Journal of the Neurological Sciences 420 (2021) 117225

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

Neuromyelitis optica spectrum disorders

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ARTICLE INFO

Keywords:
Neuromyelitis optica spectrum disorders
Aquaprin-4 antibody
MOG antibody
Demyelinating disease

ABSTRACT

The disease concept of Neuromyelitis Optica Spectrum Disorders(NMOSD) has undergone a significant change over the last two decades including the detection of Myelin Oligodendrocyte Glycoprotein(MOG) antibody in patients who are seronegative for aquaporin-4 antibody. Aquaporin-4 antibody positive NMOSD is now regarded as an immune astrocytopathy. Conversely, MOG antibody associated disease is known to target myelin rather than astrocytes, leading to an NMOSD syndrome with distinct clinical and radiological features. Incorporation of clinical features like area postrema syndrome, brainstem syndrome, diencephalic syndrome and cortical manifestations as core clinical characteristics into the revised diagnostic criteria has widened the clinical spectrum of NMOSD. With the development of these criteria, it is possible to make the diagnosis at an earlier stage so that effective immunosuppression can be instituted promptly for a better long-term prognosis. Newer therapeutic agents have been introduced for aquaporin-4 seropositive NMOSD disease; however, challenges remain in treating seronegative disease because of limited treatment options.

1. Introduction

Neuromyelitis Optica spectrum disorders (NMOSD) is referred to as an inflammatory disease of CNS predominantly involving optic nerves and spinal cord. Devic and Gault were the first to report a series of patients presenting with bilateral or sequential optic neuritis and myelitis [1,2]. Neuromyelitis optica or Devic's disease required optic neuritis, myelitis and no other CNS disease as diagnostic criteria. The term NMOSD was first introduced in 2007 to include recurrent or bilateral optic neuritis and longitudinally extensive transverse myelitis (LETM) apart from the classical NMO. In 2015, NMOSD was proposed as a unifying term to cover the entire clinical spectrum of this disease including limited forms of Neuromyelitis Optica(NMO) like recurrent optic neuritis or first attack of Longitudinally Extensive Transverse Myelitis (LETM) who are at high risk of recurrence and different brain manifestations like area postrema syndrome, brainstem syndrome and diencephalic syndrome [3]. Recent years have seen several advances in the field of this unique disorder ranging from a better understanding of pathogenic mechanisms of this disease and detection of subclinical disease by newer diagnostic tools to the development of novel therapeutic agents targeting various molecules in the inflammatory cascade. Several studies have shown that aquaporin-4 antibody may be absent in 20–30% of NMOSD depending on the assay used [4,5]. With the help of cell-based assays, MOG antibody has been detected in a good proportion of AQP4 seronegative cases of NMOSD. Although having overlapping clinical and radiological features with AQP4 positive NMOSD, MOG-associated disease is now seen as a distinct disease entity [6]. Assessment of retinal nerve fibre layer thickness and macular volume by means of optic coherence tomography (OCT) has made a significant impact on diagnostic evaluation and follow up of optic neuritis in different subtypes of this disorder [7]. Various recent randomized trials have demonstrated the efficacy of different monoclonal antibodies targeting complement protein C5, IL-6 receptor, CD19 and others; although there is a need for larger studies to establish these results [8]. The purpose of this review is to deliberate upon the recent developments and their impact on improving the disease outcome in light of updated literature

Abbreviations: NMOSD, Neuromyelitis Optica Spectrum Disorders; NMO, Neuromyelitis Optica; AQP4, Aquaporin-4; AQP4-Ab, Aquaporin-4 antibody; MOG, Myelin Oligodendrocyte Glycoprotein; MOGAD, MOG Associated Disease; CNS, Central Nervous System; LETM, Longitudinally Extensive Transverse Myelitis; STM, Short Transverse Myelitis.

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https://doi.org/10.1016/j.jns.2020.117225
Received 9 September 2020; Received in revised form 5 November 2020; Accepted 9 November 2020
Available online 12 November 2020
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and point towards the scope of future research.

2. Pathogenesis/pathology

2.1. AQP4 antibody-positive NMOSD

Aquaporin-4 is a water channel protein expressed in the end-feet of astrocytes in CNS and to a lesser extent in ependymal cells. AQP4 protein has different roles to play in CNS including facilitation of water movement between the blood, brain and CSF compartments, migration of astrocytes and scar formation by glial cells, neural signal transduction, and neuroinflammation [9–11]. Antibodies to AQP4 are produced peripherally and then cross the blood-brain barrier during acute disease relapse [12]. 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 [13]. Degranulation of Natural Killer (NK) cells results in the release of perforins and granzyme which further induces astrocyte injury [14]. (Fig. 1).

2.1.1. Genetic predisposition

A probable role of genetic predisposition has been postulated as the disease is more prevalent in non-Caucasian population [15,16]. This has been further substantiated by the detection of familial NMO, although only a small proportion (3%) of cases of NMO have a family history [17]. Aquaporin-4 IgG positivity is found to be associated with HLA-DRB1*03 (DR3) in French and Brazilian populations and HLA-DPB1*0501 in Japanese and Chinese populations [18]. These HLA haplotypes are also

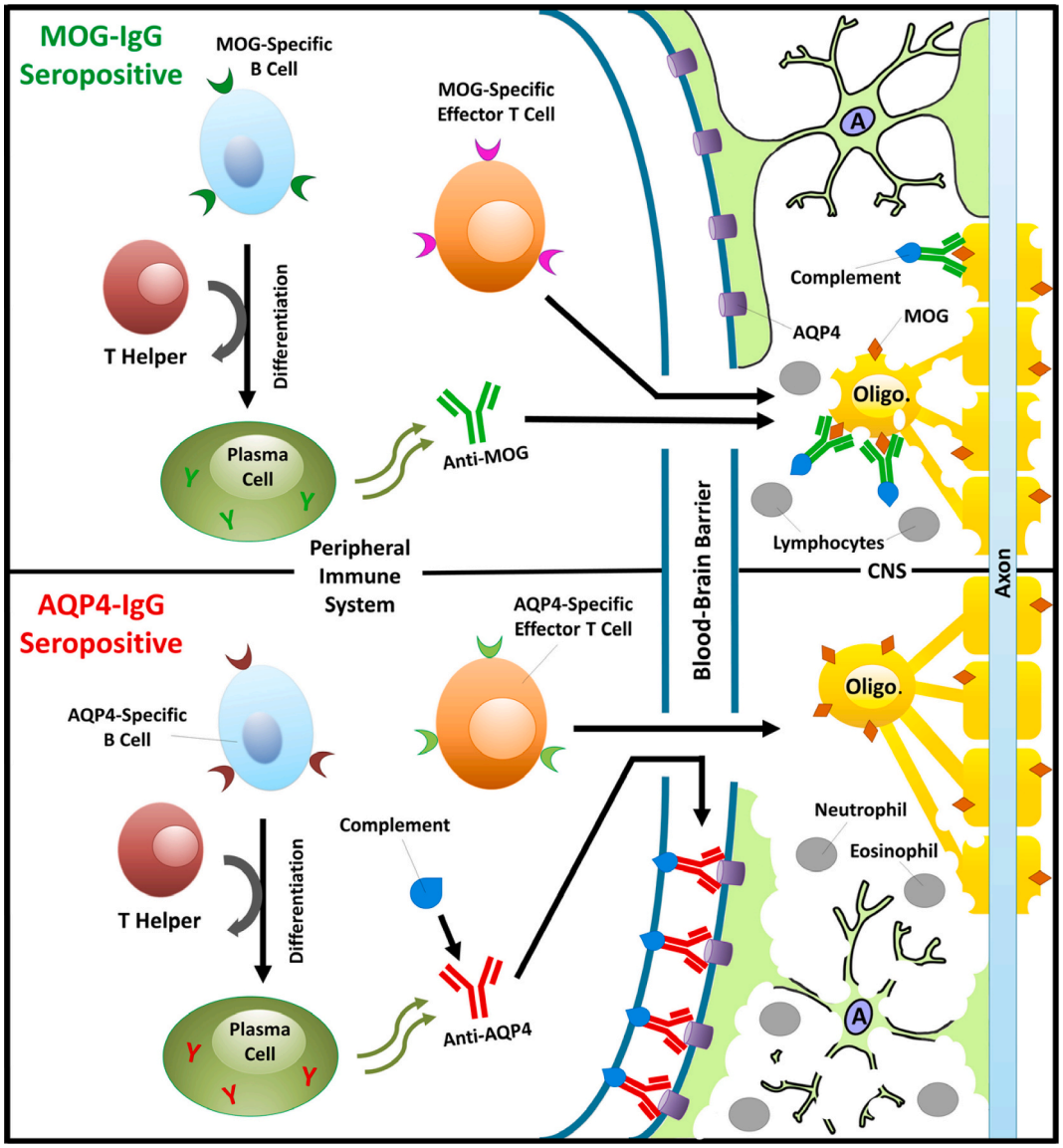


Fig. 1. Proposed model for the mechanisms by which AQP4- and MOG-specific antibodies target two different cell types in the CNS,astrocytes (A) and oligodendrocytes (Oligo) respectively. The upper panel shows that MOG-specific effector T cells may initiate CNS inflammation, which is characterized by the accumulation of lymphocytes. Once entering the CNS, MOG-specific IgG may bind to myelin and myelin-forming oligodendrocytes that express MOG. This binding promotes demyelination and damage to oligodendrocytes or myelin. The lower panel shows that the production of AQP4-specific IgG requires B cells to differentiate into plasma cells expressing AQP4-IgG with the assistance of antigen-specific T-helper cells. CNS inflammation may be initiated by AQP4-specific effector T cells, which is characterized by the accumulation of neutrophils and eosinophils. Along with complement, AQP4-IgG1 binds to AQP4 water channels (abundantly expressed on astrocyte end-feet processes) and exacerbates astrocyte injury. *Source*: [200].

associated with other autoimmune disorders such as systemic lupus erythematosus (SLE) and Graves' disease [19]. Autoimmune conditions such as SLE, Myasthenia Gravis and Sjogren's syndrome are found in association with NMO [23] and these disorders are also more common in family members of patients with NMO [17].

2.1.2. Triggers for autoimmunity

Infections are known to trigger the disease onset and relapses in NMOSD. Viral infections are known to precede NMOSD in 15–35% of cases. Among the viral infections, VZV often in combination with HIV is most common. Others include CMV, EBV, Dengue and Hepatitis A virus. Among the bacterial infections, *Mycobacterium tuberculosis*, Mycoplasma pneumonia and Treponema pallidum have been reported in the literature [20]. Pathogenesis of para-infectious NMO is believed to involve one of the following mechanisms:

1. Bystander activation - inflammatory reaction elicited by systemic infection results in damage to AQP4 expressing epithelial cells. This in turn starts a process leading to antigen presentation of AQP4 to T cells and activation of AQP4 specific B cells [21].
2. Molecular mimicry- similarity between structural epitopes from an infectious agent and self-proteins leads to antibody misdirection against self-proteins (AQP4) [22].
3. Systemic infection may trigger independent CNS disease by causing secretion of pro-inflammatory cytokines capable of damaging astrocytes and endothelial cells [23].

2.1.3. Pathology

Significant loss of immunostaining for AQP4 and glial fibrillary acidic protein (GFAP) in NMO lesions indicating the astrocyte damage has been demonstrated in various pathological studies [24]. This is also supported by the detection of remarkably high levels of GFAP in the CSF of AQP4-seropositive NMOSD patients during acute exacerbations [25]. Myo-inositol and Myo-inositol/creatinine ratio(the marker of astrocyte activity) is detected to be lower in the cervical cord of AQP4-Ab-seropositive NMOSD than in multiple sclerosis on Magnetic Resonance Spectroscopy [26]. The results of these studies indicate that astrocytic destruction rather than demyelination is the pathological hallmark of NMOSD disease.

Six types of pathological lesions are known to exist in NMOSD. Type 1: active lesions accompanied by complement activation and granulocyte infiltration. Type 2: cystic and necrotic lesions with severe tissue destruction. Type 3: lesions characterized by Wallerian degeneration in lesion associated tracts. Type 4: lesions with selective loss of AQP4 with no structural damage. Type 5: active lesions of astrocytes, with cytoplasmic swelling and vacuolation, beading and dissolution of their processes and nuclear alterations resembling apoptosis, a process termed as clasmatodendrosis Type 6: astrocyte dystrophy and demyelination [27]. Lesions in cortical gray matter are detected to have patchy loss of cortical neurons in layer II-IV, loss of AQP4 immunoreactivity on astrocytes in layer I, microglial activation in layer II and meningeal infiltration of lymphocytes without any evidence of cortical demyelination [28]. Mechanism of pathological injury in AQP4 deficient regions such as peri-plaque white matter areas include abnormalities of astrocytic Na + dependent excitatory amino acid transporter or downregulations of NR1 subunit of the NMDA receptor [29]. Microglial/macrophage activation, mitochondrial damage and axonal energy failure are other postulated mechanisms [30–32].

IFN-β which is a type of IFN-I and used as a treatment modality in multiple sclerosis (MS) has been found to worsen the disease in patients with NMOSD [33]. Also elevated TH17 signatures have been found in NMOSD patients and studies have shown that such patients have increased frequency of relapses once treated with IFN- β [33–35]. Studies have revealed that binding of AQP4-IgG to AQP4 protein on astrocytes leads to AQP4 internalization and production of IL-6 [36] and that astrocytes express IL-6 in neuroinflammation [37]. IL-6 downregulates EC tight junction molecules, [38] decreases barrier function, [39] and induces chemokines - CCL2 and CXCL8 [40].

2.2. AQP4 antibody-negative NMOSD

73–90% of cases of NMOSD fulfilling 2015 diagnostic criteria were found to be seropositive for the Aquaporin 4 antibody in a study of 132 patients by Hamid et al. Therefore,10–27% of NMOSD cases were categorized as seronegative. A significant proportion (42%) of these seronegative cases were shown to express antibodies against Myelin Oligodendrocyte Glycoprotein [41]. Myelin oligodendrocyte glycoprotein (MOG) is a myelin protein present in the outermost layer of the myelin sheath. MOG has been used as an antigen to induce experimental autoimmune encephalomyelitis (EAE) in rodents [42]. Older MOG-antibody detection assays ELISA and Western blot have been disregarded because of low specificity. The reason for the low specificity of these tests was due in part to the detection of IgM antibodies; however, using the IgG-1 specific antibody substantially improved the specificity [43]. O'Connor et al. developed a MOG-transfected cell-based assay to detect conformation-sensitive MOG-IgG [44]. Using cell-based assay, MOG antibody has been detected in 6 to 23% of patients in AQP4-antibody-seronegative NMO and other disease phenotypes, such as optic neuritis, LETM, acute disseminated encephalomyelitis (ADEM), and brainstem and cerebral cortical encephalitis [45–47]. Markus Reindl et al. demonstrated that Live MOG-IgG CBAs showed excellent agreement(96%) for high positive and negative samples [48].

2.2.1. Pathology

Histopathological studies of MOG-AD reveal type 2 MS pattern demyelinating lesions and well-demarcated areas of myelin loss with relative preservation of axons and astrocytes. An abundance of lipid-laden macrophages containing myelin debris is seen. The inflammatory infiltrate is composed predominately of perivascular T cells and some B-cells. Complement deposition with terminal complex C9 is also noted [48–50].

Demyelination in MOG-AD can be either perivenular or ADEM pattern with partial axonal preservation and reactive gliosis in the white and gray matter [51]. Cortical demyelination is also present, predominant lesions being intracortical rather than leukocortical [52]. The inflammatory infiltrate in MOG associated disease lesions is CD4+ T cell dominant in contrast to MS where CD8+ T cell predominate [53]. Complement deposition within the active white matter lesions has been noted in MOG associated disease on histopathology or autopsy [50,54].

MOG associated disease has also been shown to differ with AQP4-Ab positive NMOSD with regards to serum biomarkers. Serum tau level was seen to be higher during relapse in MOG associated disease whereas in AQP4-Ab positive NMOSD, serum NfL and GFAP were found to be higher in relapse than in remission [55]. Because of different pathophysiology, serum biomarkers, clinical and radiological manifestations and disease outcome, MOG associated disease is now seen as a distinct disease entity.

There is a subset of cases with typical NMO who are seronegative for AQP4 and MOG antibodies [45]. Some of them may be false-negative based on the currently available assays but it remains unclear whether a third NMO-associated autoantibody is present and this issue is under study.

3. Epidemiology

The prevalence range of NMOSD is 0.5–4/100,000 and may reach up to 10/100,000 in certain racial groups. Higher prevalence (3.5/100,000) has been noted in East Asians with a study from Japan recording a prevalence of 4.1/100,000 [56]. Blacks have been shown to have a higher prevalence than whites across various population studies with a study from UK reporting a prevalence rate of 1.8/100.000 among blacks [57]. The prevalence rate among Whites has been consistently

shown to be around 1/100,000 in various nationwide and region-wide studies. Annual incidence among Whites is reported to be 0.5 to 0.8/million [58,59]. A higher incidence is noted in populations with a higher prevalence (1.32/million in Hungarians) [60]. The incidence of MOG associated disease was reported to be 1.6/million with 1.3/million in adults and 3.1/million in children in a recent Dutch study [61]. No racial preponderance has been noted for MOG associated disease.

Differences in clinical features have been noted among different races. The mean age of onset is lower in Blacks and Asians than Whites (28–33 years for Blacks, 35–40 for Asians and 44 for Whites) [62,63]. Brain and brainstem attacks have been reported more likely in Black and Asian patients. Severe attacks are more frequent in Blacks and therefore have a higher risk of severe disability [63]. 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%) [64]. Men and women are affected equally in monophasic NMOSD but in typical recurrent NMOSD, female to male ratio ranges from 5:1 to 10:1 [65]. The median age of onset is 32 to 41 years, but the disease, particularly the MOG variant is seen in children and cases have been reported in the elderly as well [66].

4. Clinical features

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 [67,68]. 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 [69]. Optic neuritis which can be bilateral in NMOSD leads to severe visual impairment and significant loss of vision-related quality of life. The severity of vision-related quality of life loss has been seen to correlate with bilateral and more severe optic neuritis. Optic neuritis in NMOSD is accompanied by more profound neuro-axonal damage and loss of visual function than in MS [70]. Myelitis in NMOSD usually manifests as longitudinally extensive transverse myelitis (LETM) i,e. it involves three or more vertebral segments on magnetic resonance imaging (MRI) [66,68]. LETM may represent a limited form of NMOSD in a high proportion of patients [71]. A shorter extent of spinal cord involvement can also be seen in a small number of patients [72]. Area postrema syndrome presenting clinically as nausea and vomiting or hiccups, with associated medullary lesions on MRI occurs has been reported in 16 to 43% of cases [3,71]. Brainstem involvement may manifest with oculomotor dysfunction or other cranial nerve palsies. It may also lead to acute neurogenic respiratory failure and death [68]. Other reported manifestations of brainstem involvement include hearing loss, vertigo, facial palsy, trigeminal neuralgia and pruritus of neurologic origin [73]. Extra-axial cranial nerve involvement was reported in a study of 273 cases of MOG-associated disease at a frequency of 1.1% (3 cases). Oculomotor, trigeminal and vestibulocochlear were the cranial nerves involved with involvement occurring at the cisternal level in oculomotor and root level in the other two cranial nerves [74]. Diencephalic syndrome manifesting as symptomatic narcolepsy, hypothermia, bradycardia and hypotension has been reported in NMOSD. Unusual manifestations in the form of encephalopathy, fulminant cerebral demyelination, posterior reversible leukoencephalopathy can be seen occasionally [69,75–77].

NMOSD has a significant impact on the quality of life. Nearly two-thirds of NMOSD patients report a strong negative impact on physical health with a relatively preserved emotional well-being. Factors imposing a greater negative impact on physical and emotional well-being include pain, bowel/bladder dysfunction, sexual dysfunction and inability to work [78]. Moderate to severe depression exists in 28% of NMOSD patients. The severity of depression is found to be significantly associated with neuropathic pain and about 40% of depressed patients may not be receiving antidepressant treatment [79]. Pain is a very frequent symptom occurring at a frequency of 86% in MOG-Ab positive NMOSD and 83% in AQP4-Ab positive NMOSD. Neuropathic pain is seen in both entities whereas headache is more common in MOG associated disease [80]. Cognitive impairment in NMOSD has gained less attention as compared to MS although patients report it as one of the most relevant concerns. The prevalence of cognitive impairment varies between 30 and 70% in different studies [81,82]. Meng et al. in his meta-analysis showed that NMOSD patients performed worse than healthy controls particularly in domains of attention, language, memory, processing speed and executive function [82].

NMOSD has a relapsing course in majority of the patients [66,68,83]. Relapses are known to occur within three years in 90% of cases [68]. Annual relapse rates of 0.77 occur in NMOSD despite maintenance therapy which is more than double the relapse rate in MS. Transverse myelitis is the most frequent presentation of relapse followed by optic neuritis. The time between relapses is shorter in NMOSD as compared to MS. Relapse duration and maximal disability level are also more in NMOSD. NMOSD relapses are more likely to be treated with IVIG or plasma exchange [84]. Studies have shown that the progression of EDSS in NMOSD indicative of disability mainly takes place at the timing of each relapse and it does not deteriorate significantly if there is no relapse. This shows the impact of the increased frequency of relapses on disability progression [85].

Key points regarding the clinical features of NMOSD are highlighted in Table 1.

5. Imaging findings

5.1. Optic nerve/chiasm

Optic neuritis in NMOSD involves a long segment of optic nerve, usually affecting more than half its length. The involvement of the posterior optic pathway including chiasm and the optic tract is characteristic [86,87]. 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 [3,88,89].

5.2. Spinal cord

The classical spinal cord lesion in NMOSD is LETM-Longitudinally Extensive Transverse Myelitis which is characterized by longitudinal involvement of three or more contiguous vertebral segments of the spinal cord [90]. The central gray matter is commonly affected, representing the area with the most prominent expression of the AQP4 antigen [91]. On MRI, these lesions are central in location or may involve both central and peripheral areas [92,93]. Cervical and dorsal spinal segments are usually involved [93]. Bright spotty lesions on T2-weighted images and corresponding hypointense lesions on T1-weighted images are the typical imaging features on MRI [93,94]. In the acute phase of myelitis, cord swelling and irregular enhancement on T1-weighted images are seen. Ring enhancement pattern, having a distinct lens-shaped appearance on sagittal images is reported

Table 1
Key points about the clinical Features of NMOSD.

- ➢ Sequential optic neuritis in rapid succession or bilateral simultaneous optic neuritis is highly suggestive of NMOSD.
- ➢ Myelitis in NMOSD is symmetrical and is 3 or more vertebral segments in length and often leaves residual deficit.
- ➢ Area postrema syndrome characterized by nausea and vomiting or intractable hiccups is the classical presentation of brain involvement.
- ➢ Brainstem or diencephalic syndrome can be other manifestations.
- ➢ ADEM is a more common manifestation in children and is associated with MOG antibody.

uncommonly [95] (Fig. 2). Short transverse myelitis (STM) can be the other pattern of myelitis in NMOSD. It refers to a spinal cord lesion that extends less than three vertebral segments. Studies have shown that STM could represent 14.5% of the initial manifestations of myelitis in NMOSD patients [76,96]. The points that differentiate STM lesions in NMOSD from those in MS include the location of the former in central gray matter and involving more than half of the cross-sectional area and being longer than the corresponding MS lesions [79,143]. In STM, testing AQP4-IgG status is recommended for accurate diagnosis [72,96], even in the absence of additional features of NMOSD. The timing of spinal MRI may be relevant to detect LETM as the patient may present with symptoms initially suggestive of brain involvement but may evolve to spinal cord involvement within 1 to 2 weeks [97]. LETM lesions may evolve into multiple shorter lesions during remission or after treatment with high-dose steroids. This has been demonstrated on follow-up MRI studies of LETM cases [98]. Studies have shown that relapses in NMOSD tend to recur in the same anatomical sites within the CNS [99] (168). Spinal cord atrophy is seen in cases with recurrent myelitis and may correlate with neurologic disability [98].

5.3. Brain

Brain lesions occur variably in 24%–89% of NMOSD patients [100–103]. The typical brain lesions of NMOSD are not commonly seen. The sites of typical brain lesions include the peri-ependymal regions, subpial region, circumventricular organs, brainstem, chiasm/hypothalamus, and corpus callosum which are the sites of high AQP4 expression [90,103,104]. Classical MR imaging findings in NMOSD are confluent hyperintensities on FLAIR/T2WI in periependymal areas, along the ependymal lining of the lateral, third, and fourth ventricles, particularly close to the cerebral aqueduct (Fig. 3). Ependymal surfaces of the corpus callosum, diencephalic region, and brainstem are the other commonly affected regions [90]. In acute phases, heterogeneous hyperintensity on FLAIR/T2WI is usually seen giving rise to a marbled or "arch bridge" appearance [105,106]. Hypothalamic, thalamic lesions, and the periaqueductal area can be involved less frequently [88,105]. Periependymal lesions in the dorsal brainstem involving the area postrema are a characteristic MRI finding in NMOSD disease, observed in 7%–46% of patients [88]. These medullary lesions may merge with the periependymal lesions in the upper cervical spinal cord, assuming a linear shape with variable hyperintensity on FLAIR/T2-weighted images [3,88]. The involvement of the corticospinal tract has been observed in 23%–44% of NMOSD patients even though the corticospinal tract is not a region with high AQP4 expression. The pathogenesis of this finding remains unknown. Extensive and confluent hemispheric white matter lesions known as tumefactive lesions(>3 cm in the longest diameter) may be seen [105]. Such lesions, however, are more common in multiple sclerosis rather than NMOSD. Nonspecific punctate or small (<3 mm) dots or patches of hyperintensities on T2-weighted or FLAIR sequences in the subcortical or deep white matter are seen in 35–84% of brain imaging studies and are usually asymptomatic [103,105,107].

Contrast enhancement on T1-weighted images is seen in 9%–36% of cases [88]. Cloud-like enhancement, characterized as patchy and inhomogeneous with poorly defined margins is the most common pattern of enhancement [88,101,105,108]. Periependymal linear pattern also called pencil-thin enhancement can be the other enhancement pattern. Less commonly, leptomeningeal and nodular enhancement may be observed [88,105]. A study showed that leptomeningeal enhancement on MRI in AQP4 IgG positive NMOSD patients may be associated with concomitant breakdown of intraparenchymal blood-brain barrier. Leptomeningeal enhancement demonstrated on postcontrast T1-weighted and FLAIR images was accompanied by periependymal enhancement in about 45% of cases and intraparenchymal enhancement in 100% cases. [109]. Ring and "open ring" enhancement very rare in NMOSD [108].

In the chronic phase, large lesions may shrink and even disappear, but in some cases, cystic-like or cavitary changes are known to occur. Results from a follow-up MRI study in NMOSD patients revealed that 47% of lesions showed focal T1-hypointensity and 18% in particular, showed focal cystic changes. Cystic changes were more frequent in corticospinal tract and corpus callosal lesions. Most of the lesions in the cerebellum, basal ganglia and temporal white matter resolved

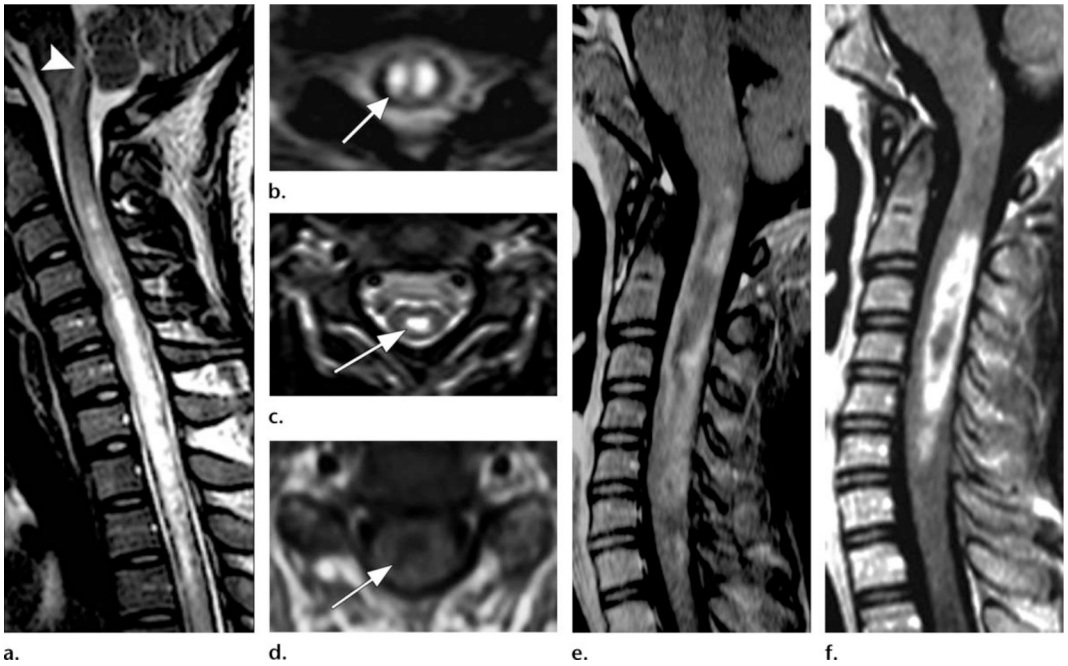


Fig. 2. Typical spinal cord involvement in NMOSD. (**a**) Sagittal T2-weighted image shows LETM extending into the area postrema (arrowhead). **(b)** Axial T2-weighted image shows characteristic involvement of the central gray matter (arrow). **(c)** Axial T2-weighted image shows a bright spotty lesion (arrow). **(d)** Axial T1-weighted image shows a corresponding dark lesion (arrow). **(e, f)** Sagittal contrast-enhanced T1-weighted images in patients with acute LETM show patchy areas of enhancement **(e)** and a lens-shaped pattern of enhancement **(f)**. *Source:* [201].

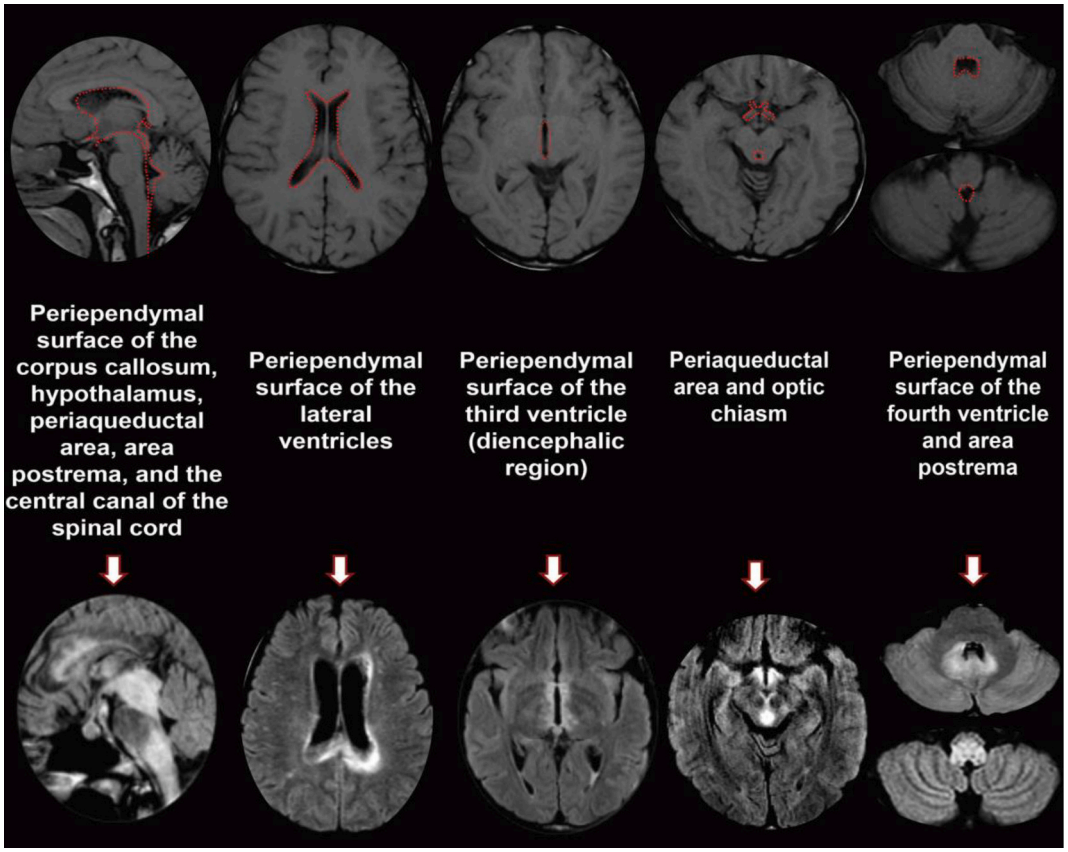


Fig. 3. Typical brain involvement in NMOSD. Top: Representative brain MR images show AQP4 antigen distribution. Bottom: Fluid-attenuated inversion-recovery (FLAIR) images show the corresponding lesions. The hyperintense lesions on the FLAIR images have the same distribution as AQP4, reinforcing the involvement of these water channels in NMOSD pathophysiology. *Source:* [201].

completely [110].

7 Tesla MRI used in small studies has been shown to detect reduced myelin signal in normal-appearing white matter(NAWM) in NMOSD patients and subclinical optic radiation damage in MS patients [111,112]. However, these results need to be confirmed in larger studies

Key points regarding the radiological characteristics of NMOSD are highlighted in Table 2.

5.4. Optical coherence tomography

OCT is a biomicroscopic device that uses the property of tissues to backscatter light to produce high-resolution cross-sectional images. Measurement of retinal peripapillary nerve fibre layer thickness(pRNFL) by means of OCT is proving to be a reliable marker for diagnostic evaluation and progression of optic neuritis in MS and NMOSD [113,114]. Although characteristics like RNFL thickness and macular volume on OCT have been established in MS as markers of axonal and neuronal integrity respectively, OCT features in NMOSD are currently ill-defined [115,116]. OCT studies in acute optic neuritis show a highly swollen pRNFL [117]. As optic nerve is commonly affected at optic chiasma in AQP4 seropositive NMOSD, contralateral optic nerve may get involved clinically or radiologically [87]. Recurrent optic neuritis in NMOSD leads to severely thinned RNFL and GCIPL(Ganglion Cell Internal Plexiform Layer) [118]. Macular thinning is known to be more severe in NMOSD-ON than in MS-ON. Also, RNFL thickness is significantly lower in NMOSD related optic neuritis compared to patients with MS-ON [119–122]. While RNFL thickness is reduced on an average by 7 μm in MS patients with no history of ON, NMOSD patients without a history of ON have normal RNFL thickness [119,123,124]. However, GCIP loss has been demonstrated in NMOSD patients with AQP4-Ab seropositivity without a history of optic neuritis [125]. Microcystic alterations in the inner nuclear layer called microcystic macular edema (MME) are seen in 20% of NMOSD patients after optic neuritis [126]. However, MME is not specific for NMOSD and can be seen in a range of neuropathies including MS and non-inflammatory neuropathies [127]. RNFL thickness has been found to correlate well with visual function in both MS and NMOSD [123,128]. It has also been shown to correlate well with pericalcarine cortex thickness in NMOSD supporting the concept of transsynaptic degeneration being responsible for some detectable brain atrophy [129].

Optic neuritis in AQP4 seropositive NMOSD is associated with worse visual outcomes compared with MOG-ON and MS-ON, even with similar severity of macular GCIPL thinning [130]. This suggests that macular structure-function correlation, as defined by evaluation of macular GCIPL thickness and visual acuity, may vary by ON etiology. Macular microcystoid pathology has been proposed as a factor contributing to poor visual outcome following ON as this pathology is more frequent in AQP4-Ab positive NMOSD compared to MS and MOG [126,127,131]. 3D foveal morphometry has depicted wider and flatter foveas in AQP4

Table 2
Key points about the radiological Features of NMOSD.

- ➢ Optic nerve involvement is usually longitudinally extensive, preferentially involving the posterior optic pathway.
- ➢ 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.
- ➢ Typical brain MR imaging findings in NMOSD include confluent hyperintensities on FLAIR/ T2-weighted images in peri-ependymal areas.
- ➢ Lumbosacral myelitis is more typical of MOG-associated disease.
- ➢ Cerebellar peduncle lesions are detected with high frequency in children with MOG associated disease.

positive NMOSD compared to MS which is independent of optic neuritis supporting the primary retinopathy in AQP4 positive NMOSD [132]. Diffusion tensor imaging (DTI) has been used to study microstructural changes in the optic radiation (OR). Microstructural changes in the form of fractional anisotropy reduction have been detected in AQP4 seropositive NMOSD without a history of optic neuritis [133].

6. Distinct features of MOG associated disease

MOG associated disease is known to occur in all age groups with the median age of onset in early to mid-thirties [47,134–136]. Optic neuritis is the most common presentation, followed by myelitis and acute disseminated encephalomyelitis (ADEM). Optic neuritis is frequently bilateral and associated with optic nerve head swelling [87,137]. Results from a large retrospective study of MOG associated disease have shown that MOG associated disease was more frequent in children and elderly, most patients have a relapsing disease, attacks may follow infection or vaccination in 40% of cases, bilateral optic neuritis and simultaneous optic neuritis and myelitis are common at the onset, perioptic contrast enhancement may be seen in one-third of cases, short segment myelitis can occur and should not preclude MOG IgG positivity and plasma exchange is often followed by full or partial recovery (146). There have been case reports of MOG IgG positive NMOSD presenting with unilateral cortical encephalitis with seizures [138]. Lesions in the brain are usually bilateral with subtentorial lesions found in nearly one-third of patients [135]. Typically lesions are few (< 3), fluffy on T2WI [135,139]. Optic nerve on MRI is more edematous and shows perioptic contrast enhancement. Chiasma and optic tract are spared [137]. Thalamic and pontine lesions are more common [135]. Cerebellar peduncle lesions are typically seen in children with MOG-IgG positive disease. There have been case reports of MRI in MOG-IgG-positive patients depicting curvilinear and punctuate enhancement in pons mimicking CLIPPERS-chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids [140]. T2 hyperintense lesions in the spinal cord are reported in nearly 50% of patients with MOG-associated disease. Most lesions are short and predominantly occur in cervical and thoracic regions [141]. Lumbosacral myelitis has been reported more commonly than in AQP4 seropositive NMOSD [27]. However, LETM lesions are common in children. MOG-associated disease is known to relapse in 44–83% of patients [135,141,142]. 50–80% of patients end up having a residual disability. Transverse myelitis at onset is considered an important predicting factor of long-term disability [141–143]. MOG seropositive patients have a lower risk of relapse than AQP4 positive patients and have better visual and motor outcomes [135,142].

7. NMOSD in children

Pediatric NMOSD is believed to represent 3–5% of all NMOSD cases. The disease is more common in girls with F: M ratio ranging from 9:1 (UK) to 1:1 (multinational) [144,145]. MOG-IgG antibody occurs at increased frequency in pediatric NMOSD. It was seen in 40% of patients with optic neuritis and LETM who were seronegative for AQP4 antibody [47]. In contrast, the frequency of AQP4 IgG seropositivity is much lower in pediatric onset NMOSD [146]. Disease course and outcome may vary in different age groups. Children show better recovery of visual acuity, lower annual relapse rate and more intracranial optic nerve involvement than young and middle-aged groups [147]. Recurrent isolated optic neuritis(RION) and chronic relapsing inflammatory optic neuropathy with corticosteroid dependence(CRION) are associated with high seropositivity for MOG-IgG antibodies [148,149]. Area postrema syndrome and acute brainstem syndrome may be found with similar frequency in children and adults [150]. Cognitive impairment with a frequency of 7% has been noted in children with MOG associated disease under 10 years of age [47]. However, the frequency of cognitive deficit in the leukodystrophy phenotype of pediatric MOG-associated disease was reported to be 57% [151].

LETM is a frequent clinical presentation in children, seen in 88% of patients with monophasic transverse myelitis [152].MOG antibody is reported to have a more frequent association with LETM in children. In one case series, 58% of children presenting with NMO or limited forms of NMOSD were positive for MOG antibody [145]. Conversely in adults, more than half of LETM patients are AQP4 antibody positive [100,153]. Lesions in the cerebellar peduncle distinguish children with MOG-IgG from those with AQP4-IgG [134]. Children with optic neuritis in presence of MOG IgG antibody may have involvement of any part of the optic nerve, but intracranial involvement is more common than those who are seronegative [147].

8. Diagnosis

The diagnosis of NMOSD is made by using the revised diagnostic criteria for NMOSD laid by IPND (International Panel for NMO Diagnosis) in 2015 [4]. The IPND diagnostic criteria for NMOSD are given in Table 3.

Although these criteria have helped in early detection of cases and improving the disease outcome, there are some points that warrant further debate. The clinical manifestations of MOG associated disease like ADEM and recurrent optic neuritis have not been included in the diagnostic criteria of NMOSD. MOG associated disease is currently being considered a distinct disease entity and it may need to be segregated from NMOSD considering its different pathogenesis, clinic-radiological

Table 3
2015 International Consensus diagnostic criteria for NMOSD [4].

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
Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
b. Dissemination in space (2 or more different core clinical characteristics)
c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses
Core clinical characteristics
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions
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 1/2 optic nerve length or involving optic chiasm
2. Acute myelitis: requires associated intramedullary MRI lesion extending over at least 3 contiguous segments (LETM) OR at laest 3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

manifestations and response to treatment. Also, double seronegative patients presenting for the first time with LETM or optic neuritis suggestive of NMOSD may not fit into these criteria. At present, there is no mechanism to estimate their risk of relapse and whether they also need to be started on maintenance therapy is a point that needs further research.

Evaluation of NMOSD often involves MRI of the brain, orbits and spinal cord, serum AQP4 antibody and MOG antibody and CSF analysis.

8.1. CSF findings

CSF in NMOSD cases shows mild pleocytosis in the range of 6–380 cells/μl (median 19 cells/μl). CSF white cell count>50 cells/μl is reported in 13 to 35% of patients with the predominant cell type being lymphocytes followed by monocytes and neutrophils. Elevated protein usually in the range of 50–100 mg/dl is seen in half of the patients. Oligoclonal bands are reported in less than 20% of patients [66,69,154]. CSF in MOG associated disease has revealed elevated total CSF protein in the range of 50–100 mg/dl in about 60% of patients which may be present during attacks as well as in remission. Increased WBC count (<50 cells /μl) is seen in nearly half of the patients. 20% of patients may have >50 cells/μl. OCB is absent in 90% of CSF samples in MOG associated disease. Intrathecal IgG synthesis is low and transient and restricted to acute attacks. Elevated CSF albumin/serum albumin ratio is seen in 48% [155].

8.2. Antibody detection tests

Various assays are used for the detection of AQP4 antibody and MOG antibody. All AQP4 antibody assays are highly specific (97% for ELISA, 99.7% for tissue Indirect Immunofluorescence assay and 100% for Cell-based assay). However, sensitivity is only 60% for ELISA, 78% for indirect immunofluorescence assay and 90–94% for both fixed and live cell-based assay [156]. The specificity of cell-based assays for detecting MOG antibody ranges from 98 to 100%. Established Cell-based assays for MOG antibody include Oxford live CBA, Euroimmun fixed CBA and Mayo live fluorescence-activated cell sorting assay [157]. Considering the high sensitivity and specificity, Cell-based assays are currently used for the detection of AQP4 and MOG antibody.

AQP4 and MOG serostatus and antibody levels may change during the disease course. AQP4 antibodies usually remain detectable even during remission, although the titer may decrease with immunosuppression [158]. In MOG-AD, approximately 80% of patients remain seropositive during remission [47]. Some studies have shown that antibody titres were associated with relapse and treatment status [158–160]. However, the level of AQP4 antibody titer does not predict the long term disease course [161]. Response to immunotherapy in NMOSD does not depend on serostatus. This was established in a study by Mealy et al. who showed that annualized relapse rates were reduced significantly with rituximab or mycophenolate mofetil in both seropositive and seronegative NMOSD with minimal differences [162].

8.3. Differential diagnosis

Sarcoidosis, vasculitis, infections like HIV or syphilis, and paraneoplastic conditions may mimic NMOSD and need to be excluded if the presentation is not typical of NMOSD. Other diseases which could represent differentials on neuroimaging for MS/NMOSD include small vessel disease in the elderly, neuro-Behcet disease, CADASIL, Susac syndrome, adrenoleukodystrophy, CLIPPERS, migraine, B12 deficiency and copper deficiency for spinal cord lesions, HTLV associated myelopathy, spinal cord infarction, dural AV fistula and others [163].

Table 4 highlights the comparison of MOG associated disease, Neuromyelitis optica and Multiple sclerosis.

Red flag signs described a decade ago by European Magnetic Resonance Network in MS (MAGNIMS) are useful when considering a diagnosis of MS. These signs include meningeal enhancement, increasing lesions, indistinct lesions, macrobleeds, microbleeds, infarcts, cavities, complete ring enhancement, symmetrical lesions, sparing of U-fibres, siderosis and extensive spinal cord lesions [163]. Central vein sign on 3 T MRI has been found useful in differentiating MS from non-MS pathologies. Using a 35% central vein sign proportion threshold had a sensitivity of 68.1% and specificity of 82.9% for distinguishing MS from non-MS pathologies [164].

9. Management

The clinical course of NMOSD patients is typically relapsing. Only 4% of cases show a monophasic course [63]. The goals of management are to perform an early diagnosis, to treat acute attacks and to start long-term maintenance therapy to reduce the risk of relapses [165].

9.1. Treatment of acute attack

Acute NMOSD attacks are treated with high-dose corticosteroids, typically intravenous methylprednisolone 1 g/day for 3–5 days, followed by oral steroids to avoid an early relapse. All patients, particularly those with AQP4 antibody positivity should be treated over a long

Table 4
Comparison of MOG-Associated Disease, NMO and MS.

	MOG-AD	NMO	MS
Age of onset	Early to mid-30s	Around 40	Around 30
Sex	Slight predominance in women	AQP4 − NMO: equal distribution AQP4 + NMO: more common in women	More common in women
Clinical phenotype	Commonly ON at onset (better visual field outcomes compared to AQP4-positive ON); other presentations include myelitis, ADEM and ADEM-like events	ON, usually severe with limited recovery; transverse myelitis; intractable nausea with hiccups or vomiting	ON, usually with good recovery; other neurological systems involved
Disease course	Monophasic or relapsing	Relapsing	Relapsing or progressive
Type of relapses	Commonly ON (more than in NMO)	ON; LETM	Any, with relapse phenotype predicted by previous relapse phenotypes
MRI brain	Abnormal in 45–77%; fluffy T2 hyperintense lesions;few lesions (e.g., ≤ 3); bilateral lesions at onset (about 50% of cases); thalamic and pontine lesions more common compared to NMO; more oedematous and extensive inflammatory lesions in the optic nerve,sparing chiasm and optic tracts	Abnormal in 60%; T2 hyperintense lesions around the 3rd and 4th ventricle and the aqueduct of Sylvius; area postrema lesions	Always abnormal; presence of Dawson's fingers, subcortical S-shaped or U-fibre lesions
MRI spinal cord	Abnormal in about 50% of cases; lesions more commonly short; in children, LETM more common	LETM (≥ 3 vertebral segments)	Lesions more commonly short
CSF	Pleocytosis variable; OCBs uncommon	Commonly ≥50 WCC/mm3; glial fibrillary acidic protein at relapse; OCBs in 10–25%	Commonly <50 WCC/mm3; OCBs in up to 95% of RRMS patients

period following clinical remission to avoid relapses [165]. Patients not responding to IVMP should be managed by plasmapharesis which may warrant 4 to 8 treatments. Plasma exchange (PLEX) is considered mandatory for the treatment of relapses. Early plasmapheresis is associated with nearly full recovery in the first attack. PLEX in combination with steroids has been shown to result in the improvement of post-relapse Expanded Disability Status Scale (EDSS) in 65% of patients [166]. A similar benefit has been demonstrated in the treatment outcome of optic neuritis [167]. It is pertinent to mention here that the timely administration of relapse treatment with IVMP and PLEX/IA is key to the success of the interventions. Both the techniques of apharesis including therapeutic plasma exchange and immunoadsorption (IA) are equally effective in the treatment of relapses in NMOSD and complete remission was achieved with early apharesis [168,169]. Early institution of IVMP has been found to significantly influence the visual recovery in AQP4 and MOG-ON and delay of greater than 1 week is associated with a higher risk for poor visual recovery [168].

9.2. Maintenance treatment

Maintenance therapy is necessary for NMOSD to prevent progressive disability and mortality. Although there is no consensus about the duration of preventive therapy, five years of maintenance treatment are recommended for patients with AQP4 IgG seropositive status and presenting with an attack of LETM [170,171]. However, many experts believe that maintenance therapy should be continued life-long given the fact that recurrence can occur even after 5 years. Various agents that are used in maintenance therapy include azathioprine (AZA), Mycophenolate Mofetil (MMF), and less commonly, Methotrexate and Cyclophosphamide.

Rituximab (RTX) is a chimeric monoclonal antibody directed against the CD20 epitope expressed on B cells. The safety and efficacy of Rituximab in NMOSD were demonstrated in a meta-analysis recently [172] lending further support to the previous evidence [165,173,174]. Rituximab treatment in NMOSD patients has been demonstrated to cause improvement and/or stabilization of disability in 93% of patients and prevention of relapse during a five-year follow-up in 60% of patients [174]. A comparison of RTX and Azathioprine (AZA) was studied in a randomized trial by Nikoo et al. Compared to the AZA treated group, Rituximab treated group had a significantly greater decline in annual relapse rates (ARR) (1.09 vs. 0.49), a greater decline in EDSS (0.98 vs. 0.54) and a significant increase in relapse-free patients (78.8 vs. 54.3%) from baseline to month 12 [175]. Results from another study by Kim et al. showed that non-responders to AZA or MMF often had fewer relapses when switched to RTX [176].

Azathioprine and Mycophenolate mofetil have shown a similar level of efficacy in reducing the relapse rates when used as maintenance therapy in NMOSD patients. The tolerablity of Mycophenolate mofetil, however, has been better compared to azathioprine considering the haematologic adverse effects of azathioprine [177]. Therefore, RTX is considered a more efficacious option than other conventional maintenance therapy such as Azathioprine and Mycophenolate.

Eculizumab is a humanized monoclonal antibody that blocks the complement protein C5 and prevents activation of the complement cascade. An open-label pilot study, evaluating the safety and efficacy of Eculizumab, demonstrated an improvement of disability (EDSS 4.3 to 3.5) in 12/14 NMOSD patients [178]. Eculizumab was found to be effective in reducing the relapse rates in a randomized trial of NMOSD patients who were seropositive for aquaporin-4 (AQP4) IgG antibodies. Treatment with eculizumab reduced the risk of relapse with absolute risk reduction [ARR] of 33% [179]. Inebilizumab is a humanized monoclonal antibody against the CD19 surface antigen of B cells. Inebilizumab was found to be effective in a small trial [180]. However, further studies are warranted to establish the long-term efficacy. Satralizumab is a humanized monoclonal antibody against interleukin-6 (IL-6) receptor. It is reported to be effective in reducing the number of relapses significantly in patients who were seropositive for AQP4 antibody [181]. Tocilizumab is a recombinant humanized monoclonal antibody against the interleukin-6 (IL-6) receptor [182]. Tocilizumab reduces AQP4-Ab production by decreasing the plasmablast survival [183]. It has been shown to cause stabilization and improvement of the disease in several small retrospective and prospective trials [184,185]. Subcutaneous tocilizumab is as effective as IV formulation and has an advantage of at-home administration [186]. Aquaporumab is a recombinant human monoclonal antibody against AQP4. Animal experiments have demonstrated the potential of aquaporumab to inhibit the development of brain lesions in NMOSD [187]. It can be a promising therapeutic agent in future. Bortezomib, an inhibitor of the 26S proteasome, was found to reduce relapses in an uncontrolled case series on five NMOSD patients [188]. Stem cell-based therapies are currently being investigated. Bone marrow-derived autologous mesenchymal stem cells were demonstrated to be effective and safe up to 2 years after treatment in NMOSD in an open-label pilot study [189].

Potential tolerization strategies that have been tried in animal and human studies include autoreactive T cell vaccine, Dendritic cell vaccine, Tc receptor engineering, regulatory T cell induction, regulatory B cell induction, anti-idiotypic network and others. These studies have yielded ambiguous results and have proven incomplete in phase-III trial design. Such experimental studies, however, may prove to be productive for novel therapy [190].

9.2.1. Treatment of MOG associated disease

There is a scarcity of data regarding the management of MOG-associated disease and no definite therapeutic guidelines exist. Patients with MOG associated disease are steroid responsive. It is still controversial whether MOGAD should be treated with immunotherapy from first event on, although most experts would agree on a recommendation for immunotherapy after 2 or more attacks [191]. IVMP course needs to be followed by oral steroids for a period of upto 6 weeks to reduce the chance of relapse. Maintenance therapies including oral prednisolone, monthly IVIG, rituximab and mycophenolate mofetil all have shown improvements in absolute risk ratio in limited studies. However, failure rates on maintenance steroids were less(5%) compared to other therapeutic agents [143]. The persistence of MOG antibody was found to be associated with relapses in a longitudinal analysis of CNS inflammatory diseases with 2 year follow-up [192]. Long term efficacy of mycophenolate mofetil was studied by Shengde Li et al. in a cohort of 79 patients with MOG associated disease. Results confirmed the efficacy of MMF in reducing the annual relapse rate (7.4% in the MMF+ group and 44.0% in the MMF− group) [193]. Rituximab has shown a less beneficial effect as maintenance therapy in MOG associated disease as compared to MS and AQP4 IgG positive NMOSD. 37% decline in relapse rate was noted with Rituximab and 33% of patients achieved remission after 2 years of treatment. Better treatment effect (63% reduction in relapse rate) was observed in those who received rituximab as first-line maintenance therapy. Adults showed a better response as compared to children(42% vs 29% reduction in relapse rate) [194].

Due to the rarity of double seronegative NMOSD disease and very limited available data, a treatment approach similar to that of AQP4 or

Table 5
Key Points about treatment of NMOSD.

- ➢ Intravenous methyl prednisolone 1 g/day for 3–5 days followed by a course of oral steroids or plasma exchange are the treatment of choice for acute attacks.
- ➢ Azathioprine (AZA) or Mycophenolate Mofetil (MM) are commonly used agents for maintenance therapy.
- ➢ Rituximab is more effective in reducing relapse rates than azathioprine/mycophenolate.
- ➢ Eculizumab may be highly effective in reducing the relapse rate in patients seropositive for AQP4-IgG antibodies.
- ➢ Immunosuppression is continued for at least five years, though life-long treatment may be warranted.

MOG seropositive disease is being currently followed.

Key points regarding the management of NMOSD are given in Table 5.

10. Prognosis

Stepwise deterioration occurs during the course of NMOSD due to accumulating deficits from recurrent attacks. Prognosis is predicted by older age at onset, the number of relapses in the first 2 years, the severity of first attack and association with other autoimmune diseases and autoantibody status [62,66,68,195]. Mortality rates were reporteddd to be high ranging from 25 to 50% in earlier studies [195–197]. However, with early diagnosis and early start of maintenance treatment, the prognosis of this disease has improved significantly. In a long term follow up study of Serbian patients with NMOSD, 58.5% of patients reached EDSS of 4.0, 48.6% reached EDSS of 6.0 and 43.2% reached EDSS of 7.0 over a 6.9-year follow-up at a median interval of 6.5 years,11.9 years and 22.0 years for these respective impairments. Higher EDSS at onset was an independent predictor for reaching severe disability. Survival probabilities were 98.6%, 94.6%, 82.7% and 63.0%, at 5,10,15 and 20 years respectively [198]. Rituximab has significantly reduced the disability and improved the survival in NMOSD when started early in the course. This is also accompanied by a reduction in the number of relapses [199].

11. Conclusion

Current clinical concept of NMOSD is based on AQP4-antibody-seropositive cases and newly detected MOG antibody-associated disease. The clinical spectrum and disease course of MOG associated disease are different from AQP4-antibody-seropositive NMOSD. As single site diseases like optic neuritis or myelitis and multisite diseases like ADEM and cerebral cortical encephalitis do not fit into 2015 diagnostic criteria for NMOSD, more research needs to be done regarding the need for maintenance therapy for such patients. Also, the need to study the clinical and immunopathological characteristics of double seronegative NMOSD seems indispensable. Most of the studies regarding the management have involved AQP4-seropositive-NMOSD cases. The data on the management of MOG antibody-positive NMOSD and double seronegative cases is limited. Therefore, more randomized studies are needed in the future to develop standardized therapeutic guidelines that take into account all the clinical subtypes of NMOSD.

Declaration of Competing Interest

None.

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