Neuromyelitis optica

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Abstract | Neuromyelitis optica (NMO; also known as Devic syndrome) is a clinical syndrome characterized by attacks of acute optic neuritis and transverse myelitis. In most patients, NMO is caused by pathogenetic serum IgG autoantibodies to aquaporin 4 (AQP4), the most abundant water-channel protein in the central nervous system. In a subset of patients negative for AQP4-IgG, pathogenetic serum IgG antibodies to myelin oligodendrocyte glycoprotein, an antigen in the outer myelin sheath of central nervous system neurons, are present. Other causes of NMO (such as paraneoplastic disorders and neurosarcoidosis) are rare. NMO was previously associated with a poor prognosis; however, treatment with steroids and plasma exchange for acute attacks and with immunosuppressants (in particular, B cell-depleting agents) for attack prevention has greatly improved the long-term outcomes. Recently, a number of randomized controlled trials have been completed and the first drugs, all therapeutic monoclonal antibodies, have been approved for the treatment of AQP4-IgG-positive NMO and its *formes frustes*.

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Neuromyelitis optica (NMO) is characterized by simultaneous or consecutive attacks of acute optic neuritis (ON) and transverse myelitis (TM)[1–3]. In ≥80% of cases, NMO is caused by pathogenetic IgG autoantibodies to aquaporin 4 (AQP4-IgG), the most abundant water channel protein in the central nervous system (CNS)[4–6]. Around 10–40% of individuals with NMO who lack AQP4-IgG have IgG autoantibodies to myelin oligodendrocyte glycoprotein (MOG-IgG)[7–9]; of note, MOG-IgG is also present in a subset of patients (mostly children) with acute disseminated encephalomyelitis (ADEM)[10–12]. AQP4-IgG-positive NMO is primarily an autoimmune astrocytopathy, although secondary damage to oligodendrocytes and neurons occurs as a result of astrocyte dysfunction and loss and, probably, bystander inflammation[13,14]. By contrast, primary demyelination is found in those with MOG-IgG. NMO has also been described in patients with sarcoidosis, infectious disease, connective tissue disorders (CTDs) and paraneoplastic neurological disorders, although cases are rare. In a small subgroup of patients, the cause remains unknown (known as idiopathic NMO).

AQP4-IgG-positive and MOG-IgG-positive NMO usually have a relapsing disease course with no major disease progression between attacks, although cases of monophasic MOG-IgG-positive disease have been reported. Untreated NMO can lead to severe, persisting visual and motor dysfunction owing to incomplete recovery from acute attacks[15]; however, improvements in treatments over the past few years mean that NMO can be controlled in many patients. High-dose corticosteroids and plasma exchange (PEX) or immunoadsorption (IA) are the therapeutic mainstay for acute attacks[16,17], whereas rituximab, azathioprine, mycophenolate mofetil (MMF) and other immunosuppressants are used for long-term stabilization[16,17]. The approval of eculizumab, satralizumab and inebilizumab has substantially expanded the spectrum of available drugs for patients with AQP4-IgG.

Many unresolved nosological and terminological issues for NMO exist, resulting both from the heterogeneous pathogenesis of NMO, which it shares with other neuroimmunological syndromes, and from the fact that some patients do not present, at least initially, with the full clinical syndrome but with isolated ON, TM or, more rarely, brainstem or brain inflammation. Indeed, the latter finding has led to the introduction of the term 'neuromyelitis optica spectrum disorders' (NMOSD), which is used to refer to NMO and its *formes frustes*[18,19]. Isolated ON may be even more common than NMO in those with MOG-IgG-associated disease, although the proportion of patients with a history of both ON and myelitis increases over time.

This Primer provides an up-to-date review of the epidemiology, immunopathogenesis, diagnosis and treatment of NMO. Although the Primer largely focuses on NMO in the context of AQP4-IgG-associated and MOG-IgG-associated autoimmunity, other differential diagnoses are also briefly discussed.

Epidemiology

Incidence and prevalence

NMO occurs worldwide and in all ethnicities[20]; however, significant regional differences in incidence and prevalence rates have been reported, with higher

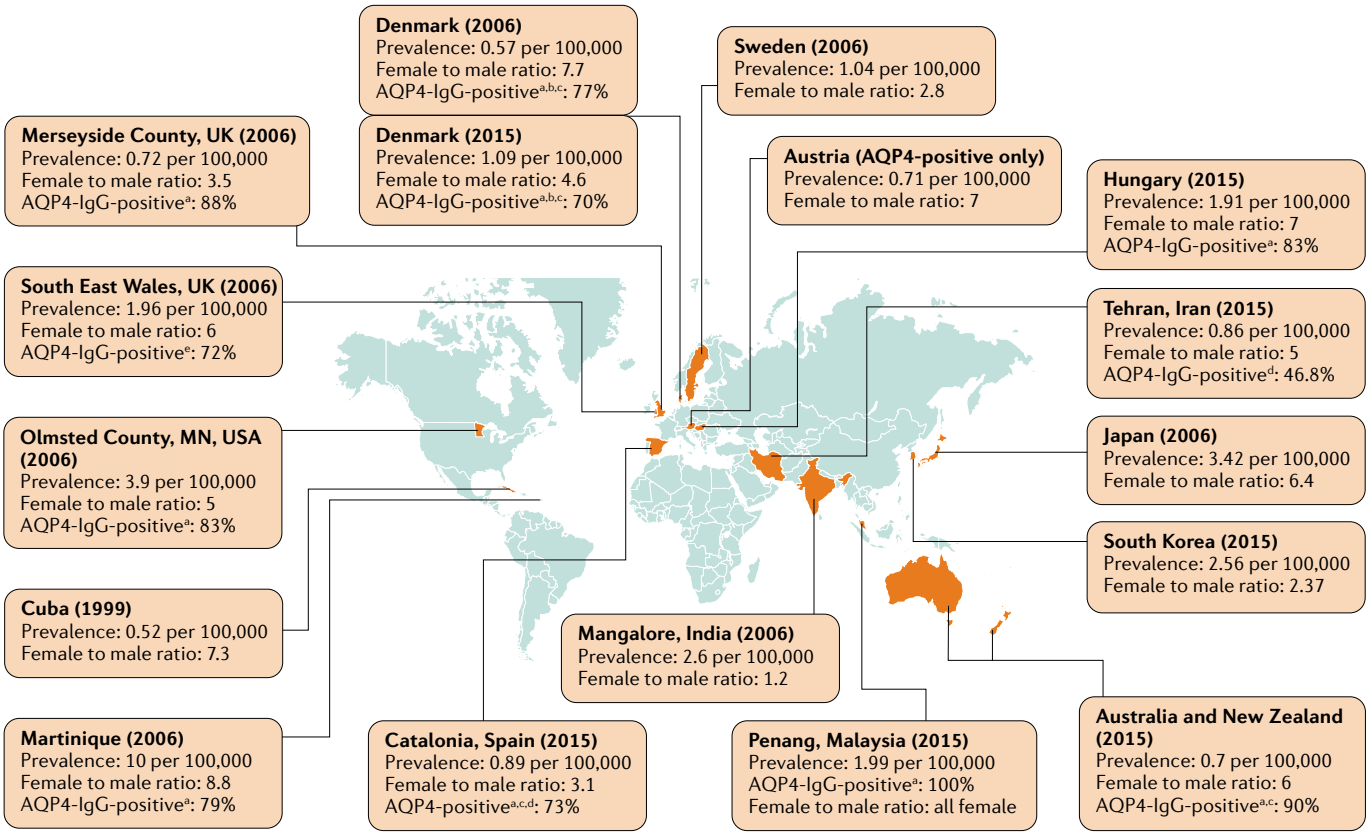


Fig. 1 | **Prevalence estimates.** Reported prevalence estimates, aquaporin 4 (AQP4)-IgG seropositivity rates and sex ratios vary between countries. The diagnostic criteria used in each study is indicated by the year after the region name (2015: neuromyelitis optica spectrum disorders (NMOSD) according to REF.[19]; 2006: neuromyelitis optica (NMO) according to REF.[343] plus *formes frustes* (varying definitions); 1999: NMO according to REF.[192] plus *formes frustes*); one study[24] took into account exclusively AQP4-IgG-positive cases. Prevalence dates varied between studies (2004–2017). Data retrieved from REF.[22] (Australia and New Zealand), REF.[24] (Austria), REF.[358] (Catalonia, Spain), REF.[359] (Cuba), REF.[38] (Denmark), REF.[360] (Hungary), REF.[361] (Japan), REF.[362] (Mangalore, India), REF.[21] (Martinique), REF.[363] (Merseyside County, UK), REF.[21] (Olmsted County, MN, USA), REF.[23] (Penang, Malaysia), REF.[364] (South East Wales, UK), REF.[26] (South Korea), REF.[25] (Sweden) and REF.[365] (Tehran, Iran). [a]AQP4 antibody status determined using cell-based assay. [b]AQP4 antibody status determined using immunoprecipitation assay. [c]AQP4 antibody status determined using tissue-based immunofluorescence assay. [d]AQP4 antibody status determined using ELISA. [e]Method to identify AQP4 antibody status not described.

prevalence and incidence rates in non-white individuals[20–22] (FIGS 1,2). This finding suggests that genetic and/or environmental factors may have a role in the aetiopathogenesis of NMO. Indeed, one population-based study found a 2.6-times higher prevalence of NMOSD in Martinique (in which 90% of the population is Black) than in Olmsted County in the USA (in which 82% of the population is white)[21], and a study from Australia and New Zealand found a 3-times higher prevalence in Asian individuals than in non-Asian individuals[22], although significant differences were also noted between different Asian ethnicities within the same country[23]. Accordingly, significant differences in the proportion of patients with NMO among those with inflammatory demyelinating diseases (IDD) of the CNS have been described between different ethnicities and regions. Although only 1–2% of adult white individuals with IDD have AQP4-IgG-related or MOG-IgG-related disorders[21,24,25], patients with these antibodies accounted for 25–45% of all adult patients with IDD in some studies in Asia[26–28]. Besides the reported higher prevalence of NMOSD in non-white individuals, this difference likely also reflects the well-known lower prevalence of classic multiple sclerosis (MS) in Asian populations. Two studies have not found evidence for a latitudinal gradient in incidence and prevalence as observed in MS[22,29]; however, more and larger studies are needed to properly address this topic.

Of note, a higher seroprevalence of MOG-IgG than of AQP4-IgG has been noted in children with IDD[30–32], with the opposite result in adults[27,28,33–36]. Indeed, three large paediatric studies found a 5–8-times higher frequency of MOG-IgG than of AQP4-IgG, whereas AQP4-IgG was 3–8-times more frequent among adults with IDD in four large studies that included exclusively adult patients (and 4-times more frequent based on a pooled analysis considering all cases reported in these studies)[27,33,35,36]. Nationwide studies assessing the incidence of AQP4-IgG-associated and MOG-IgG-associated disorders are scarce. One nationwide study found an incidence of 0.16 cases per 100,000 person-years per year

Optic neuritis
(ON). Inflammation of the optic nerve.

Transverse myelitis
(TM). Inflammation of the spinal cord.

Acute disseminated encephalomyelitis
(ADEM). Sudden onset, widespread, polyfocal inflammatory demyelination of the brain and spinal cord, typically following infection or vaccination.

Autoimmune astrocytopathy
An autoimmune disorder primarily directed against astrocytes.

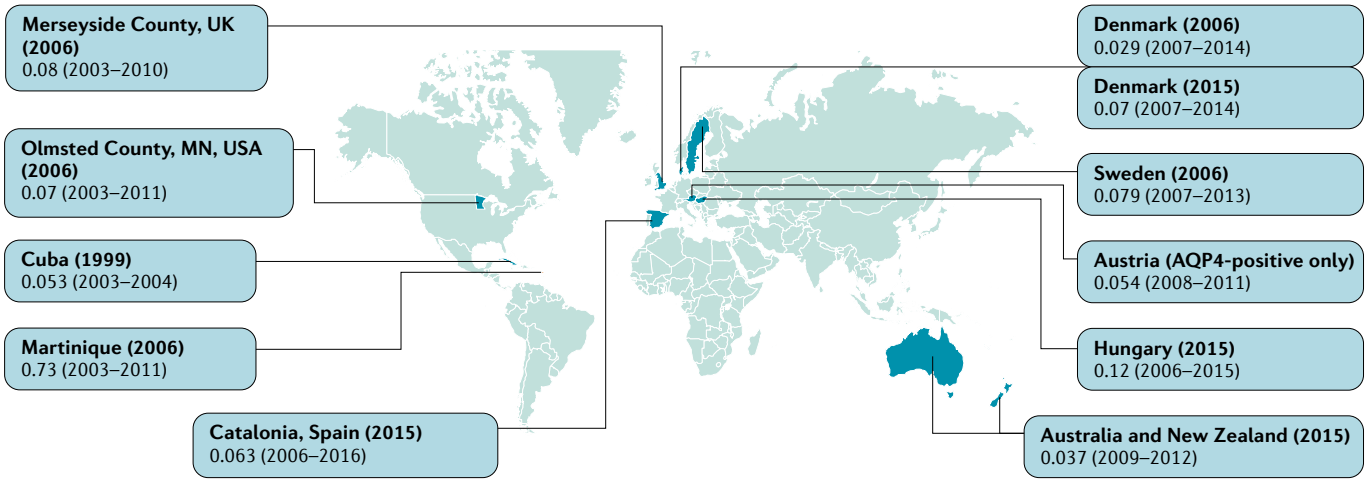


Fig. 2 | **Incidence estimates.** Reported annual incidence estimates (per 100,000 person-years) vary between countries. The diagnostic criteria used in each study is indicated by the year after the region name (2015: neuromyelitis optica spectrum disorders (NMOSD) according to REF.[19]; 2006: neuromyelitis optica (NMO) according to REF.[343] plus *formes frustes* (varying definitions); 1999: NMO according to REF.[192] plus *formes frustes*); one study[24] took into account exclusively AQP4-IgG-positive cases. Years analysed are given in brackets. Data retrieved from REF.[22] (Australia and New Zealand), REF.[24] (Austria), REF.[358] (Catalonia, Spain), REF.[359] (Cuba), REF.[38] (Denmark), REF.[360] (Hungary), REF.[21] (Martinique), REF.[363] (Merseyside County, UK), REF.[21] (Olmsted County, MN, USA) and REF.[25] (Sweden).

for MOG-IgG-associated disorders in the Netherlands[37], with a higher incidence in children (0.31 cases per 100,000 person-years) than in adults (0.13 cases per 100,000 person-years)[37]. In Denmark and Austria, the nationwide incidence of AQP4-IgG-associated disorders was 0.02 and 0.054 cases per 100,000 person-years, respectively[24,38].

In general, the incidence and prevalence of NMO are expected to increase in the future due to increasing awareness of the disease, improved diagnosis owing to better distinction from its mimics, and the wider accessibility of tests for AQP4-IgG and MOG-IgG. In addition, decreasing mortality owing to earlier diagnosis and therapeutic improvements may also lead to increasing prevalence estimates.

In addition to genetic and environmental factors, the observed heterogeneity in prevalence and incidence estimates between studies may, to some extent, also reflect differences in data sources, case ascertainment, diagnostic criteria and antibody assays used. Moreover, confidence intervals were broad in some studies, and some reported age-adjusted data on prevalence and incidence while others did not. Accordingly, the available epidemiological data should be interpreted with caution.

Demographics

NMO can occur at any age. The median age at onset was 40 years for patients with AQP4-IgG and 31 years for patients with MOG-IgG in two large European cohorts comprising mainly adults[9,15] but may be lower in Asian and Black patients positive for AQP4-IgG[9,15]. NMO is more common in women than in men, particularly in those with AQP4-IgG (male to female ratio 1:9 to 1:10)[15,39,40]. The female preponderance is much less pronounced in patients with seronegative NMO and in those with MOG-IgG[9,15,33,41] (FIG. 1).

Risk factors

The strongest risk factor for NMO is female sex, particularly for AQP4-IgG-positive NMOSD. Several studies have found a significant association between human leukocyte antigen (HLA) alleles and NMO (either compared with MS or with healthy controls), such as HLA-DRB1*03, which was found in patients with AQP4-IgG in the Netherlands (in addition to HLA-A*01 and HLA-B*08)[42], Spain (together with HLA-DRB1*10)[43], Mexico[44], India (with a trend for HLA-DRB1*10 in the total NMO population)[45], Brazil[46,47] and in French Afro-Caribbean patients with NMO[48]. Of note, different HLA associations were reported in some populations, namely with HLA-DPB1*0501 in southern Han Chinese individuals positive for AQP4-IgG[49] and HLA-DPB1*0501 and HLA-DRB1*1602 in Japanese patients positive for AQP4-IgG (but not in those negative for AQP4-IgG)[50,51]. No association with HLA-DPB1*0501 was found in European patients[52]. Other reportedly associated alleles include HLA-DQA1*05:03 in Japanese patients with NMOSD[53] and HLA-DRB1*04:04 and HLA-DRB1*10:01 in Muslim Arab Israeli patients positive for AQP4-IgG (alongside a strong negative association with HLA-DRB1*07 and HLA-DQB1*02:02)[54]. In line with the HLA associations, one genome-wide association study suggested that genetic variants in the MHC region contribute to the aetiology of AQP4-IgG-positive NMO in patients of European ancestry[55]. By contrast, only one study has investigated HLA alleles in patients with MOG-IgG, which found no association[42]. This finding could indicate a role for T cell-independent B cell activation; alternatively, multiple HLA class II/peptide complexes might be capable of triggering a $CD4^+$ T cell response in MOG-IgG-associated autoimmunity. However, more and larger studies are needed before any definite conclusions can be drawn.

Several other risk or protective factors for NMO have been discussed. Polymorphisms in *IL17A* have been suggested to influence the risk for NMO[56]. In addition, exposure of children to other young children has been postulated to be a protective factor against the development of NMO, compatible with a potential role of infections in early life in modifying disease risk[57]. Several other environmental (such as dietary) risk factors have been proposed but lack independent confirmation[58]. Smoking has been suggested to adversely affect disease progression and severity[59–61] and is associated with AQP4-IgG seropositivity in patients with NMO[62]. Multiple studies have found low vitamin D levels in patients with NMO[63–65] and some studies have found an inverse relationship between 25-hydroxyvitamin D serum levels and attack severity, disease progression[66] and/or therapeutic response[63,66], although conflicting data have been reported[67,68]. However, it is still not completely clear whether low vitamin D levels predispose to NMO or are secondary to neurological disability. Acute attacks (including the initial attack) are preceded by acute (mostly respiratory) infections in a substantial number of cases in both patients with AQP4-IgG and in patients with MOG-IgG[9,15]; however, no specific infections have been convincingly linked to the induction of NMO or to the recurrence of NMO attacks. A number of reports on NMO with post-vaccinal onset exist, but the overall incidence is low[9,69].

Mechanisms/pathophysiology

AQP4-IgG-associated disease

Antigen. AQP4 is a bidirectional, osmosis-driven water channel that is impermeable to anions and glycerol and is found at highest concentrations in perivascular and peripial astrocytic endfeet that are in direct contact with the basal lamina of the endothelium and pia, respectively[70]. AQP4 is also present in ependymal cell membranes but not in oligodendrocytes, neurons or choroidal epithelial cells[71]. Five isoforms of AQP4 have been reported but it is unclear whether all are expressed in humans. The two isoforms of relevance in humans are the a isoform (M1-AQP4) and c isoform (M23-AQP4)[13,72]. AQP4 M1 and M23 monomers can form heterotetramers and homotetramers in membranes, with each monomer containing a water-selective pore. M23 homotetramers and M1/M23 heterotetramers further assemble into orthogonal arrays of particles[73]. Each monomer consists of six membrane-spanning α-helices and two pore helices. Recombinant AQP4-IgG derived from patients with NMO bound to the extracellular loops of the water channel and required specific conserved amino acids in loops C and loop E for binding[74].

Histopathology. CNS lesions in individuals positive for AQP4-IgG are characterized by vasculocentric IgG and IgM deposits, which are most prominent around the blood vessels (corresponding to the high AQP4 expression at the glia limitans interna[75–77]), complement deposits and cellular infiltrates consisting of macrophages/microglia, neutrophils, eosinophils granulocytes, B cells, and a few T cells[75] (FIG. 3). The hallmark diagnostic histopathological features include a substantial loss of astrocytes, with either preservation or secondary loss of oligodendrocytes and neurons depending on lesion stage and attack severity[76–78]. Secondary loss of neurons and oligodendrocytes occurs owing to astrocyte dysfunction and/or inflammatory bystander damage[79].

In some lesions, AQP4 is lost but other astrocytic markers, such as glial fibrillary acidic protein (GFAP), are still detectable, indicating that the disappearance of AQP4 precedes astrocyte loss. Some studies suggest that the initial (and potentially reversible) loss of AQP4 may be the result of AQP4 internalization and endolysosomal degradation[80–84], although conflicting data have been reported[85]. Interestingly, one study reported a loss in AQP4 reactivity on Müller cells in the retina in the absence of complement activation[86]. In severe cases, large areas of necrosis and cavitation may be present and thickened and hyalinized walls have been observed in both active and inactive lesions[75].

Lesion distribution and severity in patients with AQP4-IgG may reflect differences in AQP4 expression levels (higher in the optic nerve, spinal cord, diencephalon and area postrema[87] than in other CNS regions), the proportion of supramolecular AQP4 aggregates between brain areas (higher in the spinal cord and optic nerves[88]) and blood–brain barrier (BBB) permeability, which is much greater in the circumventricular organs, including the area postrema. The relative lack of inflammation outside the CNS despite high AQP4 expression in some tissues and organs, such as the kidneys, has been proposed to be partly caused by greater co-expression of regulators of complement activation (that is, CD46, CD55 and CD59) in the periphery than in the CNS[89–91]. In addition, although the colocalization of AQP4 and regulators of complement activation has been reported in cultured human astrocytes, it seems to be largely absent in astrocytic endfeet in contact with endothelial cells, in cell culture and in normal human brain and spinal cord, which would render the endfeet at the BBB particularly vulnerable to complement-mediated damage[89]. The dependence of regulators of complement activation expression on astrocyte–endothelial cell contact could also account for the milder pathology observed in animal models in the area postrema, with its relative lack of a proper BBB[92], and for reports of reversible MRI lesions in patients with AQP4-IgG-positive NMOSD and intractable nausea, vomiting or hiccups due to an area postrema lesion (so-called area postrema syndrome)[93].

Pathophysiology. Besides histopathology, several further lines of indirect evidence support a role of AQP4-IgG in the pathogenesis of NMO (summarized in REFS[14,94,95]). For example, the presence of AQP4-IgG is highly specific for NMO and its *formes frustes*[4] and the serum concentrations of AQP4-IgG and AQP4-IgG-producing plasmablasts[96] coarsely correlate with NMO disease activity. Indeed, serum AQP4-IgG levels typically increase shortly before relapse and decline during remission (although this is not always the case, such as in patients receiving immunosuppressants)[97–99]; accordingly, median AQP4-IgG serum concentrations were found to be higher during acute attacks[97–99]. In Japanese patients with AQP4-IgG, high antibody serum titres

Area postrema syndrome (APS). Intractable nausea, vomiting or hiccups caused by a lesion in the dorsal medulla oblongata.

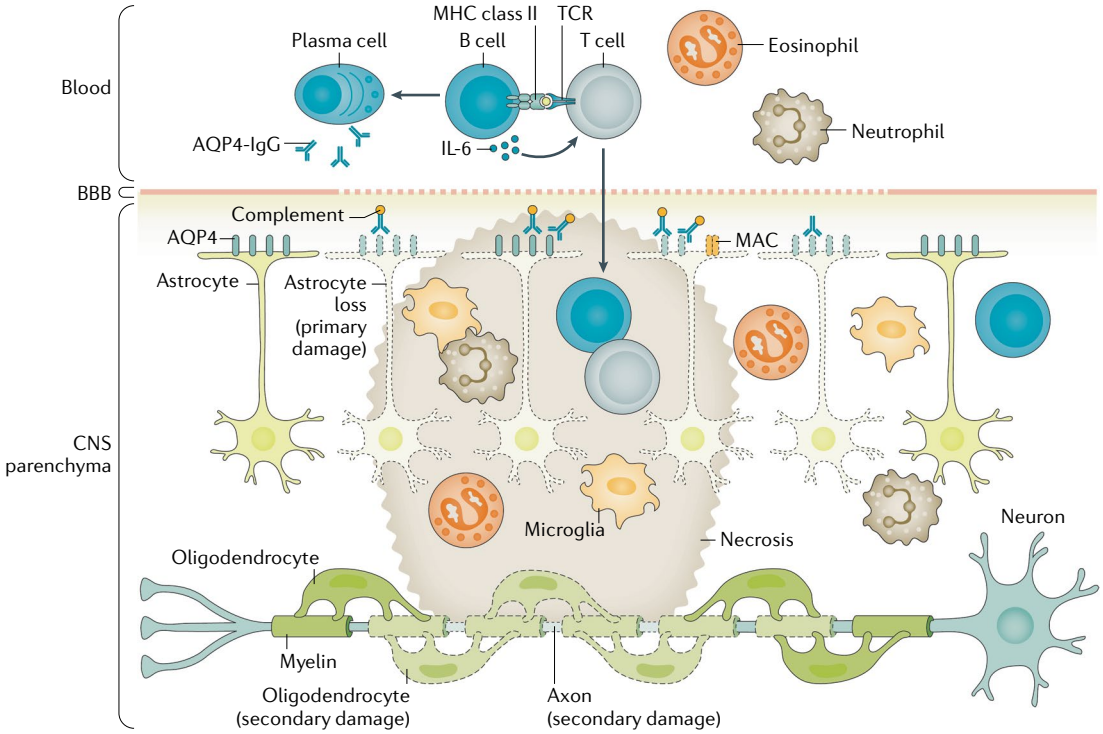


Fig. 3 | **Mechanisms of disease in individuals with AQP4-IgG.** Lesions in aquaporin 4 (AQP4)-associated neuromyelitis optica spectrum disorders are characterized by IgG and complement deposition — mainly on astrocyte endfeet — together with astrocyte loss and, often, secondary oligodendrocyte and neuronal loss. Complement deposits include C9neo, which indicates activation of the terminal complement pathway leading to the formation of the membrane attack complex (MAC)[75–77]. Various types of infiltrating immune cell — namely, macrophages/microglia, neutrophils, eosinophils, B cells and T cells — are present within the lesions. Severe inflammation may result in necrotic, cavitary lesions. BBB, blood–brain barrier; CNS, central nervous system; MHC, major histocompatibility complex; TCR, T cell receptor.

were associated with complete blindness and extensive or large cerebral lesions on MRI, and titres were positively correlated with spinal cord lesion length on MRI[98]. Of note, the increase in AQP4-IgG levels during relapse is not paralleled by an increase in other autoimmune autoantibodies[99]. In addition, the presence of AQP4-IgG predicts future relapses as well as later conversion to NMO in patients initially presenting with isolated ON, TM or brainstem encephalitis[15,100,101].

Further evidence supporting a pathogenetic role for AQP4-IgG is that they belong to the complement-activating IgG1 subclass[102] and their presence during clinical attacks is accompanied by increased complement C5a concentrations in cerebrospinal fluid (CSF)[103]. AQP4-IgG is also more frequently present in the CSF during relapse than during remission[104]. Moreover, treatments that eliminate antibody serum levels (such as PEX or IA[105,106]), those that target B cells, plasmablasts and plasma cells[107–111], and those that inhibit the terminal complement cascade[112] are effective for AQP4-IgG-positive NMOSD. In addition, recurrence of B cells in patients treated with rituximab is associated with an increase in AQP4-IgG levels and breakthrough attacks[113]. Finally, the predilection sites for MRI lesions in NMO correlate with sites of high AQP4 expression[87,88].

More direct evidence of a pathogenetic role of AQP4-IgG is from animal experiments, in which intravenous or intraperitoneal transfer or intracerebral injection of patient IgG and human complement caused a decreased AQP4 expression, followed by astrocyte loss, complement deposits, demyelination and necrosis[114–117], which can be prevented by complement inhibitors[114]. Similarly, sera from patients with AQP4-IgG applied together with human complement can destroy primary mouse astrocytes[118] and AQP4-transfected human cells[102,119] in vitro and can reproduce NMOSD-typical lesion pathology in spinal cord slice cultures from wild-type mice but not from AQP4-null mice[120]. Sterically blocking the interaction between AQP4-IgG and AQP4 or preincubation with engineered non-pathogenetic AQP4 antibodies can inhibit the pathogenetic process in vitro in AQP4-IgG-transfected cells[121,122], an ex vivo spinal cord slice model[123] and in a mouse model[123]. Modification of the Fc region of AQP4-IgG, which is essential for the binding of immune cell receptors and complement proteins, can also block the pathogenetic process[123–125], further supporting a role of antibody-dependent and complement-dependent cytotoxicity.

Interestingly, differences in epitope specificity between individual AQP4-IgG antibodies may result in differences in C1q binding or activation and, in consequence, in the extent of complement-dependent cytotoxicity[126]. Although other factors are likely to also play a role in this process, such as BBB function and antibody affinity, it could help explain why low AQP4-IgG

titres can induce acute attacks in some patients but not in others[99]. Moreover, it would indicate that monitoring AQP4-IgG subpopulations rather than titration of total IgG might be required for reliable relapse prediction[126].

Complement activated by AQP4-IgG is thought to attract granulocytes through the BBB[84]; indeed, neutrophils and eosinophils are both increased in the CSF of patients with NMOSD[75,127,128]. Moreover, the astrocyte-bound Fc region of AQP4-IgG might activate macrophages, neutrophils and eosinophils, all of which are present in lesions with some indication of degranulation, in patients with NMOSD and in animals exposed to AQP4-IgG[75,129–131]. In support of a pathogenetic role of granulocytes, granulocyte (toxin) inhibitors and eosinophil depletion reduce lesion severity in animal models[131,132], whereas hypereosinophilia or treatment with granulocyte colony-stimulating factor results in disease exacerbation[132,133]. Neutrophils are thought to exacerbate disease via the secretion of neutrophil elastase, whereas eosinophils promote disease by promoting antibody or complement-dependent cellular cytotoxicity[131,132]. Eosinophils secrete IL-4, which promotes a type 2 T helper (T_H2) cell response, thereby favouring autoantibody synthesis.

Further cell types involved in the pathogenesis of NMO are B cells[134] and plasma cells, the presence of which is promoted by a B cell-friendly environment (that is, increased BAFF, APRIL and CXCL13 levels in CSF), which might result from both astrocyte and immune cell activation in the brain[135,136] and T_H cells, which are needed for B cell isotype switching and affinity maturation. Impaired B cell regulatory properties owing to a lack of regulatory B cells or reduced expression of IL-10 alongside a preponderance of activated intrathecal B cells may also contribute to pathogenesis[137]. Similarly, the generation of $FOXP3^+$ regulatory T cells might be disturbed owing to excessive IL-6 production by immune cells and astrocytes[138,139], which may promote IL-17-secreting T_H17 cells, therefore contributing to neutrophil recruitment[140–142]. In fact, an increase in the proportion of T_H17 cells and the concentration of T_H17-related cytokines has been reported in the CSF and serum of patients with NMOSD[143]. NMOSD lesions also contain a few cytotoxic $CD3^+$ and $CD8^+$ T cells[75]. Further evidence for a contribution of T cells to pathogenesis is based on the association of NMOSD with HLA alleles that have been reported to enhance B cell and T cell cooperation[47,52]. Moreover, AQP4-reactive T cells are sufficient to induce an NMOSD phenotype in mouse models[144]. These models also suggest that loss of tolerance to AQP4 is a key step in the development of an autoreactive disease process against this self-protein[145].

CNS antigen-specific T cells could also support the entry of AQP4-IgG into the CNS via opening of the BBB. In fact, circulating AQP4-IgG could induce CNS damage only in the presence of CNS antigen-specific T cells in several passive transfer animal models[92]. However, this theory was challenged by another study that demonstrated NMO-like lesion formation after pre-treatment with complete Freund's adjuvant in the absence of encephalitogenic T cells[117]. Moreover, IgG can enter the CNS on its own via the circumventricular organs, which have fenestrated capillaries, and via meningeal or parenchymal blood vessels. Although the relatively low amount of AQP4-IgG entering the CNS through the intact BBB might not induce major tissue damage, they could lead to barrier disruption given that the astrocytic endfeet, which are the main target of AQP4-IgG, form a constitutive element of the BBB, resulting in a self-amplifying process[92]. Accordingly, in a more recent passive transfer rat model, CNS antigen-specific T cells were not required to induce AQP4-IgG-induced damage when species-specific recombinant antibodies with high affinity and pathogenicity were used and longer exposure times applied[92]. However, of note, the presence of an encephalitogenic T cell response significantly enhanced lesion formation[92]. It is plausible to assume that the amplified CNS/AQP4-specific T cells observed in NMOSD exert similar effects in human disease[142,146].

A potential role of natural killer cells and antibody-dependent cellular cytotoxicity in the pathogenesis of NMOSD has been discussed but is controversial[130,147]. Other pathogenetic mechanisms possibly involved in NMOSD include glutamate-mediated excitotoxicity[82,85], inflammatory bystander damage[148], and disturbed water homeostasis owing to blocking or loss of AQP4 due to internalization[81,83]. Some groups have proposed that the predominant effector mechanism may differ between brain regions, depending, for example, on differences in the local ratio of M1 and M23 AQP4. This could partly explain the diverse pathological features in AQP4-IgG-positive NMO[81,148] and might also account for the absence of demyelinating lesions in the cortex despite evidence for meningeal inflammation, cortical microglial activation and cortical neuronal loss[148].

One study has suggested that defects in both central and peripheral B cell tolerance checkpoints in AQP4-IgG-positive NMOSD lead to an excess of polyreactive and autoreactive new emigrant/transitional and mature naive B cells, as also seen in myasthenia gravis, systemic lupus erythematosus (SLE) and other autoimmune diseases. These cells may provide a pool of cells more prone to antigen-driven B cell somatic mutations that lead to AQP4-reactive cells and would explain two fundamental aspects of AQP4-IgG-positive NMOSD: the presence of antigen-specific AQP4-IgG and an excess of systemic autoimmunity[149].

MOG-IgG-associated disease

Antigen. MOG belongs to the immunoglobulin superfamily and is an intrinsic membrane glycoprotein with two transmembrane domains, two extracellular domains and one cytoplasmic domain. MOG is expressed on the surface of oligodendrocytes and on the outermost surface of myelin sheaths but accounts only for a small portion of all myelin proteins[150,151]. Although its precise function has not been entirely elucidated, a role in cellular adhesion, oligodendrocyte stability, myelin/immune system interactions and as a binding partner of nerve growth factor (NGF) has been postulated[150–152].

Histopathology. Lesions in patients with MOG-IgG are characterized by demyelination with dominant loss of MOG (compared with other myelin proteins such as

myelin basic protein and myelin-associated glycoprotein (MAG))[153] and relative preservation of axons and oligodendrocytes[153–158] (although axonal spheroids, which indicate some axonal damage probably secondary to demyelination or inflammation, and occasional apoptotic oligodendrocytes have been described[154]. In addition, lesions are characterized by cellular infiltrates consisting of macrophages/microglia, T cells (with a preponderance of $CD4^+$ T cells), granulocytes and relatively few B cells, and IgG and complement deposition (FIG. 4). Different from MS, lesions in patients with MOG-IgG have preserved or even increased AQP4 with no dystrophic astrocytes and rather have hypertrophic, reactive astrocytes (including occasional Creutzfeldt–Peters cells[154]) and a dense GFAP-positive network.

Although a substantial overlap with so-called pattern II MS lesions exists[154,159,160], perivascular demyelination, similar to that seen in ADEM, seems to be a characteristic finding that clearly distinguishes lesions in patients with MOG-IgG from the typically confluent MS lesions. However, the frequency of additional confluent demyelination is still controversial owing to inconsistent findings between studies[153,154]; to explain the discrepancy, it has been hypothesized that the fusion pattern may form only at later disease stages. Moreover, confluent lesions in patients with MOG-IgG are thought to be caused by fusion of adjacent perivenous lesions rather than by radial diffusion as seen in MS[153,154]. Interestingly, the co-occurrence of perivascular and confluent demyelination has also been observed in a subset of patients with ADEM[161], which is also associated with MOG-IgG in some cases.

Similar to AQP4-IgG-positive NMOSD, CNS lesions outside the optic nerves and spinal cord are not uncommon in MOG-IgG-associated disease and children tend to present with brain lesions more often than adults in both conditions. The exact reasons for the latter observation are unknown but could involve differences regarding spatial expression patterns, BBB configuration, antibody (epitope) specificity, conformation sensitivity and affinity. Importantly, cortical demyelination, which is virtually absent in AQP4-IgG-positive NMOSD, is relatively frequent in patients with MOG-IgG with brain involvement and is often topographically associated with meningeal inflammation[154]. Subpial lesions have been observed in some patients with MOG-IgG[153,154] and are frequent in MS (then characteristically extensive)[162] and occasionally occur in patients with ADEM[161] but are mostly absent in other inflammatory CNS disorders[163].

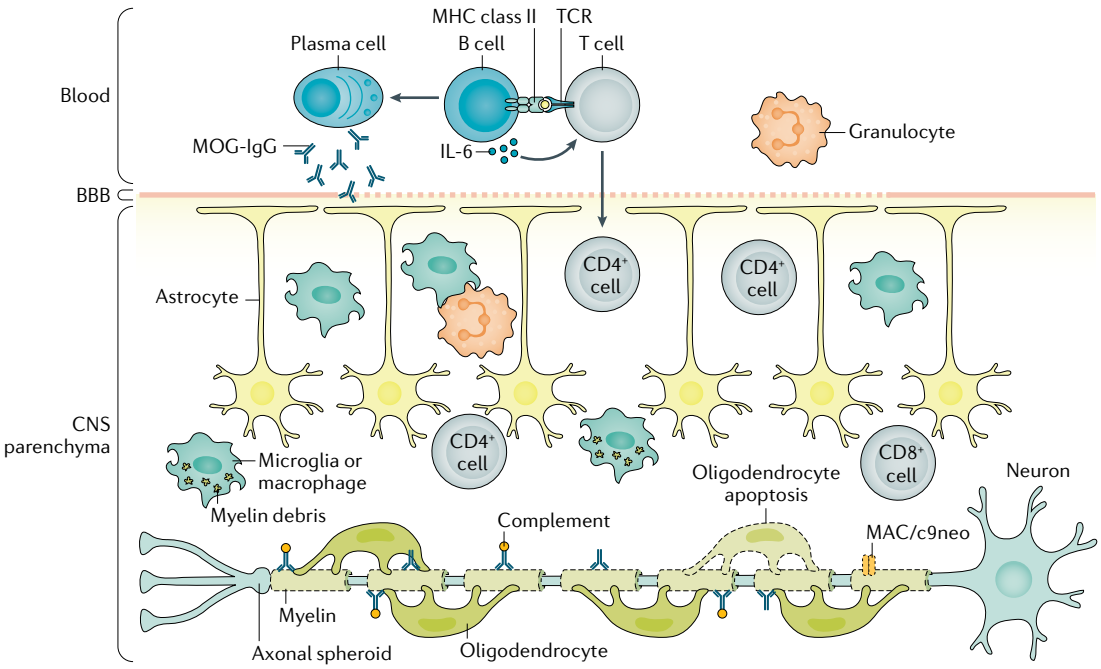


Fig. 4 | **Supposed mechanisms of disease in patients positive for MOG-IgG.** Cellular infiltrates in individuals with myelin oligodendrocyte glycoprotein (MOG)-IgG consist mainly of microglia/macrophages (some containing MOG-positive myelin degradation products[153,154]), T cells (predominantly $CD4^+$ rather than $CD8^+$, in contrast to multiple sclerosis[153,154]) and granulocytes (neutrophils and possibly eosinophils)[154,155,175]. The number of B cells within the lesions is low compared with T cell numbers[154,366]. Immunoglobulin deposits are typically IgG (not usually IgM) and complement (including C9neo) can be detectable within macrophages and along myelin sheaths in areas of active demyelination but not in a vasculocentric fashion as seen in aquaporin 4 (AQP4) neuromyelitis optica spectrum disorder. Both IgG and complement deposition are less pronounced and less frequent in patients with MOG-IgG than in those with AQP4-IgG[153]. The thickened vessel walls described in AQP4-IgG-associated lesions have not been noted in patients positive for MOG-IgG. Interestingly, some areas with absent MOG staining but no marked infiltration of phagocytic macrophages have been observed, which leaves the possibility that other pathomechanisms, such as internalization or downregulation of MOG, might be involved in the pathogenesis[153]. BBB, blood–brain barrier; CNS, central nervous system; MAC, membrane attack complex; MHC, major histocompatibility complex; TCR, T cell receptor.

Moreover, strictly intracortical lesions seem to be prominent and more common than in MS patients of similar disease duration[154].

Pathophysiology. Microinjection of MOG-IgG from patients with NMO into mouse brains has been shown to cause altered myelin basic protein expression and reduced expression of contactin-associated protein 1 and Ankyrin 3, axonal proteins required for the integrity of the nodes of Ranvier and action potential firing; these effects were independent of human complement or were associated with only faint C5b-9 immunoreactivity[164]. Similar to human MOG-IgG disease (but in contrast to AQP4-IgG-positive NMOSD), lesion pathology was mild, with no oligodendrocyte, astrocyte or neuronal death and no axonal degeneration, and lesions were reversible within 2 weeks[164]. This finding is consistent with clinical observations that MOG-IgG-positive disease tends to cause reversible CNS damage in some patients but not with the severe and permanent disability seen in others[9,165,166]. One reason for the mild changes in this animal model might be the fact that only a small portion of human MOG-IgG is reactive to rodent MOG as demonstrated by cell-based assays (CBAs) and immunohistochemistry[41,167,168]. In addition, the assays used in this study to detect MOG-IgG in human serum did not use full-length human MOG as an antigenic substrate (as recommended[169]) and no leukocyte infiltration was observed in the mice.

In a different study, purified IgG from a patient with high titres of MOG-IgG that were reactive to rodent MOG caused significant and human complement-dependent myelin degradation, indicated by myelin basic protein loss, and signs of axonal disturbances and swellings in an ex vivo mouse model[167]. However, these findings could not be reproduced with other sera reactive to rodent MOG. Differences in epitope specificity, titres and IgG subclass composition have been hypothesized to determine the extent of complement activation and therefore account for the differential effects of IgG from different patients observed in animal models[167,170]. These differences might potentially also influence phenotype, course and severity in human disease[170], all the more as epitope recognition was found to stabilize over time in many patients[168,170]. Notably, MOG-IgG from most patients has reactivity to an immunodominant region at Proline42 in the CC′ loop[168,170] but MOG-IgG from 15% of paediatric and 25% of adult patients recognizes other epitopes[170]. Additional factors besides the antibody itself, such as BBB disruption or T cell activation, may be required for lesion formation in human disease. The latter hypothesis is supported by the fact that MOG-IgG, similar to AQP4-IgG, remains detectable, in part at relatively high titres, also during remission[8,99]. The interplay with T cells was highlighted by one study in which affinity-purified antibodies from patients with MOG-ON that recognized epitopes on the CC′ and the FG loop of MOG caused demyelination associated with deposition of C9neo and increased T cell and macrophage infiltration in vivo when co-transferred together with myelin-reactive T cells[171].

At the cohort level, median MOG-IgG levels are higher during active disease than during remission[9,170] and high titres were associated with a more severe phenotype of ON in adults, as defined by a bilaterality of symptoms[170,172]; these findings are compatible with a direct pathogenetic role of the antibody in human disease.

MOG antibodies have been shown to affect cell function or viability in several ways. In one in vitro study using MOG-transfected HEK293 cells, IgG to human full-length MOG resulted in surface binding of IgG colocalizing with MOG-EmGFP, formation of the membrane attack complex, internalization of the antibody and complement-mediated cell lysis[7]. Additional pathogenetic mechanisms proposed include blocking the binding of NGF to MOG, resulting in compromised axon growth and survival[152]; and opsonization of MOG, which is then recognized by myeloid antigen-presenting cells, internalized, processed and presented, subsequently leading to the activation of MOG-reactive, encephalitogenic T cells (known as autoantibody-boosted T cell activation)[173,174].

Although MOG-IgG is mostly produced extrathecally[8,104,170], MOG protein is expressed only in the CNS. This finding has led to the hypothesis that MOG drained via the CSF into peripheral lymph nodes may trigger the process[174,175]; MOG presentation on CNS-resident phagocytes may then facilitate the reactivation of T cells within the CNS[173].

The pathophysiology of NMO in patients seronegative for both AQP4-IgG and MOG-IgG has still to be elucidated and is likely heterogeneous.

Mechanisms of pain

Various mechanisms have been proposed to underlie neuropathic pain in NMO[176]. For example, AQP4-IgG-mediated loss of excitatory amino acid transporter 2 (which colocalizes with AQP4) might result in a disbalance between excitation and inhibition in nociceptive pathways prompted by extracellular glutamate accumulation[177]. MOG-IgG-mediated loss of MOG could lead to NGF depletion and might result in increased local NGF concentrations leading to aberrant sprouting of unmyelinated TrkA-expressing nociceptive spinal cord fibres, including in the posterolateral tract of the spinal cord[152]. Moreover, inflammatory lesions may affect pain generating pathways in the brainstem, which is frequently involved in patients with AQP4-IgG and those with MOG-IgG.

Diagnosis, screening and prevention

Clinical presentation

As previously mentioned, NMO predominantly causes attacks of ON and TM but cerebral and brainstem lesions occur in some patients (FIG. 5). NMO-related ON typically causes hazy vision and a decline in high-contrast visual acuity (VA) as assessed by a Snellen chart, although only low-contrast VA or colour vision (resulting in colour desaturation) is affected in some patients[9,15]. Moreover, NMO frequently leads to scotomas (an area in the visual field of diminished VA), both in patients with AQP4-IgG[178] and those with MOG-IgG[9].

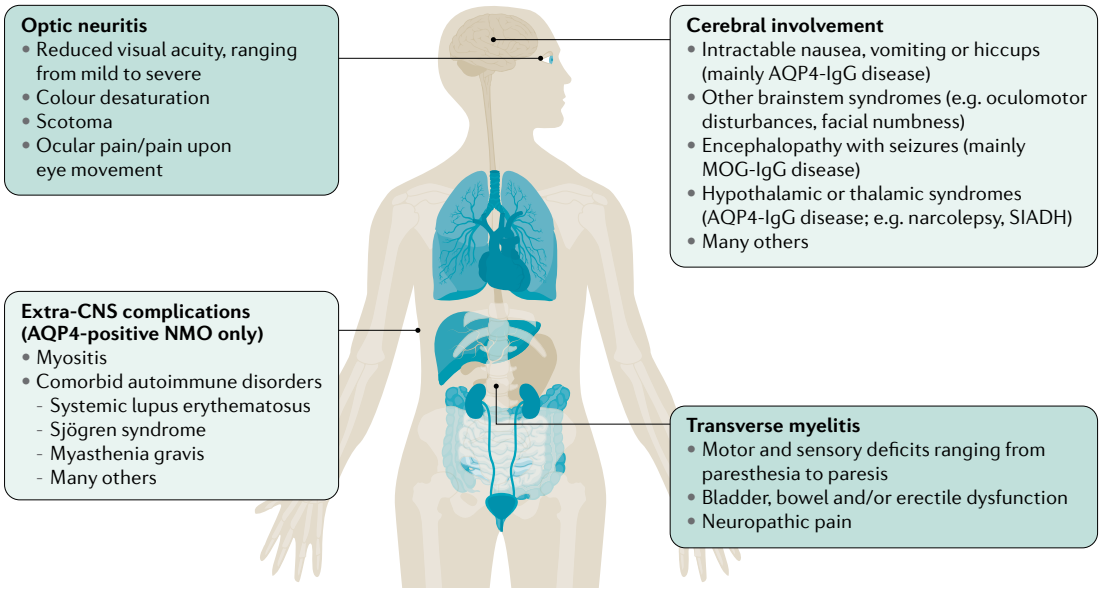


Fig. 5 | **Manifestations of NMO.** Optic neuritis and transverse myelitis are the predominant symptoms of neuromyelitis optica (NMO), although some patients can also have brain or brainstem involvement, which can manifest with a variety of different symptoms. Optic neuritis (either alone or in combination with other symptoms) was present at onset in 50% of patients with aquaporin 4 (AQP4)-IgG and in 74% of those with myelin oligodendrocyte glycoprotein (MOG)-IgG in two European studies[9,15] and transverse myelitis at onset in 52% of patients with AQP4-IgG and in 34% of patients with MOG-IgG[9,15]. CNS, central nervous system; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Visual loss during acute ON can be mild but can progress to complete (yet mostly transient) functional blindness (defined by VA ≤0.1) in one or both eyes during acute attacks both in patients with AQP4-IgG[15] and in those with MOG-IgG[9,179]. The onset of ON is often preceded or accompanied by ocular pain and/or pain on eye movement, especially if the retrobulbar portion of the optic nerve is affected. Simultaneous ON in both eyes occurs more often in patients with NMO than in those with MS, and possibly more frequently in those with MOG-IgG[9] than in those with AQP4-IgG[15]. In the long term, both the right and the left eye will be affected in most individuals with AQP4-IgG[15] and MOG-IgG[9].

Symptoms associated with TM range from mild sensory symptoms to very severe sensorimotor spastic tetraparesis. Symptoms typically ascend from the feet to a 'sensory level' on the trunk and are often heralded by pain at the site of the lesion. TM can also cause bladder, bowel and/or erectile dysfunction[180], with symptoms including an overactive bladder and urinary retention (which often requires catheterization), reduced quality of life (QOL) and required modification of lifestyle[180]. The Lhermitte sign (a brief electric shock or paraesthesia-like sensation running down the spine and occasionally the limbs, that is precipitated by neck flexion and caused by stretching of demyelinated fibres in the spinothalamic columns) is not specific for MS but may also occur in patients with AQP4-IgG-positive[15,181] or MOG-IgG-positive TM[9,165].

Symptomatic brain involvement is more common than previously thought and may occur both in patients with MOG-IgG and in those with AQP4-IgG. ADEM-like disease is a frequent manifestation in young children with MOG-IgG, which is characterized by encephalopathic (impaired consciousness, altered behaviour, seizures) and polyfocal neurological symptoms that are associated with multifocal and often large inflammatory brain lesions. However, children older than ~9 years and adults present more frequently with ON and myelitis but without encephalopathy[12]. Cerebral symptoms are thought to be more common in children than adults in AQP4-IgG-positive NMOSD[182]. The brainstem is commonly affected in both AQP4-IgG-positive and MOG-IgG-positive disease and spinal cord lesions often extend into the medulla oblongata. Common symptoms associated with brain involvement include epileptic seizures (which are more common in children with AQP4-IgG than adults and are more common in patients with MOG-IgG than with AQP4-IgG)[183], psychiatric symptoms (such as depression and encephalopathic presentations)[184] and neuropsychological deficits (such as decline in attention and memory performance, both during acute attacks and in the long-term course)[185]. Other common symptoms suggestive of brain involvement include headache, intractable vomiting or hiccups owing to dorsal bulbar lesions involving the area postrema (typically in those with AQP4-IgG[93,186] but also occurring in 2–5% of those with MOG-IgG[9,187,188]), and symptomatic narcolepsy and other symptoms attributable to diencephalitis (typically in AQP4-IgG-positive NMOSD) such as inappropriate antidiuretic hormone secretion, hypothyroidism, hyperprolactinemia, secondary amenorrhoea, galactorrhoea, hypothermia, hypotension, obesity and behavioural changes[189]. In addition, brain involvement can cause hemiparesis due to hemispheric white matter lesions, cerebellar ataxia due to lesions in either the cerebellar peduncles or, more rarely, the cerebellar hemispheres[9,165,190], and

olfactory deficiency[191]. Brainstem and/or upper cervical cord lesions can cause respiratory insufficiency, which can be life-threatening if not treated early and effectively[9,165,192,193].

Pain and dysesthesia (unpleasant abnormal sensation) are frequent and can constitute a significant burden. ON is often preceded by headaches[194] and was accompanied by pain upon eye movement in 86% of patients with MOG-IgG and ON in one study[179]. Myelitis in NMO is often accompanied or followed by painful tonic spasms that can be mistaken for spasticity[195,196]. Of note, asymptomatic damage to the optic nerve or spinal cord detected by MRI, optical coherence tomography (OCT) or evoked potentials (visual evoked potential (VEP)/somatosensory evoked potential) is not uncommon in patients with AQP4-IgG and in those with MOG-IgG[9,189,197].

Owing to the expression of AQP4 outside the CNS, myositis[198,199], internal otitis[200], gastritis[201] and vitamin B_{12} deficiency have all been discussed as possible extra-CNS complications of AQP4-IgG-related autoimmunity. Moreover, AQP4-IgG-positive NMOSD is often associated with other autoimmune diseases, including CTDs such as SLE, Sjögren syndrome, antiphospholipid syndrome, rheumatoid arthritis, myasthenia gravis[202,203], coeliac disease[204,205] and, in rare cases, other CNS autoimmune disorders such as *N*-methyl-D-aspartate receptor encephalitis[206]. The presence of such comorbidities can alter the clinical presentation and needs to be considered when making treatment decisions in patients with NMO.

Disease course

In most cases, NMO starts with an acute attack of ON (in ~45% of those with AQP4-IgG[15] and in 64% of those with MOG-IgG[9]) or TM (in 47% of those with AQP4-IgG[15] and in 24% of those with MOG-IgG[9]). Simultaneous ON and TM at onset is relatively rare (in 4.4% of patients with AQP4-IgG[15] and in 10% of patients with MOG-IgG[9]). Simultaneous bilateral ON is not uncommon at onset of NMO and occurs more often in patients with MOG-IgG[9,15]. The first attack is sometimes accompanied by brain or brainstem lesions, which may or may not be symptomatic. Isolated brain or brainstem disease occurs at onset in a few cases[9,15].

Relapse rate. Although almost all patients with AQP4-IgG relapse if the disease is untreated[15], a monophasic disease course has been described in a subset of patients with MOG-IgG[9,34,197]. The interval between the first and the second attack varies considerably between patients; the median interval was 9 months in patients with AQP4-IgG in one study[15] and 5 months in patients with MOG-IgG in another study[9], but the second attack occurred several years after the first attack in some patients in both studies. Thus, diagnosing 'monophasic' disease (and therefore deciding against long-term treatment) should be done with caution. Similarly, the time to conversion to NMO in patients with isolated ON or TM at onset may range between less than a week and several years[9,15]. Accordingly, the proportion of patients with recurrent MOG-IgG-associated disease in a given cohort depends on observation time; in one study, 60% of patients had a recurrent course at 12 months, almost 80% after 48 months and 93% at ≥8 years[9]. Similarly, 80% had relapsed after 60 months in a North American cohort[179]. In two large European studies, a higher median annualized relapse rate (ARR) was found in patients with MOG-IgG than in those with AQP4-IgG[9,15], with the median ARR highest in patients with MOG-IgG with relapsing disease and a history of both ON and myelitis[9]. After a median of 60 months for patients with AQP4-IgG and 52 months for those with MOG-IgG, 66% and 44% of patients, respectively, had experienced at least one attack of ON and one of TM in these studies[9,15].

Recovery from acute attacks. Although symptoms can completely resolve after acute attacks, especially if treated early, two European studies reported no or incomplete recovery after 66% of ON attacks and after >80% of TM attacks in patients with AQP4-IgG[15] and in 48% of ON attacks and in 65% (with at least a partial recovery in all patients) of myelitis attacks in patients with MOG-IgG[9]. Although these data suggest an overall lower attack severity in MOG-IgG-positive disease, it should be considered that severity definitions and observation times differed between the two studies. Moreover, the higher ON attack rate in the MOG-IgG-positive cohort may counterbalance the overall lower degree of tissue damage sustained per attack, as suggested by an OCT study[166]. In addition, flare-ups after intravenous methylprednisolone (IVMP) therapy as well as steroid-dependent symptoms (including chronic relapsing inflammatory optic neuropathy) are commonly seen in patients with MOG-IgG[9,207–209]. If patients rather than attacks are considered, 34% of patients with AQP4-IgG had at least one attack with no recovery and 46% of patients with MOG-IgG had at least one attack with no or little recovery[9,15]. In both studies, complete recovery was most common after the first attack, with lower recovery rates with more subsequent attacks[9,15].

Factors associated with disease course. Antibody serostatus, genetic background and age at onset can determine differences in clinical presentation, attack severity and prognosis in NMO[210]. Some studies have suggested a higher frequency of severe attacks in Black patients than in Asian and white patients, whereas white patients had a lower incidence of brain or brainstem involvement than Asian and Black patients[211]. Brain involvement is more common in children[12,182] but late onset (>50 years of age) is associated with a trend towards more motor disability and, possibly, higher mortality[212,213].

Accrual of disability over time. Incomplete recovery from acute attacks results in the accrual of disability over time, which is traditionally measured using the Expanded Disability Status Scale (EDSS), which was originally developed for use in MS. However, one limitation of the EDSS is that it strongly focuses on ambulation deficits and does not sufficiently reflect visual impairment; patients with isolated ON cannot reach an EDSS score higher than 4, even if complete bilateral visual loss is present.

Box 1 | **2015 IPND criteria for NMOSD with AQP4-IgG**

Criteria A, B and C must all be met.

Criterion A

Aquaporin 4 (AQP4)-IgG-positive serostatus

Criterion B

At least one of the following 'core characteristics' (which may be the result of one or more clinical attacks)

1. Clinical evidence for acute optic neuritis
2. Clinical evidence for acute myelitis
3. Clinical evidence for acute area postrema syndrome
4. Clinical evidence for acute brainstem encephalitis other than area postrema syndrome
5. Clinical evidence for acute diencephalitis or symptomatic narcolepsy plus MRI evidence of
   - a periependymal lesion at the level of the third ventricle, or
   - a lesion in the thalamus or hypothalamus
6. Clinical evidence for acute (tel)encephalitis plus MRI evidence of
   - an extensive periependymal lesion at the level of the lateral ventricles, or
   - a large/confluent deep or subcortical white matter lesion (often with gadolinium enhancement), or
   - a longitudinally extensive (≥1/2 of its length), diffuse, heterogeneous or oedematous corpus callosum lesion, or
   - a longitudinally extensive (contiguously from the internal capsule to the cerebral peduncles) corticospinal tract lesion

Criterion C

Exclusion of alternative diagnoses

Note the 'red flags' for AQP4-IgG-positive neuromyelitis optica spectrum disorders (NMOSD)[19] (Supplementary Box 1); the presence of any of these findings should prompt re-testing for AQP4-IgG and a thorough investigation for competing differential diagnoses. Data from REF.[19]. IPND, International Panel for NMO Diagnosis.

A median annualized EDSS increase of 0.65 was found in one study of European patients positive for AQP4-IgG who had a disease duration of ≥12 months, with a median EDSS of 5 (that is, disability severe enough to impair full daily activities, ambulatory without aid or rest for about 200 meters) at the last follow-up examination (median disease duration 60 months, range 0–390 months). In those with a disease duration of ≥100 months, the median EDSS was 6.5 (that is, requiring constant bilateral assistance, such as canes, crutches or braces, to walk ~20 metres without resting); of note, however, 20% of patients were still fully ambulatory (EDSS <4). Pure sensory symptoms were associated with a better long-term prognosis and tetraparesis was associated with a worse long-term prognosis in patients presenting with myelitis at onset. At the last follow-up, 4% of patients had died from NMO-related causes (which included dyspnoea and cardiac arrest associated with acute disease), 6–284 months after disease onset.

Possibly owing also to the under-representation of VA in the EDSS, the higher ratio of ON to TM attacks in patients with MOG-IgG and differences in observation times between studies, EDSS scores were lower at last follow-up in European patients with MOG-IgG, with a reported median of 2.5 (equating to minimal disability in two functional systems), than in the AQP4-IgG-positive cohort[9,15]. Among patients with an observation period of ≥100 months, the median EDSS was 3 (that is, fully ambulatory but moderate disability in one functional system or mild disability in three or four functional systems).

The main long-term sequela in patients with MOG-IgG is visual impairment. Indeed, functional blindness in at least one eye was present in around one-quarter of all patients with a history of ON in one European cohort (80% of whom had experienced >3 attacks of ON) with severe visual deficiency in another 10% of patients[9]. Some degree of visual loss was noted in ~50% of all patients with MOG-IgG in a European cohort after a median of 50 months[9]. In >80% of patients, both eyes had been affected by ON at least once[9]. By contrast, in a North American cohort, only 6% of patients had a VA of ≤20/200, corresponding to legal blindness, at last presentation[179]. The exact reasons for this discrepancy remain unknown but might include differences in observation time, the proportion of children included, clinical setting and treatment. Some degree of paresis was noted in ~30% of patients with MOG-IgG after a median of 50 months in the European cohort[9]. Ambulation was impaired at last follow-up owing to paresis and/or gait ataxia in 25% of patients with a history of myelitis but severe paresis was rare (4%)[9]. In addition, 69% of patients had bladder, bowel and/or erectile disturbances at last follow-up. In a large North American cohort (median follow-up 24 months), a gait aid was required at last presentation in 6% of patients, with relatively frequent bladder or bowel dysfunction (44%) and erectile dysfunction (33%)[9]. Only 1 of 50 patients with MOG-IgG had died, from brainstem encephalitis, at last follow-up in the European study.

Diagnostic criteria

Most patients with NMO are positive for AQP4-IgG, but some of these patients present with isolated ON or myelitis (or, more rarely, brainstem encephalitis) at onset. Accordingly, in 2015, the International Panel for NMO Diagnosis (IPND) proposed a set of diagnostic criteria that covers both patients with AQP4-IgG and 'full' NMO and patients presenting with AQP4-IgG and inaugural forms or *formes frustes*, which are now summarized under the umbrella term NMOSD[19] (BOX 1). As antibody tests have limited reliability, these criteria take into account clinical presentation and MRI findings in addition to AQP4-IgG serology[19] and are accompanied by a list of 'red flags' which, if present, should prompt thorough investigation for competing differential diagnoses and re-testing (Supplementary Box 1).

Criteria for patients with unknown or negative AQP4-IgG status were also established by the IPND[19] (BOX 2). However, these criteria are based on clinical and radiological features deemed typical for AQP4-IgG-mediated disease and are therefore not perfectly fitted to cover all patients who have a different underlying pathology. Accordingly, most experts agree that patients with MOG-IgG should be diagnosed with MOG-IgG-associated NMO (or MOG-IgG-associated ON or MOG-IgG-associated TM, etc.) or, more generally, with 'MOG-IgG-positive encephalomyelitis' (EM) or 'MOG-IgG-associated autoimmune disease', rather than 'NMOSD with unknown or negative AQP4-IgG

Box 2 | **IPND criteria for NMOSD with negative or unknown AQP4-IgG serostatus**

Owing to the lack of availability of aquaporin 4 (AQP4)-IgG testing in some regions and the possibility of false-negative AQP4-IgG test results, the International Panel for NMO Diagnosis (IPND) proposed a second set of criteria that permits a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) in patients with suspected AQP4-IgG-mediated autoimmunity but unknown or negative AQP4-IgG serostatus.

Criteria A, B and C must all be met.

Criterion A

Negative or unknown AQP4-IgG serostatus

Criterion B

Two or more different[a] core characteristics (which may be the result of one or more clinical attacks) from the following list, at least one of which has to be acute optic neuritis, myelitis or area postrema syndrome.

1. Clinical evidence for acute optic neuritis plus MRI showing
   - a longitudinally extensive (≥1/2 of the distance from orbit to chiasm) optic nerve lesion, or
   - an optic nerve lesion that involves the optic chiasm, or
   - no brain lesions or only non-specific brain white matter lesions
2. Clinical evidence for acute myelitis plus MRI evidence for a longitudinally extensive (contiguously extending over three or more complete vertebral segments) intramedullary spinal lesion, or three or more contiguous segments of sharply demarcated spinal cord atrophy (with or without T2 signal) in patients with a history compatible with acute myelitis
3. Clinical evidence for acute area postrema syndrome plus MRI evidence for an associated dorsal medulla/area postrema lesion (often, but not always bilateral)
4. Clinical evidence for acute brainstem encephalitis plus MRI evidence for an associated periependymal lesion at the level of the fourth ventricle
5. Clinical evidence for acute diencephalitis (for example, symptomatic narcolepsy) plus MRI evidence for a periependymal lesion at the level of the third ventricle or a lesion in the thalamus or hypothalamus
6. Acute (tel)encephalitis plus MRI evidence of
   - an extensive periependymal lesion at the level of the lateral ventricles, or
   - a large/confluent deep or subcortical white matter lesion, or
   - a longitudinally extensive (≥1/2 of its length), diffuse, heterogeneous or oedematous corpus callosum lesion, or
   - a longitudinally extensive (contiguously involving the internal capsule and the cerebral peduncles) corticospinal tract lesion

Criterion C

Exclusion of alternative diagnoses

[a]That is, dissemination in space (but not in time) is a prerequisite. Data from REF. [19].

serostatus'. This is important given that patients with MOG-IgG may differ with regard to treatment needs and prognosis. Accordingly, international recommendations on MOG-IgG testing and diagnostic criteria for MOG-EM (or MOG-IgG-associated autoimmune disease) have been proposed by a panel of experts[169] (BOX 3). MRI findings in MOG-IgG-associated disease are less characteristic than those in AQP4-IgG-related disease; therefore, these criteria and recommendations lay more emphasis on the proper selection of patients for MOG-IgG testing (Supplementary Box 2), test methodology (Supplementary Box 3), and the definition of red flags to minimize the number of false-positive diagnoses (Supplementary Box 4).

Longitudinally extensive transverse myelitis (LETM). Spinal cord inflammation that extends over three or more vertebral segments.

Serology

There is general consensus among experts that CBAs using full-length human protein as an antigenic substrate and Fcγ-specific or IgG1-specific secondary antibodies should be used to detect AQP4-IgG[19,214] and MOG-IgG[12,169] and that serum is the specimen of choice[215,216]. Live CBA had a higher sensitivity than two commercial formalin fixed-cell assays for AQP4-IgG and MOG-IgG in three studies[217–219]; however, the pronounced difference for MOG-IgG seen in one study[170] was not observed in three multi-centre studies[217,218,220]. Despite their seemingly higher sensitivity, live CBAs are only offered by few centres worldwide owing to relatively high technical demands, whereas fixed CBA are readily available and can be standardized more easily. Some experts recommend that positive AQP4-IgG and, especially, MOG-IgG test results should be confirmed using a second, methodologically different assay given the far-reaching prognostic and therapeutic consequences of a positive test result. Re-testing individuals who are negative for both AQP4-IgG and MOG-IgG is also advisable if clinical and paraclinical findings still suggest NMO, ideally during acute attacks and/or treatment-free intervals, to ensure that these patients are truly 'negative' and that this is not just a false-negative result. In case of doubt, ideally, a live CBA employing Fcγ-specific or IgG1-specific secondary antibodies should be used. ELISA is currently not considered suitable for detecting MOG-IgG[169,217] and not recommended for detecting AQP4-IgG for clinical purposes[221,222]. Some patients also have serum AQP4-IgM or MOG-IgM antibodies[7,8,128]; however, their pathogenetic relevance is unknown. Making a diagnosis of seropositive NMOSD or MOG-associated disease strictly requires the presence of IgG antibodies to AQP4 or MOG, respectively; the presence of AQP4-IgM or MOG-IgM antibodies is not sufficient.

Broad, non-selective screening for AQP4 and MOG autoantibodies bears considerable risks as AQP4-IgG-associated and MOG-IgG-associated NMO are rare and no immunoassay has perfect specificity. Accordingly, unselected screening of patients with suspected CNS autoimmunity may result in an unacceptable rate of false diagnoses and mistreatment[4,169]. To reduce these risks, the use of highly specific assays as well as the careful selection of patients for serological testing is essential. International recommendations[169] suggest that testing for MOG-IgG should be mainly considered in patients with monophasic or relapsing acute ON, TM, brainstem encephalitis, encephalitis, or any combination thereof, and radiological (or only in patients with a history of ON, electrophysiological (VEP)) findings that are compatible with CNS demyelination in whom at least one of the clinical or paraclinical features listed in Supplementary Box 2 is present.

Although no consensus recommendations have been published for AQP4-IgG testing, it is widely accepted that AQP4-IgG should be tested for in patients with longitudinally extensive transverse myelitis (LETM), recurrent or severe TM, area postrema syndrome, or any combination thereof, and in patients exhibiting any of the clinicoradiological features considered typical for NMOSD in the 2015 IPND recommendations[19]. Whether all patients with isolated ON should be tested for AQP4-IgG is controversial, partly as the reported prevalence of AQP4-IgG in such individuals

is inconsistent between studies, but AQP4-IgG testing seems to be justified in patients with longitudinally extensive ON, ON involving the optic chiasm, or severe (including bilateral) or recurrent ON. Negative CSF-restricted oligoclonal bands (OCBs) and a brain MRI that does not meet the Paty criteria for MS further support the decision to test for AQP4-IgG. Moreover, most of the methodological recommendations given for MOG-IgG in REF.[169] (Supplementary Box 3) are also applicable to AQP4-IgG testing, and confirmatory testing, particularly if titres are low or any of the red flags defined in REF.[19] (Supplementary Box 1) are met, is also recommended in this indication.

Monitoring antibody levels for relapse prediction is not routinely carried out as AQP4-IgG and MOG-IgG levels during acute attacks vary substantially within the same individual and between individuals. Moreover, rising antibody levels do not always lead to acute exacerbation and some relapses are not associated with a significant rise in titres, for example, under immunosuppressive treatment[97–99]. In addition, very close monitoring intervals would be required as AQP4-IgG levels were shown to increase only relatively shortly before attack onset, which further challenges the feasibility of serological monitoring[97–99].

Retrospective studies on stored samples have shown that AQP4-IgG may be present years before clinical onset of symptoms[203,223]; however, the 2015 IPND criteria do not cover asymptomatic patients with AQP4-IgG. If the positive antibody status is confirmed in a second assay, such patients should be closely monitored and briefed to present swiftly to a hospital in the event that symptoms suggestive of NMO occur.

MRI

MRI is used to identify and characterize lesions in patients with suspected NMO and helps to differentiate between NMO and MS.

Spinal cord. The MRI feature that discriminates with highest accuracy between NMO and MS is the presence of an LETM lesion[9,224,225] (FIG. 6); however, shorter lesions occur in ~15%[15,226] of patients with AQP4-IgG-positive and in 44–52%[9,224] of patients with MOG-IgG-positive myelitis at least once[227]. Both axial and sagittal plane images should be used to judge the extent of the spinal cord lesion. In very rare cases, routine MRI does not show a distinct lesion despite the presence of symptoms compatible with myelitis; however, in such cases, antibody testing should be repeated to exclude a false-positive result[228]. On the other hand, non-contiguous yet confluent short lesions may mimic LETM in patients with long-standing MS. Lesions in patients with AQP4-IgG predominantly involve the grey matter[189] and lesions in those with MOG-IgG are often confined to the grey matter (the so-called axial H-sign, typically lacking gadolinium enhancement)[188], whereas lesions in patients with MS predominantly affect white matter. AQP4-IgG-positive NMOSD can cause inflammatory oedema (visible as spinal cord expansion or swelling on MRI), necrosis and cavitations[189]; therefore, T1 hypointense spinal cord lesions are not rare in AQP4-IgG-positive NMOSD[229]. MRI may also show (often longitudinally extensive) spinal cord atrophy or reduced mean upper cervical cord area, which seems to occur more frequently in patients with AQP4-IgG than in those with MOG-IgG[230]. Cervical spinal cord lesions often extend into the brainstem. Conus involvement is more common in those with MOG-IgG[230] but can also occur, although rarely, in AQP4-IgG-positive NMOSD and MS. Leptomeningeal enhancement has been reported occasionally in patients with AQP4-IgG[231] and in those with MOG-IgG[232].

Optic nerve. AQP4-IgG-positive and MOG-IgG-positive ON are frequently characterized by longitudinally extensive lesions. These lesions do not normally occur in MS, which is characterized by short-length lesions. Similar to MS, AQP4-ON predominantly affects the posterior portions of the optic nerve (but often including the chiasma) whereas MOG-ON more frequently involves the anterior portion; however, posterior lesions (or long lesions involving also the posterior parts, including the chiasm) can occasionally occur in MOG-ON[233]. Longitudinally extensive ON is defined by the current criteria for NMOSD[19] as acute ON associated with a T2 or gadolinium-T1 lesion extending over more than half of the distance from the orbit to the chiasm. However, several other definitions have been proposed[169]. One study suggested that involvement of >6/12 optic nerve segments may distinguish MOG-ON and MS-ON[233]. Interestingly, perioptic gadolinium enhancement, which is not typically seen in MS, has been described in some patients with MOG-ON[9,234,235]. Simultaneous bilateral ON is more common at onset in MOG-ON than in AQP4-ON and is relatively rare in MS.

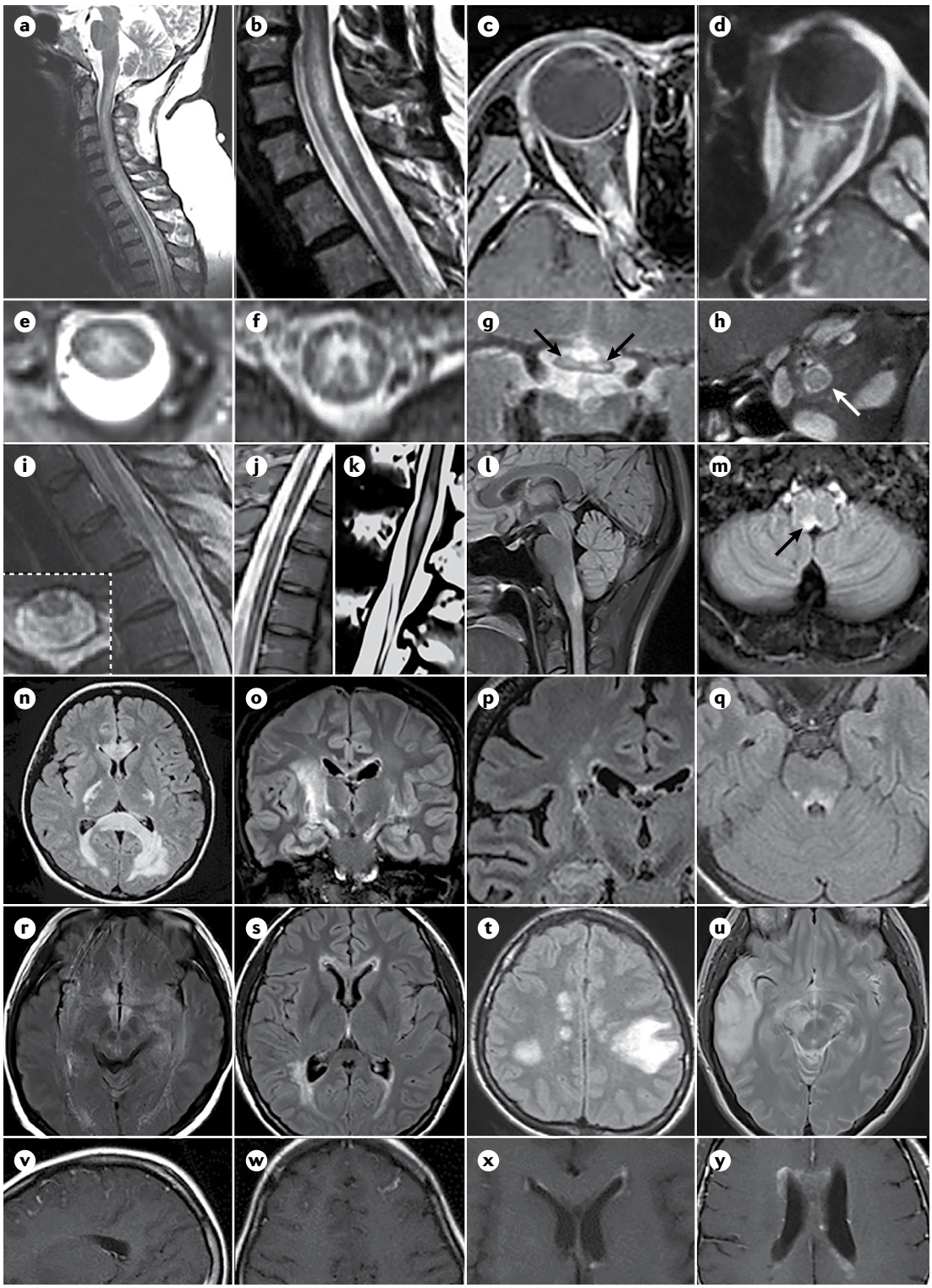
Brain. Periependymal lesions are typical of AQP4-NMOSD (FIG. 6) and can be extensive and gadolinium enhancing. They may occur at the lateral ventricles and the third or fourth ventricle. By contrast, periventricular MS lesions are typically ovoid or perpendicular (Dawson fingers)[236]. White matter lesions in MS are typically relatively small and circumscribed, whereas large, confluent, unilateral or bilateral subcortical or deep white matter lesions are more typical of AQP4-NMOSD (often with 'cloud-like' gadolinium enhancement)[189]. However, large, tumefactive lesions also rarely occur in MS and can be difficult to distinguish, especially in patients negative for AQP4-IgG. Lesions in the

Box 3 | **Diagnostic criteria for MOG-IgG-positive encephalomyelitis**

All four criteria must be met.

1. Monophasic or relapsing acute optic neuritis, myelitis, brainstem encephalitis or encephalitis, or any combination of these syndromes
2. MRI or electrophysiological (visual evoked potential in patients with isolated optic neuritis) findings compatible with central nervous system demyelination
3. Seropositivity for myelin oligodendrocyte glycoprotein (MOG)-IgG as detected by means of a cell-based assay employing full-length human MOG as target antigen
4. Absence of 'red flags' (see Supplementary Box 4) or, if red flags are present, confirmation of the patient's MOG-IgG serostatus in a second, methodologically different assay (or, only if no other assay is available, in a second sample)

Data from REF.[169].



circumventricular organs (most commonly in the area postrema) are also suggestive of AQP4-IgG-positive NMOSD but can occasionally occur also in patients with MOG-IgG or those with MS[165,237,238]. Brainstem lesions are frequent in both patients with AQP4-IgG and MOG-IgG and are often contiguous, especially in patients with AQP4-IgG, with an upper cervical spinal cord lesion. In AQP4-IgG-positive NMOSD, both brain and brainstem lesions can occur bilaterally, and brain lesions tend to be longitudinally extensive, including corticospinal tract lesions and corpus callosum lesions[189,239].

Cortical lesions are usually absent in patients with AQP4-NMOSD but are common in MS. By contrast, FLAIR-detectable cortical involvement in patients with MOG encephalitis with seizures (for which the acronym FLAMES has been proposed[240,241]) has begun to emerge as a characteristic feature[183,242,243]. MS lesions mostly form around central venules, which is less frequent (but does

◀ Fig. 6 | **MRI findings in NMO.** Spinal cord lesions are often longitudinally extensive both in patients with aquaporin 4 (AQP4)-IgG (panel **a**) and, although at lower frequency, in patients with myelin oligodendrocyte glycoprotein (MOG)-IgG (panel **b**), and can extend into the brainstem (panel **a**). Optic neuritis often involves the posterior parts of the optic nerve in patients with AQP4-IgG (panel **c**) but tend to affect more often the anterior parts in patients with MOG-IgG (panel **d**). Lesions affect predominantly the central portion of the spinal cord (panel **e**; AQP4-IgG) and are typically H-shaped in patients with MOG-IgG (panel **f**). Optic chiasm lesions are more common in AQP4-IgG-positive neuromyelitis optica spectrum disorder (NMOSD) but may occur also in MOG-IgG-associated disease (as shown in panel **g**). Perineural gadolinium (Gd) enhancement is a common feature of MOG-IgG-positive optic neuritis (panel **h**). Severe and/or recurrent myelitis may result in (often longitudinally extensive) spinal cord atrophy, especially in patients with AQP4-IgG (panel **i**) and more rarely in patients with MOG-IgG (panel **j**). Conus involvement in MOG-IgG-associated myelitis (panel **k**). Dorsal medulla oblongata lesions causing area postrema syndrome (APS) are a typical finding in AQP4-IgG-positive NMOSD (panel **l**) but may also occur (although more rarely) in MOG-IgG-positive disease (panel **m**). Longitudinally extensive corpus callosum lesion (panel **n**). Longitudinal lesion following the pyramidal tract (panel **o**). Cavitary pyramidal lesion (panel **p**). Periependymal hyperintensity adjacent to the fourth ventricle (panel **q**). Diencephalic lesions adjacent to the third ventricle involving the hypothalamus (panel **r**). Periependymal lesion delineating the posterior and anterior horns of the lateral ventricles (panel **s**). Large white matter lesion (panel **t**). Cortical lesions in a patient with MOG-IgG and epilepsy (panel **u**). Leptomeningeal Gd enhancement (panels **v** and **w**). Pencil-thin ependymal Gd enhancement (panel **x**). Patchy, 'cloud-like' Gd enhancement (panel **y**). NMO, neuromyelitis optica. Panels **n**–**t** and **w**–**x** all show typical findings in patients with AQP4-IgG. Panels **e**, **o**, **t**, **v** and **w** adapted from REF.[189], Kim, H. J. et al. MRI characteristics of neuromyelitis optica spectrum disorder: an international update. *Neurology* **84**(11), 1165–1173 (https://n.neurology.org/). Panels **f**–**h** and **m** adapted from REF.[9], CC BY 4.0. Panel **x** adapted from REF.[367], CC BY 4.0. Panel **y** republished with permission of American Journal of Neuroradiology, from Conventional and advanced imaging in neuromyelitis optica, Barnett, Y. et al. **35**(8), 1458–1466, 2014, REF.[368]; permission conveyed through Copyright Clearance Center.

occur) in AQP4-NMOSD[244], and can help discriminate MS from differential diagnoses, including NMOSD[245]. Although brain lesions were previously believed to be rare in NMO, particularly at onset, more recent studies have found brain lesions in the first available MRI in up to 48% of patients with AQP4-IgG, although only a minority of these patients meet the Barkhof MRI criteria for MS[15,246]; of note, most of these lesions are clinically silent, which is also a very frequent finding in MS. In rare cases, MS with only spinal cord involvement at onset has been described, but a normal brain MRI in patients presenting with acute ON or myelitis is generally suggestive of NMOSD or MOG-EM. Diffusion tensor imaging may reveal tissue alterations outside T2 lesions in AQP4-NMOSD, which may be a surrogate of anterograde and retrograde neuronal degeneration, and voxel-based morphometry analysis has demonstrated a reduction in density and volume of the sensorimotor and the visual cortex[247,248]. The occurrence of the widespread damage in normal-appearing white matter[249,250] and (deep) grey matter[251,252] volume reductions typically seen in MS is still contentious[253]. Myo-inositol and *N*-acetyl-aspartate may be promising markers of astrocyte and myelin damage[254]. Brain lesions in patients with MOG-IgG are less typically distributed than in NMOSD. However, the following combination of brain MRI features have been proposed to substantially increase the odds for MOG-EM compared with MS: no lesion adjacent to a lateral ventricle that is ovoid/round or associated with an inferior temporal lobe lesion and no Dawson finger-type or juxtacortical U fibre lesions (Matthews–Jurynczyk criteria)[190,255,256]. Of note, the Barkhof criteria for MS have been found to be met in up to 40% of patients positive for AQP4-IgG and in around 15% of those positive for MOG-IgG at least once over the course of disease[9,15,255].

Lumbar puncture

CSF examination is not required for diagnosing NMO but is useful to confirm CNS inflammation, to identify patients with non-MS-related CNS demyelination and to rule out important differential diagnoses.

Although CSF-restricted OCBs are a diagnostic mainstay in MS, they are absent in most patients with NMO, in line with the fact that AQP4-IgG and MOG-IgG are mainly produced outside the CNS[127,257,258]. However, positive OCBs do not exclude the diagnosis. In addition, the polyspecific, oligoclonal humoral immune response to measles virus, rubella virus and varicella zoster virus (so-called MRZ reaction), which is detectable in ~70% of adults with MS[259], is absent in virtually all patients with AQP4-IgG[260] or MOG-IgG[257,258]. Low levels of intrathecally produced IgG are sometimes detectable by isoelectric focusing, especially during acute attacks, or even by IgG CSF/serum ratio calculation, and AQP4-IgG-producing plasma cell clones were identified in the CSF from few patients with NMO[115]. If present at all, OCB may appear and disappear dependent on disease activity[127,257,258], unlike in MS.

A CSF white cell count of >50 cells/µl is extremely rare in MS and should prompt physicians to challenge the diagnosis, but is not infrequent in patients with AQP4-IgG-associated or MOG-IgG-associated acute myelitis, in which it sometimes exceeds 100 cells/µl (REFS[9,127]). Importantly, granulocytes are found in almost half of individuals with AQP4 and MOG disease but are practically never found in those with MS. Similarly, eosinophils are mostly absent in patients with MS (and rare in MOG-EM) but are present in ~10% of CSF samples in AQP4-IgG-positive NMOSD, which is also characterized by elevated CSF levels of eosinophil attractants[261]. An elevated albumin CSF to serum ratio (QAlb), indicating blood–CSF barrier dysfunction, is very rare (<10%) in MS and virtually never exceeds 12×10^{-3} but is present in ~50% of samples from patients with AQP4-IgG and MOG-IgG and exceeds 12×10^{-3} in ~25% of samples[127,257,258]. Accordingly, CSF total protein values are also usually higher in NMO than in MS. Moreover, CSF L-lactate levels (which are independent of blood–CSF barrier function) are elevated during acute attacks in some patients with AQP4-IgG or MOG-IgG but not in MS and correlate with the cumulative spinal cord lesion load in patients with acute TM[127,257,258]. However, CSF white cell count can be normal or similar to those in MS both in patients with AQP4-IgG and in those with MOG-IgG, especially in patients presenting with isolated ON and in samples taken during remission[127,257,258]. In general, most CSF alterations are less frequent and less pronounced during acute ON than during acute TM[127,257,258]. Further CSF markers that have differential diagnostic and prognostic potential are IL-6 (REF.[262]), GFAP (which has been reported to correlate with spinal cord lesion length and functional outcome after 6 months[263,264]) and neurofilaments[264].

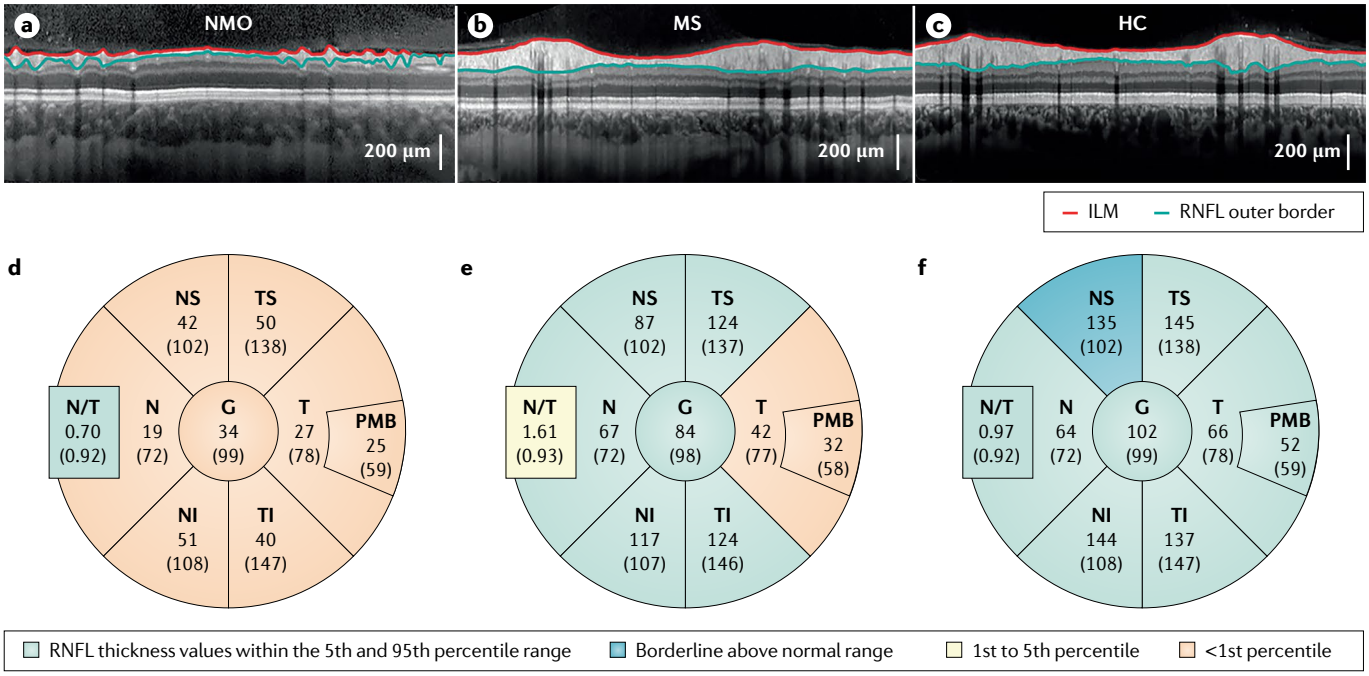


Fig. 7 | **Typical OCT findings in NMO compared with MS and a HC.** Severe thinning of the peripapillary retinal nerve fibre layer (RNFL) in a patient with aquaporin 4 (AQP4)-IgG and a history of optic neuritis (ON) (panel **a**). Moderate RNFL thinning in a patient with multiple sclerosis (MS) and a history of ON (panel **b**). Normal RNFL thickness in a heathy control (HC) (panel **c**). RNFL thinning in a patient with neuromyelitis optica (NMO) affected all areas of the retina compared with normative device data as can be seen from ring-scan data (panel **d**), whereas it involved mostly the temporal sector (and the papillomacular bundle) in the patient with MS, resulting in an increased nasal (N)/temporal (T) ratio (panel **e**); normal ring scan data were found in the HC (panel **f**). The numbers in each segment represent the thickness (µm), and the numbers in parenthesis represent the average thickness in the age-matched reference group. G, global; ILM, inner limiting membrane; NI, nasal-inferior; NS, nasal-superior; OCT, optical coherence tomography; PMB, papillomacular bundle; TI, temporal-inferior; TS, temporal-superior.

The fact that clinical attacks are often preceded by infections in patients with AQP4-IgG or MOG-IgG[9,15,165], which may result in fever or blood leucocytosis, and that granulocytes and elevated L-lactate levels may be present in the CSF, may well lead to the false suspicion of bacterial (or early viral) CNS infection in some cases. In most samples, however, CSF L-lactate levels and CSF white cell count are much lower than in typical bacterial meningitis[127,257,258].

Fundoscopy

Although MS and AQP4-IgG-positive NMOSD mostly affect the retrobulbar optic nerve, anterior ON is common in patients with MOG-IgG. Accordingly, the presence of papillitis/papilloedema increases the odds for an MOG-IgG-associated process, although a number of differential diagnoses need to be considered[9,265]. Of note, there are some reports of MOG-IgG-positive ON with retinal haemorrhages and/or a macular star; in such cases, CMV-related opportunistic retinitis, other infections, paraneoplastic disorders[266], CTDs (including vasculitis), Behçet disease, sarcoidosis, lymphomas and anterior (including non-arteritic) ischaemic optic neuropathy are relevant differential diagnoses.

Optical coherence tomography

OCT is an easily applicable, rapid and non-invasive technique that can measure retinal neuro-axonal degeneration, indicated by thinning of the retinal nerve fibre layer (RNFL) and the ganglion cell/inner plexiform layer (GCIPL) (FIG. 7). In AQP4-IgG-positive NMOSD, ON attacks usually cause severe thinning of the RNFL and GCIPL that is, on average, more pronounced than in classical MS-associated ON[267], resulting in poorer visual function and impaired visual QOL[268]. In contrast to MS[269], clinically unaffected eyes in AQP4-IgG-positive NMOSD have normal OCT values in the majority of cases, although some studies have reported thinning in unaffected eyes in some patients[270–273]. Although single ON attacks in patients with MOG-IgG seem to cause less severe retinal damage than in those with AQP4-IgG-related ON, the resultant retinal thinning over the course of the disease seems to be comparable in both conditions, presumably owing to a higher frequency of ON attacks in MOG disease[166,274]. Interestingly, visual outcomes after ON appear to be more favourable in patients who are seropositive for MOG-IgG than in those positive for AQP4-IgG despite similar severity of macular GCIPL thinning[275]. Whether progressive retinal thinning occurs in non-ON eyes of patients with MOG-IgG requires further investigation[276], as does the diagnostic and prognostic relevance of microcystic alterations of the inner nuclear layer detected after ON in a subset of patients both in MOG-IgG-associated and in AQP4-IgG-associated disease[277].

Electrophysiology

Prolonged P100 latencies, indicating delayed conduction along the optic nerve caused by demyelination, which is a typical VEP pattern in MS, were also present in 42%

of (mainly AQP4-IgG-postive) NMOSD eyes in one study and in 72% of patients with MOG-IgG in another study[9,278]. However, different from MS, the prolonged latencies were often associated with reduced amplitudes, suggestive of axonal damage, or even a complete lack of response[9,278]. One longitudinal study found an average annual increase of P100 latencies of 1.951 ms in patients with NMOSD in the absence of ON attacks, with a change of –2.149 µV/year for P100-N140 amplitudes[279], suggesting that a progressive VEP latency delay and amplitude reduction may occur independently of ON. In another study that combined OCT and VEP[280], the inverse association between RNFL thickness and VEP latency was significantly stronger in eyes from patients with MS than in those of patients with NMOSD; a decrease of 1 µm in RNFL thickness conveyed an average VEP delay of 0.48 ms in MS versus 0.14 ms in NMOSD, suggesting stronger axonal involvement in NMOSD.

Biopsy

Although several histopathological features characteristic of NMO have been described[281], CNS biopsy is rarely performed owing to the availability of non-invasive diagnostic tests. Indeed, CNS biopsy can cause serious adverse effects; for example, there are several reports of patients with persisting tetraparesis or paraparesis after spinal cord biopsy in whom AQP4-IgG was retrospectively found to be positive[282]. Thus, conducting AQP4-IgG and MOG-IgG serology and other non-invasive tests is strongly recommended prior to biopsy. One of the few indications for biopsy is the exclusion of lymphoma and other neoplasms. Coexisting brain lesions may be more accessible than spinal or optic nerve lesions and biopsy of such lesions (ideally in non-eloquent areas) may be equally informative[283].

Differential diagnoses

Simultaneous or consecutive ON and TM can occur also in patients with other neurological disorders, including paraneoplastic neurological disorders (for example, anti-Hu or anti-CV2/CRMP5-associated disease[266]), neurosarcoidosis, neurosyphilis and other infectious diseases. However, such cases must not be classified as 'seronegative NMOSD', which requires the exclusion of other disorders that better explain the patient's condition[19]. In general, diagnostic criteria specifically developed for these disorders should be used, if available. The latter also applies to cases of NMO in those with SLE and other CTDs if AQP4-IgG is negative but not of CTD-associated NMO in patients positive for AQP4-IgG. As previously mentioned, AQP4-IgG-positive NMOSD is often associated with CTDs; however, no major differences between patients with and without concomitant CTDs have been reported and AQP4-IgG is virtually never detected in patients with CTDs who do not have typical symptoms of NMOSD. This suggests that NMOSD in patients with underlying CTDs is mainly attributable to AQP4-IgG rather than to concomitant CTD-related autoimmunity, although the two diseases may share a common autoimmune predisposition. Accordingly, the diagnostic criteria for AQP4-IgG-positive NMOSD rather than those for CTD or neuro-lupus should be applied and the coexistence of CTDs should be noted as an additional diagnosis. However, CTD-related vasculitis, which is rare, should be ruled out as a precaution and rheumatological advice obtained. A comprehensive overview of the differential diagnosis of ON and TM can be found in REFS[284,285].

Management

Although multiple drugs are considered effective for NMO, there are no generally accepted treatment algorithms. An overview of acute and long-term therapies used to treat patients with NMO according to the IPND criteria and proposals on first-line treatments and treatment escalation can be found in FIGS 8 and 9 and in Supplementary Box 5. Although these schemes try to reflect common practice at specialized centres, they are not supported by strong levels of evidence. Similar yet not identical proposals have been published by members of the German Competence Network Multiple Sclerosis[286].

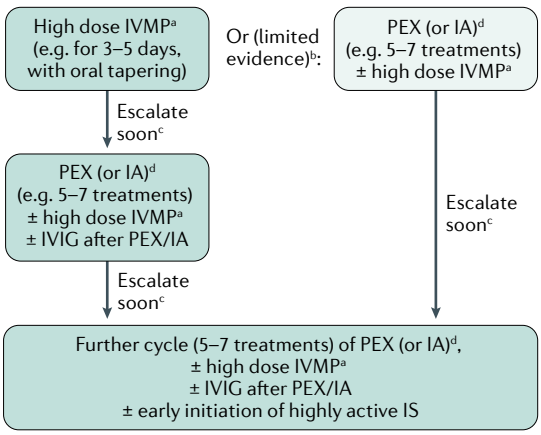


Fig. 8 | **Proposed management algorithm for acute attacks in patients with a diagnosis of NMOSD according to the IPND criteria or of MOG-IgG-associated disease.** The proposed algorithm reflects the authors' personal opinions, and is not supported by strong levels of evidence. IPND, International Panel for NMO Diagnosis; IS, immunosuppressive treatment; IVIG, intravenous immunoglobulins; IVMP, intravenous methylprednisolone. [a]Anti-ulcer and, in selected patients, anti-thrombotic co-medication is advisable with use of glucocorticosteroids; consider oral tapering (particularly relevant in patients with myelin oligodendrocyte glycoprotein (MOG)-IgG). [b]According to guidelines published by the German Competence Network Multiple Sclerosis, apheresis therapy may be considered as first-line treatment in selected patients with aquaporin 4 (AQP4)-IgG-positive neuromyelitis optica spectrum disorders (NMOSD) who previously responded well to plasma exchange (PEX) or immunoadsorption (IA) or who repeatedly did not previously respond well to high-dose steroids[286]. [c]The probability of complete recovery after apheresis rapidly declines over time; apheresis is associated with better clinical outcome, especially in patients with myelitis; response to apheresis therapy has also been observed in some patients with AQP4-IgG-negative NMOSD. [d]Escalate as promptly as possible if either treatment is insufficiently effective or symptoms deteriorate.

No such recommendations exist for patients positive for MOG-IgG so far.

Treatment of acute attacks

Acute treatment is a critically important aspect of management as neurological deficits in NMOSD result from the cumulative sequelae of attacks. The initial treatment of acute attacks consists of IVMP for at least 3–5 consecutive days[16,17]. Of note, the time to commencing treatment is important; treatment at ≤4 days of onset of AQP4-ON and MOG-ON with IVMP can increase the chance of full visual recovery, whereas treatment at ≥7 days after onset is associated with a higher risk of poor visual recovery[287]. In addition, early commencement of high-dose IVMP treatment was critical for minimizing axonal loss in NMO-associated ON in one study[288]. Although systematic data are missing, oral steroid tapering for 2–6 months may be useful when recovery is incomplete or slow[16,17] and may help to prevent early flare-ups, particularly in patients with MOG-IgG[9].

Escalatory or rescue treatments for patients who fail to recover substantially with IVMP include PEX, IA and intravenous immunoglobulin (IVIG)[289]; of these, PEX is the best studied and most widely used, whereas only very few published data exist for IA. In the only randomized, blinded sham control study of PEX in acute, severe CNS demyelinating disease, 42% of individuals with MS, 'idiopathic' TM or NMO who had failed treatment with IVMP and had a severe residual deficit recovered to a moderate or greater degree after PEX, compared with 6% in the sham group[290]. Multiple retrospective and prospective studies have supported the results of this study, some of which specifically included patients with

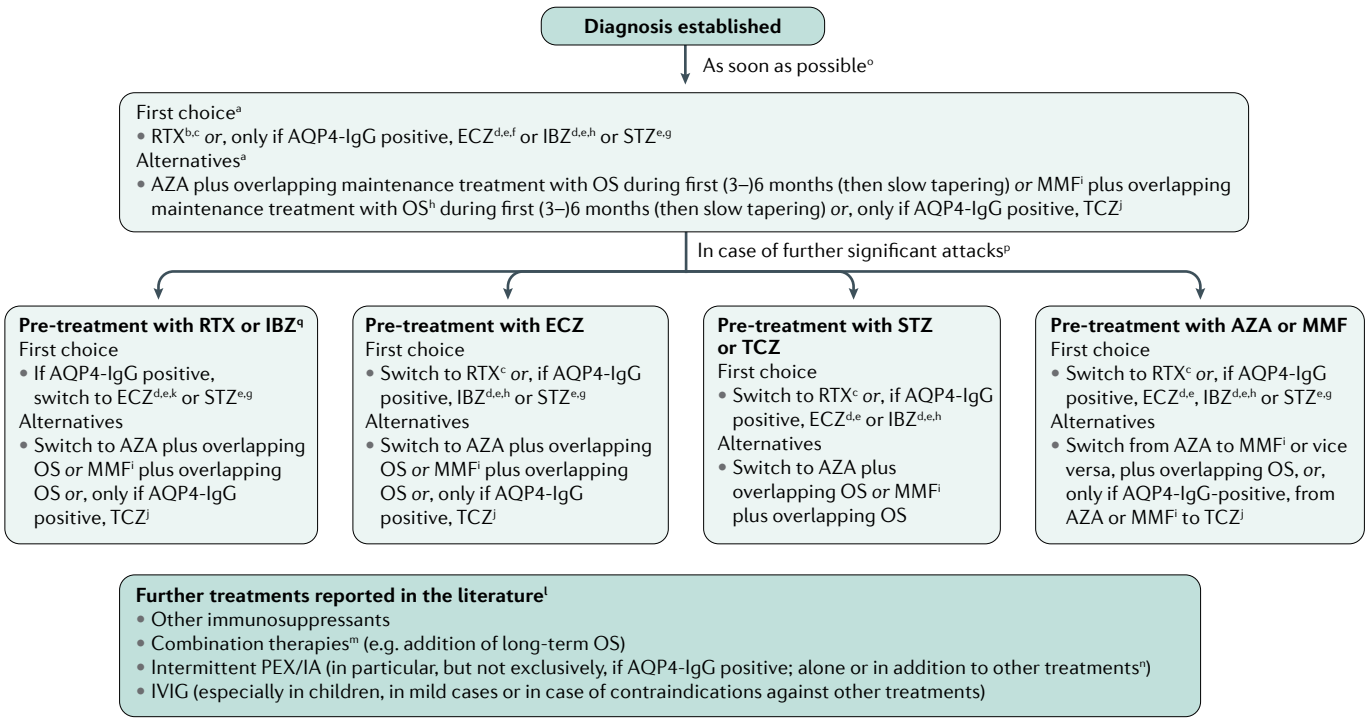


Fig. 9 | **Proposed long-term management of patients with NMOSD according to the IPND criteria except MOG-IgG-positive cases.** Note that no consensus treatment guidelines exist to date that consider the recent phase III trials. The proposed algorithm reflects the authors' personal opinion and is not supported by strong levels of evidence. AZA, azathioprine; ECZ, eculizumab; IA, immunoadsorption; IBZ, inebilizumab; IPND, International Panel for NMO Diagnosis; IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil; NMO, neuromyelitis optica; OS, oral steroids; PEX, plasma exchange; RTX, rituximab; STZ, satralizumab; TCZ, tocilizumab. [a]Only ECZ, IBZ and STZ are currently approved by the FDA; all other drugs are used off-label. [b]Especially if aquaporin 4 (AQP4)-IgG positive with severe first attack; consider RTX in women who plan to become pregnant[369] (obligatory patient counselling, careful risk–benefit assessment). [c]Consider initial co-treatment with OS (with slow tapering) to prevent early relapses. [d]Approved for use in adults. In the European Union, approved for relapsing neuromyelitis optica spectrum disorders (NMOSD) only. [e]Investigated exclusively in patients with highly active (ECZ) or active (STZ, IBZ) disease (TABLE 2); however, FDA approval is not restricted to these subgroups. [f]Limited experience with therapy-naive patients. [g]USA: approved for use in adults; Canada: approval includes adolescents; Japan: approval includes children. [h]Effective method of contraception during and for 6 months after stopping treatment required. [i]Strictly contraindicated before/during pregnancy and in women with wish for child; two contraceptional measures recommended. [j]Mainly in patients with high disease activity. [k]In the pivotal trial, 32% were on RTX for >3 months prior to inclusion; experience with switching in patients treated for ≤3 months is scarce. [l]Only very limited experience exists with these therapies. [m]Unknown whether better or as safe as monotherapy; possibly increased risk for opportunistic infections (including progressive multifocal leukoencephalopathy), consider prophylactic treatment (for example, against *Pneumocystis jirovecii*). [n]Ideally not in combination with ECZ, which may be eliminated by PEX/IA; if PEX/IA is applied, an ECZ boost is required; PEX/IA may also eliminate other monoclonal antibodies. [o]As NMOSD often takes a severe course and neurological deficits may accumulate rapidly, early initiation already after the first attack is justified, especially if AQP4-IgG positive. [p]Only very limited data regarding therapy sequences, potential risks linked to switching therapies, and the need for wash-out periods exist. [q]Switching from RTX to IBZ might be an option in selected patients, for example, if relapses under RTX are associated with insufficient depletion of B cells despite frequent administration of RTX; however, more studies addressing this topic are needed.

NMO[105,106]. Early initiation of PEX, generally within 5 days of onset, might be associated with better clinical outcome than later initiation[291,292]. Of interest, the use of antibody depletion by apheresis as first-line therapy was a predictor of complete recovery (OR 4.38, $P = 0.006$ compared with high-dose steroids) in a multivariate generalized estimating equations analysis, which analysed mainly attacks treated with PEX and a few treated with IA[289]. First-line PEX/IA might therefore be an option in patients with severe attacks who previously responded well to PEX or IA, especially in patients with isolated TM[289]; however, confirmation is required. In addition, one open-label study of 3–7 cycles of IA alone ($n = 10$) found that IA was effective in all patients, with an improvement in VA in three patients and in VEP in five patients[293]. IVIG was reported to be effective in a retrospective study of 11 acute attacks in five patients, with a 45% response rate, but the effectiveness and role of IVIG or cell-depleting therapies require more study[294].

Off-label long-term treatments

Of note, the following long-term treatments lack supporting evidence from large phase III trials.

Azathioprine. Azathioprine is an immunosuppressant that interferes with purine metabolism. In 1998, a non-controlled series found that seven patients with NMO were attack free after azathioprine treatment and experienced major improvement in neurological function, presumably due to the stability of their disease[295]. Based on these data, azathioprine became the mainstay of treatment for over a decade but, more recently, there has been a shift towards rituximab use, which has a faster onset and does not require prolonged courses of steroids (but is substantially more expensive). Moreover, the risk of lymphoproliferative and other malignant diseases is increased with azathioprine use. Of note, owing to a latency in action, azathioprine is usually combined with oral steroids during the first 4–6 months of treatment.

Data supporting the use of azathioprine for NMO comes from a case series in which 37% of treated patients remained relapse free after 2 years of follow-up, with stable or improved disability scores in just over 60% of patients treated for ≥1 year, although the discontinuation rate was 38%[296] (TABLE 1). Similar results were found in a retrospective study in which 61% of patients remained relapse free after a median time of 18 months, with a reduction in median relapse rate from 1.5 to 0 per year; however, the discontinuation rate was 46% owing to adverse events (in 62% of cases) and either death or continuing disease activity (in 34% of cases)[297]. Two retrospective studies[298,299] and one controlled clinical trial[300] have suggested the superiority of rituximab over azathioprine, although evidence from larger studies is desirable. Azathioprine is also widely used in individuals with MOG-IgG, with apparent efficacy[9,301], in particular if combined with oral steroids during the drug's latency period[9]. However, no controlled studies are available and it is difficult to estimate the relative efficacy of azathioprine compared with other immunotherapies, such as rituximab or IVIG, in patients with MOG-IgG.

Rituximab. More than 50 retrospective and prospective studies have provided compelling evidence that rituximab (a $CD20^+$ B cell-depleting monoclonal antibody) reduces the relapse rate in patients with NMOSD; 60–80% of patients will avoid relapse as long as B cell depletion is maintained[302] (TABLE 1). Approximately half of the individuals who fail rituximab treatment have B cell repletion either because of unanticipated earlier repopulation or owing to issues with redosing[298], which may be corrected by adjustment in the dosing schedule. However, the other half of the cases have no detectable circulating B cells at the time of relapse and these patients should be switched to alternative therapies. The efficacy of rituximab was confirmed in a first randomized, double-blinded, placebo-controlled (yet relatively small) trial (RIN-1)[303] (TABLE 2). Rituximab may be also effective in patients with MOG-IgG[9,304] (TABLE 1); however, relapses have been reported in some patients[9,304].

The most common treatment regimen comprises two initial administrations, 2 weeks apart. Rituximab depletes nearly all circulating B cells within hours through complement-mediated and cell-mediated mechanisms. The second dose depletes B cells that enter the circulation after the initial dose, following which circulating B cells will remain depleted for an average of 6–9 months. Repeated infusions every 6 months or upon B cell repletion are associated with optimal outcomes[16,17]. Adverse events include, aside from initial serum sickness and occasional allergic reactions, reduced IgG levels (occurring in ~20% of patients with NMOSD[305,306]), which, if severe enough, can lead to an immunosuppressed state and, in rare cases, early or delayed neutropenia[307]. As with other immunsuppressants, infections may occur during treatment with rituximab; hepatitis B, active tuberculosis and other severe infections need to be excluded before starting treatment. Rituximab is considered relatively safe during pregnancy and breastfeeding (BOX 4).

Mycophenolate mofetil. MMF has partly replaced azathioprine because of proposed better efficacy and tolerability[308]. At least five observational and controlled trials support the use of MMF to prevent relapses of NMO and its *formes frustes*[309–313]; the reported reduction in risk of relapse with treatment is 70–93% compared with pre-treatment estimates[314]. One meta-analysis suggested that the overall tolerability of MMF might be better than that of azathioprine and cyclophosphamide[315]; however, MMF is associated with miscarriage and teratogenicity (BOX 4) and it takes weeks or months to achieve the required decline in absolute lymphocyte counts, during which time patients remain at risk of relapse. To protect against relapse during this window of vulnerability, MMF is often combined with low-dose prednisone. A recent study suggests that MMF may be effective in reducing the risk of relapse also in patients with MOG-IgG[316].

Tocilizumab. Three case series have been published regarding the use of tocilizumab (a humanized monoclonal antibody to the IL-6 receptor) in patients with AQP4-IgG[111,317,318] (TABLE 1), all of which reported

Table 1 | **Retrospective case studies and open-label prospective trials investigating treatment outcomes in NMO/NMOSD**

Treatment regimens	*N*	Antibody status	Study design	Main outcomes	Ref.
Azathioprine					
2 x 500 mg IVMP per day for 5 days, followed by PD 1 mg/kg for 2 months with very slow tapering and, from week 3, AZA 2 mg/kg/day	7	Not determined	P	All patients remained relapse-free with a mean EDSS reduction from 8.2 to 4.0 at 18 months ($P < 0.0001$)	295
Variable (≥2 mg/kg/day in more than two-thirds of patients with available data)	70[a]	65% AQP4-IgG positive	R	ARR declined from 2.18 to 0.64 ($P < 0.0001$); 37% of patients relapse free at a median of 22 months; a lower post-treatment ARR was reported if dose ≥2.0 mg/kg/day; stable or improved EDSS in 61%	296
Initial dosage 2–3 mg/kg/day AZA for a median of 23.5 months, plus PD 5–60 mg/day for median of 6 months	32	78% AQP4-IgG positive	R	ARR declined from 2.26 to 0.63; HR relative to RTX 2.12 (1.12–4.01; $P = 0.02$) 53% ≥1 relapse	298
Median 125 mg/day, plus PDL in 63% of patients (median 4.5 mg/day) for a median of 18 months	103	All AQP4-IgG positive	R	ARR improved in 89% of patients from 1.5 (IQR 0.6–4.0) to 0 (IQR 0–0.27) ($P < 0.0001$); 61% of patients were relapse-free, 78% of patients had improvement or stabilized impairment; of note, discontinuation occurred in 46% of patients owing to adverse events in 62%, death in 19%, ongoing disease activity in 15% and pregnancy in 2%	297
Various treatment regimens	22	64% AQP4-IgG positive	R	ARR declined from 0.92 to 0.56 with AZA, compared with 1.17 to 0.25 with RTX ($P = 0.02$), implying superiority of RTX; EDSS declined significantly from 7 to 6 with AZA and from 7 to 5 with RTX, median follow-up 21 months	299
50 mg/day AZA escalated to 2–3 mg/kg/day, plus PDL 1 mg/kg/day for 3–5 months tapered over 6 months to 10–20 mg/day for 12 months	35	57% AQP4-IgG positive	RCT, open-label	ARR declined from 1 (s.d. 0.38) to 0.51 (s.d. 0.55) with AZA ($P < 0.001$), compared with 1.30 (s.d. 0.68) to 0.21 (s.d. 0.42) with RTX ($P < 0.001$), implying superiority of RTX; 54% of patients were attack-free with AZA compared with 79% with RTX, with an improvement in EDSS by 0.98 (s.d. 1.14) with RTX vs 0.44 (s.d. 0.54) with AZA	300
Various treatment regimens for a median of 10 months	17	All MOG-IgG positive	R	≥1 relapse in >80% of patients; 14/34 attacks during latency period, with 12 of these attacks in patients who were not cotreated with OS, PEX or IS during that period	9
150 mg AZA/day for a median of 2.1 years	11	All MOG-IgG positive	R	Mean ARR was reduced from 1.05 (s.d. 1.20) to 0.43 (s.d. 0.79) with AZA ($P = 0.041$) and 55% of patients were relapse-free; EDSS was unchanged in all patients	313
Rituximab					
375 mg/m^2 weekly 4× or 1,000 mg every 2 weeks 2×; varying number of reinfusions; other regimens in 6%	438	83% AQP4-IgG positive	M	Mean 0.79 (SE 0.15; 95% CI –1.09 to –0.50) reduction in the mean ARR ratio and mean 0.64 (SE 0.27; –1.18 to –0.10) reduction in mean EDSS at an average of 27.5 (3–272) months follow-up	302
1,000 mg every 2 weeks 2×, reinfusion every 6 months	13	92% AQP4-IgG positive	R	8/13 patients were relapse free after RTX, with a mean ARR reduction from 2.61 to 0.09 ($P < 0.001$) at an average of 5 years of follow-up	352
Not specified	52	Not determined	R	No association between RTX use and risk of or time to all-cause rehospitalization 12 months after treatment in children	353
Various treatment regimens	9	All MOG-IgG positive	R	Decline in RR in 3/9 patients, with ≥1 attack on therapy, mostly 1–3 months after infusion, in the remainder	9
Not specified	26	All MOG-IgG positive	R	ARR declined from 1.08 to 0.43 ($P < 0.02$), with 73% of patients relapse-free; no EDSS progression in 88.5% of patients after a median of 1.7 years after treatment	313
1,000 mg on days 0 and 15 or 375 mg/m^2 weekly for 4 weeks; 6-month intervals or CD19$^+$ or CD19$^+$/CD27$^+$ B cell-guided intervals	121	All MOG-IgG positive	R	Relapsing subgroup ($n = 101$): 37% reduction in ARR (95% CI 19–52%; $P < 0.001$) overall, 63% reduction (95% CI 35–79%; $P = 0.001$) when used first line ($n = 47$) and 26% (95% CI 2–44%; $P = 0.038$) when used after other IS ($n = 54$); median ARR declined from 1.18 to 0.56 if ≥12 months observation pre-RTX and post-RTX, and from 1.18 to 0.00 overall Monophasic subgroup ($n = 20$): 14/20 patients were relapse-free after a median of 11.2 (IQR 6.3–14.1) months. Caveat: effect of pre-treatment with other IS cannot be fully excluded, as no defined wash-out period was required before RTX	304

Table 1 (cont.) | **Retrospective case studies and open-label prospective trials investigating treatment outcomes in NMO/NMOSD**

Treatment regimens	N	Antibody status	Study design	Main outcomes	Ref.
MMF					
Median dose of 2,000 mg/day for a median of 27 months	24	92% AQP4-IgG positive	R	Median ARR dropped from 1.3 to 0.09 ($P<0.01$), with a stabilization or reduction in disability in 91% of patients	309
1,000–2,000 mg/day for a median of 20 months	58	90% AQP4-IgG positive	R	Median ARR reduced from 1.5 to 0 ($P<0.001$); reduction of ARR in 88%; improvement or stabilization of EDSS in 91%	311
2,000 mg/day	67	67% AQP4-IgG positive, ≥8% MOG-IgG positive	R	Median ARR decreased from 1 (range 0.1–3.2) to 0 (0–3) ($P<0.05$); EDSS improved or stabilized in 44/53 with available data ($P<0.05$); 47% of AQP4-IgG positive, 4/5 MOG-IgG positive and 47% of seronegative patients were relapse-free at last follow-up; 51% of all patients relapsed despite treatment with MMF (median follow-up 24 months)	312
1,500–2,000 mg/day with or without titration to a goal absolute lymphocyte count of 1.0–1.5 × 10^3/μl or to a target weight-based dose of 30 mg/kg/day for a median of 3 years	103	83% AQP4-IgG positive	R	Mean ARR dropped from 1.79 in AQP4-IgG positive and 1.45 in patients negative for AQP4-IgG to 0.29 and 0.30, respectively ($P<0.0001$ and $P<0.005$, respectively); no difference in efficacy was observed between patients positive for AQP4-IgG and seronegative patients	310
Not specified; median treatment duration 1.7 years	11	All MOG-IgG positive	R	ARR dropped from 1.20 to 0.23 ($P<0.04$), with no relapse in 8 patients and no EDSS progression in 11 patients	313
≥14 years of age: 2 × 750 mg/day; <14 years: 2 × 600 mg/m^2, maximum 1.5 g/day; median follow-up 473 (MMF^+) vs 261 days (MMF^-)	54	All MOG-IgG positive	P	Relapse rate 7.4% (4/54) in the MMF-treated group and 44% (11/25) in the control group (HR unadjusted 0.14, 95% CI 0.05–0.45; HR adjusted for age, sex, disease course and antibody titre 0.08, 95% CI 0.02–0.28; $P<0.001$)	316
Tocilizumab					
6 mg/kg, every 4–6 weeks for a median of 18 months	3	All AQP4-IgG positive	R	Median ARR reduced from 3 (range 2.3–3) to 0.6 (0–1.3)	111
8 mg/kg monthly in addition to existing therapy (2 × AZA plus OS, 2 × CyA plus OS, 1 × AZA, 1 × OS, 1 × tacrolimus plus OS) for 12 months	7	All AQP4-IgG positive	P	Mean ARR in the total cohort reduced from 2.9 ± 1.1 to 0.4 ± 0.8 ($P<0.005$) with a mean EDSS improvement from 5.1 ± 1.7 to 4.1 ± 1.6; 71% of patients were relapse-free at last follow-up and a reduction in neuropathic pain and fatigue was reported	317
6–8 mg/kg, monthly for an average of 31 months	8	All AQP4-IgG positive	R	Median ARR reduction from 4.0 to 0.4 ($P<0.01$), and median EDSS reduction from 7.3 to 5.5 ($P=0.03$); 38% of patients were relapse-free	318
TCZ monotherapy or add-on (36%) therapy (OS, AZA, MTX or RTX), 6–8 mg/kg i.v. every 4–6 weeks	45	71% AQP4-IgG positive, 13% MOG-IgG positive	R	Mean ARR decreased from 1.83 to 0.58 ($P<0.001$) and mean EDSS decreased from 5.2 to 4.7 ($P=0.015$) after 3–100 months of follow-up; includes 8 patients from REF.[318]	354
8 mg/kg TCZ every 4 weeks (plus 12 weeks OS or IS) vs 2–3 mg/kg/day AZA (plus 0–24 weeks OS or IS)	118	103 AQP4-IgG positive, 1 MOG-IgG positive	P	Longer median time to first relapse in the TCZ group (78.9 weeks, IQR 58.3–90.6) vs in the AZA group (56.7 weeks, IQR 32.9–81.7; $P=0.0026$); 8/59 TCZ-treated and 28/59 AZA-treated patients had a relapse by the end of the study (HR 0.236, 95% CI 0.107–0.518; $P<0.0001$); a lower risk of relapse was found in the TCZ group at week 60 (HR 0.274, 95% CI 0.123–0.607; $P=0.0006$); 1 death was reported in each group (reportedly unrelated to study drugs); caveat: numerous patients in the AZA arm were pre-treated with AZA at inclusion and had active disease (non-responders?)	319
162 mg subcutaneous every 1–2 weeks depending on body weight	12	7 AQP4-IgG positive, 2 MOG-IgG positive, 3 seronegative	R	Median ARR declined from 2 (IQR 1.29–5.75) before therapy to 0 (IQR 0–1.0; $P=0.0015$) with TCZ; mean follow-up 31.8 ± 18.8 months; 1 death following acute myelitis (AQP4-IgG positive); caveat: 5 patients co-treated for some part of the follow-up period with OS and/or MMF, or OS and IVIG	355
IVIG					
0.7 g/kg/day for 3 days (4–21 infusions/patient) for an average of 19 months	8	25% AQP4-IgG positive	P	Mean ARR dropped from 1.8 to 0.0006 ($P=0.01$), with a mean EDSS reduction from 3.3 to 2.6 ($P=0.04$)	322
0.4 g/kg/day for 5 days, then 0.4–1.0 g/kg/day every 2 to 3 months for a median of 4 years	6	67% AQP4-IgG positive; 33% unknown	R	Median ARR decreased from 0.75 to 0.15 ($P<0.05$); EDSS (median 6.5) remained stable; 50% of patients were relapse-free at last follow-up	324
Mitoxantrone					
3 or 6 monthly cycles of 12 mg/m^2 MITOX plus 1,000 mg MP, 3 months interval, then 12 mg/m^2 MITOX every 3 months up to 2 years or cumulative dose of 100 mg/m^2	5	Not determined	P	Two relapses in 2 patients; decrease in EDSS in 4/5 (mean 4.4 at baseline, 2.25 at 24 months follow-up); caveat: 3/5 patients had LETM with unknown antibody status and did not meet criteria for NMO	325

Table 1 (cont.) | **Retrospective case studies and open-label prospective trials investigating treatment outcomes in NMO/NMOSD**

Treatment regimens	N	Antibody status	Study design	Main outcomes	Ref.
Mitoxantrone (cont.)					
Three-monthly cycles of 12 mg/m^2 MITOX, followed by 6–12 mg/m^2 every 3 months (n = 7), 6 monthly cycles of 12 mg/m^2, followed by 6–12 mg/m^2 every 3 months (n = 13) for a mean of 17 months	20	All AQP4-IgG positive	R	Decrease of median ARR from 2.8 (range 1–5.7) to 0.7 (0–2.3) (P < 0.001), with a decrease in mean EDSS from 5.6 (1.5–9) to 4.4 (1–7) (P < 0.001)	326
Monthly cycles of 12 mg/m^2 MITOX plus 1 g MP for 3 months, then 3 quarterly infusions with same dosage; target dose met in 41/51 for 12 months	51	50% AQP4-IgG positive	P	ARR decreased from 1.82 at 1 year before treatment to 0.37 at 1 year after treatment (P < 0.0001), with a reduction in mean EDSS from 5.8 to 4.5 at 1 year (P < 0.001)	327
Median 12 mg (10–12 mg) MITOX/m^2 every 3 months for a mean of 345 days	34	86% AQP4-IgG positive	R	HR 0.9 (95% CI 0.5–1.6, P = NS) for attack risk vs IFNβ	328
Methotrexate					
Methotrexate up to 50 mg once weekly, prednisone 1 mg/kg with taper for a mean of 50 months	8	Not determined	R	7 patients clinically stabilized without new Gd MRI lesions; mean EDSS reduction from 6.6 at initiation to 4.56 at 24 months	334
Median maintenance dose 17.5 mg/week (7.5–25 mg/week) plus 11 × OS, 1 × RTX, 1 × tacrolimus for a median of 22 months	14	All AQP4-IgG positive	R	Decrease of median ARR from 1.39 to 0.18 (P < 0.01), with stabilization or improvement of EDSS in 11/14 patients (median EDSS 5.25 at baseline vs 5.0 at last follow-up)	332
Dose increase from 7.5 mg to 17.5 mg weekly, plus OS 5–10 mg/day for a mean of 40 months	9	All AQP4-IgG positive	R	ARR decreased by 64% from 3.11 at 18 months before MTX treatment to 1.11 at 18 months post-treatment (P < 0.01), with EDSS stabilization or improvement in 6/9 patients	333
Tacrolimus					
2–3 mg/day of tacrolimus for a median of 11 months (plus OS 2.5–20 mg/day in 15 patients for >6 months)	25	88% AQP4-IgG positive	R	86% decrease in ARR, with an improvement in mean EDSS from 4.5 to 2.3 (P < 0.001)	356
Oral prednisolone					
8 periods with >10 mg/day and 18 ≤10 mg/day (median 19 and 45 months, respectively)	9	5/9 AQP4-IgG positive	R	Lower ARR (median 0.49 during treated vs 1.48 during untreated periods) in all but 1 patient negative for AQP4-IgG; significantly more relapses in the <10 mg/day subgroup (OR 8.75, P = 0.049)	335
Cyclophosphamide					
1 g CYC every 2 months for a mean of 10 months	7	1/7 AQP4-IgG positive	R	5 patients had ongoing disease activity (ARR ranging from 0.8 to 5.0); 1 death occurred owing to severe NMO relapse and only 1 patient was stable	336
750–1,200 mg CYC/patient for a mean of 17 months	4	All AQP4-IgG positive	R	Median EDSS improvement from 8 to 5.75; caveat: 3/4 patients had coexisting connective tissue disorders (SS, SLE, APLS)	357
Treatment for a median of 19 months	5	1/5 AQP4-IgG positive	R	Median ARR decreased from 1.30 to 0.92 (P = NS); EDSS was unchanged and remained at 6.5	299

Reports that included <3 patients were not considered. Note that REF.[302] is a meta-analysis of 46 single studies and case series on the efficacy of rituximab published between 2000 and 2015. ARR, annualized relapse rate; APLS, antiphospholipid syndrome; AQP4, aquaporin 4; AZA, azathioprine; CYC, cyclophosphamide; CyA, cyclosporine A; EDSS, Expanded Disability Status Scale; Gd, gadolinium; IFNβ, interferon-β; IS, immunosuppressive treatment; i.v., intravenous; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; LETM, longitudinally extensive transverse myelitis; M, meta-analysis; MITOX, mitoxantrone; MMF, mycophenolate mofetil; MOG, myelin oligodendrocyte glycoprotein; MP, methylprednisolone; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; NS, not significant; OS, oral steroids; P, non-randomized prospective study; PEX, plasma exchange; PD, prednisone; PDL, prednisolone; R, retrospective case series/cohort study; RCT, randomized controlled trial (open-label); RR, relapse rate; RTX, rituximab; SLE, systemic lupus erythematosus; SS, Sjogren syndrome; TCZ, tocilizumab. [a]Ninety-nine patients in total; ARR and EDSS data based on a subgroup of 70 patients treated ≥12 months.

a decrease in ARR, with a decline in EDSS scores in two studies[317,318]. In addition, one prospective, multicentre, randomized, open-label phase II study demonstrated a longer time to relapse with tocilizumab than with azathioprine[319] (TABLE 1). Only one patient with MOG-IgG was included in the study and treated with tocilizumab and this patient was relapse free at the end of the study period[319]. In two other patients with MOG-IgG who were unresponsive to previous therapies in separate studies, tocilizumab also resulted in clinical stabilization or improvement[320,321].

Intravenous immunoglobulin. Four case series on IVIG treatment in NMOSD and in patients with MOG-IgG have been published[301,322–324] (TABLE 1). All studies reported a significant reduction in ARR, with a decline in EDSS scores in two studies[301,322]. One study reported no change in EDSS scores[324].

Other agents. Three studies of mitoxantrone reported significant reductions in relapse rates in patients with NMO and its *formes frustes*, the majority of whom was positive for AQP4-IgG, compared with relapse rates

Table 2 | **Phase III and phase II/III multi-centre, randomized, double-blind, placebo-controlled trials in patients with NMO/NMOSD**

Drug and clinical trial design	Study population	Treatment	Main outcomes	Study acronym (ref.)
Eculizumab as add-on or monotherapy, phase III with open-label extension	143 (2:1[a]), m:f = 1:10, adult (mean age 44.3 ± 13.27 years), worldwide recruitment, AQP4-IgG-positive "NMO or NMOSD" with active disease (≥2 attacks in the last 12 months or ≥3 attacks in the last 24 months, including ≥1 in the last 12 months) and EDSS ≤7	900 mg weekly for the first 4 doses starting on day 1, followed by 1,200 mg every 2 weeks starting at week 4; co-treatment: continuation of any previous stable-dose IST allowed (including with >1 IST and/or with up to 20 mg/day CS); used by 78% of patients in the experimental arm and by 72% in the placebo arm	Primary end point (time to first adjudicated on-trial relapse) met, reduction of risk of relapse by 94.2% (at week 48, 3% (3/96) of patients had experienced a relapse vs 43% (20/47) in the placebo arm; HR 0.06, 95% CI 0.02–0.20; $P < 0.001$); significantly lower ARR (0.02 vs 0.35, rate ratio 0.04, 95% CI 0.01–0.15; $P < 0.001$); 96.4% and 51.9% were relapse free at week 96; no significant between-group difference in EDSS progression, with higher rates of upper respiratory tract infection in the eculizumab group (including one death from pulmonary empyema)	PREVENT[112]
Satralizumab as add-on therapy, phase III with open-label extension	83 (1:1[a]), m:f = 1:13, adult/juvenile (13–73 years), Asia (41%)/Europe and USA (59%), NMO 2006 (REF.[343]) or AQP4-IgG-positive s/rLETM or AQP4-IgG-positive r/bilON with active disease (≥2 attacks in the last 2 years, including ≥1 in the last 12 months) and EDSS <7	120 mg s.c. at weeks 0, 2, and 4 and subsequently at 4-week intervals; co-treatment: mandatory stable-dose IST (adults: AZA, MMF or CS; juveniles: AZA plus CS, or MMF plus CS; stable dose required during at last 8 weeks before baseline) in both arms	Primary end point (time to first adjudicated on-trial relapse) met, reduction of risk of relapse by 62% (attacks in 20% (8/41) vs 43% (18/42) in the control group; HR 0.38, 95% CI 0.16–0.88; $P = 0.02$); 78% vs 59% were relapse free at 96 weeks; a difference in risk reduction of 79% (HR 0.21, 0.06–0.75) vs 34% (HR 0.66, 0.20–2.24) was observed between patients positive for and those negative for AQP4-IgG; effect on pain, fatigue, EDSS and SAE frequency did not differ between groups	SAkuraSky[108]
Satralizumab as monotherapy, phase III with open-label extension	95 (2:1[a]), m:f = 1:4.3, adult (20–70 years), 85% non-Asian, NMO 2006 (REF.[343]) or AQP4-IgG-positive s/rLETM or AQP4-IgG-positive s/rON, plus ≥1 attack in the last 12 months and EDSS <7	120 mg s.c. at weeks 0, 2, and 4 and subsequently at 4-week intervals; co-treatment: no additional IST allowed	Primary end point (time to first adjudicated on-trial relapse) met, reduction of risk of relapse by 55% (attacks in 30% (19/63) vs 50% (16/32); HR 0.45, 95% CI 0.23–0.89; $P = 0.018$); 72% in the active treatment arm and 51% in the placebo arm were relapse free at 96 weeks; a difference in risk reduction (74% (HR 0.26, 0.11–0.63) vs −19% (HR 1.19, 0.3–4.78)) was observed between patients positive for and those negative for AQP4-IgG; similar proportion of SAE in the two groups (but more severe SAE in the active treatment group); no apparent effect on pain and fatigue after 24 weeks	SAkuraStar[109]
Inebilizumab as monotherapy, phase II/III with open-label extension	230 (3:1[a]), m:f = 1:1.9, adult (18–74 years), worldwide recruitment, NMO 2006 (REF.[343]) or AQP4-IgG-positive NMOSD 2007 (REF.[18]) and active disease (≥1 attack requiring rescue therapy in the last year or ≥2 such attacks in the last 2 years) and EDSS ≤8	300 mg i.v. on days 1 and 15; co-treatment: no additional IST allowed	Primary end point (time to first adjudicated on-trial relapse) met, reduction of risk of relapse by 73% (12% (21/174) vs 39% (22/56); HR 0.272, 95% CI 0.150–0.496; $P < 0.0001$) in the overall population and by 77% in patients positive for AQP4-IgG (HR 0.227; $P < 0.0001$) after 28 weeks of treatment; significant effects also with regard to EDSS worsening ($P < 0.005$), NMOSD-related hospitalizations ($P = 0.01$; rate ratio 0.286) and the number of active MRI lesions ($P = 0.0034$); SAE in 5% vs 9%; no difference in VA	N-MOmentum[110]
RTX plus oral prednisolone vs placebo plus oral prednisolone	38 (1:1[a]), m:f = 1:18, aged 37–65 years, patients in Japan with AQP4-positive NMOSD taking 5–30 mg/day oral steroids with EDSS ≤7.0	375 mg/m² i.v. every week for 4 weeks, then 6-month interval dosing (1,000 mg every 2 weeks, at 24 weeks and 48 weeks after randomization) or placebo i.v.; concomitant oral prednisolone (gradually reduced to 2–5 mg/day)	The primary outcome (time to first relapse) met with no relapse in the RTX arm and 7 relapses in the control arm (group difference 36.8%, 95% CI 12.3–65.5; logrank $P = 0.0058$) after 72 weeks; no significant difference in change in EDSS from visit 2 to the last study visit between groups (−0.32 (95% CI −0.62 to −0.01) vs −0.26 (−0.77 to 0.25); $P = 0.85$); SAE in 16% vs 11%; caveats: small sample size and relatively mild disease, exclusively Japanese patients included	RIN-1 (REF.[303])

In all studies, patients could enter an optional open-label extension trial after first relapse or, if no relapse occurred, at the end of the randomized controlled period (RCP). Per protocol, the end of the RCP was at 24 protocol-defined relapses (PDR) in PREVENT, at 26 PDR in SAkuraSky, at 44 PDR or after 1.5 years after enrolment of the last patient in SAkuraStar, and at 67 PDR in N-MOmentum. The RCP of the N-MOmentum study was stopped before complete enrolment because of clear demonstration of efficacy. AQP4, aquaporin 4; ARR, annualized relapse rate; AZA, azathioprine; CS, corticosteroids; EDSS, Expanded Disability Status Scale; IST, immunosuppressive therapy; i.v., intravenous; LETM, longitudinally extensive transverse myelitis; MMF, mycophenolate mofetil; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; r/bil, recurrent or simultaneous bilateral; RTX, rituximab; SAE, severe adverse events; s.c., subcutaneous; s/r single or recurrent; VA, visual acuity. [a]Randomization ratio (active treatment group:control group).

Box 4 | **NMO and pregnancy**

Aquaporin 4 (AQP4) is expressed by placental cells and AQP4-IgG is likely capable of causing placentitis, with the risk of miscarriage[370–372]. Moreover, AQP4-IgG-positive (but not typically myelin oligodendrocyte glycoprotein (MOG)-IgG-positive) disease is frequently associated with connective tissue disorders such as systemic lupus erythematosus, Sjögren syndrome, antiphospholipid syndrome and rheumatoid arthritis[373–375], some of which are also associated with an increased risk of spontaneous miscarriage. Some studies have found an increase in relapse rate after delivery, especially in the first 6 months post-partum, in women with AQP4-IgG-positive neuromyelitis optica spectrum disorders (NMOSD)[369]. In addition, pregnancy-related attacks have also been reported in women with MOG-IgG-positive disease, most of which occurred post-partum[9]. Immunotherapy tends to reduce the risk of such attacks[369].

Treatment considerations

Rituximab has been successfully used in pregnant and breastfeeding women with neuromyelitis optica (NMO) or NMOSD (summarized in REF.[369]). The manufacturer advises that effective contraception is required in women during treatment with rituximab and for 12 months after the last dose, together with avoidance of breastfeeding. However, physicians have to balance the risk of fetal loss and pre-eclampsia apparently associated with NMOSD and that of pregnancy-associated NMOSD relapses against the risk of transient haematological disturbances, primarily B cell depletion, in the fetus or neonate[369]. Eculizumab treatment did not seem to have any adverse effects on pregnancy outcomes in patients with paroxysmal nocturnal haemoglobinuria or HELLP syndrome, although data on NMOSD are widely missing[369]. Azathioprine, non-fluorinated glucocorticoids, plasma exchange and immunoadsorption are also thought to be relatively safe in pregnancy but should also be used only after careful risk–benefit evaluation[369]. Tocilizumab might be an option in women with very severe NMOSD[369]. Mycophenolate mofetil (MMF) is associated with first-trimester pregnancy loss in up to 45% of cases and it has a well-documented and relatively characteristic profile of teratogenicity, causing limb and organ system anomalies, microtia, and cleft lip and palate in 26–33% of exposed newborns. Accordingly, MMF is strictly contraindicated during pregnancy. Two negative pregnancy tests are obligatory before the first dose; in the case of accidental conception, the patient should be switched to a safer option. MMF should be stopped at least 6 weeks before planned conception. As 90% of patients with AQP4-IgG and the majority of patients with MOG-IgG are women, many in their childbearing years, counselling patients regarding the potential risks and optimum treatment is of paramount importance. See REF.[369] for a comprehensive review of NMSOD and pregnancy.

1–2 years before treatment initiation, and improved or stabilized EDSS in a subgroup of the cohort[325–327] (TABLE 1); however, one retrospective cohort study did not find a reduction in relapse rate compared with interferon-β (IFNβ)[328]. Owing to the potentially severe cardiotoxic and myelotoxic side effects[329,330] and the availability of multiple alternative therapies, the use of mitoxantrone is generally discouraged[331]. Only a few patients with MOG-IgG treated with mitoxantrone have been reported[9,313], with no convincing effect in preventing relapses.

Similarly, data on methotrexate for the treatment of NMO are scarce. Three retrospective studies[332–334] reported favourable effects on relapse rates and disease stabilization in patients with NMOSD (TABLE 1). In addition, methotrexate was also beneficial in some patients with MOG-IgG in one study[9] but no effect on relapse rates was found in another study[313].

Other evaluated treatments include prednisolone monotherapy and cyclophosphamide. One small study of patients with NMO, according to the 1999 Wingerchuk criteria, suggested a beneficial effect of oral prednisolone monotherapy on the ARR[335]. Cyclophosphamide has not been shown to prevent relapses[99,336], including in patients with MOG-IgG[9,313], and should be considered only as a reserve treatment when other drugs are unavailable or have failed (TABLE 1).

New long-term treatments

Eculizumab. Eculizumab is a humanized therapeutic monoclonal antibody that inhibits the terminal complement cascade; it prevents the cleavage of C5, thereby reducing inflammation and inhibiting the formation of the cytolytic membrane attack complex. In a worldwide phase III study (PREVENT), eculizumab was highly effective in reducing the risk of relapse in patients with NMOSD[112] (TABLE 2) and, accordingly, was approved in June 2019 for the treatment of adult patients with AQP4-IgG-positive NMOSD in the USA, and shortly thereafter in the European Union and Japan. The adverse effects of eculizumab include increased susceptibility to infections, particularly with encapsulated bacteria, and upper respiratory tract infections; in one study, one patient with NMOSD developed meningococcal sepsis[337]. Immunization with meningococcal vaccines is mandatory; vaccination must be carried out at least 2 weeks before the first dose of eculizumab, unless the risks associated with delaying therapy outweigh the risk of developing a meningococcal infection; if treatment is started, by way of exception, less than 2 weeks after vaccination, careful monitoring during therapy for early signs of meningococcal infection is required and patients should receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. In addition, one death from pulmonary empyema (a build-up of pus in the pleural space) occurred in the eculizumab group in the phase III study. In the USA, an obligatory Risk Evaluation and Mitigation Strategy programme has been instituted.

Satralizumab. Satralizumab is a humanized anti-IL-6 receptor monoclonal antibody with a longer half-life than tocilizumab, which is administered by subcutaneous injection. Two phase III studies that evaluated the efficacy and safety of satralizumab as add-on (SAkuraSky)[108] or monotherapy (SAkuraStar)[109] both demonstrated a significant reduction in relapse risk in patients with AQP4-IgG-positive NMOSD and active disease (TABLE 2). Based on the results of these studies, the FDA approved the drug for the treatment of adult patients with AQP4-IgG-positive NMOSD, including by self-injection, in August 2020. The proportion of patients experiencing serious adverse events was similar in the treatment and control arm in both studies and no anaphylactic reactions, opportunistic infections or deaths were reported.

Inebilizumab. Inebilizumab is a $CD19^+$ cell-depleting humanized monoclonal antibody that also targets plasmablasts and CD19-expressing plasma cells, which are the main sources of AQP4-IgG. A large, worldwide phase III study (N-MOmentum)[110] reported a significant reduction in relapse risk in the AQP4-IgG-positive subgroup with inebilizumab treatment (TABLE 2). The efficacy of inebilizumab was less clear in seronegative patients but lack of power precludes definitive conclusions. Inebilizumab was approved for the treatment of AQP4-IgG-positive NMOSD in adults by the FDA in June 2020.

Duration of therapy

How long immunotherapy has to be maintained is unknown. No data are available to indicate the circumstances that would allow the safe interruption or cessation of maintenance therapy in patients with AQP4-IgG-positive NMOSD. By contrast, there are reports on the rapid reoccurrence of attacks after B cell-repopulation in patients treated with rituximab after cessation of therapy or following overly long treatment intervals[9,99]. Similarly, relapses were noted after stopping treatment with other drugs such as eculizumab or tocilizumab. It should be kept in mind that some patients with MOG-IgG-associated disease may have a monophasic disease course and that the disease may take a milder course in some cases; however, no parameters that would reliably predict such course are known to date and patients positive for MOG-IgG with rapid accrual of severe visual and/or motor deficits have been described[9,165].

Symptomatic treatment

Central neuropathic pain has no generally accepted standard of care but the most frequently used medications include antiepileptics, antidepressants and NSAIDs[338]. However, these medications are not fully effective, resulting in frequent breakthrough opioid use[177,338]. Notably, tocilizumab reduced neuropathic pain severity in patients with AQP4-IgG-positive NMOSD[317]. For painful tonic spasms, the use of carbamazepine or topiramate has been recommended[339,340]. Potassium channel blocking using fampridine or extended-release fampridine is beneficial in some patients with TM and can improve ambulation[341]. Residual bladder dysfunction after myelitis is common in patients with NMO[9] and can be treated with anticholinergic, α-blocking and antispasmodic agents, serotonin/noradrenaline reuptake blockers, β3-adrenoreceptor agonists, cannabinoids, botulinum toxin, and desmopressin, often together with intermittent self-catheterization, depending on the type of neurogenic bladder disorder[342]. Fatigue is often multifactorial. Pharmacological and/or psychological management of fatigue has to take into account coexistent spasticity, sleep impairment related to uncontrolled pain or micturition, and the adverse effects of symptomatic and other treatments. Spasticity is treated by oral antispasticity medications alone or in combination with cannabinoids and, when focal, by botulinum toxin. Continuous intrathecal baclofen administration or intermittent triamcinolone may be required in severe cases of spasticity. Remyelination therapies with proven efficacy in NMO are not currently available. More detailed data on symptomatic treatment can be found in REF.[342].

MS-approved drugs and NMO

Most disease-modifying drugs approved for the prophylactic treatment of MS have not been systematically tested in NMO and should be avoided in this disorder. Glatiramer acetate did not affect the relapse rate in two retrospectively assessed cohorts meeting the 2015 (REF.[19]) and the 2006 (REF.[343]) Wingerchuk criteria. Importantly, a detrimental influence on the course of disease has been consistently reported for IFNβ. Exacerbation of NMOSD has also been reported following treatment with fingolimod, natalizumab, alemtuzumab, dimethyl fumarate and autologous haematopoietic stem cell transplantation in single patients (Supplementary Table 1). As mentioned above, limited data suggest that mitoxantrone might be effective to some degree; however, the drug should rather be avoided in NMO owing to the availability of other treatment options with a better safety profile. Similarly, available evidence suggests that individuals positive for MOG-IgG may not benefit from MS disease-modifying drugs, as treatment with IFNβ, natalizumab, glatiramer acetate and alemtuzumab has been mostly associated with failure or worsening (for example, REFS[9,344]) (Supplementary Table 1). No data exist for ocrelizumab, a B cell-depleting monoclonal antibody that theoretically might be effective in both disorders.

Socioeconomic aspects

The new FDA-approved drugs are among the most expensive drugs worldwide. Owing to this high cost, these drugs may not be affordable to many patients. Moreover, eculizumab and inebilizumab are both administered intravenously and satralizumab subcutaneously, which may preclude using these therapies in some regions. By contrast, azathioprine, MMF and oral steroids are available as tablets, which may be more practicable in countries with developing medical systems and unfavourable climatic and infrastructural conditions. Accordingly, treatment recommendations and algorithms should continue to cover the established and more reasonably priced 'off-label' treatments in the future. In one study, which was performed before approval of the new, expensive long-term teatments, the mean self-reported burden owing to monthly out-of-pocket NMOSD-related expenses was rated 5.71 ± 3.12 on a 10-point scale (1: no burden; 10: significant burden) and prescription medicines accounted for the largest portion of NMOSD-related medical costs for 46% of patients ($n = 193$)[345].

Quality of life

Despite the severe effects of NMO on motor and visual function, patients with AQP4-IgG or with MOG-IgG have reported that pain is among the most prevalent and debilitating symptoms[177,346,347]. Central neuropathic pain, which can be pervasive, severe and intractable to treatment, occurs in 62–91% of patients with NMO[177,348]. Central neuropathic pain is described as an agonizing burning, stabbing, shooting, tingling or squeezing sensation in the face, arms, torso and legs that is distressing, persistent and incapacitating[177,338]. NMO lesions in the spinal cord are characteristically long and severe, and pain is more prevalent and severe in NMO than in most other neurological diseases[177,346]. Research on the effect of persistent pain on QOL in NMO has found major depression to occur in more than half of patients with severe pain, pain scores to be higher in patients with clinically significant depression, and chronic neuropathic pain to be associated with less enjoyment of life and more difficulty with ambulation[338,346].

Owing to the increasing awareness of the dangers of polypharmacy, exploring non-pharmacological interventions that can be used in combination with pharmacological therapies broadens the options for central neuropathic pain treatment. In NMO, adverse effects from off-label medications, particularly at higher doses, are independently associated with slower reaction times and fatigue[346]. Central neuropathic pain in patients with NMO is often refractory to treatment[177,338] and, accordingly, pain treatment in NMO remains a huge area of unmet need. Although pain may be the strongest independent predictor, other commonly occurring symptoms, especially motor and visual disability[268], fatigue, depression, anxiety, and bowel and bladder dysfunction, are correlated with reduced QOL[345,349]. Nonetheless, symptoms such as depression are under-recognized and undertreated[184]. Furthermore, dissatisfaction with treatment options and economic burden correlate with poorer QOL[345].

Outlook

Diagnostic criteria and nosology

Some potential confusion in nomenclature stems from the use of the term NMOSD; this term was originally used by some to refer to the limited or inaugural forms of NMO, whereas others used the term to refer to both NMO and its *formes frustes*. The 2015 IPND criteria use this term in the latter sense but, importantly, do not restrict its application to AQP4-IgG-positive cases. Some have proposed revising the nomenclature to be based on immunopathology, for example, 'AQP4-IgG-related encephalomyelitis' (in analogy to MOG-EM) or 'AQP4-IgG-related autoimmune disease' and would use the terms 'NMO' and 'NMOSD' only to denote a syndrome or a spectrum of syndromes, respectively. Seronegative cases would then be referred to as 'NMO (or LETM or ON) of unknown origin'. However, as a practical limitation to this nomenclature, routine AQP4-IgG testing is not available in all countries and antibody results may be incorrectly negative. The current category of 'NMOSD with unknown or negative AQP4-IgG' status covers these patients and helps with choosing the right treatment if the clinical and radiological features suggest AQP4-IgG-positive NMOSD despite a negative test result. Accordingly, it is likely that future revisions of the NMOSD diagnostic criteria will not introduce a completely new nomenclature but will rather focus on sharpening the distinction between seronegative NMOSD and MOG-IgG-associated disease. Moreover, given the diagnostic significance of a positive antibody result, such revisions should include strict recommendations on indications and methodology of antibody testing to further reduce the risk of incorrect diagnoses. There is also still an unmet need for developing standardized serological assays and for the establishment of quality control measures such as regular national round robin tests.

Treatment

The first phase III clinical trials were completed in 2019, which is a major step forwards. Considering the lack of robust data on the old treatments, one could argue that treatments found to be effective in these phase III trials should become the future standard of care for all patients. However, there are several limitations to this approach, for example, a lack of rigorous head-to-head comparison trials proving superiority of the newer agents (or combinations) over the established ones. Determining superiority by direct comparison of relapse suppression using summary measures across studies is potentially misleading owing to differences regarding inclusion criteria, attack definitions, duration, co-treatments and comparator (placebo versus pre-treatment). Large head-to-head superiority studies (which should include the already established drugs), although highly desirable, may be difficult to perform owing to the prevalence of NMO and the frequency of relapse with the available therapies. Other limitations include the lack of controlled data proving long-term efficacy and the lack of long-term safety of each of the newer agents. Moreover, some patients are stable on the older drugs and studies on the risks and benefits of switching such patients to one of the newer treatments have not been performed. Furthermore, patients seronegative for AQP4-IgG meeting the 2015 criteria do not seem to respond to satralizumab and are less likely to respond to inebilizumab, whereas seronegative patients were not included in eculizumab trials. Whether the newer drugs are effective in patients positive for MOG-IgG is also unknown.

Eculizumab is one of the most expensive drugs in the world and the prices for satralizumab and inebilizumab are also very high. As these drugs will not be affordable to many patients, publicly funded randomized trials are needed to better define the efficacy and safety of the currently used immunosuppressants in patients with NMO. We recommend that future trials assess novel outcomes, including the severity of clinical attacks as well as frequency, in addition to biomarkers of subclinical astrocyte damage such as GFAP.

All current treatments require long-term administration and likely have a risk of long-term toxicity due to immunosuppression; therefore, there is continuing interest in the long-term modulation of presumed defects in immune tolerance in NMO. Indeed, defects in central and peripheral immune tolerance checkpoints for B cells have been documented in patients with NMO and it seems that the expanded pool of autoreactive and polyreactive B cells that result from these defects, which are not unique to NMO but occur in many other autoimmune diseases, provide the necessary substrate of cells that may be subverted by antigen-driven mechanisms to generate AQP4-reactive B cells[149]. Several potential approaches to immune tolerance induction have been proposed that can be explored and may prove useful adjunctive or potential replacement treatments for those currently available and which may have longer effects on underlying fundamental defects in immune tolerance[350,351]. However, this approach to treatment is nascent for NMO in particular and for autoimmunity in general.

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Competing interests
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