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NEUROMYELITIS OPTICA: CURRENT CONCEPTS

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1. ABSTRACT

Neuromyelitis optica (NMO; Devic's syndrome or Devic's disease) is a clinically defined disorder consisting of optic neuritis (ON) in combination with myelitis. Its nosological relationship to other central nervous system demyelinating diseases remains uncertain. Advances in understanding of its natural history and pathophysiology may eventually allow determination of whether idiopathic NMO represents a specific disease. This article summarizes recent progress in these areas of NMO research.

2. INTRODUCTION

The term "neuromyelitis optica" (NMO; also known as Devic's syndrome or Devic's disease) describes the coexistence of optic neuritis and myelitis. Recognized for over a century (1), the concept of NMO as a distinct entity has engendered much unresolved controversy. Often diagnosed and classified as a severe form of multiple sclerosis (MS), arbitrary diagnostic criteria that take into account unique clinical, laboratory, and neuroimaging characteristics allow identification of an NMO syndrome that appears to have a natural history and treatment response distinct from "typical" MS (2,3). Recent immunological and immunopathological studies derived from patients with clinical NMO add supportive evidence to the concept of idiopathic NMO as a distinct disease, or at least a distinct entity within the nosological conceptualization of idiopathic demyelinating diseases of the central nervous system.

3. WHAT IS NEUROMYELITIS OPTICA?

3.1. Epidemiology and Disease Associations

The clinical combination of optic neuritis and myelitis has been reported in association with many systemic autoimmune disorders (systemic lupus erythematosus, Sjögren syndrome, mixed connective tissue disease, among others), infectious diseases (pulmonary tuberculosis and a myriad of viral illnesses), and immunizations (3-5). The NMO syndrome, therefore, includes a wide spectrum of para-infectious disorders and complications of systemic autoimmunity. In some instances, the neurological symptoms evolve as a complication of a systemically active connective tissue disorder. Most commonly, however, NMO is the most prominent or only clinically apparent disease and the markers of systemic autoimmunity are found during its investigation. It is not clear whether the same pathophysiological basis is operative in these overlapping syndromes.

Neuromyelitis optica is predominantly a disorder of women (80-90% of cases) and the median age of onset is late in the fourth decade, about 10 years later than for typical MS (6). Most North American NMO patients are Caucasian but there is a distinct overrepresentation of people with Asian and African ancestry compared with typical MS. Although familial cases have been reported, NMO is generally a sporadic disease (7-10). It may differ genetically from typical MS in that most studies do not find an association with the HLA-DRB1*1501 allele that is associated with typical MS (11-13).

Table 1. Various Proposed Diagnostic Criteria for Neuromyelitis Optica

Mandler et al. (16)
• Clinical: Acute involvement of spinal cord and ON, either coincidental or separated by months or years, independent of subsequent progression, but without other clinical features at any time during disease course • Imaging: Normal-appearing brain MRI. Enlargement and cavitation on spinal cord MRI • CSF: Decreased serum/CSF albumin ratio, normal IgG synthesis rate and usually absence of oligoclonal bands
O'Riordan et al. (17)
• Severe (more or less complete) transverse myelitis • An acute unilateral or bilateral optic neuropathy • No clinical involvement beyond the spinal cord and optic nerves • Illness may be monophasic or multiphasic
Wingerchuk et al. (6)
Diagnosis requires all absolute criteria AND one major supportive criterion OR two minor supportive criteria
❑ **Absolute criteria**
• Optic neuritis • Acute myelitis • No clinical disease outside of the optic nerves and spinal cord
❑ **Major Supportive Criteria**
• Negative brain MRI at disease onset (normal or not meeting • radiological diagnostic criteria for MS) • Spinal cord MRI with T2 signal abnormality extending over >3 vertebral segments • CSF pleocytosis (>50 WBC/mm3) OR > 5 neutrophils/mm3
❑ **Minor Supportive Criteria**
• Bilateral optic neuritis • Severe ON with fixed visual acuity worse than 20/200 in at least one eye • Severe, fixed, attack-related weakness (MRC grade 2 or less) in one or more limbs

3.2. Diagnosis and Discrimination from Multiple Sclerosis

Neuromyelitis optica is generally classified as one of the subtypes of idiopathic inflammatory demyelinating diseases of the central nervous system (CNS), of which MS is the prototype. The term NMO is applied to patients who have experienced optic neuritis (unilateral or bilateral) and myelitis without clinical evidence of demyelination affecting brain white matter. It used to be considered a monophasic disorder (for a summarized account of the history of NMO, see Wingerchuk and Weinshenker (3)) but is more often relapsing-remitting. This was recognized early on in Japan, where cases of relapsing NMO were diagnosed as "opticospinal" or "Asian" variants of MS, distinguishing it clearly from "Western" or typical MS. The "opticospinal variant" observed in Asia appears to have the same demographic, clinical, neuroimaging, and pathological characteristics as cases of relapsing NMO reported from North America with the exception that systemic autoimmunity is recognized much more commonly in the West (14). The characteristics of a "pure" subgroup of opticospinal MS (clinical opticospinal disease, normal head MRI except for optic nerve abnormalities, and more than 5 years of clinical follow-up) are virtually identical to cases of relapsing NMO (13).

Classification problems persist because many patients with NMO meet MS diagnostic criteria and some patients with MS may present with ON and myelitis (15). Gradually revised (but still arbitrary and largely unvalidated) diagnostic criteria attempt to discriminate NMO from MS by emphasizing several apparent clinical, laboratory, and neuroimaging differences (Table 1) (6,16,17). Clinically, NMO usually presents with more dramatic acute exacerbations. Optic neuritis attacks are generally severe and exhibit poor recovery; a minority of patients experience simultaneous bilateral ON but the frequency is significantly higher than in MS. Myelitis attacks in NMO are often fulminant, bilateral, "complete transverse myelitis" and accompanied by pain and a greater degree of residual neurological impairment.

Although very severe attacks suggest NMO, there is substantial overlap in clinical severity between NMO and MS; therefore, other factors assume greater diagnostic importance. Laboratory features suggestive of NMO include lack of cerebrospinal fluid (CSF) oligoclonal banding and immunoglobulin abnormalities and seropositivity for multiple autoimmune markers such as antinuclear antibody (ANA), extractable nuclear antigen (ENA), and thyroid autoantibodies (6,17). However, magnetic resonance imaging (MRI) studies of the head and spinal cord appear to have the highest discriminative value. In most cases, head MRI is normal (except for possible optic nerve abnormalities) or demonstrates only a few punctate nonspecific abnormalities that do not fulfill radiological criteria for MS. Over time, brain MRI may reveal an increasing number of cerebral white matter lesions but only in a small minority of cases will these meet MRI criteria for MS and they are rarely symptomatic.

Spinal cord MRI is probably the most useful discriminative test. Most patients with NMO have a contiguous, longitudinally extensive, gadolinium-enhancing cord lesion that spans three or more vertebral segments (Figure 1). Spinal cord plaques in MS uncommonly exceed two segments in length and lesions over more than three segments are exceedingly rare.

The specificity of these criteria for discrimination of NMO from MS is not known. This is in part due to the lack of a gold standard for NMO diagnosis. Prospective studies that evaluate clinical symptoms and signs, CSF and MRI findings at disease onset and correlate them with a gold standard for NMO diagnosis are needed. An objective biological or pathological marker that is associated with NMO but not with MS is needed. A potentially important advance in NMO research was reported in April, 2003 (18,19). Investigators at Mayo Clinic presented data

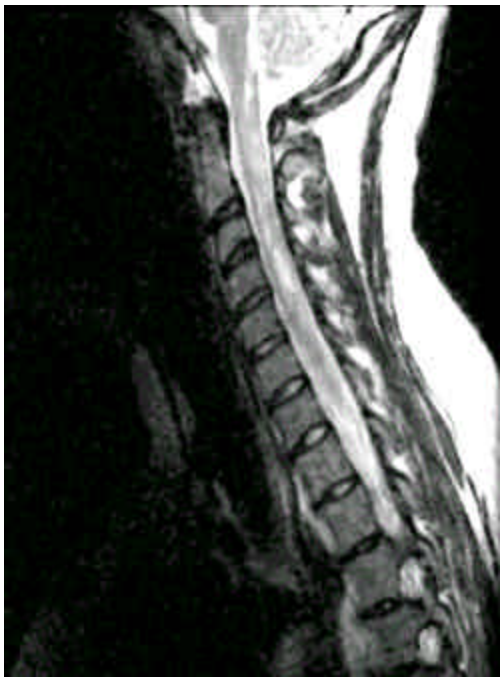

Figure 1. Magnetic resonance imaging of the cervical spinal cord (sagittal T2-weighted images) demonstrates a longitudinally extensive cord lesion extending beyond the cervicomedullary junction.

regarding a serum autoantibody that appears to discriminate NMO from typical multiple sclerosis. This indirect immunofluoresence assay reveals a distinct staining pattern (termed 'NMO-IgG') that appears to selectively bind a target associated with CNS capillaries, pia, and subpia (18). Within a group of 48 patients with definite or probable NMO, 54.2% were seropositive for NMO-IgG compared with none of 20 patients with typical MS (19). This finding represents the first specific biological marker for NMO and, if validated, may be a powerful diagnostic tool available at disease onset.

4. WHAT IS THE NATURAL HISTORY OF NMO?

Neuromyelitis optica remains a construct, i.e., an empirically derived diagnostic entity conceived from clinical experience that suggests that patients with NMO behave differently than those with "typical" MS. Patients fulfill NMO diagnostic criteria if they have presumed demyelinating isolated optic nerve and spinal cord lesions, negative head MRI and CSF oligoclonal banding, and a longitudinally extensive spinal cord lesion of three or more vertebral segments. Patients who fulfill this syndrome definition proceed along either a monophasic or a relapsing course. A monophasic course, which probably occurs in less than 25% of patients, is defined by co-occurrence of either unilateral or bilateral ON and a single episode of myelitis and extended follow-up (several years) that reveals no further exacerbations. Most patients experience a relapsing course, in which the index events of ON and myelitis may be many weeks or even years apart but attacks of ON, myelitis, or both recur over the next months to years. Those patients destined for a relapsing course usually declare it relatively early: after fulfilling NMO diagnostic criteria, 55% have their first optic nerve or spinal cord relapse within one year; this proportion increases to 78% at three years and 90% at five years (6).

For the purposes of prognostication and long-term treatment, clinical and laboratory features that are available early in the disease course and are highly discriminative between the relapsing and monophasic NMO varieties would be very useful. Unfortunately, there are no CSF or imaging variables that independently allow course and severity prediction, but some clinical features are useful. The clinical impression that patients who present with a combination of ON and myelitis simultaneously or in rapid succession (over a few days) are much more likely have a monophasic course was recently confirmed by observational data utilizing a longitudinal database of 80 NMO patients (20). In the largest contemporary series, the median interval between the first clinical event and the development of bilateral ON and myelitis (traditional definition of NMO) was 5 days (range 0 to 151 days) in the monophasic group versus 166 days (range 2 to 730 days) for the relapsing group (6). This single variable is quite powerful; the relative risk of relapsing disease is increased by 2.16 for every month increase in the first inter-attack interval. Other independent predictors include female sex (relative risk = 10.0 female versus male) and less severe motor impairment with the initial myelitis event (relative risk = 0.48 for every point decrease on a motor weakness scale). Complete paraplegia occurs at the clinical nadir of the first myelitis attack in 70% of monophasic patients compared with only 31% of those who later develop relapsing disease. Although the first ON attacks are also typically more severe in those with a monophasic course, with complete loss of light perception occurring in more than 50% versus about 28% of relapsing patients, this is not an independent risk factor for disease course prediction. These prognostic variables may be useful when considering the use of preventative immunosuppressant therapies early in the disease course and in planning epidemiological and therapeutic studies.

Although the ON and myelitis attacks that define monophasic NMO may be more severe, long-term neurological impairment and disability is measurably less in this group than for relapsing disease. This is because most patients with monophasic disease experience some recovery and then remain neurologically stable because no further relapses occur. Although 22% remained functionally blind (20/200 vision or worse) in at least one affected eye, more than 50% of ON episodes demonstrated eventual recovery to 20/30 visual acuity or better. Permanent neurological impairment in monophasic disease is more often related to myelitis; most patients experience at least a moderate degree of both limb weakness and bowel and/or bladder dysfunction. Permanent monoplegia or paraplegia occurs in 31%. Five-year survival of this group is approximately 90% and cause of death is usually unrelated to NMO or a medical complication of immobility (6,20).

Relapsing NMO follows an unpredictable course consisting of clusters of attacks months or years apart. When considering only exacerbation frequency, this disease course resembles its relapsing-remitting "typical MS" counterpart. When attack severity and cumulative disability are considered, however, the natural history of relapsing NMO is markedly different from that of a typical MS cohort (6). A mere five years from disease onset, more than 50% of people with relapsing NMO have at least one eye with less than 20/200 acuity or are nonambulatory due to attack-related paraplegia or quadriplegia. This is in contradistinction to MS, in which most patients recover from early attacks completely or nearly so and suffer mild disability until the secondary progressive phase of the disease takes hold about 10-15 years later. Progressive disease is not a feature of NMO. While the prognosis for most monophasic patients is to maintain some degree of independence (despite moderate visual and motor deficits), those with relapsing disease face early, stepwise accumulation of greater disability.

As in typical MS, relapse frequency is extremely variable in NMO. Several attacks may strike over a few months or remissions lasting a more than a decade may occur. In one series followed over a median of 16.9 years, the median number of relapses was five (range 1 to 18) (6). As in monophasic NMO, a progressive phase of neurological deterioration is uncommon, although there are many patients who seem to have rapid, sometimes stepwise, deterioration when they embark on a taper following a period of continuous corticosteroid therapy.

The long-term survival rate for relapsing NMO is probably the lowest of all relapsing-remitting CNS demyelinating syndromes. Severe, ascending cervical myelitis causing respiratory failure affected as many as one-third patients in one series (though the true incidence is probably lower given improvements in diagnostic accuracy and widening of the NMO spectrum). In one longitudinal series, five-year survival was 68% with all deaths secondary to myelitis-related respiratory failure (6). Improvements in medical and supportive care have likely reduced these estimates but the point is that the disease has the potential for both serious morbidity and mortality. Predictors of mortality in relapsing NMO include a history of systemic autoimmune disease (relative risk = 4.15), greater exacerbation frequency during the first two years of disease (relative risk = 1.21 per attack) and better motor recovery following the first myelitis attack (20).

In summary, the natural history of disease for patients who fulfill NMO diagnostic criteria is markedly different than that of typical MS. Progress has been made in predicting the course and its severity, and this may be useful ultimately in study design and clinical practice.

5. WHAT IS THE PATHOLOGICAL BASIS OF NMO?

The cause of NMO is not known. Its clinical and basic pathological features have led many to conclude that it represents a severe, topographically restricted MS variant. The fact that multiple infectious and systemic autoimmune diseases have been associated with NMO suggests that a single pathological basis for the clinical syndrome is unlikely. The situation is complicated by cases of the NMO phenotype occurring as an apparent complication of classic autoimmune diseases such as systemic lupus erythematosus and Sjögren syndrome (21,22). In addition, serum autoantibodies (antinuclear antibody, extractable nuclear antigen, etc.) associated with those systemic diseases are often found in patients with NMO who do not have clinically evident systemic disease (6,17). These associations suggest that at least some cases may be caused by B-cell mediated processes.

5.1. General Pathology

Pathological studies of NMO optic nerve specimens are limited and generally yield nonspecific demyelination that is more extensive than seen in most MS cases of similar duration (23,24). Brain parenchyma is usually normal but may reveal scattered areas of minor perivascular infiltrates and patchy demyelination or gliosis.

Study of NMO spinal cord lesions at various stages of maturity has been more informative. Acute lesions often expand the cord and are associated with softening, cavitation, and necrosis (24-27). The inflammatory infiltrate is vigorous and includes a high proportion of polymorphonuclear cells. Depending on the severity of the myelitis attack, pathological findings range from modest perivascular inflammatory demyelination to complete hemorrhagic, necrotic destruction of both gray and white matter. In many cases, large numbers of eosinophils are often found in the inflammatory infiltrate (27). The intense eosinophilic and neutrophilic inflammatory response is quite distinct from findings in typical MS. The role of the distinct eosinophilic response in NMO is unknown; it may be a primary response or reflect secondary activation by the C5a component of complement (27).

A potentially discriminative gross pathological abnormality in NMO is the presence of hyalinized medium-sized spinal cord arteries (16,17,27-29). This vascular feature is usually found in conjunction with parenchymal necrosis and a macrophage-predominant inflammatory infiltrate and is not observed in MS. It is not known whether these vascular abnormalities are a clue to the primary immunopathogenesis of NMO lesions or are a nonspecific secondary phenomenon.

5.2. Immunopathology

Immunopathological advances have strengthened the case for humoral immunity underlying the pathogenesis of NMO. Using spinal cord biopsy and autopsy tissue samples, Lucchinetti *et al* discovered prominent IgG and C9 neoantigen (a marker of complement activation) deposits within regions of active myelin destruction and around vessel walls where there was vascular proliferation and fibrosis (27). This finding provides an early indication that the hyalinized vasculature seen on gross examination may be relevant to NMO pathophysiology.

The autoantigen(s) responsible for NMO pathogenesis are not known. The recent discovery of the NMO-IgG serum autoantibody marker (described in Section 3.2) is an important first step in antigen

identification (18,19). This highly specific staining pattern is associated with capillaries in cerebellar cortex and midbrain but the spectrum of CNS regions involved and the precise antigen associated with this marker are not yet known.

Animal models of MS, such as experimental allergic encephalomyelitis (EAE), assist in the understanding of CNS inflammatory demyelination mechanisms. The clinical and pathological phenotype of varies depending upon the genetic strain of the animal and the type, timing, and route of antigen exposure. Induction of EAE using the antigen myelin oligodendrocyte glycoprotein (MOG) can result in inflammatory lesions restricted to the optic nerve and spinal cord (30). MOG-induced EAE can actually produce several other patterns of CNS pathology resembling clinically recognizable MS phenotypes such prototypic MS, optic neuritis, and the acute Marburg variant of MS (31). Therefore, other genetic or environmental factors may be more important in determining the pathological and clinical expression of such idiopathic inflammatory CNS demyelinating disorders.

It is not known why the optic nerves and spinal cord are preferentially affected in NMO. Over years of follow-up, brain MRI can detect dissemination of cerebral white matter lesions, but these are generally asymptomatic, punctate, and subcortical in location. Lucchinetti *et al* postulated that antibody-mediated injury might be more likely in sites of a less effective blood-brain barrier (27); this is indirectly supported by various EAE models that have a predominance of optic nerve and spinal cord lesions.

6. THERAPY

6.1. Acute Exacerbations and Supportive Care

Acute therapy is often the foremost consideration at disease presentation, especially when patients experience rapidly progressive, ascending paraplegia, quadriplegia, or respiratory failure. There are no reports of structured therapeutic trials of first-line treatment for NMO exacerbations. Parenteral corticosteroids are empirically used and appear effective. Many clinicians use intravenous methylprednisolone 1000 mg daily for five consecutive days. I usually begin oral prednisone afterward if the patient is not already taking it as part of an immunosuppressive regimen for NMO attack prevention.

Corticosteroid-refractory attacks are not an uncommon occurrence in NMO. Although various second-line therapies such as intravenous immune globulin have been employed, the only existing controlled evidence supports the use of plasmapheresis. A randomized, double-blind, crossover trial that included many NMO patients demonstrated that compared with sham exchanges, plasmapheresis (seven exchanges, each of ≅55 ml/kg, administered every other day) resulted in clinically meaningful improvement in 42% of patients with various forms of severe, idiopathic inflammatory demyelinating disease (32). A retrospective review found that six of ten NMO patients with severe, corticosteroid-refractory NMO attacks demonstrated moderate or marked clinical improvement shortly after plasmapheresis was initiated (33). Predictors of response included early treatment initiation, male sex, and preserved muscle stretch reflexes. Therefore, if patients with severe attacks worsen during corticosteroid therapy or do not demonstrate improvement very shortly after treatment completion, immediate implementation of plasmapheresis is recommended.

Patients with severe myelitis attacks requiring hospitalization become exposed to the medical risks immobility poses. Prevention of these complications is important and the clinician must be aware of the possibility that an ascending cervical myelitis may cause neurogenic respiratory failure. Patients at risk for this complication require close intensive care unit observation, ongoing monitoring of respiratory and bulbar status, and ventilatory assistance when necessary. Measures to prevent thromboembolic events, decubitus ulceration, aspiration pneumonia, and urinary tract infections are also required.

6.2. Preventative Immunotherapy

Therapy aimed at attack prevention is required for patients with relapsing NMO but not for those with monophasic disease. Perhaps the strongest argument for distinguishing between NMO and MS is that they each appear to require quite different chronic immune-based therapies. The treatments of choice for reduction of MS attack frequency are interferon-beta and glatiramer acetate (34). Although there are some exceptions, such as a report that interferon beta-1b seemed to benefit Japanese opticospinal MS (35) and a case report of clinical stability associated with glatiramer acetate treatment (36), anecdotal evidence from experienced clinicians suggests that these agents fail to significantly alter attack rate for most relapsing NMO patients.

There are no preventative therapies with proven efficacy for relapse suppression in NMO. In the only published prospective treatment study, seven newly diagnosed NMO patients remained stable for at least 18 months after initiation of a combination of azathioprine (2 mg/kg/d) and oral prednisone (1 mg/kg/d) (37). After two months, the prednisone dose was gradually reduced (by 10 mg every three weeks to 20 mg/d, then an even slower reduction to a maintenance dose of 10 mg/d). Most patients received maintenance doses of 75-100 mg azathioprine and 10 mg prednisone daily. During the 18-month follow-up period, no attacks were recorded and neurological impairment scores improved marginally. I usually employ a similar approach for patients with recently active disease, aiming for an initial target dose of 2.5 to 3 mg/kg/d of azathioprine and 40-60 mg/d of prednisone. If clinical stability is achieved and lasts for more than 8 weeks, I slowly taper the prednisone dose on alternate days (e.g., 5 mg every 2 weeks) in an attempt to reduce corticosteroid adverse effects. Once there is hematological evidence that azathioprine is active (mild decrease in leukocyte count and increase in mean corpuscular volume), the dose prednisone is reduced even more slowly (e.g., 5 mg every 4 weeks). Some patients are able to sustain remissions on azathioprine monotherapy but

others will develop steroid dependence, either because of perceived neurological worsening or documented new exacerbations when attempts to reduce the prednisone dose are made.

Various other immunosuppressive drugs have been used but in limited numbers and outside the realm of a structured study. Mycophenolate mofetil may be used in place of azathioprine though its onset of action may be no more rapid. For patients who "fail" the azathioprine and prednisone combination, I consider a trial of mitoxantrone, which is approved for use in rapidly worsening secondary progressive or relapsing-remitting MS. There are no data concerning the use of mitoxantrone in NMO. In some instances, such as when a cluster of attacks has recently occurred, I consider the use of mitoxantrone as first –line therapy to try to achieve a rapid remission. Other therapies aimed at B-cell modulation should be studied in the future based on the recent immunopathological discoveries in NMO. There may be a role for different drugs of this type to induce remission and to sustain it.

The importance of early diagnosis and treatment of relapsing NMO cannot be overstated. The dismal natural history of the disorder, which causes almost exclusively attack-related disability, mandates early and carefully monitored treatment aimed at relapse prevention. Controlled trials, planned and managed by multicenter collaborative efforts, are needed to determine optimal long-term therapy for NMO.

7. CONCLUSION

Significant advances in the last five years have allowed us to better understand the nosology, natural history, and treatment of NMO. We have taken major steps toward unraveling the immunohistochemistry and immunopathology of NMO and solidifying its place as a distinct clinic entity. Relapsing NMO needs to be recognized early in its course to allow early initiation of therapy and to prevent attack-related disability. The recent discovery of a serum autoantibody marker, if validated, may assist in achieving this goal and represents a milestone in the evolution of our knowledge about this uncommon but devastating disorder.

8. REFERENCES

1. E Devic: Myelite subaigue compliquee de neurite optique. *Bull Med* 8,1033-1034 (1894)
2. B Weinshenker: Neuromyelitis optica: what it is and what it might be. *Lancet* 361, 889-890 (2003)
3. Wingerchuk, D.M. & B.G. Weinshenker: Neuromyelitis Optica. In: Multiple Sclerosis 2. Eds: McDonald WI, Noseworthy JH, Butterworth-Heinemann, Woburn, MA 243-258 (2003)
4. Cree, B.A. Goodin, D.S. & S.L. Hauser: Neuromyelitis optica. *Semin Neurol* 22, 105-122 (2002)
5. Papais-Alvarenga, R.M., Miranda-Santos, C.M. Puccioni-Sohler, M. de Almeida, A.M.V. Oliveira, S. Basilio De Oliveira, C.A. Alvarenga, H. & C.M. Poser: Optic neuromyelitis syndrome in Brazilian patients. *J Neurol Neurosurg Psychiatry* 73, 429-435 (2002)
6. Wingerchuk, D.M. Hogancamp, W.F. O'Brien, P.C. & B.G. Weinshenker: The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology* 53, 1107-1114 (1999)
7. D. McAlpine: Familial neuromyelitis optica: its occurrence in identical twins. *Brain* 61, 430-438 (1938)
8. Ch'ien, L.T. Medeiros, M.O. Belluomini, J.J. Lemmi, H. & J.N. Whitaker: Neuromyelitis optica (Devic's syndrome) in two sisters. *Clinical Electroencephalography* 13, 36-39 (1982)
9. Yamakawa, K. Kuroda, H. Fujihara, K. Sato, S. Nakashima, I. Takeda, A. Suzuki, K. & Y. Itoyama: Familial neuromyelitis optica (Devic's syndrome) with late onset in Japan. *Neurology* 55, 318-320 (2000)
10. Keegan, B.M. & B. Weinshenker: Familial Devic's disease. *Can J Neurol Sci* 27(Suppl2), S57-S58 (2000)
11. Ono, T. Zambenedetti, M.R. Yamasaki, K. Kawano, Y. Kamikawaji, N. Ito, H. Sakurai, M. Nishimura, Y. Kira, J. Kanazawa, I. & T. Sasazuki: Molecular analysis of HLA class (HLA-A and -B) and HLA class II (HLA-DRB1) genes in Japanese patients with multiple sclerosis (Western type and Asian type). *Tiss Antigens* 52, 539-542 (1998)
12. Yamasaki, K. Horiuchi, I. Minohara, M. Kawano, Y. Ohyagi, Y. Yamada, T. Mihara, F. Ito, H. Nishimura, Y. & J. Kira: HLA-DPB1*0501-associated opticospinal multiple sclerosis: clinical, neuroimaging and immunogenetic studies. *Brain* 122, 1689-1696 (1999)
13. Misu, T. Fujihara, K. Nakashima, I. Miyazawa, I. Okita, N. Takase, S. & Y. Itoyama: Pure optico-spinal form of multiple sclerosis in Japan. Brain 125, 2460-2468 (2002)
14. J Kira: Multiple sclerosis in the Japanese population. Lancet *Neurology* 2, 117-127 (2003)
15. de Seze, J. Stojkovic, T. Ferriby, D. Gauvrit, J.-Y. Montagne, C. Mounier-Vehier, F. Verier, A. Pruvo, J.-P. Hache, J.-C. & P. Vermersch: Devic's neuromyelitis optica: clinical, laboratory, MRI and outcome profile. *J Neurol Sci* 197, 57-61 (2002)
16. Mandler, R.N. Davis, L.E. Jeffery, D.R. & M. Kornfeld: Devic's neuromyelitis optica: a clinicopathological study of 8 patients. *Ann Neurol* 34, 162-168 (1993)
17. O'Riordan, J.I. Gallagher, H.L. Thompson, A.J. Howard, R. S. Kingsley, D. P Thompson, E. J. McDonald, W. I. & D.H. Miller: Clinical, CSF, and MRI findings in Devic's neuromyelitis optica. *J Neurol Neurosurg Psychiatry* 60, 382-387 (1996)
18. Lennon, V.A. Lucchinetti, C.F. & B.G. Weinshenker: Identification of a marker autoantibody of neuromyelitis optica. *Neurology* 60(Suppl1), A519-A520 (2003)
19. Weinshenker, B.G. Wingerchuk, D.M. Lucchinetti, C.F. & V.A. Lennon: A marker autoantibody discriminates neuromyelitis optica from multiple sclerosis. *Neurology* 60(Suppl1), A520 (2003)
20. Wingerchuk, D.M. & B.G. Weinshenker: Neuromyelitis optica: Clinical predictors of a relapsing course and survival. *Neurology* 60, 848-853 (2003)
21. Bonnet, F. Mercie, P. Morlat, P. Hockes, C. Vergnes, C. Ellie, E. Viallard, J.F. Faure, I. Pellegrin, J.L. Beylot, J. & B. Leng: Devic's neuromyelitis optica during pregnancy

in a patient with systemic lupus erythematosus. *Lupus* 8, 244-247 (1999)
22. Mochizuki, A. Hayashi, A. Hisahara, S. & S. Shoji: Steroid-responsive Devic's variant in Sjogren's syndrome. *Neurology* 54, 1391-1392 (2000)
23. Achard, C. & L. Guinon: Sur un cas de myelite aigue diffuse avec double nevrite optique. *Arch de Med Exper er d'Anat Path* 1, 696-710 (1889)
24. F.C. Stansbury FC: Neuromyelitis optica (Devic's disease). Presentation of five cases with pathological study and review of the literature. *Arch Ophthalmol* 42, 292-335;465-501 (1949)
25. C. Goulden: Optic neuritis and myelitis. *Trans Ophthal Soc UK* 34, 229-252 (1914)
26. G.M. Beck: A case of diffuse myelitis associated with optic neuritis. *Brain* 50, 687-703 (1927)
27. Lucchinetti, C.F. Mandler, R.N. McGavern, D. Bruck, W. Gleich, G. Ransohoff, R.M. Trebst, C. Weinshenker, B. Wingerchuk, D. Parisi, J.E. & H. Lassmann: A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. *Brain* 125:1450-1461 (2002)
28. Ortiz de Zarate, J.C. Tamaroff, L. Sica, R.E. & J.A. Rodriguez: Neuromyelitis optica versus subacute necrotic myelitis. II. Anatomical study of two cases. *J Neurol Neurosurg Psychiatry* 31, 641-645 (1968)
29. Lefkowitz, D. & J.N. Angelo: Neuromyelitis optica with unusual vascular changes. *Arch Neurol* 41, 1103-1105 (1984)
30. Stefferl, A. Brehm, U. Storch, M. Lambracht-Washington, D. Bourquin, C. Wonigeit, K. Lassmann, H. & C. Linington: Myelin oligodendrocyte glycoprotein induces experimental autoimmune encephalomyelitis in the 'resistant' Brown Norway rat: disease susceptibility is determined by MHC and MHC-linked effects on the B cell response. *J Immunol* 163, 40-49 (1999)
31. Storch, M.K. Stefferl, A. Brehm, U. Weissert, R. Wallstrom, E. Kerchensteiner, M. Olsson, T. Linington, C. & H. Lassmann: Autoimmunity to myelin oligodendrocyte glycoprotein in rats mimics the spectrum of multiple sclerosis pathology. *Brain Pathol* 8, 681-694 (1998)
32. Weinshenker, B.G. O'Brien, P.C. Petterson, T.M. Noseworthy, J.H. Lucchinetti, C.F. Dodick, D.W. Pineda, A.A. Stevens, L.N. & M. Rodriguez: A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol* 46, 878-886 (1999)
33. Keegan, M. Pineda, A.A. McClelland, R.L. Darby, C.H. Rodriguez, M. & B.G. Weinshenker: Plasma exchange for severe attacks of demyelination: Predictors of response. *Neurology* 58, 143-146 (2001)
34. Noseworthy, J.H. Weinshenker, B.G. Lucchinetti, C. & M. Rodriguez: Multiple sclerosis. *N Engl J Med* 343:938-952 (2000)
35. Itoyama, Y. Saida, T. Tashiro, K. Sato, T. Ohashi,Y. & The Interferon-beta Multiple Sclerosis Research Group in Japan: Japanese multicenter, randomized, double-blind trial of interferon beta-1b in relapsing-remitting multiple sclerosis: two year results. *Ann Neurol* 48,487 (2000)
36. Bergamaschi, R. Uggetti, C. Tonietti, S. Egitto, M.G. and V. Cosi: A case of relapsing neuromyelitis optica treated with glatiramer acetate. *J Neurol* 250, 359-361 (2003)
37. Mandler, R.N. Ahmed, W. & J.E. Dencoff: Devic's neuromyelitis optica: a prospective study of seven patients treated with prednisone and azathioprine. *Neurology* 51, 1219-1220 (1998)

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