

Update on neuromyelitis optica: natural history and management

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Abstract: Neuromyelitis optica or Devic disease is an inflammatory disorder of the central nervous system. It is caused by antibodies that attack aquaporin 4 water channels in the cell membrane of astrocytic foot processes at the blood brain barrier. It can involve the optic nerve, the spinal cord and beyond. Here we review its pathophysiology, clinical features, and therapy.

Keywords: Neuromyelitis optica, Devic disease, NMO-IgG, optic neuritis, transverse myelitis, NMO spectrum disorders

Introduction

Neuromyelitis optica (NMO) or Devic disease is an inflammatory disorder of the central nervous system characterized by episodes of optic neuritis and transverse myelitis. The condition was defined by Dr Eugene Devic, a physician practising in Lyon, France, in 1894.¹⁻³ It was subsequently thought that there was no clinical involvement beyond the optic nerve and spinal cord and that the disorder might be, where monophasic, a variant of acute disseminated encephalomyelitis (ADEM) and, where relapsing, a variant of classic multiple sclerosis (MS). However symptoms in other neurological axes have been repeatedly reported in NMO cases. NMO is also currently considered as an entity distinct from classic multiple sclerosis because it has clinical manifestations, antibodies, radiological and pathological features that differ from MS.⁴ The prognosis of NMO has been poor without appropriate treatment as many patients were left with severe disability and many died within weeks or months.⁵ Early recognition and treatment of NMO, therefore, are essential. In this article we review the pathogenesis and clinical manifestations of NMO with an emphasis on the optic nerve and spinal cord involvement, and beyond. Clinicopathological correlation and treatment are also discussed.

Optic nerve and spinal cord involvement Pathophysiology

In NMO, the involvement of the spinal cord and optic nerves or chiasm has been commonly reported but there is increasing evidence that isolated or multiple cerebral lesions can occur.⁶ NMO is characterized by neuronal destruction with glial (astrocyte and oligodendrocyte) and connective tissue reaction in the spinal cord and optic nerve or chiasm.^{6,7} In the acute phase, leukocytes, particularly neutrophils and eosinophils, infiltrate perivascular areas.^{7,8} Demyelination, axonal loss, and macrophage infiltration are commonly seen in the optic nerve and the grey and white matter of

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the spinal cord.⁶⁻¹² The changes vary in degree from lacunar degeneration to frank necrosis which has been observed particularly in the spinal cord.^{7,13} Small foci of necrosis have been demonstrated in the optic nerve.⁷ In severely affected cases resulting in blindness or paraplegia, swelling and softening of the affected parenchyma has been identified at an early stage in the evolution of an attack.^{6,10,13} The inflammation usually occurs over several cord segments.^{6,9,10} The spinal cord may be affected partially or entirely in cross-section and the inflammation may extend to the pial surface.^{6,9,10} In some chronic cord lesions, a cyst or a long cavity is formed.^{6,10,14} Astrocytosis and atrophy develop in later stages,^{7,10,14,15} up to 10 months after the onset in one study.¹⁶ The walls of medium-sized vessels in the cord lesions appear thick and hyalinized, giving a 'rubber band' appearance.⁶ Studies have revealed hyalinization of small arteries and veins as they enter affected parenchyma with the lumen greatly obliterated.^{10,13} The sclerosis of the vessels is located in close proximity to the necrotic cord area and also observed in degenerated nerve roots.¹³ However the vascular changes have not been observed in every case.¹⁶ It is notable that patients in postmortem studies were severely affected and their pathological findings seem to be at the extreme end of the spectrum of the disorder. More recent reports indicate that NMO may manifest in a lesser clinical severity.¹⁷ To aid the understanding of the clinical syndrome, we include two examples of clinical and pathological correlation from the literature (Figure 1).

Ortiz de Zarate et al⁶ described a 49-year-old man who presented with bilateral blurred vision and became blind within 5 days. Cerebrospinal fluid (CSF), urine, and blood tests were all unremarkable except for a high erythrocyte sedimentation rate. Two and a half months later, right lower limb weakness developed, followed by paraplegia after a further week. Sensory impairment to the level of the costal margin began a month later and progressed to the second rib within the next few days. CSF remained normal. He died from sepsis in the 5th month of his illness. A postmortem study revealed T2 to L1 spinal cord damage with the entire thickness of the cord affected in the central portion of the lesion, and necrosis was evident from T6 to T12. Myelomalacia was prominent centrally in the spinal cord. All stages of neuronal degeneration, astrocyte hyperplasia, plenty of scavenger cells (white blood cells that engulfed debris), and interstitial edema were widespread. The walls of medium-sized vessels within the lesions appeared thick and hyalinized, giving a "rubber tube" appearance. Similar to the cord lesions, there was central



Figure 1 Sections from the 11th thoracic and 3rd lumbar segments, using Loyez myelin stain, revealed irregular regions of degeneration in the white matter.

Notes: Typical histopathological findings of NMO are identified. The results were from a woman who presented with a 4 week history of marked right leg weakness and numbness, followed by burning pain in the same area and urinary incontinence. She developed left leg weakness 4 days prior to admission. On examination, both legs were flaccid and weak without muscle wasting. Deep tendon reflexes in the arms were intact, knee and right ankle jerks were absent, but the left ankle jerk was present. The abdominal reflexes and plantar responses were not elicited. Sensation in all modalities was impaired. Cerebrospinal fluid (CSF) showed WBC 18 cells/mm³, neutrophils 80%, lymphocytes 20%, and raised protein.

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malacia and several scavenger cells were observed in the optic chiasm. Groups of lymphocytes were demonstrated in the hypothalamus and crus cerebri.

The NMO antibody and aquaporin 4

Evidence of humoral immunity such as perivascular deposition of immunoglobulin and complement in a vasocentric pattern around thickened hyalinized blood vessels, and the infiltration of neutrophils or eosinophils, is prominent in NMO lesions.⁸ In 2004 researchers at the Mayo Clinic discovered an NMO immunoglobulin (NMO-IgG, not IgM), later referred to as anti-aquaporin 4 (AQP4) antibody, that is specific to NMO.^{18,19} CSF protein electrophoresis in NMO is often negative for oligoclonal bands in patients with NMO,¹⁹ however, there is at least one study demonstrating evidence for pos-

sible intrathecal production of AQP4 specific autoimmunity.²⁰ AQP4 Ab is not detected in MS patients. The antibody selectively binds to the extracellular domain of (AQP4) water channels in the cell membrane of astrocytic foot processes at the blood–brain barrier.^{19,21} AQP4 forms a macromolecular complex with excitatory amino acid transporter 2 (EAAT2) on astrocyte plasma membranes.²² It regulates CNS water and ion homeostasis.^{23,24} The distribution of AQP4 in the brain is wide. It occurs along the entire surface of plasma membrane of the astrocytic foot processes that face vessels and the pia mater; on the basolateral membrane of ependymal cells; and in the glia lamellae of the supraoptic nucleus and other osmosensitive regions in the hypothalamus.²⁴ A recent study has revealed that AQP4 is prominent at the glia limitans externa, the cerebral cortex, the grey-white matter junction, the subependymal region, the abluminal surface of penetrating cortical blood vessels in a rim pattern, the astrocytic foot processes abutting vessels in a rosette pattern, the floor of the fourth ventricle including the area postrema, but is minimal in normal cerebral white matter.²⁵ AQP4 is diffusely expressed in the entire spinal cord with the greatest concentration in the central grey matter and pia mater,²⁶ and EAAT2 is found abundantly in the grey matter.^{22,25} AQP4 is also highly present in the optic nerve and retinal Müller cells, a type of astrocyte; but absent in myelin, neurons, and oligodendrocytes.^{19,24,25} Characteristic NMO lesions, with or without necrosis, lack AQP4 and show vasocentric depositions of IgG, IgM, and complement.^{22,25,27} These findings coincide with the inflammation, edema, necrosis, cavitation, cord atrophy, perivascular cuffing, and thickened vessel walls.²⁶ The regions of AQP4 depletion colocalize with the immune complex deposition in NMO lesions.²⁵ The loss of AQP4 parallels the loss of EAAT2 in NMO.^{22,28} In contrast to the stage-dependent loss of AQP4 in MS lesions, the loss of AQP4 in NMO lesions depends on neither stage of disease nor CNS region.²⁵ The binding of NMO-IgG to AQP4 initiates two events: AQP4 endolysosomal degradation; and complement activation.¹⁹ In the presence of active complement in vitro, the binding of NMO-IgG to the AQP4 channel in astrocytes increases plasma membrane permeability.²² In the absence of active complement in vitro, the astrocytic membranes are still intact but NMO-IgG down-regulates AQP4, Na⁺-dependent glutamate transport, and EAAT2, leading to glutamate homeostasis impairment.²² Hinson et al have hypothesized that the disrupted EAAT2 would increase extracellular glutamate levels in AQP4-rich regions, which is toxic to oligodendroglia and neurons leading to subsequent demyelination.¹⁹

Seropositivity for NMO-IgG is useful to differentiate NMO from MS²¹ and is 76% sensitive and 94% specific to NMO.²⁹ It predicts relapses and NMO development in patients with a first episode of severe longitudinally extensive transverse myelitis (LETM).³⁰ Around 70% of NMO patients have antibody detectable in the serum. A Japanese group has recently developed a new NMO-IgG assay which has 91% sensitivity and 100% specificity to NMO.¹⁷ The serum NMO-IgG titre correlates with the severity of the disease with higher titers in patients with complete blindness, LETM, or extensive cerebral lesions and low titers following corticosteroid and immunosuppressive treatments.¹⁷ The NMO-IgG titer in the serum is consistently higher than in the CSF.¹⁷ A study revealed that CSF NMO-IgG was detectable in three seronegative cases and that this measurement might improve the sensitivity of the test.³¹

Demyelination and axonopathy develop in both MS and NMO but astrocytic damage or astrocytopathy predominates only in NMO.³² Misu et al revealed that the depletion of AQP4 was associated with astrocytic impairment as decreased glial fibrillary acidic protein or GFAP, an astrocyte specific protein, accompanies the loss of AQP4, particularly where there is immune complex deposition in the early stage of NMO lesions.²⁶ However myelin basic protein (MBP) staining is relatively intact, suggesting that demyelination is not the primary pathology. These findings differ from what has been observed in ischemic infarction and MS lesions. The surrounding areas of NMO lesions exhibit reactive gliosis as AQP4 and GFAP expressions rise. However the relationship between AQP4 expression, GFAP expression, and perivascular deposition of activated complement and immunoglobulin was found to be heterogeneous.³³ A recent NMO study revealed AQP4 and GFAP loss in demyelinating areas in some patients, but total preservation of AQP4 in areas with demyelination and GFAP loss in other patients even in cases seropositive for NMO-IgG.³³ The findings indicate that AQP4 loss is independent of the presence of the NMO-IgG antibody.³³ In addition, perivascular immune complex deposition was demonstrated in active and chronic NMO lesions but not tightly related to perivascular AQP4 depletion; and not found in any demyelinating MS lesions.³³ Matsuoka et al, hence, have hypothesized that there might be two pathological types of NMO: AQP4 autoimmunity-related and AQP4 autoimmunity-unrelated, and the latter may account for seronegative NMO.³³

Two studies revealed that the GFAP level in the CSF (CSF-GFAP) increased during clinical relapse and

remarkably decreased following intravenous methylprednisolone treatment.^{32,34} The level was greater in myelitis than optic neuritis and cerebral lesions. The level in NMO was significantly higher than that in MS; acute disseminated encephalomyelitis (which is identified by monophasic encephalomyelitis with multifocal white matter lesions by brain and spinal MRI); neuro-Behçet disease; meningitis; cord infarction; headache; sinusitis; and conversion disorder.³² The findings are suggestive of astrogliopathy in NMO but not in the other conditions stated above. CSF-GFAP in NMO correlates well with the Expanded Disability Status Scale (EDSS) and has 90% sensitivity and 76.9% specificity when compared with the other conditions.³² CSF-GFAP level has a potential role as a biomarker for NMO activity. It is noted that the level is also high in cerebral ischemia and mildly elevated in Alzheimer's disease.³² Additionally, serum GFAP was found to be significantly higher in patients with NMO-related optic neuritis (ON) as compared to MS-type ON in one recent study.³⁵

Clinical manifestations: world studies

Since the discovery of NMO-IgG, various additional clinical manifestations of NMO have been identified. Revised NMO criteria have been proposed by Wingerchuk et al in 2006.²⁹ The criteria include optic neuritis, acute myelitis, and at least two out of three supportive criteria: contiguous spinal cord MRI lesion extending over three or more vertebral segments; brain MRI not meeting MS diagnostic criteria; and seropositivity for NMO-IgG. NMO-IgG seropositivity has been incorporated in recent diagnostic criteria for NMO.³⁶ It can therefore include limited forms, including isolated or recurrent optic neuritis,³⁷ isolated or recurrent transverse myelitis, and a wide range of clinical presentations (NMO spectrum disorders).

Prevalence of NMO is greater in females. Mean age of onset is the late 30s in NMO as opposed to the early 30s in MS. However both childhood and elderly onset (up to 80 years of age), has been reported.^{8,18,38} NMO is usually sporadic but familial occurrences have been reported, involving about 3% of all NMO patients in a series.³⁹ The clinical course of NMO patients is mostly relapsing-remitting rather than monophasic.^{4,38,40} Conversion to a secondary progressive course is uncommon.⁴⁰⁻⁴² A series showed that patients with a relapsing course had a poorer prognosis than the less common monophasic type and one third of these patients died from respiratory failure as a consequence of cervical cord lesions.⁴³ Patients can present with either ON or transverse myelitis or both.^{38,40} The mean interval between the first

two attacks was significantly shorter if the initial lesion was bifocal (11.1 months), compared to either a spinal cord (33.1 months) or an isolated optic nerve lesion (34 months) in a French cohort.⁴⁰ The mean number of relapses decreased after the first two years in this study.⁴⁰ The median time from the onset of NMO to EDSS score 4, 6, and 7 was 7, 10, and 21 years respectively.⁴⁰ Serum NMO-IgG was detectable in 54% of 111 cases tested.⁴⁰

In a Caucasian study from Denmark 163 cases were ascertained who had diagnoses of ON, MS, NMO, and TM without MR changes of MS. Twenty-six percent were diagnosed as NMO on clinical criteria (62% of whom were AQP4 positive).⁴⁴ In a Thai series, seropositive NMO-IgG was demonstrated in almost 40% of patients (53/135 cases) with idiopathic inflammatory demyelinating CNS disease which included NMO, other NMO spectrum disorders, conventional MS, optico-spinal MS (OSMS), and clinical isolated syndromes.⁴⁵ NMO-IgG was detected in 9% of Western MS patients¹⁸ and 15% of northern Japanese conventional MS (CMS) patients.⁴⁶ A study in Cuba and the French West Indies (an ethnically mixed population) revealed seropositivity to NMO-IgG in 33.3% of relapsing NMO cases and 4.8% of relapsing remitting MS.⁴⁷ It was shown in this study that seropositive patients had more attacks and more disability as evaluated by EDSS than seronegative cases, particularly in the motor and sensory systems.

OSMS was considered as an Asian form of MS in the past but recent studies have shown otherwise. It has been suggested that there is no important difference between OSMS and NMO and that they are the same disease.⁴⁸ A study in the northern part of Japan revealed that NMO-IgG was detected in 63% (12/19) of OSMS cases who experienced optic neuritis, myelitis, and fulfilled Wingerchuk criteria, and 15% (2/13) of CMS cases.⁴⁷ The majority of these patients showed long spinal cord involvement (>3 vertebral segments) and no perception of light in one or both eyes. A study in Kyushu, the southernmost part of Japan, recruited relapsing remitting MS patients according to Poser criteria and subdivided them into OSMS (58 cases) and CMS (90 cases).⁴⁹ Patients who had both optic nerve and spinal cord involvement, without any clinical evidence of disease in either the cerebrum or the cerebellum, were considered to be OSMS. They could manifest additionally with minor brainstem signs, such as transient double vision and nystagmus. Patients who were not included in the criteria, were considered as CMS. None was seropositive for human T-cell leukemia virus type I (HTLV-1). Half of the OSMS patients fulfilled Wingerchuk 1999 NMO criteria. The AQP4 antibody positivity rate was 36.2% in

patients with OSMS, 6.7% in CMS, and 0% in healthy individuals.⁴⁹ AQP4 antibody-positive patients with OSMS and CMS showed higher relapse rate and EDSS than AQP4 antibody-negative CMS patients and were mostly female. The AQP4 antibody-negative OSMS patients had results for these parameters in between the two groups. Both clinical features and peripheral blood cytokine production patterns of low-titer anti-AQP4 antibody patients were similar to those of anti-AQP4 antibody-negative OSMS patients with LETM. Thus it is clear that the precise case definition for OSMS will result in a differing proportion of cases fulfilling diagnostic criteria for classical NMO on the one hand and classical MS on the other.

In classical NMO the CSF usually shows pleocytosis ($50\text{--}1000 \times 10^6$ WBC/L) with neutrophil predominance and infrequent oligoclonal bands.⁴¹ Syndromic NMO is found in other autoimmune disorders such as SLE and Sjögren disease.⁴¹

Optic neuritis (ON)

Optic neuritis presents with subacute loss of vision with or without orbital pain (especially on eye movement), decreased colour vision, and signs of optic neuropathy.⁵⁰ It is a clinical diagnosis but MRI of the optic nerves is confirmatory in most cases (Figure 2).⁵⁰ Involvement of different segments of the anterior visual pathway influences the clinical presentation. For instance, pain usually occurs with involvement of the intraorbital segment of the optic nerve; is quite severe in optic nerve sheath inflammation; but is not a feature of disease limited to the intracranial segment of the optic nerve. In optic chiasm involvement, the presentation

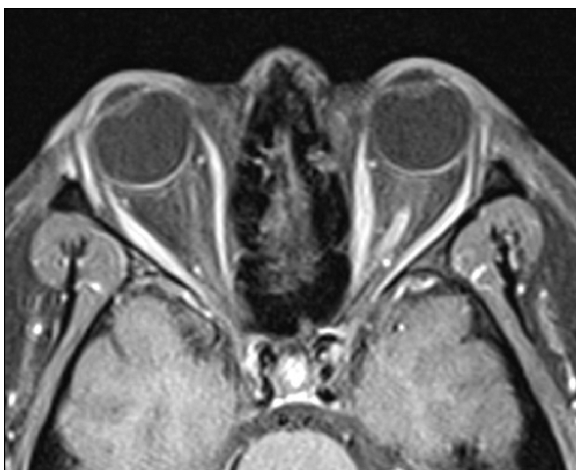


Figure 2 A postcontrast axial T1-weighted fat-suppressed MRI of the orbits in a NMO patient showed enhanced left optic nerve. The finding was consistent with acute left optic neuritis.
Abbreviations: MRI, magnetic resonance imaging; NMO, neuromyelitis optica.

may mimic bilateral simultaneous optic neuritis. Clinical ophthalmic assessments include visual acuity; Ishihara colour test; visual field; pupillary light reaction; anterior segments; retina; and optic disc. ON has been classified as typical and atypical types. The “typical” type implies ON as seen in MS but it should be noted that this is typical only in Caucasian populations and it would preferable to use a more specific designation such as DON (demyelinating ON) or MS-ON, depending on whether criteria for MS are fulfilled.⁵⁰ Other alternative ON phenotypes are considered as atypical including NMO; chronic relapsing inflammatory optic neuropathy (CRION); ADEM; neuroretinitis; post-infection and post-vaccination ON; infectious diseases such as neuroborreliosis, tuberculosis, syphilis, and cytomegalovirus; and other systemic diseases such as sarcoidosis, autoimmune disease such as systemic lupus erythematosus, Sjögren syndrome, and Behçet disease.⁵⁰ Features of typical and atypical ON in adults are shown in Tables 1 and 2 respectively and more reviews on MS-ON can be consulted.^{50–55} A question that should be addressed in a first presentation of optic neuritis is whether the case is typical or not, as the management differs.⁵³ When atypical ON is suspected, further investigations are recommended such as MRI of the brain and orbits with gadolinium, lumbar puncture, chest x-ray, blood tests including full blood count, liver function, renal function, calcium and electrolyte, erythrocyte sedimentation rate, autoimmune screening, ACE, syphilis and viral serological studies. An investigation of the pattern of visual field defect in NMO revealed that both central and non-central scotoma (altitudinal, quadrant, three quadrant, hemianopia, and bitemporal hemianopia) were observed in seropositive NMO patients and the incidence of non-central scotoma was higher than in MS patients.⁵⁶ Among non-central scotomata in NMO cases, an altitudinal defect was the most common.⁵⁶

Patients with NMO-type ON have a poorer visual outcome and a thinner peripapillary retinal nerve fibre

Table 1 Summary of typical symptoms and signs of optic neuritis⁵⁴

Typical symptoms

Orbital pain with pain on eye movement
Pain can occur before visual loss
Progressive visual loss over a few days
Spontaneous improvement of vision
History of multiple sclerosis

Typical signs

Normal or swollen optic disc
Normal macular and peripheral retina
Uveitis or retinal periphlebitis might be observed

Table 2 Summary of features of atypical optic neuritis⁵⁴

Severe visual loss for more than 2 weeks after the onset
Severe orbital pain
No early visual improvement (within 3 weeks after the onset)
African patients with vision < 6/12 and no early recovery
Visual deterioration after stopping steroid
Past history of cancer
Optic atrophy on acute presentation without previous history of ON
Severe optic swelling with vitreous reaction
Optic disc hemorrhage

Abbreviation: ON, optic neuritis.

layer, measured with optical coherence tomography, than MS-ON.⁵⁷ Furthermore the NMO-IgG titer in ON patients with permanent complete blindness at least in one eye has been shown to be higher than that in ON patients without blindness.¹⁷ A study of ON in patients with NMO in an African population showed that ON was the first manifestation in 23 cases (76.6%), being retrobulbar ON in 20 cases, and papillitis in 3.⁵⁸ Seventy percent of patients had bilateral involvement. Thirty percent of patients with a first episode of ON experienced a residual loss of visual acuity $\leq 20/200$.⁵⁸ In the cohort studied by Collongues et al, this visual acuity loss affected 22% of patients.⁴⁰ Patients in this study who first presented with bifocal disease experienced a worse visual prognosis than those who first presented with either an isolated cord or optic nerve lesion.⁴⁰ Moreover, a high number of lesions on brain MRI was related to a shorter duration from the onset of NMO to severe residual visual loss.⁴⁰ A study performed in central London revealed that African and African-Caribbean patients who presented with acute isolated ON had a threefold increase in the risk of developing NMO-type ON than Caucasian patients.⁵⁹ Optic neuritis in Chinese patients seems to be aggressive and normal MRI scans of the brain were commonly observed in one study.⁶⁰

Isolated ON with clinical, radiological, and serological evidence of neither MS nor NMO can be subdivided into three groups: CRION; recurrent isolated ON (RION); and a solitary episode of isolated ON (SION). CRION has been defined in an article published in 2003 based in London.⁶¹ It is a form of ON which is usually bilateral but sequential rather than simultaneous associated with pain and with no clinical myelitis at extended follow up. It is characterized by repeated ON relapses immediately or soon after withdrawing immunosuppression, which is a feature of neither MS nor NMO nor RION. In CRION, MRI of the brain is normal; the optic nerves reveal hyperintensity on T2 weighted images and contrast enhancement; and CSF oligoclonal bands are rare.⁶¹ RION refers to relapsing remitting isolated ON in one or both optic nerves in patients who have no clinical or laboratory-supported evidence

of MS.⁶² SION is a unilateral or bilateral ON in patients with evidence of neither MS nor NMO, who do not require immunosuppression to prevent relapse, and do not have recurrence of ON or another neurological episode after extended follow up.⁵¹ A RION series from the Mayo clinic demonstrated that 20% of 34 patients were seropositive for NMO-IgG and 50% (6/12) of the seropositive cases developed a myelitis attack and fulfilled criteria for a diagnosis of NMO within 8.9 years (median) following the first ON episode.⁶³ MRI brain of all cases was unremarkable or showed nonspecific abnormalities. Non-Caucasian patients were more commonly seropositive than seronegative. Another study revealed that 20.8% (5/24) of patients with RION converted to NMO due to the occurrence of myelitis within 2–12 years follow-up (mean 5.8 years) and 25% (6/24) of RION cases had seropositive NMO-IgG.⁶⁴ Four of 21 French patients (19%) with bilateral ON and/or RION were seropositive for NMO-IgG.⁶⁵ In a Japanese cohort, 26.9% (7/26) of RION patients had positive serum NMO-IgG.⁴⁹ A study in Cuba and the French West Indies (mixed population) revealed seropositivity to NMO-IgG in 16.6% of 12 RION cases.⁴⁷ In a prospective series involving 114 ON patients from London, serum NMO-IgG was detected in 5% of SION, 6% of RION, 5% of CRION, 56% of NMO-ON, and no MS-ON cases.⁶² In an investigation performed in China, the rate of seropositivity was 50% in patients who presented with RION⁶⁶ and 32% (11/34) in patients with severe ON (acuity 20/200 or worse).⁶⁷ Higher titers had significantly more ON relapses than lower titers and 18.2% (2/11) of seropositive ON cases developed transverse myelitis within 32 months.⁶⁷ Using a recently developed fluorescence immunoprecipitation assay employing recombinant human AQP4 in 224 subjects from multiple centers in Europe,⁶⁸ seropositive NMO-IgG was demonstrated in 5.8% of SION, 58.8% of NMO-ON, and 0% in MS-ON and normal subjects. Seropositive NMO-IgG in SION was rare with a high rate of NMO conversion according to Wingerchuk's revised criteria; whereas none of the seronegative SION cases (0/60) converted to NMO within 26 month follow-up (median) and 13/60 NMO-IgG negative SION patients were diagnosed with MS later in the disease course.⁶⁸ Seropositive NMO-IgG predicted a poor visual outcome.⁶⁸ The Danish study revealed that serum NMO-IgG was detectable in 3/12 (25%) of RION, 1/28 (0.04%) of SION, and 1/4 (25%) of bilateral ON.⁴⁴ In summary, seropositive NMO-IgG in isolated ON confidently excludes an MS type of ON but seronegativity does not rule out subsequent NMO conversion.⁶² Seropositive NMO-IgG RION is a limited form of NMO and predicts a potentially poor visual outcome.⁶³ Moreover, these patients are at high risk of developing transverse myelitis and severe disability

in the future.⁶³ Hence long-term immunosuppression should be considered in RION patients seropositive for NMO-IgG.⁶³

Transverse myelitis

Acute transverse myelitis (ATM) is a focal inflammation of the spinal cord having numerous potential causes and resulting in motor, sensory, and autonomic dysfunction.⁶⁹ It is paramount to exclude compressive lesions and secondary ATM which includes autoimmune disorders such as NMO, systemic lupus erythematosus (SLE), Sjögren's syndrome, and antiphospholipid syndrome; inflammation such as MS, ADEM, Behçet disease, and sarcoidosis; infection; neoplasm; metabolic disorders such as B12 deficiency and copper deficiency; vascular conditions such as infarction and dural fistula; and radiation myelopathy.^{30,69,70} Idiopathic ATM refers to the situation where no cause has been found.⁶⁹ Patients with NMO usually present subacutely over weeks to months with moderate to severe spinal cord involvement.⁷¹ When the condition involves three or more vertebral segments, it is termed LETM which is a part of the Wingerchuk 2006 criteria (Figure 3).²⁹ Such lesions may extend from the level of C2 to the conus medularis.⁷² NMO patients complain of sensory disturbance such as numbness, tingling, dissociated sensory loss, pain, weakness, and bowel and bladder dysfunction.^{6,13,16} These symptoms can involve one leg initially before progressing to the other leg and arms⁶ over a matter of weeks¹³ or the two legs simultaneously.⁹ Patients present with signs of white matter dysfunction such as spasticity, hyperreflexia and



Figure 3 A sagittal T2-weighted MRI of the spinal cord in a NMO patient showed hyperintense signal and swelling of several cervical and thoracic cord levels. The finding was consistent with acute myelitis.

Abbreviations: MRI, magnetic resonance imaging; NMO, neuromyelitis optica.

a positive Babinski sign.^{72–74} Mild muscle wasting along with pyramidal tract signs, a mixed picture of gray and white matter dysfunction, has been reported.¹³ A study of myelitis in SLE revealed that patients with clinical “white matter” myelitis were more likely to fulfill NMO criteria than those with “gray matter” myelitis.⁷⁵ Paroxysmal symptoms can occur, such as intermittent sensory disturbance becoming constant,¹³ tonic spasms, and Lhermitte's symptom.⁴³ Spinal MRI usually reveals T2 signal hyperintensity, edema, and gadolinium enhancement of acutely inflamed regions. Unlike MS, NMO lesions tend to be located at the central region rather than the peripheral white matter^{26,76} and holocord involvement is also observed.⁴⁷ In chronic cases, MRI scans demonstrate atrophic spinal cord and occasionally cavities.^{15,77} Recurrent transverse myelitis, commonly seen in NMO,³⁰ can occur in the same location in the spinal cord.⁷⁴ A progressive course is unusual but still possible. For example, in one report a NMO-IgG seropositive female experienced a 4-month history of progressive quadriplegia and respiratory failure following nausea, vomiting, and hiccups.⁷⁸ Her weakness worsened in spite of intravenous steroids but improved with plasma exchange. The case represents an extreme end of the clinical spectrum of myelitis in NMO.

Serum NMO-IgG was detected in 52% (14/27) of patients with recurrent isolated longitudinal extended transverse myelitis (R-LETM) in North American Caucasian series.¹⁸ The rate of seropositivity in R-LETM varied in other studies, rates being 33% in a French study,⁶⁵ 60% in a Japanese study,⁷⁶ 23.5% in another Japanese series,⁴⁹ and 14.2% in a Cuban and French West Indies series (mixed population).⁴⁷ Thirty-eight percent (11/29) of patients in a Mayo clinic series who presented with single episode of LETM were seropositive for NMO-IgG; 56% of these seropositive cases developed a second episode, either TM or ON, within a year.³⁰ Serum antinuclear antibody and extractable nuclear antigen were demonstrated in three of these relapsed cases. No further relapse occurred in seronegative LETM cases.³⁰ R-LETM may be considered another limited form of NMO.³⁰ Early immunosuppression has been recommended in patients who present with single LETM and seropositive NMO-IgG in order to prevent the second event.³⁰

In contrast to LETM, patients who presented with acute partial transverse myelitis (APTM) involving ≤ 2 vertebral segments and who had normal cerebral MRI scans showed a much lower frequency of NMO-IgG seropositivity (5% or 1/22 in one study).⁷⁹ However the NMO-IgG titre of APTM appeared low in another study.¹⁷ NMO cannot be ruled out completely in cases with APTM as it could represent another end of the clinical spectrum.

Beyond the optic nerve and spinal cord

Brain MRI scans are usually normal or show nonspecific white matter lesions at the onset of NMO.⁴³ There is increasing evidence for the occurrence of lesions outside the optic nerve and spinal cord (Figure 4). A pathological study of a NMO case with seropositive NMO-IgG, who presented with generalized numbness, tongue numbness, vomiting, hiccups, and double vision, has been reported.¹¹ MRI brain demonstrated several lesions in the dorsal medulla, basal ganglia, and an enhancing lesion in the right temporal lobe. She recovered spontaneously. Within two years she had exhibited two episodes of LETM. A MRI brain during the last attack showed new brain lesions with a recurrent gadolinium-enhancing right temporal lobe lesion. Similar to the spinal cord pathology reported above, a temporal lobe biopsy revealed lymphocyte, macrophage and eosinophil infiltration, myelin and axonal loss, and perivascular complement deposition. The patient responded well to Rituximab. Other cerebral lesions that have been reported so far include periventricular and white matter lesions.⁴⁷ A large cavity in the white matter of the right frontal lobe associated with meningitis,¹⁴ and extensive cerebral white matter lesions along with lesions in the corpus callosum.¹² Extensive brain lesions are frequent in children with NMO.⁸⁰

Posterior reversible encephalopathy has been reported in five seropositive NMO patients.⁸¹ These patients, who presented with confusion, double vision, and cortical

blindness, had bilateral T2-weighted hyperintense signals in the frontal, parietal and occipital lobes, and cerebellum. These might be due to NMO or medication related.⁸² An unenhanced tumefactive lesion in the left temporo-parietal region and ovoid lesions in the pericallosal areas with normal CSF profiles have been observed in a NMO-IgG seropositive case who experienced motor aphasia, finger agnosia, right-left disorientation, and right hand paresis.⁸³ Extensive brain lesions like tumors or ADEM and MS-like ovoid lesions on MRI have been identified in other reports on NMO.^{76,84}

Brainstem lesions have included a typical NMO case with right deviation of the tongue and right lower facial weakness;¹⁶ lesions in the floor of fourth ventricle involving the subependymal region and area postrema associated with intractable vomiting;^{25,84,85} periaqueductal lesions associated with intractable hiccup and nausea;⁸⁶ medulla oblongata lesions associated with nausea, vomiting, and acute respiratory failure;⁴³ abnormal eye movement such as opsoclonus, down-beat nystagmus, upbeat nystagmus, central vestibular nystagmus;⁸⁷ one and a half syndrome;⁸⁸ and bilateral internuclear ophthalmoplegia.⁸⁹ Hypothalamic and thalamic lesions have also been reported in patients presenting with hypersomnia and confabulation, weight loss, and behavioral change.^{84,90,91}

Treatment

One investigation demonstrated that the serum NMO-IgG level was associated with clinical disease activity, in that it rose

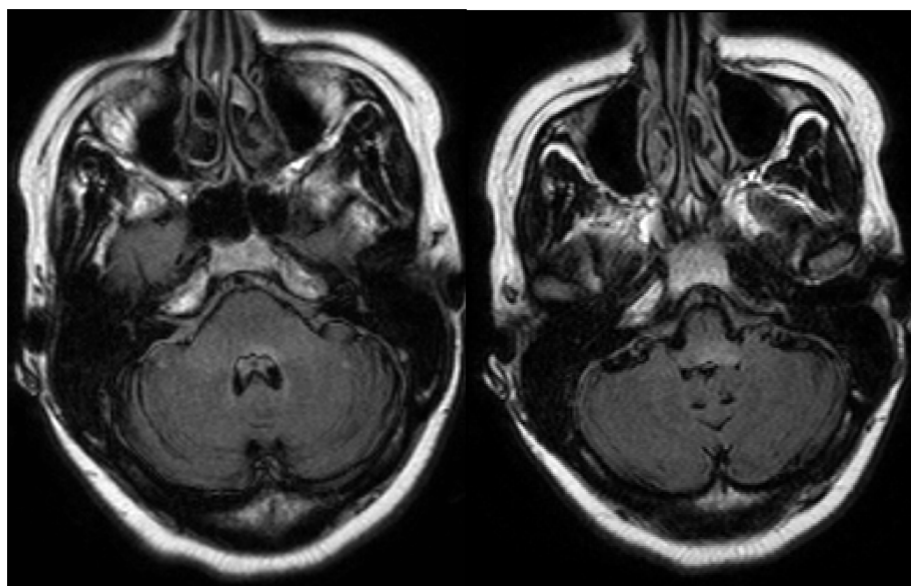


Figure 4 Axial fluid-attenuated inversion recovery (FLAIR) MRI scans of the brain showed hyperintense signal in the pons and medulla in a NMO patient who presented with ataxia, nausea, and vomiting.

Abbreviations: MRI, magnetic resonance imaging; NMO, neuromyelitis optica.

Table 3 Treatment summary

Study	Drug	Dose	Follow-up	Outcome
Falcini ¹⁰⁷ (9 YOF, LETM + ON, normal brain MRI, relapses during AZA 2.5 mg/kg/d)	MMF (n = 1)	2000 mg/day for 16 months	2 years	No further relapse Clinical and radiological improvement
Jacob 2009 ¹⁰⁶ (NMO spectrum disorders)	MMF (n = 24)	2000 mg/day (median)	28 months (median)	Reduced relapse rate in 79% of patients Improved or stabilized EDSS in 91% of patients One death from disease complications
Cree ¹⁰⁹ (ATM and ON)	RTX (n = 8)	375 mg/m ² IV once a week for 4 weeks Monitor peripheral blood CD19 B cells bimonthly Retreated, when these B cells became detectable, with two infusions of RTX 1000 mg, 2 weeks apart	12 months (average) CD19 = 0 after the 2nd dose and was sustained for 6–12 months	Reduced annual relapse rate and relapse-free in 75% of patients Improved EDSS in 88% of patients
Capobianco ¹²³ (ATM and ON)	RTX (n = 2)	Case 1: 375 mg/m ² IV once a week for 4 weeks, then PLEX every 3 weeks for 4 months, then two infusions of RTX 1000 mg, 2 weeks apart Case 2: 375 mg/m ² IV once a week for 4 weeks	First case: 13 months	Case 1: a clinical relapse after the first RTX while CD19 = 0; another relapse after PLEX and positive CD 19; no relapse within 2 months after second infusion Case 2: a clinical relapse at 6 months after the infusion and positive CD 19
Jacob ¹¹⁷ (NMO or LETM, most patients were refractory to other treatments)	RTX (n = 25)	I) 375 mg/m ² IV once a week for 4 weeks (n = 18) or II) Two infusions of RTX 1000 mg, 2 weeks apart (n = 4) III) No record (n = 3) Retreated at 6- to 12-month intervals or after relapse or when CD19 became detectable; Median interval 8 months	19 months (median)	Reduced annual relapse rate Stabilized or improved EDSS in 80% of patients two deaths, one from brainstem relapse and the other from septicemia
Jarius ⁹² (LETM ± ON)	RTX (n = 5)	As in Cree et al ¹⁰⁹	62 months (median)	Reduced relapse rate in 80% of patients but relapse occurred at day 260, 311, and 364 post- infusion in three case. Therapy interval was shortened in two cases, resulting in no further relapses. Failure in one case: (relapse at day 27 and 99 post infusion)
	CYC (n = 1)	50 mg/day orally then 50 mg on every other day	8 years	Pre-treatment Ten relapses in 1295 days; post-treatment one in 1610 days
	MiTX (n = 3)	No data	Long-term	Reduced relapse only in one case; increased relapse in the other two

(Continued)

Table 3 (Continued)

Study	Drug	Dose	Follow-up	Outcome
Nasir ¹²⁵ (NMO/SLE, LETM + ON, 19 myelitis relapses, NMO-IgG+)	AZA (n = 3)	No data	268, 235, and 673 days	Reduced relapse
	RTX (n = 1)	Two infusions of RTX 1000 mg, 2 weeks apart after the 17th relapse	CD 19 and 20 depletion at 5 months after the infusion	Two myelitis relapses with enhanced cord lesions on MRI, 3 and 4 months after the infusion, resulting in complete paraplegia
Kim ¹¹⁰ (NMO or NMO spectrum disorders)	RTX (n = 30)	I) 375 mg/m ² IV once a week for 4 weeks or II) Two infusions of RTX 1000 mg, 2 weeks apart Retreated with RTX 375 mg/m ² IV once when CD27 B cells > 0.05% of peripheral blood mononuclear cells by flow cytometric analysis	Over 24 months	Reduced relapse rate by 88%, relapse-free in 70% of patients Improved or stabilized EDSS in 97% of patients
Bedi ¹¹¹ (NMO)	RTX (n = 23)	I) 375 mg/m ² IV once a week for 4 weeks, followed by 2 planned infusions of the same dose biweekly every 12 months (n = 4) or II) Two infusions of RTX 1000 mg, 2 weeks apart, followed by 1000 mg every 6 months (n = 19)	32.5 months (median)	Reduced relapse rate in all cases and relapse- free in 74% of patients Improved or stabilized EDSS in all patients
Pellkofer ¹¹² (NMO, refractory to other treatments)	RTX (n = 10)	Two infusions of RTX 1000 mg, 2 weeks apart Retreated when reappearance of B cells initially but later at fixed interval every 6–9 months up to five courses in total B cell (CD20) depletion was identified as $<0.01 \times 10^9/L$ by flow cytometry	35–40 months The rise of B cells accompanied clinical relapse	Reduced relapse in 80% of patients 2 patients had infection, associated with decreased Ig 1 death from cardiovascular failure 3 days after infusion
Qian ¹¹⁴ (ON, LETM, white matter lesions; NMO-IgG 1:1920; refractory to AZA and MMF)	RTX (n = 1)	No record	64 months of several drug trials	Four more relapses within 5 months after RTX infusion when CD19 = 0, resulting in paraplegia
Mahmood ¹²⁵ (Case 1: 10-year-old female, LETM + ON, normal MRI brain, NMO-IgG was + then negative during a relapse, RTX = first prophylaxis drug; Case 2: 15-year-old female, LETM + ON, AZA trial)	RTX (n = 2)	Two infusions of RTX 1000 mg, 2 weeks apart; 3 cycles of infusion with 6–9 month interval; monitored B cells every 6–9 months, aiming at <10% of lower normal limits	2 years	Case 1: No relapse Case 2: Relapsed when B cells rose and relapse- free when B cells reached the target
Arabshahi ¹²² (11-year-old female, NMO/Sjögren, chiasmitis, LETM, No NMO-Ig test)	CYC (n = 1)	PLEX, steroid, and CYC, then monthly infusion (dose: no record) and oral prednisolone	7 months	Visual loss recurred after the first dose of CYC and tapering steroid, resulting in counting fingers in both eyes 6 months after the repeated doses
Mok ¹¹⁸ (NMO/SLE, refractory to treatment including IVMP)	CYC (n = 1)			No relapse

(Continued)

Table 3 (Continued)

Study	Drug	Dose	Follow-up	Outcome
Birnbaum ¹²¹ (NMO/SLE, LETM, ON, headache, hearing loss, NMO-IgG ⁺ , white matter lesions)	CYC RTX (n = 1)	CYC 1000 mg/m ² monthly for 6 months followed by RTX 1000 mg infusion at week 0, 2, 26, and 28	27 months	Myelitis relapse following CYC but relapse free following RTX
Gadze ⁷² (NMO/ R-LETM, abnormal VEP, normal brain MRI, NMO-IgG ⁺)	AZA CYC (n = 1)	CYC 1000 mg/m ² IV with IVMP 1000 mg once a month for 6 months	2 years	No clinical improvement (bed-bound) after a course of AZA and prednisolone; but partial remission and improved neurological signs (could stand with a stick) and cord MRI after CYC and IVMP
Polgár ¹¹⁹ (Case 1: NMO/SLE/APS, NMO-IgG ⁺ , LETM, brainstem and temporal lesions, sigmoid sinus thrombosis, Case 2: NMO/SLE, ON, ATM, 2 relapses pre- and 1 relapse post- AZA/ chloroquine)	Case 1 AZA Glatiramer CYC Case 2 AZA Chloroquine CYC	Case 1: CYC 500 mg/m ² IV once a month for 6 months. Three months after the last infusion: quarterly maintenance CYC therapy for 18 months Case 2: CYC 500 mg/m ² IV once a month for 6 months, followed by AZA 100 mg/day; no CYC maintenance therapy	Case 1: 6 years Case 2: 9 years	Case 1: relapses with AZA or glatiramer but relapse free with CYC Case 2: 2 relapses pre- and 1 relapse post- AZA/ chloroquine; no relapse during 6-month CYC infusion and a relapse after the last dose of CYC
Chia ¹²⁰ (NMO/SLE, ON, LETM, NMO-IgG ⁺ , treatment naive)	CYC (n = 1)	CYC 750 mg/m ² monthly for 3 months, stopped, then CYC 750 mg/m ² monthly for 6 months and a course of 5–20 mg of prednisolone	Almost a year	Clinical improvement following the first 3 doses of CYC; myelitis after discontinuing it; no relapse after 6 months of CYC

Abbreviations: RTX, rituximab; CYC, cyclophosphamide; MiTX, mitoxanthrone; AZA, azathioprine; MMF, mycophenolate mofetil; PLEX, plasma exchange; Ig, immunoglobulin; SLE, systemic lupus erythematosus; APS, Antiphospholipid syndrome; MRI, magnetic resonance imaging; LETM, longitudinally extensive transverse myelitis; ON, optic neuritis; NMO, neuromyelitis optica; EDSS, Expanded Disability Status Scale; ATM, acute transverse myelitis.

during relapse and decreased during remission or following treatment with steroid and immunosuppressive drugs such as azathioprine, rituximab, and cyclophosphamide.⁹² The low antibody titer was sustained for about a year in two patients who received a combination of azathioprine and prednisolone following intravenous methylprednisolone for acute relapse.⁹²

Acute relapse

Intravenous methylprednisolone

Intravenous methylprednisolone 1 g daily for 3–6 days has been recommended for acute myelitis or optic neuritis, following by a course of oral prednisolone.^{93,94} A prospective case series revealed that hyperacute treatment with corticosteroids may prevent visual loss in patients with optic neuritis who present with prodromal retro-orbital pain but no visual deterioration.⁹⁵ The patients included NMO cases, all had a prior history of optic neuritis, and the acute recurrence was confirmed by MRI.

Plasma exchange

Plasma exchange should be carried out quickly in a severe progressive steroid refractory event, as a rescue therapy.^{93,94} The response rate was 42% in one study.⁹⁶ The usual regimen is five exchanges of 1.5 plasma volumes over 10 days.⁹⁷ Early treatment seems to be associated with moderate to marked improvement.⁹⁸ It was also found to be useful in other smaller studies.^{99–101} The improvement in responsive cases appears to occur rapidly after the treatment and to be sustained.⁹⁸

Prophylactic immunosuppressive treatment

Azathioprine

Azathioprine is effective in preventing relapses in NMO spectrum disorders when used alone or in combination with prednisolone and has been classified as a class IV treatment.¹⁰² Annualized relapse rate reduction was 76% in a Mayo Clinic study¹⁰² and 70% in a Brazilian study.¹⁰³ EDSS and visual

scores of NMO patients have been shown to improve.^{102–104} The suggestion is to initiate the medication after the first attack in all seropositive patients and seronegative cases with a high chance of NMO relapse.¹⁰² Thiopurine methyl transferase (TPMT) should be checked in all cases. If the TPMT level is within a normal range, the recommended dose is 2.5–3 mg/kg/day in patients.¹⁰² A lower dose should be initiated in case of low TPMT (heterozygous) and an alternative treatment should be sought if the level is very low (homozygous deficiency).¹⁰² Full blood count, liver function, and renal function tests are conducted regularly. The target is a rise in mean corpuscular volume for at least 5 points from the baseline¹⁰² or a slight decline in lymphocyte count. Adverse effects include immunosuppression, myelosuppression, allergy, gastrointestinal disturbance, hepatic toxicity, and myalgia.⁹⁴

Mycophenolate mofetil (Table 3)

Mycophenolate mofetil is a noncompetitive inhibitor of the enzyme inosine 5'-monophosphate dehydrogenase. It inhibits purine synthesis and controls lymphocyte proliferation and T-cell-dependent antibody.¹⁰⁵ A few studies (class IV) showed a good efficacy on reducing relapse rate and improving disability.^{106,107} Side effects include immunosuppression, myelosuppression, gastrointestinal disturbance, infection, early pregnancy loss and congenital malformation.^{94,108}

Rituximab (Table 3)

Rituximab is a chimeric monoclonal antibody directed against antiCD20 which is expressed on pre-B cells and mature B cells.¹⁰⁹ Its use in NMO treatment was first described by Cree et al in 2005 and was found to be effective in reducing the relapse rate and improving disability.¹⁰⁹ Further studies showed more or less the same results.^{109–111} It is recommended to monitor CD19, CD27, or CD 20 B cells regularly and to maintain the level at zero.^{108,110–112} A study demonstrated that CD19 reappeared within 251–350 days following the last rituximab infusion, which correlated well with the rise of NMO-IgG and clinical relapse.⁹² A repeat treatment should be given when the number of these B cells increases, regardless of clinical relapse.¹¹² The NMO-IgG titer declined markedly and rapidly following re-infusion, consistent with clinical improvement;^{92,110} but did not disappear even when CD19 was undetectable in a study.⁹² It is notable that a seropositive NMO patient experienced agammaglobulinemia due to the depression of B-lymphocytes associated with carbamazepine and was relapse-free when CD19 was low (0.11%).¹¹³ However resistance was demonstrated in a

case with CD19 cell depletion.¹¹⁴ Plasma cells produce a variety of antibodies and do not express CD20. Perhaps the resistance might be because rituximab does not suppress plasma cells.¹¹⁴ Side effects include immunosuppression, myelosuppression,⁹⁴ progressive multifocal leukoencephalopathy¹¹⁵ and posterior reversible encephalopathy syndrome.¹¹⁶ Transient hypotension and influenza-like symptoms have been reported and can be managed with intravenous methylprednisolone.¹¹⁰ Infection has been recorded, including urinary and respiratory tract infection, and septicemia.^{110,117}

Cyclophosphamide (Table 3)

Cyclophosphamide is an antineoplastic alkylating agent. Its active metabolite binds with the guanine bases of DNA to interfere with mitosis.⁹⁴ Some case reports revealed that it was useful especially when a patient did not show any response to other medications and had other autoimmune diseases,^{72,118–120} whereas two reports showed a non-satisfactory outcome.^{121,122} The relapse rate declined significantly in one study, consistent with a decrease in serum NMO-IgG level.⁹² Side effects include immunosuppression, myelosuppression, alopecia, gastrointestinal disturbance, hemorrhagic cystitis, bladder cancer, leukemia, and infertility.⁹⁴

Conclusion

NMO is an inflammatory disorder of the central nervous system. Following the discovery of the NMO-IgG (anti AQP4) antibody, it has become evident that the spectrum of the disease is wider than previously thought and not limited to the optic nerve and the spinal cord. It can behave aggressively and fatalities occur from respiratory failure. Blindness is also a significant risk. Early recognition and treatment, when clinical symptoms are mild, could prevent further severe disability and relapses. In addition, not all patients with clinical NMO have NMO-IgG seropositivity. Perhaps this is due to low titers of NMO-IgG or alternatively there might be other unidentified antibodies or causes.

Disclosure

The authors report no conflicts of interest in this work.

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