From Devic disease to the ‘neuromyelitis optica spectrum’: an unfinished tale bridging three centuries

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ABSTRACT

Background and objectives. Eugène Devic (1858-1930) made medical and neurological history in 1894 when he described neuromyelitis optica (NMO). This article describes how the concept of this disease has evolved over the centuries since being described by the well-known doctor from Lyon.

Methods. To describe the history of NMO, we performed a literature search in PubMed, ScienceDirect, and Google Scholar; keywords were ‘Devic syndrome/disease’ and ‘neuromyelitis optica’.

Results and conclusions. Although the histopathological findings in Devic’s case were clearly distinct from those in multiple sclerosis (MS), Devic disease was nonetheless regarded as a mere variant of MS during most of the 20th century. In the early 21st century, aquaporin-4 antibodies (AQP4-Abs) were identified as the cause of NMO and other diseases that are now recognised as making up the ‘NMO spectrum’. These diseases may coexist with other autoimmune and paraneoplastic disorders. The situation has become more complex now that similar syndromes are known to be caused by myelin oligodendrocyte glycoprotein antibodies (MOG-Abs), while others arise in seronegative patients. Clinical presentation (myelitis, severe neuritis optica, intractable hiccups, brainstem and hypothalamic dysfunction, encephalopathy syndrome), CSF results (absence of oligoclonal bands and polymorphonuclear pleocytosis), and magnetic resonance and optical coherence tomography findings provide the bases for suspecting an NMO spectrum disorder. Further steps will then entail requesting specific serology studies (AQP4-Abs and MOG-Abs) and administering the appropriate immunosuppressant treatment, keeping in mind that disease-modifying therapies used in MS may aggravate NMO.

KEYWORDS
Devic disease, AQP4-Abs, neuromyelitis optica, history of neurology, multiple sclerosis, MOG-Abs

Introduction

Eugène Devic was born in 1858 in La Cavalerie-Aveyron, in the Midi-Pyrénées region of the south of France; he was an only son, born to a wealthy winegrowing family. He studied medicine in Lyon. Devic began his specialist training in 1882 and graduated in 1886 upon presenting a thesis titled ‘Des rachutes de la fièvre typhoïde’. His most important mentors were the professors Bouveret and Tripier. His career would introduce him to a variety of medical fields, especially anatomical pathology, paediatrics, cardiology, gastroenterology, and neurology. His list of contributions touched on different topics in neurology, including infantile chorea, polyneuritic psychosis, post-typhoid insanity, and brain tumours.1-4 He died in 1930.

A discreet, hard-working man, Devic’s admirable qualities distinguished him from the rest, both in clinical medicine and in the classroom.1 Although the Parisian school was unrivalled, E. Devic and J. Froment were the finest exponents of the Lyon school of neurology between the last two decades of the 19th century and the first two of the 20th.5 Devic’s son André and his grandson Michel continued to advance his research, and his great-grandson-in-law Christian Confavreux, a recognised
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expert in demyelinating disease, also investigated neuromyelitis optica (NMO) (Figure 1, A and C).

Eugène Devic made a name for himself as a doctor and neurologist at the First French Congress of Medicine, held in Lyon in 1894, when he gave an oral presentation on a new syndrome, ‘acute neuromyelitis optica’, based on a histopathology study of one of his own cases plus the review of another 16 previously published similar cases.\(^6,7\)

Not long after that, Devic’s student Fernand Gault (1873-1936) defended his thesis in which he theorised that NMO might arise from an infection causing two distinct ‘hotspots’ in the central nervous system: ophthalmic on the one hand and spinal on the other.\(^8\)

The main purpose of this study is to present a historical description of NMO, classically considered a variant of multiple sclerosis (MS) but now recognised as an independent entity. The study is based on a literature search of PubMed, Science Direct, and Google Scholar (keywords: Devic disease/syndrome, neuromyelitis optica).

Development

Devic’s case study

The patient was a 45-year-old white woman examined in Hospital Hôtel-Dieu de Lyon in December 1892 due to general malaise, headache, and depressed mood. On 27 January 1893, she exhibited urinary retention and paraparesis progressing to paraplegia in about 10 days; in the same period of time, she also developed amaurosis with bilateral papilloedema. She died on 4 March 1893 and her death was attributed to infection secondary to pressure ulcers. While her brain was histopathologically normal, her spinal cord exhibited a lesion 5 cm long in the inferior thoracic region, with an additional lesion in the lumbar area and in both optic nerves. Spinal cord lesions affected both white and grey matter without occupying the entire cross-section; they displayed necrosis and inflammation with cell infiltration. Vessels appeared to be enlarged, with no signs of thrombosis or haemorrhage. Demyelination was predominant in the optic nerves.\(^6,7\)

Selected cases of myelitis and neuritis optica published before Devic’s study

S. Jarius and B. Wildemann\(^4\) have researched possible cases of Devic syndrome predating Devic’s own description. In 1804, A. Portal, first physician to Louis XVIII and founder of the Académie Nationale de Medicine, published the case of the Marquis de Causan, who exhibited amaurosis and spinal cord inflammation.\(^9\)

In *Pathological and practical research on diseases of the brain and spinal cord* (1829), John Abercrombie describes a case of vision loss with intractable vomiting and hiccups; he was also one to coin the term ‘neuroencephalitis optica’.\(^4\) An 1844 article published by Giovanni B. Pescetto in the *Giornale delle scienze mediche della Società medico-chirurgica di Torino* describes a reversible case, treated with bloodletting, of amaurosis and cervical myelitis.\(^10\) Christopher M. Durrant’s 1850 article in the British Medical Journal describes a case of bilateral amaurosis and tetraplegia.\(^11\) In 1862, Jacob A.L. Clarke

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**Figure 1.** Photo gallery: A) E. Devic. B) W.R. Brain. C) C. Confavreux. D) V.A. Lennon
published a case of bilateral neuritis optica with extensive transverse myelitis in *The Lancet*. Thomas C. Allbutt, the inventor of the clinical thermometer, may deserve the same recognition as Devic according to English-speaking historians. In 1870, he reported a case of acute myelitis with “a sympathetic eye disorder” and highlighted that an ophthalmoscope was a useful tool for examining patients with spinal disease. In 1876, the journal *Przeglad Lekarski* published a case report by Adolf Wurst describing a 30-year-old woman with bilateral neuritis optica and transverse myelitis.

Devic syndrome and Devic disease

Devic and Gault showed that the lesions in neuromyelitis optica differed from those in ‘sclerose en plaques’, the French term for EM, in both structure and location (NMO lesions were seen in the spinal cord and optic nerve, although some patients also displayed brainstem lesions). Perhaps Devic’s major accomplishment was having introduced the term ‘neuromyelitis optica’ for what he recognised as a syndrome, that is, an anatomical-clinical entity potentially stemming from multiple causes. In contrast with the French author’s ideas on the subject, the association of optic neuritis and extensive myelitis began to be called Devic disease in 1907. This change came about when Turkish doctor Peppo Acchioté presented another case of bilateral optic neuritis and paraplegia with sphincter dysfunction to the *Société Neurologique de Paris*; in doing so, he proposed the name ‘Devic disease’, which was met with widespread approval.

The 20th century saw many more case descriptions referred to as ‘Devic disease’, although with many terminological variations describing the association between optic neuritis and myelitis: *neuroppticomyélite* (Devic), *neuro-myélite diffuse aiguë* (Gault), *neuro-optic myelitis*, *neuromyelitis optica* (Erwin Stransky), acute neuro-optic myelitis, *neuromielite ottica*, *oftalmomielitis*, *neuromielitis óptica*, and *mielitis oftálmica*.

With the publication in 1933 of *Diseases of the nervous system*, the influential and ubiquitous textbook by W.R. Brain (Figure 1B), neuromyelitis optica or Devic disease came to be considered a variant of MS, and this paradigm endured to the end of the 20th century. McAlpine was the one to publish the first familial cases of NMO.

Nevertheless, many authors observed and emphasised the distinguishing features of NMO. Some were clinical

<table>
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<th>Author(s)</th>
<th>Observations/description/discovery</th>
<th>L. C.</th>
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<td>1804</td>
<td>A. Portal</td>
<td>Case of the Marquis de Causan, afflicted with amaurosis and myelitis</td>
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<td>1829</td>
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<td>1844</td>
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<td>Case of amaurosis and cervical myelitis</td>
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<td>1850</td>
<td>C.M. Durrant</td>
<td>Bilateral amaurosis and tetraplegia</td>
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<td>J.A.L. Clarke</td>
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<td>First Congress of Medicine (Lyon): neuromyélite optique aigué</td>
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<td>1894</td>
<td>F. Gault</td>
<td>Doctoral thesis: ‘De la neuromyélite optique aigué’</td>
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<td>2015</td>
<td>D. Wingerchuk et al.</td>
<td>NMO spectrum disorders and the 6 clinical variants: diagnostic criteria</td>
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L. C.: literature citations.
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(Severe, occasionally bilateral optic neuritis, extensive myelitis, and lack of response to interferons); others were paraclinical (frequent polymorphonuclear pleocytosis in excess of 50 cells/mm³ with no oligoclonal bands in CSF; furthermore, brain MRI studies did not show the lesions typical of MS in these cases). Published cases include some of paraneoplastic origin and others associated with autoimmune diseases such as Sjögren syndrome, Hashimoto thyroiditis, systemic lupus erythematosus, type 1 diabetes, coeliac disease, and myasthenia gravis.

Little by little, the older concept of Devic syndrome was being recovered. In Spain, three cases of Devic disease appeared in Anales de Medicina y Cirugía in 1949, reported by de Gispert Cruz, who believed them to represent an independent entity among the demyelinating diseases. In 1969, López-Nieto and Noya-García published a case of neuromyelitis optica in Archivos de la Sociedad Oftalmológica Hispanoamericana; since it was possibly of tuberculous origin, they opted for treatment with tuberculostatic drugs.

In 1999, Dean Wingerchuk and other authors at the Mayo Clinic, mindful of the marked differences between NMO and MS, decided to review the medical histories of 71 patients diagnosed with Devic disease and treated between 1950 and 1997. Of these patients, 23 presented a monophasic illness and 48 had recurrences. Recurrent cases were associated with pronounced cumulative disability after attacks; a third of these patients died of respiratory failure caused by cervical myelitis. They also examined MRI studies and found that most patients presented no changes in the brain, but displayed longitudinally extensive spinal cord lesions spanning 3 vertebral bodies or more. This large series was also able to confirm typical CSF changes: pleocytosis greater than 50 cells/mm³ with a predominance of polymorphonuclear neutrophils. Based on the findings from the clinical review study, the same group proposed the first diagnostic criteria for NMO, listed here in Table 2. At a later date, some of the authors from this group suggested antibody-mediated disease as a hypothesis; the separation of NMO and MS was approaching quickly.

In 2004, Vanda A. Lennon (Figure 1D) and other researchers published their discovery of an antibody, which they named IgG-NMO, in the serum of patients with a phenotype indicative of NMO (102 from the USA and 12 from Japan). This antibody was characterised by its ability to bind to and mark the glia limitans, pia mater, ependyma, and subpial penetrating vessels surrounded by Virchow-Robin spaces; in other words, structures related to the blood-brain barrier. One year later, the same authors established that the specific target antigen of this IgG-NMO antibody was the aquaporin-4 water channel. This discovery prompted researchers to issue a revised version of the NMO diagnostic criteria. Since then, multi-centre studies based on these criteria have been published. Additionally, a study in a group of patients with isolated clinical syndromes suggesting MS detected AQP4-Abs in 4% of the cases. We now know that AQP4-Abs can bind to two different forms of AQP4 protein: when binding to the M1 isoform, the receptor is internalised, whereas binding to the M23 isoform results in complement activation, including the degranulation of eosinophils with participation by neutrophils and NK cells.

### Table 2. Initial diagnostic criteria for neuromyelitis optica before the discovery of AQP4-Abs (Wingerchuk et al., 1999)

<table>
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<th>Absolute criteria</th>
<th>Major diagnostic criteria</th>
<th>Minor diagnostic criteria</th>
</tr>
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<tbody>
<tr>
<td>Optic neuritis</td>
<td>Normal brain MRI</td>
<td>Bilateral optic neuritis</td>
</tr>
<tr>
<td>Acute myelitis</td>
<td>MRI showing extensive spinal cord hyperintensities (in 3 or more vertebrae)</td>
<td>Severe optic neuritis with visual acuity &lt; 20/200</td>
</tr>
<tr>
<td>Absence of NS disease except in optic nerve and spinal cord</td>
<td>CSF: &gt; 50 leukocytes/mm³ or &gt; 5 neutrophils/mm³</td>
<td>Severe weakness in one or more limbs (≤ 2 on the MRC scale)</td>
</tr>
<tr>
<td>All required, always</td>
<td>At least one absolute criterion required</td>
<td>At least two absolute criteria required</td>
</tr>
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NS: nervous system; MRC: Medical Research Council.
The NMO spectrum

As the technique for detecting AQP4-Abs became more available, researchers observed that these antibodies were not always present in patients whose clinical and neuroimaging profiles were entirely compatible with NMO, and that other patients with very different clinical presentations tested positive.

A panel of experts, led by D. Wingerchuk, established the concept of ‘NMO spectrum disorders’ (NMOSD), comprising 6 core clinical characteristics: 1) optic neuritis; 2) acute myelitis; 3) area postrema syndrome with hiccups/vomiting; 4) acute brainstem syndrome; 5) narcolepsy or acute diencephalic syndrome with NMOSD-typical lesions (MRI); 6) symptomatic cerebral syndrome with NMOSD-typical brain lesions (MRI). The authors stated that a diagnosis of an NMOSD must be based on the presence of one of the above clinical syndromes plus positivity for AQP4-Abs, and they recommended using a cell-based serum assay as the detection method. In addition, they indicated that where two of the core clinical syndromes are present but AQP4-Abs are negative, NMOSD may still be diagnosed if one of the clinical syndromes is longitudinally extensive myelitis, optic neuritis, or postrema syndrome; the patient will also have to exhibit

Figure 2. MRI study of a case of NMO (author’s personal files) with AQP4-Abs: extensive hyperintensities in the cervical spinal cord (arrow) and hypothalamus (arrow)
multiple attacks and dissemination in space viewed by MRI, and of course other alternative diagnoses must be ruled out.\textsuperscript{49}

Beyond the NMO spectrum

The concept of the NMO spectrum, as outlined in the preceding section, has provided diagnostic guidance for a variety of cases, based on the clinical syndromes and AQP4-Ab status. Nevertheless, we must recognise that the overall situation has not yet been fully explained and accounted for, in light of the following issues: 1) NMO overlaps with other autoimmune disorders, including systemic lupus erythematosus,\textsuperscript{29} Sjögren syndrome,\textsuperscript{28} paraneoplastic syndromes,\textsuperscript{26,27} and others; 2) some patients with a clinical syndrome indicative of an NMOSD lack AQP4-Abs, but they do show myelin oligodendrocyte glucoprotein antibodies (MOG-Abs)\textsuperscript{50,51}; 3) in Eastern and Latin American countries in which NMO is more prevalent, this new entity must be distinguished from optic-spinal forms of MS.\textsuperscript{52-56}

Differential diagnosis for optic-spinal forms of MS and NMOSD is aided by the CSF profile,\textsuperscript{53} images from MR (Figure 2)\textsuperscript{57,58} and optical coherence tomography (OCT),\textsuperscript{59} the relapsing clinical course and greater severity of NMO, and especially, presence or absence of APQ4 antibodies. Distinguishing between these entities is crucial; doctors know that many disease-modifying treatments used in MS (interferon beta,\textsuperscript{60} glatiramer acetate,\textsuperscript{61} natalizumab,\textsuperscript{62} and fingolimod\textsuperscript{63}) may aggravate NMO.

A recent study comparing MOG-Abs syndrome to NMOSD found more male patients of younger ages, as well as lesions located predominantly in the conus medullaris and grey nuclei, in the first group.\textsuperscript{20,51} The study concluded that all patients with a syndrome resembling NMOSD but absence of should be checked for MOG-Abs. The aetiologic and prognostic spectrum in longitudinally extensive transverse myelitis has been examined in a Spanish multicentre study. Here, AQP4-Abs were detected in only 9% of the 23 patients included in the study, which did not test for MOG-Abs.\textsuperscript{84}

Corticoids, immunoglobulins, and plasmapheresis are the main treatment options for attacks of NMOSD disorders; various immunosuppressants, ranging from azathioprine\textsuperscript{65} to rituximab are used to modify the course of the disease.\textsuperscript{46,48,66}

Conclusions

Devic syndrome, described in the second half of the 19th century as acute neuromyelitis, was considered a variant of MS throughout most of the 20th century. In the early 21st century, were identified as the cause of NMO and other diseases now recognised as elements of the ‘NMO spectrum’. These diseases may coexist with additional autoimmune and paraneoplastic disorders. In any case, the situation has grown more complex since there have been reports of very similar cases in which some are produced by MOG-Abs and others are seronegative. Clinical presentation with myelitis, severe optic neuritis, intractable hiccups and vomiting, brainstem and hypothalamic dysfunction, encephalopathy syndrome; CSF with absent OCB and polymorphic pleocytosis; and findings from MRI and OCT studies are the pillars for suspecting an NMOSD. The next step entails serology testing (patients negative for AQP4-Abs are checked for MOG-Abs) and starting treatment with an immunosuppressant different from those used in MS.

Conflicts of interest

The author has no conflicts of interest to declare.

References

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