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Neuromyelitis Optica Spectrum Disorders – from pathophysiology to treatment

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ABSTRACT
Neuromyelitis optica spectrum disorders (NMOSD) are a group of autoimmune diseases characterized by severe, inflammatory attacks predominantly affecting the optic nerves and spinal cord and central nervous system. NMOSD presents with clinical features such as optic neuritis, acute myelitis, and area postrema syndrome, making it a challenging condition to diagnose due to its varied clinical manifestations. Untreated, approximately 50% of NMOSD patients will be wheelchair users and blind, and a third will have died within 5 years of their first attack. Historically considered a variant of multiple sclerosis, NMOSD is now recognized as a distinct entity, largely due to the discovery of the pathogenic role of aquaporin-4 (AQP4) antibodies. Approximately 75% of patients have antibodies against aquaporin-4, a water channel expressed on astrocytes. These antibodies target astrocytes, leading to complement activation, inflammation, and subsequent damage to the central nervous system. Relapses are treated with high-dose steroids and plasma exchanges to prevent residual disability. Advances in understanding the pathophysiology of NMOSD have paved the way for targeted therapies, including monoclonal antibodies that inhibit complement activation, B-cell depletion strategies, and interventions targeting interleukin-6 signaling. Four preventive immunotherapies have now been approved for AQP4-IgG-positive NMOSD in many regions of the world: eculizumab, ravulizumab inebilizumab, and satralizumab. These treatments have significantly improved disease outcomes, offering hope for better management of NMOSD, although challenges remain in early diagnosis, treatment accessibility, and preventing relapses. Further research is essential to refine therapeutic approaches and explore novel targets to enhance patient care.

Keywords: Neuromyelitis Optica Spectrum Disorders, demyelinating disease, Aquaporin-4-antibody, immunosuppressive therapies, Acute treatment, Long-term management

1. Introduction

Neuromyelitis Optica Spectrum Disorders (NMOSD) are autoimmune conditions characterized by inflammatory involvement of the optic nerve, spinal cord, and central nervous system. These disorders involve severe axonal damage and demyelination in the Central Nervous System.[1] NMOSD presents with clinical features such as optic neuritis, acute myelitis, and area postrema syndrome, making it a challenging condition to diagnose due to its varied clinical manifestations.[2] Patients with NMOSD commonly experience recurrent attacks of optic neuritis and transverse myelitis, leading to severe disability.[3]

The presence of anti-aquaporin-4 antibodies (AQP4-abs) is diagnostically characteristic of NMOSD and its spectrum disorders.[4] However more recently another antigenic target, myelin oligodendrocyte glycoprotein (MOG) has been identified in patients with NMOSD.[5] The frequency of MOG-ab and AQP4-ab coexistence was exceptionally reported, suggesting that both have different immunopathogenic mechanisms.[6] AQP4-ab-positive NMOSD is characterized by AQP4 loss, dystrophic astrocytes, and absence of cortical demyelination.[7] By contrast, MOGAD pathology is characterized by the coexistence of perivenous and confluent primary demyelination with partial axonal preservation and reactive gliosis in the white and gray matter, with particular abundance of intracortical demyelinating lesions.[8] These findings, added to the clinical and radiological differences, clearly demonstrate that AQP4-ab-positive NMOSD and MOGAD are two different entities.[9] Currently, there is no known curative treatment for NMOSD.[10] NMOSD treatment is divided into treatment of acute episodes, individual symptom management, and long-term relapse prevention.[11] Consequently, the main target of therapy is to counteract acute attacks promptly and effectively and to prevent future attacks by initiating immunotherapy as soon as a definite diagnosis of NMOSD is established.[12]

We want to present a review about the Neuromyelitis Optica Spectrum Disorders, especially AQP4-ab-positive, from pathophysiology, clinical features, epidemiology, imaging findings to acute and long-term treatment with trials of new drugs for treating this condition.

2. Pathophysiology

NMOSD is an inflammatory disease that primarily affects the optic nerve and spinal cord; the brainstem, specifically the area postrema, can also be involved.[13] IgG antibodies against aquaporin-4 are noted in more than 60% to 90% (specificity 90%, sensitivity 70%-90%) of patients with NMOSD.[14] AQP4 is the most widely expressed water channel in the brain, spinal cord, and optic nerves. Within the brain, AQP4 is located in regions in contact with cerebrospinal fluid, and is specifically localized to the foot processes of astrocytes at the blood brain barrier.[15] AQP4 is also present in the collecting ducts of the kidney, parietal cells of the stomach, airways, secretory glands, and skeletal muscle.[16] However, these organs are relatively protected from antibody-mediated damage due to local complement inhibitors which are absent in the brain.[17]

The AQP4-IgG is an antibody from the G1 subclass, thus a competent complement activator. It is mainly produced in the periphery and enters the CNS through the blood-brain barrier, the capillaries of the circumventricular organs, the meninges, or the parenchymal blood vessels.[11] The binding of the AQP4 antibody to AQP4 protein on the surface of astrocytes results in various functional consequences including target internalization, impairment of AQP4 function, complement-mediated cytotoxicity and antibody dependent cell-mediated cytotoxicity (ADCC). Complement activation leads to the recruitment of activated macrophages, releasing cytokines and oxygen free radicals which leads to the destruction of neurons and oligodendrocytes.[18, 19] The astrocytic loss is the main histological finding, evidenced by the loss of aquaporin-4 and the astrocytic marker glial fibrillary acidic protein.[20] Depending on the severity of the tissue injury and the stage of the disease, it can be followed secondarily by the death of oligodendrocytes and neurons.[11, 21]

3. Epidemiology and risk factors

The prevalence range of NMOSD is 0.5–4/100,000 and may reach up to 10/100,000 in certain racial groups.[22] It depends on the studied population and geographic area but are higher in black and Asian populations compared with Caucasians.[23] Among demyelinating diseases, there is an increased prevalence of NMOSD in those with Asia or African ancestry, and a lower prevalence in those with European ancestry.[24, 25]

A US-based study showed that patients with African ancestry tend to have a higher mortality rate (15.4%) as compared to the overall mortality rate (7.0%).[26]

Neuromyelitis Optica Spectrum Disorder is more common in the female sex, with a ratio varying from 3:1 to 9:1. The female prevalence is especially significant in patients seropositive to AQP4-IgG. In contrast, this ratio decreases to near 1:1 in patients with NMOSD and MOG-IgG.[27] Average age of onset is between 30-40 years old.[28]

NMOSD can correlate with autoimmune diseases such as systemic lupus erythematosus (SLE), celiac disease, Sjögren syndrome, and sarcoidosis.[10]Moreover, the disease, particularly the MOG variant is seen in children and cases have been reported in the elderly as well.[13] NMOSD attacks have been shown to occur in 20% to 30% of cases after an environmental trigger, such as post-vaccination or infection.[29] To date, there is no evidence of a clear association of NMOSD attacks with specific infections.[30]

4. Clinical features

Transverse myelitis and optic neuritis are the classic features of NMOSD.[31] Optic neuritis attacks in NMOSD although clinically similar to the attacks seen in Multiple sclerosis or isolated optic neuritis, are characterized by a more severe visual loss.[32] NMOSD primarily affects the optic nerve and spinal cord, leading to paralysis and blindness, with a relapsing course and severe outcomes.[33] Patients with NMOSD commonly present with symptoms such as optic neuritis, characterized by vision loss, eye pain, and visual disturbances.[34] Bilateral ON is more typical of MOG-associated disease than NMOSD. Although optic neuritis attacks in NMOSD mostly unilateral, sequential optic neuritis or bilateral simultaneous optic neuritis is considered a distinct feature of NMOSD.[35]

Additionally, individuals with NMOSD may experience acute myelitis, leading to weakness, numbness, and paralysis in the limbs, as well as bladder and bowel dysfunction.[36] Longitudinally extensive transverse myelitis is characterized by a contiguous spinal cord lesion that extends to 3 or more vertebral segments. Many patients with myelitis report bladder dysfunction, paraparesis, quadriparesis, and visual impairment of sudden onset (less than 7 days).[37] Brainstem syndromes, and area postrema syndrome can also occur in NMOSD.[38] Brainstem involvement may manifest with oculomotor dysfunction or other cranial nerve palsies. It may also lead to acute neurogenic respiratory failure and death.[32] Other reported manifestations of brainstem involvement include hearing loss, vertigo, facial palsy, trigeminal neuralgia and pruritus of neurologic origin.[38]

Area postrema syndrome occurs in up to 10 to15% of NMOSD patients positive for AQP4-IgG. Its clinical presentation is characterized by nausea, vomiting, and hiccups persisting for more than 72 hours (median of 14 days) and can result in weight loss.[39] Furthermore, diencephalic syndromes with symptoms like altered consciousness and hormonal imbalances may manifest in patients with NMOSD.[40]

Diencephalic syndrome is less frequent. Patients present with hypersomnia, narcolepsy, hypo or hyperthermia, syndrome of inappropriate antidiuretic hormone secretion, anorexia, obesity, anhidrosis, decreased level of consciousness.[30]

The presence of anti-aquaporin-4 antibodies (AQP4-abs) is a hallmark of NMOSD and is associated with a more severe disease course and poorer outcomes.[41] NMOSD can also present with atypical symptoms such as cortical oscillopsia without nystagmus, indicating diverse ocular manifestations due to brain abnormalities.[42] In some cases, NMOSD may lead to hypoglossal nerve involvement, resulting in symptoms like a wasted tongue, hypogeusia, hypersalivation, and other brainstem manifestations.[43]

5. Imaging findings

5.1 Optic nerve

Optic nerve is a core clinical characteristic of NMOSD. Simultaneous or sequential involvement of both optic nerves on MR imaging of the orbits is highly suggestive of NMOSD with lesions sometimes being asymptomatic.[44] It is typically characterized as bilateral and longitudinally extensive optic nerve involvement, usually affecting more than half the length of the optic nerve.[45] The involvement of the posterior optic pathway including chiasm and the optic tract is characteristic.[46] Acute stage of optic neuritis is characterized by thickened optic nerve with hyperintensity on T2-weighted images and enhancement on gadolinium-enhanced T1-weighted

images. In the chronic stage, atrophy of the optic nerves and variable hyperintensity on T2-weighted images is seen.[47]

5.2 Spinal cord

LETM is the most typical spinal cord lesion and is characterized by longitudinal involvement of the spinal cord at three or more contiguous vertebral segments.[48] The central gray matter is commonly affected, representing the area with the most prominent expression of the AQP4 antigen.[49] The most common sites are in the cervical region and upper to midthoracic region.[50] When the cervical spine is involved, extension into the brainstem, typically to the area postrema, is commonly observed.[51] Bright spotty lesions on T2-weighted images and corresponding hypointense lesions on T1-weighted images are the typical imaging features on MRI.[52] These imaging features have been described as relatively specific for distinguishing NMO from other entities, including multiple sclerosis.[52] NMOSD the most common axial distribution of lesions is a central location with radiation to the outer ependymal surface.[53] All four quadrants are affected equally and may be associated with significant cord swelling.[54] What is interesting, studies have shown that relapses in NMOSD tend to recur in the same anatomical sites within the CNS.[55] Spinal cord atrophy is seen in cases with recurrent myelitis and may correlate with neurologic disability.[56]

5.3 Brain

The prevalence of brain lesions is variable, occurring in 24%–89% of NMOSD patients.[57] These lesions have typical imaging features that should be promptly recognized, particularly in the absence of optic neuritis or LETM.[48] To recognize typical brain lesions in NMOSD, one must primarily remember the areas where AQP4 is consistently expressed.[58] The sites of high AQP4 expression include the periependymal regions, subpialregion, circumventricular organs, brainstem, chiasm/hypothalamus, and corpus callosum which are the sites of typical brain lesions.[59]

Cortical lesions are usually considered a “red flag” imaging feature suggesting the possibility of a diagnosis other than NMOSD.[51]

6. Treatment od NMOSD

6.1 Acute treatment

6.1.1. Glucocorticoids

Acute treatment is critically important in NMOSD as exacerbations result in severe residual disability. Therefore, relapse therapies should be started early and aggressively.[60] Intravenous corticosteroid therapy is commonly the initial treatment for acute attacks of optic neuritis or myelitis.[61] A common approach begins with corticosteroid pulses (e.g., methylprednisolone 1000 mg intravenous daily for 3 – 5 days).[62] Complete recovery after relapse has been observed in up to 35% of patients treated with intravenous methylprednisolone (IVMP).[63] The proposed mechanisms of IVMP include the (i) inhibition of pro-inflammatory cytokine production, (ii) downregulation of expression of cell adhesion molecules and receptors, (iii) augmentation of anti-inflammatory cytokine secretion, (iv) reduction and modulation of T-cell activity by inducing T cell apoptosis and causing expansion of myeloid-derived suppressor cells, (v) restoration of the integrity of the blood–brain barrier by downregulating the matrix metalloproteinases, and (vi) repression of nitric oxide production by myeloid cells.[64]

6.1.2. Plasma exchange

If the initial response to steroids is inadequate, then plasmapheresis should be considered.[62] Plasma exchange (PLEX) every other day for 2 weeks (5–7 treatments) or immunoadsorption are recommended within 5 days from NMOSD relapse onset, when response to IVMP is poor or absent.[60] Other studies have shown the efficacy of PLEX as an add-on treatment to IVMP to reduce disability in severe spinal attacks.[65] Possible mechanisms of PLEX include removal of the autoantibodies and proinflammatory factors, and regulation of the lymphocytic function and proliferation.[66] An independent, single-center retrospective analysis of patients with syndromes reminiscent of NMOSD found that the probability of complete recovery from relapse decreased as the time interval between relapse onset and PLEX increased.[67] In conclusion, PLEX should be started early in patients

who show suboptimal improvement with IVMP, and use of IVMP and PLEX together may be considered as an initial treatment in severe attacks of NMOSD.

6.1.3 Immunoadsorption

Immunoadsorption (IA) is an alternative apheresis therapy to PLEX when PLEX is contraindicated or unavailable. [10] During IA, the plasma fraction is separated and then passed through an IA device where tryptophan or protein A is used as an absorber. This process provides a rapid removal of immunoglobulins and complements, while the albumin and clotting factors are mostly preserved. [68] However, IA has been used less frequently, and no clear difference has been established between PE and IA in terms of therapeutic outcomes, but data are limited, and more experience exists for PE.[69]

6.1.4 Intravenous immunoglobulin-G therapy (IVIgG)

IV immunoglobulin-G therapy (IVIgG) can be used if response is poor. In a retrospective study on 10 NMOSD patients unresponsive to IVMP, IVIgG was effective in 50% of patients. [70] The potential mechanisms of its immunomodulatory effects include a blockade of cellular receptors, neutralization of cytokines, complements and autoantibodies, and modulation of the immune effector cells.[71] Recently, a retrospective study reported high-dose IVMP plus IVIgG was superior to high-dose of IVMP alone.[72]

6.2 Long-term treatment

Untreated, approximately 50% of NMOSD patients will be wheelchair users and blind, and a third will have died within 5 years of their first attack.[32] To minimize permanent neurologic disability, long-term relapse prevention treatment is recommended for all patients who are diagnosed with NMOSD. [60] Various agents that are used in maintenance therapy include azathioprine (AZA), Mycophenolate Mofetil (MMF), and less commonly, Methotrexate and Cyclophosphamide.[73] The B-cell depleting monoclonal antibody, rituximab (RTX) is used as a second-line medication. [28] The IL-6 receptor (IL-6-R) antibody tocilizumab has also been increasingly used as rescue therapy, showing benefits in several case series. [74] Four therapies, eculizumab, inebilizumab, and satralizumab and most recently ravulizumab have been approved for use in AQP4-IgG-positive NMOSD since 2019.[10] In the following section, we summarize and discuss specific therapies that have been widely used in the long-term treatment.

6.2.1 Azathioprine and mycophenolate mofetil

The most commonly used first line immunosuppressants (IS) in NMOSD are mycophenolate mofetil (MMF; 2–3 grams/day) and azathioprine (AZA; 2.5–3 mg/kg). Retrospective data suggest that MMF may be superior to AZA (reduction in relapse rate 87.4% versus 72.1% respectively) but prospective data are lacking. [75] AZA is often selected in younger female patients as MMF is contraindicated in pregnancy. It should also be noted that MMF can have spermatotoxic effects. Oral prednisolone (5–10 mg) is often given long-term as the combination may be more protective than MMF/AZA alone.[76]

6.2.2 Rituximab

Rituximab - B cell depletion with RX has been demonstrated as effective in the treatment of NMO in several clinical case series and retrospective analyses. [77] RX treatment can be initiated using one of two different regimens: either two 1 g infusions of RX at an interval of 2 weeks or four weekly 375 mg/m^2 body surface area (BSA) applications. To prevent infusion-related side effects, premedication (1 g paracetamol, 100 mg prednisolone, 4 mg dimethindene maleate i.v.) should be dispensed. [10] RTX reduces relapse rates up to 88.2% and is either given 6-monthly or according to monitored B-cell counts (CD19$^+$ lymphocytes). [78] Thus, RX is another option for first-line treatment in NMO/NMOSD and for patients who have not responded to previous immunosuppressive therapy.[10]

6.2.3 Tocilizumab

Retrospective and prospective case series since 2013 have reported that IL-6-R blockade with tocilizumab can effectively prevent attacks in NMOSD, mostly after standard immunotherapies, including rituximab. [79, 80] It improved fatigue and neuropathic pain in a small trial of NMOSD patients, suggesting that the IL-6 pathway

may be involved in these mechanisms.[81] However, data on tocilizumab as a first-line therapy for NMOSD are scarce, and tocilizumab has not been granted regulatory approval for NMOSD.[10] The onset of action can be expected after a few weeks.
One study investigating tocilizumab treatment within 2 weeks after an NMOSD attack showed favorable effects on the disease course.[82] Moreover, data on the long-term use of tocilizumab in NMOSD remain scarce and mainly arise from other indications.[10]

6.2.4 Satralizumab

Satralizumab is a subcutaneously administered humanized monoclonal antibody targeting the interleukin-6 (IL-6) receptor. It binds to both the membrane-bound and soluble IL-6 receptors and prevents the binding of IL-6, hence blocking IL-6 signaling pathways that are involved in inflammation.[83] In the clinical trial (Sakura-Sky) at 96 weeks, 78% of patients receiving satralizumab were relapse-free, compared to 59% receiving placebo. At 48 and 96 weeks, 92% of AQP4-ab-positive patients on satralizumab were relapse-free. No change was observed in pain or fatigue scores from baseline.[84, 85] Satralizumab was effective in patients with AQP4-IgG-positive but not in patients with AQP4-IgG-negative NMOSD in clinical trials. However, they did not have sufficient power to draw definitive conclusions for AQP4-IgG-negative patients.[86]

6.2.5 Eculizumab

Eculizumab is a humanized monoclonal antibody that blocks the complement protein C5 and prevents activation of the complement cascade.[22] The results of the study trial (PREVENT) showed that eculizumab, as a monotherapy or add-on therapy, significantly reduced the risk of attacks and was effective across all subgroups compared to placebo. These studies included only adult AQP4-IgG-positive patients with high disease activity.[87, 88] Eculizumab was approved by the FDA as treatment to prevent relapse in AQP4-IgG-seropositive adults with NMOSD in 2019, followed by the European Union and in Japan.[62] Adverse effects include infection, especially by encapsulated bacteria and upper respiratory tract infections. Immunization with the meningococcal vaccine is mandatory before the initiation of therapy, at least 2 weeks before the first dose of eculizumab.[11] However, patients on eculizumab remain at risk for meningococcal disease even after receipt of meningococcal vaccines and some health care providers in the USA as well as public health agencies in other countries recommend prophylactic treatment with appropriate antibiotics for the duration of eculizumab treatment.[89]

6.2.6 Inebilizumab

Inebilizumab is a humanized monoclonal antibody against the CD19 surface antigen of B cells. Inebilizumab was found to be effective in a small trial (*N*-Momentum).[90] Data from this trial showed that inebilizumab significantly reduced the attack rate in patients with NMOSD.[90] Moreover, the trial showed that the risk of an EDSS-based disability progression confirmed after 3 months was lower in patients who received inebilizumab.[91] This effect was more robust in AQP4-ab-positive patients.[84] However, further studies are warranted to establish the long-term efficacy.

6.2.7 Ravulizumab

Ravulizumab is a long-lasting monoclonal antibody that targets the complement factor C5. It has been engineered to exhibit altered intracellular antibody recycling and has a four times longer half-life than eculizumab. Therefore, it needs to be administered i. v. only once every 8 weeks.[92] The results of the study trial suggest ravulizumab monotherapy is more efficacious than satralizumab and inebilizumab monotherapies in preventing relapse. Moreover, while ravulizumab + immunosuppressive therapy is more efficacious than satralizumab + immunosuppressive for this endpoint in the combination therapy setting. Findings between eculizumab and ravulizumab were largely comparable.[93] In patients with AQP4+ NMOSD, ravulizumab significantly reduced relapse risk compared with placebo.[94] Building on existing experience with eculizumab in this setting, ravulizumab represents a potential new therapy for adults with AQP4+ NMOSD that combines strong efficacy, a well-established safety profile, and an 8-week dosing interval.[94]

7. Conclusion

In conclusion, Neuromyelitis Optica Spectrum Disorders (NMOSD) represent a complex and challenging group of autoimmune conditions that predominantly affect the central nervous system, leading to significant neurological disabilities if not properly managed.

Advances in diagnostic techniques, particularly the identification of anti-AQP4 and anti-MOG antibodies, have significantly improved our ability to differentiate NMOSD from other demyelinating diseases like multiple sclerosis. This, in turn, has facilitated the development of more targeted therapeutic approaches, improving outcomes for many patients.

Despite these advancements, NMOSD remains a condition with significant physical and emotional burdens for those affected. Early diagnosis and prompt initiation of appropriate therapies are crucial in minimizing relapses and preventing long-term disability. Ongoing research into the underlying mechanisms of NMOSD, as well as the development of novel treatments, holds promise for further enhancing patient care and quality of life. As awareness of NMOSD grows within the medical community, there is hope for continued progress in the fight against this debilitating disease.

Author's contribution

Conceptualization, JK; methodology, JK, AN, MK; software, OB, AK, KR, OK, MS; check, AK, KR; formal analysis, AN, OB, MK; investigation, AK, KR, OK; resources, MS, ZS, KP; data curation, ZS, KP; writing – rough preparation, JK, AN, MK; writing-review and editing, JK, OK; visualization, MK; supervision, MS, KP; project administration, ZS

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