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Review

Neuromyelitis optica

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The combination of optic neuritis and myelitis, the so-called Neuromyelitis optica is an uncommon pattern of demyelinating disorder. In 1870, Sir Thomas Clifford Allbutt first reported the association and Erb published a comparable report. Gowers and Dreschfeld described other instances in the 19th century. This paper attempts to review the syndrome to consider whether it merits recognition as a disease, sui generis, or rather as a syndrome symptomatic of multiple sclerosis, acute disseminated encephalomyelitis, and other immunological disorders. Two forms are distinguished: a monophasic illness, and a relapsing form. The claimed differential features separating it from classical multiple sclerosis are appraised. Modern immunology suggests an antibody-dependent, complement-mediated pathogenesis.
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Introduction

Neuromyelitis optica (NMO) has been a source of controversy for over a century. This paper seeks briefly to appraise the syndrome as exposed both by its history and by more recent developments.

NMO is the combination of optic neuritis with myelitis. This can occur in multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), Sjögren's syndrome, systemic lupus erythematosus, and in many viral and other infections. However, sometimes, no cause is found.[1] The optic neuritis precedes the myelitis in 80% of cases, usually by less than 3 months. The clinical course is variable. Often a monophasic, sometimes fulminating illness, it can run polyphasic courses with relapses and remissions.

Whether NMO is a distinct disease or part of the wide spectrum of multiple sclerosis is debated. Differences are: the severe sequelae occur after an acute episode – more frequent in NMO than in MS; MS infrequently presents as transverse myelitis; oligoclonal bands in the CSF, and white matter lesions on brain MRI are uncommon in NMO but occur in over 90% of MS patients.

History

In 1870, Sir Thomas Clifford Allbutt first reported an association between myelitis and an optic nerve disorder.[2] He described a case of myelitis followed by optic nerve changes approximately 3 months later; however, details of his case report are scant and pathology was not presented. Erb[3] published a report of a 52-year-old man who developed recurrent optic neuritis followed by subacute myelitis. The patient partially recovered from his myelopathy but remained with impaired vision. Steffan described a similar patient. Seguin[4] reviewed Erb's case, one case of the ophthalmologist HD Noyes,[5] and a third personal case of optic neuritis and subacute transverse myelitis. He mistakenly considered the association accidental. Dreschfeld[6] in 1882 described the first pathologically examined case of optic neuritis and myelitis and showed inflammation in both the spinal cord and optic nerves; the brain was normal. Dreschfeld credited Gowers whose classic textbook discloses:

> In rare cases of myelitis, optic neuritis has been observed, without any intracranial complication to cause it. It is probably not the result of the inflammation of the spinal cord, but is an associated and similar lesion, the result cause of the myelitis…most of the cases thus accompanied have been instances of disseminated myelitis….[7]

Gowers plainly recognized that the optic neuritis and the myelitis were both the result of a common cause.

Several additional cases were also described in the 19th century literature. Devic[8] (little is written about Devic.[8] He also described 'Lhermitte's sign' in MS some 6 years before Lhermitte (Bereil T, Devic E. Sur un cas

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de douleurs à type de décharge dans la sclérose en plaques. *Lyon Med* 1918; **141**: 559)) (1858–1930)[9] and his student Gault[10] in 1894 reviewed 16 previously reported similar cases, and Gault studied another case for his doctoral thesis. Gault and Devic believed that cases of optic neuritis and myelitis constituted a distinct clinical entity. Many case reports were later chronicled. Beck[11] reviewed 70 and Stansbury[12] 20 cases but some had pathology in the brainstem and cerebrum more suggestive of ADEM or MS than a discrete entity.

Clinical features

About one-third of cases have a prodromal fever, myalgia, or headache. The typical patient presents with an acute and severe paraparesis or tetraparesis with both pyramidal and sensory signs, often with sphincter involvement, evolving over 1–14 days, with a sensory level. Neuroimaging excludes cord compression. This is preceded or succeeded by an acute unilateral or bilateral optic neuropathy with impaired acuity and colour vision and central or caecocentral scotomata, but there are no signs beyond the spinal cord or optic nerves. Some measure of improvement in a few weeks is the rule, but residual signs and disability often persist.

In about 80% cases, involvements of the cord and optic nerves occur within 3 months of each other. About two-thirds of cases have a relapsing course, and one-third a monophasic illness, most with incomplete recovery and variable persisting disabilities; 90% survive 5 years. When optic neuritis and myelitis occur simultaneously within a few days of each other, the illness is more likely to be monophasic.

The main clinical features are summarized in Table 1.

Neuropathology

Stansbury[12] reviewed the neuropathology of 20 cases of NMO and proposed that the lesions progressed through a series of stages. The earliest stage is characterized by acute inflammation: with prominent perivascular exudates of polymorphonucleocytes, and plasma cells. The next stage is characterized by tissue destruction and demyelination in the perivascular foci: smaller lesions seem to coalesce into larger lesions, and axis-cylinder destruction is noted. Necrotic lesions are observed in the cord, and smaller necrotic foci are sometimes found within the optic nerves. Reactive microglial cells characterize the next stage, with lipid-laden phagocytes containing myelin. The final stage is characterized by astrocytosis and the formation of glial scars. Stansbury noted that glial scarring is less frequent and usually only partial, in contrast to typical MS plaques.

Several cases of NMO in the early literature had many or diffuse brain lesions, which in retrospect, may have been instances of MS or ADEM. Indeed, Miller and Evans suggested[13] that NMO was a form of ADEM. Both NMO and ADEM can produce both grey and white matter involvement, perivascular infiltration, and areas of focal necrosis. However, such an explanation fails to account for those cases that have a relapsing–remitting course.

More recent work has shown that early demyelinating lesions in NMO are associated with perivascular deposition of immunoglobulins, in particular IgM, and with local activation of the complement cascade and an eosinophilic infiltrate. This combination is relatively specific for early lesions, but is also accompanied by immunopathological changes in the CNS such as macrophage/microglial activation and axonal damage that also occur in MS. The immunopathology of NMO is suggestive of an antibody-dependent, complement-mediated pathogenesis 'extenuated by the recruitment and degranulation of eosinophils'.[14] There is evidence associating HLA-DRB1-1501 with MS in contrast to NMO associated with DRB1-802, DPB1 501, but this indicates susceptibility rather than cause.

Table 1 Clinical features of NMO combined from recent series[19–23]

Feature	*Number*
Women/men	87/36
Monophasic/polyphasic	72/40
Optic neuritis presentation	50 (45%)
Transverse myelitis presentation	43 (38%)
Combined ON/TM presentation	19 (17%)
Autoimmune disease/antibodies	28/104 (27%)
Antecedent infection	22/91 (24%)
Normal brain (MRI)	48/63 (76%)
Abnormal spinal cord (MRI)	55/58 (95%)
CSF pleocytosis	63/85 (74%)
>50 cells/mm^3	27/84 (32%)
CSF oligoclonal bands	23/77 (30%)

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; ON/TM, optic neuritis/transverse myelitis [after Cree *et al*[1]]

Symptomatic neuromyelitis optica

NMO has been associated with many systemic diseases, which include collagen vascular diseases, autoantibody syndromes, Behcet's Syndrome, thymoma, Sjögren's syndrome, infections – Varicella-zoster virus, Epstein-Barr virus, and HIV, and exposure to Clioquinol and Antituberculous drugs. These should be investigated when clinical features are suggestive.

Neuromyelitis optica or MS variant?

Standard texts classify the relapsing type as a variant of multiple sclerosis.[15–17] It resembles the optico-spinal variant of MS (OSMS).[18] Wingerchuk *et al*[19] presented the results of a large-scale study of relapsing and monophasic NMO cases at the Mayo clinic. This showed that if a broad clinical definition of NMO is adopted, not surprisingly, a syndrome with diverse aetiologies emerges. Conversely, many writers assert that NMO is a unique disease, but many question this

concept, suggesting that relapsing NMO is a variant of multiple sclerosis.[24]

Varieties of this syndrome are common in MS, but the title NMO has been more strictly delineated, with arguable justification,[25] to bilateral severe visual loss with a transverse cord lesion. Patients who present with rapidly developing blindness and paraplegia, with a pleocytosis of several hundred cells in the CSF, certainly do not appear at the time to have multiple sclerosis; yet the subsequent course may be typical of MS.

Further, the optic-spinal form of multiple sclerosis with negative oligoclonal IgG bands, and no brain lesions on repeated MRI – termed pure OSMS, overlaps and is confused both with NMO[20] and classical MS. The alleged typical features and comparison with classical MS are shown in Table 2.

Diagnostic criteria

Diagnostic criteria for NMO have been proposed to clarify the nosological debate (Table 3). However, none has received widespread acceptance. The original criteria of Gault and Devic fail to exclude coexistent myelitis and optic neuritis caused by infection, injury, or tumour, which caused confusion in the early literature. The criteria of O'Riordan *et al* allow for polyphasic and unilateral optic neuritis cases but require the myelitis to be both rapid and transverse. The criteria of both Mandler *et al* and Wingerchuk *et al* use magnetic resonance imaging (MRI) to exclude alternative diagnoses, and to show the characteristic acute central cord swelling, $\pm$Gadolinium enhancement extending over three or more vertebral segments. A new antibody, NMO-IgG, discovered at the Mayo Clinic, is asserted to be 70% sensitive but nearly 100% specific for NMO and NMO-related disorders such as recurrent transverse myelitis and recurrent optic neuritis.[26] Widespread testing of this marker with long follow-up would be important to validate its general application.

Table 2 Features said to be characteristic of NMO *versus* MS

Typical distribution of lesions
Neuropathological necrosis
Severe optic neuritis and myelitis
Females > males
Lower frequency of oligoclonal IgG bands
Association with a specific human leucocyte antigen (HLA) class II allele (DPBl*0501)
Normal MRI scan of the head
Longitudinally extensive signal abnormality in cord in acute attacks

Treatment

Treatment for acute attacks and relapses is aimed at controlling symptoms and if possible prevention. But most trials contain small numbers, and are uncontrolled. Patients are commonly given intravenous methylprednisolone 500–1000 mg daily for 5–10 days. Seven exchanges of plasmapheresis (55 ml/kg) on alternate days have been claimed to benefit exacerbations. Intravenous immunoglobulin also has its advocates. Prevention of complicating venous thromboembolism, aspiration pneumonia, pressure sores, contractures, and urinary infections are more important. Prevention of relapses is unproven, although glatiramer acetate and interferon beta-1a and 1b have been tried, as have long-term steroids – but without proven evidence of prevention. One prospective trial, after initial high-dose intravenous methylprednisolone, prescribed maintainance prednisone 10 mg/day and azathioprine 75–100 mg/day. Disability Status Scale scores improved, and no exacerbations occurred in the 18-month treatment.[27]

Conclusions

NMO emerges as a syndrome rather than a single disease. Devic and Gault were not the first to associate

Table 3 Some definitions of NMO

Gault[10] *and Devic*[9]
Retrobulbar neuritis or papillitis accompanied by acute myelitis and occasionally other neurological symptoms or signs not restricted to the spinal cord or optic nerves

O'Riordan et al[20]
1. a severe transverse myelitis;
2. an acute unilateral or bilateral optic neuropathy;
3. no clinical involvement beyond the spinal cord or optic nerves; and
4. a monophasic or multiphasic illness.

Wingerchuk et al[19]
Diagnosis requires all absolute criterion 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
Major supportive criteria: (1) Negative brain MRI at onset (does not meet criteria for multiple sclerosis), (2) Spinal cord MRI with signal abnormality extending over $\geqslant 3$ vertebral segments, (3) CSF pleocytosis of >50 WBC/mm^3 or >5 PMNs/mm^3
Minor supportive criteria: (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 $\leqslant 2$) in one or more limbs

the combination of optic neuritis with myelitis; however, Devic's name is established as an eponym by tradition. It is clear that many conditions are associated with, or result in, NMO. Separation from classical and variant MS, and variant forms of disseminated encephalomyelitis, has been widely attempted, but no incontrovertible diagnostic features have been proved. Despite reported differences, it remains likely that these conditions are part of the same spectrum of inflammatory demyelination in which the genetic background and immune factors define the pattern of disease.

The terms NMO and Devic's syndrome retain utility and convenience for reference until the syndrome is broken down into its composite aetiologies.

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