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NEUROLOGICAL UPDATE

Contemporary management challenges in seropositive NMOSD

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Abstract
Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory disorder of the central nervous system that presents unique management challenges. Neurologic disability in NMOSD is directly linked to acute attacks, therefore, relapse prevention is an overarching goal of care. To this end, identifying effective biomarkers that predict relapse onset and severity is of critical importance. As treatment becomes more precision-based and patient-centred, clinicians will need to be familiar with managing circumstances of particular vulnerability for patients with NMOSD, including infection, pregnancy, and the post-partum phase. The discovery of the pathogenic aquaporin-4 Immunoglobulin G (AQP4 IgG) autoantibody almost 20 years ago ultimately distinguished NMOSD as an autoimmune astrocytopathy and helped spearhead recent therapeutic advancements. Targeted therapies, including eculizumab, satralizumab, and inebilizumab, approved for use in aquaporin-4 immunoglobulin G (AQP4 IgG) seropositive patients with NMOSD will likely improve outcomes, but there are formidable costs involved. Importantly, seronegative patients continue to have limited therapeutic options. Moving forward, areas of research exploration should include relapse prevention, restorative therapies, and initiatives that promote equitable access to approved therapies for all people living with NMOSD.

Keywords Neuromyelitis optica spectrum disorders (NMOSD) · Autoimmune astrocytopathy · Aquaporin-4 IgG (AQP4 IgG)

Overview

Neuromyelitis Optica Spectrum Disorders (NMOSD) was once considered a severe form of multiple sclerosis (MS) affecting the optic nerves and spinal cord [1]. The discovery of aquaporin-4 [AQP4–immunoglobulin G (IgG)], a pathogenic antibody targeting a water channel expressed on the end-feet of astrocytes, has helped to distinguish seropositive NMOSD as an autoimmune astrocytopathy. As such, NMOSD is distinct from MS, with separate diagnostic criteria (Table 1) [1–3]. NMOSD predominantly affects middle-aged women (mean age of symptom onset is 40 years; female to male ratio is approximately 9:1), and prevalence rates are higher in individuals of Afro-Caribbean and Asian descent [1, 2, 4–8]. Recurrent attacks are the key driver of neurological impairment [7, 8]. Recognition of factors known to affect relapse frequency and prognosis (Table 2) is germane to optimizing care, as is employing effective acute and long-term treatment strategies.

Acute relapse management

The most common approach to acute relapse management is immediate initiation of high-dose corticosteroids (intravenous methylprednisolone 1000 mg daily for 3–5 days), with a slow taper (i.e., oral prednisone starting at 1 mg/kg/d with a reduction of 5 mg every 2 weeks) to ameliorate neurological impairment [1, 9–16]. Yet, studies have shown that long-term outcomes from NMOSD relapses may correlate more robustly with the severity of attacks at presentation than treatment timing (within 14 days from symptom onset or later) [13]. Unfortunately, for a sizable proportion of patients, corticosteroids are not sufficient, and another immunotherapy must be quickly instituted. By convention, plasma exchange (PE)

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Table 1 NMOSD diagnostic criteria for adult patients (Modified from Table 1, Ref. [6])

Diagnostic criteria for AQP4 IgG positive NMOSD	Diagnostic criteria for AQP4 IgG negative NMOSD
1. At least 1 core clinical feature [optic neuritis (ON), transverse myelitis (TM), area postrema syndrome (APS), acute brainstem syndrome, symptomatic narcolepsy/diencephalon syndrome with typical MRI lesions, symptomatic cerebral syndrome with typical MRI lesions]	1. At least 2 core clinical features caused by 1 or more clinical attacks meeting these requirements: at least 1 core feature must be ON, acute TM with LETM, or APS; dissemination in space (2 or more core features); meeting MRI requirements
2. Positive serum AQP4 IgG	2. Negative serum AQP4 IgG (or testing not available)
3. Exclude alternative diagnoses	3. Exclude alternative diagnoses

Additional MRI requirements for NMOSD without AQP4-IgG or having unknown AQP4-IgG status include: (1) Acute ON: This requires brain MRI showing normal findings or non-specific white matter signal changes, OR optic nerve T2-hyperintense lesion or T1-weighted gadolinium enhancing lesion extending over 50% of the optic nerve length or involving the optic chiasm; Acute TM requires associated intramedullary MRI lesion extending across 3 or more contiguous segments (LETM) OR 3 or more contiguous segments of focal spinal cord atrophy in patients with a history compatible with acute TM; APS requires associated dorsal medulla/area postrema lesions; Acute brainstem syndrome requires associated periependymal brainstem lesions

Table 2 Factors known to increase the risk, severity, and recovery of NMOSD relapses [1, 7, 8]

Factors associated with increased relapse risk	Factors associated with worse relapse severity	Factors associated with poor prognosis
Female sex	Age > 50 years	Age > 50 years
Caucasian and African descent	African descent	African descent
Third trimester of pregnancy	Previous severe relapse	Infection
Postpartum period	Infection	Late pregnancy/postpartum period
Seropositive AQP4 IgG status	Late pregnancy/postpartum period	Severity of previous relapse
Recent attack	High AQP4 IgG titre	Myelitis
Painful tonic spasms	Elevated serum NFL and GFAP levels	Motor symptoms at onset
Elevated serum GFAP	Medullary lesions	Recurrent myelitis within 1 year
Extensive LETM	LETM	Medullary lesions
Brain MRI enhancement	Spinal cord atrophy	Long spinal cord lesions
Medullary lesions	Markers of neuroaxonal injury (reduced spinal cord cross sectional measures and reduced retinal nerve fiber layer measures with OCT)	Spinal cord atrophy

AQP4 IgG aquaporin 4 IgG, *GFAP* glial fibrillary acidic protein, *LETM* longitudinal transverse myelitis, *MRI* magnetic resonance imaging, *NFL* neurofilament light chain, *OCT* optical coherence tomography

and immunoadsorption (IA) are considerations, since these treatments rapidly remove serum autoantibodies, complement, and pro-inflammatory cytokines [1, 14–16]. There is uncertainty, however, about exactly when these adjunctive therapies should be started for acute relapse management. A systematic review of 561 records and 8 observational studies (including 228 NMOSD patients) showed that the mean time to the initiation of PE was 11 days, with improved EDSS scores noted 8–23 days after starting therapy [17]. In a retrospective study of 207 NMOSD interventions by Kleiter et al. [11], 40% of patients had complete relapse remission when they initiated apheresis therapy within 2 days of symptom onset. A stepwise decline in recovery occurred if PE or IA was offered three or more weeks after symptoms began [11]. Current data regarding the efficacy of IVIG therapy in NMOSD relapse management is sparse. Several small studies and retrospective analyses have failed to show robust results with IVIg as rescue treatment. Li et al. [18] evaluated 243 attacks in 198 NMOSD patients: 153 attacks were treated with high-dose steroids, 14 attacks were treated with IVIg, and the remaining events were treated with a mix of therapies. The proportion of patients with better outcomes was significantly lower for patients treated with IVIg monotherapy [18]. Elsone et al. [19] reported that less than half of patients treated acutely with IVIg for NMOSD attacks improved. Rituximab is not considered an acute treatment for NMOSD relapses since it requires induction over a 2–4 weeks (depending on the dosing regimen used) [20]. Yet, rituximab may be used if all other options have failed, although the evidence of its utility a rescue medication is unclear. For more refractory cases, use of other immunosuppressive agents may need to be considered, such as cyclophosphamide [1, 21].

Long-term management: precision versus personalized medicine

The primary goal of long-term immunosuppressive therapies is to reduce relapse-related disability among people living with NMOSD. Until recently, numerous off-label immunosuppressive agents have been used, with rituximab

showing the most encouraging results [1, 22–24]. A meta-analysis of 25 studies using rituximab in NMOSD patients (not restricted by serostatus) demonstrated mean reductions of 0.79 in relapses and 0.64 points on Expanded Disability Status Scale (EDSS) scores [22]. Gao et al. showed that 63% of rituximab-treated patients (seronegative and seropositive) achieved a relapse free state [23]. Rituximab and mycophenolate mofetil have demonstrated superior efficacy to azathioprine in annualized relapse rate reduction (97.9% and 90.2% vs. 72.1%, respectively) with lower failure rates [24].

Recently, four randomised controlled trials demonstrated the efficacy of three new targeted therapies for NMOSD, namely eculizumab, satralizumab, and inebilizumab. These studies varied with respect to relapse-definition, use of other immune therapies, and AQP4 IgG serostatus, yet all showed robust benefits in preventing relapses [1, 25–29]. Notably, these targeted therapies are currently approved only for aquaporin-4 positive NMOSD patients [1, 25–29].

The PREVENT phase III randomized add-on placebo-controlled trial showed marked benefit with eculizumab, a C5 inhibitor, in AQP-4 seropositive patients [1, 25, 26]. Patients in this multicentre international trial were allowed to maintain use of most immunosuppressive medications with eculizumab or placebo. While 43% (20/47) placebo/control patients relapsed, only 3% of participants in the eculizumab arm (3/96) experienced attacks, for an adjudicated relapse risk (ARR) of 94% (hazard ratio [HR] 0.06, 95% CI 0.02–0.20; $p < 0.001$) [25, 26]. The benefits of eculizumab treatment were sustained at 48 weeks (98% relapse-free in the treatment group versus 63% in the control group) and at 96 weeks (96% relapse-free in the treatment group versus 52% in the control group) [1, 25, 26]. One major advantage of eculizumab includes its rapid onset of action, while another is that regular laboratory monitoring (needed for B-cell targeted therapy) is not required [1, 25]. Yet, the dosing schedule of infusions every 2 weeks may be challenging for some, and the high cost is prohibitive for many people living with NMOSD [1, 25]. The drug is currently priced at approximately $710,000 USD (approximately four 300 mg vials every 2 weeks at $6830 per vial) per year [1, 25].

Satralizumab, a monoclonal antibody that blocks the IL-6 receptor, has been trialed in two international phase 3 studies [1, 25, 27, 28]. The SAkuraSky study (satralizumab added on to existing immunotherapy) showed a 62% reduction in ARR (HR 0.38, 95% CI 0.16–0.88; $p = 0.02$) for treated participants versus controls [28]. The proportion of treated participants who remained relapse-free was 89% (36/41) at 48 weeks [versus 66% (28/42) for the control group] and 78% (31/41) at 96 weeks [versus 59% of (25/42) for the control group] [28]. In the SAkuraStar study (satralizumab alone versus placebo alone), 30% (19/63) of participants in the satralizumab treatment arm relapsed compared with 50% (16/32) of controls, providing a 55% reduction in adjudicated relapse risk (HR 0.45, 95% CI 0.23–0.89; $p = 0{\cdot}018$) [27]. Seventy six percent of participants using satralizumab were relapse free (48/63) versus 62% of (20/32) for the control group, at 48 weeks. Furthermore, 72% (45/63) of treated participants versus 50% (16/32) of control subjects remained relapse free at 96 weeks [27]. Relative to eculizumab, the onset of action of satralizumab is somewhat slower [25]. Advantages of satralizumab include its subcutaneous self-administered route, and safety profile with other immunotherapies [25]. It is currently priced at approximately $219,231 USD for the first year, and $190,000 USD yearly thereafter [25].

Inebilizumab is a monoclonal antibody that targets the B-lymphocyte antigen CD19 [25]. Akin to rituximab, this agent depletes B cells and removes B cell precursors from the circulation [25]. In the NMomentum study (no background immunotherapy), 12% (21/174) of inebilizumab-treated participants relapsed compared with 39% (22/56) in the control arm, resulting in a 73% reduction in adjudicated relapse risk (HR 0.27; 95% CI 0.15–0.50; $p < 0{\cdot}001$) [25, 29]. Inebilizumab eliminates plasmablasts and B cells, thus reducing immunosurveillance activity and potentially rendering patients more vulnerable to developing certain cancers and infections (e.g., progressive multifocal leukoencephalopathy) similar to ocrelizumab [1, 25]. The treatment schedule for inebilizumab mirrors that of rituximab (two infusions at induction two weeks apart, followed by two infusions per year) [25]. The cost of inebilizumab for the first year of treatment is approximately $393,000 USD for three infusions (two loading doses, followed by a single 300 mg dose 6 months later) and $262,000 USD per year, for two yearly doses [25]. In contrast, rituximab and biosimilars are relatively modestly priced: $19,452 USD for two 6-month infusions per year) [30].

As the armamentarium of targeted NMOSD treatments increases, so too will be the need to establish optimal sequencing strategies and ensure affordable care. To this end, autologous hematopoietic stem cell bone marrow transplantation therapy (AHSCT) as an immune-reconstitution strategy may play a role [31]. Theoretically, halting relapses in NMOSD could stop disease. Small trials employing AHSCT have shown mixed findings, with some studies showing relapse abrogation, and others failing to do so. Regimen selection may have much to do with these outcomes, as use of adjuvant B-cell therapies (such as rituximab) appear to result in better outcomes [31, 32]. Immune reconstitution therapies provide long-term efficacy, with minimal risk for opportunistic infections and malignancy [1, 31, 32]. Importantly, AHSCT is considerably more affordable than the newer targeted NMOSD therapies: the cost of AHSCT has been estimated to be less than $4700 per quality-adjusted life year in MS patients [32]. Yet, there are inherent short-term and long-term risks associated with AHSCT, including a

loss of fertility and future risk of myelofibrosis [33]. In time, NMOSD immunosuppressive therapies may be selected with a view to controlling the complement system (eculizumab), transitioning to immunomodulation (satralizumab), and providing longer term immunosuppression (inebilizumab), in a manner that is tailored to the needs of the patient [31]. A key step towards precision medicine for people living with NMOSD will be the development of better biomarkers and utilization of patient reported outcome measures (PROMs) to capture relevant information about a person's health [34].

Predicting relapses: the need for biomarkers

A NMOSD relapse has been aptly characterized as a "neuro-immunological stroke" [35], with a poor prognosis for recovery. Prior to the era of targeted therapies, 41% of AQP4 + NMOSD patients became legally blind, and 22% required a walker within 5 years of disease onset [1, 35–37]. Developing biomarkers that facilitate diagnosis, predict relapses, and prognosticate recovery is paramount, because these tools may help tailor treatment strategies for people living with NMOSD [1]. From a diagnostic perspective, approximately 75% of patients are seropositive for AQP4 IgG [1]. Yet, serum AQP4 IgG titres may not predict long-term disease course or response to therapy, potentially limiting the use of this biomarker beyond the diagnostic phase [1, 38–43]. Jitprapaikulsan et al. [38] studied 336 serial serum specimens from 82 AQP4-lgG–seropositive patients. NMOSD activity at blood draw was defined as preattack (7.1%, drawn within 30 days preceding an attack), attack (32.1%, drawn at attack onset or within 30 days after), or remission (59.2%, drawn > 90 days after attack onset and > 30 days preceding a relapse). There was no significant difference in the estimated mean AQP4-IgG titers between these three phases of disease ($p = 0.21$) [38].

Serum neurofilament light chain (sNFL), a scaffolding protein in the neuronal cytoskeleton, has shown promise in detecting relapses [44]. As a biomarker, sNfL may be useful in quantifying relapse severity, however sNfL levels do not necessarily differ between patients with NMOSD, MS, or myelin oligodendrocyte glycoprotein antibody disease (MOGAD) [45–48].

Glial fibrillary acidic protein (GFAP) is a principal intermediate filament that forms the astrocyte cytoskeleton. Higher CSF and serum GFAP levels have been reported during NMOSD attacks, which may implicate a role in relapse prediction [6, 46–50]. Moreover, GFAP levels typically increase before the development of clinical relapse symptoms and may remain elevated in the early remission phase [49]. Serum GFAP may also serve as a diagnostic indicator of NMOSD, as GFAP levels are significantly higher in patients with NMOSD as compared to those in healthy controls [46]. GFAP coupled with sNFL and other diagnostic markers such as MRI may prove to be optimal in both diagnosing and monitoring disease and response to treatment.

Magnetic resonance imaging (MRI) criteria are useful in the diagnosis NMOSD, particularly in seronegative cases (Table 1). The so-called gold standard for relapse definition is met when clinical findings are accompanied by evidence of a new or enhancing MRI lesion [1, 7, 51, 52]. The length of optic nerve and spinal cord lesions may also help prognosticate recovery after optic neuritis and transverse myelitis attacks, respectively, since longer lesions correlate with worse functional outcomes [1, 51].

NMOSD: special circumstances

COVID-19 and NMOSD

The COVID-19 pandemic has significantly impacted the care of patients with autoimmune disorders, particularly those using immunomodulatory therapies; NMOSD is no exception. As of June 2021, there were 77 patients with NMOSD reported in the COViMS (COVID-19 Infections in MS and Related Diseases) Registry [53]. At the time of COVID-19 diagnosis, 62% of NMOSD patients were using rituximab, and 60% had harboured a comorbidity that could contribute to severe outcomes. Sixteen percent of patients with NMOSD and COVID infections were hospitalized, 9% required intensive care, and 10% died [53]. It is noteworthy that patients with NMOSD who harboured a co-existing diagnosis such as diabetes, hypertension, or obesity were 6 times more likely to have a poor clinical COVID-19 related outcome compared their counterparts without these comorbidities (OR = 6.0, 95% CI 1.79–19.98) [53]. These findings highlight the importance of optimizing overall medical management for people living with NMOSD. In the REDONE. br (Brazilian Registry of Neurological Diseases) platform disease modifying therapies and comorbidities did not predict worse outcomes from COVID-19 related infection, yet people with NMOSD had a higher frequency of hospitalizations (but not death) relative to the general Brazilian population [54]. During the pandemic, registries have shown that use of rituximab and corticosteroids are factors associated with slightly greater odds of hospitalization, intensive care admissions, and ventilation requirements among patients with MS [55, 56], and these findings may be extendable to patients with NMOSD. Notably, there have been cases of COVID-19 related infection potentially precipitating NMOSD disease-onset [57, 58]; infections are known to be a relapse-related risk factor in NMOSD [1, 7, 8, 60]. Vaccinations have also been reported to precede NMOSD attacks [59, 60] . In the balance, when one considers the risks of

infection related relapses, discontinuing immunosuppressive treatment likely poses greater risks than benefits to people living with NMOSD.

Pregnancy and lactation for people living with NMOSD

Pregnancy offers potential benefits to MS related disease activity but, unfortunately, the same cannot be said for NMOSD [60]. In fact, pregnancy and the post-partum period are factors known to increase relapse risk (Table 2) [1, 7, 8, 60]. Specifically, patients with AQP4 IgG positive NMOSD are at considerable risk of pregnancy associated complications, particularly if pre-pregnancy disease activity is high and immunosuppressive therapy is not utilized [61–63]. From the standpoint of general management, pregnancy outcomes in NMOSD may be impacted by factors such as maternal age, concomitant diagnoses, and medication use. Spontaneous abortion and miscarriage are increased in the NMOSD patient population [61, 62]. There may also be a higher risk of pre-eclampsia and posterior reversible encephalopathy syndrome due to osmotic changes associated with AQP4 activity [64]. Several immunopathological factors may render patients with NMOSD more vulnerable during pregnancy and the post-partum period: AQP4 is expressed on placental syncytiotrophoblasts (highest during mid-gestation) [65]; IL-6 activity and secondary plasmablast survival increases during the intrapartum period [63]; and, higher estrogen levels promote B-cell activating factor [63]. Collongues et al. [66] studied a retrospective cohort of NMOSD patients and reported a rebound in the annualized relapse rate during the first postpartum trimester that was higher than the pre-pregnancy period in AQP4 IgG antibody positive patients. These findings highlight the need to optimize the utility and safety of immunotherapy during pregnancy and lactation periods. During the intrapartum period, patients can safely be given high-dose non-fluorinated corticosteroids [67], plasmapheresis, and even IVIg for acute attacks. Ongoing maintenance therapy with azathioprine with or without corticosteroids does not appear to have a significant impact on neonatal outcomes and is not appreciably detected in breast milk [68]. Given their teratogenic potential, mycophenolate mofetil and methotrexate are contraindicated in pregnancy [1, 63]. Notably, the use of monoclonal therapies, including rituximab, poses potential challenges. Das et al. [69] studied outcomes after rituximab exposure in a systemic review of 102 pregnancies. When checked, B-cell counts were low in 39% of newborns but normalized within 6 months without adverse clinical events [69]. Disease mitigation during pregnancy is an important factor in the decision to continue treatment, with careful monitoring in the post-natal phase. Krysko et al. [70] studied concentrations of rituximab in breast milk and found that levels were less than 0.4% (well below theoretically acceptable levels of less than 10%). Low oral bioavailability might also limit the absorption of rituximab in the newborn, suggesting that resumption of rituximab, if stopped during pregnancy should be reinstituted soon after delivery, even if the patient plans to breastfeed. Data are lacking with respect to the newer, targeted NMOSD therapies. Eculizumab treatment in patients with paroxysmal nocturnal hemoglobinuria and other non-NMOSD disorders does not seem to negatively impact pregnancy outcomes. Drug levels detected in umbilical cord blood have been insufficient to cause adverse outcomes [71]. Additionally, eculizumab has not been detected in breast milk samples from treated mothers [71]. Experiences with satralizumab will likely parallel those of tocilizumab, which appears to have a reasonable safety profile during pregnancy and lactation. Inebilizumab is mechanistically and pharmacologically very similar to rituximab and ocrelizumab, although there is limited drug-specific data. As our knowledge of the new treatments for NMOSD evolves, so too will our understanding of the management challenges associated with using these agents during pregnancy and the post-partum period.

Conclusions

Insights into the immuno-pathobiology of NMOSD have evolved over the past two decades, spearheading the discovery of new targeted therapies. Consequently, NMOSD has become more than just a diagnostic dilemma, and now presents significant management challenges. Moving forward, better biomarkers will be needed to optimize relapse-prevention and mitigate risks to patients with NMOSD. Future research efforts should focus on reparative strategies to ameliorate the effects of attack related disability. Finally, greater advocacy will be needed to ensure accessible and affordable care for all people living with NMOSD.

Declarations

Conflicts of interest The authors have no known conflicts of interest with the content of this paper.

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