Neuromyelitis optica and myelin oligodendrocyte glycoprotein

Angela Huang[1], Aroucha Vickers[2], Claudia M. Prospero Ponce[2], Andrew G. Lee[2,3,4,5,6,7,8]

[1]Baylor College of Medicine, Houston, TX, USA; [2]Department of Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, Houston, TX, USA; [3]Department of Ophthalmology and Visual Sciences, The University of Texas Medical Branch, Galveston, TX, USA; [4]Departments of Ophthalmology, Neurology, and Neurosurgery, Weill Cornell Medicine, New York City, NY, USA; [5]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Texas A and M College of Medicine, College Station, Bryan, TX, USA; [7]The University of Iowa Hospitals and Clinics, Iowa City, IA, USA; [8]The University of Buffalo, Buffalo, NY, USA

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Correspondence to: Andrew G. Lee, MD. Blanton Eye Institute, Houston Methodist Hospital, Scurlock Tower, 6560 Fannin St. Ste 450, Houston, TX 77030, USA. Email: aglee@houstonmethodist.org.

Abstract: Neuromyelitis optica (NMO) refers to an antibody mediated, inflammatory disorder of the central nervous system (CNS) characterized by recurrent or monophasic attacks of optic neuritis and myelitis. Most patients with NMO possess a specific serum immunoglobin, NMO-IgG, which can serve as a biomarker for NMO. The autoantibodies target aquaporin-4 (AQP4), the main water channel protein found in the CNS including the brain, spinal cord, and optic nerve. The remaining 10–25% of patients are seronegative for NMO-IgG despite meeting the diagnostic criteria for NMO. Recent studies have shown that a subset of these patients is seropositive for antibodies against myelin oligodendrocyte glycoprotein (MOG). This paper will provide an overview of the current English scientific literature published regarding the history, epidemiology, AQP4 biomarker, MOG biomarker, diagnosis, clinical features, related diseases in NMO spectrum disorder (NMOSD), and treatments of NMO.

Keywords: Neuromyelitis optica (NMO); Devic disease; aquaporin-4; myelin oligodendrocyte glycoprotein (MOG)

Introduction

Neuromyelitis optica (NMO), also called Devic syndrome, is a heterogeneous inflammatory disorder of the central nervous system (CNS) characterized by recurrent or monophasic episodes of optic neuritis and myelitis. Optic neuritis refers to inflammation and demyelination of the optic nerve. Myelitis refers to inflammation of the spinal cord. NMO spectrum disorders (NMOSD) describes a wider clinical spectrum of manifestations of NMO including limited or related forms of NMO, including recurrent isolated optic neuritis (RION), recurrent myelitis associated with longitudinally extensive spinal cord lesions, optic neuritis or myelitis associated with systemic autoimmune disease, Asian optic-spinal multiple sclerosis (MS), other brain syndromes, and combinations. This review article aims to summarize the knowledge and data of NMO in the current English published scientific literature. This paper will provide an overview of the history, epidemiology, AQP4 biomarker, MOG biomarker, diagnosis, clinical features, related diseases in NMOSD, and treatments of NMO.

History

The earliest reports to describe relationships between myelitis and optic nerve occurred during the 19th century. The term NMO, later Devic syndrome, originated from an 1894 review published by French neurologist Eugène Devic and his student Fernand Gault who analyzed 16 patients with both myelitis and amaurosis (1). NMO was thought to

be a variant of MS for the next century, until distinguishing clinical, immunological, pathological characteristics were found to separate NMO from MS as its own disease entity.

Epidemiology

Epidemiological studies from various countries indicate that NMO has a prevalence rates of around 0.52/100,000 to 4.4/100,000 (2,3). NMO has been found in higher frequency in individuals of Asian or African descent than in Caucasians populations (2). A study on a multicenter cohort of patients in the United States with NMO-IgG seropositive NMO, NMO-IgG seronegative NMO, and NMO-IgG seropositive NMOSD revealed that 29.4% of the cases were incorrectly diagnosed as MS, especially before the availability of the AQP4-IgG antibody tests (3). Therefore, the true prevalence of NMO may be greater than reported. As the availability of AQP4-IgG antibody tests increases and the test becomes more widely used, it is expected that the prevalence of NMO will also increase in the future.

NMO has been found in higher frequency overall in women than in men with a female:male ratio of 1:9 (4). NMO with a recurrent course has been found to be more frequent in females than males with a female:male ratio of 5:1–10:1, whereas NMO with a monophasic course has been found to exist in equal frequency between females and males (5). While NMO can become symptomatic in any age group including children and the elderly, the mean age at which relapsing NMO is diagnosed is 39 years old, whereas it is 29 years old for monophasic NMO (6). NMO may occur with antecedent factors such as postpartum period, and is associated with a higher frequency of relapses during last trimester of pregnancy and postpartum (7).

Clinical features

Optic neuritis

In around 90% of patients with NMO, NMO occurs in relapsing episodes with attacks of ON, myelitis, or both (8). In the remaining 10% of patients, NMO takes on a monophasic course generally with simultaneous presentation of optic neuritis and myelitis (9). NMO attacks are often severely debilitating and can cause increasing disabilities if left untreated due to incomplete remission (10). Benign forms of NMO are rare and difficult to define, especially since a disabling attack may occur

unpredictably after a long remission period. Symptoms of NMO relapses usually increase over a span of several days before tapering off over the next few weeks or months. Attacks of optic neuritis and myelitis are more likely to occur at different periods of time than to occur simultaneously (10). Long-term outcomes in visual acuity, motor strength, and sensory function are generally better for patients who experience a monophasic course rather than a relapsing course of NMO (9).

Optic neuritis in NMO patients typically presents unilaterally, but it can also present bilaterally as vision loss and pain with eye movement. Over 50% of patients who experience a relapsing course of NMO develop blindness in at least one eye after 5 years of initial onset of disease or require ambulatory aid (11).

Transverse myelitis

Myelitis in NMO patients usually presents as spinal cord lesions in the cervical portion of the spine. The spinal cord lesions are generally in the form of longitudinal extensive transverse myelitis (LETM) involving three or more vertebral segments (12). Compared to MS, patients with myelitis caused by NMO experience greater frequency of complete transverse myelitis with tetraplegia or paraplegia. They will typically experience loss of sensation below the lesion and dysfunction of the bladder sphincter (7). Acute myelitis can be accompanied by pain, paroxysmal tonic spasms of the trunk and extremities, radicular pain, and Lhermitte sign, especially in relapsing attacks (7).

Miscellaneous

NMO has been reported to affect the brain in addition to the optic nerves and spinal cord. There have been reports of up to 59% of NMO patients who experienced attacks to the CNS not limited to the optic nerves or spinal cord. Lesions in the brain stem can lead to characteristic brainstem symptoms of intractable hiccups, nausea, and respiratory failure (7). Most deaths associated with NMO are caused by respiratory failure in the brainstem from extended cervical myelitis. Other symptoms reported associated with the brainstem, include hearing loss, diplopia, nystagmus, trigeminal neuralgia, facial numbness, and symptomatic narcolepsy (13). NMO has also been reported in association with endocrine pathologies caused by diencephalic lesions (14). There is also association with seizures, encephalopathies, posterior reversible encephalopathy

syndrome (15).

Patients with relapsing course of NMO generally experience older onsets, longer time interval between the first two episodes, less debilitating motor impairment upon the initial myelitis episode, have other autoimmune diseases, and are more frequently female than male. Around 55% of patients experience their first relapse of optic neuritis and or myelitis within 1 year after the initial onset (9). Around 90% of patients experience their first relapse within 5 years.

The prognostic characteristics of NMO are affected by the age of onset and by genetic factors. A cohort study comparing NMO disease courses among different populations in the UK and Japan showed that older-onset patients had greater risk of motor disability, whereas younger-onset patients in the UK had greater risk of visual disability (16).

Patients with NMO-IgG disease rarely experience seizures or encephalitis-like presentation, whereas they are more common in patients with MOG-IgG disease. In a single-center study on 34 MOG-IgG patients and 100 NMO-IgG patients, around 15% of MOG-IgG patients experience seizures or encephalitis-like presentation, compared to 1% of NMO-IgG patients (17). The MOG-IgG patients with seizures show associated inflammatory cortical brain lesions on magnetic resonance imaging (MRI). The encephalitis in MOG-IgG patients can be severe with lasting damage. The seizures and encephalitis-like presentations in MOG-IgG patients are thought to be caused by demyelination events. In contrast, the incidence of seizure disorders in patients with MS is 2.28% and the prevalence is 3.09% (18).

Biomarkers

AQP4-IgG biomarker

Originally, NMO was thought to be a subtype of MS as a monophasic disease with simultaneous bilateral optic neuritis and acute transverse myelitis. Later studies showed that NMO is more frequently relapsing than monophasic (8), and can involve the brain in addition to the optic nerve and spinal cord (19). In 2004, the important discovery of the serum autoantibody NMO-IgG or AQP4-IgG heavily supported the separation of NMO from MS as different disease entities (20). The autoantibody is rarely found in patients who are healthy or who have other neurological diseases (21). NMO-IgG binds to aquaporin-4 (AQP4), the main water channel protein in the brain, spinal cord, and optic nerve (22). The NMO-IgG antibodies are detectable in the serum of up to 80% of patients with the clinical phenotype of NMO (23). The serum autoantibody shows 76% sensitivity and 94% specificity for NMO (12). Therefore, NMO-IgG is currently recognized as a highly specific biomarker for NMO. Its discovery has led to better diagnosis of NMO and understanding of its pathogenesis. NMO-IgG can be detected through different methods including cell-based assay, indirect immunofluorescence, enzyme-linked immunosorbent assay (ELISA), and flow cytometry assay. According to the 2015 international consensus diagnostic criteria, cell-based assay is the most recommended method based upon sensitivity and specificity for the wider clinical manifestations of NMO in NMOSD including limited or related forms of NMO.

Populations of different geographies and ethnicities demonstrate different levels of seropositive status for AQP4-IgG. Seropositive status for AQP4-IgG has been shown in 70–76.9% of Chinese, 63–90% of Japanese, 56–73% of Caucasians, 47% of Italians, and 33.3% of Caribbean patients with NMOSD (24).

AQP monomers typically contain six long helical segments that span the cell membrane and two helical segments that do not span the cell membrane (25). The monomers contain water pores that allow water molecules to move through the membrane through structural and electrostatic design. AQP4 are unique in that the tetramers of AQP4 channels can form supra-molecular assemblies in the plasma membrane called orthogonal arrays of particles (OAPs) (26). AQP4 exists as two major isoforms, a long M1 isoform and a short M23 isoform. OAPs are formed through interactions between the M23 isoforms. In patients with NMO, AQP4-IgG binds more to AQP4s of the M23 isoform than the M1 isoform, possibly due to preferred binding to OAPs formed by the M23 isoform (27).

In the brain, AQP4 is primarily located in the astrocyte foot processes at the blood brain barrier and the interfaces of the CNS with cerebrospinal fluid (CSF) (28). The locations of the AQP4s allow them to regulate water homeostasis in the brain through water movement into the brain (22). In regions of the brain not involved in the blood brain barrier and the hippocampus, AQP4 is located throughout the plasma membrane of astrocytes. In the hippocampus, AQP4s may be involved in water fluxes that affect ion movements during electrical activity (29). In the spinal cord and optic nerve, AQP4 are also located in perivascular astrocyte foot processes. AQP4 expression is reduced in patients with AQP4-IgG positive status.

Patients with NMO-IgG serum positive status are thought to have NMO caused by autoimmune attacks that damage the astrocytes in the optic nerves and spinal cord. AQP4-IgG is believed to enter CNS, bind to AQP4, cause down-regulation of AQP4 through endocytosis, and lead to disruptions in water movements and homeostasis in the CNS. AQP4-IgG is also believed to activate complement produced by local astrocytes, which leads to an increase in the permeability of the blood brain barrier and an influx of eosinophils and neutrophils into the CNS. The events cause cell death of astrocytes, oligodendrocytes, and neurons (11).

AQP4-IgG levels in patients with NMO fluctuate depending on the disease course and treatment. AQP4-IgG levels have been found to increase with relapses and decrease following treatment (30). Patients with more severe NMO tend to have higher AQP4-IgG levels, such as in patients with permanent complete blindness in at least one eye or with extensive or large cerebral lesions in MRI (31).

MOG-IgG

AQP4-IgG antibody is still debated as a measure for the clinical parameters of NMO as 12–24% of NMO patients are AQP4-IgG seronegative (32). While the high percentage may be due to insufficient sensitivity of the assays, some of the AQP4-IgG seronegative patients are proposed to have other antibodies which cause NMO. The target of autoimmune response in these seronegative patients is mostly unknown. However, recent studies indicate that myelin oligodendrocyte glycoprotein (MOG) autoantibodies may be associated with NMO in AQP4-IgG seronegative patients (33). In addition to its presence in a subset of NMO patients, MOG-IgG is also detected in patients with recurrent optic neuritis, LETM, acute disseminated encephalomyelitis (ADEM), and MS (34). In most studies, MOG-IgG serum positive status has not been found in NMO patients who also have AQP4-IgG serum full-length human MOG (FL-MOG) antibody has been shown to also be positive in MS and healthy patients. Using the anti-human IgG secondary antibody (IgG1-specific secondary antibody) may improve the specificity of the test (35). However, further research is needed on the optimal detection method.

MOG is a glycoprotein located on the outer surface of myelin sheaths in the CNS. It makes up approximately 0.05% of total myelin protein (33). It is encoded by the MOG gene in humans and is highly conserved. MOG is proposed to play a role in the maintenance or structure of myelination of nerves. MOG-IgG binds to the extracellular domains of MOGs, which can cause temporary reversible damage to the myelin and axons. The changes may affect the structure of the nodes of Ranvier and impact potential firing of the nerves (33). The exact effect of MOG-IgG *in vivo* is unknown. Studies indicate that MOG-IgG binding may cause conformational changes that directly impair the myelin structure, and that there is a lack of complement activation (33).

While patients with MOG-IgG seropositive status share some clinical and demographical features with AQP4-IgG seropositive patients and patients seronegative for both antibodies, there are also some marked differences. A study of patients in Brazil and Japan showed that around 20% of NMOSD patients seronegative for AQP4-IgG were positive for MOG antibodies (36). The attacks showed better recovery after first attack when compared to AQP4 seropositive patients or NMOSD patients who were seronegative for both antibodies. In this study, patients with MOG antibodies demonstrated male predominance, simultaneous optic neuritis, optic nerve lesions more than spinal cord lesions. More specifically, MRI spinal cord lesions were exhibited by 37% of MOG-IgG seropositive patients compared to the higher frequency of 92% in AQP4-IgG seropositive patients or 71% in seronegative patients (36). Whereas AQP4-IgG patients tend to possess spinal lesions in the cervicothoracic region, MOG-IgG seropositive patients tend to possess spinal lesions in the thoracolumbar region (36).

The median age of NMO onset in MOG-IgG positive patients was also found to be a few years older than in the AQP4-IgG seropositive patients and seronegative patients. Another study evaluated 23 patients with NMOSD with negative AQP4 antibody in Sydney, Australia, indicated a small female predominance (12/23) of MOG seropositive status. They also found a greater frequency of bilateral and recurrent optic neuritis and observed that all MOG seropositive patients had prominent optic nerve swelling; most of the patients responded to steroids (37).

A study reviewing patients with anti-MOG optic neuritis found that these patients had significantly higher percentages of best-correct visual acuity (BCVA) 6 months after the attack than patients with anti-AQP4 optic neuritis or patients seronegative for both MOG and AQP4 (38). There was no significant difference of the average peripapillary retinal nerve fiber layer (RNFL) thickness after 6 months between anti-MOG optic neuritis

patients and anti-AQP4 optic neuritis patients, but both were thinner than in optic neuritis patients seronegative for both MOG and AQP4. The recovery of visual acuities was as good in anti-MOG optic neuritis patients as in patients seronegative for both MOG and AQP4, whereas anti-AQP4 optic neuritis patients have significantly thinner RNFL of the optic nerve head (38). A study reviewing 87 patients with anti-MOG optic neuritis from Mayo Clinic and collaborating neuro-ophthalmologist determined an average outcome of 20/30 vision with only 5 (6%) of the patients experiencing 20/200 vision or worse (personal communication). Analysis of the Optic Neuritis Treatment Trial (ONTT) shows 3 anti-MOG optic neuritis patients, 2 with recurrent optic neuritis and 1 with single optic neuritis, with 20/20 vision outcome without chronic immunosuppression (personal communication). Anti-MOG optic neuritis does not necessarily lead to poor outcomes or necessitate chronic immunosuppression. Whereas anti-AQP4 optic neuritis patients should always be treated, anti-MOG optic neuritis patients do not require treatment if patient has complete recovery. If patient with anti-MOG optic neuritis does not show complete recovery to 20/20, then consideration should be made for the patient to receive chronic immunosuppression due to the high risk of relapse (personal communication with John Chen MD, Mayo Clinic).

Glial fibrillary acid protein (GFAP)

GFAP is a highly sensitive biomarker for astrocytosis and gliosis that has received consideration as an additional diagnostic marker for NMO. In NMO, binding of AQP4 antibodies to the astrocytic foot processes is believed to damage astrocytes causing release of astrocytic proteins into the CSF, including GFAP (39). During a NMO relapse, the CSF GFAP levels are detected about a thousand times more in NMO than in patients with MS (40). In contrast to CSF GFAP levels, blood GFAP levels are not as markedly elevated. CSF GFAP levels in patients with NMO in the acute phase have been shown to correlate with Expanded Disability Status Scale (EDSS) or spinal lesion length (41). CSF GFAP levels have also been shown to return to normal after intravenous methylprednisolone treatment (40).

Diagnosis

NMO

A diagnosis of NMO should be considered in patients with severe attacks of optic neuritis or myelitis. In 1999, a diagnostic criterion was developed by Wingerchuk et al. to diagnose NMO and to distinguish NMO from MS (9). In their diagnosis, a patient must experience ON, myelitis, and meet one supporting criterion including LETM on spinal cord MRI, neutrophilic pleocytosis in CSF, or failure of the brain MRI to meet the diagnostic criteria for MS.

In 2006, the diagnostic criteria for NMO was updated by Wingerchuk et al. after the discovery of NMO-IgG (12)—The updated criteria factors in the specific NMO-IgG marker. The 2006 Wingerchuk et al. criteria are continued to be used today to diagnose NMO. The criteria are 99% sensitive and 90% specific for NMO. A diagnosis of NMO can be made according to the following conditions:

2006 Proposed Diagnostic Criteria for NMO by Wingerchuk et al.:

- ❖ Required conditions:
    - ◆ At least one episode of ON;
    - ◆ At least one episode of myelitis.
- ❖ Two of the three conditions below must be met:
    - ◆ Contiguous spinal cord MRI lesion extending over three or more vertebral segments;
    - ◆ Brain MRI not meeting the revised Paty's diagnostic criteria for MS;
    - ◆ NMO-IgG seropositive status.

As knowledge of NMO continues to grow, the diagnostic criteria for NMO can be expected to receive more updates in the future.

NMOSD

In recent years, there has been recognition of wider clinical manifestations of NMO that do not fulfill the 2006 Wingerchuk diagnostic criteria. These forms of NMO are termed NMOSD. The presence of anti-AQP4-IgG antibody has been found to be associated with ranges of CNS symptoms greater than just NMO. The wider clinical spectrum of NMOSD includes limited forms of NMO, including RION, recurrent myelitis associated with longitudinally extensive spinal cord lesions, optic neuritis or myelitis associated with systemic autoimmune disease, Asian optic-spinal MS (42), other brain syndromes, and combinations. NMOSD can be stratified based on serological testing for AQP4-IgG seropositive or seronegative status. AQP4-IgG seropositive NMOSD is associated with damage to astrocytes, whereas AQP4-IgG seronegative NMOSD is associated with damage to myelin.

The clinical diagnostic criteria for NMOSD were

updated by the International Panel for NMO Diagnosis in 2015 (43). For AQP4-IgG seropositive NMOSD, the criteria included positive test for AQP4-IgG, exclusion of other differential diagnoses, and presence of at least one core clinical characteristic of NMOSD in optic nerve, spinal cord, area postrema, brainstem, cerebrum, or diencephalon. For AQP4-IgG seronegative NMOSD, the criteria were more stringent with more neuroimaging required. The increased stringency is due to a larger number of other differential diagnoses such as neoplasms, sarcoidosis, and paraneoplastic disorders. The long-term outcome and treatment response can differ among NMOSD patients based upon presence of AQP4-IgG (44).

With the discovery of the AQP4-IgG antibody, clinical syndromes outside of the CNS were also included as possible disease characteristics. Inflammation of the area postrema that presents as intractable vomiting, nausea, or hiccups was recognized as a hallmark characteristic of NMOSD with AQP4-IgG (45).

Patients with NMO may have co-existing autoimmune inflammatory diseases (44,46), including but not limited to systemic lupus erythematosus (SLE) or Sjogren syndrome (46). It is true that some autoimmune diseases may directly cause transverse myelitis and/or optic neuritis, but these cases do not show a positive NMO-IgG (46). Optico-spinal MS and NMO share similar clinical features and MRI findings, and are debated to be the same disease due to the similar immunopathology in Asian population (42).

ADEM

In addition to AQP4 seronegative NMOSDs, MOG has also been found in patients with ADEM. ADEM is an acute autoimmune neurological disorder that shares clinical and pathological characteristics with other acute demyelinating syndromes such as MS or NMOSD (47). Demyelination occurs in the CNS including the brain, spinal cord, and sometimes the optic nerve. The etiology is thought to stem from inflammation, usually from prior infection or sometimes from immunization (48). Like NMO, ADEM can present with LETM, deep gray matter lesions, bilateral optic neuritis, bilateral multiple cerebral lesions of white matter. ADEM can be distinguished from NMO in that ADEM typically occurs in children, although it can be found in other age groups as well (49). In addition, ADEM does not have AQP4 autoantibodies and is usually monophasic rather than relapsing. ADEM can also be

distinguished by its main symptom of encephalopathy instead of optic neuritis and transverse myelitis for NMO. Although ADEM currently lacks a specific biomarker for identification, ADEM seems to share an association with MOG. A comparison of MOG seropositive status between patients with MS, ADEM, and AQP4-seronegative patients with ON, TM, or NMOSD revealed 36.4% of ADEM patients were sensitive for MOG antibodies, whereas around 5% of MS and 2% of AQP4-seronegative patients were sensitive for MOG antibodies, similar to healthy patients (50). For both ADEM and MS patients, MOG antibodies were more likely to be found in pediatric patients than older patients.

Chronic relapsing inflammatory optic neuropathy (CRION)

NMO should be compared to other underlying inflammatory diseases also characterized by optic neuritis beyond MS, especially as treatment and outcomes are different for other diseases. In 2003, Kidd *et al.* described a unique form of inflammatory optic neuropathy without demyelination and named the disorder as CRION (51). CRION is characterized by typically painful, severe, and bilateral visual loss with relapses and remissions which respond well to corticosteroid treatments and usually necessitating long-term immune suppression. Early recognition of CRION can reduce risk of blindness from inappropriate treatment. A 2011 study found that only 5% of patients with CRION are seropositive for NMO-IgG, which supports the separation of CRION as a distinct entity from NMO (52). Testing of NMO-IgG in patients with severe or recurrent optic neuritis is strongly supported for its high diagnostic specificity for the underlying disease. CRION patients also do not exhibit glial damage characteristic of NMO as detected through laboratory tests for the CSF GFAP biomarker for glial damage (53).

Like NMO, CRION is found more frequently in female populations and non-Caucasian populations (54). Both NMO and CRION also have worse outcomes than MS in terms of visual recovery. NMO and CRION patients have worse visual acuity and worse damage to the RNFL than patients with relapsing remitting MS although there is no significant difference between visual acuities and RNFL damage between NMO and CRION patients. High-dose corticosteroid treatment can be used at the onset of pain to prevent vision loss from optic neuritis attacks from CRION, NMO, and MS (55). Steroid withdrawal

tends to lead to relapse in CRION patients, so long-term immunosuppression should be considered.

Whereas CRION describes attacks of optic neuritis dependent upon steroids to prevent further attacks, RION describes attacks of optic neuritis independent of steroids (56). Both CRION and RION are thought to lack a demyelinating etiology.

Radiographic modalities

MRI

MRI findings can help differentiate between NMO and MS. Unlike MS, MRI images of the brain during the onset of NMO are usually normal but can show atypical brain lesions for MS including aquaporin-4 rich areas of involvement. The brain lesions can exist by itself or as extensions of cervical myelitis (13). The MRI brain lesions can be found in around 60% of patients with NMO during later course of disease of a mean of 6 years (7). The MRI brain lesions are typically found in locations with high AQP4 expression, which would be in the periependymal areas such as the hypothalamus, periaqueductal grey, and area postrema (13). In patients with NMO, MRI imaging of the spinal cord may show longitudinally extensive lesions that typically span at least three vertebral segments. In patients with MS, MR imaging of the spinal cord typically does not span more than one or two vertebral segments (57). Common MRI features of MS are the presence of cortical, U-fibre, or Dawson's finger lesions, whereas common MRI features of NMO are the presence of hypothalamic, periaqueductal grey and area postrema lesions (58). NMO patients commonly show infratentorial lesions, especially in the medulla, but also in the pons, cerebellar peduncles, mesencephalon, and diencephalon. Lesions that are typical for MS include ovoid lesions perpendicular to the lateral ventricles, isolated ovoid and round cortical lesions, and isolated juxtacortical lesions in the U-fibers (59). These types of lesions are not typical for NMOSD patients.

CSF Analysis

CSF findings can help differentiate between NMO and MS. Oligoclonal bands (OCB) appear in approximately 90% of MS patients during the entire disease course, whereas OCBs only appears in around 16% of AQP4-IgG seropositive NMO patients and usually only appear during relapse (60).

NMO patients can also be checked for levels of myelin basic protein (MBP) in the CSF. MBP are structural myelin proteins which form polymers between the myelin membrane layers to create compact myelin sheaths. The disassembly of the MBP network has been proposed to trigger the pathological breakdown of myelin sheaths in NMO patients (61). NMO patients display significantly higher levels of MBP in the CSF as compared to MS patients (62). IgG index is significantly higher in MS patients than in NMO patients. The IgG index in NMO patients is within the range of normal IgG index range with no intrathecal IgG synthesis (63).

The distinction between NMO and MS can be further made by analyzing a polyspecific antiviral immune reaction to the measles, rubella, and varicella zoster virus (MRZ) reaction. A positive reaction, defined as a combination of at least two out of the three positive antibody indices, is seen in over 80% of MS patients and only around 5% of NMO patients (64).

NMO patients may also show pleocytosis with increased proportion of neutrophils or eosinophils, whereas pleocytosis is lower in MS patients and neutrophils and eosinophils are normally absent in the CSF of MS patients. NMO patients also show increased levels of inflammatory molecules in the CSF. NMO patients may also show greater levels of total protein levels in the CSF, especially during acute attacks (65).

No significant differences have been determined in OCB, MRZ, or white cell counts between AQP4-IgG seropositive and seronegative NMO patients (44).

The presence of elevated GFAP levels in the CSF suggests an NMO relapse rather than MS (40).

EPs and nerve conduction studies (NCS)

Visual evoked potentials (VEP) can be used to aid in the distinction between NMO patients and MS patients. MS patients typically display an abnormal VEP from healthy controls with the main characteristic of MS being an absolute increase in latency of the P100 wave (66). Between NMO and MS patients, NMO patients are less likely to display a latency in the P100 wave. NMO patients are more likely to have a decreased amplitude in the wave or absence of visual responses. Between NMO-IgG seronegative and seropositive patients, NMO-IgG seronegative patients are less likely to display a lack of visual response than NMO-IgG seropositive patients (66). NMO-IgG seronegative patients also display a significantly higher delay in latency of the P100 wave than NMO-IgG seropositive patients.

In addition to VEPs, motor and somatosensory evoked potentials (MEPs and SSEPs) have also been used to assess MS patients and can help differentiate from NMO patients. MEPs and SSEPs can provide data on disease activity and predict future clinical disabilities, such as the use of lower limb SSEPs to aid in the detection of clinical abnormalities in MS patients. A study of NMO patients in a tertiary university center showed that 69.2% and 69.0% of NMO patients with severe relapses present abnormal MEPs and SSEPs during relapses, respectively (67). Patients with abnormal lower limb MEPs and SSEPs had worse disabilities as represented by higher EDSS scores and Kurtzke's pyramidal functional system scores than patients with normal lower limb MEPs and SSEPs (67). NMO patients with abnormal lower limb SSEPs were also more likely to experience new relapses than those with normal responses. Therefore, lower limb MEPs and SSEPs can be used in NMO patients to predict disability and relapse.

NCS can be used to detect the existence of peripheral neuropathy in patients. A study that compared NCS between NMO and MS patients indicated no significant difference between the frequency of abnormal NCS between NMO and MS patients (68). In the analysis, 10.3% and 10.7% of MS and NMO patients displayed abnormal NCS findings, respectively.

Treatment

Steroids

There is no current cure for NMO; however, various treatments can improve management of symptoms of attacks and can help prevent future attacks. NMO treatments should be initiated immediately after an attack, as the attack can lead to severe disabilities. Acute attacks are routinely treated with high dose intravenous corticosteroid methylprednisolone, followed by suggested tapering with oral steroids (69,70). The slow tapering has been indicated to potentially prevent early rebounds. About 80% of patients respond well to intravenous corticosteroid treatment within 2 weeks.

Plasma exchange and IVIG

For patients with insufficient response or resistance to the steroid treatment, plasma exchange is recommended (69).

About 60% of patients respond well to plasma exchange by 6 months after treatment (71). Initial treatment of future attacks with plasma exchange is recommended for patients who have previously improved from plasma exchange. IV steroid and plasma exchange treatments are indicated to work well in MOG-IgG seropositive NMO patients as well (33). For patients with insufficient response to steroids and plasma exchange, intravenous immunoglobulins or cytoablative therapy has been proposed in patients present with idiopathic transverse myelitis (72).

Immunosuppression

For prevention of future attacks, long-term immunosuppression is recommended to be initiated immediately after an NMO relapse, especially for patients who are seropositive for NMO-IgG, a good indicator of future relapse. Agents that target B cells should be considered, including oral azathioprine and oral prednisone, to decrease the frequency of relapses (73). Aggressive forms of NMO can be countered with rituximab (74). Alternative treatment options include other immunosuppressant agents, such as mycophenolate mofetil (75), methotrexate (76), or mitoxantrone (77). One of the main treatments for MS, interferon-β (INF-β), has repeatedly demonstrated lack of efficacy for NMO patients, and has been indicated to exacerbate the disease (78). Therefore, INF-β is not recommended for treatment of NMO. However, glatiramer acetate also called Copaxone, a first-line immunomodulatory treatment for MS, has been shown to be potentially effective treatment agent in NMO (79). It is suspected that its efficacy is due to its protective effects on myelin. Another main treatment for MS, natalizumab, also demonstrates inefficiency and harm when used on NMO patients (80). It is suspected that natalizumab exacerbates NMO by enhancing secretion of AQP4 antibodies.

Conclusions

The introduction of AQP4-IgG has greatly improved knowledge about NMO and its distinction from MS and led to the recognition of a wider clinical spectrum of NMO. Further research on AQP4-IgG and MOG-IgG can provide greater knowledge on NMO, categorization of similar disorders or subsets or disorders, better understanding of their pathogenesis, and appropriate treatments in clinical settings.

Footnote

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