DEVIC’S NEUROMYELITIS OPTICA

A critical review

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Abstract – Devic’s neuromyelitis optica (NMO) is an idiopathic inflammatory demyelinating and necrotizing disease characterized by predominant involvement of the optic nerves and spinal cord. In Asian countries relapsing NMO has been known as opticospinal multiple sclerosis. It has long been debated if NMO is a variant of multiple sclerosis (MS) or a distinct disease. Recent studies have shown that NMO has more frequently a relapsing course, and results from attack to aquaporin-4 which is the dominant water channel in the central nervous system, located in foot processes of the astrocytes. Distinctive pathological features of NMO include perivascular deposition of IgG and complement in the perivascular space, granulocyte and eosinophil infiltrates and hyalinization of the vascular walls. These features distinguish NMO from other demyelinating diseases such as MS and acute demyelinating encephalomyelopathy. An IgG-antibody that binds to aquaporin-4, named NMO-IgG has high sensitivity and specificity. Magnetic resonance imaging (MRI) studies have revealed that more frequently there is a long spinal cord lesion that extends through three or more vertebral segments in length. Brain MRI lesions atypical for MS are found in the majority of cases. Treatment in the acute phase includes intravenous steroids and plasma exchange therapy. Immunosuppressive agents are recommended for prophylaxis of relapses.

KEY WORS: Devic’s neuromyelitis optica, opticospinal multiple sclerosis, recurring optic neuritis, transverse myelitis, aquaporin-4, NMO-IgG antibody.

Neuromielite óptica de Devic: revisão crítica

Resumo – Neuromielite óptica ou doença de Devic (NMO) é uma doença inflamatória com desmielinização e necrose envolvendo preferencialmente os nervos ópticos e a medula espinal. Desde sua descrição inicial tem havido controvérsia se a NMO é uma variante da esclerose múltipla (EM) ou se é uma entidade independente. Na Ásia a doença é conhecida como esclerose múltipla óptico-espinal. Recentes avanços têm demonstrado que na maioria dos casos a NMO é recorrente e resulta de alterações inflamatórias por ataque à aquaporina-4, uma proteína localizada nos pés dos astrócitos na barreira hemato-encefálica. Patologicamente a NMO difere da EM pela presença de necrose e cavitação no centro da medula, deposição perivascular de IgG e complemento, infiltração de neutrófilos e eosinófilos, assim como por hiperplasia e hialinização dos vasos. O anticorpo contra a aquaporina-4 (IgG-NMO), detectado no soro dos pacientes, tem alta sensibilidade e especificidade. Imagem por ressonância magnética demonstra lesão medular que se estende três ou mais segmentos vertebrais. Na maioria dos casos há lesões cerebrais atípicas para EM. Corticosteróide venoso em altas doses e plasmaférese são usados no tratamento das fases agudas, enquanto os imunossupressores devem ser usados na profilaxia das recorrências.

PALAVRAS-CHAVE: neuromielite óptica, doença de Devic, esclerose múltipla óptico-espinal, neurite óptica recorrente, mielite transversa, aquaporina-4, IgG-NMO.

Devic’s neuromyelitis optica (NMO) or Devic’s disease is a severe idiopathic immuno-mediated inflammatory demyelinating and necrotizing disease that predominantly involves the optic nerves and spinal cord. Recent immunopathological evidences suggest that the target antigen is aquaporin-4, the dominant water channel in the central nervous system (CNS), located in the astrocyte foot processes at the blood-brain barrier.

The distinction between NMO and multiple sclerosis (MS) has long been unclear. For many decades NMO
was considered a variant of MS, characterized most commonly by a monophasic course of bilateral optic neuritis and transverse myelitis occurring concomitantly or within a short interval, and no evidence of disease outside the optic nerves and the spinal cord. Studies of MS in Asia revealed that compared with MS in Western countries, Asian MS patients had more frequent and severe involvement of the optic nerves and spinal cord, and a relatively more rapid progression. These observations led Japanese authors to divide their patients who did not meet the criteria for classical Devic's disease, into two other different subtypes of MS. Patients who had a relapsing-remitting course with involvement of the optic nerves and spinal cord and no clinical evidence of disease either in the cerebrum or the cerebellum were considered to have opticospinal MS. Those with minor brainstem signs, such as nystagmus and diplopia in addition to the opticospinal involvement were included in this group. Patients with signs of multiple involvement of the central nervous system, including the cerebrum and cerebellum were considered to have conventional MS. It was suggested that classical Devic's NMO and conventional MS represent two extremes of a spectrum of the same condition.

Recent clinical, pathological, immunological and imaging studies, however, have suggested that most patients with NMO have a relapsing course, the disease has distinctive histopathological and immunopathogenetic features, and that most patients have magnetic resonance imaging (MRI) brain lesions which are atypical for MS. It has also been shown that opticospinal MS and relapsing NMO are most likely the same disease.

In addition to the idiopathic and pure form of NMO the co-occurrence of optic nerve disease and transverse myelopathy has been described in association with a variety of conditions such as connective tissue disorders, bacterial and viral infections, and others. These observations suggest that NMO would be more appropriately considered as a clinical syndrome rather than a single disease.

This review focuses on the historical aspects, epidemiology, genetics, pathology and immunopathogenesis, clinical features, cerebrospinal fluid (CSF) abnormalities, MRI findings, diagnostic criteria and current treatment of Devic’s NMO.

**HISTORICAL OVERVIEW**

The association between acute myelitis and optic nerve disorder was first described by Albutt in 1870. Nine years later Erb reported a 52-year-old man with recurring optic neuritis in whom transverse myelitis supervened three months later. The patient ultimately made a complete recovery from the myelitis and a practically complete recovery of visual function. Seguin in 1880 was the first author to report a case in America. Other cases with this association were also reported in 1880 by Stefan and Noyes. In 1882 Chisholm recorded a case in which death occurred only 12 days after the onset drawing attention to the severity of the disease. In the same year, Dreschfeld demonstrated for the first time in an autopsied case the occurrence of inflammatory infiltrates in the optic nerves and spinal cord but no brain abnormalities. He credited Gowers for recognizing that optic neuritis and myelitis were both the result of a common cause.

In 1884 Eugène Devic reported the case of a 45-year-old French woman seen at the Hôtel-Dieu Hospital of Lyon because of intractable headache and depression in addition to general asthenia. One month later she developed urinary retention, complete paraplegia and blindness, and died few weeks later. Autopsy disclosed severe demyelinating and necrotic lesions extending for 4-5 cm length in the lower thoracic and lumbar spinal cord.

The lesions involved both the white and gray matter and were associated with cellular infiltrates and thickening of the vessels walls. There was demyelination of the optic nerves but gross examination of the brain was unrevealing. Devic presented this case at the First Congress of Internal Medicine in Lyon, and mentioned 16 other cases reported in the literature. In his paper Devic proposed the identity of the pathological process involving both the spinal cord and the optic nerves, named the syndrome “neuro-myélite optique” or “neuroptico-myélite”, and discussed its relationship with MS.

Fernand Gault, a disciple of Devic’s, reviewed in detail these 17 cases in his doctoral thesis named “De la neuromyélie optique aiguë” and suggested that they represented a distinct nosological entity. The eponym “Devic’s disease” was suggested by Acchiote in 1907.

In 1914 Goulden reviewed 51 cases in the literature fulfilling the diagnostic criteria as proposed by Devic, and added one case of his own. Beck in 1927 reviewed 71 cases and described rarefaction of the optic nerves and spinal cord, polymorphonuclear infiltrates, extensive demyelination and necrosis extending over multiple segments of the spinal cord. He emphasized that these pathological abnormalities were distinct from those found in MS.

Other authors as Hassin and Lowenberg et al. in 1937 described involvement of both white and gray matter in the spinal cord, marked inflammatory infiltrates, and the absence of gliosis. Stansbury in 1949, based upon review of over 200 cases and analysis of 20 autopsied cases, concluded that NMO occurs at any age, but is most common in persons between 30 and 50 years of age; that the initial disability is distributed equally between the optic nerves and the spinal cord; that the severe binocular loss of vision is a characteristic of the disease, although the visual loss may be monocular. Finally he suggested that the disease outcome is extremely poor as patients in his anal-
yasis usually died few months after onset of the disease. He proposed that the lesions progressed through a series of different stages. At onset there are prominent perivascular infiltrates of polymorphonuclear cells, leucocytes and plasma cells. Then perivascular foci of demyelination and necrosis ensue to coalesce into larger lesions with axonal damage. The spinal cord gray matter may be distinctively affected or may be involved by extension of the adjacent white matter lesions. Necrotic areas are commonly seen in the spinal cord and less frequently within the optic nerves. Finally, glial scars are formed although scarring is less frequent and usually only partial in contrast to typical MS lesions. Scott\textsuperscript{10} in 1952, commenting on Stanbury’s review, disagreed over his conclusion about the inexorably poor outcome of the disease and drew attention to cases with good functional recovery. He described cases with visual loss associated with minimal spinal cord dysfunction and even the occurrence of “abortive types” with binocular loss of vision not followed by paraplegia. Similar observations had been previously reported by Walsh\textsuperscript{11}. By 1958 over 300 cases of Devic’s disease had already been reported in the literature and the condition was considered more frequent than previously thought\textsuperscript{12}.

In Latin America NMO was first reported by Aluizio Marques\textsuperscript{13} in 1943 who described two cases in Rio de Janeiro. The first patient was a 21-year-old mulattoe female who developed simultaneous bilateral blindness and paralysis in the course of mumps. Cerebrospinal fluid examination disclosed 17 cells /mm\textsuperscript{3}. Clinical examination three months later revealed partial recovery of the vision and complete recovery of the motor, sensory, and sphincter functions. The second case was of a 45-year-old white woman who presented acute transverse myelitis followed a month later by bilateral optic neuritis. Examination nine months after the onset of the disease disclosed no recovery.

The concept of Devic’s NMO has been debated since Devic formulated his famous questions “Why such a peculiar localization?” “What is the intimate nature of the process?” To overcome these unanswered questions many clinical criteria for the diagnosis of the disease have been set forth by different investigators. Initially, the monophasic course of bilateral optic neuritis and myelitis as well as the simultaneity or short interval between the index events were emphasized. In 1894, Gault and Devic\textsuperscript{25} proposed that the diagnosis should be restricted to cases with bilateral optic neuritis and acute myelitis occurring simultaneously or within a few weeks apart. Other signs of CNS involvement could be occasionally observed. Shibasaki et al.\textsuperscript{24} in a study of the differences between British and Japanese MS considered as having Devic’s disease patients with both acute bilateral optic neuritis and acute myelitis – with no other signs of involvement of nervous system - occurring in a monophasic course within an interval of four weeks.

Imaging, CSF and pathological features were added to clinical findings in the diagnostic criteria suggested by Mandler et al.\textsuperscript{35} in 1994. Additionally to the occurrence of optic neuritis and myelitis, which could be coincidental or separated by an interval of months to years, patients should not have signs of involvement beyond the optic nerves and spinal cord. Magnetic resonance imaging (MRI) criteria included normal brain and the presence of signs of cavitation in the spinal cord. CSF analysis should reveal decreased serum/CSF albumin ratio; normal IgG synthesis and usually absent oligoclonal bands. Pathological features included necrosis and cavitation of the spinal cord with absent or scant inflammatory infiltrates. There should be signs of demyelination in the optic nerves, with or without cavitation whereas no lesions were to be found in the brain, brainstem and cerebellum.

In 1996 O’Riordan et al.\textsuperscript{36} reviewed the case records of patients seen at the National Hospital of Neurology and Neurosurgery, Queen Square and Moorfield’s Eye Hospital between 1986 and 1994. The disease was defined as a complete acute and severe transverse myelitis associated with acute unilateral or bilateral optic neuritis and no signs of brain involvement beyond the optic nerves. The disease could follow a monophasic or relapsing course. Interestingly in five of their 12 cases a probable etiology could be identified. Two patients had probable “acute disseminated encephalomyelitis” two weeks after a non-specific infectious illness and MRI showed swelling and abnormal sign extending over many segments of the spinal cord. One patient had systemic lupus erythematosus, another mixed connective tissue disease, and a third pulmonary tuberculosis. Six other patients exhibited a variety of organ-specific autoantibodies, further pointing to an immunological mechanism for the disease.

Starting in 1999 a series of investigations conducted at the Mayo Clinic have changed the very concept of NMO and clarified a number of issues concerning its clinical features, pathology, immunological mechanisms, and imaging.\textsuperscript{8,12-37} In a study of 71 patients with the association of optic neuritis (unilateral or bilateral), acute myelitis and no evidence of clinical disease outside of the optic nerve spinal cord Wingerchuk et al.\textsuperscript{9} showed that the great majority of cases have a relapsing course; that patients with monophasic course have more severe index events; that over one third of patients have CSF pleocytosis with more than 50 cells/mm\textsuperscript{3}; and that a spinal cord MRI with signal abnormality extending over three or more vertebral segments could be found in almost 90% of the cases. The authors proposed new diagnostic criteria according to these findings. Lucchinetti et al.\textsuperscript{7} in 2002 broadened the knowledge of the NMO pathology and emphasized its dif-
ferences from MS. Distinctly from MS, in NMO there are a pronounced perivascular deposition of immunoglobulin and complement, eosinophilic infiltration and prominent vascular fibrosis and hyalination within the lesions. They concluded that these findings support a major role of humoral immunity in the pathogenesis of NMO. The next work in this line of investigation was published by Lennon et al., in 2004 who identified a serum autoantibody marker of NMO named NMO-IgG, which can distinguish NMO from MS and other demyelinating disorders. The following year Lennon et al. demonstrated that the NMO-IgG selectively binds to aquaporin-4 (AQP-4), the predominant water channel within the CNS located in foot processes of the astrocytes in the blood-brain barrier. Aquaporins have been known since the seminal study by Peters Agre in 1988 who discovered the first water channel, termed aquaporin 1 and was awarded the Nobel Prize of Chemistry in 2003. Finally Pittcock et al. reported the finding of nonspecific brain MRI lesions in the majority of patients with NMO.

EPIEDEMOLOGY

Studies on epidemiology of NMO are still scanty and the data may be misleading as different authors have used distinct terminology, definition of the disease, diagnostic criteria and methods of survey.

Cases of Devic’s NMO have been reported in all continents and races although the disease is more prevalent in areas with Black, Asian and Indian populations, where MS prevalence is usually low. In Africa and Asia classical MS is rare. In Africa and Asia classical MS is rare. In Nigeria, Osuntokun reported 95 cases of NMO among 97 cases of MS. In South Africa recurrent NMO was observed in seven of eight black patients with demyelinating disease. In Asia, low prevalence rates of MS have been reported in Japan, China, Taiwan, Korea, India, Malaysia and Thailand. Two recent studies in Japan, quoted by Kira, reveal prevalence rates of 8-9/10, a much higher figure than those revealed by early epidemiological studies which suggested rates of 0.7-4.0/10.

On the other hand there have been many reports about the higher rate of NMO in Asians than in Western populations. In the first Japanese study Okinaka found that out of the 270 cases of demyelinating disease collected in Japan, there were 175 cases of NMO and 66 cases of conventional MS. Kuroiwa et al. in 1975 conducted a nationwide survey of demyelinating diseases in Japan and found strict Devic’s disease in 7.6% of the 1084 cases collected. In the MS group analysis of the site of involvement disclosed lesions in the optic nerves and spinal cord in 80% of the cases, whereas the cerebrum was affected in 43%, the brainstem in 70% and the cerebellum in 47%. In an analysis of 488 cases of demyelinating diseases in Asian countries, using the same definitions and diagnostic criteria, the authors found strict Devic’s disease in 7% of the multiple sclerosis group. In a comparison study between British and Japanese MS patients, Shibasaki et al. found Devic’s disease in none of 204 British cases, in comparison with 5% in the Japanese group. Additionally, their study showed that the proportion of the opticospinal form among all cases of MS was 42% in Japan and 6% in Britain.

The higher proportion of strict Devic’s disease among MS cases has also been reported in India (11%-42%), Korea (7%), and Philippines (13%-20%).

One study of MS in Algonkian and Athapaskan indigenous people in Manitoba, Canada, identified five cases with the NMO phenotype among seven cases of MS. Autopsy in one of these patients showed marked demyelination and necrosis of the spinal cord with inflammatory infiltrates of lymphocytes and eosinophils, similar histopathological features to those more recently described by Lucchineti et al.

The frequency of the opticospinal MS has been reported as 36% of MS cases in Hong Kong, 43% in Taiwan, and 40% to 57% in Japan, although lower (16%) in northern Japan. Interestingly opticospinal MS has not been reported in Mediterranean Arab but is frequent among MS cases in Arabs from Gulf countries.

In the Caribbean basin the relative frequency of NMO has been studied in the African descent population of Martinique. In a population-based study in French Afro-Caribbeans, using the Wingerchuk et al. original diagnostic criteria Cabre et al. found 13 cases (17.3%) of relapsing NMO among 75 cases of demyelinating diseases. Recently they described a series of 35 (17%) cases in a cohort of 206 cases of demyelinating diseases in which isolated optic neuritis cases were included. In Argentina one study showed that among 134 cases of definite MS 10 (7.5%) fulfilled the Wingerchuk et al.’s criteria for NMO. In Brazil Lana-Peixoto et al. in a study of 67 consecutive patients with demyelinating disease found 39 patients with classical MS, 20 with opticospinal MS and eight with strict Devic’s disease, suggesting that the optic nerves and spinal cord are more frequently affected in the Brazilian population than in the Caucasian population of North America and Europe. A more recent Brazilian study from a hospital in Rio de Janeiro describes the features of a series of 24 NMO patients (20 women and four men; ages at onset 14 to 55 years, mean 32.8) but the relative frequency of the disease among other demyelinating disorders is not mentioned. In their series Blacks comprised 14 cases and 22 patients had relapsing disease.

The age of onset ranges from childhood to late adulthood, with the incidence tapering off after the fifth decade. In Wingerchuk et al. series the age at onset ranged from 1 to 72 years. The median age at onset...
was 41 years in the relapsing and 29 years in the monophasic group.

One recent study of 17 cases under 18 years of age revealed that the median age in pediatric cases was 4.4 years\(^\text{20}\). On the other hand cases with late onset have been also reported\(^\text{8}, \text{78}\). The eldest reported patient at the onset of the disease was an 81-year-old woman who developed NMO one month after influenza immunization\(^\text{81}\).

Although the gender distribution is variable in different series women are affected more frequently than men, usually in a ratio higher than in MS. This trend is most evident in China where a study\(^\text{86}\) showed female to male ratio as high as 9:1\(^\text{46}\). Female to male ratio was 5:1 in a Brazilian series\(^\text{72}\); whereas in the Mayo Clinic series\(^\text{8}\) it varied according to the clinical type of the disease, being 1:1 in monophasic NMO and 5:1 in recurrent NMO. Similarly 28 (93%) of the 35 French-Afro-Caribbeans in Martinique with NMO were women and had the relapsing type of the disease\(^\text{69}\).

In the pediatric group female to male ratio was 3.2:1\(^\text{18}\).

**GENETICS**

In the Japanese population the frequency of HLA-DRB1*0501 allele was found to be significantly greater (93%) in patients with opticospinal MS than in healthy controls (63%) but not in patients with conventional MS (66%)\(^\text{82}\).

A more recent study\(^\text{81}\), however, suggested that opticospinal MS is not necessarily associated with the DPB1*0501 allele. The authors determined the frequencies of the DRB1*1501, DPB1*0501 and DPB1*0301 in 26 patients with opticospinal MS, 167 with conventional MS and 156 normal subjects. All opticospinal MS patients were negative for DPB1*0301 whereas the frequency of the DPB1*0501 allele was similar in opticospinal MS and conventional MS yet higher than in the healthy controls. In DPB1*0301 positives a frequency of the DPB1*0501 was low but similar in conventional MS and controls. They also found that the DPB1*0301 allele was strongly associated to the development of periventricular lesions which were found in 97% of the conventional MS patients who were DPB1*0301 positive in contrast with only 16% of those who were DPB1*0301 negative, and 8% of the opticospinal MS patients.

It is somewhat surprising that given the genetic underpinning of the disease only five pairs of familial cases have been reported in the literature. McAlpine\(^\text{84}\) in 1938 described two identical twins with severe cervicothoracic myelitis and bilateral optic neuritis, occurring in one at age 24 and the other at age 26. Both patients died 18 and 26 months after onset. Autopsy showed marked demyelination of both optic nerves and spinal cord with mild or no inflammatory infiltrates. In one case there was a demyelinating lesion in the lower medulla, whereas in the other case examination of the brain was unrevealing. Ch’len et al.\(^\text{85}\) reported two sisters aged 10 years and 6 years who developed NMO at ages 3 years and 2 years 9 months respectively. Both presented bilateral optic neuritis followed by myelitis five months later. Another paper\(^\text{86}\) described NMO in two elderly Japanese sisters with onset at 59 and 62 years of age. The cases of two other sisters of Spanish –American ancestry who developed NMO at ages 26 and 28 were also documented\(^\text{87}\). Recently Bradley and Mikol\(^\text{88}\) reported by the first time a mother-daughter pair with NMO. Differently from other familial cases these patients developed NMO in different stages of life; the daughter at 29 years of age whereas the mother at 62.

An additional feature in these cases was the previous history of thymectomy for myasthenia gravis in the daughter. The occurrence of NMO following thymectomy for myasthenia gravis has been well documented\(^\text{89}\).

**PATHOLOGY AND IMMUNOPATHOGENESIS**

The basic structural pathological features of NMO have long been known\(^\text{31}, \text{90}, \text{91}\). In the acute phase of the disease gross pathology of the spinal cord includes diffuse swelling and softening extending over multiple spinal segments and occasionally over the entire extension of the cord. Histopathological examination discloses necrosis of both grey and white matter with macrophage infiltration associated with myelin and axonal loss. There is variable perivascular inflammatory infiltration. Late in the course of the disease atrophy and cavitation of the involved spinal cord segments and optic nerves ensue, with marked gliosis and cystic degeneration. In necrotic and perinecrotic areas the walls of the microvessels are thickened and hyalinized.

In a study of nine autopsied NMO patients Lucchinetti et al.\(^\text{7}\) investigated the role of humoral mechanisms in the pathogenesis of the necrotizing demyelination of the spinal cord and optic nerves. They found extensive demyelination across multiple spinal cord levels, associated with necrosis, cavitation and acute axonal pathology in both grey and white matter. Lesions were typically located in the central portions of the spinal cord with peripheral rims of myelin preservation. The number of blood vessels within the lesion was increased and their walls were thickened but with no fibrinoid necrosis or granulocyte infiltration as usually found in necrotizing vasculitis. There were a prominent loss of oligodendrocytes and acute axonal swelling and spheroids within all the lesions. In acute active lesions there were extensive macrophage infiltration, many B lymphocytes and few CD3+ and CD8+ T lymphocytes, usually associated with eosinophilic and granulocyte perivascular infiltrates. These lesions showed a marked deposition of immunoglobulins (mainly IgM) and complement in a characteristic perivascular rosette pattern, and along the outer rim of the thickened vessel walls.
The structural and immunopathological features of NMO were compared with cases of MS, acute demyelinating encephalomyelitis (ADEM) and acute spinal cord infarction. It was observed that T-cells and macrophages were present to a variable degree in all of them. However, 52% of the MS cases and none of the ADEM and spinal cord infarction cases showed deposition of IgG and activated complement. In MS the pattern of deposition was different from that seen in NMO as it was less pronounced and found in degenerating myelin sheaths, along with macrophages and oligodendrocytes in the plaque edge, as opposed to the perivascular pattern described in NMO lesions. In an earlier study Lucchinetti et al. identified four immunohistochemical types of MS lesions. The most common type is the “pattern 2” type characterized by deposits of complement and immunoglobulins. However, immune complexes in “pattern 2” MS lesion are characteristically located at sites of myelin destruction. No complement activation and immunoglobulin reactivity was seen in acute spinal cord infarctions or ADEM cases. Eosinophils and granulocytes are observed in rare cases of fulminant Marburg MS (4% of MS cases) compared with 56% of NMO cases. All early active NMO lesions contained eosinophils whereas no eosinophils were present in ADEM or spinal cord infarction cases. Hyalinized vessels were present in all NMO cases but absent from MS, ADEM or spinal cord infarction cases.

The pattern of tissue inflammation in early demyelinating active NMO with a unique perivascular pattern supported a role for humoral autoimmunity in the pathogenesis of the disease. The abnormalities of the perivascular region with macrophage infiltrate and massive deposition of complement and immunoglobulin associated with the prominent vascular hyalinization definitely led the authors to suggest the perivascular space as the primary target site of the pathogenic process.

In addition to the lesion pathological features different lines of evidence favor humoral immune mechanisms in the pathogenesis of NMO. Firstly, there are striking similarities between NMO and a variant of MOG-induced experimental allergic encephalomyelitis (EAE) in Brown Norway rats which develop a marked antibody response associated with pronounced demyelination mainly affecting the optic nerves and the spinal cord. Secondly, NMO patients have a number of circulating autoantibodies and many of them have autoimmune co-morbidities such as Sjögren syndrome, systemic lupus erythematosus and mixed connective tissue disease. Finally, some treatment peculiarities such as improvement of corticosteroid-refractory acute attacks following plasma exchange and a better response with general immunosuppression than with standard MS immunomodulatory drugs strongly support the role of autoantibodies in the disease process.

On the basis of the immunopathological observations a cascade reaction initiated by the presence of a peripheral antibody directed against a perivascular antigen activating the classical complement pathway was proposed. Activated macrophages, eosinophils and neutrophils generate cytokines, proteases and free radicals leading to vascular and parenchymal damage. Increased vascular permeability will cause further parenchymal lesion via secondary ischemia. This mechanism may account for the typical location of the lesion within the spinal cord. Novel antigens liberated during the destructive process may further extend the immune response (Fig 1).

A large number of patients with NMO have brain lesions on MRI, most of them asymptomatic, but some are clinically evident. Two autopsy reports by different investigators describe the pathological features of brain lesions in NMO patients. Nakamura et al. found marked tissue destruction, cavities and inflammatory changes typical of NMO in the cerebrum, optic nerves and spinal cord of a 63-year-old patient who had an encephalopathy with a cerebral tumefactive lesion 30 years earlier, followed by repeated attacks of optic neuritis and myelitis. More recently Hengstman et al. found typical NMO histopathological abnormalities in brain lesions at autopsy of a 35-year-old woman with NMO and multiple brain lesions on MRI. In some of these lesions there were perivascular infiltrates with large number of eosinophils. These cases show that symptomatic brain lesions may occur in NMO and that the histopathological features of these brain lesions are identical to those found in the spinal cord and optic nerve.

The reason for the preferential involvement of the optic nerves and spinal cord in NMO remains to be discovered. It is probable, however that these structures may harbor unique antigenic characteristics driving the immune response.
mune response, and through epitope spreading following lesions in these sites the immune response may broaden damaging other central nervous system structures. The NMO autoantibody marker

Accumulating evidences of humoral mechanisms in the pathogenesis of NMO prompted the identification of a specific IgG autoantibody (NMO-IgG) that localizes to blood-brain barrier. Indirect immunofluorescence with a composite substrate of mouse tissue showed that NMO-IgG yields a characteristic immunohistochemical pattern of binding in mouse central nervous system. It was prominent in pia and subpia, and outlined the Virchow-Robin space and microvessels in white and grey matter of the cerebellum, midbrain, and spinal cord. It binds to an antigen in the abluminal face of cerebral microvessels, an area represented by astrocytic foot processes.

Lennon et al. tested masked serum samples from 102 North American patients with either NMO, high risk syndrome for NMO or MS (presented with myelitis and optic neuritis but did not meet the Wingerchuk et al.’s criteria for the diagnosis of NMO), and 22 Japanese patients (11 with opticospinal MS, one with high risk syndrome for MS, five with classical MS and five with cerebral infarction). They identified 33 (73%) of the 45 patients with NMO and 16 (45%) of the 35 with high risk syndrome for NMO who were seropositive for this antibody. Two (9%) of the 22 patients with diagnosis of MS were also seropositive for NMO-IgG. Thus this test showed a sensitivity of 73% and specificity of 91% to differentiate patients with clinically definite NMO from those with myelitis and optic neuritis but could not define the criteria for the diagnosis of NMO. When NMO and high risk syndrome are considered together the sensitivity drops to 61.3% and the specificity to 90.9%. The 56 control patients with miscellaneous autoimmune and paraneoplastic neurologic disorders were all seronegative. In the Japanese group none of the patients with classical MS or cerebral infarction was seropositive. Of the 12 patients with opticospinal MS or high risk syndrome for NMO seven (55%) were seropositive. In this group, therefore the sensitivity of the test was 58% and the specificity 100%.

Since the substrates of the NMO-IgG detection assay were not human but mouse brain tissue, there has been a concern that the non-human substrates could be affecting its sensitivity and specificity. To clarify this issue Japanese investigators studied the sensitivity and specificity of a new test using human AQP4-transfected cells as substrates of the indirect immunofluorescence assay. They tested 148 sera of patients with NMO, high risk syndrome, MS, clinically isolated syndrome suggestive of MS and miscellaneous diseases. The sensitivity of the assay, named anti-AQP4 antibody assay, increased to 91% for NMO and 85% for high risk syndrome, and the specificity was 100% for NMO and high risk syndrome as compared with the assay with non-human antigen. Changes from initial negativity to later positivity over some years have also been observed in some patients with typical clinical and imaging features of the disease.

Anti-AQP4 antibodies can be also detected in patients with the diagnosis of classical MS who have longitudinally extensive spinal cord lesions on MRI scans. In the Matsuo-Ka et al.’s series two of 17 (11.8%) of these patients were seropositive, and the antibody was detected only in those with spinal cord lesions extending over 10 vertebral segments in length. The anti-AQP4 antibody assay was consistently negative in all classical MS patients with longitudinally extensive spinal cord lesions shorter than 10 segments in length. The anti-AQP4 titer had no correlations with disease duration, number of exacerbations or effects of immunotherapies, but had an inverse correlation with both the EDSS score and the progression index.

Aquaporin-4 water channel

NMO-IgG from NMO-positive patients’ serum was found to bind to distal urine-collecting tubules and to basolateral membranes of the epithelial cells of the gastric mucosa. This distribution suggested the water channel protein, aquaporin 4 (AQP4) as the target autoantigen in NMO. Aquaporin 4 is an integral protein of astrocytic plasma membranes and is highly concentrated in the astrocyte foot processes.

Aquaporins constitute a family of water channels that regulate the transport of water in many organs including the nervous system, kidney, gastrointestinal tract, secretory glands, inner ear and muscles. Aquaporin 4 is a homotetrameric integral plasma membrane protein found in electrically excitable tissues including brain and spinal cord, retina, inner ear and skeletal muscles. In general it is not expressed in excitable cells, but is found in supporting cells (astrocytes and ependyma in the nervous system; Müller cells in the retina; Hensen’s and inner sulcus cells in the ear). It is the most abundant aquaporin in mammalian brain and is concentrated at the blood-brain barrier, anchored in the astrocytic foot process membrane by the dystroglycan complex. Aquaporin-4 is also present on ependymal cells, and in lower levels, on brain endothelial cells. It is highly expressed in the supraoptic nucleus of the hypothalamus and periventricular structures such as area postrema and the vascular organ of lamina terminalis, which lack blood-brain barrier and contain osmosensitive neurons that regulate fluid homeostasis and release arginine-vasopressin which facilitates this process. At the astrocyte end foot process, AQP4 co-localizes with the inward rectifying potassium channel (Kir 4.1), which is involved in clearance of extracellular K⁺. This co-local-
ization suggests that water and K⁺ flux are coupled. It also co-localizes with the glutamate transporter-1 (GLT-1), which is one of the two main astrocytic excitatory amino acid transporters, that prevent excessive accumulation of extracellular glutamate. The strategic localization of AQP4, together with Kir 4.1 and GLT-1 at the perivascular and subependymal end-feet provides several potential mechanisms by which loss of AQP4 may result both in severe damage of myelin and axons in vulnerable areas, such as the spinal cord and optic nerves, as well as reversible edema in other brain regions, such as the hypothalamus and periventricular structures. Perivascular AQP4 allows a bi-directional water flow between the blood and the brain and has been implicated in the pathogenesis of cerebral edema. Aquaporin-4 is up-regulated in astrocytes in the setting of hypoxia, brain injury, meningitis and encephalitis, high grade astrocytomas, and around metastatic adenocarcinoma. Aquaporin-4-null mice, which lack AQP4 expression at astrocyte end feet, are relatively resistant to the development of brain edema in the setting of hypoplasmolarity or stroke.

The distribution of AQP4-rich areas in the central nervous system, especially in the central part of the spinal cord, hypothalamus, periventricular area and periaqueductal areas is highly compatible with that of NMO lesions. Recent studies have demonstrated loss of AQP4 in lesions of the spinal cord in NMO patients but not in MS lesions. On the opposite, AQP4 expression may be increased in and around MS plaques. Misu et al. reported a case of typical NMO which showed a loss of AQP4 and glial fibrillary acidic protein (GFAP) immunostaining especially in active spinal cord lesions. In a subsequent study Misu et al. conducted an immunohistochemical analysis of 12 cases of NMO, six of MS, 7 of brain and spinal cord infarction, and eight normal controls. They observed loss of AQP4 in 90% of the acute and chronic NMO lesions, which were more pronounced in the active perivascular lesions where immunoglobulins and complements were deposited. In contrast, AQP4 immunoreactivity was increased in MS lesions. In normal controls and and infarctions AQP4 was diffusely expressed but the staining in the spinal cord was stronger in the grey matter than in the white matter. In NMO cases the areas surrounding the AQP-4-absent lesions had AQP4 expression similar to that of controls.

Similarly one study demonstrated loss of AQP4 in optic nerve and spinal cord lesions of a NMO case as well as increased expression of AQP4 in all active and some inactive lesions from seven cases of secondary progressive MS. They also observed higher expression of AQP4 in normal-appearing white matter of MS patients than in controls.

Roemer et al. analysed and compared patterns of AQP4 immunoreactivity in nervous tissues of nine patients with NMO, 13 with MS, nine with infarcts and five normal controls. In normal brain, optic nerve and spinal cord the distribution of AQP4 expression resembles the vasculocentric pattern of immune complex deposition observed in NMO lesions. Cerebral white matter showed limited AQP4 reactivity whereas the reactivity was most intense at glia limitans and subependyma. Within the cortex AQP4 reactivity was concentrated in astrocytic foot processes extending to abluminal surface of blood vessels. Within the brainstem AQP4 predominated in subependymal regions of the fourth ventricle, in a rim or rosette pattern. In the spinal cord it was prominent within both grey and white matter in a rim or rosette pattern. In the optic nerve the staining was also in a rim and rosette pattern. Therefore the rim and rosette patterns found in NMO lesions just represent the normal patterns at sites of AQP4 concentration.

AQP4 expression in MS lesions correlates with the stage of demyelinating activity. In acute MS lesions AQP4 is diffusely increased in the periplaque white matter of active lesions, whereas chronic inactive lesions are devoid of AQP4. In some MS cases there are foci of inflammatory infiltrates lacking demyelination, associated with AQP4 loss. Loss of AQP4 is not due to necrosis and cavitation. In NMO two basic pathology patterns can be found. The most prevalent lesion pattern involves the spinal cord and optic nerves. Loss of AQP4 occurs in the context of vasculocentric immune complex deposition, active demyelination and vascular hyperplasia with hyalinization. These lesions are frequently cavitary and involve both the grey and white matter in the spinal cord. The less frequent lesion pattern is found in the spinal cord and medulla extending into the area postrema, and is highly inflammatory but with no evidence of demyelination. The area postrema has high expression of AQP4 and lacks a blood-brain barrier. It is related to control of osmoregulation and brain homeostasis including control of blood flow autoregulation, edema and immune regulation.

Although it has been suggested that AQP4 autoantibodies cause NMO, probably by inhibiting AQP4, other authors keep a more skeptical view pondering that this causality still lacks definite proof as NMO has not been produced in experimental animals through administration of the antibody. In addition to that a number of questions such as why other organs which highly express AQP4 as the kidneys, lung, inner ear and intestine are not affected in the disease; why the lesions are predominantly located in the spinal cord and optic nerves, although AQP4 is ubiquitously expressed throughout the nervous system; what the preceding event opening the blood-brain barrier to allow the peripheral anti-AQP4 antibody enter the brain is; and why a NMO-like phenotype does not follow AQP4 deletion in mice, remain to be answered.
CLINICAL FEATURES

Neuromyelitis optica may present either with the simultaneous occurrence of acute transverse myelitis and optic neuritis or with these index events occurring separately by an indeterminate time interval. Following installation of disease by the presence of both myelitis and optic neuritis, its course may be either monophasic with no further events, or relapsing with additional attacks of either transverse myelitis, optic neuritis or both. In the Wingerchuk et al. series 48 (68%) of the 71 NMO cases had a relapsing and 23 (32%) a monophasic course. Relapsing course is more frequently associated with female sex, older age at onset, longer time interval between index events, less severe motor impairment with the first myelitis attack, and the presence of systemic autoimmunity. A first attack interval longer than six months almost always predicts relapsing disease. The relapsing course in this Western series is compatible with the characteristic polyphasic course of the opticospinal MS described in Asian countries. Patients with relapsing NMO tend to have a greater number of attacks than relapsing-remitting MS patients in similar follow-up duration.

In rare cases viral illnesses or immunizations precede the clinical onset. Simultaneous bilateral optic neuritis and myelitis occurred at onset in about one third of the monophasic cases and in none of the relapsing cases in Wingerchuk et al.’s series. Bilateral optic neuritis and myelitis occurring within one month usually point to a monophasic course. Optic neuritis and myelitis are equally frequent index events at the onset in Caucasians, whereas in patients of African origin, optic neuritis is more frequently the presenting symptom of the disease. Neurologic impairment is usually more severe in the monophasic than in the relapsing group. Blindness developed in over 50% of patients of the monophasic group and in 28% in the relapsing group. Patients with unilateral optic neuritis are indistinguishable from those with bilateral optic neuritis; the visual loss is usually more severe in NMO than in MS and may not be as responsive to high-dose steroid therapy.

Spinal cord involvement occurs usually in the form of transverse myelitis with paraparesis, bilateral sensory loss and sphincter dysfunction. Radicular pain, paroxysmal tonic spasms and Lhermitte’s symptom occur in one third of the relapsing cases but are rare or absent in patients with monophasic NMO.

Neurologic symptoms indicating disease outside the optic nerves and spinal cord have been observed in about 15% of patients and include symptoms of encephalopathy, brainstem dysfunction and hypothalamic abnormalities. In 10% of the cases NMO affects the hypothalamus and brainstem, especially the areas around the fourth ventricle, nucleus tractus solitarius, area postrema and the subependymal regions. Brainstem symptoms include vomiting, vertigo, hearing loss, facial weakness, trigeminal neuralgia, diplopia, ptosis and nystagmus. Some patients have nausea and intractable hiccups. In one study respiratory failure occurred in eight (17%) of 47 cases. Most patients with brainstem and hypothalamic symptoms have brain MRI and positive Ig-NMO antibodies.

Endocrine dysfunction associated with relapsing NMO (Vernant’s syndrome) was first described by Vernant et al. in 1997 who reported eight women from Martinique and Guadeloupe with recurring attacks of transverse myelitis and optic neuritis associated with endocrine dysfunction. Seven of them had secondary amenorrhea that coincided with exacerbations of NMO. One postmenopausal woman and two others had galactorrhea with hyperprolactinemia. Four patients had hypothyroidism, one diabetes insipidus and three patients were obese and had hyperphagia, probably due to hypothalamic dysfunction. Brain MRI showed gadolinium enhancement of the hypothalamic-hypophyseal region in three patients. In a series of nine cases of NMO one patient was incidentally noted to have gadolinium enhancement of the hypothalamic-hypophyseal region associated with clinical evidence of central hypothyroidism and an elevated prolactin level. More recently Poppe et al. described two patients with relapsing NMO who presented hypersomnolence, hyponatremia and hyperthermia in association with brain MRI lesions that selectively involved the hypothalamus. Hyperprolactinemia has also been reported in Asian patients with opticospinal MS.

Neuromyelitis optica has been associated with many other autoimmune diseases, and even more frequently with the presence of circulating autoantibodies in the absence of clinical manifestations of their associated conditions (Table 1). Wingerchuk and Weinshenker found autoimmune disorders and serum autoantibodies associated with neuromyelitis optica.

<table>
<thead>
<tr>
<th>Table 1. Autoimmune disorders and serum autoantibodies associated with neuromyelitis optica.</th>
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<tbody>
<tr>
<td>• Systemic lupus erythematosus</td>
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<tr>
<td>• Sjögren’s syndrome</td>
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<td>• Mixed connective tissue disease</td>
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<td>• Hypothyroidism</td>
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<tr>
<td>• Myasthenia gravis</td>
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<tr>
<td>• Polyarteritis nodosa</td>
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<td>• Pernicious anemia</td>
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<td>• Ulcerative colitis</td>
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<tr>
<td>• Primary sclerosing cholangitis</td>
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<td>• Idiopathic thrombocytopenic purpura</td>
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<tr>
<td>• Antinuclear antibodies</td>
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<tr>
<td>• Anti-SSA and anti-SSB antibodies</td>
</tr>
<tr>
<td>• Anticardiolipin antibodies</td>
</tr>
<tr>
<td>• Perinuclear antineutrophil cytoplasmic antibodies (p-ANCA)</td>
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<tr>
<td>• Anti-thyroid peroxidase antibodies</td>
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toimmune diseases in 19 (36%) of 57 patients with relapsing NMO and in only one (4%) of 23 patients with monophasic NMO. Interestingly patients with systemic lupus erythematosus or Sjögren’s syndrome who never developed optic neuritis or myelitis are NMO-IgG seronegative whereas those with optic neuritis or myelitis are usually seropositive[138,139]. Patients with myasthenia gravis who undergo thymectomy may develop NMO probably by dysregulation of B-cell autoimmunity in myasthenia, exacerbated by thymectomy[140].

Typically NMO has a worse outcome than MS[8,68,69,79]. Notwithstanding the index events are more severe in the monophasic than in relapsing NMO, in the long run the outcome is worse in relapsing disease as patients tend to accumulate neurologic impairment with repeating relapses. Relapses tend to occur early, in clusters and at unpredictable intervals[6]. Within five years of disease onset 50% of patients in the relapsing group are unable to walk without assistance and 32% die from respiratory failure secondary to acute cervical spinal cord lesion. The 5-year survival rate was 90% in the monophasic group and 68% in the relapsing group[5]. Predictors factors for poor outcome include presence of other autoimmune disorder, high frequency of attacks during the first two years of disease, and poor motor recovery following the index event[79]. The prognosis is still worse in patients of African origin than in whites. In the Afro-Caribbean series[69] 63% of the patients had EDSS score ≥ 6 at the final examination, and 33% died after a mean time of 8.7 years. In the Brazilian series[72] most of the white patients had a low EDSS score, but six of the 12 melanodermic patients died after a mean disease duration of 12 years. In children the prognosis may be more favorable than in adults. An analysis of 17 children (onset before age 18 years) with NMO showed that after a median disease duration of three years 16 patients were ambulatory without need for assistance[80].

Neuromyelitis optica and infections

Viral and bacterial diseases preceding or occurring in temporal association with NMO have been described. In the Mayo Clinic series[6] a nonspecified antecedent viral event occurred in 30% of the patients in the monophasic and 23% in the relapsing group. In other studies the infectious agent could be identified. In the first reported case in Brazil the disease occurred in the course of mumps[141]. Acute infectious mononucleosis preceded NMO for three weeks in a 29-year old man who had a complete recovery[141] and cases of varicella-zoster virus infections in association with NMO were reported by some investigators[142-145].

We had the opportunity to examine a 65-year-old wheelchair-bound woman with paraparesis and sphincter disturbances who developed severe optic neuritis 16 years after the onset of the myelitis. Spinal cord MRI disclosed a cervicothoracic lesion whereas the CSF showed three lymphocytes/mm³ and a protein content of 77 mg%. ELISA and Western blot test for HTLV I-II were positive in both the serum and CSF. The patient made no recovery.

Another interesting viral association with NMO referred to our MS Center occurred in a 39-year old man who was HIV-seropositive for three years. He suddenly developed severe paraparesis, dysesthesia in the lower limbs, a T10 sensory level and sphincter disturbances. Sequential optic neuritis occurred on the right and then on the left three and six months later. Spinal cord MRI disclosed a lesion extending over the entire thoracic cord. Laboratory work-up was unrevealing except for HIV seropositivity. A previous case of NMO in a HIV-seropositive patient had been reported in an African woman[146] in whom a spinal cord MRI scan disclosed four gadolinium-enhancing lesions on T6, T7, T10, and T12 levels.

Neuromyelitis optica has also been observed in patients with pulmonary tuberculosis[136,72,147,149] and syphilis[150,151]. Three of the 24 patients in the Brazilian series[72] had pulmonary tuberculosis.

We documented a rather unique association in a 34-year-old mulattoe man who experienced bitemporal loss of the visual field and headache. His visual acuity evolved to hand movement in both eyes in 3 days. Brain MRI showed a gadolinium-enhanced lesion in sellar region and thickening of the optic chiasm. Biopsy of the lesion disclosed “non-specific granulomatous reaction”. His vision improved after a course of IV methylprednisolone. Fourteen months later he developed lumbar pain, severe paraparesis and bladder dysfunction. Spinal cord MRI showed a T2- hyperintense lesion in thoracic and lumbar levels. Cerebrospinal fluid examination revealed 35 WBC/mm³ (38% eosinophils), a protein content of 60 mg%, and a strong positive immunoreaction for schistosomiasis mansoni. The patient had full recovery after corticosteroid treatment[152].

CEREBROSPINAL FLUID

In most NMO patients CSF analysis exhibits some abnormalities. In the Mayo Clinic series[6] pleocytosis (>5 WBC/mm³) was present in 79% of the patients and was greater than 50 WBC/mm³ in 35%. Cell count varies broadly and can reach figures over 2000 cells/mm³. This striking abnormality had long been observed[154]. Neutrophils are commonly found, and even the presence of eosinophils can be noted[154]. Protein content and some cytokines as interleukin (IL)-17 and IL-8, and the numbers of IL-5 and IL-6, IgG and IgM secreting cells are increased[154,155].

CSF features may be helpful in distinguishing NMO from MS. Pleocytosis greater than 50 WBC/mm³ rarely occurs during MS relapses, and oligoclonal bands, present in over 90% of MS patients, are found in less than 20% of pa-
tients with NMO\textsuperscript{5}. Similarly, IgG index which is usually elevated in MS is normal in patients with NMO\textsuperscript{56}. An additional difference is the higher levels of matrix metalloproteinase-9 in the CSF of MS as compared with NMO patients\textsuperscript{57}.

**MRI ABNORMALITIES**

Neuroimaging has expanded the very concept of Devic’s NMO defining the typical features of the spinal cord lesion (Fig 2) and disclosing asymptomatic cerebral lesions in the majority of patients (Fig 3). Furthermore, it provides clinicians with the most reliable element for the diagnosis of NMO – the longitudinally-extensive transverse myelitis lesion – distinguishing it from MS. Imaging of the spinal cord typically shows a gadolinium-enhanced lesion extending through several vertebral segments, and in the acute phase, marked swelling of the cord\textsuperscript{36,158,159}. Cavity-like longitudinally-extensive lesions are seen in cases with relatively severe disease, and cervical lesions may extend to lower medulla\textsuperscript{160}. In late stages of the disease spinal cord atrophy will ensue. On the opposite, spinal cord lesions in MS patients usually do not extend beyond two vertebral segments in length, do not occupy the entire cord transverse area, and are not associated with cord swelling or atrophy\textsuperscript{161-163}.

One study\textsuperscript{122} correlated the MRI features of optico-spinal MS with the NMO-IgG seropositivity. Longitudinally-extensive spinal cord lesions (LESCL) were found in all but one of the 12 NMO-IgG-positive optico-spinal MS patients and in 57% of the NMO-IgG-negatives. The only NMO-IgG-positive patient without LESCL had extensive spinal cord atrophy suggesting the previous existence of a longitudinally-extensive lesion. A similar observation was reported in another study\textsuperscript{164} which detected the presence of anti-AQP4 antibodies in 25 of 28 patients with LESCL and in 12 of 17 optico-spinal MS patients with long atrophy of the spinal cord. Although the LESCL are more frequently seen in optico-spinal MS than in conventional MS some authors\textsuperscript{165-167} have found them in one-fourth of Asian patients with conventional MS reflecting the greater susceptibility of these populations to more severe spinal cord damage\textsuperscript{168}.

![Fig 2. MRI scans of the spinal cord in patients with neuromyelitis optica. (A) Swollen cervical spinal cord with a longitudinally-extensive lesion mainly involving the central area of the cord. (B) Longitudinal-extensive irregular lesion from T4 to T9 levels. (C) Axial imaging of thoracic cord showing central pattern of involvement. (D) Extensive atrophy of the thoracic spinal cord in a late stage of the disease.](image1)

![Fig 3. Abnormal brain MRI in patients with neuromyelitis optica. (A) Isolated gadolinium-enhancing periventricular lesion. (B) Tumefactive gadolinium-enhancing lesion involving upper pons and cerebellum. (C) Lesion in the third ventricle region.](image2)
Longitudinally-extensive spinal cord lesions in anti-AQP4-positive patients predominantly involve the upper-to-middle thoracic cord with a predominant central grey matter pattern. Even short lesions in anti-AQP4 antibody-positive patients tend to show this central involvement preference. On the other hand, in anti-AQP4 antibody-negative opticospinal MS patients the lesions are usually extremely long extending from the upper cervical cord to the middle thoracic cord and have a holocord pattern. Even in cases with short spinal cord lesions this holocord pattern can be observed. Finally, in anti-AQP4 antibody-negative conventional MS patients both short spinal cord lesions and LESCL most frequently affect the cervical cord and present a peripheral pattern of involvement. This heterogeneity of the anti-AQP4 antibodies in patients with LESCL may reflect differences in their pathogenesis. In anti-AQP4 antibody-positive cases there may be predominance of humoral mechanisms, whereas in patients with LESCL and absence of anti-AQP4 antibodies T-cell mediated immune mechanisms may predominate.

It was long held that the presence of brain lesions at onset of disease outside the optic nerves ruled out the diagnosis of Devic’s NMO. However, the recent development of the Wingerchuk et al.’s diagnostic criteria\(^8\) prompted a new look at this issue\(^12\). A review of 60 cases satisfying these criteria, except for the absolute criterion of lacking symptoms beyond the optic nerves and spinal cord, and the supportive criterion of having a normal brain MRI at onset, disclosed MRI brain abnormalities in 60% of the patients. IgG-NMO antibodies were detected in 41 (68%) patients. In 30 patients the initial brain MRI was normal although half of them developed brain abnormalities in subsequent scans. Most of the lesions were small and nonspecific, not fulfilling the Barkof’s diagnostic criteria for MS. Some of the lesions were hemispheric and confluent extending to subcortical areas; others involved the hypothalamus, thalamus, region around the fourth ventricle, and the cerebral peduncle or cerebellum. Six patients (10%) had MS-like lesions and four fulfilled Barkof’s criteria for MS.

In a subsequent study Pittcock et al.\(^{123}\) described the brain MRI findings in eight out of 89 (9%) NMO patients who had lesions in the hypothalamus and in areas surrounding the third and fourth ventricles which have high expression of aquaporin-4. All but one of these patients had symptoms not related to optic nerve and spinal cord involvement. They showed that although most brain lesions found in NMO patients are nonspecific, lesions in the hypothalamus and brainstem are typical of the disease. Lesions in these structures in NMO patients had already been described by others\(^{134,136,139}\).

In Brazil, Domingues et al.\(^{169}\) in 2004 drew attention to the presence of brain lesions on MRI scans of a child with NMO. They reported the case of a 10-year-old mulatto boy with recurring optic neuritis and myelitis. His brain MRI disclosed multiple periventricular lesions, including a large one with a confluent pattern extending to the parieto-occipital subcortical area. The spinal cord lesion extended throughout the cord, and the CSF examination revealed marked pleocytosis (1675/mm\(^3\), with predominance of neutrophils). Papais-Alvarenga et al.\(^{22}\) had also observed the presence of nonspecific brain lesions in their series.

**THE SPECTRUM OF DEVIC’S NEUROMYELITIS OPTICA**

Recent advances in the understanding of the immunopathogenetic mechanisms of NMO and the discovery of the NMO-IgG as a marker of the disease have provided evidences suggesting that the disease may encompass a number of different phenotypic expressions sharing common immunological and pathological grounds.

The traditional view of Devic’s NMO as a monophasic condition in which bilateral optic neuritis and myelitis occurs simultaneously or within an interval of few weeks with no evidence of brain lesions just defines a narrow band of a broad spectrum of clinical expressions which may be determined by the influence of different genetic factors. At present time, the spectrum of Devic’s NMO includes patients whose clinical features can be categorized into a number of phenotypic subtypes such as:

1. **Classical or strict Devic’s NMO** — This group is characterized by monophasic bilateral optic neuritis and acute myelitis with clinically estimated lesions confined to the optic nerves and spinal cord and no brain lesions on MRI outside the optic nerves. In Asian countries the term “Devic’s disease” is strictly used to identify these cases\(^131\). Wingerchuk et al.\(^8\) have demonstrated that patients with unilateral optic neuritis are indistinguishable from those with bilateral optic neuritis and the interval over which patients develop the index events has no diagnostic significance. Rather, patients with NMO can be classified into a monophasic and a relapsing type.

2. **Relapsing NMO** — Patients in this group develop repetitive attacks of unilateral or bilateral optic neuritis and myelitis with clinically estimated main lesions confined to the optic nerves and spinal cord. Interestingly, in the same year (1894) Devic\(^23\) reported the case of his single patient with a monophasic course, he and Gault\(^23\) described other patients who had relapsing course. As compared with monophasic NMO relapsing NMO has distinctive features such as marked female preponderance, higher age at onset, higher frequency of associated autoimmune disorders and serum autoantibodies, and less severe index events but worse outcome\(^6\). This group also includes patients with minor brainstem signs as nystagmus, diplopia, nausea, dysarthria and dysphagia.
Table 2. Differential features of relapsing NMO (opticospinal multiple sclerosis) as compared with conventional multiple sclerosis.

- Preponderance in non-white populations
- Higher preponderance in females
- Higher age at onset
- Greater disability (higher EDSS scores)
- Longitudinally-extensive spinal cord lesions (≥ vertebral segments in length)
- Lower proportion of secondary progressive disease
- Disability determined by relapses rather than by progression of the disease
- Lower number of brain MRI lesions
- Brain MRI lesions usually do not meet criteria for MS
- CSF with greater pleocytosis and higher protein content
- CSF may have neutrophils and eosinophils
- CSF usually with negative oligoclonal bands and normal IgG index

For a long time Japanese authors\(^7\) have identified patients with clinical features of relapsing NMO as having “opticospinal MS”, emphasizing that they differ from conventional MS patients in a number of features (Table 2). More recently one study\(^16\) showed that 28% of the opticospinal MS patients have a “pure opticospinal MS” subtype as they had normal brain MRI except for lesions in the optic nerves and spinal cord in repeated examinations for a minimal follow-up of five years.

(3) Relapsing NMO with asymptomatic brain lesions on MRI not meeting diagnostic criteria for MS – These patients comprise most of the NMO cases in both Eastern and Western populations\(^12,160\). Brain MRI lesions are largely nonspecific and usually involve the brainstem and the hypothalamus or may present as large tumefactive and coalescent lesions in the cerebral hemispheres\(^12\). Most of these patients are seropositive for NMO-IgG.

(4) Relapsing NMO with asymptomatic brain lesions on MRI meeting diagnostic criteria for MS – These patients are usually seropositive for NMO-IgG and comprise 10% of the cases of relapsing NMO\(^12\). They may represent the extreme portion of the spectrum of conditions as described by Shibasaki et al.\(^3\) in 1974, which ranges from classic Devic’s disease to conventional MS.

(5) Relapsing NMO with symptomatic brain lesions – Patients with NMO may present symptoms of cerebral involvement such as consciousness disturbances, agitation, emotional liability, in addition to brainstem signs as eye movement disorders, facial weakness, nausea and dysarthria. Histopathology examination of these lesions reveal the typical changes described in the spinal cord of NMO patients\(^3\). In one autopsy-proven case the disease started with signs of encephalopathy due to a brain tumefactive lesion, followed by repeated relapses of optic nerve and spinal cord involvement\(^109\).

(6) Relapsing NMO with autoimmune diseases – Over a third of NMO patients have either symptoms of other autoimmune conditions or seropositivity for other circulating autoantibodies\(^4\).

(7) Isolated recurring optic neuritis or isolated recurrent acute myelitis (high-risk syndromes for NMO) – Patients with either isolated recurrent optic neuritis or recurring isolated longitudinally-extensive spinal cord disease are in high risk of developing the second index event that characterizes the fully-developed disease. The condition is known as forme fruste or limited forms of NMO. NMO-IgG antibody was detected in 25% of the patients with recurrent optic neuritis and 52% of the patients with recurrent transverse myelitis; 46% when both conditions are considered together\(^10\). Anti-AQP4 antibody assay with human antigen yielded a sensitivity of 85% and specificity of 100% in these cases\(^110\). Isolated transverse myelitis and isolated optic neuritis may be either high-risk syndromes for NMO or clinically isolated syndromes heralding MS. Table 3 depicts the differences between high-risk syndromes for NMO and clinically isolated syndromes which may convert to MS.

In one study of 72 patients with recurrent optic neuritis Pirko et al.\(^170\) found that the 5-year conversion rate to NMO was 12.5% and to MS, 14.4%. Among 5 patients with two or more lesions consistent with MS on brain MRI, two converted to MS and none to NMO, while among 11 patients without such lesions, none converted to MS and two converted to NMO. Conversion to NMO occurred earlier than conversion to MS, more often in women than in men and in those with a higher relapse rate. Visual outcome was worse in NMO group.

**DIAGNOSIS**

In 1999 Wingerchuk et al.\(^8\) reviewed 71 cases of NMO examined at the Mayo Clinic between 1950 and 1993. The cases fulfilled either the “strict criteria” for diagnosis of NMO (bilateral optic neuritis and myelitis occurring within two years of one another without symptomatic disease outside of the optic nerve and spinal cord) or “not meeting strict criteria” (unilateral optic neuritis or development of a second index event over a period greater than two years). They observed that there was no difference between the two groups regarding demographics, clinical or paraclinical features and outcome. Therefore this distinction makes no sense. On the other hand there are important differences between the monophasic and relapsing groups regardless of the index event interval and if optic nerve involvement is unilateral or bilateral. Based on the clinical, laboratory and imaging data from both groups they designed a set of diagnostic criteria for NMO (Table 4) which includes three absolute criteria (optic neuritis, myelitis and absence of clinical evidence of disease outside of the optic nerve and the spinal cord), and six sup-
Devic’s neuromyelitis optica

Lana-Peixoto

Porte criteria (three major and three minor criteria). Diagnosis requires the presence of all absolute criteria and either one major or two minor supportive criteria.

Recently Wingerchuk et al.\textsuperscript{132} revised their previous diagnostic criteria for NMO not to exclude patients with neurologic symptoms implicating lesions outside the optic nerves and spinal cord and those whose brain MRI lesions meet MS imaging criteria (Table 5). In a new analysis of 96 NMO patients including the detection of NMO-IgG antibodies they found that the 1999 diagnostic cri-

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**Table 3. Differences between high-risk syndrome for neuromyelitis optica and clinically isolated syndromes heralding multiple sclerosis.**

<table>
<thead>
<tr>
<th></th>
<th>High-risk syndrome</th>
<th>Clinical isolated syndrome</th>
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<tr>
<td>Age (more commonly)</td>
<td>Adults</td>
<td>Young adults</td>
</tr>
<tr>
<td>Female:male ratio</td>
<td>&gt;3:1</td>
<td>≤ 3:1</td>
</tr>
<tr>
<td>Location</td>
<td>Spinal cord</td>
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<td></td>
<td>Optic nerve</td>
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<tr>
<td></td>
<td>–</td>
<td>Brainstem</td>
</tr>
<tr>
<td>Functional impairment</td>
<td>Severe</td>
<td>Mild to moderate</td>
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<tr>
<td>Functional outcome</td>
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<td>Good</td>
</tr>
<tr>
<td>Spinal cord MRI</td>
<td>LESCL</td>
<td>Small lesions</td>
</tr>
<tr>
<td>Optic nerve MRI</td>
<td>Long lesion; thickening</td>
<td>Small lesion</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>Absent or unspecific</td>
<td>Periventricular; compatible with MS</td>
</tr>
<tr>
<td>CSF abnormalities</td>
<td>Pleocytosis</td>
<td>No pleocytosis</td>
</tr>
<tr>
<td></td>
<td>Negative OB</td>
<td>Positive OB</td>
</tr>
<tr>
<td></td>
<td>Normal IgG index</td>
<td>Elevated IgG index</td>
</tr>
<tr>
<td>NMO-IgG/Anti-QP4 (%)</td>
<td>46/85</td>
<td>0/0</td>
</tr>
<tr>
<td>Recurrence rate</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Recurrence interval</td>
<td>Shorter</td>
<td>Longer</td>
</tr>
</tbody>
</table>

LESCL, longitudinally extensive (≥3 vertebral segments) spinal cord lesion; OB, oligoclonal bands.

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**Table 4. Wingerchuk et al.’s 1999 diagnostic criteria for neuromyelitis optica.**

Diagnosis requires all absolute criteria and one major supportive criterion or two minor supportive criteria

**Absolute criteria**

1. Optic neuritis
2. Acute myelitis
3. No evidence of clinical disease outside of the optic nerve or spinal cord

**Supportive criteria**

**Major**

1. Negative brain MRI at onset (does not meet criteria for MS)
2. Spinal cord MRI with signal abnormality extending over ≥3 vertebral segments
3. CSF pleocytosis of >50 WBC mm\(^3\) OR >5 neutrophils/mm\(^3\)

**Minor**

1. Bilateral optic neuritis
2. Severe optic neuritis with fixed visual acuity worse than 20/200 in at least one eye
3. Severe, fixed, attack-related weakness (MRC grade ≤ 2) in one or more limbs

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**Table 5. Wingerchuk et al.’s revised diagnostic criteria for neuromyelitis optica.**

Definite neuromyelitis optica

- Optic neuritis
- Acute myelitis

At least two of three supportive criteria

1. Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-seropositive status
teria were 85% sensitive but only 48% specific for NMO. The evidence of a LESCL had the strongest discriminative power with sensitivity of 98% and specificity of 83%. The combination of such a lesion with an onset brain MRI scan that does not satisfy Paty’s criteria for MS increased the sensitivity to 94% and specificity to 96%.

**TREATMENT**

**Treatment of acute attacks**

Initial or recurrent index events are usually treated with high-dose intravenous methylprednisolone, one gram daily for five consecutive days. It has been observed, however, that relapses resistant to corticosteroid therapy are not uncommon, mainly in NMO-IgG-seropositive patients. Recent studies suggest that plasma exchange therapy is helpful for the recovery from acute attacks of NMO but does not prevent further relapses.

In one study of acute central nervous system demyelinating diseases including NMO and myelitis of unknown etiology Weinschenker et al. reported improvement in eight of 19 (42.1%) patients receiving active plasma exchange and only in one of 17 (5.9%) receiving sham exchange. In an extension of this study Keegan et al. observed functional improvement in six of 10 NMO patients following plasma exchange therapy. They found that male gender, preserved reflexes and early initiation of plasma exchange were associated with better prognosis.

Watanabe et al. reported the therapeutic efficacy of plasma exchange on six NMO-IgG-seropositive patients who were not responsive to high-dose intravenous methylprednisolone regimen. Four of them had significant functional improvement, one a mild improvement and two no improvement following plasma exchange. The clinical improvement started to appear quickly, usually after one or two exchanges, confirming the important role of humoral immune mechanisms play in the pathogenesis of NMO. Removal of antibodies, immune complexes and activated complement from the blood circulation probably contribute to decrease the inflammatory response within the central nervous system and consequently may provide rapid functional recovery.

Particular pathological features of NMO as prominent IgG and immune complex deposition, and complement activation provide the rationale for the early initiation of plasma exchange in acute exacerbations of NMO. As it has been previously observed plasma exchange is only effective in cases of MS that share these pathological features (type II MS).

Lymphocytapheresis is a procedure that removes only lymphocytes but not plasma from the blood. As it reduces clonally expanding pathogenic T-lymphocytes in the circulation it has been used as an adjunct therapy to standard immunosuppressive treatment for acute transplant rejection. It was effective as treatment of a NMO-IgG-seronegative patient with bilateral blindness and tetraplegia who was unresponsive to high-dose intravenous steroids and intravenous immunoglobulin treatments. This case suggests that in some patients opticospinal MS may be related to a shift in the Th1:Th2 balance towards Th1 dominance as observed by some authors.

**Prophylactic treatment**

Early prophylactic treatment of patients who present with acute attacks of NMO or high risk syndrome and are seropositive for NMO-IgG is recommended as NMO-IgG is a strong predictor of future relapses after isolated transverse myelitis.

Azathioprine (2.5-3 mg/Kg daily) usually associated with oral prednisone (1 mg/Kg/daily) has proven effective over a period of 18 months. The therapeutic benefit related to azathioprine is usually delayed up to six months, which may explain the occurrence of relapses in shorter periods of time. Intravenous methotrexate (50 mg weekly) in association with oral prednisone was reported to be effective in some patients.

As NMO is mainly an antibody-mediated disease intravenous immunoglobulins may be effective in preventing attacks and possibly enhancing neurological recovery. One study reported two patients with NMO whose disease stabilized following initiation of monthly intravenous immunoglobulin infusion. Randomized controlled trials will be needed to confirm this observation and determine optimal dosing and treatment duration.

Experience with mitoxantrone in the prophylactic treatment of relapsing NMO is also limited. The rationale for its use in NMO is related to its suppressive effect on the humoral immune system via both macrophage and B-cell attenuation. One study showed that mitoxantrone helped to stabilize relapsing NMO in four of five patients who underwent monthly intravenous infusion of the drug (12 mg/m²) for six months, followed by three additional infusions every three months. During the two year-period of treatment two patients each had an attack once within the interval of five months of treatment. Improvement was seen clinically and on MRI in four patients. Patients generally tolerated the treatment well, although one patient had a reversible decrease in cardiac ejection fraction. Careful monitoring for adverse effects such as cardiac toxic reactions and myeloid leukemia - by performing cardiac and hematological evaluations before each mitoxantrone treatment - may increase the therapeutic safety profile of the drug for prophylaxis of relapsing NMO.

Rituximab, a chimeric, murine/human monoclonal antibody that targets CD20 antigen expressed on both pre-B-cells and mature B-cells, was shown to decrease the relapse rate and improve EDSS scores in eight patients previ-
ously treated with high-dose intravenous methylprednisolone for acute attacks of NMO. Each patient received four infusions of intravenous rituximab dosed at 375 mg/m², administered once per week. Rituximab retreatment was conducted when B-cells counts became detectable again, and consisted of two infusions of 1,000 mg administered two weeks apart. Six of eight patients remained attack-free during an average of 12 months. There was a significant decrease of the median post-treatment attack rate as compared to pretreatment rates. Recovery of the neurologic function as measured by the EDSS score was observed in seven of eight patients. Very aggressive NMO cases may have relapses after rituximab treatment even when CD19+ cells (pre-B-cells) are not detected. This observation suggests that different immune mechanisms may be involved in the NMO pathogenesis.

Immunomodulators used for prophylactic treatment of relapsing MS appear ineffective for the treatment of NMO and may even increase the relapse rate. One study showed that three of six NMO patients experienced increased relapse rate following treatment with interferon beta 1-b. However remission of the MRI cervical lesion as well as of the clinical attacks during a follow-up of 36 months was reported in a patient with relapsing NMO who had been unresponsive to high-dose intravenous steroids and monthly cycles of cyclophosphamide.

Mycophenolate mofetil (MMF) was efficacious in the treatment of a 9-year-old girl with severe relapsing NMO. The child had a dramatic and sustained improvement over a 2-year period of treatment with significant regression of the typical NMI lesion and no further relapses. Mycophenolate mofetil is a non-competitive inhibitor of the enzyme inosine 5’-monophosphate dehydrogenase that controls lymphocyte proliferation and T-cell-dependent antibody responses through purine synthesis inhibition. A prospective study of MMF as an alternative immunosuppressive approach in preventing relapses of Devic’s NMO seems warranted.

In conclusion, therapeutic studies in NMO are still scanty and most of the reported observations are anecdotal. Now as the disease’s concept is better established and the current diagnosis criteria more widely accepted, larger randomized prospective trials with presently available and emerging agents are urgently needed.

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