Review Article

A Narrative Review On Neuromyelitis Optica

ABSTRACT

Neuromyelitis Optica, also known as Devic's disease, is a central nervous system (CNS) autoimmune inflammatory disease that primarily affects the optic nerve and spinal cord. The mechanism of the disease is given by the generation of IgG antibodies, whose major target is the aquaporin channel 4 (AQP4), causing an inflammatory and demyelinating process in the aforementioned tissues. In this study, we discussed extensively this disease entity by describing the epidemiology, pathogenesis, clinical features, management, and prognosis.

Keywords: Neuromyelitis Optica, Devic's disease, IgG Autoantibodies to Aquaporin 4, Neuromyelitis Optica Spectrum Disorder

1. INTRODUCTION

"Neuromyelitis Optica (NMO), also known as Devic's disease, is an autoimmune inflammatory disorder of the central nervous system (CNS), characterized by recurrent debilitating episodes of optic neuritis (ON) and/or transverse myelitis (TM)" 1. "The more encompassing term Neuromyelitis Optica Spectrum Disorders (NMOSD), proposed in the international consensus diagnostic criteria in 2015, incorporates cerebral syndromes (such as area postrema and brainstem syndromes) whether associated or not with relapsing episodes of ON (often severe and simultaneous bilateral) or acute transverse myelitis (mostly longitudinally extensive transverse myelitis (LETM), >3 vertebral segments)" 2.

"NMO is caused by pathogenic IgG autoantibodies to aquaporin 4 (AQP4-IgG), the most abundant water channel protein in the central nervous system (CNS) in more than 80% of cases. About 10–40% of those lacking AQP4-IgG have IgG autoantibodies to myelin oligodendrocyte glycoprotein (MOG-IgG)" 6. "However, MOG-IgG is also present in a subset of patients (mostly children) with acute disseminated encephalomyelitis (ADEM)" 7. "NMO has also been described in patients with sarcoidosis, connective tissue diseases, and paraneoplastic neurological disorders, although these cases are rare 8. In a small subgroup of patients, the cause remains unknown (idiopathic NMO)" 8.

The aim of this study is to discuss the concepts of the pathogenesis of neuromyelitis optica, clinical presentation, diagnosis, and treatment options.

2. PREVALENCE

"The prevalence of NMOSD ranges from 0.5 to 4/100,000, and it may be up to 10/100,000 in some racial groups. This prevalence is small compared to that of multiple sclerosis, which ranges from 1 to 2/100,000 in the equatorial region to 150 to 200/100,000 in places like Canada and the Northern part of Europe" 9, 10.

The prevalence of NMOSD among the White population has consistently been ~1/100,000. Studies were done in Australia and New Zealand gave a prevalence of 0.55/100,000 11, 12, other studies gave the prevalence as thus: Catalonia (1.09/100,000), and 1.04/100,000 in Sweden 9,10,13,14. "A study from South Denmark reported the prevalence of AQP4-antibody-positive NMOSD as 1.68/100,000 and the prevalence of the total clinical phenotype, including AQP4-antibody-negative and MOG-antibody-positive subsets as 4.4/100,000" 15.

The prevalence of NMOSD seems to be higher in the Asian population, especially the east Asians (around 3.5/100,000) 16 “This is in line with genetic studies that showed that Japanese and Chinese share the same HLA risk genes for NMOSD, namely, HLA-DPB1*05:01 and HLA-DRB1*16:02” 17. Studies also done in the black population shows that the prevalence is higher than in the white population. A study done in Ibadan, Nigeria, in 1971 found a prevalence of 0.4/1000 among the hospital population 18. “A study conducted in Liverpool, UK, reported a prevalence rate of 1.8/100,000 among Blacks” 19.

3. PATHOGENESIS

3.1 AQP4-IgG related disease

“In AQP4-IgG seropositive NMOSD, the presence of AQP4-IgG in the blood is the critical pathogenic component” 20. “AQP4 is a bidirectional, osmosis-driven water channel impervious to anions and glycerol; it is found in the highest quantities of perivascular and peripial astrocytic endfeet in direct contact with the endothelium's basal lamina and pia, respectively” 21. “AQP4 is also found in the membranes of ependymal cells but not in those of oligodendrocytes, neurons, or choroidal epithelial cells” 22.

“CNS lesions in individuals positive for AQP4-IgG are characterized by vasculocentric IgG and IgM deposits, which are most prominent around the blood vessels (corresponding to the high AQP4 expression at the glia limitans interna), complement deposits, and cellular infiltrates consisting of macrophages/microglia, neutrophils, eosinophils granulocytes, B cells, and a few T cells” 23. “Complement-dependent cytotoxicity is produced when AQP4-IgG breaches the blood-brain barrier (BBB) and reacts with AQP4 in astrocyte feet and the recruitment and activation of complement. Furthermore, effector cells such as natural killer cells are activated, resulting in antibody-dependent cytotoxicity and astrocyte damage” 20. “Complement activation and astrocyte-derived cytokines attract inflammatory cells such as eosinophils, neutrophils, and macrophages, causing further BBB destruction and increasing AQP4-IgG access into the CNS 20. In addition, inflammatory cell degranulation and astrocyte destruction cause oligodendrocyte injury, resulting in rapid myelin sheath loss, axonal damage, and neurological impairments” 24. “The interaction of AQP4-IgG with astrocytic AQP4 causes brain water movement dysfunction, glial scarring, and neuroexcitation” 25.
“Depending on the stage of the lesion and the intensity of the attack, the hallmark diagnostic histopathological findings include a significant loss of astrocytes, with either preservation or secondary loss of oligodendrocytes and neurons” 25.
“Astrocyte dysfunction and/or inflammatory bystander injury cause secondary loss of neurons and oligodendrocytes” 26.

“The detection of AQP4-IgG in cerebrospinal fluid (CSF) is less sensitive than in serum, implying that a significant fraction of AQP4-IgG originates in peripheral lymphoid tissues” 27. “Serum AQP4-IgG testing is the most efficient way of seropositive NMO diagnosis because AQP4-IgG penetration into the CNS requires a crucial serum/CSF gradient to achieve a pathogenic level” 27. “Furthermore, before relapses, AQP4-IgG titers have a greater positive connection with disease activity than during remission” 28. “Differences in AQP4 expression levels (higher in the optic nerve, spinal cord, diencephalon, and area postrema than in other CNS regions), the proportion of supramolecular AQP4 aggregates between brain areas (higher in the spinal cord and optic nerves), and blood-brain barrier (BBB) permeability (higher in the circumventricular organs, including the area postrema) may explain the distribution and severity of lesions in patients with AQP4-IgG” 29. “The lack of inflammation outside the CNS, despite high AQP4 expression in specific tissues and organs like the kidneys, the lack of inflammation outside the CNS has been attributed to stronger co-expression of complement activation regulators (CD46, CD55, and CD59) in the periphery in the CNS” 30. “Other astrocytic markers, such as glial fibrillary acidic protein (GFAP), are still detectable in some lesions, indicating that AQP4 disappearance precedes astrocyte loss” 8. “However, serum AQP4-IgG is not an accurate indicator of the severity of astrocytopathy” 20. “Still, astrocytic damage may be more accurately reflected by elevated CSF levels of glial fibrillary acidic protein (GFAP), which is related to the clinical severity and primary pathologic process in NMO, and are more severely affected than demyelination-related biomarkers” 20.

“The presence of plasma AQP4-IgG alone is inadequate to cause the BBB to be disrupted. Antigen presentation, synthesis of pro-and anti-inflammatory cytokines, and immunoglobulin formation are all functions of B cells in NMO” 31. “A B-cell subpopulation produces AQP4-IgG with the CD19, CD27, and CD38 phenotype in patients with NMO, which is selectively enhanced in the peripheral blood during NMO relapse and has morphological characteristics comparable to plasmablasts” 32. “Pathogenesis may potentially be aided by impaired B cell regulatory qualities caused by a scarcity of regulatory B cells or diminished IL-10 production in the presence of activated intrathecal B cells” 33. “Furthermore, some human B cell germline clones may express AQP4-specific B cell receptors (BCRs) that behave as antigens that cross-react with antigens from other species. CXCL13 and B-cell activating factor (BAFF) levels in the CSF are significantly higher in NMO, implying increased recruitment and activation of intrathecal B cells” 33.

“As AQP4-specific B and T cells migrate between lymph nodes, the initial B cell reaction may occur in CNS-draining or non-draining lymph nodes” 34. “When antigen-presenting cells (APCs) such as dendritic cells (DCs) and macrophages in the perivascular space, choroid plexus, or leptomeninges stimulate autoantigen presentation, astrocytes may trigger T cells migrating into the CNS” 34.

The BBB is then disrupted by the activated AQP4-specific T cells, allowing more AQP4-IgG and other immune effectors to enter tissues harboring astrocytes with AQP4 in their membranes. Even a tiny number of AQP4-specific T cells can disrupt the BBB and recruit sustained levels of pathogenic effectors. Also, activated AQP4-specific B cells function as effective APCs and play an essential role in activating AQP4-specific T cells via BCR-internalized AQP4 34.

According to studies, patients with NMO have Th17-dominant AQP4-specific T-cells, with such cells being substantially more prevalent in NMO than in MS 35. In addition, NMO sera included high quantities of Th17-related cytokines such as interleukin-21 (IL-21), IL-23, and IL-17 in cultured cells from patients with NMO 35, 36. T cell proliferation was found with limited production of Th1 cytokines 36. Furthermore, because the generation of Th17-related cytokines was substantially more resistant to glucocorticoids in patients with NMO, these individuals were likely more resistant to glucocorticoid therapy. As a result, in patients with NMO, the predominant Th17-mediated response was positively connected with neurological impairment, as was the significant release of Th17-related cytokines 36.

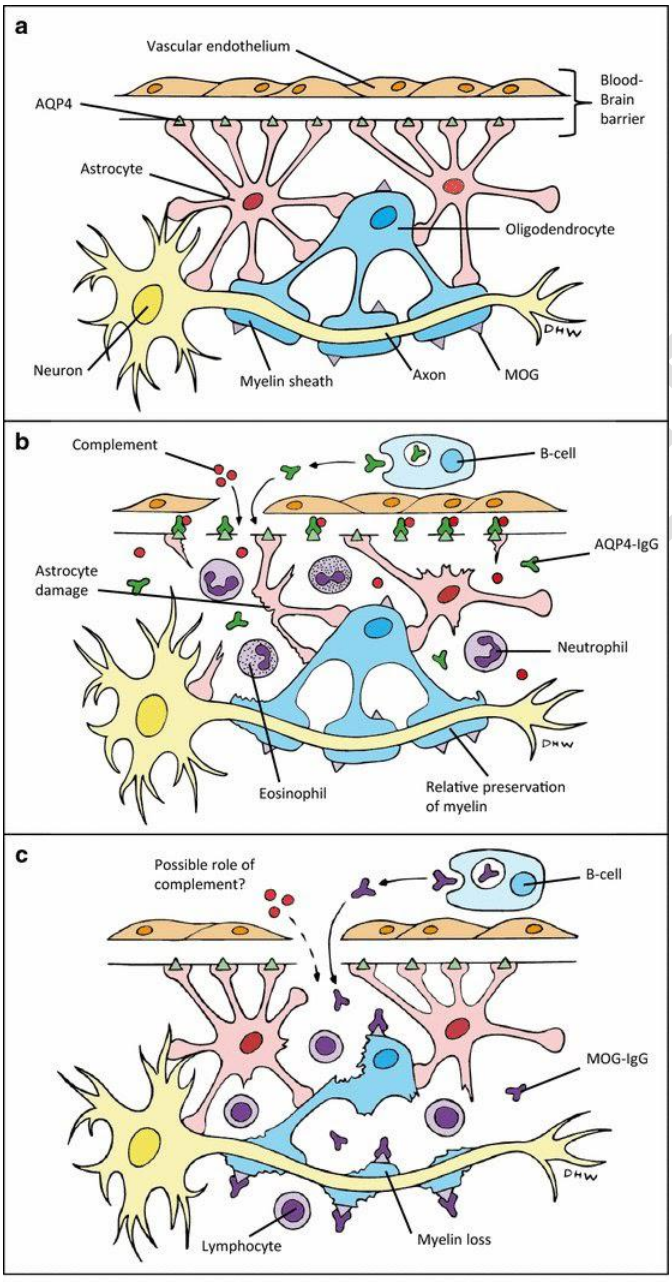

Fig. 1. a) This schematic diagram illustrates the sites of expression of aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) within the CNS: AQP4 is expressed at the blood–brain barrier, on the "foot-like" processes of astrocytes, whereas MOG is expressed by oligodendrocytes and on the outermost surface of myelin sheaths. b) AQP4-IgG is synthesized 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 demyelination, but the mechanism is less well understood. Adapted from 37.

3.2. MOG-IgG related disease

Found in the surface lamellae of oligodendroglial myelin; myelin oligodendrocyte glycoprotein (MOG) is more immunogenic than other CNS myelin proteins like proteolipid and myelin essential proteins 38. "It is an intrinsic membrane glycoprotein with two transmembrane domains, two extracellular domains, and one cytoplasmic domain that belongs to the immunoglobulin superfamily" 8. "MOG is found on the surface of oligodendrocytes and the outermost surface of myelin sheaths, but it only makes up a minor part of the total number of myelin proteins" 39, 40.

"Lesions in patients with MOG-IgG are characterized by demyelination with dominant loss of MOG 41 and relative preservation of axons and oligodendrocytes" 41. "Also, lesions are characterized by cellular infiltrates consisting of macrophages/microglia, T cells (with a preponderance of CD4+ T cells), granulocytes and relatively few B cells, and IgG and complement deposition" 8.

Unlike MS, lesions in MOG-IgG patients have intact or even increased AQP4 and no dystrophic astrocytes, but hypertrophic, reactive astrocytes (containing occasional Creutzfeldt–Peters cells) and a dense GFAP-positive network 8. Although there is some overlap with so-called pattern II MS lesions, perivascular demyelination, similar to that found in ADEM, appears to be a distinguishing feature that separates MOG-IgG lesions from normally confluent MS lesions 8, 42–44. "CNS lesions beyond the optic nerves and spinal cord are common in MOG-IgG-associated disease, as they are in AQP4-IgG-positive NMOSD, and children present with brain lesions more frequently than adults in both conditions" 8. "Notably, cortical demyelination, rare in AQP4-IgG-positive NMOSD, is common in MOG-IgG patients with brain involvement and is frequently topographically related to meningeal inflammation" 42.

4. CLINICAL MANIFESTATIONS

4.1 Optic neuritis

"Optic Neuritis (ON) is an optic nerve inflammation that causes vision loss and eye pain aggravated by eye movement" 43. "Compared with MS, ON in NMO is more severe and more likely to present with simultaneous bilateral or rapidly sequential eye involvement" 45. NMO-related ON is associated with cloudy vision and a decrease in high-contrast visual acuity (VA) as measured by a Snellen chart 46, 47. In some cases, only low-contrast VA or color vision (resulting in color desaturation) is affected 46, 47, in patients with AQP4-IgG and those with MOG-IgG 48.

"Visual loss can be mild during acute ON, but it can develop to complete functional blindness (defined by VA 0.1) in one or both eyes" 46. "Ocular pain and/or pain in eye movement are frequently preceded by the onset of ON, significantly if the retrobulbar portion of the optic nerve is affected" 46. "Simultaneous ON in both eyes occurs more regularly in NMO patients than in MS patients and possibly more frequently in MOG-IgG patients than in AQP4-IgG patients" 47.

"MRI during an acute episode may demonstrate a more significant signal on fat-suppressed T2-weighted sequences or T1 gadolinium enhancement in the optic nerve or optic chiasm" 2, 45. "The lesions are frequently lengthy, spanning more than half the distance between the orbit and the optic chiasm, and they impact the chiasm's posterior aspect" 2, 45. "Eighty-four percent of patients with acute ON had increased signal intensity on the optic nerve's T2-weighted short-tau inversion recovery scans, and 94 percent have gadolinium enhancement on T1-weighted spin-echo sequences" 49.

4.2 Transverse myelitis

The term "transverse myelitis" (TM) refers to a group of inflammatory disorders characterized by bilateral sensorimotor and autonomic spinal cord dysfunction, spinal cord inflammation as determined by cerebrospinal fluid (CSF) analysis or magnetic resonance imaging (MRI), and the exclusion of compressive, post-radiation, and vascular causes 50–52. The majority of the lesion resides in the central gray matter, and acute lesions cover most of the cross-sectional area with associated swelling and gadolinium enhancement 45, 53, 54.

Symptoms usually start in the feet and progress to a sensory level on the trunk and are commonly preceded by discomfort at the lesion site. TM can also result in an overactive bladder and urine retention (which typically necessitates catheterization) and a decreased quality of life, and the need for lifestyle changes. 55. The Lhermitte sign (a brief electric shock or paraesthesia-like sensation running down the spine and occasionally the limbs, precipitated by neck flexion and caused by stretching of demyelinated fibers in the spinothalamic columns) is not unique to MS patients, but it can occur in patients with AQP4-IgG-positive or MOG-IgG-positive TM 46,47,56,57.

4.3 Brain syndromes

“Cerebral symptoms are more common in children than adults in AQP4-IgG-positive NMOSD” 58. “The ADEM-like disease is a frequent manifestation in young children with MOG-IgG, characterized by encephalopathy (impaired consciousness, altered behavior, seizures) and polyfocal neurological symptoms associated with inflammatory brain lesions” 8.
“Symptomatic brain involvement is more common than previously thought and may occur both in patients with MOG-IgG and in those with AQP4-IgG 8. The brainstem is commonly affected in both AQP4-IgG-positive and MOG-IgG-positive disease, and spinal cord lesions often extend into the medulla oblongata” 8.

Intractable hiccups, nausea, and vomiting are some of the most common brain symptoms, and they are caused by lesions affecting the area postrema in the medulla 59. In certain NMOSD patients, these symptoms may precede acute aggravation or relapses of myelitis; hence patients with these symptoms should be examined for medullary lesions 60. Some patients may have lesions in the brainstem that are not in the region postrema; these lesions could be in any portion of the brainstem, including the cerebral peduncles, cerebellar peduncles, and the medulla 61. Those lesions in the brainstem are most likely asymmetrical 61. Hemiplegia, vertigo, dysphagia, respiratory disturbances, and other symptoms induced by brainstem lesions differ depending on where the lesion is located 61.

“In a rare number of anti-AQP4-Ab-seropositive patients with NMOSD, diencephalic lesions (particularly those in the hypothalamus) can arise” 17. “These lesions may occur in the areas surrounding the basilar cistern or the third ventricle. Diencephalic lesions are more likely to occur on both sides of the brain” 61. “The syndrome of inappropriate antidiuretic hormone secretion, narcolepsy, irregular menstruation, hyperprolactinemia, hypothyroidism, secondary amenorrhoea, galactorrhoea, hypothermia, hypotension, obesity, and behavioral abnormalities are all possible symptoms” 62.

4.4 **Others**

Pain and dysesthesia (abnormal unpleasant sensation) are common and can be a considerable burden 8. In NMO, painful tonic spasms typically accompany or follow myelitis, which can be confused for spasticity 63,64.

Myositis, internal otitis, gastritis, and vitamin B12 insufficiency have all been mentioned as probable extra-CNS consequences of AQP4-IgG-related autoimmunity due to AQP4 expression outside the CNS 65–67. “AQP4-IgG-positive NMOSD is also frequently linked to other autoimmune diseases, including CTDs like SLE, Sjögren syndrome, antiphospholipid syndrome, rheumatoid arthritis, myasthenia gravis, coeliac disease, and in rare cases, other CNS autoimmune disorders such as N-methyl-d-aspartate receptor encephalitis” 68–70. The presence of such comorbidities can modify a patient's clinical presentation and should be taken into account while making treatment recommendations 8.

5. DIAGNOSTIC CRITERIA

The International Panel for NMO Diagnosis (IPND) developed a set of diagnostic criteria in 2015 that defines the unifying term NMOSDs, divided into the seropositive and seronegative diseases by serologic testing 2. The updated criteria describe six "core clinical characteristics" that recognize clinical signs of the disease beyond optic nerve and spinal cord damage 2.

Table 1. Diagnostic criteria for neuromyelitis optica spectrum disorder (NMOSD)

Core clinical characteristics
1. Optic neuritis. 2. Acute myelitis. 3. Area postrema syndrome: an episode of otherwise unexplained hiccups or nausea and vomiting. 4. Acute brainstem syndrome. 5. Symptomatic narcolepsy or acute diencephalic clinical syndromes with NMOSD-

typical diencephalic MRI lesions. 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions.
Diagnostic criteria for NMOSD with AQP4-IgG
1. At least 1 core clinical characteristic. 2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended). 3. Exclusion of alternative diagnoses.
Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status
1. 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 lesion extending over >½ optic nerve length or involving optic chiasm. 2. Acute myelitis: requires associated intramedullary MRI lesion extending over >_ 3 contiguous segments (LETM) OR >_ 3 contiguous segments of focal spinal cord atrophy in patients with a history compatible with acute myelitis. 3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions Acute brainstem syndrome: requires associated periependymal brainstem lesions.

Adapted from Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders 2.

6. INVESTIGATIONS

These include serologic testing for AQP4-IgG, neuroimaging of the brain and spine, CSF analysis, and ophthalmologic evaluation.

6.1 Serologic testing for AQP4-IgG

Although specific test features vary depending on the assay utilized, serum AQP4-IgG testing has moderate sensitivity and high specificity for the disease 71. The initial indirect immunofluorescence assay has a reported sensitivity of 58% - 75% and specificity of 85% - 99%, but cell-based assays offer both higher sensitivity (74%–83%) and specificity (100%) 4,72–74. Because a small percentage of seronegative individuals are later discovered to be AQP4-IgG positive, it is advised that they be retested at the time of recurrent attacks 71. “According to the international recommendation, MOG-IgG testing should be considered primarily in patients with monophasic or relapsing acute ON, TM, brainstem encephalitis, encephalitis, or any combination thereof, and radiological findings that are compatible with CNS demyelination in whom at least one of the clinical or paraclinical features listed in diagnostic criteria are present” 8.

6.2 Neuroimaging

“Neuroimaging is an essential aspect of the diagnostic evaluation, particularly in patients with clinical features consistent with NMOSD who are AQP4-IgG negative 71. Patients with suspected NMO should have MRI with and without gadolinium enhancement of the brain and spine and optic nerve MRI to identify, characterize lesions, and discriminate between NMO and MS” 71.

6.2.1 The spinal cord

The presence of an LETM lesion is the MRI feature that best distinguishes NMO from MS; however, shorter lesions occur in ~15% of patients with AQP4-IgG-positive and 44–52% of patients with MOG-IgG-positive myelitis at least once 46, 75, 76. The extent of the spinal cord lesion should be assessed using both axial and sagittal plane images 77. In sporadic cases, routine MRI does not show a distinct lesion despite symptoms compatible with myelitis; hence, in such cases, antibody testing should be repeated to exclude a false-positive result 77. Lesions in individuals with AQP4-IgG and MOG-IgG primarily damage grey matter (the so-called axial H-sign, which often lacks gadolinium enhancement), but lesions in MS patients primarily affect white matter 78.

Inflammatory edema (visible as spinal cord extension or swelling on MRI), necrosis, and cavitations are all possible outcomes of AQP4-IgG-positive NMOSD; hence, T1 hypointense spinal cord lesions are not uncommon 78. MRI may also reveal (often longitudinally extensive) spinal cord atrophy or a reduced mean upper cervical cord area, which appears to

be more common in AQP4-IgG patients than in MOG-IgG individuals 79. Lesions of the cervical spinal cord frequently spread into the brainstem. Conus involvement is more common in MOG-IgG patients, although it can also happen in AQP4-IgG-positive NMOSD and MS patients 79.

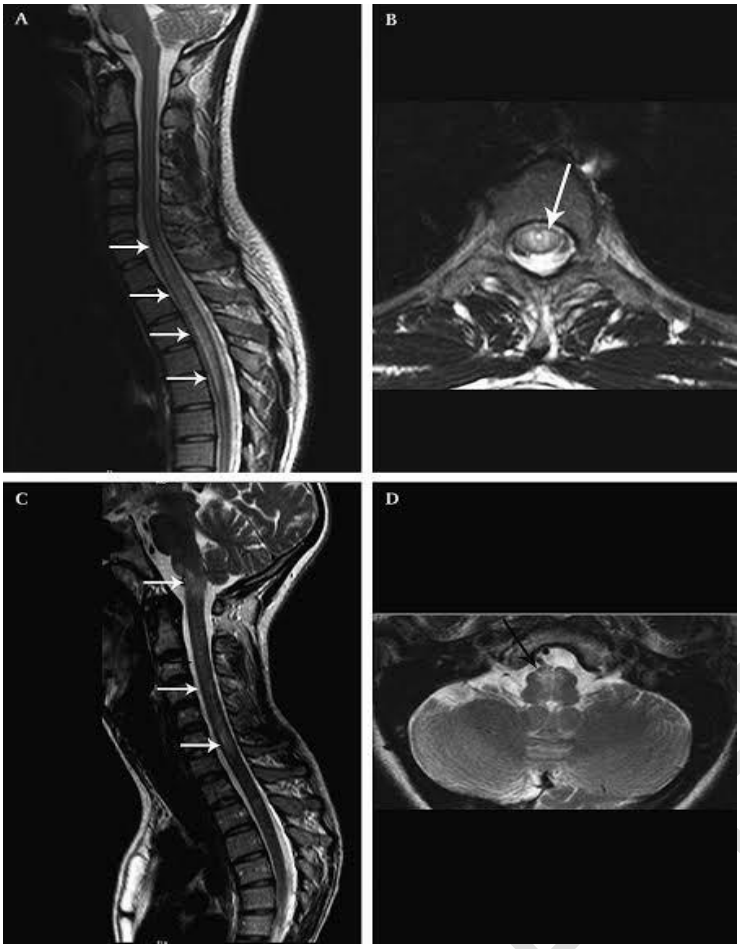

Fig. 2. (A) Sagittal T2-weighted MRI scan of cervicothoracic spinal cord showing longitudinally extensive myelitis in a case of neuromyelitis optica (NMO). Note that the lesion spans six vertebral segments with cord expansion. (B) Axial T2-weighted MRI scan (corresponding axial image of (A)) showing the transverse extent of the lesion, which involves more than half of the cord. (C) Sagittal T2-weighted spinal MRI scan of another patient with NMO showing a medullary lesion in contiguity with cervical myelitis. (D) Axial T2-weighted MRI scan (corresponding axial image of (C)) showing the medullary lesion. White and black arrows point to the intrinsic lesions. Adapted from 80.

6.2.2 The optic nerve

AQP4-ON, like MS, primarily affects the posterior portions of the optic nerve (including the chiasma), whereas MOG-ON primarily affects the anterior portion; however, posterior lesions (or long lesions also involving the posterior parts, including the chiasm) can occur in MOG-ON on rare occasions 81. Acute ON associated with a T2 or gadolinium-T1 lesion extending over more than half of the distance from the orbit to the chiasm is defined by the current NMOSD criteria as longitudinally extensive ON. Simultaneous bilateral ON is more common in MOG-ON than AQP4-ON at the outset, and it is relatively uncommon in MS 8.

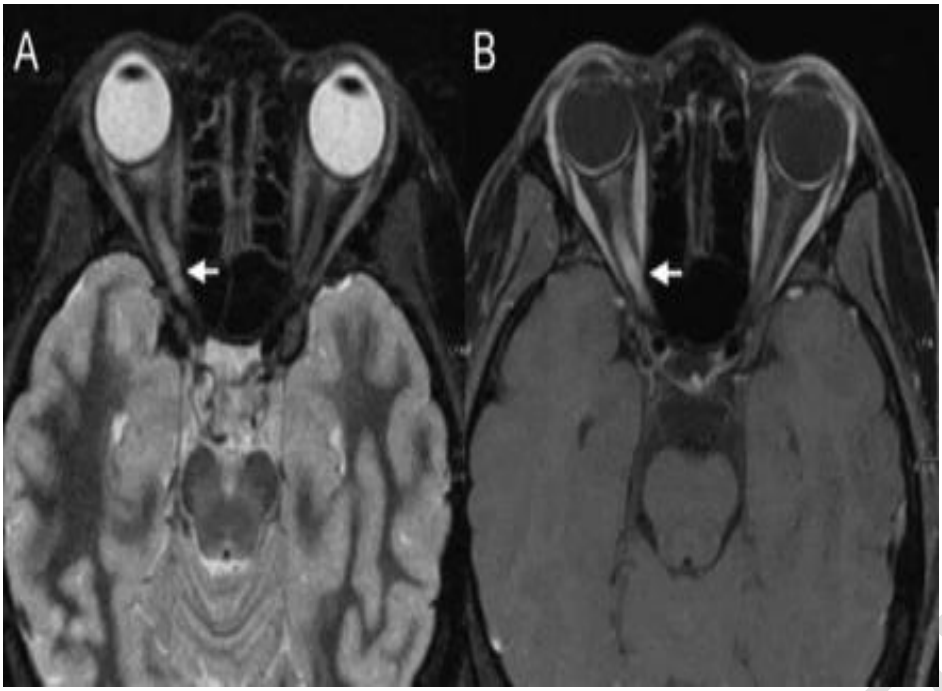

Fig. 3. MRI short tau inversion recovery, axial, high-intensity edematous lesion in the right optic nerve (A) with contrast enhancement (B) in a patient with the first episode of optic neuritis and aquaporin-4 (AQP4) antibody positivity. Adapted from 82.

6.2.3 The brain

AQP4-NMOSD is characterized by periependymal lesions that can be severe and gadolinium-enhancing 8. The lateral ventricles, as well as the third and fourth ventricles, may be affected. Periventricular MS lesions, on the other hand, are usually ovoid or perpendicular (Dawson's fingers) 83.

White matter lesions in MS are usually modest and restricted, whereas AQP4-NMOSD patients have more extensive, confluent, unilateral, or bilateral subcortical or deep white matter lesions (sometimes with 'cloud-like' gadolinium enhancement) 78. On the other hand, large, tumefactive lesions are uncommon in MS and might be challenging to spot, particularly in patients without AQP4-IgG 78.

Circumventricular organ lesions (most typically in the area postrema) also indicate AQP4-IgG-positive NMOSD, but they can also occur in patients with MOG-IgG or MS 84–86. Brainstem lesions are common in both AQP4-IgG and MOG-IgG patients, and they are frequently contiguous, especially in AQP4-IgG patients, with an upper cervical spinal cord lesion 8. Both brain and brainstem lesions can occur bilaterally in AQP4-IgG-positive NMOSD, and brain lesions are usually longitudinally extensive, including corticospinal tract lesions and corpus callosum lesions 78, 87.

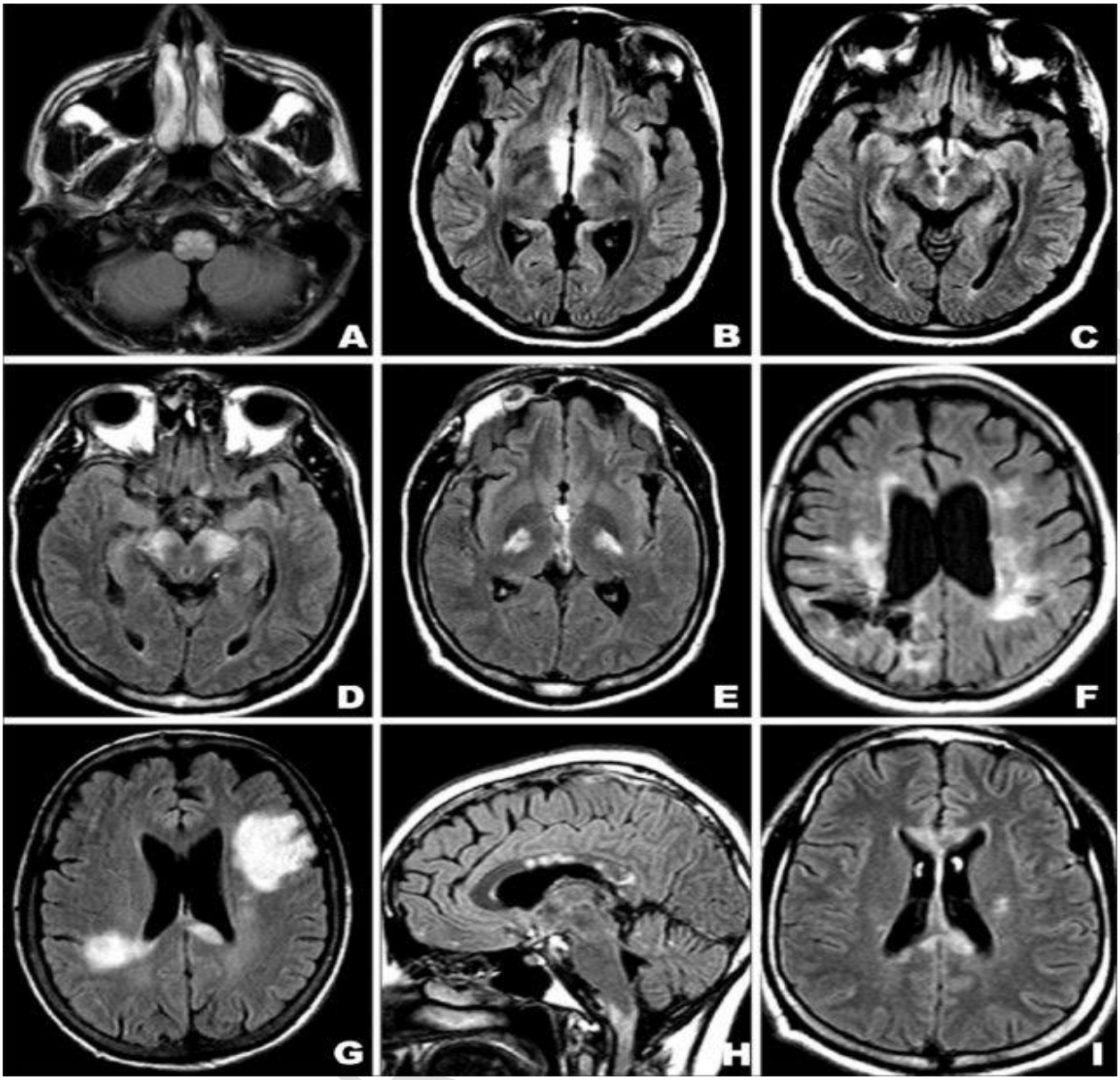

Fig. 4. Brain lesion distribution in our patients with Neuromyelitis Optica. MRI FLAIR images. (A) medulla involvement. (B, C) lesions in diencephalon and optic chiasm. (D, E) signal abnormalities in middle cerebellar peduncles, midbrain and internal capsule. (F) white matter abnormalities with cavitations suggesting early axonal loss. (G) lesions in the periventricular and subcortical cerebral white matter and corpus callosum. (H) corpus callosum, optic chiasm and medulla involvement. (I) corpus callosum lesions and slight signal abnormalities in periventricular cerebral white matter. Adapted from 88.

6.3 Cerebrospinal fluid analysis

CSF investigation is not essential for diagnosing NMO, but it can help confirm CNS inflammation, identify individuals with non-MS-related CNS demyelination, and rule out other significant illnesses 8. Although CSF-restricted oligoclonal bands are a diagnostic cornerstone in MS, they are lacking in most NMO patients, which is consistent with the fact that AQP4-IgG and MOG-IgG are produced primarily outside the CNS 89–91. Patients with NMOSD have a higher CSF IL-6, which is not seen in MS patients 92. Pleocytosis is more common in NMOSD (about 35%), especially when neutrophils or eosinophils are present 92. A CSF white cell count of more than 50 cells/µl is uncommon in MS and should cause physicians to question the diagnosis, but it is not unusual in patients with AQP4-IgG-associated or MOG-IgG-associated acute myelitis, where it can reach 100 cells/µl. Granulocytes are seen in nearly half of people with AQP4 and MOG illness, whereas they are rarely found in people with MS 93. In AQP4-IgG-positive NMOSD, which is also characterized by elevated CSF levels of eosinophil attractants, eosinophils are primarily absent in patients with MS (and rare in Myelin oligodendrocyte glycoprotein encephalomyelitis (MOG-EM)), but they are present in 10% of CSF samples in AQP4-IgG-

positive NMOSD, which is also characterized by elevated CSF levels of eosinophil attractants 93. In MS, an increased albumin CSF to serum ratio (QAlb), indicating blood-CSF barrier dysfunction, is extremely infrequent (less than 10%) and rarely surpasses 12×10-3 but it is found in 50% of samples from patients with AQP4-IgG and MOG-IgG and exceeds 12×10-3 in ~25% of samples 89–91.

In individuals with AQP4-IgG and those with MOG-IgG, CSF white cell counts can be average or similar to those in MS, especially in patients presenting with isolated ON and in samples taken after remission 89–91. Other CSF markers with differential diagnostic and prognostic potential are IL-6, GFAP (which has been reported to correlate with spinal cord lesion length and functional outcome after six months), and neurofilaments 94.

6.4 Opthalmologic evaluation

Patients with ON will have impaired color vision or "red desaturation" (red objects seem orange or gray when viewed through the affected eye) 71. On fundus examination, they may also have bland optic disc enlargement and, if there is unilateral involvement, an afferent pupillary defect 71. Although MS and AQP4-IgG-positive NMOSD mainly impact the retrobulbar optic nerve, MOG-IgG patients frequently experience anterior ON. As a result, the presence of papillitis/papilloedema raises the likelihood of a MOG-IgG-related disease; however, various other diagnoses must be evaluated 46, 95.

6.4.1 Optical coherence tomography (OCT)

“OCT is an easily applicable, rapid, and non-invasive technique that can measure retinal neuro-axonal degeneration, indicated by thinning of the retinal nerve fiber layer (RNFL) and the ganglion cell/inner plexiform layer (GCIPL)” 8. In AQP4-IgG-positive NMOSD, ON attacks usually cause severe thinning of the RNFL and GCIPL that is, on average, more pronounced than in classical MS-associated ON 96, resulting in poorer visual function and impaired visual quality of life 97. In contrast to MS, clinically unaffected eyes in AQP4-IgG-positive 98.

“Although single ON attacks in MOG-IgG patients appears to cause less severe retinal damage than in AQP4-IgG-related ON patients, the resultant retinal thinning over the disease seems to be comparable in both conditions, presumably due to a higher frequency of ON attacks in MOG disease” 99, 100. “Whether progressive retinal thinning occurs in non-ON eyes of patients with MOG-IgG requires further investigation, as does the diagnostic and prognostic relevance of microcystic alterations of the inner nuclear layer detected after ON in a subset of patients both in MOG-IgG-associated and in AQP4-IgG-associated disease” 101.

7. MANAGEMENT

7.1 Treatment of acute attacks

Since neurological abnormalities in NMOSD result from the cumulative consequences of attacks, acute treatment is necessary. Intravenous Methylprednisolone (IVMP) 1g daily for at least 3–5 days is the first line of treatment for acute attacks, followed by an oral steroid taper 102, 103. Treatment with IVMP within four days of commencement of AQP4-ON and MOG-ON can enhance the possibility of full visual recovery 104. In contrast, treatment within seven days after onset is linked to a higher risk of poor visual recovery 104.

In one investigation, early initiation of high-dose IVMP therapy was also crucial for limiting axonal damage in NMO-associated ON 105. When recovery is inadequate or slow, oral steroid tapering for 2–6 months may be beneficial and may help to prevent early flare-ups, especially in patients with MOG-IgG 102, 103. In instances unresponsive to high-dose steroids, therapeutic plasma exchange (PEX) is indicated as part of acute therapy, and it should also be considered in episodes involving spinal cord demyelination 105, 106. Immunoadsorption (IA) and intravenous immunoglobulin (IVIG) therapy are other options for patients who do not improve significantly with IVMP 8.

7.2 Preventive immunosuppressive therapy

Long-term immunosuppression should be started as soon as the diagnosis of NMOSD is confirmed. In this case, therapy goals are to lower the intensity of future attacks, delay relapse, and minimize permanent impairment 107. Several immunosuppressive drugs, including rituximab, mycophenolate mofetil (MMF), azathioprine (AZA), and mitoxantrone, have enhanced outcomes in observational studies 102, 103, 108.

7.2.1 Rituximab

Many studies have shown that rituximab (a CD20+ B cell-depleting monoclonal antibody) lowers the recurrence rate in individuals with NMOSD, with 60–80% of patients avoiding relapse if B cell depletion is maintained 109. Rituximab treatment begins with either two of 1 g infusions spaced two weeks apart or four weekly 375 mg/m2 body surface area administrations. Redosing every 6 to 9 months, when the CD19 population exceeds 0.1 percent, or with the therapeutic target of 0.05 percent circulating peripheral memory B cells (CD271 cells in peripheral blood mononuclear cells) have all been tested maintenance therapy regimens 110,111. Through complement-mediated and cell-mediated processes, rituximab depletes nearly all circulating B lymphocytes within hours 102, 103, 108. Following the initial dosage, the second dose depletes B cells that reach the circulation, with circulating B cells remaining decreased for an average of 6–9 months 102, 103, 108. The best outcomes are related to repeated infusions every six months or upon B cell repletion 102, 103, 108. Reduced IgG levels (occurring in 20% of patients with NMOSD), which, if severe enough, can lead to an immunosuppressed condition and, in rare circumstances, early or delayed neutropenia, are among the adverse effects 112,113.

Infections can occur while taking rituximab, just like they might with other immunosuppressants; hepatitis B, active tuberculosis, and other serious diseases must be ruled out before starting treatment. During pregnancy and lactation, rituximab is thought to be relatively safe 8. “The adverse events of rituximab in the setting of NMOSD are similar to those observed in other conditions, such as rheumatoid arthritis, including infusion reactions and infections” 110,111.

7.2.2 Azathioprine

Azathioprine is an immunosuppressive drug that disrupts purine metabolism 8. “The use of azathioprine for NMO is supported by data from a case series in which 37% of treated patients remained relapse-free after two years of follow-up, with stable or improved disability scores in just over 60% of patients treated for one year, despite a 38% discontinuation rate” 114. “A retrospective study found that 61% of patients remained relapse-free after a median of 18 months, with a reduction in median relapse rate from 1.5 to 0 per year; however, 46% of patients discontinued due to adverse events (in 62% of cases) and either death or continued disease activity (in 34% of cases)” 115.

Although evidence from larger trials is required, two retrospective investigations and one controlled clinical trial have suggested that rituximab is superior to azathioprine. Azathioprine is also commonly used in those with MOG-IgG, and it appears to be effective when taken with oral steroids during the drug's latency period 46,116. Due to its latency in action, azathioprine is frequently used in conjunction with oral steroids for the first 4–6 months of treatment 8.

7.2.3 Mycophenolate mofetil

Some observational and controlled trials support the use of MMF to prevent NMO relapses; the reported reduction in relapse risk with therapy is 70–93% compared to pretreatment estimates. According to a meta-analysis, MMF may have better overall tolerability than azathioprine and cyclophosphamide; however, MMF is linked to teratogenicity, and it takes weeks or months to achieve the required decrease in absolute lymphocyte counts, during which time patients are at risk of relapse. MMF is frequently used with low-dose prednisone to prevent recurrence during this vulnerable period 102, 103, 108.

7.3 New long-term therapies

7.3.1 Tocilizumab

Tocilizumab is an IL-6 receptor humanized monoclonal antibody 8. Increased IL-6 levels have been identified in the serum and CSF of patients with NMOSD, notably during relapses suggesting that IL-6 may have a role in the etiology of NMOSD 107. Plasmablasts produce and secrete AQP4-IgG in response to IL-6 107. Tocilizumab, given for 12 to 24 months, reduced clinical and MRI disease activity in NMO, according to several case reports and a prospective pilot trial 117–119. These findings were verified in a retrospective study of 8 individuals with severe relapsing illness who had been unresponsive to previous treatments, including rituximab, treated with tocilizumab for up to 51 months 120.

7.3.2 Eculizumab

“Eculizumab is a humanized therapeutic monoclonal antibody that inhibits the terminal complement cascade, preventing C5 cleavage and the production of the cytolytic membrane attack complex” 8. “Eculizumab was found to be highly effective in reducing the risk of relapse in patients with NMOSD in a global phase III study (PREVENT) and was approved in June 2019 for the treatment of adult patients with AQP4-IgG-positive NMOSD in the United States, and shortly after in the European Union and Japan” 121. “Increased susceptibility to infections, particularly with encapsulated bacteria, and

upper respiratory tract infections are among the side effects of eculizumab; in one trial, one patient with NMOSD had meningococcal sepsis" 122.

Meningococcal vaccines are required; immunization must be done at least 2 weeks before the first dose of eculizumab unless delaying treatment outweighs the risk of getting a meningococcal infection 8.

7.3.3 Satralizumab

"Satralizumab is a humanized anti-IL-6 receptor monoclonal antibody with a longer half-life than tocilizumab, which is given subcutaneously" 8. "In patients with AQP4-IgG-positive NMOSD and active disease, a phase III studies evaluated the efficacy and safety of satralizumab as an add-on (SAkuraSky) or monotherapy (SAkuraStar) both showed a significant reduction in relapse risk" 123. In August 2020, the FDA approved the medicine to treat adult patients with AQP4-IgG-positive NMOSD, including by self-injection, based on the findings of these studies 8. In both investigations, the number of patients who experienced significant adverse events was identical, and no allergic reactions, opportunistic infections, or deaths were observed 8.

8. CONCLUSION

Despite the fact that the underlying mechanism of NMO has been established, with AQP4-IgG antibodies found in the majority of NMO patients, ethnic and environmental factors play a substantial role in the disease's clinical features and prognosis. Improved understanding of NMO pathogenesis is critical for developing diagnostic tools for earlier detection and developing novel effective treatments. NMO is currently incurable, and patients may suffer from devastating disability for the duration of their condition. Multiple biochemical therapies (corticosteroids, immunosuppressants, monoclonal antibodies, and plasma exchange) reduce relapse rates and, in certain cases, anti-AQP4 blood levels.

DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES

1. van Pelt ED, Wong YYM, Ketelslegers IA, Hamann D, Hintzen RQ. Neuromyelitis optica spectrum disorders: comparison of clinical and magnetic resonance imaging characteristics of AQP4-IgG versus MOG-IgG seropositive cases in the Netherlands. *Eur J Neurol*. 2016;23(3):580-587. doi:10.1111/ene.12898
2. Wingerchuk DM, Banwell B, Bennett JL, Cabre, P., Carroll, W., Chitnis, T., et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189. doi:10.1212/WNL.0000000000001729
3. Jarius S, Wildemann B. Aquaporin-4 antibodies (NMO-IgG) as a serological marker of neuromyelitis optica: a critical review of the literature. *Brain Pathol*. 2013;23(6):661-683. doi:10.1111/bpa.12084
4. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock, S. J., Lucchinetti, C. F., Fujihara, K., et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet*. 2004;364(9451):2106-2112. doi:10.1016/S0140-6736(04)17551-X
5. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med*. 2005;202(4):473-477. doi:10.1084/jem.20050304
6. Mader S, Gredler V, Schanda K, Rostasy, K., Dujmovic, I., Pfaller, K., et al. Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders. *J Neuroinflammation*. 2011;8:184. doi:10.1186/1742-2094-8-184
7. O'Connor KC, McLaughlin KA, De Jager PL, Chitnis, T., Bettelli, E., Xu, C., et al. Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. *Nat Med*. 2007;13(2):211-217. doi:10.1038/nm1488

8. Jarius S, Paul F, Weinshenker BG, Levy M, Kim HJ, Wildemann B. Neuromyelitis optica. *Nat Rev Dis Primers*. 2020;6(1):85. doi:10.1038/s41572-020-0214-9

9. Evans C, Beland S-G, Kulaga S, Wolfson, C., Kingwell, E., Marriott, J., et al. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. *Neuroepidemiology*. 2013;40(3):195-210. doi:10.1159/000342779

10. Kingwell E, Marriott JJ, Jetté N, Pringsheim, T., Makhani, N., Morrow, S. A., et al. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. *BMC Neurol*. 2013;13:128. doi:10.1186/1471-2377-13-128

11. Bukhari W, Khalilidehkordi E, Mason DF, Barnett, M. H., Taylor, B. V., Fabis-Pedrini, M., et al. NMOSD and MS prevalence in the Indigenous populations of Australia and New Zealand. *J Neurol*. Published online July 2, 2021. doi:10.1007/s00415-021-10665-9

12. Bukhari W, Prain KM, Waters P, Woodhall, M., O'Gorman, C. M., Clarke, L., et al. Incidence and prevalence of NMOSD in Australia and New Zealand. *J Neurol Neurosurg Psychiatr*. 2017;88(8):632-638. doi:10.1136/jnnp-2016-314839

13. Sepúlveda M, Aldea M, Escudero D, Llufriu, S., Arrambide, G., Otero-Romero, S., et al. Epidemiology of NMOSD in Catalonia: Influence of the new 2015 criteria in incidence and prevalence estimates. *Mult Scler*. 2018;24(14):1843-1851. doi:10.1177/1352458517735191

14. Jonsson DI, Sveinsson O, Hakim R, Brundin L. Epidemiology of NMOSD in Sweden from 1987 to 2013: A nationwide population-based study. *Neurology*. 2019;93(2):e181-e189. doi:10.1212/WNL.0000000000007746

15. Asgari N, Lillevang ST, Skejoe HPB, Falah M, Stenager E, Kyvik KO. A population-based study of neuromyelitis optica in Caucasians. *Neurology*. 2011;76(18):1589-1595. doi:10.1212/WNL.0b013e3182190f74

16. Miyamoto K, Fujihara K, Kira J-I, Kuriyama, N., Matsui, M., Tamakoshi, A., & Kusunoki, S. Nationwide epidemiological study of neuromyelitis optica in Japan. *J Neurol Neurosurg Psychiatr*. 2018;89(6):667-668. doi:10.1136/jnnp-2017-317321

17. Wang H, Dai Y, Qiu W, Zhong, X., Wu, A., Wang, Y., et al. HLA-DPB1 0501 is associated with susceptibility to anti-aquaporin-4 antibodies positive neuromyelitis optica in southern Han Chinese. *J Neuroimmunol*. 2011;233(1-2):181-184. doi:10.1016/j.jneuroim.2010.11.004

18. Osuntokun BO. The pattern of neurological illness in tropical Africa. Experience at Ibadan, Nigeria. *J Neurol Sci*. 1971;12(4):417-442. doi:10.1016/0022-510x(71)90110-9

19. Jacob A, Panicker J, Lythgoe D, Elsone, L., Mutch, K., Wilson, M., et al. The epidemiology of neuromyelitis optica amongst adults in the Merseyside county of United Kingdom. *J Neurol*. 2013;260(8):2134-2137. doi:10.1007/s00415-013-6926-y

20. Wu Y, Zhong L, Geng J. Neuromyelitis optica spectrum disorder: Pathogenesis, treatment, and experimental models. *Mult Scler Relat Disord*. 2019;27:412-418. doi:10.1016/j.msard.2018.12.002

21. Nielsen S, Nagelhus EA, Amiry-Moghaddam M, Bourque C, Agre P, Ottersen OP. Specialized membrane domains for water transport in glial cells: high-resolution immunogold cytochemistry of aquaporin-4 in rat brain. *J Neurosci*. 1997;17(1):171-180. doi:10.1523/JNEUROSCI.17-01-00171.1997

22. Jung JS, Bhat RV, Preston GM, Guggino WB, Baraban JM, Agre P. Molecular characterization of an aquaporin cDNA from brain: candidate osmoreceptor and regulator of water balance. *Proc Natl Acad Sci USA*. 1994;91(26):13052-13056. doi:10.1073/pnas.91.26.13052

23. Lucchinetti CF, Mandler RN, McGavern D, Bruck, W., Gleich, G., Ransohoff, R. M., et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. *Brain*. 2002;125(Pt 7):1450-1461. doi:10.1093/brain/awf151

24. Jarius S, Wildemann B, Paul F. Neuromyelitis optica: clinical features, immunopathogenesis and treatment. *Clin Exp Immunol*. 2014;176(2):149-164. doi:10.1111/cei.12271

25. Tradtrantip L, Jin B-J, Yao X, Anderson MO, Verkman AS. Aquaporin-Targeted Therapeutics: State-of-the-Field. *Adv Exp Med Biol*. 2017;969:239-250. doi:10.1007/978-94-024-1057-0_16

26. Tradtrantip L, Yao X, Su T, Smith AJ, Verkman AS. Bystander mechanism for complement-initiated early oligodendrocyte injury in neuromyelitis optica. *Acta Neuropathol*. 2017;134(1):35-44. doi:10.1007/s00401-017-1734-6

27. Majed M, Fryer JP, McKeon A, Lennon VA, Pittock SJ. Clinical utility of testing AQP4-IgG in CSF: Guidance for physicians. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(3):e231. doi:10.1212/NXI.0000000000000231

28. Valentino P, Marnetto F, Granieri L, Capobianco M, Bertolotto A. Aquaporin-4 antibody titration in NMO patients

treated with rituximab: A retrospective study. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(2):e317. doi:10.1212/NXI.0000000000000317

29. Matiello M, Schaefer-Klein J, Sun D, Weinshenker BG. Aquaporin 4 expression and tissue susceptibility to neuromyelitis optica. *JAMA Neurol*. 2013;70(9):1118-1125. doi:10.1001/jamaneurol.2013.3124

30. Yao X, Verkman AS. Marked central nervous system pathology in CD59 knockout rats following passive transfer of Neuromyelitis optica immunoglobulin G. *Acta Neuropathol Commun*. 2017;5(1):15. doi:10.1186/s40478-017-0417-9

31. Etemadifar M, Salari M, Mirmosayyeb O, Serati, M., Nikkhah, R., Askari, M., & Fayyazi, E. Efficacy and safety of rituximab in neuromyelitis optica: Review of evidence. *J Res Med Sci*. 2017;22:18. doi:10.4103/1735-1995.200275

32. Chihara N, Aranami T, Sato W, Miyazaki, Y., Miyake, S., Okamoto, T., et al. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. *Proc Natl Acad Sci USA*. 2011;108(9):3701-3706. doi:10.1073/pnas.1017385108

33. Quan C, Yu H, Qiao J, Zhao, G., Wu, Z., Li, Z., & Lu, C. Impaired regulatory function and enhanced intrathecal activation of B cells in neuromyelitis optica: distinct from multiple sclerosis. *Mult Scler*. 2013;19(3):289-298. doi:10.1177/1352458512454771

34. Graber DJ, Levy M, Kerr D, Wade WF. Neuromyelitis optica pathogenesis and aquaporin 4. *J Neuroinflammation*. 2008;5:22. doi:10.1186/1742-2094-5-22

35. Li M, Yan Y. Experimental models of neuromyelitis optica: current status, challenges and future directions. *Neurosci Bull*. 2015;31(6):735-744. doi:10.1007/s12264-015-1552-6

36. Linhares UC, Schiavoni PB, Barros PO, Kasahara, T. M., Teixeira, B., Ferreira, T. B, et al. The ex vivo production of IL-6 and IL-21 by CD4+ T cells is directly associated with neurological disability in neuromyelitis optica patients. *J Clin Immunol*. 2013;33(1):179-189. doi:10.1007/s10875-012-9780-2

37. Whittam D, Wilson M, Hamid S, Keir G, Bhojak M, Jacob A. What's new in neuromyelitis optica? A short review for the clinical neurologist. J Neurol. 2017;264(11):2330-2344. doi:10.1007/s00415-017-8445-8

38. Ungureanu A, de Seze J, Ahle G, Sellal F. Myelin oligodendrocyte glycoprotein antibodies in neuromyelitis optica spectrum disorder. *Rev Neurol (Paris)*. 2018;174(10):675-679. doi:10.1016/j.neurol.2018.01.378

39. Vourc'h P, Andres C. Oligodendrocyte myelin glycoprotein (OMgp): evolution, structure and function. *Brain Res Brain Res Rev*. 2004;45(2):115-124. doi:10.1016/j.brainresrev.2004.01.003

40. Johns TG, Bernard CC. The structure and function of myelin oligodendrocyte glycoprotein. *J Neurochem*. 1999;72(1):1-9. doi:10.1046/j.1471-4159.1999.0720001.x

41. Takai Y, Misu T, Kaneko K, Chihara N., Narikawa K., Tsuchida S, et al. Myelin oligodendrocyte glycoprotein antibody-associated disease: an immunopathological study. *Brain*. 2020;143(5):1431-1446. doi:10.1093/brain/awaa102

42. Höftberger R, Guo Y, Flanagan EP, Lopez-Chiriboga AS, Endmayr V, Hochmeister S, et al. The pathology of central nervous system inflammatory demyelinating disease accompanying myelin oligodendrocyte glycoprotein autoantibody. *Acta Neuropathol*. 2020;139(5):875-892. doi:10.1007/s00401-020-02132-y

43. Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol*. 2000;47(6):707-717. doi:10.1002/1531-8249(200006)47:6<707::aid-ana3>3.0.co;2-q

44. Jarius S, König FB, Metz I, Ruprecht K, Paul F, Brück W, Wildemann B. Pattern II and pattern III MS are entities distinct from pattern I MS: evidence from cerebrospinal fluid analysis. *J Neuroinflammation*. 2017;14(1):171. doi:10.1186/s12974-017-0929-z

45. Sellner J, Boggild M, Clanet M, Hintzen RQ, Illes Z, Montalban X, et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. *Eur J Neurol*. 2010;17(8):1019-1032. doi:10.1111/j.1468-1331.2010.03066.x

46. Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, Pache F, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. *J Neuroinflammation*. 2016;13(1):280. doi:10.1186/s12974-016-0718-0

47. Jarius S, Ruprecht K, Wildemann B, Kuempfel T, Ringelstein M, Geis C, Kleiter I, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients. *J*

Neuroinflammation. 2012;9:14. doi:10.1186/1742-2094-9-14

48. Nakajima H, Hosokawa T, Sugino M, Kimura F, Sugasawa J, Hanafusa T, Takahashi T. Visual field defects of optic neuritis in neuromyelitis optica compared with multiple sclerosis. *BMC Neurol*. 2010;10:45. doi:10.1186/1471-2377-10-45

49. Kupersmith MJ, Alban T, Zeiffer B, Lefton D. Contrast-enhanced MRI in acute optic neuritis: relationship to visual performance. *Brain*. 2002;125(Pt 4):812-822. doi:10.1093/brain/awf087

50. Beh SC, Greenberg BM, Frohman T, Frohman EM. Transverse myelitis. *Neurol Clin*. 2013;31(1):79-138. doi:10.1016/j.ncl.2012.09.008

51. West TW, Hess C, Cree BAC. Acute transverse myelitis: demyelinating, inflammatory, and infectious myelopathies. *Semin Neurol*. 2012;32(2):97-113. doi:10.1055/s-0032-1322586

52. West TW. Transverse myelitis--a review of the presentation, diagnosis, and initial management. *Discov Med*. 2013;16(88):167-177.

53. Nakamura M, Miyazawa I, Fujihara K, Nakashima I, Misu T, Watanabe S, et al. Preferential spinal central gray matter involvement in neuromyelitis optica. An MRI study. *J Neurol*. 2008;255(2):163-170. doi:10.1007/s00415-008-0545-z

54. Krampla W, Aboul-Enein F, Jecel J, Lang W, Fertl E, Hruby W, et al. Spinal cord lesions in patients with neuromyelitis optica: a retrospective long-term MRI follow-up study. *Eur Radiol*. 2009;19(10):2535-2543. doi:10.1007/s00330-009-1425-3

55. Mutch K, Zhao S, Hamid S, Methley A, Elsone L, Singh G, et al. Bladder and bowel dysfunction affect quality of life. A cross sectional study of 60 patients with aquaporin-4 antibody positive Neuromyelitis Optica spectrum disorder. *Mult Scler Relat Disord*. 2015;4(6):614-618. doi:10.1016/j.msard.2015.07.015

56. Jarius S, Kleiter I, Ruprecht K, Asgari N, Pitarokoili K, Borisow N, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 3: Brainstem involvement - frequency, presentation and outcome. *J Neuroinflammation*. 2016;13(1):281. doi:10.1186/s12974-016-0719-z

57. Etemadifar M, Mehrbod N, Dehghani L, Golabbakhsh A, Fereidan-Esfahani M, Akbari M, et al. Prevalence of Lhermitte's sign in multiple sclerosis versus neuromyelitis optica. *Iran J Neurol*. 2014;13(1):50-51.

58. McKeon A, Lennon VA, Lotze T, et al. CNS aquaporin-4 autoimmunity in children. *Neurology*. 2008;71(2):93-100. doi:10.1212/01.wnl.0000314832.24682.c6

59. Misu T, Fujihara K, Nakashima I, Sato S, Itoyama Y. Intractable hiccup and nausea with periaqueductal lesions in neuromyelitis optica. *Neurology*. 2005;65(9):1479-1482. doi:10.1212/01.wnl.0000183151.19351.82

60. Takahashi T, Miyazawa I, Misu T, Takano R, Nakashima I, Fujihara K, et al. Intractable hiccup and nausea in neuromyelitis optica with anti-aquaporin-4 antibody: a herald of acute exacerbations. *J Neurol Neurosurg Psychiatr*. 2008;79(9):1075-1078. doi:10.1136/jnnp.2008.145391

61. Akaishi T, Nakashima I, Sato DK, Takahashi T, Fujihara K. Neuromyelitis optica spectrum disorders. *Neuroimaging Clin N Am*. 2017;27(2):251-265. doi:10.1016/j.nic.2016.12.010

62. Kim HJ, Paul F, Lana-Peixoto MA, Tenembaum S, Asgari N, Palace J, et al. MRI characteristics of neuromyelitis optica spectrum disorder: an international update. *Neurology*. 2015;84(11):1165-1173. doi:10.1212/WNL.0000000000001367

63. Kim S-M, Go MJ, Sung J-J, Park KS, Lee K-W. Painful tonic spasm in neuromyelitis optica: incidence, diagnostic utility, and clinical characteristics. *Arch Neurol*. 2012;69(8):1026-1031. doi:10.1001/archneurol.2012.112

64. Liu J, Zhang Q, Lian Z, Chen H, Shi Z, Feng H, Miao X, et al. Painful tonic spasm in neuromyelitis optica spectrum disorders: Prevalence, clinical implications and treatment options. *Mult Scler Relat Disord*. 2017;17:99-102. doi:10.1016/j.msard.2017.07.004

65. Deguchi S, Deguchi K, Sato K, et al. HyperCKemia related to the initial and recurrent attacks of neuromyelitis optica. *Intern Med*. 2012;51(18):2617-2620. doi:10.2169/internalmedicine.51.7898

66. Di Filippo M, Franciotta D, Massa R, Yunoki T, Omote Y, Morimoto N, et al. Recurrent hyperCKemia with normal muscle biopsy in a pediatric patient with neuromyelitis optica. *Neurology*. 2012;79(11):1182-1184. doi:10.1212/WNL.0b013e3182698d39

67. Jarius S, Paul F, Ruprecht K, Wildemann B. Low vitamin B12 levels and gastric parietal cell antibodies in patients with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorders. *J Neurol*. 2012;259(12):2743-2745. doi:10.1007/s00415-012-6677-1

68. Jarius S, Paul F, Franciotta D, de Seze J, Münch C, Salvetti M, et al. Neuromyelitis optica spectrum disorders in patients with myasthenia gravis: ten new aquaporin-4 antibody positive cases and a review of the literature. *Mult Scler*. 2012;18(8):1135-1143. doi:10.1177/1352458511431728

69. Leite MI, Coutinho E, Lana-Peixoto M, Apostolos S, Waters P, Sato D, et al. Myasthenia gravis and neuromyelitis optica spectrum disorder: a multicenter study of 16 patients. *Neurology*. 2012;78(20):1601-1607. doi:10.1212/WNL.0b013e31825644ff

70. Titulaer MJ, Höftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, et al. Overlapping demyelinating syndromes and anti–N-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2014;75(3):411-428. doi:10.1002/ana.24117

71. Milo R, Kahana E. Multiple sclerosis: geoepidemiology, genetics and the environment. *Autoimmun Rev*. 2010;9(5):A387-94. doi:10.1016/j.autrev.2009.11.010

72. Hor JY, Asgari N, Nakashima I, Broadley SA, Leite MI, Kissani N, Jacob A, et al. Epidemiology of neuromyelitis optica spectrum disorder and its prevalence and incidence worldwide. *Front Neurol*. 2020;11:501. doi:10.3389/fneur.2020.00501

73. Marignier R, Bernard-Valnet R, Giraudon P, Collongues N, Papeix C, Zéphir H, et al. Aquaporin-4 antibody-negative neuromyelitis optica: distinct assay sensitivity-dependent entity. *Neurology*. 2013;80(24):2194-2200. doi:10.1212/WNL.0b013e318296e917

74. Fryer JP, Lennon VA, Pittock SJ, Jenkins SM, Fallier-Becker P, Clardy SL, et al. AQP4 autoantibody assay performance in clinical laboratory service. *Neurol Neuroimmunol Neuroinflamm*. 2014;1(1):e11. doi:10.1212/NXI.0000000000000011

75. Mariotto S, Ferrari S, Monaco S, Benedetti MD, Schanda K, Alberti D, et al. Clinical spectrum and IgG subclass analysis of anti-myelin oligodendrocyte glycoprotein antibody-associated syndromes: a multicenter study. *J Neurol*. 2017;264(12):2420-2430. doi:10.1007/s00415-017-8635-4

76. Baumann M, Grams A, Djurdjevic T, Wendel EM, Lechner C, Behring B, et al. MRI of the first event in pediatric acquired demyelinating syndromes with antibodies to myelin oligodendrocyte glycoprotein. *J Neurol*. 2018;265(4):845-855. doi:10.1007/s00415-018-8781-3

77. Macaron G, Ontaneda D. MOG-related disorders: A new cause of imaging-negative myelitis? *Mult Scler*. 2020;26(4):511-515. doi:10.1177/1352458519840746

78. Wang H, Wang K, Wang C, Xu F, Qiu W, Hu X. Increased plasma interleukin-32 expression in patients with neuromyelitis optica. *J Clin Immunol*. 2013;33(3):666-670. doi:10.1007/s10875-012-9837-2

79. Chien C, Scheel M, Schmitz-Hübsch T, Borisow N, Ruprecht K, Bellmann-Strobl J, et al. Spinal cord lesions and atrophy in NMOSD with AQP4-IgG and MOG-IgG associated autoimmunity. *Mult Scler*. 2019;25(14):1926-1936. doi:10.1177/1352458518815596

80. Nandhagopal R, Al-Asmi A, Gujjar AR. Neuromyelitis optica: an overview. Postgrad Med J. 2010;86(1013):153-159. doi:10.1136/pgmj.2009.091389

81. Ramanathan S, Prelog K, Barnes EH, Tantsis EM, Reddel SW, Henderson AP, et al. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. *Mult Scler*. 2016;22(4):470-482. doi:10.1177/1352458515593406

82. Sato DK, Nakashima I, Takahashi T, et al. Aquaporin-4 antibody-positive cases beyond current diagnostic criteria for NMO spectrum disorders. Neurology. 2013;80(24):2210-2216. doi:10.1212/WNL.0b013e318296ea08

83. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. *Brain*. 2019;142(7):1858-1875. doi:10.1093/brain/awz144

84. Wei Q, Yanyu C, Rui L, Caixia L, Youming L, Jianhua H, et al. Human aquaporin 4 gene polymorphisms in Chinese patients with neuromyelitis optica. *J Neuroimmunol*. 2014;274(1-2):192-196. doi:10.1016/j.jneuroim.2014.07.003

85. Shosha E, Dubey D, Palace J, Nakashima I, Jacob A, Fujihara K, et al. Area postrema syndrome: Frequency, criteria, and severity in AQP4-IgG-positive NMOSD. *Neurology*. 2018;91(17):e1642-e1651. doi:10.1212/WNL.0000000000006392

86. Dubey D, Pittock SJ, Krecke KN, Flanagan EP. Association of extension of cervical cord lesion and area postrema syndrome with neuromyelitis optica spectrum disorder. *JAMA Neurol*. 2017;74(3):359-361. doi:10.1001/jamaneurol.2016.5441

87. Geraldes R, Ciccarelli O, Barkhof F, De Stefano N, Enzinger C, Filippi M, et al. The current role of MRI in differentiating multiple sclerosis from its imaging mimics. *Nat Rev Neurol*. 2018;14(4):213. doi:10.1038/nrneurol.2018.39

88. Bichuetti DB, Rivero RLM, Oliveira DM, et al. Neuromyelitis optica: brain abnormalities in a Brazilian cohort. Arq Neuropsiquiatr. 2008;66(1):1-4. doi:10.1590/s0004-282x2008000100001

89. Jarius S, Paul F, Franciotta D, Ruprecht K, Ringelstein M, Bergamaschi R et al. Cerebrospinal fluid findings in aquaporin-4 antibody positive neuromyelitis optica: results from 211 lumbar punctures. *J Neurol Sci*. 2011;306(1-2):82-90. doi:10.1016/j.jns.2011.03.038

90. Jarius S, Pellkofer H, Siebert N, Korporal-Kuhnke M, Hümmert MW, et al. Cerebrospinal fluid findings in patients with myelin oligodendrocyte glycoprotein (MOG) antibodies. Part 1: Results from 163 lumbar punctures in 100 adult patients. *J Neuroinflammation*. 2020;17(1):261. doi:10.1186/s12974-020-01824-2

91. Jarius S, Lechner C, Wendel EM, Baumann M, Breu M, Schimmel M, et al. Cerebrospinal fluid findings in patients with myelin oligodendrocyte glycoprotein (MOG) antibodies. Part 2: Results from 108 lumbar punctures in 80 pediatric patients. *J Neuroinflammation*. 2020;17(1):262. doi:10.1186/s12974-020-01825-1

92. Uzawa A, Mori M, Kuwabara S. Neuromyelitis optica: concept, immunology and treatment. *J Clin Neurosci*. 2014;21(1):12-21. doi:10.1016/j.jocn.2012.12.022

93. Correale J, Fiol M. Activation of humoral immunity and eosinophils in neuromyelitis optica. *Neurology*. 2004;63(12):2363-2370. doi:10.1212/01.wnl.0000148481.80152.bf

94. Uzawa A, Mori M, Ito M, Uchida T, Hayakawa S, Masuda S, et al. Markedly increased CSF interleukin-6 levels in neuromyelitis optica, but not in multiple sclerosis. *J Neurol*. 2009;256(12):2082-2084. doi:10.1007/s00415-009-5274-4

95. Biotti D, Bonneville F, Tournaire E, Ayrignac X, Dallière CC, Mahieu L, et al. Optic neuritis in patients with anti-MOG antibodies spectrum disorder: MRI and clinical features from a large multicentric cohort in France. *J Neurol*. 2017;264(10):2173-2175. doi:10.1007/s00415-017-8615-8

96. Bennett JL, de Seze J, Lana-Peixoto M, Palace J, Waldman A, Schippling S et al. Neuromyelitis optica and multiple sclerosis: Seeing differences through optical coherence tomography. *Mult Scler*. 2015;21(6):678-688. doi:10.1177/1352458514567216

97. Schmidt F, Zimmermann H, Mikolajczak J, Oertel FC, Pache F, Weinhold M et al. Severe structural and functional visual system damage leads to profound loss of vision-related quality of life in patients with neuromyelitis optica spectrum disorders. *Mult Scler Relat Disord*. 2017;11:45-50. doi:10.1016/j.msard.2016.11.008

98. Petzold A, Balcer LJ, Calabresi PA, Costello F, Frohman TC, Frohman EM, et al. Retinal layer segmentation in multiple sclerosis: a systematic review and meta-analysis. *Lancet Neurol*. 2017;16(10):797-812. doi:10.1016/S1474-4422(17)30278-8

99. Pache F, Zimmermann H, Mikolajczak J, Schumacher S, Lacheta A, Oertel FC, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 4: Afferent visual system damage after optic neuritis in MOG-IgG-seropositive versus AQP4-IgG-seropositive patients. *J Neuroinflammation*. 2016;13(1):282. doi:10.1186/s12974-016-0720-6

100. Akaishi T, Sato DK, Nakashima I, Takeshita T, Takahashi T, Doi H, et al. MRI and retinal abnormalities in isolated optic neuritis with myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies: a comparative study: Table 1. *J Neurol Neurosurg Psychiatry*. 2016;87(4):446-448. doi:10.1136/jnnp-2014-310206

101. Oertel FC, Outteryck O, Knier B, Zimmermann H, Borisow N, Bellmann-Strobl J et al. Optical coherence tomography in myelin-oligodendrocyte-glycoprotein antibody-seropositive patients: a longitudinal study. *J Neuroinflammation*. 2019;16(1):154. doi:10.1186/s12974-019-1521-5

102. Trebst C, Jarius S, Berthele A, Paul F, Schippling S, Wildemann B, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). *J Neurol*. 2014;261(1):1-16. doi:10.1007/s00415-013-7169-7

103. Romeo AR, Segal BM. Treatment of neuromyelitis optica spectrum disorders. *Curr Opin Rheumatol*. 2019;31(3):250-255. doi:10.1097/BOR.0000000000000603

104. Stiebel-Kalish H, Hellmann MA, Mimouni M, Paul F, Bialer O, Bach M, et al. Does time equal vision in the acute treatment of a cohort of AQP4 and MOG optic neuritis? *Neurol Neuroimmunol Neuroinflamm*. 2019;6(4):e572. doi:10.1212/NXI.0000000000000572

105. Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke KD, Wegner B, et al. Neuromyelitis optica: Evaluation of 871

attacks and 1,153 treatment courses. *Ann Neurol*. 2016;79(2):206-216. doi:10.1002/ana.24554

106. Watanabe S, Nakashima I, Misu T, Miyazawa I, Shiga Y, Fujihara K, Itoyama Y, et al. Therapeutic efficacy of plasma exchange in NMO-IgG-positive patients with neuromyelitis optica. *Mult Scler*. 2007;13(1):128-132. doi:10.1177/1352458506071174

107. Patterson SL, Goglin SE. Neuromyelitis Optica. *Rheum Dis Clin North Am*. 2017;43(4):579-591. doi:10.1016/j.rdc.2017.06.007

108. Montcuquet A, Collongues N, Papeix C, Zephir H, Audoin B, Laplaud D, et al. Effectiveness of mycophenolate mofetil as first-line therapy in AQP4-IgG, MOG-IgG, and seronegative neuromyelitis optica spectrum disorders. *Mult Scler*. 2017;23(10):1377-1384. doi:10.1177/1352458516678474

109. Damato V, Evoli A, Iorio R. Efficacy and Safety of Rituximab Therapy in Neuromyelitis Optica Spectrum Disorders: A Systematic Review and Meta-analysis. *JAMA Neurol*. 2016;73(11):1342-1348. doi:10.1001/jamaneurol.2016.1637

110. Collongues N, de Seze J. An update on the evidence for the efficacy and safety of rituximab in the management of neuromyelitis optica. *Ther Adv Neurol Disord*. 2016;9(3):180-188. doi:10.1177/1756285616632653

111. Kim S-H, Huh S-Y, Lee SJ, Joung A, Kim HJ. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. *JAMA Neurol*. 2013;70(9):1110-1117. doi:10.1001/jamaneurol.2013.3071

112. Tallantyre EC, Whittam DH, Jolles S, Paling D, Constantinesecu C, Robertson NP, et al. Secondary antibody deficiency: a complication of anti-CD20 therapy for neuroinflammation. *J Neurol*. 2018;265(5):1115-1122. doi:10.1007/s00415-018-8812-0

113. Marcinnò A, Marnetto F, Valentino P, Martire S, Balbo A, Drago A, et al. Rituximab-induced hypogammaglobulinemia in patients with neuromyelitis optica spectrum disorders. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(6):e498. doi:10.1212/NXI.0000000000000498

114. Costanzi C, Matiello M, Lucchinetti CF, Weinshenker BG, Pittock SJ, Mandrekar J, et al. Azathioprine: tolerability, efficacy, and predictors of benefit in neuromyelitis optica. *Neurology*. 2011;77(7):659-666. doi:10.1212/WNL.0b013e31822a2780

115. Elsone L, Kitley J, Luppe S, Lythgoe D, Mutch K, Jacob S, et al. Long-term efficacy, tolerability and retention rate of azathioprine in 103 aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder patients: a multicentre retrospective observational study from the UK. *Mult Scler*. 2014;20(11):1533-1540. doi:10.1177/1352458514525870

116. Hacohen Y, Wong YY, Lechner C, Jurynczyk M, Wright S, Konuskan B, et al. Disease Course and Treatment Responses in Children With Relapsing Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. *JAMA Neurol*. 2018;75(4):478-487. doi:10.1001/jamaneurol.2017.4601

117. Araki M, Matsuoka T, Miyamoto K, Kusunoki S, Okamoto T, Murata M, et al. Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: a pilot study. *Neurology*. 2014;82(15):1302-1306. doi:10.1212/WNL.0000000000000317

118. Ayzenberg I, Kleiter I, Schröder A, Hellwig K, Chan A, Yamamura T, Gold R, et al. Interleukin 6 receptor blockade in patients with neuromyelitis optica nonresponsive to anti-CD20 therapy. *JAMA Neurol*. 2013;70(3):394-397. doi:10.1001/jamaneurol.2013.1246

119. Kieseier BC, Stüve O, Dehmel T, Goebels N, Leussink VI, Mausberg AK, et al. Disease amelioration with tocilizumab in a treatment-resistant patient with neuromyelitis optica: implication for cellular immune responses. *JAMA Neurol*. 2013;70(3):390-393. doi:10.1001/jamaneurol.2013.668

120. Ringelstein M, Ayzenberg I, Harmel J, Lauenstein AS, Lensch E, Stögbauer F, et al. Long-term Therapy With Interleukin 6 Receptor Blockade in Highly Active Neuromyelitis Optica Spectrum Disorder. *JAMA Neurol*. 2015;72(7):756-763. doi:10.1001/jamaneurol.2015.0533

121. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. *N Engl J Med*. 2019;381(7):614-625. doi:10.1056/NEJMoa1900866

122. Pittock SJ, Lennon VA, McKeon A, Mandrekar J, Weinshenker BG, Lucchinetti CF, et al. Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. *Lancet Neurol*. 2013;12(6):554-562. doi:10.1016/S1474-4422(13)70076-0

123. Yamamura T, Kleiter I, Fujihara K, Palace J, Greenberg B, Zakrzewska-Pniewska B, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381(22):2114-2124. doi:10.1056/NEJMoa1901747