

What's new in neuromyelitis optica? A short review for the clinical neurologist

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Abstract The evolution of neuromyelitis optica spectrum disorder (NMOSD) from a rare, incurable and misunderstood disease with almost universally poor outcomes to its present state in just over a decade is unprecedented in neurology and possibly in medicine. Our knowledge of NMOSD biology has led to the recognition of wider phenotypes, new disease mechanisms, and thus clinical trials of new and effective treatments. This article aims to update readers on the recent developments in NMOSD with particular emphasis on clinical advances, the 2015 diagnostic criteria, biomarkers, imaging, and therapeutic interventions.

Keywords Optic neuritis · Myelitis · Aquaporin · Myelin oligodendrocyte glycoprotein

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing and often severely disabling autoimmune disease, which predominantly targets the spinal cord, optic nerves and brainstem. Three quarters of patients with NMOSD have serum immunoglobulin-G (IgG) autoantibodies to the aquaporin-4 channel (AQP4-IgG), which is highly

expressed on the 'foot-processes' of astrocytes at the blood–brain barrier [1, 2].

2015 diagnostic criteria

The 2015 international consensus diagnostic criteria for NMOSD have accepted the central role of AQP4-IgG in causing NMOSD [3]. Wide availability and use of reliable AQP4-IgG testing has identified heterogeneity of seropositive phenotypes beyond the optic neuritis and myelitis, which were traditionally used to define NMO.

The 2015 criteria are outlined in Table 1. The term 'NMO' has been discarded and 'NMOSD' adopted with a significant distinction now existing between NMOSD with and without detectable AQP4-IgG. For AQP4-IgG seropositive individuals, at least one of six sites within the CNS must be affected (spinal cord, optic nerves, area postrema, brainstem, diencephalon or cerebrum). Seronegative patients must have at least two affected sites, of which one must be clinical involvement of the spinal cord, optic nerves, or area postrema (a region within the dorsal medulla, also recognised as a particularly characteristic site of involvement). For the seronegative group there are additional MRI requirements to fulfil (Table 1) [3].

Compared to the 2006 criteria [4], the 2015 criteria increase the diagnostic rates of NMOSD by 76% in the UK [5] and by 85% in South Korea [6]. The time to diagnosis is shortened to 11 months using the new criteria, compared to 53 months with the 2006 criteria [6]. The larger patient numbers will have an impact on delivery of care, while earlier diagnosis (and hopefully treatment) should reduce the number of people with disability from repeated attacks. The number of patients eligible for recruitment to clinical trials should also increase.

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Table 1 Summary of the 2015 international consensus diagnostic criteria for neuromyelitis optica spectrum disorders in adult patients [3]

Diagnostic criteria for NMOSD with AQP4-IgG:

- At least one core clinical characteristic
- Positive test for AQP4-IgG using best available method
- Exclusion of alternative diagnoses (e.g. sarcoidosis, neoplastic or paraneoplastic disease, chronic infection)

Diagnostic criteria for NMOSD without AQP4-IgG or unknown AQP4-IgG status:

- At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
 - (a) At least one core clinical characteristic must be optic neuritis, longitudinally-extensive acute myelitis or area postrema syndrome
 - (b) Dissemination in space (two or more different core clinical characteristics)
 - (c) Fulfilment of additional MRI requirements, as applicable
- Negative tests for AQP4-IgG using best available methods, or testing unavailable
- Exclusion of alternative diagnoses

Core clinical characteristics:

- Optic neuritis
- Acute myelitis
- Area postrema syndrome
- Brainstem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status:

- Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesions extending over more than half of optic nerve length or involving optic chiasm
- Acute myelitis: requires associated intramedullary MRI lesions extending over more than three contiguous segments OR more than three contiguous segments of focal spinal cord atrophy in patients with a history compatible with acute myelitis
- Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
- Acute brainstem syndrome: requires associated periependymal brainstem lesions

Clinical advances

Greater severity and poorer recovery typify the clinical course of transverse myelitis in NMOSD as compared with MS. Neuropathic pain is more prevalent (62–86%), frequently intractable and has a major impact on quality of life [7, 8]. Neuropathic pruritis (itch) was experienced by 27.3% of patients in a UK cohort [9] and paroxysmal tonic spasms occur in 14–25% of NMOSD patients compared to less than 3% of patients with MS or idiopathic transverse myelitis [10, 11]. The latter are recurrent brief episodes of muscle hypertonia causing abnormal posturing and pain, which are most common during recovery from a first episode of myelitis [10].

Traditionally it was thought that relative sparing of brain parenchyma helped define NMOSD, but we now know that 60% of brain MRI scans are abnormal at onset [12]. Periventricular brain regions with high expression of AQP-4 are most commonly affected. The most characteristic site is the area postrema of the dorsal medulla. Lesions here commonly cause intractable nausea, vomiting and hiccups—‘area postrema syndrome’. These symptoms are rare

in MS but occur in approximately a fifth of NMOSD patients [13, 14] and may be the initial presentation [15]. Diencephalic lesions are also well described and may be asymptomatic or cause a spectrum of clinical features from hypersomnolence and narcolepsy [16, 17] to various endocrinopathies resulting from disturbances of the hypothalamic-pituitary axis, such as the syndrome of inappropriate antidiuretic hormone secretion [18, 19].

Finally, about half to two-thirds of patients with NMOSD with brain lesions have evidence of cognitive impairment at psychometric testing, which is comparable to MS [20–25]. Particularly affected in NMOSD are processing speed, executive function, memory, attention and verbal fluency [22, 24, 26, 27]. It must be highlighted, however, that the marked cognitive dysfunction seen in advanced MS is not seen in NMOSD, probably reflecting the effect of treatments, lack of progressive disease or major cortical pathology in NMOSD. Lifetime prevalence of depression in NMOSD is also similar to patients with MS, but with higher rates of recurrent depression and suicidality [25]. Anxiety is also common soon after diagnosis [25, 28]. These factors all have a significant impact on health-related quality of life [29] and

Table 2 Which patients to test for AQP4-IgG (modified from Waters et al. [33])

1. Longitudinally extensive transverse myelitis
2. “Idiopathic” acute transverse myelitis lacking other features of MS
3. Severe optic neuritis with poor visual recovery
4. Bilateral simultaneous optic neuritis
5. Longitudinally extensive optic neuritis or involvement of the chiasm detected on MRI
6. Intractable nausea, vomiting or hiccups in the absence of gastro-intestinal pathology
7. Dorsal medullary lesion detected on MRI
8. Diencephalic clinical syndromes
9. Cryptogenic leukoencephalopathy
10. Presumed ‘MS’ with unexplained severe relapses after starting standard disease modifying drugs
11. In the above situations, if the initial test was negative, retesting patients at 3–6 months will improve sensitivity, especially if the initial test was done during clinical remission, treatment with immunosuppression or immediately following plasma exchange

highlight the need for cognitive and psychiatric assessment as part of comprehensive care in NMOSD.

Biomarkers

Anti-aquaporin-4 antibody (AQP4-IgG)

Detection of AQP4-IgG in serum is a central diagnostic tool in NMOSD as it predicts future relapse [30–32]. Table 2 outlines the usual clinical indications for serum AQP4-IgG testing. But in practice, if the features of an apparent demyelinating disease do not fit with typical relapsing MS or clinically isolated syndrome (clinically, radiologically or in response to treatment), then testing is justifiable. Available assay techniques include live and fixed cell-based assays using fluorescence microscopy or flow cytometry, protein-based assays such as enzyme-linked immunosorbent assay (ELISA), and tissue-based methods including indirect immunofluorescence and immunohistochemistry. Of these methods, cell-based assays have the highest sensitivity (76.7%) and specificity (99.8%) [33]. Transfection of cells with the M23 (rather than the M1) isoform of AQP4 further increases the sensitivity of these cell-based assays [34, 35].

CSF testing for AQP4-IgG is comparatively less sensitive [36] and if cell-based assays are used for serum testing, then there is little to be gained from routine CSF AQP4-IgG testing in general [3, 33]. For patients who are AQP4-IgG seronegative at initial testing but for whom the clinical suspicion of NMOSD remains high, retesting at 3–6 months may yield some additional seropositive cases (see Table 2). More research is needed to clarify whether serial titres of AQP4-IgG will be useful for predicting future clinical relapses in seropositive patients.

Roughly a quarter of patients meeting the clinical criteria for NMOSD remain seronegative on repeated testing

with cell-based assays. It is quite plausible that several additional (and possibly pathogenic) biomarkers exist.

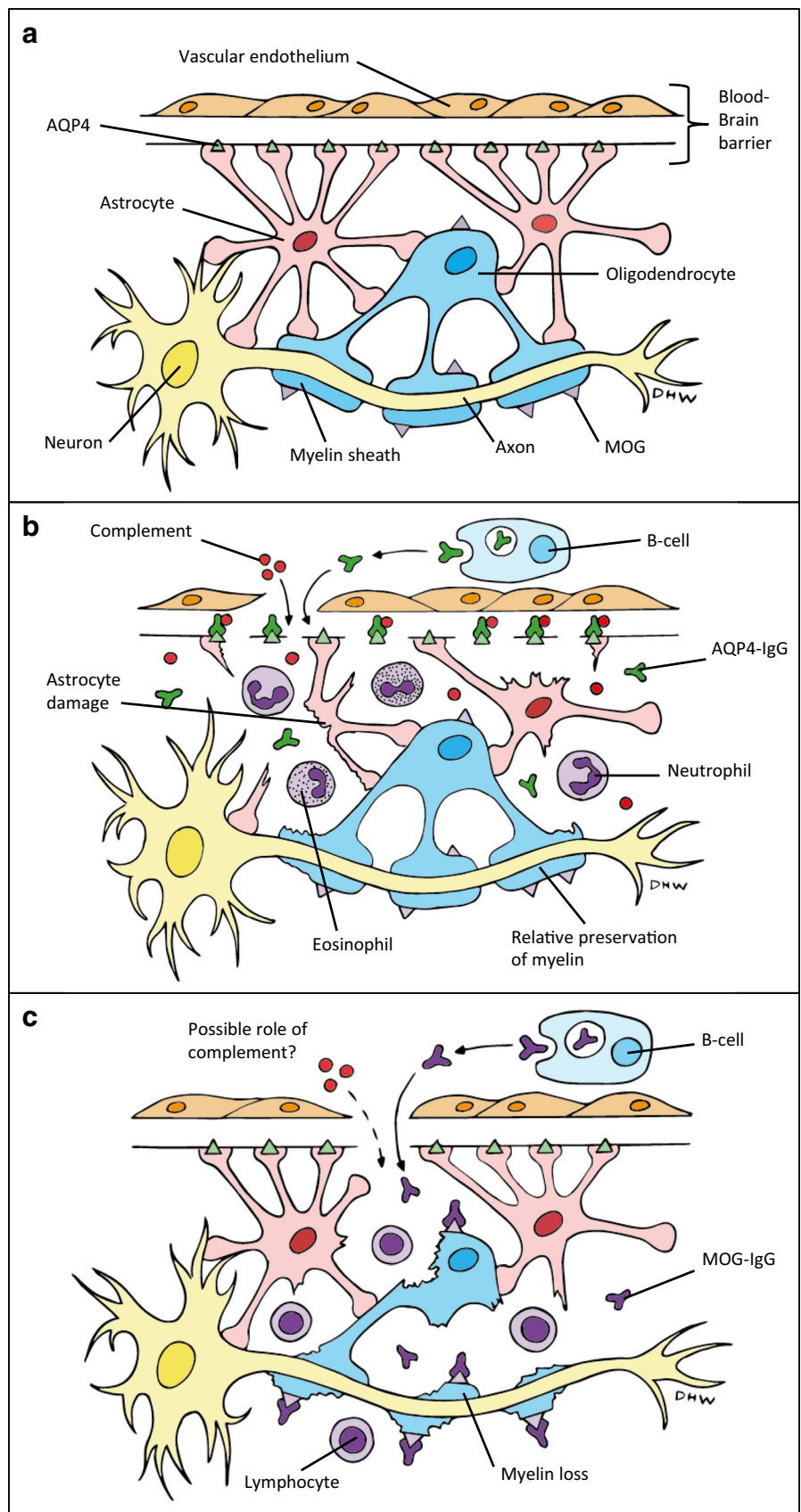
Anti-myelin-oligodendrocyte glycoprotein antibody (MOG-IgG)

A proportion of patients with AQP4-IgG seronegative NMOSD and NMOSD-like syndromes (e.g. relapsing optic neuritis or relapsing transverse myelitis) have been found to have serum antibodies against myelin-oligodendrocyte glycoprotein (MOG-IgG). In contrast to AQP4-IgG seropositive NMOSD, which is an astrocytopathy, MOG-IgG targets a protein expressed by oligodendrocytes and on the outermost surface of myelin sheaths [37, 38] (see Fig. 1). MOG-IgG has also been linked with other demyelinating diseases, including paediatric forms of multiple sclerosis and acute disseminated encephalomyelitis (ADEM) [37, 39, 40]. Whether these apparent MS cases are truly the same as adult relapsing MS will be borne out only on long-term follow-up.

Evidence for the pathogenicity of MOG-IgG comes from *in vitro* studies demonstrating complement-mediated cytotoxicity [37] and from the development of NMOSD-like syndromes in rodent models [41, 42]. However, an *in vivo* mouse study found that MOG-IgG caused reversible alterations to myelin without complement activation or inflammatory cell infiltration [43]. This is in contrast to AQP4-IgG, and may explain why some MOG-IgG patients have better recovery from attacks [44, 45].

The recent and largest published cohort of fifty MOG-IgG positive patients found that 80% of patients follow a relapsing disease course and 40% experience significant disability [46], making a case for long-term immunosuppressive therapy, similar to AQP4-IgG patients. This cohort also highlighted some interesting demographic and clinical differences between MOG-IgG and AQP4-IgG-positive patients. AQP4-IgG seropositive NMOSD has a high

Fig. 1 a This schematic diagram illustrates the sites of expression of aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) within the CNS: AQP4 is expressed at the blood–brain barrier, on the “foot-like” processes of astrocytes, whereas MOG is expressed by oligodendrocytes and on the outermost surface of myelin sheaths. **b** AQP4-IgG is synthesised in the bloodstream by mature B-cells. On crossing the blood–brain barrier it activates complement-mediated astrocyte damage with relative preservation of myelin initially. The inflammatory response involves accrual of neutrophils and eosinophils. **c** MOG-IgG is also produced outside of the CNS. It causes a demyelination, but the mechanism is less well understood



female predominance (as high as 8:1) and high rates of co-existent autoimmune disease (25% of patients) or auto-antibodies (45% of patients) [47]. In MOG-IgG disease the sex difference is less (M:F, 1:3) and only 9% of patients have a second autoimmune disorder. Optic neuritis (affecting 88% of patients) is more common than myelitis (affecting 56% of patients) and patients are more likely to have significant permanent visual deficits than impaired ambulation. Complete recovery from attacks appears more common with MOG-IgG. There is a tendency for relapse on withdrawal of corticosteroids and immunosuppressive medications are often effective in preventing relapses [46].

There is huge research interest in defining the role of MOG-IgG in idiopathic inflammatory demyelination, either as a subtype of NMOSD or as a separate disease entity, with important implications for management. Improved awareness and testing of MOG-IgG will help to further our understanding over the coming years.

Glial fibrillary acidic protein (GFAP)

Glial fibrillary acidic protein (GFAP) is an astrocyte-specific protein important for maintaining the structural integrity of white matter and the blood–brain barrier [48]. GFAP titres are significantly higher in the CSF of individuals with NMOSD than those with MS or other non-inflammatory neurological disorders [49, 50]. Furthermore, titres rise during relapses and fall with administration of corticosteroids, as well as demonstrating correlation with Expanded Disability Status Scale (EDSS) scores [49, 50]. This may reflect the extensive complement-mediated astrocyte damage that occurs in NMOSD but not in MS. As a serum marker, however, GFAP shows less promise, with levels failing to differentiate between NMOSD and other causes of optic neuropathy in a large multicentre study [51].

Interestingly, a novel neuronal autoantibody against GFAP has recently been described in a cohort of North American patients with steroid-responsive meningoencephalomyelitis, and may be a biomarker for a new and distinct autoimmune CNS disorder [52].

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that has been reproducibly found at high levels in the serum and CSF of individuals with NMOSD as compared with MS and other neurological disorders [53–55]. There is mounting evidence for its role in the pathogenesis of NMOSD, its value as a prognostic biomarker and as a target for therapy.

IL-6 promotes the development and maintenance of the Th17 subset of CD4⁺ T-helper cells, which are involved in the induction of pro-inflammatory mediators and

neutrophil recruitment, as well as being implicated in organ-specific autoimmunity [56]. IL-6 has also been demonstrated to augment plasmablast survival and secretion of AQP4-IgG [57].

At relapse, individuals with low levels of IL-6 in their CSF are more likely to have improved recovery [58]. In clinical remission, serum levels of IL-6 directly correlate with relative risk of relapse over a 2-year follow-up period [59]. There is also a correlation between neurological disability and ex vivo production of IL-6 by T-cells sampled from the patients in clinical remission [56]. Finally, IL-6 may induce resistance to glucocorticoids in lymphocytes, as blocking the IL-6 receptor amplifies the effect of hydrocortisone in inhibiting Th17-related cytokines [59]. There have been several series of patients treated successfully with the IL-6 receptor antibody, tocilizumab, and a randomised clinical trial is now in progress, as discussed below.

Imaging

Table 3 highlights the main imaging features of NMOSD, which may help to differentiate it radiographically from MS. These should be considered as guidance and not hard and fast rules. For example, it is important to remember that while longitudinally extensive transverse myelitis is the most common radiographic sign of NMOSD, short myelitis (less than three vertebral segments) does occur (Fig. 2). In a large cohort of AQP4-IgG-positive patients, short myelitis represented 14% of initial myelitis episodes [60] and that figure may be higher for MOG-IgG-positive cohorts [46]. AQP4-IgG and MOG-IgG testing should, therefore, be considered in cases of short myelitis if there are other clinical clues to NMOSD or if additional evidence of MS is lacking.

The other key message is that contrary to historical reports, most patients with NMOSD have brain lesions (Fig. 3). These lesions may satisfy Barkhof criteria for MS in 11–27% of cases [12, 61]. Closer examination of the distribution and morphology of lesions may help discriminate between the two conditions, though no one pattern is diagnostic. For example, MS-typical ovoid lesions in perpendicular alignment to the lateral ventricles (“Dawson’s fingers”) and juxtacortical U-fibre lesions are uncommonly seen in NMOSD [61].

Treatment/therapeutics

Medical therapy for NMOSD is focussed on the treatment of acute clinical relapses and then prevention of future relapses with long-term immunosuppression. Due

Table 3 Imaging features of NMO vs. MS [3, 12, 14, 61–64]

CNS site	Common characteristics of MRI lesions in NMOSD	Common characteristics of MRI lesions in MS
Spinal cord	Long (3 or more vertebral segments) Central cord involvement Cord expansion Extension into the medulla T1-hypointensity during the acute phase Usually symptomatic	Multiple and short Cord usually not expanded Dorsolateral predominance May be asymptomatic
Optic nerves	Long Involvement of the posterior aspects of the nerve and/or chiasm Unilateral or bilateral	Short More commonly unilateral
Brainstem	Area postrema/dorsal medulla involvement May be contiguous with cervical cord lesions Poorly defined borders	Any location Ventral or dorsal pontine lesions Well defined borders
Diencephalon	Hypothalamic, thalamic or periependymal regions of 3rd ventricle	Uncommon
Corpus callosum	Long and diffuse Involve both anterior and posterior corpus callosum Extend into cerebral hemispheres Often disappear in remission	Smaller lesions Often at the callosal-septal interface in the middle and posterior thirds of the corpus callosum
Cerebral hemispheres	Large, confluent subcortical or deep white matter lesions Long corticospinal tract lesions	Ovoid lesions perpendicular to the lateral ventricles (Dawson's fingers) Juxtacortical U-fibre lesions

to the rarity of the condition and ethical concerns about using placebo therapies to treat a condition resulting in permanent disability, there has been a lack of randomised placebo-controlled trials to inform treatment decisions. Nevertheless, standards of care have emerged to guide present treatment, based on a growing body of largely retrospective evidence. Corticosteroids, azathioprine, mycophenolate mofetil and rituximab remain the drugs of choice, though the order of preference varies on both patient and physician preferences and cost globally. Several clinical trials are nearing completion that should add several drugs to our treatment armoury (see Table 4).

The burgeoning interest in NMOSD as an 'orphan' disease has spurred drug development. There are several ongoing small non-randomised studies using bortezomib (proteasome inhibitor that eliminates plasmablasts), ublituximab (anti-CD20 antibody causing B cell depletion), cetirizine (blocks the action of eosinophils) and maintenance plasma exchange for relapse prevention. Alpha1-antitrypsin (protease inhibitor that protects cells from neutrophil-mediated damage) and bevacizumab (blocks angiogenesis by inhibiting vascular endothelial growth factor A) are being evaluated as adjunctive therapies for acute relapses (<http://www.clinicaltrials.gov>) [65].

Treatment of acute relapses

Acute relapses in NMOSD are treated with high dose corticosteroids and with plasma exchange (PLEX) or immunoadsorption. The combination of intravenous methylprednisolone (IVMP) and PLEX appears to be superior to IVMP alone in restoring neurological function [66] and a retrospective review of 871 relapses supports that it improves outcomes, particularly in transverse myelitis relapses [67].

A retrospective case series of ten patients treated with intravenous immunoglobulin (IVIg), after inadequate response to IVMP with or without PLEX, reported subsequent improvement in five patients and no further deterioration in the other five [68]. Unfortunately, the multicentre randomised controlled TRial of IntraVENous immunoglobulin versus standard therapy for the treatment of acute transverse myelitis (STRIVE), which was to include a subset of patients with NMOSD, was discontinued due to poor recruitment [69].

Finally, on the basis that NMOSD lesions are increasingly understood to involve classical complement-mediated astrocyte injury, a proof-of-concept trial has used purified human C1-esterase inhibitor Cinryze[®] as an adjunct to IVMP in the treatment of ten patients with acute

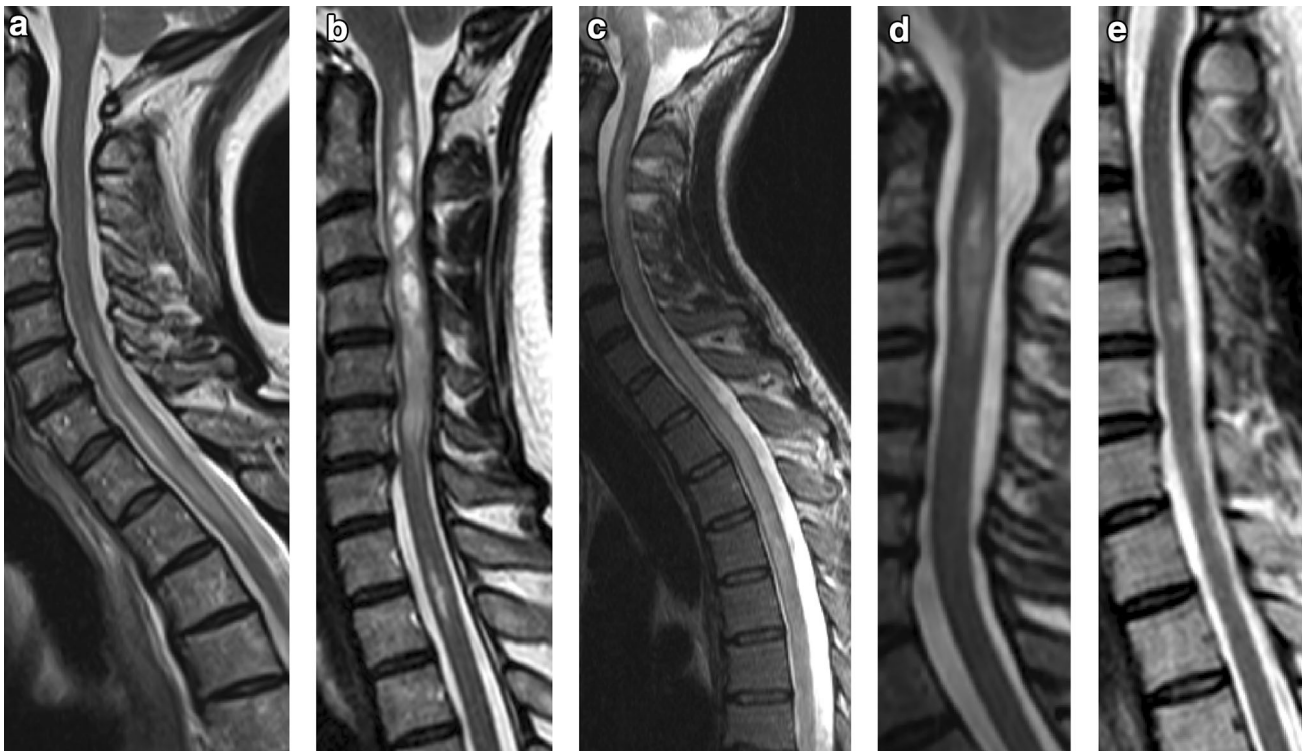


Fig. 2 T2-weighted sagittal spinal cord images of patients with NMOSD (all AQP4-IgG positive) demonstrating **a** typical longitudinally extensive myelitis (LETM); **b** LETM with cystic components

and cord expansion; **c** LETM extending over the entire length of the spinal cord; **d** short myelitis extending over 2½ vertebral segments; **e** short myelitis spanning less than one vertebral body

NMOSD relapses [70]. All but one patient returned to their pre-relapse EDSS or better, only two patients required escalation to PLEX, and there were no adverse events. As with IVIg, these findings need verifying with a randomised controlled trial.

Drugs that are ineffective or worsen NMO

There has been concern for some time that the immunomodulatory therapies used in relapsing remitting multiple sclerosis, particularly interferon beta [71, 72], natalizumab [73–75] and fingolimod [76], may be ineffective or even provoke relapses in NMOSD. Glatiramer acetate is also not beneficial in NMOSD [77]. Alemtuzumab too appears ineffective and may be harmful [78].

Prevention of future relapses

Standard immunosuppressive drugs are the first choice agents in NMOSD. Azathioprine and mycophenolate mofetil have the most evidence of efficacy. These agents may be combined with long-term corticosteroid therapy in high-risk patients. Methotrexate, cyclophosphamide, intravenous immunoglobulin and mitoxantrone are used less often, with the latter in particular being limited by serious side effects. There are several excellent reviews

covering these treatments in detail [79–81] including a 2012 national guideline for the treatment of NMOSD developed by the UK NMO Service [82]. In the rest of this article, we focus on the more recent and targeted therapies for NMOSD: monoclonal antibodies and stem cell therapies.

Rituximab

Rituximab is a chimeric monoclonal anti-CD20 antibody that acts by causing B-cell depletion, as well as reducing T-cell activation [83, 84]. Its efficacy in NMOSD has been reproducibly demonstrated in numerous case series. Annualised relapse rates are reduced by 74–97%, with around two-thirds of patients achieving complete remission [85–92]. In one retrospective analysis, it was found to be superior to mycophenolate and azathioprine [88].

Much attention has been given to individual factors that may influence the efficacy of rituximab in NMOSD. It destroys B-cells mainly through antibody-dependent cellular cytotoxicity, binding both the CD20 receptor on the B-cell and the fragment c gamma receptor 3A (FCGR3A) on natural killer cells. Some patients have polymorphisms in the gene for FCGR3A and these patients are more likely to relapse on rituximab therapy [89]. Another variable factor is the time taken to repopulate B-cells following

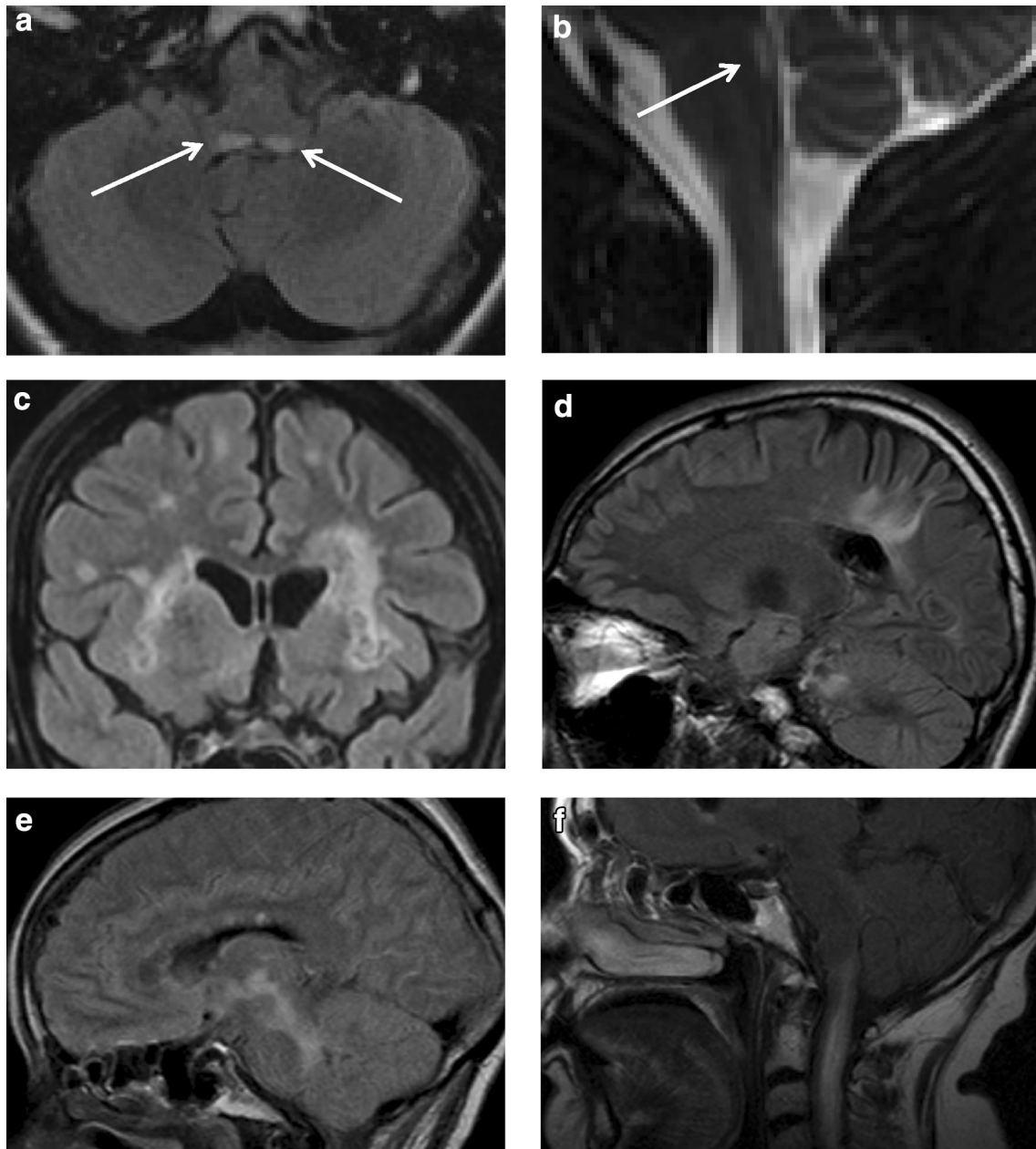


Fig. 3 MRI brain images of patients with NMOSD (all AQP4-IgG positive): **a** Axial FLAIR image showing signal hyperintensity within the dorsal medulla (area postrema). **b** Further area postrema lesion demonstrated on a sagittal T2-weighted sequence (images **a** and **b** courtesy of Brian G Weinschenker, Mayo Clinic, Rochester, Minnesota). **c** Coronal FLAIR image showing bilateral

periventricular, deep white matter and subcortical cerebral lesions. **d** Sagittal FLAIR image showing deep white matter lesions spreading to the corpus callosum. **e** Sagittal FLAIR image showing diencephalic involvement spreading to the dorsal midbrain and pons. **f** Sagittal FLAIR image demonstrating a high cervical myelitis extending into the medulla

administration of a rituximab dose, which can be established by monitoring counts of peripheral CD19⁺ cells (most B-cells) or CD19⁺ CD27⁺ cells (memory B-cells) [88, 93–95]. This means that rather than the traditional regime of six-monthly infusions, individually tailored regimes can be offered to ensure adequate immunosuppression, while limiting side effects and improving cost-effectiveness. Repeated doses as low as 100 mg were

sufficient to deplete B cell populations and maintain remission in Chinese NMOSD patients for a period of 12 months [95].

Rituximab is generally well tolerated, but given the long duration of therapy required in NMOSD, there are concerns about the potential increased risk of progressive multifocal leukoencephalopathy (PML) due to reactivation of the John Cunningham virus (JCV), as has been reported in

Table 4 Ongoing pivotal phase 3 randomised controlled trials in NMOSD [65]

Drug	Mechanism of action	Route	Trial design	Primary outcomes
Eculizumab	Humanized monoclonal antibody Target: complement protein C5	IV	Add-on therapy Randomized Double-blind Placebo-controlled	Time to first relapse
SA237	Humanized monoclonal antibody Target: IL-6 receptor	SC	Two trials: Monotherapy Add-on therapy Randomized Double-blind Placebo-controlled	Time to first relapse
MEDI-551	Humanized monoclonal antibody Target: CD19 (B-cell depletion)	IV	Monotherapy Randomized Double-blind Placebo-controlled	Time to first relapse

IV intravenous, *SC* subcutaneous

individuals treated with rituximab for other autoimmune diseases [96]. To date, there are no reports of PML in rituximab-treated NMOSD patients. In a cohort of 78 Korean patients treated for a mean duration of 4 years, no patients developed PML and none of the 24 patients who were seronegative for JCV converted to seropositive [97].

An anti-CD19 monoclonal antibody, MEDI-551, that also causes B-cell depletion, is currently being evaluated in a double blind study (see Table 3).

Tocilizumab

Tocilizumab is a humanized monoclonal IgG1 antibody that targets the IL-6 receptor (CD126). It is licensed for the treatment of rheumatoid arthritis [98]. IL-6 has been implicated in Th17-mediated inflammation and glucocorticoid-resistance in NMOSD. Several case reports and case series have been published describing the successful treatment of refractory NMOSD patients with tocilizumab [99–105]. In the largest of these case series, eight NMOSD patients were treated and followed up for a mean of 30.9 months. Median relapse rates fell from 4.0 to 0.4 with improvement in median EDSS [103].

SA-237 is a monoclonal antibody against the IL-6 receptor and is currently being tested in NMOSD in a phase III clinical trial (see Table 3). The manufacturers claim a prolonged plasma half-life, which is achieved by applying “recycling antibody technology[®]” to the drug. Once bound to the cell surface IL-6 receptor, the drug-receptor complex is internalised. In contrast to tocilizumab, once SA-237 enters the cell, it dissociates from the IL-6 receptor and is recycled back into the plasma allowing repeated binding to more IL-6 receptors [106].

Eculizumab

Eculizumab is a humanized monoclonal IgG antibody that neutralises the complement protein C5, preventing formation of the C5b-9 membrane attack complex [107]. This is the terminal stage of the complement cascade that is activated by AQP4-IgG and causes astrocyte membrane lysis [108]. 14 AQP4-IgG seropositive patients with highly active disease (median of 3 relapses in the preceding 12 months) were treated with eculizumab for 12 months [109]. 12 patients became relapse-free and two had possible relapses. Despite prior vaccination, one patient developed meningococcal sepsis, which is an uncommon but recognised risk of eculizumab. She was treated successfully with antibiotics [109]. A double-blind placebo controlled trial is now ongoing (see Table 3).

Stem cell therapies

Autologous or allogenic haematopoietic stem cell transplantation (HSCT), which requires pre-transplant immune conditioning with cytotoxic agents, is a common procedure in the treatment of hematologic malignancies, and more recently, aggressive, treatment-resistant multiple sclerosis. In an initial case in 2011, HSCT failed to prevent relapses of NMOSD [110]. The European Group for Blood and Marrow Transplantation Autoimmune Diseases Working Party conducted a retrospective survey, identifying 16 treatment-refractory NMOSD patients treated with HSCT. Relapse-free survival at 3 and 5 years was 31 and 10%, respectively, indicating that HSCT allows only for temporary disease control [111].

Mesenchymal stem cells (MSC) may possess immunomodulatory properties, inhibiting pathogenic B- and T-cell responses and secreting neurotrophic factors that foster tissue repair [112, 113]. Recent pilot studies using either bone marrow or umbilical cord-derived MSC infusions in NMOSD patients report early benefits. A total of 20 patients were treated and observed for 18–24 months. Reduction in relapse frequencies, decrease of lesions on serial MRI scans and improvement of EDSS scores have been reported by both trials, with no major adverse events [114, 115]. Peripheral B-cell levels fell for several weeks following treatment, but the exact mode of action is unknown and the optimum frequency of infusions is yet to be determined [115].

Perhaps the most alluring use of stem cell therapy is as a potential strategy for repair of existing CNS damage by replacing lost cells, thereby restoring neurological function. This concept has been put to the test in traumatic spinal cord injury and MS, though there is currently insufficient evidence of definite clinical benefit [116]. There have been no published studies of regenerative stem cell therapies in NMOSD.

Symptom control

There is little evidence specific to NMOSD to guide symptomatic treatment. However, the most frequent symptomatic complaints are treated similarly to MS. These include impaired mobility, visual impairment, spasticity, pain, bladder and sexual dysfunction, fatigue, anxiety and depression.

Neuropathic pain is a major problem for many patients with NMOSD [7, 8]. First line medications include anti-epileptic drugs (gabapentin, pregabalin, carbamazepine), or low-dose tricyclic antidepressants (amitriptyline and nortriptyline). It is important to escalate doses to ensure maximum benefit, though many patients require multimodal analgesia and all agents may cause sedation at higher doses. Painful tonic spasms usually respond to carbamazepine or topiramate [11, 117].

Fampridine, a medication that blocks potassium channels and improves ambulation in a proportion of patients with MS, has been safely used in a few patients with NMOSD and may be similarly beneficial [118, 119]. Antispasticity medications including baclofen and tizanidine can also be effective in NMOSD but may exacerbate weakness, so appropriate selection of patients is important.

Bladder dysfunction is common and troublesome after NMOSD myelitis. Antimuscarinic agents (oxybutynin, tolterodine and solifenacin) and mirabegron, which activates the β 3-adrenoceptor, cause detrusor relaxation, thereby improving urinary frequency and urgency.

Intermittent self-catheterisation and injection of botulinum toxin into the bladder wall (repeated every 3–6 months) are very helpful. For patients whose predominant symptom is nocturia, cautious use of desmopressin nasal spray at bedtime will reduce the volume of urine produced overnight. It is usually possible to help patients significantly with one or a combination of these strategies, but a permanent suprapubic catheter (SPC) may be the preferred option for some.

Anxiety, depression and fatigue are common in NMOSD, and may be partially alleviated by improving pain, bladder dysfunction and their effect on sleep.

Fatigue in NMO is multifactorial. Corticosteroids may cause sleep and mood disturbance and analgesic agents can exacerbate fatigue. It is important to also consider possible co-existent autoimmune diseases, for example pernicious anaemia and hypothyroidism. Depression in NMOSD may benefit from both psychological and pharmacological therapy.

The breadth, severity and complexity of the symptoms experienced by patients with NMO necessitate multidisciplinary teams such as the UK NMO service (<http://www.nmouk.nhs.uk>). The neurologist is ideally supported by specialist nurses, physiotherapist, occupational therapist, urologist, ophthalmologist/orthoptist, dietician and psychologist in providing holistic care.

Capturing changes in self-reported health status as part of trial outcomes or evaluation of services is important and the first patient-reported outcome measure for NMOSD has recently been published [120].

Conclusion

This article has highlighted many of the recent advances in the rapidly evolving field of NMOSD. In just over a decade unprecedented collaboration between basic scientists, immunologists, clinical neurologists, clinical trialists and pharmaceutical industries, funding organisations and governmental agencies has led to this remarkable progress. A special mention has to be made about the central role played by the Guthy-Jackson Charitable Foundation (<http://www.guthyjacksonfoundation.org>) in facilitating and accelerating this change, particularly in engendering collaborations across the globe.

We look forward to the outcomes of prospective, placebo-controlled and head-to-head trials, which should usher in a new era of evidence-based treatment. Exciting as that is, the hefty price tags that seem to universally accompany new monoclonal antibody drugs is evoking anxiety amongst clinicians, patients and the governmental and insurance agencies that fund healthcare globally.

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Compliance with ethical standards

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