# 12 Neuromyelitis Optica Spectrum Disorders

Jonathan F. Cahill

## Clinical Presentation

Optic neuritis (ON) and transverse myelitis (TM) have long been considered the core clinical characteristics of neuromyelitis optica spectrum disorder (NMOSD). The optic neuritis of NMOSD presents similarly to that of multiple sclerosis (MS) and other inflammatory ON with decreased visual acuity, loss of color vision, and pain with eye movement developing subacutely over hours to days. The episodes or attacks of optic neuritis are most commonly severe and of a relapsing and remitting course. Unilateral ON is most typical, although simultaneous bilateral ON is not uncommon [1, 2]. There is frequently incomplete recovery from attacks with a stepwise accrual of disability (loss of visual acuity and constriction of visual fields) over time. Similarly, the clinical presentation of TM with NMO is similar to that of MS, with paraparesis, bladder dysfunction, and a sensory level on the trunk being common symptoms. Lhermitte sign and tonic spasms, other symptoms of myelopathy, are also common. Compared to MS, severe symptoms and incomplete recovery are more common in NMOSD [3]. A third clinical presentation in NMOSD, which is included as a core clinical characteristic in the 2015 NMOSD criteria [4], is that of the area postrema syndrome (APS). Lesions of the area postrema, the chemosensitive vomiting center of the brain in the dorsal medulla, can be caused by the extension of longitudinally extensive cervical cord lesions. APS is characterized by intractable hiccups, nausea, and vomiting [5].

About half of all patients with NMO have a relapse of symptoms within 1 year of diagnosis, and up to 90% have a clinical relapse within 3 years [6, 7]. Because residual symptoms after each attack are common and disability accrues with time, approximately half of all patients develop severe visual loss or inability to ambulate without assistance after 5 years [7, 8]. With the effect on neurological disability leading to other complications such as respiratory failure from high cervical lesions, the median survival for patients with NMO is less than 18 years [7, 9]. Factors associated with more severe disease and shorter survival include higher attack frequency during the first year of disease, incomplete recovery from the first attack, blindness at disease onset, and the presence of other autoimmune diseases [7, 9].

The main difference between typical MS and typical NMOSD is the lack of significant brain disease in NMOSD. The disease primarily affects the optic nerves and spinal cord, with relative sparing of the brain, although some specific brain

J. F. Cahill (✉)
Rhode Island Hospital and Alpert Medical School of Brown University, Brown Neurology, Providence, RI, USA
e-mail: jonathan_cahill@brown.edu



S. A. Rizvi et al. (eds.), *Clinical Neuroimmunology*, Current Clinical Neurology,
https://doi.org/10.1007/978-3-030-24436-1_12

areas are increasingly recognized as being affected in NMOSD. Another key clinical difference between NMOSD and MS is that NMOSD does not have a secondary progressive phase of illness [10]. NMOSD is a disease characterized almost exclusively by relapses, sometimes with incomplete recovery, which can be more severe than relapses of MS [1, 11, 12].

## Epidemiology

The median age of onset of symptoms in NMOSD is about 10 years later than in MS (39 years compared to 29 years) and the female-to-male ratio is significantly higher (range 3:1 to 9:1 in NMOSD) than in MS [11, 13, 14]. Other autoimmune diseases, especially systemic lupus erythematosus (SLE) and Sjogren syndrome (SS), have been associated with NMOSD and longitudinally extensive myelitis [15–18]. The serological markers of these systemic autoimmune disorders (antinuclear antibodies and Sjogren syndrome A antibodies) are also common in patients with NMOSD who do not have clinical manifestations of SLE or SS. In one study of 78 patients with NMOSD, 66.7% of them had aquaporin-4 antibodies, antinuclear antibodies were found in 43.8%, and Sjogren syndrome A antibodies in 15.7% [19]. Only five of the aquaporin-4 antibody-positive patients had coexisting clinical SLE, SS, or both.

## Pathology and Pathophysiology

The pathology of NMOSD is primarily demyelination. The degree of demyelination within lesions is frequently more extensive than in MS, and there is more commonly associated necrosis, cavitation, and acute axonal pathology (spheroids) [20, 21]. There is significant oligodendrocyte loss in both gray matter and white matter. In active lesions, there is perivascular inflammation with macrophages and T-cells, as well as neutrophils and eosinophils.

With the discovery of specific autoantibodies to the aquaporin-4 channel on astrocytes in NMOSD [22], a biomarker for the disease was found. Aquaporin-4 is an astrocyte water channel found in the periventricular and periaqueductal brain and the gray matter of the spinal cord [23, 24]. The aquarorin-4 channel is one of a family of channels that allow for movement of water across cell membranes [25]. The channel is highly represented in the optic nerve, the spinal cord, and the area postrema. In NMOSD, specific autoantibodies to the aquaporin-4 channel have been shown to be pathogenic [26, 27]. Measurable aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) can be found in 75–90% of patients with NMOSD, and when found, the AQP4-IgG is 91–100% specific for NMOSD [11].

## MOG Antibodies

In a subset of patients with a clinical presentation of NMOSD but without AQP-4-IgG, antibodies to the membrane-embedded myelin oligodendrocyte glycoprotein (MOG) have been found [28, 29]. MOG-IgG is also found in children with acute disseminated encephalomyelitis [30], but in those cases, the antibody seropositivity is not persistent and MOG-IgG cannot be detected after the monophasic illness. MOG-IgG is not found in patients with multiple sclerosis or AQP-4-IgG seropositive NMOSD [31]. The clinical presentation of MOG-IgG-positive NMOSD is like that of AQP-4-IgG-positive cases, with ON and TM as the most common presenting syndromes. Though the severity of symptoms is similar between the two, the degree of recovery from attacks of ON or TM in patients with MOG-IgG disease is generally greater than for those with AQP-4-IgG disease. Patients with MOG-IgG-positive disease are more likely to have simultaneous bilateral ON, rapidly sequential ON, or simultaneous ON and TM [32]. In one large cohort of 252 patients, 56% of MOG-IgG seropositive patients had a monophasic presentation [33]. Involvement of the cerebellum and brainstem is also more common in MOG-IgG-positive patients, and cases of seizures, encephalitis, and meningitis have been described [34–36]. Because of the greater degree of phenotypic variability in MOG-IgG-positive patients, some have

suggested it be considered a separate entity outside of NMOSD, and the terms MOG-IgG-associated optic neuritis, encephalitis, and myelitis (MONEM) have been suggested [37]. The natural history of MOG-IgG seropositive NMOSD is not fully understood, owing to the limited follow-up time and the low number of described cases. In clinical practice, most patients with MOG-IgG seropositive NMOSD are treated with long-term immunotherapy in a similar way to patients with AQP-4 IgG seropositive NMOSD [38].

## Imaging NMOSD

MRI is a valuable diagnostic tool for the diagnosis and monitoring of disease activity in NMOSD. Just as how the clinical presentation of NMOSD is similar but with notable specific differences from MS, the imaging abnormalities of the two diseases are distinct. A large majority of patients with NMOSD presenting with ON have gadolinium enhancement of the optic nerve visible on MRI [11]. Bilateral optic neuritis, chiasmatic involvement, and enhancement of more than half of the length of the optic nerve (longitudinally extensive optic neuritis—LEON) are features more typical of NMOSD than MS [4, 39].

At the time of diagnosis, brain MRI in NMOSD patients is normal in nearly 80%, and the remainder usually have nonspecific white matter T2 hyperintensities not meeting diagnostic criteria for MS [1]. Over time, the brain MRI in most patients with NMOSD demonstrates the accumulation of white matter T2 hyperintensities, but typically they remain nonspecific and not meeting MS criteria [1]. The brain MRI is useful in differentiating MS from NMOSD, but not in differentiating different antibody-mediated forms of NMOSD from one another [40]. At disease onset, several patterns of brain MRI lesions specific to NMOSD have been described, including lesions that are longitudinally extensive within the corticospinal tract, extensive hemispheric lesions, periependymal lesions surrounding the lateral ventricle, and cervicomedullary lesions [41]. With further follow-up imaging, a minority of patients (16%) ultimately develop typical MS-like lesions which satisfy MS criteria [42, 43].

In NMOSD patients presenting with myelitis, a large majority (90%) have abnormal spinal cord MRI showing T2 hyperintensity most often in the central gray matter, which usually (88%) spans three or more vertebral body levels within the spinal cord [1]. Although longitudinally extensive transverse myelitis (LETM) is typical, lesions spanning less than three levels are also described [44]. Cord edema (50%) and gadolinium enhancement (64%) are common during the acute presentation, and over time, many patients develop cord atrophy [1].

## 2015 Criteria

Previous diagnostic criteria for NMOSD [1, 45] have defined NMOSD by the clinical presentation of ON and acute myelitis, with supportive evidence of AQP4-IgG seropositivity and MRI findings. Recognizing the role of AQP4-IgG in the pathogenesis of NMOSD, some have reported cases of AQP4-IgG seropositive patients not meeting previous NMOSD criteria [44, 46]. Many of these cases were first attacks or monophasic presentations of ON or acute myelitis. Some were cases of short-segment myelitis, hypothalamic, or brainstem syndromes.

With increasing recognition of several different CNS syndromes as within the spectrum of NMOSD, a consensus panel revised the diagnostic criteria in 2015 [4]. These criteria dichotomize NMOSD cases into those APQ4-IgG seropositive and those seronegative. Because of the specificity of the AQP4-IgG, the requirements for diagnosis of NMOSD are fewer in seropositive cases. Table 12.1 summarizes the 2015 NMOSD diagnostic criteria.

These criteria may facilitate earlier and more accurate diagnosis of NMOSD, often after only one clinical attack (in the AQP4-IgG-positive patients). The criteria may also prove helpful in diagnosing NMOSD in a subset of patients with atypical MS. As treatment for NMOSD with immunotherapy becomes more widespread, the importance of early and accurate diagnosis becomes clear.

**Table 12.1** 2015 NMO-spectrum disorders diagnostic criteria

| AQP4-IgG seropositive | AQP4-IgG seronegative or unknown |
|---|---|
| At least one core clinical characteristic[a] | At least two core clinical characteristics[a], occurring as a result of one or more clinical attacks, and meeting the following requirements:<br>1. One of the core clinical characteristics must be ON, myelitis with LETM, or APS<br>2. Dissemination in space (two or more different core clinical characteristics)<br>3. MRI findings consistent with NMOSD[b] |

[a]*Core clinical characteristics*: (1) Optic neuritis (ON), (2) Acute myelitis, (3) Area postrema syndrome (APS), (4) Acute brainstem syndrome, (5) Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions[b], (6) Symptomatic cerebral syndrome with NMOSD-typical brain MRI lesions[b]

[b]*MRI findings consistent with NMOSD*: (1) Brain MRI normal or only nonspecific white matter lesions, (2) Optic nerve MRI with T2-hyperintensity or gadolinium enhancement extending over half the optic nerve length (LEON) or involving optic chiasm, (3) Spinal cord MRI with lesion extension over three contiguous segments (LETM), or three contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis, (4) Area postrema syndrome requires associated dorsal medulla/area postrema lesions, (5) Acute brainstem syndrome requires associated periependymal brainstem lesions

## Immunotherapy for NMOSD

Like with MS, there are several goals of treatment for NMOSD. First, one should consider treating acute attacks of NMOSD with immunotherapy to reduce CNS damage and enhance repair. Second, long-term immunotherapy should be considered to reduce the frequency and severity of subsequent attacks in order to reduce disability in the long term. A third consideration, though not reviewed in detail here, is the use of pharmacological agents and other therapies to reduce chronic symptoms of NMOSD, much in the same way as MS.

The primary goals in treating acute attacks of NMOSD are to restore neurological function and to limit irreversible damage of the CNS. The mainstay of treatment for acute attacks of optic neuritis and transverse myelitis, the two most common presenting symptoms of NMOSD, is high-dose corticosteroids [47]. A typical dose is 1000 mg of intravenous methylprednisolone daily for 3–5 days. Intravenous methylprednisolone has been the treatment of choice since the Optic Neuritis Treatment Trial demonstrated the superiority of intravenous steroids over low-dose oral steroids [48]; but several recent studies have shown high-dose bioequivalent oral steroids to be as effective as intravenous doses [49, 50]. Oral tapering doses of steroids following the high-dose course are optional, but have not be evaluated in a systematic way. An oral taper over 2–6 months may be considered in cases of limited recovery or instances when the long-term immunotherapy to be started has a delayed onset of action.

Because acute attacks of NMOSD can be severe and poorly responsive to corticosteroids, additional treatment options may be necessary. In cases of severe optic neuritis, severe transverse myelitis, and NMOSD attacks, plasmapheresis has been shown to be helpful in achieving better functional recovery [51–54]. The benefit of plasmapheresis is independent of AQP-4 IgG seropositivity in patients with NMOSD [55]. A typical regimen would be five to seven exchanges of 1–1.5 volumes of circulating plasma every other day [56]. Other acute immunotherapies such as intravenous immune globulin (IVIG) have not been shown to be effective in treating acute NMOSD attacks.

Because incomplete recovery from attacks is common, and the accrual of disability in NMOSD over time is largely dependent on the attack severity and frequency, long-term immunotherapy to reduce attacks is warranted in most patients. Unlike MS, NMOSD does not have a secondary progressive phase, and the therapeutic target in NMOSD is for reduced attack frequency only. Prior to 2019 no randomized controlled trials of preventative immunotherapy agents in NMOSD had been completed, though many different agents had shown benefit in small prospective and retrospective series, including oral corticosteroids, azathioprine, mycophenolate, methotrexate, mitoxantrone, and rituximab. Immunomodulating

agents used to treat MS, such as beta-interferon, natalizumab, and fingolimod, have largely been unsuccessful in NMOSD or shown to be harmful [57–59].

A small retrospective study showed long-term corticosteroid therapy in NMOSD to reduce relapse rates [60], but the side effects of long-term corticosteroid use limit its widespread adoption as first-line therapy. Several steroid-sparing agents have been investigated and used for NMOSD. Azathioprine, which inhibits de novo purine synthesis and prevents T-cell and B-cell proliferation, has been used to treat NMOSD for decades [61]. It has been shown to decrease annualized relapse rates in NMOSD patients when used alone or in conjunction with oral corticosteroids [62]. Because of the delayed onset of action of azathioprine, a typical approach is to treat with a target dose of 2–3 mg/kg/day in conjunction with oral prednisone, and to taper the prednisone over several months. Mycophenolate, an inhibitor of de novo guanosine synthesis, which prevents T-cell and B-cell proliferation, also has also been shown in a retrospective series to reduce relapse rates and reduce or stabilize disability in NMOSD [63]. Target doses for mycophenolate are 1000 mg twice daily. Like with azathioprine, there is a delayed onset of action with mycophenolate and a prolonged oral corticosteroid taper may be warranted. Long-term immunosuppression with azathioprine or mycophenolate has been associated with increased risk of infection, myelosuppression, and secondary malignancy. Small studies have shown benefits in NMOSD with the use of methotrexate [64] and mitoxantrone [65, 66], but the significant side effects of these drugs and the availability of other immunotherapeutic options have limited their use.

The understanding of the antibody-mediated pathogenesis of NMOSD has led to the use of rituximab, an anti-CD20 monoclonal antibody that depletes peripheral B-cell populations. Rituximab, dosed either as four weekly 375 mg/m$^2$ infusions or as 1000 mg biweekly infusions, reduces relapse rates in NMOSD [67, 68]. Disability scores in patients with NMOSD treated with rituximab also either stabilize or decrease over the course of treatment, up to 2 years [69, 70]. A typical approach is to dose rituximab every 6 months, or alternatively to monitor circulating B-cells, and re-dose based on repopulation of CD19+ B-cells or CD27+ memory B-cells. Rituximab is generally well tolerated, with the most common side effect being allergy or infusion reaction, which can generally be avoided with pre-treatment with corticosteroids, diphenhydramine, and/or acetaminophen. Infections, including severe infections, are more common in patients treated with rituximab. And although cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients being treated with rituximab for other autoimmune conditions (risk estimated 1:25,000) [56], to date, there have been no reports of PML in patients treated with rituximab monotherapy for NMOSD or MS.

In 2019, the results of clinical trials of three different monoclonal antibodies were presented, showing a reduction in relapse rates in NMOSD subjects. Eculizumab is a humanized monoclonal antibody which inhibits the terminal complement protein C5. As an add-on therapy to existing immunomodulating therapy, eculizumab reduced the likelihood of relapse in AQP4-IgG positive NMOSD subjects. Only 3% of subjects in the eculizumab group experienced an adjudicated relapse compared to 43% of placebo treated subjects [71]. Based on these results, eculizumab became the first drug approved by the US Food and Drug Administration for the treatment of AQP4-IgG positive NMOSD patients in June 2019. Inebilizumab, a monoclonal antibody targeting the B-cell marker CD19, reduced relapse rates by 73% in NMOSD subjects, the majority of whom were AQP4-IgG positive [72]. And satralizumab, an anti-IL-6 receptor monoclonal antibody, reduced relapse rates by 62% in a group of AQP4-IgG positive and negative subjects with NMOSD, although the treatment benefit was less evident in the antibody negative subjects [73]. The success of these three monoclonal antibodies in reducing relapse rates in NMOSD represents a breakthrough in the treatment of this disease and reinforces the importance of immunotherapy in NMOSD.

The optimal duration of immunotherapy treatment for NMOSD is not well studied. In part, this is because of the relatively recent recognition of the disease as a specific entity and the lack of a known cure. In this way, NMOSD is like MS, and most immunotherapy is continued for the long term depending on tolerability and the development of adverse effects. The decision to stop immunotherapy for NMOSD should be based on consideration of multiple factors including pre- and post-treatment relapse rates, relapse severity, disability, treatment tolerability, treatment duration, and other patient-specific factors (e.g., age, other comorbidities, considerations for potential pregnancy).

## Conclusion

Over the past two decades, neuromyelitis optica spectrum disorder has come to be understood as a unique disease entity distinct from multiple sclerosis. The unique pathology, pathophysiology, imaging, epidemiology, and responses to treatment set the disease apart. But NMOSD also has significant phenotypic heterogeneity, and new information, such as additional pathogenic autoantibodies, is coming to light each year.

## References


1. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology. 1999;53:1107–14.
2. O'Riordan JI, Gallagher HL, Thompson AJ, et al. Clinical, CSF, and MRI findings in Devic's neuromyelitis optica. J Neurol Neurosurg Psychiatry. 1996;60:382–7.
3. Weinshenker BG. Neuromyelitis optica: what it is and what it might be. Lancet. 2003;361:889–90.
4. Wingerchuk DM, Banwell B, Bennett JL, International Panel for NMO Diagnosis, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177–89.
5. Popescu BF, Lennon VA, Parisi JE, et al. Neuromyelitis optica unique area postrema lesions: nausea, vomiting, and pathogenic implications. Neurology. 2011;76(14):1229–37.
6. Kitley J, Leite MI, Nakashima I, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. Brain. 2012;135:1834–49.
7. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica: clinical predictors of a relapsing course and survival. Neurology. 2003;60:848–53.
8. Ghezzi A, Bergamaschi R, Martinelli V, et al. Clinical characteristics, course and prognosis of relapsing Devic's neuromyelitis optica. J Neurol. 2004;251:47–52.
9. Cabre P, González-Quevedo A, Bonnan M, et al. Relapsing neuromyelitis optica: long term history and clinical predictors of death. J Neurol Neurosurg Psychiatry. 2009;80(10):1162–4.
10. Wingerchuk DM, Pittock SJ, Lucchinetti CF, Lennon VA, Weinshenker BG. A secondary progressive clinical course is uncommon in neuromyelitis optica. Neurology. 2007;68:603–5.
11. Wingerchuk DM, Lennon VA, Lucchinetti CF, et al. The spectrum of neuromyelitis optica. Lancet Neurol. 2007;6:805.
12. de Seze J, Lebrun C, Stojkovic T, Ferriby D, Chatel M, Vermersch P. Is Devic's neuromyelitis optica a separate disease? A comparative study with multiple sclerosis. Mult Scler. 2003;9:521–5.
13. Asgari N, Lillevang ST, Skejoe HP, Falah M, Stenager E, Kyvik KO. A population-based study of neuromyelitis optica in Caucasians. Neurology. 2011;76:1589–95.
14. Cabrera-Gomez JA, Kurtzke JF, Gonzalez-Quevedo A, Lara-Rodriguez R. An epidemiological study of neuromyelitis optica in Cuba. J Neurol. 2009;256:35–44.
15. Giorgi D, Balacco Gabrieli C, Bonomo L. The association of optic neuropathy with transverse myelitis in systemic lupus erythematosus. Rheumatology. 1999;38:191–2.
16. Lehnhardt FG, Impekoven P, Rubbert A, et al. Recurrent longitudinal myelitis as primary manifestation of SLE. Neurology. 2004;63:1976.
17. Ferreira S, Marques P, Carneiro E, D'Cruz D, Gama G. Devic's syndrome in systemic lupus erythematosus and probable antiphospholipid syndrome. Rheumatology. 2005;44(5):693–5.
18. Chan AY, Liu DT. Devic's syndrome in systemic lupus erythematosus and probable antiphospholipid syndrome. Rheumatology. 2006;45:120–1.
19. Pittock SJ, Lennon VA, De Seze J, et al. Neuromyelitis optica spectrum disorders and non-organ-specific autoimmunity. Arch Neurol. 2008;65(1):78–83.
20. Lucchinetti CF, Mandler RN, McGavern D, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. Brain. 2002;125:1450–61.
21. Mandler RN, Davis LE, Jeffery DR, Kornfeld M. Devic's neuromyelitis optica: a clinicopathological study of 8 patients. Ann Neurol. 1993;34:162–8.
22. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis

optica: distinction from multiple sclerosis. Lancet. 2004;364:2106.
23. Takahashi T, Fujihara K, Nakashima I, et al. Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: a study on antibody titre. Brain. 2007;130:1235.
24. 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;202:473–7.
25. Yukutake Y, Yasui M. Regulation of water permeability through aquaporin-4. Neuroscience. 2010;168(4):885–91.
26. Hinson SR, Pittock SJ, et al. Pathogenic potential of IgG binding to water channel extracellular domain in neuromyelitis optica. Neurology. 2007;69(24):2221–31.
27. Papadopoulos MC, Verkman AS. Aquaporin 4 and neuromyelitis optica. Lancet Neurol. 2012;11:535–44.
28. Mader S, Gredler V, Schanda K, et al. Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders. J Neuroinflammation. 2011;8:184.
29. Kitley J, Woodhall M, Waters P, et al. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. Neurology. 2012;79(12):1273–7.
30. Probstel AK, Dornmair K, Bittner R, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. Neurology. 2011;77(6):580–8.
31. Kitley J, Waters P, Woodhall M, et al. Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: a comparative study. JAMA Neurol. 2014;71(3):276–83.
32. Jarius S, Ruprecht K, Kleiter I, in cooperation with the Neuromyelitis Optica Study Group (NEMOS), 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.
33. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. Brain. 2017;140(12):3128–38.
34. Fujimori J, Takai Y, Nakashima I, Sato DK, Takahashi T, Kaneko K, et al. Bilateral frontal cortex encephalitis and paraparesis in a patient with anti-MOG antibodies. J Neurol Neurosurg Psychiatry. 2017;88(6):534–6.
35. Hamid SHM, Whittam D, Saviour M, Alorainy A, Mutch K, Linaker S, et al. Seizures and encephalitis in myelin oligodendrocyte glycoprotein IgG disease vs aquaporin 4 IgG disease. JAMA Neurol. 2018;75(1):65–71.
36. Sarangi S, Wong B, Cahill J. Clinical episode of aseptic meningitis with leptomeningeal enhancement in patient with anti-MOG antibodies. Presented at the annual meeting of the American Academy of Neurology (AAN), Los Angeles, CA, April, 2018. P5.420; 2018.
37. dos Passos GR, Oliveira LM, da Costa BK, et al. MOG-IgG-associated optic neuritis, encephalitis, and myelitis: lessons learned from neuromyelitis optica spectrum disorder. Front Neurol. 2018;9:217.
38. Weber MS, Derfuss T, Bruck W. Anti-myelin oligodendrocyte glycoprotein antibody-associated central nervous system demyelination—a novel disease entity? JAMA Neurol. 2018;75(8):909–10.
39. Mealy MA, Whetstone A, Orman G, Izbudak I, Calabresi PA, Levy M. Longitudinally extensive optic neuritis as an MRI biomarker distinguishes neuromyelitis optica from multiple sclerosis. J Neurol Sci. 2015;355(1–2):59–63.
40. Jurynczyk M, Geraldes R, Probert F, et al. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. Brain. 2017;140(3):617–27.
41. Huh SY, Min JH, Kim W, Kim SH, Kim HJ, Kim BJ, Kim BJ, Lee KH. The usefulness of brain MRI at onset in the differentiation of multiple sclerosis and seropositive neuromyelitis optica spectrum disorders. Mult Scler. 2014;20(6):695–704.
42. Pittock SJ, Lennon VA, Krecke K, Wingerchuk DM, Lucchinetti CF, Weinshenker BG. Brain abnormalities in neuromyelitis optica. Arch Neurol. 2006;63:390–6.
43. Matthews L, Marasco R, Jenkinson M, et al. Distinction of seropositive NMO spectrum disorder and MS brain lesion distribution. Neurology. 2013;80:1330–7.
44. Flanagan EP, Weinshenker BG, Krecke KN, et al. Short myelitis lesions in aquaporin-4-IgG-positive neuromyelitis optica spectrum disorders. JAMA Neurol. 2015;72:81–7.
45. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology. 2006;66:1485–9.
46. Sato DK, Nakashima I, Takahashi T, et al. Aquaporin-4 antibody-positive cases beyond current diagnostic criteria for NMO spectrum disorders. Neurology. 2013;80:2210–6.
47. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica. Curr Treat Options Neurol. 2008;10:55–66.
48. Beck RW, Cleary PA, Anderson MM Jr, Keltner JL, Shults WT, Kaufman DI, Buckley EG, Corbett JJ, Kupersmith MJ, Miller NR, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. N Engl J Med. 1992;326(9):581–8.
49. Ramo-Tello C, Grau-Lopez L, Tintore M, et al. A randomized clinical trial of oral versus intravenous methylprednisolone for relapse of MS. Mult Scler J. 2014;20(6):717–25.
50. Morrow SA, Fraser JA, Day C, et al. Effect of treating acute optic neuritis with bioequivalent oral vs intravenous corticosteroids. JAMA Neurol. 2018;75(6):690–6.
51. Weinshenker BG, O'Brien PC, Petterson TM, Noseworthy JH, Lucchinetti CF, Dodick DW, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol. 1999;46(6):878–86.

52. Keegan M, Pineda AA, McClelland RL, Darby CH, Rodriguez M, Weinshenker BG. Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology. 2002;58(1):143–6.
53. Ruprecht K, Klinker E, Dintelmann T, Reickmann P, Gold R. Plasma exchange for severe optic neuritis: treatment of 10 patients. Neurology. 2004;63(6):1081–3.
54. Watanabe S, Nakashima I, et al. Therapeutic efficacy of plasma exchange in NMO-IgG-positive patients with neuromyelitis optica. Mult Scler. 2007;13(1):128–32.
55. Bonnan M, Valentino R, et al. Plasma exchange in severe spinal attacks associated with neuromyelitis optica spectrum disorder. Mult Scler. 2009;15(4):487–92.
56. Kimbrough DJ, Fujihara K, Jacob A, et al. Treatment of neuromyelitis optica: review and recommendations. Mult Scler Relat Disord. 2012;1:180–7.
57. Papeix C, Vidal JS, de Seze J, et al. Immunosuppressive therapy is more effective than interferon in neuromyelitis optica. Mult Scler. 2007;13:256–9.
58. Min JH, Kim BJ, et al. Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder. Mult Scler. 2012;18(1):113–5.
59. Kleiter I, Hellwig K, et al. Failure of natalizumab to prevent relapses in neuromyelitis optica. Arch Neurol. 2012;69(2):239–45.
60. Watanabe S, Misu T, et al. Low-dose corticosteroids reduce relapses in neuromyelitis optica: a retrospective analysis. Mult Scler. 2007;13(8):968–74.
61. Mandler RN, Ahmed W, et al. Devic's neuromyelitis optica: a prospective study of seven patients treated with prednisone and azathioprine. Neurology. 1998;51(4):1219–20.
62. Costanzi C, Matiello M, et al. Azathioprine: tolerability, efficacy, and predictors of benefit in neuromyelitis optica. Neurology. 2011;77(7):659–66.
63. Jacob A, Matiello M, et al. Treatment of neuromyelitis optica with mycophenolate mofetil: retrospective analysis of 24 patients. Arch Neurol. 2009;66(9):1128–33.
64. Minagar A, Sheremata WA. Treatment of Devic's disease with methotrexate and prednisone. Int J MS Care. 2000;2(4):43–9.
65. Weinstock-Guttman B, Ramanathan M, et al. Study of mitoxantrone for the treatment of recurrent neuromyelitis optica (Devic disease). Arch Neurol. 2006;63(7):957–63.
66. Kim SH, Kim W, et al. Efficacy and safety of mitoxantrone in patients with highly relapsing neuromyelitis optica. Arch Neurol. 2011;68(4):473–9.
67. Cree BA, Lamb S, Morgan K, Chen A, Waubant E, Genain C. An open label study of the effects of rituximab in neuromyelitis optica. Neurology. 2005;64:1270–2.
68. Jacob A, Weinshenker BG, et al. Treatment of neuromyelitis optica with rituximab: retrospective analysis of 25 patients. Arch Neurol. 2008;65(11):1443–8.
69. Kim SH, Kim W, et al. Repeated treatment with rituximab based on the assessment of peripheral circulating memory B cells in patients with relapsing neuromyelitis optica over 2 years. Arch Neurol. 2011;68(11):1412–20.
70. Bedi GS, Brown AD, et al. Impact of rituximab on relapse rate and disability in neuromyelitis optica. Mult Scler. 2011;17(10):1225–30.
71. Pittock SJ, Berthele A, Fujihara K, Kim HJ, Levy M, Palace J, Nakashima I, Terzi M, Totolyan N, Viswanathan S, Wang K-C, Pace A, Fujita KP, Armstrong R, Wingerchuk DM. Eculizumab in aquaporin-4–positive neuromyelitis optica spectrum disorder. N Engl J Med. 2019, [Epub ahead of print].
72. Cree B, Bennett J, Kim HJ, et al. A double-masked, placebo-controlled study with open-label period to evaluate the efficacy and safety of inebilizumab in adult subjects with neuromyelitis optica spectrum disorders – top line efficacy and safety results. Philadelphia: Presented at the Annual Meeting of the American Academy of Neurology (AAN); 2019. Plen02.001.
73. Yamamura T, Kleiter I, Fujihara K, et al. Efficacy of satralizumab (SA237) in subgroups of patients in SAkuraSky: a phase III double-blind, placebo-controlled, add-on study in patients with neuromyelitis optica spectrum disorder (NMOSD). Philadelphia: Presented at the Annual Meeting of the American Academy of Neurology (AAN); 2019. S43.008.