

## Neuromyelitis optica spectrum disorders with and without aquaporin 4 antibody: Characterization, differential diagnosis, and recent advances

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### Abstract

**Importance:** The term neuromyelitis optica spectrum disorders (NMOSD) currently includes neuromyelitis optica (NMO) and rare neurological disorders characterized by specific IgG autoantibodies directed against aquaporin 4 (AQP4); from a clinical perspective, optic nerves and spinal cord are the usual target tissues. The discovery and characterization of AQP4-IgG has revolutionized the diagnosis of NMOSD and can be used to predict relapses. Similarities with multiple sclerosis (MS) include immune-mediated demyelination and axonal damage but unlike MS, identification of AQP4 Ab positive and seronegative NMOSD (also called anti-MOG-Ab positive) have revolutionized the diagnosis of NMOSD leading to early diagnosis and therapeutic options. Similar to MS, the clinical presentation in NMOSD can have a relapsing-remitting disease course but some patients with NMOSD tend to run a more aggressive disease course. It is important to recognize that, despite the development of tests to identify specific autoantibodies, the diagnosis of NMOSD can be challenging and often missed, leading to delay in treatment options, particularly in the cohort of patients who do not have AQP4-IgG antibodies in serum (seronegative NMOSD). One cardinal difference in therapeutic options between NMOSD and MS is that there are no FDA-approved therapeutic interventions for NMOSD. **Objectives:** The aim of this study is to review recent changes in diagnostic criteria of NMOSD and outline challenges in characterizing patients with seronegative NMOSD. **Findings:** Depending on the assays used and the cohorts studied, 10% to 50% of NMOSD patients are AQP4-negative which can be challenging for the clinician treating the disease. Furthermore, identification of seronegative NMOSD or anti-MOG antibody positive patient cohorts can be difficult since antibody testing is available only in Japan and UK. **Conclusions:** The diagnostic criteria for NMOSD continue to evolve in this rapidly developing field. Concurrent diagnosis of systemic lupus erythematosus, Sjögren's syndrome or myasthenia gravis increase the likelihood of diagnosis of NMOSD. As compared to the AQP4-IgG positive group, MOG-Ab positive patients with NMOSD or seronegative NMOSD have distinguishing characteristics that be exploited for early treatment. Recent breakthroughs, including the discovery of Fc receptor polymorphism, will likely aid in the medical management of NMOSD patients. Patients with clinical presentation with at least one core 'syndrome' should be evaluated for possible NMOSD. Some of these are seen in MS, such as optic neuritis and acute myelitis. Others include area postrema syndrome (APS) which presents with intractable nausea and vomiting, or hiccups, acute brainstem syndrome or symptomatic narcolepsy. As always, alternate diagnoses such as MS, sarcoidosis, malignancy, paraneoplasia, and infective etiologies affecting the brain should be sought and excluded.

**Keywords:** neuromyelitis optica; neuritis; myelitis; seronegative; Aquaporin-4 channelopathies; NMO spectrum disorders

### Introduction

Neuromyelitis optica (NMO), also known as Devic's disease, is an inflammatory demyelinating autoimmune disease of the central nervous system that most commonly affects the optic nerves and spinal cord. Currently, NMOSD is the new moniker for NMO [1]. Studies show that the prevalence of NMO in the U.S. ranges from 0.5-4 per 100,000 population [2]. The F:M ratio is 9:1 in adults and but 3:1 in the pediatric population [1]. Despite over-representation of East Asians and other non-white population worldwide, most patients with NMOSD in the developed world are white [3]. However, these epidemiological statistics are primarily based on patients who tested positive for AQP4-IgG antibodies and do not include seronegative NMOSD patients.

AQP4 is a transmembrane water channel protein found in astrocytic foot processes that plays a pivotal role in

maintaining the integrity of the blood brain barrier (BBB). It is responsible for glutamate and potassium regulation in the BBB, synapses, and paranodes adjacent to the nodes of Ranvier. Interestingly, patients who are seronegative

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for AQP4-IgG antibodies do not show a pathogenic or symptomatic pattern similar to their seropositive patients.

## Methods

PubMed search for publications on NMO and NMOSD using MeSH subheadings from January, 1940 through July 31, 2015 were performed. Recent peer-reviewed basic science studies, case reports, case series reports, consensus statements, retrospective analyses, meta-analyses, and evidence-based guidelines were incorporated in this review. Emphasis was placed on patients who lacked AQP4-IgG auto-reactivity as this small subset of NMOSD patients is generally a challenge to clinicians.

## Clinical presentation and pathology

In 1870, an English physician, Thomas Clifford Allbutt, first described NMO. He noted that there was an association between unilateral optic nerve disorder and myelitis. In 1894, Eugène Devic and his student Fernand Gault described 16 patients who had lost vision bilaterally or unilaterally and within weeks developed loss of sphincter control, spastic quadriparesis or paraparesis, as well as loss of sensation.

Devic and Gault characterized NMO as an acute disorder that presented with transverse myelitis and optic neuritis occurring simultaneously or in rapid succession. This definition is called Devic's classical syndrome, or monophasic NMO. A relapsing form of NMO was later reported, which now accounts for 80-90% of NMO cases [4]. Optic neuritis may present as visual impairment with decreased visual acuity, although visual field defects or loss of color vision may occur, as well. With cord involvement, patients can present with an acute and severe spastic paresis of the legs, sensory disturbances and bladder dysfunction. Additional core clinical characteristics of NMOSD include other sites, including the area postrema, which contains specialized ependymal cells that detect toxins and causes unexplained hiccups or nausea/vomiting.

Area postrema syndrome-associated NMOSD typically presents with nausea, vomiting or hiccups and the lesions occupy the medullary floor of the fourth ventricle and area postrema; these lesions can be unilateral or bilateral, as noted on an MRI of the brain [5]. Symptoms can precede the episodes of optic neuritis or transverse myelitis. Area postrema is the emetic reflex center and is comprised of 2 symmetric structures at the floor of the rhomboid fossa and regulates fluid balance, osmoregulation and immunomodulation [5, 6].

Acute brainstem syndrome (APD), symptomatic narcolepsy, or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions in brain, and symptomatic cerebral syndrome with NMOSD-typical CNS lesions are another variant of NMOSD presentation [1, 7].

Pathology shows perivascular exudate leading to tissue destruction and ultimately, demyelination. Small lesions may aggregate to form larger lesions primarily in gray matter of the spinal cord that are characteristically referred to as longitudinally extensive myelitis to signify lesion extension

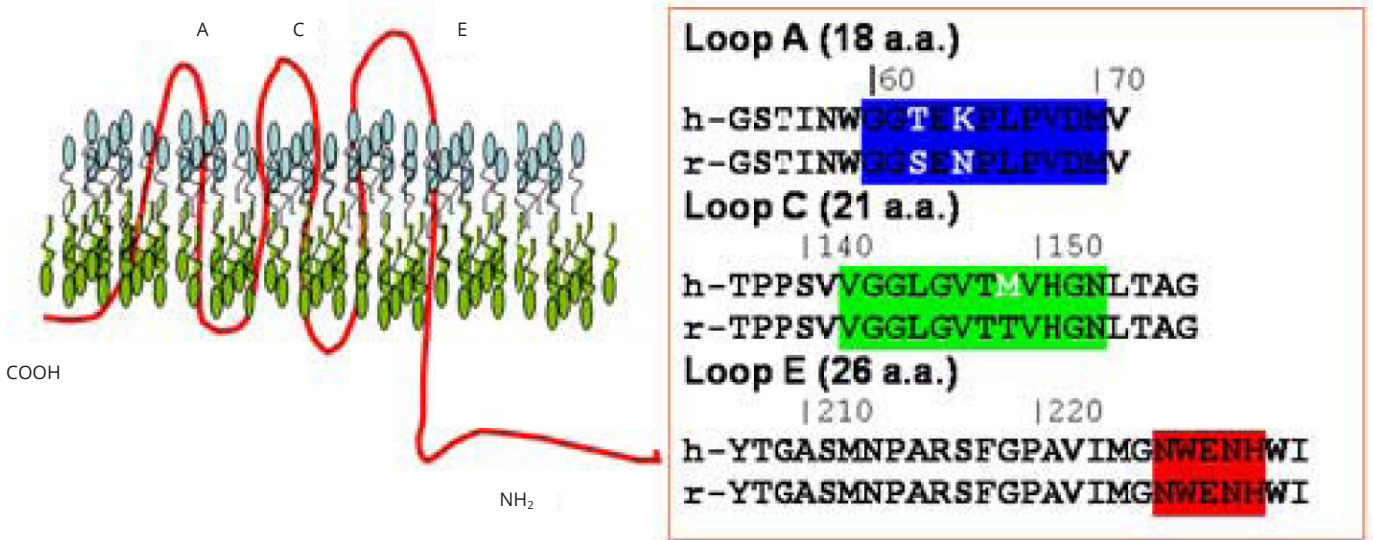
over three spinal segments. Microgliosis and subsequent astrocytosis follows, leading to the formation of glial scars [8]. Typically, NMO/NMOSD lesions are cavitory, necrotic, and infiltrated with macrophages and granulocytes [9]. Recent study findings suggest that astrocytes are injured during NMOSD attacks and this is more pronounced than demyelination or axonal injury [10]. Interestingly, experimental studies that have purified NMO-IgG antibodies from seronegative patients did not reproduce NMOSD-like pathology with astrocytic destruction as was seen with the infusion from seropositive patients [11]. These data suggest a unique pathophysiological distinction in seronegative NMOSD that remains to be defined.

Experimental evidence from both in vitro and in vivo studies have shown that the AQP4 antibody plays an important pathogenic role in NMOSD. Antibodies against AQP4 have been shown to increase BBB permeability, activate the complement cascade, and induce astrocytic cytotoxicity. Antibodies against AQP4, also known as NMO immunoglobulins (NMO-IgG), are currently the most highly specific biomarker for NMOSD. T cells are also implicated in NMO/NMOSD pathogenesis because AQP4-IgG is a T-cell-dependent IgG subclass molecule. Human anti-AQP4 antibodies are not only important in the diagnosis of NMOSD, but have also been shown to augment the disease and induce NMO-like lesions in animals with T-cell-mediated brain inflammation [12]. Studies have also shown elevations of interleukin-6 (IL-6), along with IL-1, IL-8, IL-13, and granulocyte colony-stimulating factor [13]. These data further suggest that immunological status plays an important role in the pathogenesis of NMOSD and may serve to further differentiate itself from similar disease processes.

## Biomarkers and challenges of disease definition

Once regarded and often misdiagnosed as a variant MS, NMOSD is now recognized as a pathophysiologically distinct disease. NMOSD differs from MS primarily in the severity of its attacks and its tendency to strike the optic nerves and spinal cord at the beginning of the disease and NMOSD attacks are more often associated with axonal necrosis [14], while MS is primarily associated with central demyelination. Furthermore, it has been shown that NMOSD attacks respond poorly to conventional MS therapy [15] and can worsen the disease.

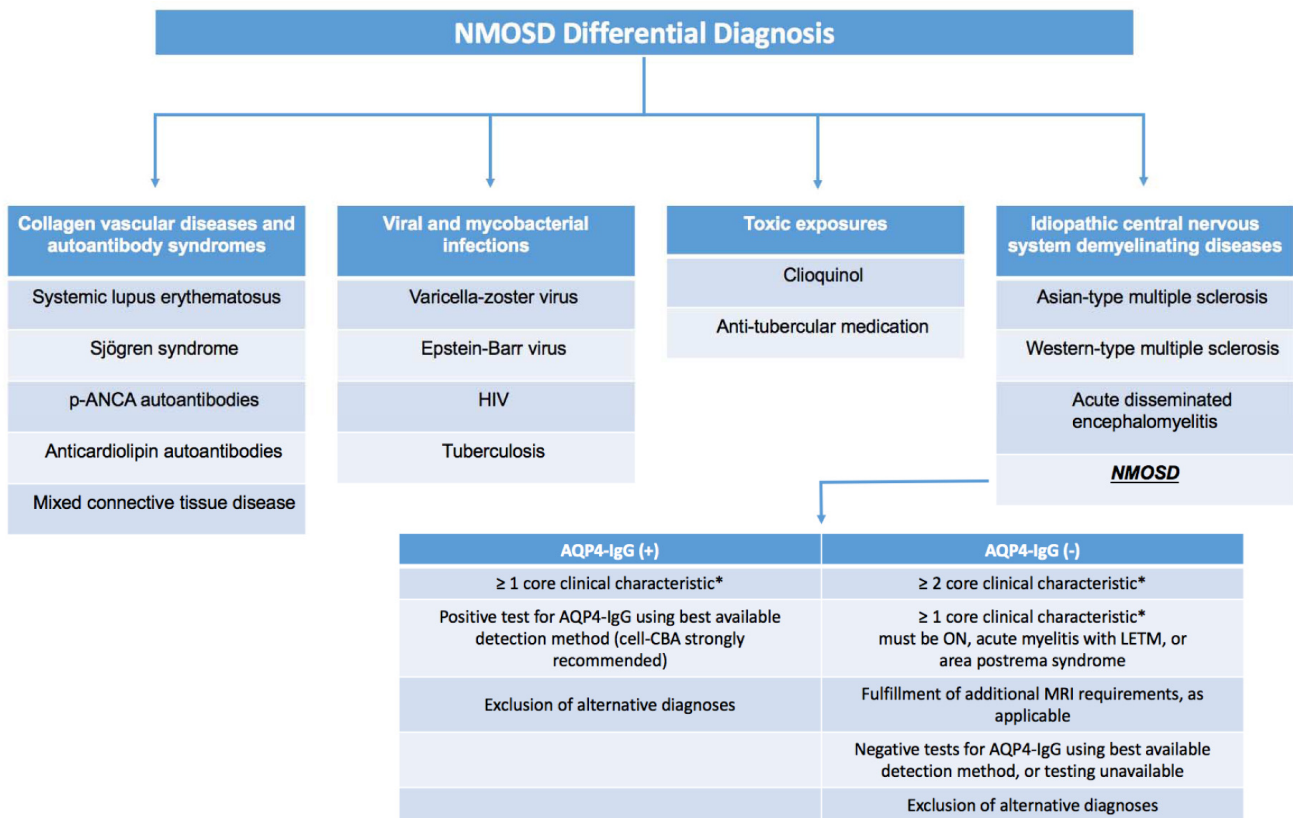
The discovery of circulating IgG antibodies against the most abundant water channel protein in the CNS, AQP4, was the main pathophysiological finding that exclusively and definitively distinguished it from MS [15]. AQP4 is a type III transmembrane water channel regulator and exists as two major isoforms, M1 and M23, in astrocytes and some epithelial tissues of both rat and human. Algorithms have been used to help elucidate AQP4 topology and have predicted that three extracellular loops (A, C, and E) connect six alpha helices spanning the membrane [16] (Figure 1). The authors suggest that clonal expansion of AQP4 sensitive B cells and subsequent activation may reflect the time interval between the clinical presentation of optic neuritis and LETM. The discovery of the crystal structure of AQP4 has also helped show that only the N- and C- termini are surface exposed, which suggest that these residues are likely the limiting factors in epitope recognition [17].



**Figure 1** Predicted isoforms of Aquaporin-4 (AQP4), a type III transmembrane water regulator channel predominantly found in astrocytes in the CNS and some epithelial tissues. Two main isoforms have been proposed, M1 and M23, that differ by 23 residues. Residues predicted in the extracellular loops are shown in one letter code. Residues based on the crystal structure that are predicted to be in the exposed extracellular loops are highlighted in either blue (Loop A) green (Loop C), or orange-red (Loop E). Differences between mouse and human sequences in the exposed loops are noted by single letter code in white.

AQP4 antibodies have been found in variants of NMOSD, including Asian opticospinal MS, optic neuritis or transverse myelitis associated with systemic autoimmune disease, and optic neuritis or myelitis associated with CNS lesions typical of NMO (hypothalamic, brainstem, corpus callosal, and periventricular) [3]. However, a capricious 10-50% of NMOSD patients are still negative for AQP4 antibodies despite the use of the most sensitive assays currently available [18, 19]. This lack of anti-AQP4 seropositivity in

a subset of NMO patients suggests that the myelitis and optic neuritis can be caused by other mechanisms, such as connective tissue disorders, paraneoplastic disorders [20], infectious diseases [21], or others, supporting the hypothesis that NMOSD is probably heterogeneous (Figure 2). It is unclear why NMOSD lesions are mainly localized in spinal cord and optic nerves rather than in the brain, and why peripheral, AQP4-expressing organs are often unaffected.



**Figure 2** Summary of key differential diagnoses as recently updated by Wingerchuk, et al. [1]. Seronegative and seropositive diagnostic criteria are also compared. Core clinical characteristics each implicate 1 of 6 CNS regions: optic nerve, spinal cord, area postrema of the dorsal medulla, brainstem, diencephalon, or cerebrum.



Heterogeneous NMOSD may include a subgroup of patients associated with other autoantibodies as well. One such autoantibody is anti-myelin oligodendrocyte glycoprotein (anti-MOG). Studies implicating MOG as a pathogenic player in NMOSD might suggest that some AQP4-IgG seronegative patients with clinical and neuroimaging features of NMOSD have a different underlying pathogenesis [22]. A small portion of patients with NMO-like symptoms, akin to all AQP4 seronegative patients, have been reported to have detectable anti-MOG and show different characteristics from those patients positive for anti-AQP4. In fact, seronegative NMO patients that are positive for anti-MOG Abs seem to have a more favorable prognosis [23]. However, the exact role of MOG or other antibodies in disease pathogenesis remains a work in progress.

As compared to the AQP4-IgG positive group, MOG-Ab positive patients with NMOSD or seronegative NMOSD have the following features: a) it tends to affect younger patients or children, b) sex ratio is equal, c) the disease is monophasic, d) the interval to the second clinical attack is longer, e) oligoclonal bands in cerebrospinal fluid (CSF) are seen more often and f) CNS lesions are MS-like in their distribution, location, and appearance on imaging studies and can be mistaken for lesions suggesting acute disseminated encephalomyelitis.

### Diagnostic criteria

The first diagnostic criteria for NMO were proposed in 1999, and have been subject to systematic modifications, such as removing the restriction on CNS involvement beyond the optic nerves and spinal cord [24]. Another key revision was that they included anti-AQP4 seropositivity, as discussed earlier. The revised diagnostic consensus included the main criteria, acute myelitis, optic neuritis and, at least, two of three supportive criteria: longitudinally extensive myelitis defined as contiguous spinal cord MRI lesions extending over three or more spinal segments, brain MRI not meeting diagnostic criteria for MS, and anti-AQP4 seropositive status.

In 2015, the authors revisited these diagnostic criteria and included some salient modifications [1], and are summarized, in figure 2.

According to the updated Wingerchuk et al. diagnostic criteria, NMOSD patients must meet a certain number of core clinical characteristics according to their AQP4 sensitivity. These core clinical characteristics are: 1) optic neuritis, 2) acute myelitis, 3) area postrema syndrome defined as an episode of otherwise unexplained hiccups or nausea and vomiting, or 4) acute brainstem syndrome defined most commonly as symptomatic narcolepsy, acute diencephalic clinical syndrome, or symptomatic cerebral syndrome. Seronegativity status must show two or more core clinical characteristics in addition to fulfilling additional MRI requirements. These requirements for NMOSD without AQP4-IgG and/or unknown AQP4-IgG include the following: a) Optic neuritis: Brain MRI showing normal findings or only nonspecific white matter lesions, OR optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over  $>1/2$  optic

nerve length or involving optic chiasm; b) Longitudinally extensive myelitis: Associated intramedullary MRI lesion extending over  $>3$  contiguous segments OR  $>3$  contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis; c) Area postrema syndrome: requires associated dorsal medulla/area postrema lesions; d) Acute brainstem syndrome: requires associated peri-ependymal brainstem lesions.

For AQP4-IgG seronegative cases diagnosed using the new NMOSD scheme, detailed clinical, neuroimaging, and laboratory descriptions of patients will be necessary to better characterize this heterogeneous population. AQP4-IgG seronegative patients must have experienced at least one of the three most common clinical characteristics of seropositive NMOSD, namely optic neuritis, longitudinally extensive myelitis (of the spinal cord), or area postrema syndrome with associated MRI lesions. This is particularly important to identify the frequencies with which seroconversion to AQP4-IgG positivity or detection of other autoantibodies of interest occur.

### Differential diagnosis

Differentiating NMOSD from other demyelinating disorders is based upon important differences in clinical course, prognosis, and underlying pathophysiology [25]. NMOSD has been associated with collagen vascular disease and infectious, viral, toxic, and other associated idiopathic etiologies (Figure 2). Additionally, other autoantibody syndromes have been strongly associated with NMOSDs, such as systemic lupus erythematosus, Sjögren's syndrome, subacute combined degeneration, Hashimoto's thyroiditis, and myasthenia gravis [4].

It is important to note that individual optic neuritis attacks in NMO are indistinguishable from isolated syndromes of optic neuritis or MS. Thus, longitudinally extensive spinal cord lesions are not specific for NMOSD, though visual loss is generally more severe in NMOSD [24-26]. The majority of optic neuritis attacks in NMOSD are unilateral as seen primarily in seropositive patients. However, sequential optic neuritis in rapid succession or bilateral simultaneous optic neuritis is highly suggestive of NMOSD, as well [25]. Seropositive and seronegative patients were found to differ with regard to important features, such as attack severity and clinical presentation. The primary key differences as recently described by Jarius et al. are summarized in table 1 [27].

### Evaluation and diagnosis of NMOSD

In addition to a complete history and physical examination, the evaluation of suspected NMOSD requires determination of AQP4 antibody status, brain and spinal cord neuroimaging with MRI, and cerebrospinal fluid (CSF) analysis. Laboratory methods to determine AQP4 sensitivity include indirect immunofluorescence, enzyme-linked immunosorbent assay (ELISA), cell-based assay (CBA), and immunoprecipitation. These assays demonstrate strong specificity, but the CBA has the highest sensitivity [28]. Anti-AQP4 assays are very specific and, if positive in other autoimmune diseases with CNS injury, concomitant NMOSD is likely [29]. CSF analysis can be utilized during acute NMOSD attacks and abnormalities

**Table 1** Summary of findings published in an exclusively Caucasian population comparing the key clinical characteristics between seropositive and seronegative patients [25].

	Seropositive	Seronegative
Female:Male ratio	↑ (10.4x)	↓ (1.9x)
Unilateral ON	+	
Bilateral ON		+
Simultaneous myelitis and ON		+
Sensory symptoms		+
Brainstem involvement	nsd	
Monophasic		+
Relapsing	+	
Median disease duration		nsd
<i>Annual relapse frequency of:</i>		
ON		nsd
Myelitis		nsd
ON:Myelitis ratio		nsd

*Abbreviations:* + = more common; nsd = no significant difference; ON = optic neuritis

may include elevated protein levels and pleocytosis, which can be detected in up to 80 percent of NMOSD patients (presumably seropositive patients). Remarkably, oligoclonal bands are usually absent in 70 to 85 percent of cases [25, 30], distinguishing NMOSD from MS.

Several brain, optic nerve, and spinal cord patterns are characteristic or highly suggestive of NMOSD. On brain imaging, lesions in NMOSD are primarily located in the central medulla, hypothalamus, and diencephalon, where AQP4 expression is the highest. In the spinal cord, imaging usually shows extensive lesions spanning greater than three spinal segments, as discussed earlier. In severe cases, cavitation of the cord may be visualized as the “owl-eye sign,” akin to acute anterior spinal artery infarction [25]. Spinal cord lesions in NMOSD typically occupy the central gray matter presenting as central hypointense regions on T1-weighted MRI as well as enhancement following IV gadolinium administration. This is in contrast to lesions in MS, which affect the peripheral or outer areas of the cord where the white matter resides.

#### Therapy recommendations

Currently there are no FDA-recommended drugs for therapy in NMOSD. The only therapeutic interventions currently approved by the FDA are treatments to mitigate an acute attack in order to reduce symptoms and prevent relapses. Generally, acute attacks and relapses are treated with ‘first line’ therapies - IV steroids, plasmapheresis or immunoglobulin infusions [31]. Recurrent attacks are treated with systemic immunosuppression or ‘second line’ drugs. In the U.S., Mycophenolate mofetil (CellCept), Rituximab (Rituxan, RTX), and Azathioprine (Imuran) have been widely used. No controlled clinical trials have been done in the evaluation of NMOSD treatment. It is important to note that IFN- $\beta$ , Natalizumab (Tysabri), and Fingolimod (Gilenya) may worsen NMOSD [32-34]. Tocilizumab (TCZ) is a humanized IL-6 receptor monoclonal antibody that

competitively inhibits the binding of IL-6 to its receptor. Prolonged tocilizumab therapy may be safe and effective from early treatment phases onward for otherwise therapy-resistant highly active NMOSD [35]. In addition, a recent study found that a novel Fc receptor polymorphism of the FCGR3A gene could determine the efficacy or lack thereof of Rituxan therapy, raising hopes for personalized medicine [36]. The FCGR3A gene encodes a receptor for the Fc portion of immunoglobulin G, and it is involved in the removal of antigen-antibody complexes from the circulation.

#### Conclusions

The diagnostic criteria of NMOSD are a continuously evolving area of research that includes multi-disciplinary efforts to define the clinical and serological aspects of the disease. Even though the stringent and ever changing adaptation of MRI criteria has been used for diagnosis of NMOSD, the use of non-conventional techniques have not helped to further elucidate pertinent clinical findings to aid in early diagnosis. The diagnosis of NMOSD continues to be refined as researchers and practitioners better understand the differentiating factors that separate it from other autoimmune diseases. In fact, the concomitant diagnosis of diseases such as Sjögren's syndrome or myasthenia gravis increases the likelihood of a diagnosis of NMOSD. From a therapeutic perspective, newer agents such as tocilizumab as well as the FCGR3A receptor polymorphism analysis have already shown promise and signal the arrival of a new genre of therapeutic approaches on the wings of strides made in the world of molecular biology.

#### Conflicts of interest

The authors declare no conflict of interest.

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