REVIEW

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Neuromyelitis optica spectrum disorders: still evolving and broadening

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Purpose of review
The diagnostic criteria of neuromyelitis optica spectrum disorders (NMOSD) has been revised in the past 20 years and pathological and therapeutic data have been accumulated. This review provides an overview of evolution and broadening of the concept of NMOSD.

Recent findings
NMOSD encompassing brain syndrome as well as optic neuritis and acute myelitis is now classified into aquaporine-4 (AQP)-antibody-seropositive and aquaporine-4 (AQP)-antibody-seronegative diseases, detecting more patients earlier than before. Seronegative NMOSD includes cases of myelin oligodendrocyte glycoprotein (MOG)-antibody-seropositive disease with its unique clinical spectrum somewhat different from AQP4-antibody-seropositive NMOSD. Pathologically, NMOSD includes AQP4-antibody-seropositive autoimmune astrocytopathic disease and MOG-antibody-seropositive inflammatory demyelinating disease. Double seronegative group needs further research. Therapeutic options of NMOSD has taken shape and first-ever clinical trials of monoclonal antibodies have been done. In retrospect, relapsing NMO in the studies preceding the discovery of AQP4-antibody had features of AQP4-antibody-seropositive NMO whereas monophasic NMO was similar to AQP4-antibody-seronegative/MOG-antibody-seropositive NMO.

Summary
The clinical, pathological and therapeutic concepts of NMOSD have evolved and broadened over the last two decades following the detection of AQP4 antibodies and MOG antibodies in the patients. Double seronegative NMOSD is a current research focus, but now we may need to reconsider how NMOSD should be defined.

Keywords
auqporin-4 antibody, myelin oligodendrocyte glycoprotein antibody, neuromyelitis optica spectrum disorders, seronegative neuromyelitis optica

INTRODUCTION

Neuromyelitis optica (NMO) is characterized by optic neuritis and myelitis and was first recognized over a century ago [1,2]. The relation between NMO and multiple sclerosis had been debated for a long time, but after the discovery of NMO-specific aquaporin 4 (AQP4)-antibody [3,4], numerous reports have clarified that NMO has clinical, MRI, laboratory, and immunopathological features distinct from multiple sclerosis [2]. Diagnostic criteria for NMO have been revised multiple times [5–7,8], and AQP4 antibody has definitely played a pivotal role in the evolution of the diagnosis of NMO [6–9]. As brain syndromes also occur in NMO, the term NMO spectrum disorders (NMOSD) to cover the entire clinical spectrum was proposed in the international consensus diagnostic criteria in 2015 [8]. Wide recognition of NMOSD has therapeutic implications as well. Some disease-modifying drugs (DMDs) for multiple sclerosis like interferon-beta, fingolimod, and natalizumab are ineffective or exacerbate NMOSD, which is also a striking difference between the two immune-mediated central nervous system (CNS) disorders and emphasize the importance of early differential diagnosis [9]. More recently, first-ever international, multicenter, double-blind, placebo-controlled clinical trials of three candidate drugs for NMOSD have been done [10–12].

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KEY POINTS

- In the 2015 diagnostic criteria, neuromyelitis optica spectrum disorders (NMOSD) is stratified by aquaporin-4 (AQP4)-antibody serostatus and encompasses brain syndrome as well as optic neuritis and acute myelitis, making earlier diagnosis possible compared with the previous criteria.
- The clinical spectrum of myelin oligodendrocyte glycoprotein (MOG)-antibody detected in some cases with AQP4-antibody-seronegative NMOSD is somewhat different from AQP4-antibody-seropositive NMOSD.
- Pathologically, AQP4-antibody-seropositive NMOSD is an autoimmune astrocytopathic disease whereas MOG-antibody-seropositive NMOSD is an inflammatory demyelinating disease.
- Immunosuppression but not disease-modifying drugs for multiple sclerosis is the treatment of choice for NMOSD.
- With evolution and broadening of the concept of NMOSD and accumulated new data, we may need to reconsider how we should define NMOSD.

After the research of AQP4-antibody-seropositive NMOSD had revealed the characteristic findings of the disease, investigators started to focus on AQP4-antibody-seronegative NMOSD [13–15]. AQP4-antibody-seronegative NMO had been known to have some clinical features distinct from AQP4-antibody-seropositive NMO, and myelin oligodendrocyte glycoprotein (MOG)-antibody was detected in a fraction of the patients [16,17,18▪▪,19▪,20,21▪▪].

In this article, the evolution or broadening of the clinical, immunopathological, and therapeutic concepts of NMOSD are reviewed and the challenges ahead are discussed.

EVOLUTION OF CLINICAL CONCEPT OF NEUROMYELITIS OPTICA SPECTRUM DISORDERS

From Devic's autopsied case to neuromyelitis optica spectrum disorders in 2007

Cases of NMO including Eugene Devic's autopsied case report of severe opticomyelitis were published in late 19th century [1,22▪,23,24]. As optic neuritis and myelitis are also common manifestations of multiple sclerosis, concurrent or sequential development of inflammatory lesions involving two separated anatomical structures in the CNS (optic nerve and spinal cord) in NMO was probably a main reason why people began to take an interest in this disease. Some NMO cases in early reports were severe opticomyelitis whereas others were relatively mild in disability [1,22▪,23,24] (Fig. 1).

As seen in Devic's case [1] and the first proposed diagnostic criteria by a group at Mayo Clinic in 1999 [5], optic neuritis (unilateral or bilateral), myelitis, and no other CNS disease had been considered to be absolute diagnostic requirements of NMO before the discovery of AQP4-antibody. In those days, in Asia and some other parts of the world where typical multiple sclerosis was relatively rare, patients with recurrent optic neuritis and myelitis alone were diagnosed with 'opticospinal MS' and those with brain manifestations with or without optic neuritis and myelitis were classified as 'conventional MS' [25].

In 2004, Lennon *et al.* [3] first reported an autoantibody unique to NMO (the 1999 criteria were applied for NMO), NMO-IgG, and the next year the target was identified as AQP4, a main water channel in the CNS, especially on the endfeet of astrocytes, AQP4-antibody [4]. Among various methods to detect AQP4-antibody, human AQP4-trasfected cell-based assay was found the most sensitive and specific [26,27]. In 2006, the Mayo group incorporated AQP4-antibody seropositivity in the criteria, but both optic neuritis and acute myelitis remained absolute requirements (additionally, fulfilling two of the following three criteria: criterion 1, contiguous spinal cord lesions longer than three vertebral segments on MRI; criterion 2, brain MRI not meeting Paty's criteria for multiple sclerosis at onset; and criterion 3, NMO-IgG or AQP4-antibody seropositive status, was needed) [6]. Then based on the studies of larger numbers of AQP4-antibody-seropositive cases, they introduced the term 'NMOSD' in 2007 [7], and in addition to typical NMO in which both optic neuritis and myelitis develop, cases of recurrent or simultaneous bilateral optic neuritis and those with single or recurrent longitudinally extensive transverse myelitis [longitudinally extensive transverse myelitis (LETM), extending over three or more vertebral segments on MRI] were also included as limited forms of NMO in NMOSD, indicating that the clinical concept was broadened from NMO to NMOSD [7]. Although it was already recognized that brain syndromes developed in some AQP4-antibody-seropositve cases, in the 2007 criteria, either optic neuritis or myelitis was required for diagnosing NMOSD [7].

The International Consensus Diagnostic Criteria of Neuromyelitis Optica Spectrum Disorders (2015)

The international panel on NMO diagnosis consisting of 18 members from 9 countries started on further revision to the diagnostic criteria of NMOSD

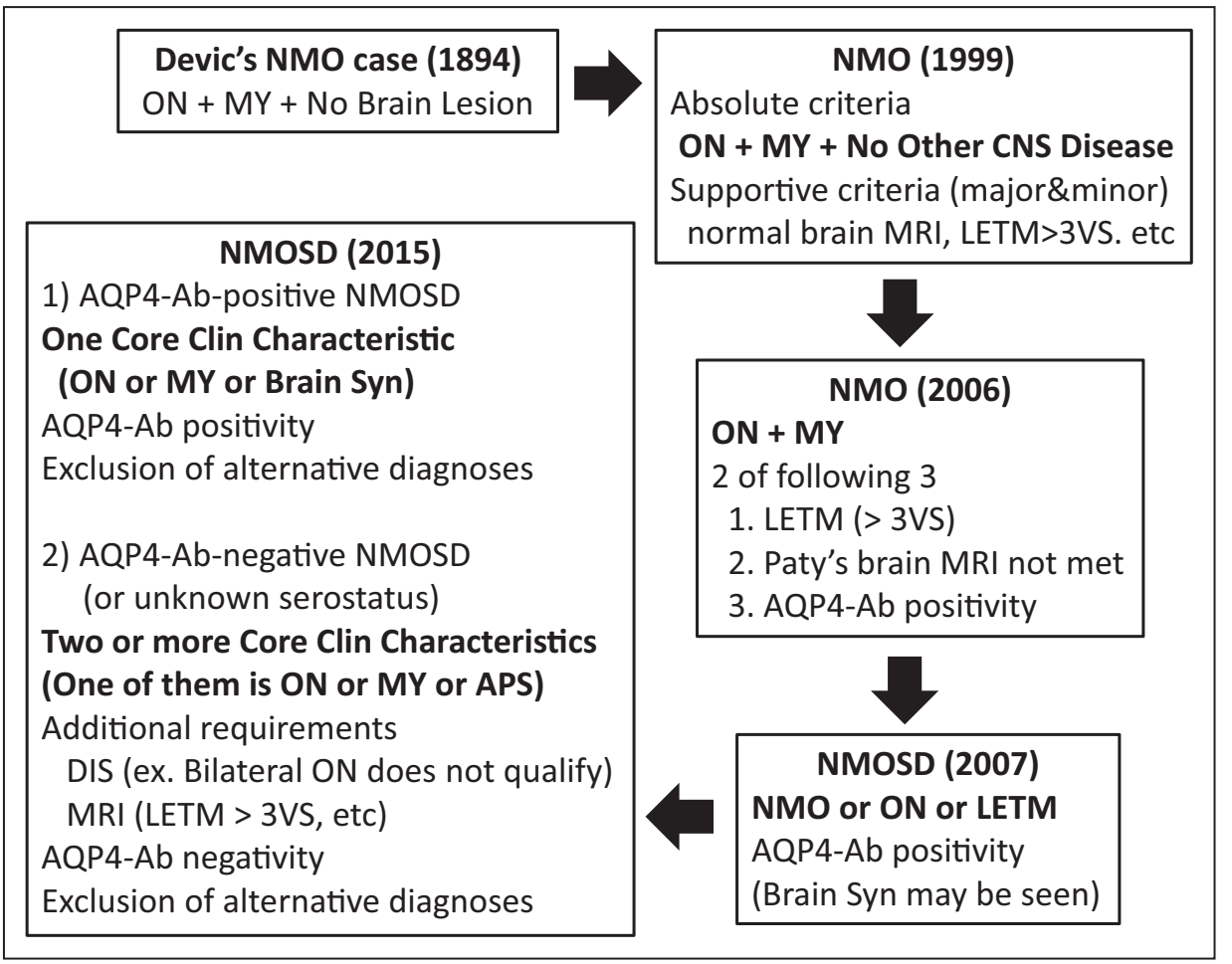

FIGURE 1. History of the diagnostic criteria of neuromyelitis optica and neuromyelitis optica spectrum disorders: evolution and broadening of the clinical concept. Devic's NMO case and other early reports of the disease were published since late 19th century. Then, in the last two decades, the diagnostic criteria of NMO and NMOSD have changed. Absolute required clinical manifestations are shown in bold letters. The clinical concept has evolved and broadened from NMO (1999 and 2006) to NMOSD (2007 and 2015), and from ON and MY with no other CNS Disease (1999) to ON and MY (2006) to NMO or ON or LETM (2007) to One Core Clinical Characteristic (ON or MY or Brain Syn) in AQP4-antibody-seropositive NMOSD and two or more core clinical characteristics (one of them should be ON or MY or APS) in AQP4-antibody-seronegative NMOSD (or serostatus unknown) (2015). With these changes, NMOSD can be diagnosed earlier in a wider range of patients. APS, area-postrema syndrome; AQP4-Ab, aquaporin 4-antibody; CNS, central nervous system; LETM, longitudinally extensive transverse myelitis; MY, acute myelitis; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorders; ON, optic neuritis; Syn, syndrome; VS, vertebral segments.

in 2011, convened seven times, and the revised consensus criteria was published in 2015 (Fig. 1) [8]. NMOSD was proposed as the unifying term for the entire clinical spectrum of NMOSD including typica NMO, the limited forms (optic neuritis and LETM), brain syndromes and the combinations. NMOSD was stratified by AQP4-antibody serostatus, that is, AQP4-antibody-serosepositive NMOSD and AQP4-antibody-seronegative NMOSD (or unknown serostatus). In AQP4-antibody-seropositive NMOSD, if AQP4-antibody is reliably positive (cell-based assay is preferred) and alternative diagnoses are excluded, only core clinical characteristic (optic neuritis, acute myelitis or brain syndrome) is required for the diagnosis. Brain syndromes, such as area postrema syndrome manifesting intractable hiccup, nausea and vomiting, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions and symptomatic cerebral syndrome with NMOSD-typical brain lesions as well as optic neuritis and myelitis in the criteria were the ones seen in AQP4-antibody-seropositive cases [8]. Only about 70% of AQP4-antibody-seeoposotive cases eventually develop typical NMO, but the experts analyzed all available data and concluded

that AQP4-antibody-seropositive NMOSD is one disease entity regardless of its clinical phenotypes [8]. On the other hand, for the diagnosis of AQP4-antibody-seronegative NMOSD, as one can imagine, more stringent criteria were set to exclude a variety of diseases mimicking NMOSD, although exclusion of alternative diagnoses was imperative (Fig. 1) [8]. Afterward studies to compare the diagnostic criteria of NMOSD have demonstrated that the 2015 criteria are able to make an earlier diagnosis of NMOSD in a wider range of cases than the 2006 criteria [28,29▪,30], which is crucial in order to institute effective immunosuppression promptly and improve the long-term prognosis.

There was no controversy over AQP4-antibody-seropositive NMOSD, but a big sticking point was how to deal with AQP4-antibody-seronegative NMOSD [8]. As a matter of fact, some panel members were reluctant to create the category of AQP4-antibody-seronegative NMOSD because NMOSD would not be a homogeneous entity by incorporating AQP4-antibody-seronegative disease into the criteria. Meanwhile, it is a fact that NMOSD is a clinical diagnosis, and if AQP4-antibody seropositivity is required for the diagnosis, NMOSD may not be diagnosed in areas where reliable AQP4-antibody assays are not readily available. Moreover, typical NMO cases consistently seronegative for AQP4-antibody despite the application of the most reliable assay did exist. The panel finally incorporated AQP4-antiibody-seronegative NMOSD in the consensus diagnostic criteria but allowed for future revisions [8].

Table 1. Pathological classification of neuromyelitis optica spectrum disorders and the evidences

NMOSD
AQP4-antibody-seropositive → autoimmune astrocytopathic disease
MOG-antibody-seropositive → inflammatory demyelinating disease
Double seronegative → unknown
Evidences of astrocytic damage in AQP4-antibody-seropositive NMOSD
Extensive loss of AQP4 and GFAP immunostaining in the CNS lesions
Remarkably high CSF-GFAP levels during relapse
Low myo-inositol/creatinine value in the cervical cord on ^{1}H-MRS
Pathogenicity of AQP4-antibody in experimental studies (*in vitro* and *in vivo*)
Significantly reduced thickness of Muller cell-rich fovea on OCT
Evidences of myelin damage in MOG-antibody-seropositive NMOSD
Inflammatory demyelination in brain-biopsied cases
High CSF-MBP level during relapse (no elevation of CSF-GFAP)

AQP4, aquaporin 4; CNS, central nervous system; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MRS, magnetic resonance spectroscopy; NMOSD, neuromyelitis optica spectrum disorders; OCT, optical coherence tomography.

AQUAPORINE-4-ANTIBODY-SEROPOSITIVE NEUROMYELITIS OPTICA SPECTRUM DISORDERS IS AN AUTOIMMUNE ASTROCYTOPATHIC DISEASE

In most articles on NMOSD, introduction starts with a sentence like 'NMOSD is a severe inflammatory demyelinating disease of the central nervous system.' In fact, neuromyelitis optica (Devic) is classified as a demyelinating disease of the CNS in the International Classification of Diseases (2019 ICD-10-CM Diagnosis Code G36.0) [31]. However, the pathological studies of AQP4-antibody-seropositive NMOSD cases clearly indicate that AQP4-expressing astrocyte is the major target of immune attack and astrocytic destruction is more severe and extensive than demyelination in the disease [2].

Currently, there are five lines of evidences to support the assertion (Table 1).

(1) Massive astrocytic damage is evident [extensive loss of immunostaining for AQP4 and glial fibrillary acidic protein (GFAP)] and is more extensive than myelin damage in the NMO lesions [32–35]. Also, there are depositions of immunoglobulins and activated complements in the perivascular regions with astrocytic damage [32–35]. In contrast, astrocyte destruction is not seen or minor at best in typical multiple sclerosis.

(2) The GFAP level is remarkably high in the CSF of AQP4-antibody-seropositive NMOSD patients during acute exacerbations whereas the CSF-GFAP is not elevated at all in typical multiple sclerosis [36–39]. CSF-myelin basic protein levels are also higher in NMOSD than in multiple sclerosis but the difference of CSF-cellular damage marker levels in the two diseases is far more significant in GFAP.

(3) Myo-inositol detected by ^{1}H- magnetic resonance spectroscopy reflects proliferation and activity of astrocytes and the myo-inositol/creatine ratio is significantly lower in the cervical cord of AQP4-antibody-seropositive NMOSD than in multiple sclerosis (actually, the value in multiple sclerosis is slightly higher than control individuals because of astrogliosis in the chronic phase of demyelinating plaques.) [40].

(4) AQP4-antibody is pathogenic to astrocytes in experimental studies [41–43]. AQP4-antibody is mainly IgG1 and can activate complements efficiently and AQP4-antibody's complement-mediated cytotoxicity is a major mechanism to damage AQP4-expressing astrocytes, although astrocytic damage in NMOSD occur in other ways (antibody-dependent cellular cytotoxicity, AQP4-reactive T cells, inflammatory cytokines [mainly Th17-related ones]) as well [43].
(5) On optical coherence tomography, foveal thickness is significantly reduced in AQP4-antibody-seropositive NMOSD than in healthy controls, and the foveal change around Muller cell-rich fovea supports a retinal astrocytopathy [44▪].

These findings strongly confirm that AQP4-antibody-seropositive NMOSD should be classified as an autoimmune astrocytopathic disease rather an inflammatory demyelinating CNS disease. This change of pathological concept of AQP4-antibody-seropositive NMOSD is expected to add a new page in neuropathology and ICD-11.

AQUAPORINE-4-ANTIBODY-SERONEGATIVE NEUROMYELITIS OPTICA SPECTRUM DISORDERS

In the 2004 *Lancet* article on NMO-IgG, a portion of patients with NMO were seronegative for NMO-IgG but the difference between NMO-IgG-seropositive and seronegative NMO were unclear [3] possibly due in part to a relatively low sensitivity of mouse brain tissue-based immunefluorescence [26]. For detecting AQP4-antibody, cell-based assay is highly specific and more sensitive than ELISA and tissue-based immunefluorescence [26], but false-positive and false-negative results can occur and they hamper distinction between seropositive and seronegative diseases.

However, some patients with typical NMO are consistently seronegative for AQP4-antibody even if the most sensitive assay of AQP4-antibody (human M23-AQP4-transfected cells, no prefixing of the transfected cells on glass slides, and no green fluorescence protein-tagging of AQP4) is applied [13–15]. A French study of AQP4-antibody-seronegative cases fulfilling the 2006 criteria of NMO revealed that no female preponderance (female/male 1.2 in AQP4-antibody-seronegative NMO vs. 9.8 in seropositive disease), Caucasian ethnicity (100 vs. 73.6%), opticomyelitis at onset (27 vs. 6%) and less frequent severe visual impairment (12 vs. 54%) [13]. The Mayo group reported essentially similar findings, the female to male ratio was 1 : 1 in seronegatives and 9 : 1 in seropositives ($P < 0.0001$), Simultaneous optic neuritis and transverse myelitis as onset attack type (within 30 days of each other) occurred in 32% of seronegatives and in only 3.6% of seropositives ($P < 0.0001$) [14]. On the other hand, relapse rate, disability outcome and other clinical characteristics did not differ significantly in their study.

MYELIN OLIGODENDROCYTE GLYCOPROTEIN-ANTIBODY-SEROPOSITIVE DISEASE INCLUDING ITS NEUROMYELITIS OPTICA SPECTRUM DISORDERS PHENOTYPE

Myelin oligodendrocyte glycoprotein (MOG) is a minor myelin protein localized at the outermost layer of myelin sheath. MOG has been used as an immunogen to induce experimental autoimmune encephalomyelitis (EAE) in rodents for more than 30 years [20]. Unfortunately, a number of previous studies of MOG-antibody with ELISA and western blot generated confusing results mainly because of low specificity (for example, a part of control individuals as well as multiple sclerosis patients were positive for MOG-antibody) [45]. The high predictive value of MOG-antibody (detected by western blot) on conversion from clinically isolated syndrome to clinically definite multiple sclerosis in an initial report [46] was not confirmed by subsequent studies [47].). But O'Connor *et al.* [48] developed a MOG-transfected cell-based assay to detect conformation-sensitive MOG-IgG. Since several years ago, multiple research groups have detected MOG-antibody detected by cell-based assay in AQP4-antibody-seronegative NMO and other disease phenotypes, such as optic neuritis, LETM, acute disseminated encephalomyelitis (ADEM)/multiphasic DEM (MDEM) and brainstem and cerebral cortical encephalitis [16,17,18▪▪,20,21▪▪]. Importantly, the onset age of MOG-antibody-associated disease is around 30 years on average (vs. 40 years old for AQP4-antibody-seropositive patients), the male : female ratio is almost 1 : 1, and MOG-antibody-associated disease is relatively mild compared with AQP4-antibodyseropositive NMOSD. Some MOG-antibody-seropositive patients do meet the 2015 criteria of AQP4-antibody-seronegative NMOSD, however, in MOG-antibody-associated disease, optic chiasmal involvement occurs only rarely and lumbosacral myelitis is relatively common, which are also different from AQP4-antibody-seropositive NMOSD [16].

There have been some evidences that MOG-antibody is directly involved in the pathogenesis of MOG-antibody-associated disease, and pathological studies of brain-biopsied cases with MOG-antibody [20,49] and CSF analyses of MOG-antibody-

seropositive patients showed that MOG-antibody-associated disease is an inflammatory demyelinating disease but not an astrocytopathic disease even if the clinical phenotype is typical NMO [50] (Table 1). This important finding has widened the pathological concept of NMOSD.

A subset of cases with typical NMO are seronegative for AQP4 and MOG antibodies [16]. Some of them may be false-negative based on the currently available assays but it remains unclear whether a third NMO-associated autoantibody is present and this issue is under study.

EVOLUTION OF THERAPEUTIC CONCEPT OF NEUROMYELITIS OPTICA SPECTRUM DISORDERS

After disease-modifying drugs (DMD) for multiple sclerosis were approved, in the beginning the patients with NMOSD were also treated with DMD for multiple sclerosis. However, such DMD for multiple sclerosis as interferon-beta, natalizumab and fingolimod were ineffective in or did exacerbate AQP4-antibody-seropositive NMOSD (Table 2) [9]. The immunological mechanisms are not fully understood, but inflammatory cytokines, especially T-helper (Th)-17-related ones like IL-6, IL-8, and so forth, are significantly upregulated in the CSF during acute exacerbations of AQP4-antibody-seropoositive NMOSD and MOG-antibody-associated disease compared with multiple sclerosis and controls [51▪▪]. In animal studies, interferon-beta is effective in ameliorating the clinical course of Th-1-induced EAE but not Th-17-induced EAE [52]. Thereby, those DMD for multiple sclerosis may not efficiently suppress Th17-related pathological processes of NMOSD relapse.

Current treatment of NMOSD is classified as follows: to hasten recovery from acute exacerbation; to prevent relapse in the long-term; and to minimize chronic sequelae.

(1) High-dose intravenous methylprednisolone (HIMP; 1000 mg/day for 3–5 days, one to two courses) is the first-line therapy in the acute phase of NMOSD. Plasma exchange (replaced with 5.0% human albumin solution, replacement volume 30–40 mg/kg, four to eight sessions) or immunoadsorption may be needed as a rescue therapy in cases refractory to HIMP.
(2) Long-term immunosuppression is needed to prevent relapses of NMOSD. Commonly used drugs for the disease include Azathioprine (2–3 mg/kg/day) (combined with prednisone, 30 mg/day, taper after 6–9 months), Mycophenolate mofetil (1000–3000 mg/day) (combined with prednisone, 30 mg/day, taper after 6 months), Rituximab (induction therapy [375 mg/m^2/week × 4 or 1000 mg × 2], followed by maintenance therapy [375 mg/m^2] whenever CD27+ memory B cels [>0.05% in peripheral blood mononuclear cells] re-emerge.), Prednisone (30 mg/day, taper after 1 year) and Tacrolimus (2–5 mg/day depending on trough value). Rituximab is more potent in preventing relapse than Azathioprine and Mycophenolate mofetil. Methotrexate (15–25 mg/week), Mitoxantrone (12 mg/m^2/month × 6, followed by monthly maintenance dose of 6 mg/m^2, total cumulative dose <120 mg/m^2) and other immunological therapies for NMOSD have also been reported in the literature (Table 2). The therapeutic efficacy of Cyclophosphamide is unconvincing at this point.
(3) Symptomatic therapies for pain including painful tonic spasm (carbamazepine 200–400 mg/day in divided doses), spasticity, dysuria, constipation, depression, fatigue and other chronic sequelae should be provided. However, such studies and the evidences remain insufficient.

Therapeutic evidences for MOG-antibody-associated disease are still limited, but immunosuppression rather than DMDs for multiple sclerosis seems to be the treatment of choice in relapsing MOG-antibody-associated disease as well as AQP4-antibody-seropositive NMOSD although the responses to immunosuppressants may not be similar in the two-autoantibody-associated CNS diseases.

A number of promising cellular and molecular targets of therapy have been identified in AQP4-antibody-seropositive NMOSD [43] (Table 2). Recently, international, multicenter, double-blind, placebo-controlled clinical trials of three monoclonal antibodies for NMOSD [SA237 (anti-IL-6 receptor), eculizumab (anti-C5), and MEDI-551 (anti-CD19)] have been done, and according to the press releases they appear to be effective in reducing the risk of NMOSD relapse [10–12]. For autoantibody-seronegative NMOSD, experts tend to choose immunosuppression as well, but we occasionally encounter patients with autoantibody-seronegative, indeterminate multiple sclerosis/NMOSD-overlapping syndrome, and even multiple sclerosis and NMOSD specialists are at a loss, which treatment to choose for those cases [53▪▪].

RETROSPECTIVE REVIEW OF NEUROMYELITIS OPTICA CASES BEFORE THE DISCOVERY OF AQUAPORINE-4-ANTIBODY

As described above, the current concept of NMOSD is based on AQP4-antibody-seropositive cases

Table 2. Immunological treatment of neuromyelitis optica spectrum disorders and the mechanism of action

Corticosteroid
Prednisone (inhibits synthesis of inflammatory cytokines and incudes T-cell apoptosis)
Antimetabolites
Azathioprine (a purine analogue, disrupts synthesis of DNA and RNA and induces T-cell apoptosis)
Methotrexate (a folic acid analogue, increases extracellular release of adenosine to mediate anti-inflammatory effect)
Mitoxantrone (a type II topoisomerase inhibitor, disrupts cellular DNA synthesis and repair by intercalation between DNA bases, inhibits proliferation of macrophages, B and T cells, induces apoptosis of B cells, monocytes and dendritic cells, decreases secretion of proinflammatory cytokines)
Mycophenolate
Mycophenolate mofetil (an inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH), a key enzyme in the de novo guanosine nucleotide synthesis, T and B lymphocytes are more dependent on this pathway than other cells)
Alkylating agent
Cyclophosphamide (its metabolite phosphoramide mustard forms DNA crosslinks, which is irreversible and causes cell apoptosis, eliminates CD4+CD25+T regulatory cells, induces T-cell growth factors including type I interferons)
Calcineurin inhibitor
Tacrolimus (an inhibitor of IL-2 that promotes the development and proliferation of T cells)
Monoclonal antibodies
Rituximab (anti-CD20, depletes CD20-expressing B cells and severs B-cell–T-cell interaction)
Tocilizumab (anti-IL-6 receptor, suppresses upregulated IL-6, a main driver of AQP4-antibody-producing plasmablasts and other pathogenetic aspects of AQP4-antibody-seropositive NMOSD)
Satralizumab* (anti-IL-6 receptor, a recycling antibody acting longer than tocilizumab)
Eculizumab* (anticomplement C5, blocks complement-mediated cytotoxicity to astrocytes, a major pathological mechanism of AQP4-antibody-seropositive NMOSD)
Inebilizumab* (anti-CD19, inhibits CD19-expressing B cells including CD20-positive ones and AQP4-antibody-producing plasmablasts)
As of March, 2019, there are no approved drugs for NMOSD. *The double-blind, placebo-controlled phases of the three international, multicenter, clinical trials were completed in 2018.
Apheresis
Plasma exchange and immunoadsorption (depletes AQP4-antibody, complements other humoral factors in blood and modulates cytokine profiles and cellular immunity)
Other potential therapeutic agents under study
Complement C1 esterase inhibitor (a blocker of C1, prevents activation of C1r and C1s and inactivates them once triggered by antibody binding, blocks downstream components of the mannan-binding lectin, fibrinolytic, clotting, and kinin pathways. An open-label phase 1b safety and proof-of-concept trial was done.)
Aquaporumab (anti-AQP4 monoclonal with a mutated Fc lacking functionality for complement-mediated and cell-mediated cytotoxicity, nonpathogenic, blocks pathogenic AQP4-antibody binding)
Sivelestat (a competitive inhibitor of human neutrophil elastase)
Cetirizine (a second-generation antihistamine, inhibits eosinophil chemotaxis), Ketotifen (an allergy medication, stabilizes mast cells)
DMD for multiple sclerosis that may exacerbate NMOSD
Interferon-beta, Natalizumab, Fingolimod, Alemtuzumab, and Dimethyl fumarate (because of inability to suppress Th-17-related response?)

AQP4, aquaporin 4; DMD, disease-modifying drug; IL-6, interleukin-6; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders; Th, T helper.

simply because AQP4-antibody was the first NMO-specific autoantibody discovered. However, if we look back at the NMO cases reported before the discovery of AQP4-antibody, we realize that at least a portion of them are unlikely to be AQP4-antibody-seropositive (Table 3).

(1) In 1894, Fernand Gault, a student of Devic, wrote his thesis on the analysis of clinical features of 17 cases of NMO. Most of them were from the literature but Devic's case was also included [24]. There were more male patients than female patients. The interval of optic neuritis and myelitis was less than 30 days in 10 cases. The course was monophasic in 14 (relapsing in three), and the outcome was no or mild sequelae in eight (fatal in eight).

Table 3. Monophasic neuromyelitis optica vs. relapsing neuromyelitis optica in early reports of the disease preceding the discovery of aquaporin 4-antibody

(a) Wingerchuk *et al.* [5]

Feature	Monophasic NMO	Relapsing NMO	*P* value
N	23	48	
Sex (female : male)	11 : 12	40 : 8	0.008
Median year of onset (range)	1975	1986	0.003
Median onset age (range)	29 years (1–54)	39 years (6–72)	
Antecedent events (%)			
Viral illness	7 (30)	11 (23)	0.437
Immunization	2 (9)	0	0.090
Autoimmune disease	0	15 (30)	0.003
Index events (%)			
Optic neuritis (ON)	6 (26)	23 (48)	0.001
Myelitis	5 (22)	20 (4)	
Bilateral ON	4 (17)	4 (8)	
Myelitis and ON	1 (4)	1 (2)	
Bilateral ON and myelitis	7 (31)	0	

(b) Miyazawa *et al.* [54]

	Monophasic NMO	Relapsing NMO
N	97	109
Sex (female : male)	1.4 : 1	6.3 : 1
Average onset age (mode)	24.5 years (5–9)	34.9 years (30–34)
Average interval of ON and myelitis	4 months	21 months
Infection	51.1%	23.6%
Autoantibody	25%	50%

AQP4, aquaporin 4; NMO, neuromyelitis optica.

(2) Friedlich Albin Schanz reported an NMO case before the Devic's case [22▪]. The patient, a 19-year-old man, developed left optic neuritis, right optic neuritis (2 weeks later) and then transverse myelitis in succession. Surprisingly, without any immunosuppressive therapy, his symptoms began to improve 10 days later and completely resolved in 3-4 months.

(3) Wingerchuk *et al.* [5] divided NMO into monophasic NMO ($n = 23$) and relapsing NMO ($n = 48$) when they proposed the diagnostic criteria of NMO in 1999 (Table 3a). Relapsing NMO was characterized by female preponderance (female : male = 40 : 8), about 40 years old at onset (6–72), relatively high frequency of coexisting autoimmune disorders (30%) and no concurrent development of optic neuritis and myelitis. These features correspond to those of AQP4-antibody-seropositive NMO. In contrast, monophasic NMO patients were younger at onset (29 years old on average, range: 1–54), no coexisting autoimmune disorders and opticomyelitis at onset in 31% of the cases. Those findings were not different from AQP4-antibody-seronegative NMO and MOG-antibody-seropositive NMO.

(4) We exhaustively collected NMO cases from the literature before AQP4-antibody was initially reported and analyzed them by classifying them into monophasic and relapsing NMO [54] (Table 3b). The results were quite similar to the ones obtained by Wingerchuk *et al.* [5], that is, relapsing NMO appeared something like AQP4-antibody-seropositive NMO whereas the features of monophasic NMO were essentially similar to those in AQP4-antibody-seronegative NMO and MOG-antibody-seropositive NMO although monophasic and relapsing NMO groups may include both AQP4-antibody-seropositive and AQP4-antibody-seronegative cases.

Taken together, these data strongly suggest that cases of AQP4-antibody-seronegative NMO and MOG-antibody-seropositive NMO were probably

included in the early reports of the disease. However, when AQP4-antibody research prevailed following the discovery of the NMO-specific autoantibody, most people, so to speak, turned a blind eye to AQP4-antibody-seronegative NMO. But after a while, investigators started to focus on AQP4-antibody-seronegative NMO and MOG-antibody was detected in some of those patients.

TIME TO RECONSIDER THE CONCEPT OF NEUROMYELITIS OPTICA SPECTRUM DISORDERS?

As aforementioned, early reports of NMO probably included MOG-antibody-seropositive NMO. As MOG-antibody-associated disease has a unique clinical spectrum, which is somewhat different from that of AQP4-antibody-seropositive NMOSD [21▪▪,22▪,55,56▪▪,57,58,59▪▪]. More specifically, single site disease like LETM and severe/bilateral/recurrent optic neuritis and multiple site/extensive diseases, such as ADEM/MDEM and cerebral cortical encephalitis (some of them are MOG-antibody-seropositive) do not fit in the 2015 diagnostic criteria of NMOSD [55]. Also, it is indispensable to study the clinical and immunopathological features of double seronegative NMOSD to see if we can extract another unique subgroup of patients defined by a biomarker.

On the basis of current understanding of AQP4-antibody-seronegative and -seronegative NMOSD, now may be the time to reconsider the concept (or definition) of NMOSD from scratch.

CONCLUSION

NMO was initially described in the late 19th century, and the clinical, pathological and therapeutic concepts of NMOSD have evolved and broadened in the past 20 years. Current clinical concept of NMOSD is based on AQP4-antibody-seropositive cases, but we have newly recognized MOG-antibody-seropositive disease including its NMOSD phenotype and double seronegative NMOSD that were probably included in early reports preceding the discovery of AQP4-antibody. Now may be the time to reconsider how we should define NMOSD.

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Conflicts of interest

K.F. serves on scientific advisory boards for Bayer, Biogen, Mitsubishi Tanabe, Novartis, Chugai, Ono, Nihon, Merck Serono, Alexion, and Medimmune; has received funding for travel and speaker honoraria from Bayer, Biogen, Eisai, Mitsubishi Tanabe, Novartis, Astellas, Takeda, Asahi Kasei Medical, Daiichi Sankyo, and Nihon; serves as an editorial board member of Clinical and Experimental Neuroimmunology (2009–present) and an advisory board member of Sri Lanka journal of Neurology; has received research support from Bayer, Biogen, Asahi Kasei Medical, The Chemo-Sero-Therapeutic Research Institute, Teva, Mitsubishi Tanabe, Teiji, Chugai, Ono, Nihon, and Genzyme.

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