering of nerve fibers. It is mainly seen in children and teens and usually presents suddenly with symptoms such as coordination problems, speech difficulties, seizures, changes in perception, and behavioral changes such as confusion and irritability (46).
The criteria of an ADEM diagnosis, designated by the International Pediatric Multiple Sclerosis Study Group (IPMSSG), are a first clinical CNS event with a suspected demyelinating origin, encephalopathy that cannot be explained by fever or systemic illness, and an abnormal brain MRI during the acute phase that is compatible with ADEM but not indicative of any other CNS disease (46). MRI scans are necessary to diagnose ADEM and will show lesions primarily in the white matter, possibly accompanied by lesions in the gray matter. The lesions tend to be large, poorly demarcated, and bilateral, which differs from MS, which is associated with smaller, well-demarcated, and predominantly localized lesions that lie periventricular in the white matter supra and infratentorial but also cortically and subcortically area, especially in the corpus callosum (47). Children with MOG antibodies have been found to have a high likelihood of spinal cord issues, like longitudinally extensive transverse myelitis (LETM) across three or more segments (48), as well as a higher probability of post-disease epilepsy (49).

Research by Cobo-Calvo et al. (50) supported these findings, noting that thalamic and brainstem problems were common in MOGAD cases. Interestingly, follow-up MRIs often revealed significantly more lesion healing in MOGAD compared to AQP4-IgG+NMOSD and MS (41, 50, 51). However, these improvements seen on MRI in the long term do not always lead to positive outcomes, as imaging does not always correlate to the clinical picture. 40% of patients in a study by Jurynczyk et al. (47) were found to have some sort of long-term cognitive impairment, such as poor visual acuity, cognitive impairment, and significant sphincter and erectile dysfunction. Additionally, a study found that children with MOG IgG antibodies had a risk of epilepsy after the disease compared to those without (49).

While most cases of ADEM follow a monophasic pattern, some patients may encounter recurring episodes, leading to a diagnosis of multiphasic ADEM (52). However, many of these patients are more likely to have MOGAD. In fact, studies indicate that around 30 to 50% of individuals with

ADEM have MOG IgG antibodies, and research (52) has shown a significant link between MOG IgG antibodies and the recurrence of episodes. Patients with consistently elevated MOG IgG are more likely to experience episodes, with an 88% recurrence rate observed in cases compared to minimal relapses in those with temporary antibody presence (52). This underlines the diverse outcomes seen in patients with MOGAD initially presenting as ADEM symptoms —some may have a one-time disease course. In contrast, others might face episodes showcasing the complexity and variations in conditions associated with MOG antibodies.

In a study by Baumann et al. (48), researchers compared pediatric patients with ADEM without MOG-abs and those with MOG-abs. They did not find a difference in symptoms experienced, gender distribution, or age when symptoms first appeared between the two groups. However, patients with MOG-abs did have higher levels of white blood cells in their cerebrospinal fluid (CSF) and more frequent initial behavioral problems.

4.4. Transverse Myelitis

Transverse myelitis is inflammation within the spinal cord, leading to neurological issues that progress rapidly, typically reaching their most severe phase within three weeks (53).
In MOGAD, episodes affecting the spinal cord can present alone events or alongside other CNS symptoms such as ADEM or optic neuritis (54, 55, 56). Patients may experience a sudden development of partial or complete paralysis, alongside a decreased sensation below the affected nerve site and a distinct sensory demarcation along the torso (57). Issues like neurogenic bladder and bowel dysfunction are expected, with a notable frequency of erectile dysfunction in affected males, likely due to the recurrent engagement of the conus medullaris (54-56). Often, issues with bowel, bladder, and sexual functions persist, overshadowing any remaining motor skill deficits (54, 55). Symptoms may also include Lhermitte's phenomenon (an electrical sensation that spreads to the limbs when bending the neck) or Uhthoff's phenomenon (a deterioration of symptoms in response to increased temperatures). The intensity of the myelitis observed is typically more severe than that associated with MS, with about a third of affected individuals unable to walk at the lowest point of their condition (54).

Sagittal T2-weighted MRI scans reveal that myelitis-related lesions in roughly 75% of cases extend over three or more spinal segments, a condition known as LETM, predominantly located in the spinal cord's central region (54-56). This aspect is crucial for distinguishing MOGAD from MS, where lesions seldom exceed three vertebral segments in length and are more likely to be positioned towards the spinal cord's posterior (54, 55, 57, 58). Nonetheless, it's common for MOGAD patients to exhibit several spinal cord lesions, with some displaying both longitudinally extensive and shorter lesions, although a few may exhibit only the shorter variants (54-56).

4.5. AQP4-IgG-Seronegative Neuromyelitis Optica Spectrum Disorder

NMOSD is a neuroinflammatory disorder of the CNS that, as the same suggests, affects the optic nerves and spinal cord. Due to inflammation, there is demyelination and axonal damage that leads to its core clinical characteristics, which include optic neuritis, acute myelitis, area postrema syndrome (characterized by hiccups, nausea, or vomiting), brain stem syndrome, diencephalic clinical syndrome, and cerebral syndrome (59).

Additionally to the clinical characteristics, AQP4 water channel protein, the target antigen of NMO-IgG, plays a significant role in the pathogenesis and is part of the diagnostic criteria for NMSOD. However, in a study conducted by Prasad et al. (60), AQP4-IgG was not detected in about 25% of patients who met the criteria for NMOSD and in another study (61), 21.1% of AQP4-IgG-NMOSD seronegative patients had MOG-IgG. In fact one-third to one-half of patients with the clinical syndrome of AQP4-IgG-seronegative NMOSD are diagnosed with MOGAD (62). However, as the ratio of AQP4-IgG-NMOSD seronegative patients to MOG-IgG is quite far from 1:1, other factors must be taken into account for a proper MOGAD diagnosis.

4.6. Cerebral Cortical Encephalitis

Identified in 2017 by Ogawa et al. (63) as a phenotype of MOGAD, Cerebral Cortical Encephalitis (CCE) typically presents clinically with seizures, aphasia, stroke-like episodes, headaches, and fever. On imaging, CCE appears as unilateral, cortical, fluid-attenuated inversion

recovery (FLAIR)-hyperintense lesions (64). These lesions and the concomitant seizures they presumably cause have been given the acronym FLAMES: FLAIR-hyperintense Lesions in Anti-MOG-associated Encephalitis with Seizures (64). Although commonly unilateral, bilateral cortical T2-FLAIR hyperintensity occurs in approximately one-third of cases, with 53% showing involvement in other brain areas. The extent of cortical T2-hyperintense lesions and leptomeningeal enhancement seen in MOGAD-associated CCE is generally more significant than that observed in MS, despite the potential for subtle MRI changes in CCE. A distinguishing feature of CCE from MS is the common resolution of cortical T2 lesions and the exclusion of seizure-related signal anomalies, which may appear similar due to the absence of pathologic cortical demyelination (65).

4.7. Brainstem Features

Brainstem involvement in MOGAD is much less common than in MS and usually occurs during a multifocal demyelinating attack that also affects other areas of the CNS (66, 67). In some cases, brainstem lesions may even be asymptomatic (67). MRI findings in MOGAD patients with brainstem lesions, about 20%, will usually show diffuse T2 hyperintense lesions in the midbrain, pons, or medulla, which can help differentiate between MOGAD and MS since in MS short focal T2-lesions are more common. Furthermore, MOGAD is often accompanied by poorly defined middle cerebellar peduncle lesions that can be unilateral or bilateral, which also helps to distinguish it from AQP4-IgG+NMOSD or MS (67, 68). The most common brainstem symptoms in MOGAD are ataxia and diplopia (67), with nausea and vomiting potentially occurring as part of ADEM or its preceding viral prodrome. Area postrema syndrome, which is typical of AQP4-IgG+NMOSD and causes isolated intractable nausea, vomiting, and hiccups, is not typically observed (69).

5. Diagnostics

5.1. Diagnostic criteria

According to recent guidelines published by Banwell et al. (70) in the Lancet Neurology, MOGAD can be diagnosed by the following: A patient exhibiting symptoms commonly linked with MOGAD such as optic neuritis, myelitis, or acute disseminated encephalomyelitis along with a confirmed serum MOG antibody result of titer ≥1;100 using a standardized Cell-Based Assay (CBA). With MOG antibody titers less than that, a positive diagnosis is still possible when supported by specific clinical or MRI findings (Fig. 2). The main objective of these criteria is to establish an approach to diagnosing MOGAD and distinguishing it from conditions like MS.

<table>
<tr><th colspan="4">Diagnosis of MOGAD (requires fulfilment of A, B, and C)</th></tr>
<tr><td>(A) Core clinical demyelinating event</td><td colspan="3">Optic neuritis*
Myelitis†
ADEM‡
Cerebral monofocal or polyfocal deficits§
Brainstem or cerebellar deficits¶
Cerebral cortical encephalitis often with seizures‖</td></tr>
<tr><td rowspan="4">(B) Positive MOG-IgG test</td><td rowspan="4">Cell-based assay: serum‡‡</td><td>Clear positive**</td><td>No additional supporting features required</td></tr>
<tr><td>Low positive††</td><td rowspan="3">• AQP4-IgG seronegative AND
• ≥1 supporting clinical or MRI feature</td></tr>
<tr><td>Positive without reported titre</td></tr>
<tr><td>Negative but CSF positive§§</td></tr>
<tr><td rowspan="3">Supporting clinical or MRI features</td><td colspan="2">Optic neuritis</td><td>• Bilateral simultaneous clinical involvement
• Longitudinal optic nerve involvement (> 50% length of the optic nerve)
• Perineural optic sheath enhancement
• Optic disc oedema</td></tr>
<tr><td colspan="2">Myelitis</td><td>• Longitudinally extensive myelitis
• Central cord lesion or H-sign
• Conus lesion</td></tr>
<tr><td colspan="2">Brain, brainstem, or cerebral syndrome</td><td>• Multiple ill-defined T2 hyperintense lesions in supratentorial and often infratentorial white matter
• Deep grey matter involvement
• Ill-defined T2-hyperintensity involving pons, middle cerebellar peduncle, or medulla
• Cortical lesion with or without lesional and overlying meningeal enhancement</td></tr>
<tr><td colspan="4">(C) Exclusion of better diagnoses including multiple sclerosis¶¶</td></tr>
</table>

Fig. 2. Proposed diagnostic criteria for MOGAD (70). *ADEM=acute disseminated encephalomyelitis. AQP4=aquaporin-4. MOG=myelin oligodendrocyte glycoprotein. MOGAD=MOG antibody-associated disease.*

The issue with these diagnostic criteria lies in the elusive nature of the disease. For example, antibody testing is central to the diagnostic criteria; however, false positives, which can result from cross-reactivity with MOG-immunoglobulin (Ig) M, occur more frequently in MOG-Ab

testing than in AQP4-Ab testing. Furthermore, many MRI characteristics are non-specific to MOGAD and can be found in other neuroinflammatory conditions. A higher positivity threshold can be employed to enhance test specificity, and tests are being developed to detect secondary antibodies. To strengthen the connection between MRI findings and MOGAD, MRI lesions should be analyzed over time since MOGAD lesions tend to recover completely compared to NMOSD or MS (41, 44, 50, 51, 71, 72).

The fluctuating nature of MOG-abs, the presenting symptoms, and MRI findings similar to other neuroinflammatory conditions highlight the importance of using clinical judgment alongside laboratory and imaging studies to diagnose MOGAD.

5.2. Diagnostic Methods and Findings

5.2.1. Magnetic Resonance Imaging

MOGAD presents with much more MRI variability compared to other CNS demyelinating diseases; 10% of patients may have a normal MRI, even with severe acute disability (45). MOGAD typically manifests with intense clinical episodes and substantial T2-lesions in the brain, spine, or orbit. These lesions appear “fluffy” due to their poorly demarcated borders, compared to MS, which has well-defined margins (47). 50 to 75% of patients have at least one gadolinium-enhanced lesion (an indirect hallmark of active inflammation on MRI). In contrast, in MS, such lesions are more common (41). Optic neuritis, if presented as a symptom, is almost always seen as enhanced on MRI and usually involves the optic nerve sheath or peribulbar fat. This finding is found so often it has even been given the name “perineural enhancement” (73).

5.2.2. Optic Nerve

Optic neuritis (ON) is the predominant clinical feature in MOGAD, often presenting as an isolated incident (74). It exhibits recurrent or bilateral/simultaneous characteristics in about 50% of instances (40) (Fig. 3). In some cases, it displays dependency on steroids, meaning a worsening after steroid withdrawal, resembling chronic relapsing inflammatory optic neuropathy

(CRION) (75). Magnetic resonance imaging (MRI) of MOG-associated ON typically reveals T2 hyperintense lesions, swelling, and gadolinium enhancement of the affected optic nerve on

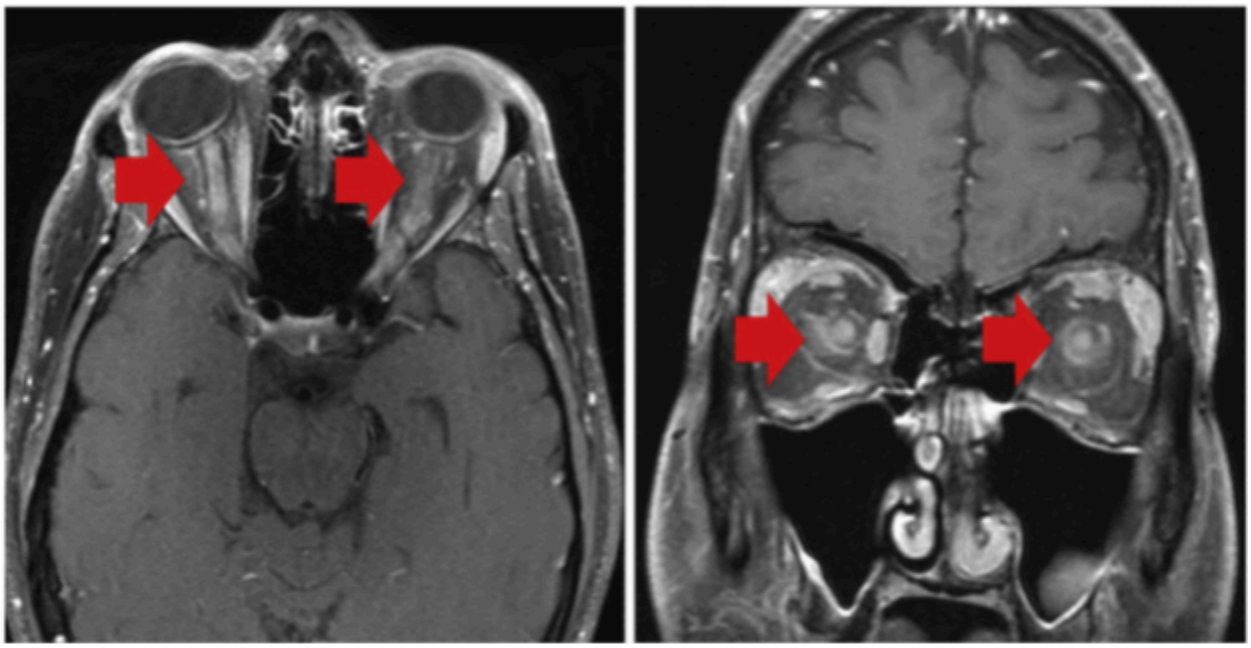

Fig. 3. MRI with contrast: Bilateral prominent enhancement of optic nerve and sheath (perineural enhancement), extending along almost the entire nerve (red arrows) (40).

T1-weighted images. MOG-ON lesions generally cover a substantial portion of the pre-chiasmatic optic nerve, referred to as longitudinally extensive optic neuritis (LEON), affecting approximately 85% of patients. 50% of these cases often show perineural enhancement that may extend into the surrounding orbital tissue (40).

While the involvement of the optic chiasm has traditionally been linked with AQP4-IgG+NMOSD, it is also observed in a small subset of MOGAD patients, rarely occurring in isolation and typically alongside extensive optic nerve involvement (76). In cases where bilateral longitudinally extensive enhancement of the optic nerve is observed without chiasmal involvement, MOGAD is often implicated (73).

Furthermore, MOG-ON primarily affects the anterior segment of the optic nerve, which likely explains the common occurrence of optic disc edema in these cases (40). This feature is

instrumental in differentiating MOG-ON from AQP4-ON, which also shows extensive lesions but primarily affects the posterior optic pathway, including the optic chiasm (73). Contrastingly, multiple sclerosis associated ON usually involves shorter segments of the optic nerve. However, bilateral ON with radiological evidence of bilateral optic nerve involvement occurs in more than 80% of MOG-ON and AQP4-ON cases, compared to only 20% in MS-ON (77). Additionally, in pediatric patients, bilateral ON has been linked with elevated MOG-IgG titers (78). A distinctive hallmark of MOG-ON includes perineuritis, marked by perineural or periorbital gadolinium enhancement within the orbital soft tissue, a feature rarely seen in MS-ON (40).

5.2.3. Brain

Observed brain lesions are found in 50% of adults diagnosed with MOGAD (78). The lesions are generally T2 hyperintense, bilateral, limited - usually no more than three - and display indistinct borders with a "fluffy" appearance (79) (Fig. 4). Approximately one-third of these lesions are located in the infratentorial area, primarily within the brainstem (78). Children diagnosed with MOGAD, however, typically show bilateral lesions in the brainstem and deep gray matter nuclei (47). Lesions in the cerebellar peduncles are characteristic (80) of pediatric patients suffering from MOGAD. Confluence of large symmetrical lesions bilaterally may sometimes occur and mimic leukodystrophy, especially in pediatric patients (81).

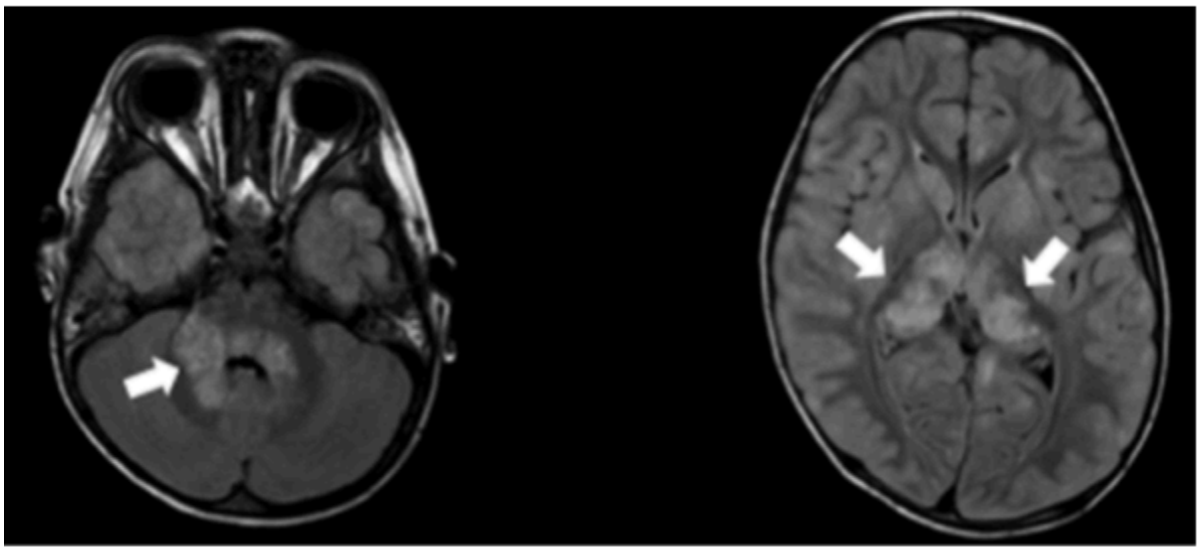

Fig. 4. Fluffy large and bilateral lesions in pons and cerebellar peduncles, adjacent to fourth ventricle, and in the thalamus of a 3 year old patient with MOG antibodies (79).

Cobo-Calvo et al. (78) noted a greater prevalence of thalamic (18.4%) and pontine (34.7%) lesions in MOGAD compared to AQP4-IgG+NMOSD, which showed higher frequencies of medulla oblongata (14.3% vs 45.5%) and area postrema (2% vs 31.8%) lesions. Apart from the pons and thalamus, MOGAD lesions in the deep white matter (49%), juxtacortical region (41%), basal ganglia (29%), periventricular white matter (27%), the area adjacent to the fourth ventricle (22%), cerebellar peduncles (18%), and cortical gray matter (16%) were identified (78), with gadolinium enhancement detected in 12% of brain lesions associated with MOGAD (78). Kitley et al. (44) found that MOGAD, compared to AQP4-IgG-positive NMOSD, frequently had more deep gray matter involvement. Although deep white matter is typically impacted in MOGAD, similar patterns are also commonly observed in NMOSD, thus not serving as a valuable tool to discriminate between the two (78). The central vein sign, a particular finding in MS brain lesions is uncommon in MOGAD and AQP4-IgG+NMOSD (82, 83, 84).

Recent studies have reported findings of lesions and leptomeningeal enhancement in MOGAD, with cranial nerve enhancement being uncommon (64, 68, 78). Although these findings are unusual, they can help physicians distinguish MOGAD from NMOSD. The encephalopathic presentation and seizures are more frequently associated with MOGAD than NMOSD (78, 85) and rarely seen in cases of MS. MOGAD encephalomyelitis or encephalitis is ADEM-like on MRI with signal changes in the gray, subcortical white, deep white, deep gray matter or a combination of these areas on T2 weighted and FLAIR sequences (86). Active lesions often display linear or nodular enhancement, sometimes accompanied by restricted diffusion (63, 85, 86).

Follow-up MRIs showing complete lesion resolution suggest a diagnosis of MOGAD rather than NMOSD or MS, where lesions tend to persist (41, 44, 50, 51, 54, 84, 87).

5.2.4. Spinal Cord

Spinal cord involvement in MOGAD tends to be severe, with symptoms such as paraparesis requiring aid and/or bladder dysfunction potentially requiring catheterization (72).

Spinal cord lesions in MOGAD tend to involve 50% or more of the axial section of the spinal cord and are T2 hyperintense, centrally located, affecting both gray and white matter (84). A sagittal T2-hyperintense line, described by Dubey et al. (71), has been deemed characteristic of MOGAD (Fig. 5). They reported a characteristic sagittal T2-hyperintense line within the spinal cord gray matter (the sagittal T2 hyperintense line) surrounded by a more hazy T2 hyperintense signal of anterior and posterior gray matter horns, the appearance of which makes the central canal appear dilated, thus being termed "pseudo-dilatation of the central canal." When seen on an axial plane, these hyperintensities make an "H" sign (71) (Figure 4). However, these signs point towards MOGAD but can be seen in other myelopathies, such as acute flaccid myelitis, viral myelitis, and idiopathic myelitis (88, 89). Thus, there must always be a high level of clinical suspicion.

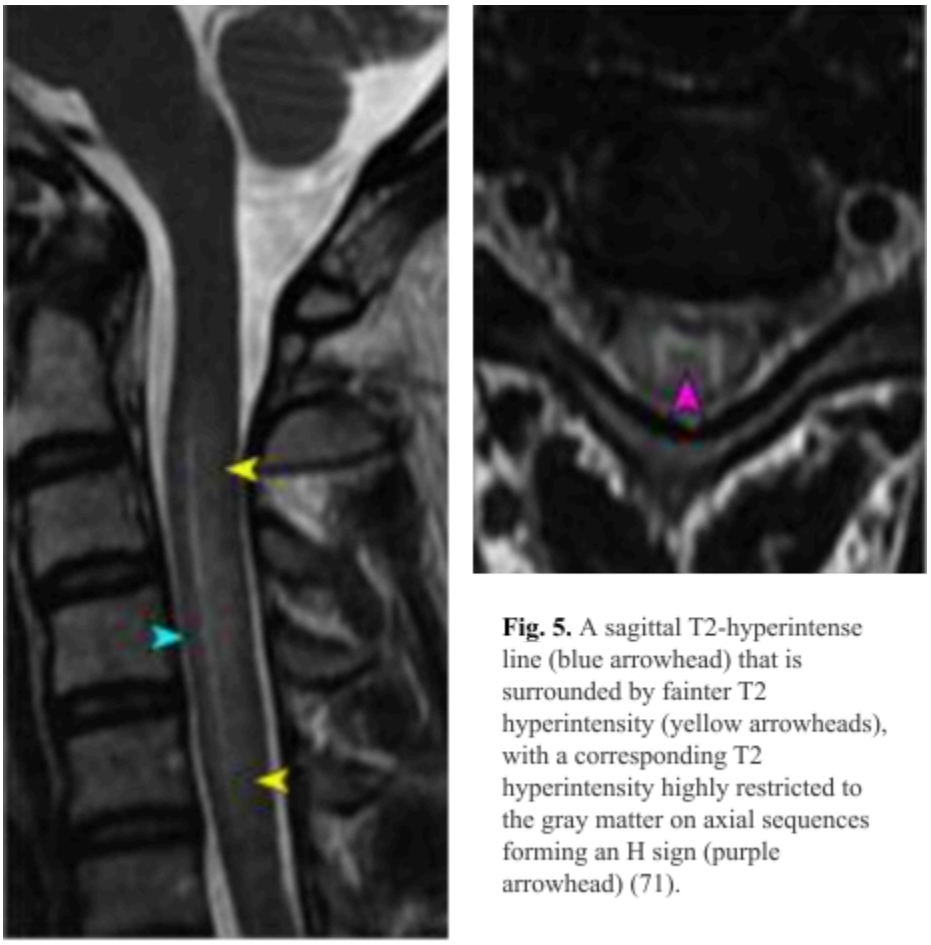

Fig. 5. A sagittal T2-hyperintense line (blue arrowhead) that is surrounded by fainter T2 hyperintensity (yellow arrowheads), with a corresponding T2 hyperintensity highly restricted to the gray matter on axial sequences forming an H sign (purple arrowhead) (71).

The length of spinal cord lesions is typically present in two patterns. LETM spans three or more vertebral segments, or shorter lesions spanning two or fewer vertebral segments (74). These patterns can be mixed with affected spinal cords containing LETM and shorter lesions (71). These lesions can help us differentiate between MOGAD and NMOSD, as two-thirds of children diagnosed with MOGAD with spinal lesions had LETM, and lesions in

NMOSD tend to be much more substantial, involving more than 50% of the cord longitudinally, even affecting the cervical or thoracic spine and are located both peripherally and centrally (90). Furthermore, spinal lesions in NMOSD usually appear more gadolinium-enhanced and show more cord edema than those in MOGAD (74). MS spinal lesions are generally shorter and longitudinally located in the periphery and involve the dorsolateral tracts (71).

A feature that is also more specific to MOGAD, compared to MS and NMOSD, is conus medullaris involvement (44, 71, 74). “Cloudlike enhancement,” which is seen as heterogenous enhancement with blurred margins, may be seen on contrast-enhanced sequences, as well as well-defined nodular enhancement or meningeal enhancement, which actually can help distinguish MOGAD from NMOSD and MS, although subtle intracranial meningeal enhancement in MS has been seen on high-resolution 7-T contrast-enhanced FLAIR scans. At the time of acute relapse, MOG-IgG myelitis lesions are frequently non-enhancing, as opposed to MS, in which new lesions are more commonly enhance (84).

5.2.5. Cerebral Spinal Fluid Findings

CSF can also be used to aid in the diagnosis of MOGAD. CSF pleocytosis (>5 white blood cells/mm3) has been found in 50% of patients during a MOGAD attack. However there is variability between degree of CSF pleocytosis and the attack phenotype in MOGAD: there is 16% CSF pleocytosis in isolated optic neuritis, 74% in isolated myelitis, 72% in isolated brain/brainstem attacks, and 50-80% with multifocal CNS involvement (91-93). Thus, depending on the symptoms, CSF pleocytosis may have a variable use when confirming MOGAD. Compared to MS, CSF pleocytosis is marked (>50 white blood cells/mm3) in 30% of patients with MOGAD; however, this can also be seen in AQP4-IgG+NMOSD (92, 93). Another distinguishing feature between MS and MOGAD is CSF-restricted oligoclonal bands (OCB), which are rare in MOGAD and found in only approximately 15% of cases, sometimes transiently. OCB are found in approximately 85% of MS cases and persist over time, except for some specific circumstances (94).

AQP4-IgG-positive-NMOSD and MOGAD's CSF cytokine profiles during acute attacks are similar, with most cytokines being Th17-related (e.g., IL-6, IL-8, IL-17). These cytokines, thus, may be potential therapeutic targets (95), which will be explored in the "Treatment" section. MS has a different cytokine profile, mainly being Th-1-related (96). Since AQP4-IgG+NMOSD affects astrocytes and MOGAD oligodendrocytes, another way to distinguish the two diseases is to look at markers of each cell type's destruction. Serum levels of glial fibrillary acidic protein (GFAP), a marker of astrocytic damage, are generally lower in MOGAD compared to AQP4-IgG-positive-NMOSD (97, 98).

In all three of these conditions, CSF concentrations of neurofilament light chains, which serve as indicators of neuroaxonal damage, are elevated during episodes, particularly at their commencement. These markers can also be identified in serum by applying highly sensitive methodologies, indicating indirect neuronal injury in both scenarios (99, 100).

5.2.6. Optical Coherence Tomography

Optical coherence tomography (OCT) is a non-invasive imaging test that takes cross-sectional retinal images, allowing the physician to analyze each distinct layer of the retina (101). It is a critical part of the diagnosis of optic neuritis and can help distinguish between MOGAD, AQP4-IgG+NMOSD, and MS (102-106).

Acute MOGAD-ON has been shown to exhibit more frequent and extensive optic disc edema than other demylinating disorders (107). Degree of optic disc edema can be quantified by using OCT and measuring the peripapillary retinal nerve fiber layer (pRNFL). Acute MOGAD-ON presents itself with a significantly thickened pRNFL:164 μm vs. MS at 103 μm, according to Chen et al. (107). Three to six months after an acute optic neuritis attack, there is progressive thinning of the pRNFL and the macular ganglion cell and inner plexiform layer (mGCIPL) (108). One study showed that there is a correlation between pRNFL thinning and worse visual outcomes if the thinning of the pRNFL is below 75 μm (109); MOGAD tends to present with

this severe thinning only after recurrent attacks, whereas in AQP4-IgG-positive-NMOSD, the thinning tends to appear after only one single attack.

Optic neuritis from AQP4-IgG+NMOSD, compared to MOGAD, is known to cause more severe vision loss with similar levels of pRNFL and mGCIPL thinning (110-112). This could be due to the different cellular targets of both diseases: AQP4-IgG+NMOSD being an astrocytopathy with the potential for more severe retinal dysfunction (112). It could also be that OCT is incapable of capturing the complete picture of optic nerve damage in AQP4-IgG+NMOSD optic neuritis compared to MOGAD.

5.2.7. Myelin Oligodendrocyte Glycoprotein IgG Testing

A positive MOG IgG test using a reliable assay with as little risk of a false positive as possible is arguably the best way to secure a proper MOGAD diagnosis. The bodily fluid usually used for testing is serum, especially at the initial appointments, as CSF is a more invasive diagnostic tool and should only be tested if a patient presents with clinical-MRI features of MOGAD but has negative serum since isolated CSF positivity for MOG-IgG is rare but possible (113, 114).

The standard assay employed is the Live CBA, which uses full-length human MOG. CBAs usually include (1) a fluorescence-activated cell sorting (FACS) assay quantifying a fluorescence ratio between MOG transfected vs non-transfected cells or (2) a visual assessment using a fluorescence microscope of transfected cells using (115).

The live CBA is highly specific for MOGAD (≈ 99%) and is thus considered the gold standard. Another assay option with a slightly slower specificity (≈ 98%), albeit superior to other non-CBAs such as enzyme-linked immunosorbent assay (ELISA), is the commercially available fixed CBA (Euroimmun). In this assay, the MOG protein may be altered due to the fixation process, thus hampering MOG-IgG recognition (115).

5.2.8. Challenges in Myelin Oligodendrocyte Glycoprotein -IgG Testing

False positives in CBAs still present a challenge in MOG IgG testing, even though the specificity is so high. They are more common when testing is done indiscriminately over large, unselected populations (116, 117). A two-year study at the Mayo Clinic found that MOG-IgG at low titer can be found in up to 2.5% of MS patients and a 28% rate of false positives in patients tested for MOG-IgG using FACS CBA, despite a specificity of 98% (116).

With such a high specificity, a positive MOG-IgG is the best and most straightforward way to diagnose MOGAD quickly. Physicians will thus test for MOG-IgG even when clinical-MRI symptoms point towards MS to rule out differential diagnoses. The Mayo Clinic, for example, reports about 20,000 samples sent into their lab per year, with one-quarter of positive results being a false positive, with MS being the overwhelming correct diagnosis (116). This was especially true at lower MOG-IgG1 titers, with the positive predictive value being 100% for titers of ≥1:1000, 82% for titers of 1:100, and 40% for titers of 1:20 (116). Features of MS — such as the presence of CSF-restricted OCBs and persistent characteristic T2 abnormalities — plus a MOG IgG titer would aid the physician in believing the positive MOG-IgG test is a false positive. However, it is simpler to avoid MOG-IgG testing in cases where MRI and clinical features strongly indicate MS to minimize the risk of diagnostic confusion (116). A thorough assessment of clinical-MRI attributes before testing will significantly increase the predictive value of MOG-IgG tests. Thus, the diagnosis of MOGAD should be made with a high level of clinical judgment.

5.2.9. Differential Diagnosis

The most important diseases to distinguish MOGAD from are MS and AQP4-IgG+NMOSD, as they are the most likely differential diagnoses.

Differentiating MOGAD from AQP4-IgG+NMOSD is simple enough as both have reliable serum biomarkers, and dual positivity of MOG-IgG and AQP4-IgG is rare (118). Differentiating MOGAD from MS is more challenging since MS does not have an antibody biomarker.

However, since MS is much more common, a MOGAD diagnosis is crucial for patients given MS treatments but who are relapsing since some disease-modifying therapies for MS appear to be ineffective for MOGAD (119).

The best way to differentiate MOGAD and MS is, of course, the MOG-IgG antibody status; however, as previously mentioned, MOG-IgG at low titer can be found in up to 2.5% of MS patients, and false positives can occur especially at lower titers (116). Thus, its findings alone are insufficient. Another discriminatory marker would be CSF oligoclonal bands; these are absent in most patients with MOGAD and are present in most patients with MS. Clinical and MRI features, particularly the evolution of T2 lesions; most MS lesions leave a residual signal abnormality, while most MOGAD T2 lesions resolve over time (50, 51, 71, 72).

AQP4-IgG-negative-NMOSD and ADEM are characteristic clinical syndromes associated with MOGAD, and clinical-MRI findings should lead to MOG-IgG testing. If seropositive with adequately high titers, the diagnosis of MOGAD should be given; if seronegative or titers are too low to provide predictive value, their syndromic descriptions are appropriate (120). Similarly, patients with single/recurrent myelitis or optic neuritis that does not fulfill the diagnostic criteria for another disease, for example, MS, can be given their syndromic descriptions unless MOG-IgG is positive, then MOGAD would be a more appropriate diagnosis (120).

In children presenting with rapidly worsening myelitis, another important disorder in the differential diagnosis is acute flaccid myelitis (AFM), which can have significant overlapping features with MOGAD, including a longitudinally extensive spinal cord lesion. With AFM, acute motor weakness is caused by dysfunction or death of anterior horn cells within the gray matter of the spinal cord; MRI of the spinal cord typically identifies T2 hyperintense lesions restricted to or predominantly involving the gray matter, as opposed to both gray and white matter in MOGAD (120). AFM is thought to be caused by viruses; thus, this diagnosis should be considered in children with recent diagnoses or symptoms of enterovirus (fever, runny nose,

sneezing, cough, skin rash, body and muscle aches). Another diagnosis to consider as well is polio since AFM and polio present similarly (121).

6. Treatment

6.1. Treatment of Acute Attacks

Since there have been no randomized controlled trials for MOGAD, treatment recommendations are mainly based on treatment for AQP4-IgG+NMOSD or retrospective studies. However, some drugs, such as rituximab, which is very effective for AQP4-IgG+NMOSD, are not as effective for MOGAG (72).

Acute attacks of MOGAD tend to be severe, so treatment is prescribed as soon as possible in almost all cases since some research has shown that early treatment may prevent lasting damage (122).

Current guidelines recommend an initial treatment of high-dose intravenous (IV) methylprednisolone (1000 mg in adults or 20 to 30 mg/kg per day in children) for five consecutive days (123). Oral prednisone has been shown to have a similar effectiveness, 1250 mg once daily for five days; thus, this may be an alternative for an acute attack in adults (124). However, this treatment plan involves taking 25 tablets daily, which may be difficult for some patients (124). Common side effects include hyperglycemia (more relevant in diabetic patients) and steroid-induced psychosis. Research has also shown the benefit of a glucocorticoid slow taper over 6-8 weeks, especially after a first attack or in patients who are starting maintenance immunotherapy since the full effect of those drugs may take weeks to months (123). A recent study by Nosadini et al. (125) found that a corticosteroid treatment of 5 weeks or longer was associated with a 6.7-fold reduced odds of relapsing disease course. More research must be done in patients with frequent relapses since prolonged glucocorticoid treatment carries the risk of many side effects such as osteoporosis, aseptic joint necrosis, adrenal insufficiency,

gastrointestinal, hepatic, and ophthalmologic effects, hyperlipidemia, growth suppression, and possible congenital malformations (126).

If glucocorticoid therapy does not provide total symptom relief, the next treatment option for adults is therapeutic plasma exchange (PLEX), one exchange every other day for five to seven exchanges (127). This may be a treatment option in children as well, as long as the treatment center is adequately trained. An alternative, especially for children, is intravenous immunoglobulin (IVIG), 2g/kg, given over two to five days (128).

In rare cases, refractory to conventional acute treatments, more aggressive immunosuppression with cyclophosphamide, rituximab, or tocilizumab can be considered (72).

6.2. Maintenance Treatment

50% of patients with MOGAD have a monophasic course, with good recovery from the disease attack (72); thus, initiating a long-term immunosuppressive treatment should be considered carefully and implemented only in those who have had two or more attacks. A particular case would be in patients who have extreme residual morbidity to prevent further disability, for example, a patient with extreme vision loss and in whom another attack would potentially cause total blindness. There is no data to support this treatment method; thus long-term treatment should be done on a patient-to-patient basis (72, 123).

6.3. IVIG

Standard long-term treatment options include a maintenance intravenous immunoglobulin (IVIG) with a loading dose of 0.4 g/kg/day for five consecutive days, followed by treatment every four weeks with a dose of 0.4 g/kg to 2 g/kg. This option can be considered for patients in whom long-term immunosuppression is especially problematic such as children or immunosuppressed individuals. A study by Chet al. al (119) showed that the relapse rate after six months or longer of immunotherapy was the lowest after IVIG (20%) and with mycophenolate mofetil, rituximab, and azathioprine were significantly higher (74%, 61%, and 59%,

respectively) (119). Another form of immunoglobulin therapy is subcutaneous Ig, which has been recently shown to be safe and effective in preventing relapses in a series of six MOGAD patients. This treatment option may be a more suitable choice as it has been shown to be more tolerable and it can be self-administered (129).

6.4. Azathioprine and Mycophenolate Mofetil

Azathioprine and mycophenolate mofetil are the most commonly prescribed glucocorticoid-sparing immunosuppressant medications for MOGAD. Their benefits are that they are oral tablets, and their cost is significantly lower. However, due to the long time they take to demonstrate effect (3-6 months), usage of these medications typically require a transitional glucocorticoid treatment (123), as previously mentioned, relapse rates are higher (119).

Azathioprine, an oral immunosuppressant that inhibits B and T cell proliferation by preventing purine synthesis, is generally administered at the dose of 2–3 mg/kg/day (123). Mycophenolate, also an oral immunosuppressant and a preventor of B and T cell proliferation by guanosine nucleotide production inhibition, is taken in adults as a 500 mg pill taken twice daily for two weeks and then increases to a maintenance dose of 1000 mg twice daily (123). In children, the goal dose is 650 mg/m2 per day. Azathioprine and mycophenolate mofetil are both associated with a 50% chance of relapse, however, this may be due to the delayed effect of the drug. Thus, relapses may occur during the 3-6 months they take to be effective (119, 130-133).

Mycophenolate is often linked to gastrointestinal issues and an increased chance of cancer after prolonged use. It's important to note that it can be harmful during pregnancy, leading to congenital disabilities. Both medications raise the risk of infections and low blood cell counts. It's crucial to monitor blood levels regularly before and during treatment. Keeping an eye on kidney and liver function is also necessary as both these drugs can be toxic in those areas. Azathioprine may cause skin rashes and high liver enzyme levels, indicating liver damage. Furthermore, there's a known long-term association with cancers like lymphoma and skin tumors (123).

6.5. Rituximab

As mentioned, treatment recommendations for MOGAD are mainly based on treatment for AQP4-IgG+NMOSD or retrospective studies (72). Thus, rituximab, an anti-CD20 monoclonal antibody, which is highly effective in preventing relapses in AQP4-IgG+NMOSD, was hoped to be equally as effective in MOGAD treatment. However, up to one-third of MOGAD patients may still experience relapses despite complete B-cell depletion (25, 66) using rituximab. When used as a first-line treatment, rituximab has increased efficacy (25, 119). For adults, rituximab is typically administered as IV with a dosage of 375 mg/m2 of body surface area/week for four weeks, followed by a similar dose weekly for 2-4 weeks at reinfusion, or as a single 1 g dose repeated after two weeks, with subsequent infusions varying based on the protocol (generally 1 g x 2 doses separated by two weeks, a single 1 g reinfusion, or 375 mg/m2/week for two weeks) (123).

Since it takes about 8-12 months for B cells to re-proliferate, infusions can be pre-scheduled, usually at 6-month intervals, or by regular measurements of CD19+ B-cells every 6-8 weeks until they consist of 1% of total mononuclear cells (134).

Rituximab is considered safe and generally deemed well-tolerated. Most common side effects are typically related to infusions and an increased risk of future infections, especially for patients who have a history of immunosuppression, lymphopenia, or hypogammaglobulinemia (135). Studies have shown occasional cases of prolonged B-cell depletion following rituximab treatment (136), which may contribute to this long-term immunosuppression. COVID-19 may be more severe, and the COVID-19 vaccine may be less effective in patients taking rituximab suffering from NMOSD. However, this association was only found in patients with comorbidities such as hypertension, diabetes, and morbid obesity (137–139).

6.6. Interleukin-6 Targeting Treatment

Interleukin-6 (IL-6), a cytokine that produces a multitude of effects, inflammation being the most pertinent in MOGAD, has been a target of treatment (140), especially for MOGAD patients who

are not responding to other immunosuppressive therapies (141-143). For example, a recent case report by McLendon et al. (144) showed a substantial response to tocilizumab in two children with malignant cerebral edema due to MOGAD (144). The drug of choice is typically tocilizumab, which is administered at a dosage of 8 mg/kg every month, with an upper limit of 800 mg per month for adults (123). An ongoing, multicenter randomized controlled trial is currently underway to assess the effectiveness of satralizumab in treating MOGAD (145).

New treatment options for MOGAD may involve exploring B cell-depleting monoclonal antibodies other than rituximab. This includes medications like ocrelizumab, ofatumumab, which targets CD20, and inebilizumab, which targets CD19 (146, 147). These drugs could serve as alternatives to rituximab since they have similar mechanisms of action. For example, in one clinical trial, inebilizumab effectively reduced relapses in patients with AQP4-IgG+NMOSD (148).

Another medication, Eculizumab, which targets C5, has proven to be highly effective in preventing relapses in AQP4 IgG+NMOSD, according to trials (149). However, its effectiveness for MOGAD is still uncertain due to data and unanswered questions about how the complement system contributes to the disease's development. Eculizumab might be considered for refractory cases of MOGAD even though there are no published case studies on its use for this condition yet (150, 151).

Furthermore, Rozanzolixizumab is a treatment option that works by inhibiting the neonatal Fc receptor, which helps break down harmful autoantibodies. This approach has been effective in treating myasthenia gravis in patients with antibodies against the acetylcholine receptor (152). Currently, a clinical trial is underway to evaluate its effectiveness in treating MOGAD (153).

6.7. Prognosis

In general, MOGAD tends to be quite responsive to glucocorticoid therapy, with rapid reversal of symptoms in most cases (154), with most children and adults only having a monophasic disease

course. Depending on the study, up to 40 – 50% will have further episodes (70, 155), with the monophasic disease being more likely among pediatric MOGAD patients if ADEM is the main symptom of their initial episode and multiphasic if optic neuritis is the first symptom (156). In general, the older the age of onset, the higher the probability of recurrence (156).

The Expanded Disability Status Scale (EDSS) is primary used in evaluation of MS severity but is used as well to measure disability following attacks of MOGAD. The scoring system ranges from 0 to 10, with a score of 6 or more indicating a need for a walking aid and 10 indicating death (157). One retrospective cohort study observed that over 60% of the MOGAD patients (61 in total over the median course of 28 years) maintained an EDSS score of less than 3, thus implying generally good outcomes (158). Also, unlike MS, where progression is the norm, MOGAD patients typically do not show such progression (159). Furthermore, MRIs done after relapses in MOGAD patients tend to show full recovery, compared to MS, where patients will have lesions even after symptoms have subsided (41, 50, 51),

Currently, there are no universally agreed-upon methods to predict who will have a relapsing disease course, and no MRI or clinical features can accurately predict future disease course (70). Furthermore, initial serum MOG-IgG titers do not predict recovery or relapse (70). However, some studies found a 2-10 fold increased likelihood of relapse with persistent MOG-IgG (160-163), particularly when the MOG-IgG titer remains high (160, 162, 163). Recent studies also indicate that recurrent attacks are more common among MOGAD patients if optic neuritis is their initial symptom, with MOGAD-ON attacks often leading to residual symptoms of optic nerve damage (28).

A study in the UK that followed patients diagnosed with MOGAD over 28 months has shown that 47% of the patients presented with permanent disabilities, such as impaired vision, restricted activity, and bladder, bowel, and erectile dysfunction (39). Another study indicated significant disability remained in 40% of the patients after a monophasic attack, with severe visual impairment (36%) and seriously impaired ambulation as the most common long-term effects

(133). There does seem to be an accumulation of symptom severity throughout multiple relapses, especially those involving vision (164), therefore highlighting the importance of an early diagnosis and treatment.

MOGAD may cause morbidity but rarely mortality. Lotan et al. (2023) calculated a crude mortality rate of 2% after conducting a retrospective study with 142 participants, which they stated is comparable to the age‐adjusted mortality rates reported for the general population in the United States (165). Upon reviewing other historical MOGAD cohorts, they also mentioned that mortality is very low. This may be because MOGAD mainly involves the optic nerves, spinal cord involvement in MOGAD often affects the thoracic region, and the conus medullaris (44, 74) may contribute to its lower mortality rate. Infections are another major cause of death in neuroinflammatory diseases, with the risk increasing significantly if treated with immunotherapy (135). MOGAD patients tend to be treated first with glucocorticoids and, thus, are less likely to develop severe disabilities (39), so they may therefore be less prone to severe and life‐threatening infections. Furthermore, mortality naturally increases with age, and the relatively younger age and low rate of comorbidities in many patients with MOGAD may also be an attribute (158).

6.8. Future Directions and Conclusion

Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD) is a recent addition to Central Nervous System (CNS) demyelinating disorders, with its recent diagnostic criteria being outlined and still under dispute (70). Previously, it slipped under the radar as Multiple Sclerosis (MS) or aquaporin-4 antibody-positive Neuromyelitis Optica Spectrum Disorder (AQP4-IgG+NMOSD) to the detriment of many patients who would have significantly benefited from a more targeted treatment plan. Due to the specific antibodies produced in MOGAD, distinct MRI-clinical features, and different treatment plans, this disease clearly needed its own designation.

One reason for MOGADs late discovery was that the antibody MOG-IgG was only elucidated in 2007 (69). Although highly specific for MOGAD, low titers and atypical presentation may lead to false positives; thus, a more dynamic clinical approach is necessary. The most significant difficulty in diagnosing MOGAD is differentiating it from MS and AQP4-IgG+NMOSD. Research has shown that differentiating MOGAD from AQP4-IgG+NMOSD can be done with seropositivity, MOG-IgG indicating MOGAD, and AQP4-IgG seropositivity suggests NMOSD. Furthermore, radiological findings of specific lesion patterns in the brain, spinal cord, and eyes can aid in differentiation. Differentiating MOGAD from MS can be done with seropositivity for MOGAD since MS does not have specific antibodies, but also analyzing lesion resolution, which is more common in MOGAD, clinical symptoms such as cognitive impairment and sphincter dysfunction, more prevalent in MOGAD and CSF findings, like the presence of Oliclonal Bands (OCB) can help differentiate MS from MOGAD since OCB are usually absent in MOGAD.

Treatment for acute attacks in MOGAD is typically IV glucocorticoids or plasma exchange. However, long-term management options still need to be further researched as treatment plans are based on NMOSD and involve further glucocorticoid use and use of immunosuppressants such as azathioprine and mycophenolate mofetil. Rituximab can be used but has shown lesser efficacy than in NMOSD. Treatments targeting Interlerukin-6 (IL-6) are being researched and utilized in some patient cases with positive results.

Research on MOGAD is evolving, and there are numerous future research options. Further elucidation of the pathogenesis of MOGAD, which will help aid in creating targeted treatment, is one necessary area of research. Larger scale studies on the epidemiology of MOGAD, genetic predispositions, gene-environment interactions, and predictors of monophasic and relapsing disease also require further exploration. Research is needed to identify and categorize radiologic features specific to MOGAD and distinguish them from other neuroinflammatory conditions like NMOSD. As mentioned previously, vitamin D and gut microbiome changes are already being explored. Specific treatments for MOGAD are necessary, either confirming the current treatment plans as ideal or discovering other drugs such as B cell-depleting monoclonal antibodies like

ocrelizumab, and improving treatment plans so that they are more personalized, taking into account the age of onset, MOG antibody titers, and comorbidities.

Multi-country and institute collaborative research and a patient-focused approach will guide the way for a more targeted and personalized diagnosis and treatment for MOGAD, improving patient morbidity. Although there is a long way to go in elucidating the mysterious and new disease, dedication seems only to garner strength, driven by the innate desire to change patients' lives and deepen our knowledge of autoimmune neurologic conditions.

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