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Update on Neuromyelitis Optica Spectrum Disorder

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Abstract

Purpose of review.—Neuromyelitis optica spectrum disorder is an autoimmune disease that caused optic neuritis and transverse myelitis. Attacks can cause severe neurological damage leading the blindness and paralysis. Understanding of the immunopathogenesis of this disease has led to major breakthroughs in diagnosis and treatment. In the past 18 months, three successful phase 3 clinical trials have been published using targeted approaches to preventing relapses.

Recent findings.—Updates in epidemiology, imaging, quality of life and treatment for acute relapse and prevention have been published in the past 18 months. Epidemiology studies are distinguishing patients based on their antigen specificity for aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG), which are increasingly recognized as separate immunological conditions. Imaging by MRI and optical coherence tomography continue to be developed as tools to distinguish NMOSD from other diseases. This is especially relevant as the recent clinical trials showed differences in response between AQP4 seropositive and seronegative patients. The three drugs that were tested for prevention of NMOSD relapses were eculizumab, inebilizumab and satralizumab. All of the trials were worldwide, placebo-controlled, double-masked studies that demonstrated a clear benefit with each approach.

Summary.—Recent research in NMOSD has resulted in improved diagnosis and approved treatments.

Keywords

neuromyelitis optica spectrum disorders; Devic's disease; optic neuritis; transverse myelitis

Introduction

Neuromyelitis optica spectrum disorder is an autoimmune disease against the aquaporin-4 (AQP4) water channel of astrocytes primarily in the optic nerves and spinal cord leading to

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blindness and paralysis.¹ NMOSD attacks often cause permanent neurological damage with accrual of morbidity with each relapse.² Since the discovery in 2005 of the AQP4-Ab biomarker associated with 70-80% of cases,³ NMOSD can be reliably distinguished from multiple sclerosis and related demyelinating diseases. New clinical criteria for NMOSD based on AQP4-Ab serostatus has improved diagnostic accuracy and reduced the delay in diagnosis⁴

Research on the immunopathogenesis has led to animal models of the disease shedding light on the roles of the adaptive and innate immune responses to aquaporin-4.⁵ Based on these models, five phase-3 clinical trials have been conducted on specific druggable targets including B cells, interleukin-6 and the complement system to prevent relapses. This review covers these recent trial results as well as updates in epidemiology/risk factors, radiology, quality of life and acute treatment of NMO relapses that have been published in the last 18 months.

Epidemiology and Risk Factors.

Estimates of NMOSD prevalence vary based on disease definition. Prior calculations relied on criteria created in 2006,⁶ which required both clinical optic neuritis and transverse myelitis. However, updated 2015 criteria require only 1 of 6 core clinical features along with AQP4-Ab positivity, or 2 clinical features if AQP4-Ab seronegative.⁴ Several recent studies have found the prevalence of NMOSD using 2015 criteria to be approximately 1.5 fold higher than with 2006 criteria,⁷⁻⁹ estimated to be between 0.7 and 10/100,000 persons across most populations around the world.⁷⁻¹²

Among demyelinating diseases, there is an increased prevalence of NMOSD in those with Asian^{8,12} or African¹⁰ ancestry, and a lower prevalence in those with European ancestry.^{10,12} However, variance based on geographic location (as seen in multiple sclerosis) remains unclear.⁸ This may be in part due to lack of data from low resource countries without access to imaging equipment or antibody testing. A survey of providers showed nearly half of African and Eastern Mediterranean countries lacked access to AQP4-Ab and MOG-Ab testing, and only 15% of World Health Organization defined low-income countries had access to these tests.¹³

Higher prevalence of NMOSD is consistently found in women, with a female to male ratio up to 9:1. Average age of onset is between 30-40 years old.^{8,14,15} Additionally, low body mass index (BMI) has been associated with a higher risk of seropositive NMOSD among women in China.¹⁶

The environmental risk factors for NMOSD remain unclear, though there may be increased risk with low fruit and vegetable consumption, low physical activity, smoking, and low levels of vitamin D.¹⁷ Clustering of NMOSD has also been seen in families. A recent whole-genome sequence study identified genetic variants that may be linked to NMOSD including a structural variation in C4a and C4b complement copy numbers similar to variants in lupus patients.¹⁸ Finally, it remains well-established that those with existing autoimmune conditions, such as lupus, myasthenia gravis, and Sjogren's Syndrome, are at higher risk of developing NMOSD.¹⁵

Imaging.

Typical MRI lesion patterns seen in NMOSD include long corticospinal tract lesions (>3 or more contiguous vertebral segments), diencephalon and dorsal brainstem lesions adjacent to the third and fourth ventricles (specifically in the area postrema of the medulla), longitudinally extensively enhancing optic nerve lesions and deep white matter lesions in the brain. Enhancement patterns in the brain are often subtle and ill-defined.¹⁹ However, as many as 50% of NMO patients have non-specific T2 white matter brain lesions and greater than 30% meet McDonald criteria for MS.²⁰ Emerging evidence suggests that a combination of typical NMOSD lesions with lesions in high AQP4 receptor expressing brain regions may be more specific in differentiating NMOSD from MS.²¹

Characteristic clinical and imaging features of optic neuritis (ON) are also seen in NMOSD. NMOSD patients are more likely to have bilateral optic neuritis or posterior involvement of the optic chiasm and optic tracts, as compared to patients with MS.²² However, MS patients may have more widespread demyelination in the posterior visual pathways such as the optic radiations,²³ and are more likely to have recurrent episodes of ON affecting the same eye.²⁴ On optical coherence tomography (OCT), more severe peripapillary retinal nerve fiber layer (pRNFL) thinning is seen in NMOSD-ON compared to MS-ON^{23,25} or idiopathic ON.²⁶ RNFL thinning may be seen specifically with ongoing disease activity.²⁷ While patients with NMOSD demonstrate prolonged latency on visual evoked potentials (VEP), severe latency delays are more common in MS.^{23,25}

FDG-PET avid lesions have classically been associated with alternative diagnoses, such as CNS lymphoma, but a striking example of FDG-uptake has been seen in an acute spinal cord lesion in NMOSD consistent with very active inflammatory activity within the lesion.²⁸

Quality of life.

Patients with NMOSD, especially those with seronegative status, report a lower than average quality of life.^{29,30,31} Pain may primarily drive reported low quality of life as measured by EQ-5D score.²⁹ Between 80-100% of NMOSD patients report chronic pain, including: neuropathic pain, pain attacks, or headache.^{31,32} Patients report that their pain interferes with work and relationships, and that they are unable to obtain relief despite treatment.^{31,32} Other symptoms shown to negatively impact quality of life in NMOSD include reduced mobility, anxiety, depression, bowel/bladder dysfunction, visual impairment,³³ and sexual dysfunction.³⁴ Dysautonomia is also experienced in NMOSD and is often more severe than in MS.³⁵ Finally, many patients with NMOSD report a high financial burden of disease largely secondary to cost of medications, travel and hospital visits.³⁰

Acute treatment of relapses.

Historically, first-line therapy for NMOSD has mirrored acute treatment for MS attacks with intravenous methylprednisolone (IVMP) 1g for 2-7 consecutive days. However, the use of IVMP as a sole treatment for relapses rarely achieves recovery back to baseline; most cases require escalated treatment with plasma exchange. According to the 2016 American Society of Apheresis clinical guidelines,³⁶ plasma exchange (PLEX) is considered a second-line therapy for acute NMOSD. PLEX and immune adsorption have been shown to be equally

efficacious and safe for treatment of MS and NMOSD in several studies.^{37,38} These treatments have been shown to reduce disability and improve visual acuity when used both as an initial treatment or in patients who did not respond to IVMP alone.³⁸⁻⁴⁰

Only recently have IVMP and PLEX begun to be compared directly. A 2016 study showed improved disability outcomes in patients with NMOSD if they received PLEX and IVMP versus IVMP alone.⁴¹ However, a recent randomized control trial of 11 patients comparing IVMP+PLEX at presentation to IVMP monotherapy at presentation with subsequent addition of PLEX only if refractory to initial steroids did not show a difference in EDSS at 1, 3, or 6 months.³⁸ Despite this, there was a trend of faster recovery and better improvement in disability level in the IVMP+PLEX treatment group.⁴²

B-cell depleting therapies are being studied for use in the acute phase of NMOSD given evidence that B-cells may be overactivated during acute relapses.⁴³ An open-label phase 1b trial of five seropositive NMOSD subjects who received a single dose of ublituximab, an anti-CD20 monoclonal antibody in addition to IVMP, demonstrated improved EDSS scores after ninety days.⁴⁰ Two subjects did not achieve B-cell depletion and relapsed within 3 months.⁴⁰ The remaining three were stable at one year.⁴⁰ No clinical adverse events were noted, though one participant experienced transient leukopenia.⁴⁴

Outcomes.

A significant amount of research has been dedicated to predicting outcomes in NMOSD based on demographic, radiologic, or serologic markers.

While late-onset NMOSD, defined as onset later than 50 years of age does not appear to differ from typical NMOSD in regards to common demographic features including gender, race, or seropositivity,^{45,46} age of disease onset may affect disability outcomes. Older age was not affiliated with relapses or disability in one study,⁴⁶ but several others have shown a higher risk of disability with older age of disease onset.^{33,45,47,48} Younger patients may present with slightly more severe NMOSD attacks, but they show improved rates of recovery (average 85% recovery at age 20) compared with older patients (60% recovery at age 60).⁴⁹ In contrast, patients with onset of NMOSD in childhood may have worse outcomes. A recent study from Brazil, reported greater disability in patients with onset of NMOSD before age 12 and death in 14% of patients who presented before age 21.⁵⁰

In addition to a higher risk of developing NMOSD, Asian and African ancestry may also have a higher likelihood of attacks^{47,46,48} and higher rate of death⁵¹ compared with other patients. Women with NMOSD have a higher percentage of pregnancy loss than expected for age.⁵² Additional clinical factors that have been associated with increased relapse risk or worse disability include brainstem-onset attacks,^{47,53} longer length of myelitis lesions,^{33,54} optic neuritis at disease onset,⁵⁵ and severity of initial attack.^{45,49} There does not seem to be a correlation between outcomes and gadolinium enhancement of CNS lesions.⁵⁴

As far as serologic testing, the titer of AQP4-IgG has not been shown to correlate with disease severity or prognosis.⁵⁶ However, in comparison with MOG antibody disease, AQP4-Ab positive and double seronegative NMOSD correlate with worse disability.⁴⁵

Time to treatment also affects disability. In one retrospective study, patients who received acute treatment within less than 14 days of onset of a relapse were more likely to return to their baseline EDSS than those who started treatment greater than 14 days from symptom onset.⁴⁵ There was no statistical difference in post-treatment EDSS whether treatment was started within 3 days versus 14 days from symptom onset but there is a sense in the NMOSD community that earlier acute treatment leads to better outcomes.⁴⁹

Preventive treatment.

Disability in NMOSD patients is due to accrued damage from each relapse. Prevention of recurrent attacks is therefore essential. Recent trials have provided a new armamentarium of available treatment options to prevent attacks in NMOSD. Each therapy targets a component of the inflammatory pathway involved in the immunopathogenesis of disease. In brief, there is a break in immune tolerance to AQP4 leading to coordinated immunological attack of the optic nerves and spinal cord. It is unclear what triggers the upstream adaptive immune response by pathogenic T and B cells to mount an inflammatory response to AQP4 on astrocytes but molecular mimicry of AQP4 with the Clostridium ABC transporter has been proposed as a possible mechanism. Once the inflammatory attack is triggered, an innate immune response comprised of neutrophils, eosinophils, and the complement system are recruited to the lesion.

One may speculate as to whether seropositivity guides management. An international, multicenter, retrospective analysis found no difference in outcomes for NMOSD populations that were either seropositive or seronegative and treated with either rituximab or myophenolate mofetil.⁵⁷ In fact, each group regardless of serostatus demonstrated statistically significant reductions in annualized relapse rates with either treatment.⁵⁷ This argues that treatment efficacy may not be entirely based upon serostatus alone. However, based on the known immunopathogenic mechanisms of NMOSD versus other autoimmune CNS diseases, treatments targeting specific mechanisms, such as complement inhibition, may be more amenable in AQP4-seropositive cases.

Preventative agents that will be discussed in this section include: eculizumab, satralizumab, tocilizumab, inebilizumab, rituximab and a brief mention of several others. Please note, disease-modifying drugs for MS have been shown to cause poor outcomes when used for NMOSD patients and should be avoided.⁵⁸

Eculizumab is a monoclonal antibody that inhibits complement C5 protein, thereby preventing division of C5 into pro-inflammatory C5a and C5b proteins. Its efficacy was demonstrated by the PREVENT trial in which seropositive, adult NMOSD patients received eculizumab or placebo, in addition to continued concurrent immunosuppressive regimen (excluding: mitoxantrone or rituximab in prior three months, IVIG in prior 3 weeks, prednisone greater than 20 mg per day).⁵⁹ The treatment group demonstrated a reduced relapse risk of 94% compared to placebo, with 98% of patients achieving remission at 1 year.⁵⁹ Eculizumab infusions can cause headaches and upper respiratory tract infections but risks of severe infections due to encapsulated organisms such as *Neisseria meningococcus* were mitigated by mandatory vaccination.⁵⁹

Satralizumab and tocilizumab are humanized monoclonal antibodies against the interleukin-6 (IL-6) receptor. IL-6 is among the pro-inflammatory cytokines implicated in disease pathogenesis, as supported by increased serum and CSF IL-6 levels in patients with active NMOSD.^{60,61} A phase 3 randomized, double-blinded, placebo-controlled trial of satralizumab versus placebo added to a stable regimen of either azathioprine or mycophenolate mofetil plus glucocorticoids evaluated the efficacy of satralizumab in both seropositive and seronegative patients.⁶² Seropositive treatment group patients demonstrated a 79% reduction in risk of relapse compared to seropositive patients who received placebo.⁶² Seronegative treatment group patients did not demonstrate a meaningful benefit compared to the placebo seronegative group.⁶² Adverse effects in the treatment and placebo group, regardless of serostatus, were of equal percentages.⁶²

Efficacy of tocilizumab for adult patients with active NMOSD was demonstrated by a Chinese multicenter, randomized, head-to-head comparison trial of tocilizumab versus azathioprine (TANGO trial). In an intention-to-treat analysis, the tocilizumab treatment group demonstrated a statistically significant reduction in relapse risk as compared to the azathioprine treatment group without a significant difference in percentage of attributable adverse effects.⁶³ Tocilizumab treated patients also showed a decrease in serum anti-AQP4 IgG titers.⁶³ Further sub-group analyses however demonstrated statistical significant reduction in relapse risk for seropositive patients and not seronegatives.⁶³ It is speculated that perhaps a reduction was not shown in the seronegative sub-group due to small seronegative small size.

Monoclonal antibodies against B cell populations continue to emerge as therapeutic options for demyelinating disease, inclusive of NMOSD. Inebilizumab, an anti-CD19+ monoclonal antibody, was compared against placebo in the N-MOMentum trial. Participants were randomly allocated to inebilizumab (n=174) monotherapy or placebo (n=56) with primary endpoint of time to first NMOSD attack within the 6-months duration of the trial.⁶⁴ The inebilizumab treatment group demonstrated a 73% reduction in risk of relapse compared to placebo with a number needed to treat (NNT) of 3.73.⁶⁴ This therapeutic benefit could not be confirmed among seronegative patients as data interpretation for seronegatives was limited due to low number.⁶⁴ Inebilizumab was shown to cause a transient neutropenia and decreased IgG levels,⁶⁴ as expected given its mechanism.

Rituximab, a chimeric monoclonal antibody that selectively targets CD20+ B cells was compared against placebo in the Japanese RIN-1 study to evaluate its efficacy and safety for preventing relapses among seropositive NMOSD patients.⁶⁵ Participants were permitted to continue an oral prednisone regimen of 5-30mg/day.⁶⁵ No relapses were reported for the rituximab treated group (total n=19), compared with 37% in the placebo group (total n=19), strongly supporting its efficacy.⁶⁵ The standard dosing interval of rituximab is every 6 months; however, recent studies argue that monitoring of B-cell populations, particularly CD19+CD27+ memory B cells may be sufficient to determine redosing intervals.^{66,67} Long-term use of depleting B-cell therapy such as rituximab leads to increased risk of hypogammaglobulinemia and associated infectious risks.⁶⁸ Due to this, measurements of immunoglobulin levels pre-treatment and at least once yearly during treatment are recommended.⁶⁸

Data pertaining to safety of immunosuppression use during pregnancy is limited. NMOSD, unlike multiple sclerosis, does not remit during pregnancy, but rather, is often more active with increased relapse risk during gestation and the postpartum period. Shared decision-making between the patient and provider regarding benefits of continued therapy versus potential risks is crucial. Case reports of continued use of rituximab during pregnancy in NMOSD patients suggest it is safe to continue.^{69,70} Reassuringly, positive outcomes in both the treated pregnant patients and their children were reported.^{69,70} A transient decrease in CD19+ B cells was reported in the newborn of a rituximab-treated NMOSD pregnant patient; however, the child's counts normalized by age 6 months without any complications.⁷⁰

Standard immunosuppressants such as azathioprine, mycophenolate mofetil and tacrolimus are also commonly used for treatment of NMOSD. Retrospective observational analyses have shown azathioprine to reduce relapse rate, and both azathioprine and mycophenolate mofetil to each slow disease progression as measured by EDSS.^{48,71} A retrospective review of NMOSD patients treated with tacrolimus and prednisone found a reduction in annualized relapse rate after one year in both seropositive and seronegative patients.⁷² A decrease in EDSS after two years was reported in treated seropositive NMOSD patients.⁷²

Other novel therapeutics warrant further investigation to support their use for prevention of NMOSD relapses. Autologous nonmyeloablative hematopoietic stem cell transplantation (HSCT) has somewhat recently been studied for treatment of NMOSD.⁷³ In an open-label cohort study, 11 seropositive and 1 seronegative NMOSD patients underwent autologous nonmyeloablative HSCT.⁷³ In this study, 80% of participants were relapse free off immunosuppression with improved EDSS and seronegative status 5 years post-HSCT.⁷³ However, one young woman in the cohort died as a result of the severe chemotherapy regimen required for transplantation. Recent Class IV evidence from a small open-label, add-on pilot study suggests that addition of daily cetirizine 10mg to an accepted immunosuppressive regimen may reduce annualized relapse rates in seropositive NMOSD patients.⁷⁴ Further investigations with larger sample size are warranted to reproduce this finding and clarify the utility of cetirizine as an add-on therapy.

Conclusions

The last two years have seen a significant improvement in understanding about NMOSD, specifically in the areas of genetics, optical coherence tomography and quality of life. But the most important highlights have been in the areas of preventive treatment with the publication of three worldwide, placebo controlled trials which have led to approved treatments, including eculizumab, satralizumab and inebilizumab.

There are areas of unmet need that have yet to make progress in NMOSD. Most importantly, patients who are disabled from relapses and have impaired quality of life due to blindness, paralysis and pain need therapies for regeneration, restoration of function and improvement in pain management.

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Key Points:

- The prevalence of neuromyelitis optica spectrum disorder is approximately 0.4 – 4.0 persons per 100,000 in most populations worldwide.
- Eculizumab proved beneficial in reducing the risk of relapse by 94% compared to controls and has been approved for use in neuromyelitis optica spectrum disorder.
- Inebilizumab and satralizumab also demonstrated significant benefits in preventing relapses in neuromyelitis optica spectrum disorder.