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Case Report

Devic's syndrome in aquaporin-4 antibody negative patient. What we need to know ...

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Abstract

Introduction: Neuromyelitis optica (NMO) is a severe demyelinating syndrome characterized by optic neuritis (ON) and acute myelitis. The NMO spectrum is actually recognized to typically evolve as a relapsing disorder that also includes patients with atypical unilateral ON and those with index events of ON and myelitis occurring weeks or even years apart (Jarius/Wildemann 2013). NMO was previously assumed to be a variant of multiple sclerosis (MS), but the discovery of aquaporin-4 antibodies in patients with neuromyelitis optica has led to this view being revised (Mandler 2006, Barnett/Sutton 2012, Wingerchuk et al. 2007). The cause of the condition is still unknown, but it has been shown that the antibodies bind selectively to a water channel expressed mainly on astrocytes at the blood-brain-barrier, which has an important role in the regulation of brain volume and ion homeostasis. However, there are some patients with NMO that are antibodies negative. The diagnosis is made on the basis of case history, clinical examination, magnetic resonance imaging (MRI) of the brain and spinal cord, analysis of cerebrospinal fluid (CSF), visual evoked potentials and a blood test with analysis of aquaporin-4 antibodies (Barnett/Sutton 2012, Wingerchuk et al. 2007, Thornton et al. 2011). This suggests that periodical revisions of established concepts and diagnostic criteria are necessary.
Purpose: The authors describe an extremely rare case of neuromyelitis optica and the aim of this paper is to call attention for the cases of NMO whith NMO-IgG negative.
Methods: The selected method is a case report.
Results: To date the patient showed partial recovery of left eye acuity and improvement of muscle strength of upper and lower limbs and does not show recurrence of the disease.
Conclusion: NMO has a distinct clinical, imaging and immunopathological features sufficient to distinguish it from MS. This distinction is essential, because the treatment and the prognosis is different.

Keywords: neuromyelitis optica, diagnostic criteria, treatment, Devic's syndrome, aquaporin-4 antibody

Introduction

Neuromyelitis optica also known as Devic's disease is a rare immune mediated demyelinating condition of the central nervous system affecting predominantly the optic nerves and the spinal cord [1]. NMO can be seen as a part of another immune-mediated syndrome, such as lupus, multiple sclerosis, but often no underlying cause can be found. It should be included as one of the central nervous system (CNS) neuroinflammatory disorders [2], [3], [4].
In the past, we have learned that NMO is far broader, and includes cases with unilateral optic neuritis, partial transverse myelitis and many cases in which optic neuritis and transverse myelitis are separated by months and years [5], [6].
Currently, NMO is considered as a central nervous system AQP4 channelopathy which causes variable damage predominantly to the optic nerves and spinal cord, although other CNS structures that highly express AQP4 may be also affected [7], [8].

Purpose

The aim of this study is to report a rare case study.

Materials and methods

We report the case of a 20-year-old Caucasian woman who presented to the Ophthalmology Emergency room, claiming progressive, painless vision loss in the left eye with 3 days of evolution and one week after she complained paresthesias in the lower extremities. The patient presented a visual acuity of 10/10 in right eye and in the left eye absent luminous perception. The direct pupillary reflex in the left eye was absent. Anterior segment in both eyes was normal. The intraocular pressure was 13 mmHg in both the eyes and fundoscopy in the left eye showed edema of optic nerve and venous engorgement and tortuosity bilaterally (Figure 1). Ocular motility was normal.
The patient performed in the emergency room a CT and blood tests. On the same day she was admitted to the Neurology Department where she performed MRI (Figure 2, Figure 3), lumbar punction with analysis of CSF. More specific tests and chest CT for screening of thymoma were requested. On the next day our patient was seen at the Ophthalmology Department where she made the following imaging tests: optical coherence tomography, angiography, visual fields and electrophysiological tests.

Results

The complementary exams realized in emergency room (brain and orbits CT and blood tests) were normal, except the slight increase of the inflammatory parameters.
On the next day, angiography, retinography and OCT confirm the ON edema on the left eye. Visual evoked response was absent in the LE.
Visual fields were performed and the left eye showed a discrete arcuate scotoma and lower decrease in sensitivity thresholds in the superior temporal quadrant, right eye was normal.
The CSF was analysed to identify the presence of serum proteins, evidence of blood-brain barrier breakdown and the presence of oligoclonal banding that were negative; quantitative analysis of the total protein, the total white cell count, differential white cell and cytology. The investigation emphasize the negativity of NMO AQ4.

Discussion

NMO is more frequent in women than in men (>80%). The onset of the syndrome varies, from adolescent to young adulthood, with a median peak incidence in the late 30s [8], [9], [10].
NMO is often associated with other autoimmune disorders in the patient or in the family. NMO manifests the sole clinical syndrome, with serological markers of autoimmunity, like a positive ANA, rheumatic factor or thyroglobulin antibody. Association with infectious disorders, like tuberculosis, viral infections and immunizations have been observed.
Nowadays, all studies suggest that neuromyelitis optica is distinct from MS. This distinction is based on clinical, imaging, pathological and serological criteria and has practical implications, in the prognosis and therapies [10].
Since 2004 with the discovery of the NMO-specific antibody and AQP4, as its targeted antigen,it is recognized as a turning point in the concept and understanding of the disease [11]. Aquaporin-4 is the most abundant water channel in the central nervous system, expressed in the foot processes of astrocytes in contact with blood vessels throughout the brain, spinal cord and optic nerves. The periventricular area, the hypothalamus and the brainstem are also considered sites of high expression of AQP-4. Although AQP-4 predominates in the CNS, it is also found in other organs such as kidneys, stomach, airways, glands and skeletal muscle. However, the paucity of clinical abnormalities outside the CNS remains to be explained, as well as the underlying mechanisms of AQP4-IgG seronegative status in some patients [10], [12], [13]. Presumed reasons include, suboptimal sensitivity of the currently available assays (specific for 91% of cases, but not very sensitive yet, 73%, of this could be explained because the substrates of the immunofluorescence assay were not human, but are from mousse brain tissues), very low serum concentration of the antibodies or their absence at some periods in the disease course, and the inhibitory effect of previous treatment with corticosteroids or immunosuppressive agents. It is also possible that in some NMO patients other antigens may play a role in the pathogenesis of the disease. Therefore, notwithstanding

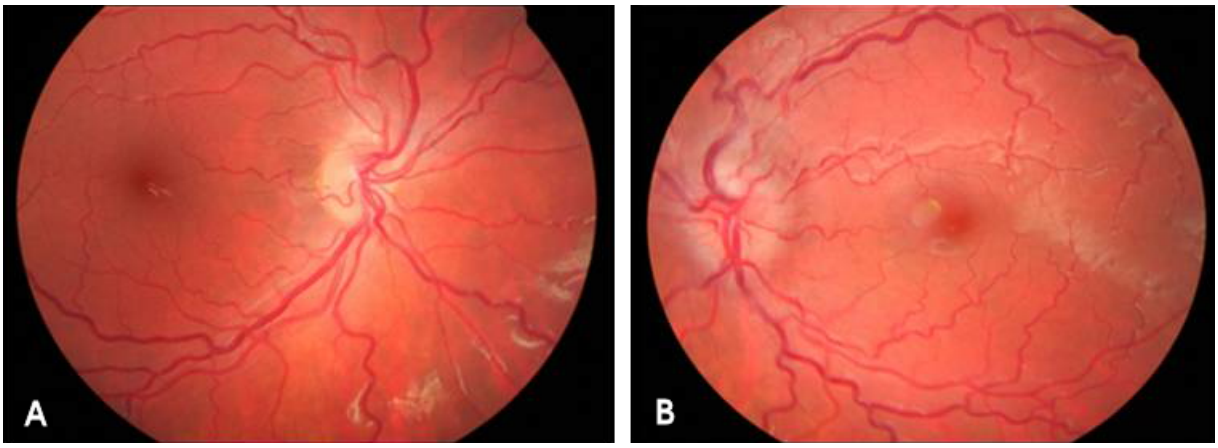

Figure 1: Retinography (day 1) – RI: tilted disc and vascular tortuosity (A); LE: ON edema, venous engorgement and vascular tortuosity (B)

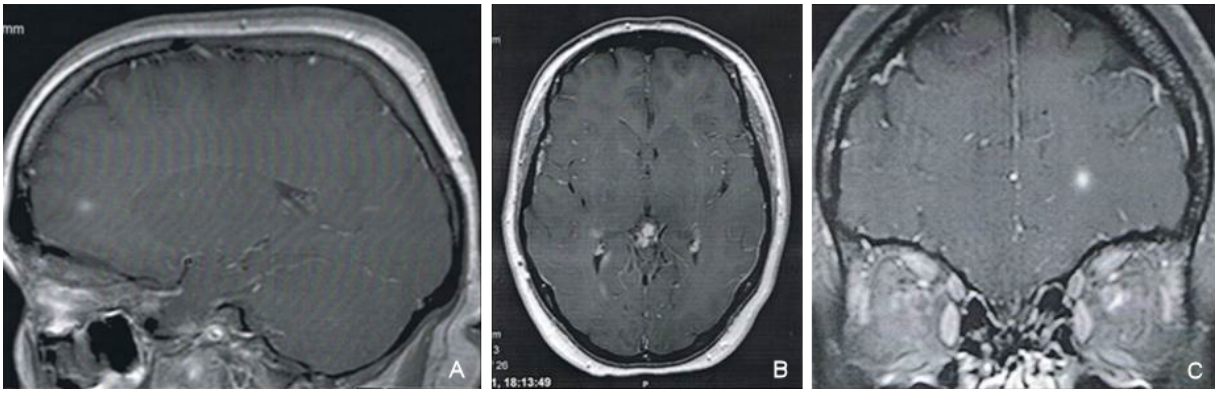

Figure 2: Brain MRI (day 2) (A, B and C) showed small areas of increased signal intensity on left temporal lobe and right periventricular area in cerebral white matter; with gadolinium uptake in the left optic nerve.

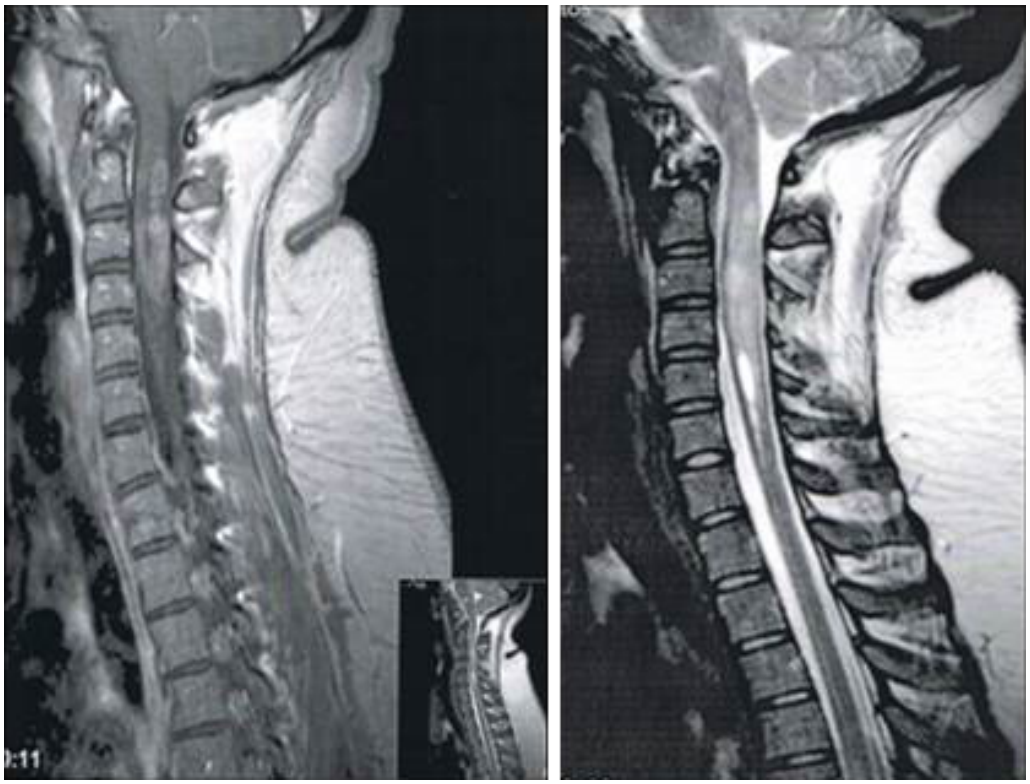

Figure 3: Sagittal T2 weighted MRI of spinal cord showing swelling of the cervical segments (more than 3 contiguous segments) with high signal intensity.

a positive serum AQP4-IgG test is of utmost importance for the diagnosis of NMOSD, a negative result alone cannot rule out the diagnosis [6], [13].
For this reason new diagnostic criteria for NMO were proposed by Mandler [10].

Complete NMO

1. *Temporal*. Acute or relapsing involvement of the optic nerves and spinal cord, coincidental or separated by months or years
2. a. *Serology*. Positive serum NMO-IgG antibody

Or

1. *Temporal*. Acute or relapsing involvement of the optic nerves and spinal cord, coincidental or separated by months or years
2. b. *Serology*. Absent serum NMO-IgG antibody
3. *Spatial*. Myelitis can be total or partial. Optic neuritis can be unilateral or bilateral.
4. *Absence in general, of central nervous system symptoms and signs outside the spinal cord and optic nerves, with exception of hypothalamic and lower brainstem dysfunction*
5. *Course*. The disease can either be monophasic or recurrent.
6. *Spinal cord MRI*. Can be normal, but often T2 signal abnormalities with cavitation and sometimes swelling, extending over 3 or more consecutive segments might reinforce the criteria
7. *Brain MRI*. In general, normal brain MRI. No white matter abnormalities in the brain, brainstem or cerebellum. White matter anomalies might sometimes be seen in hypothalamus and lower brainstem and rarely in the brain parenchyma.

Partial NMO

1. *Clinical*. Either optic neuritis or transverse myelitis
2. *Serology*. Positive serum NMO-IgG

This new classification with revised diagnostic criteria represent an important advance in NMO research and clinical practice. They discriminate NMO from MS and allow the diagnosis of partial forms and negative NMO-IgG forms, like our patient.
In general, NMO is more acute, sometimes fulminant. Myelitis, like optic neuritis, can also be fulminant, with acute urinary retention, paraparesis or quadriparesis, severe tonic flexor spasms and severe back pain [9].
Supportive laboratory features in NMO are absence of CSF oligoclonal bands and pleocytorrachia.
Brain MRI generally shows no white matter abnormalities in the brain, brainstem and cerebellum. Anomalies might be found in the optic nerves. Spinal cord RMI can be supportive when continuous lesions with gadolinium enhancement extend over 3 or more vertebral segments.
The prognosis of NMO is, in general, more guarded than that of MS patients. Patients with NMO can die from acute ventilator failure produced by necrosis of the cervical cord and its complications. Predictors of mortality in relapsing NMO include a history of systemic autoimmune disease, greater exacerbation frequency during the first 2 years of disease and better motor recovery after the first myelitis attack [9], [10].
The treatment of the acute attack need hospitalization, particularly when rapid developing paraplegia or quadriplegia occurs. For those attacks the customary treatment is giving IV methylprednisolone, 1,000 mg q/day for 5 days continue with steroids in the form of oral prednisone, with very slow tapering over months in the relapsing forms of the disease. IVIG treatments have also been used in acute attacks that are refractory to steroids. Plasmapheresis has been found to help in patients with severe attacks that worsen during corticosteroid therapy or do not demonstrate improvement. Predictors of response included early treatment initiation, male sex and preserved deep tendon reflexes.During the relapsing disease, patients with NMO can receive prednisone (1 mg/Kg/d) and azathioprine (2–3 mg/Kg/d) [2], [10], [14]. According to some studies there is a stabilization of the disease for at least 18 months. Most patients receive a maintenance doses of azathioprine of 75–150 mg together with 10 mg of prednisone dose q/o/d. Other treatments like rituximab and mitoxantrone have been studied [14].
Our patient during hospitalization received methylprednisolone, 1,000 mg q/day (IV) for 5 days, following with steroids in the form of oral prednisone (1 mg/Kg/d). At hospital discharge (three weeks later), our patient showed partial recovery of left eye acuity and improvement of muscle strength of upper and lower limbs.
Five weeks later, the patient repeated the MRI, that showed swelling diminished and sign change became less intense and smaller (Figure 4A and B), however the left frontal lesion maintains (Figure 4C) and the vascular tortuosity and the NO edema in the fundus had improved (Figure 4F).
In the follow-up visit, four months later, the dilated fundus examination showed a sectorial optical atrophy in the left eye (Figure 5B), confirmed by OCT (Figure 5C) with a visual acuity 20/20 in each eye. At the moment she was receiving prednisone 40 mg/d and azathioprine 150 mg/d.

Conclusion

NMO has a distinct clinical, imaging, pathological and immunopathological features sufficient to distinguish it from MS. This distinction is not just academic, because the treatment and the prognosis is different too, NMO optic neuritis can be fulminant and devastating. Because a small proportion of cases nevertheless fulfill the criteria for both NMO and MS, challenges persist for clear definitions, especially concerning the roles of immunomodulatory and immunosuppressive treatment [15]. Early recognition of the relapsing form may allow expeditious acute and long-standing treatment and prevent significant morbidity and mortality.

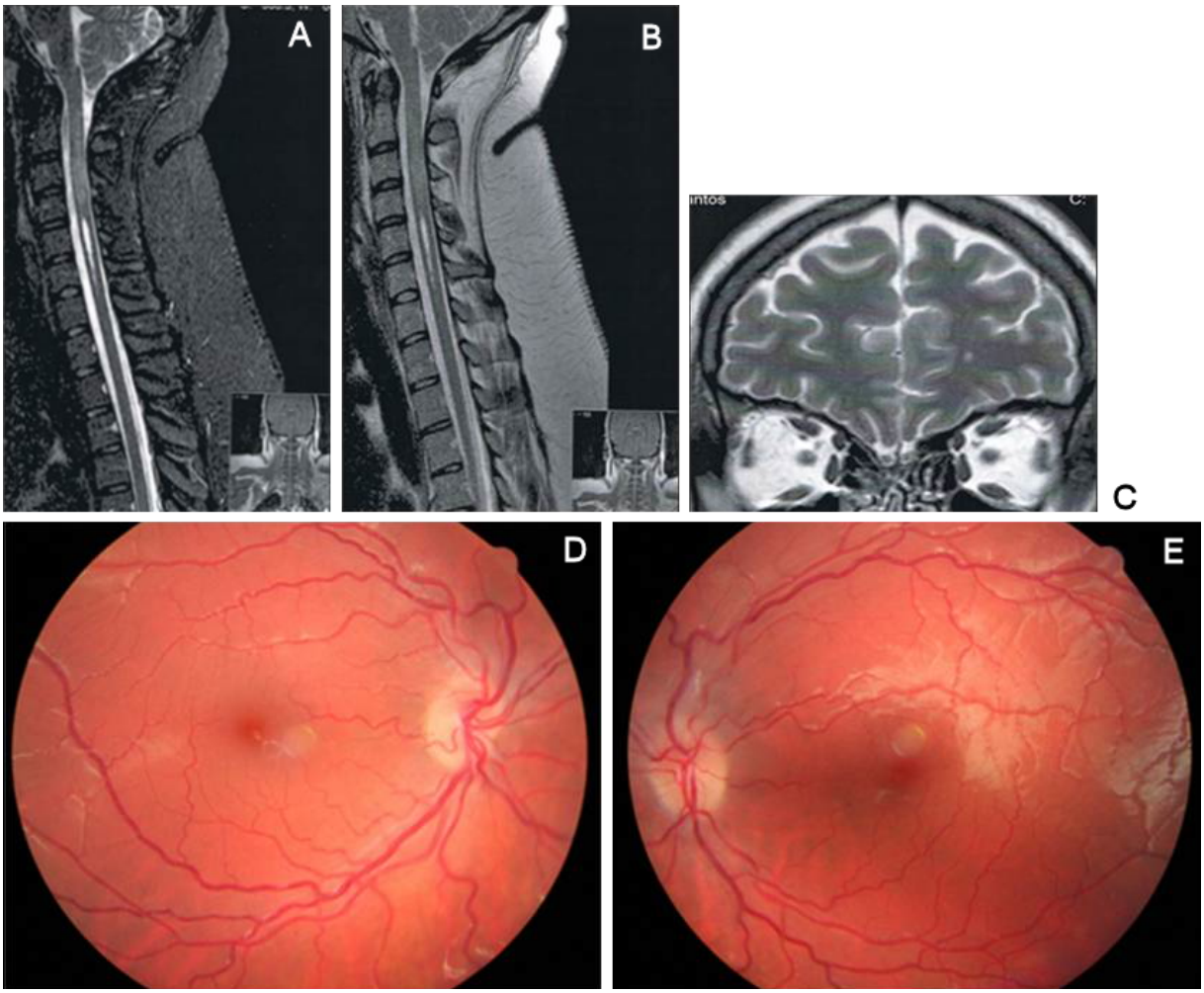

Figure 4: After the acute phase (5 weeks later), MRI showed swelling diminished and sign change became less intense and smaller (A and B), however the left frontal lesion maintains and the vascular tortuosity and the NO edema in the fundus had improved (D and F).

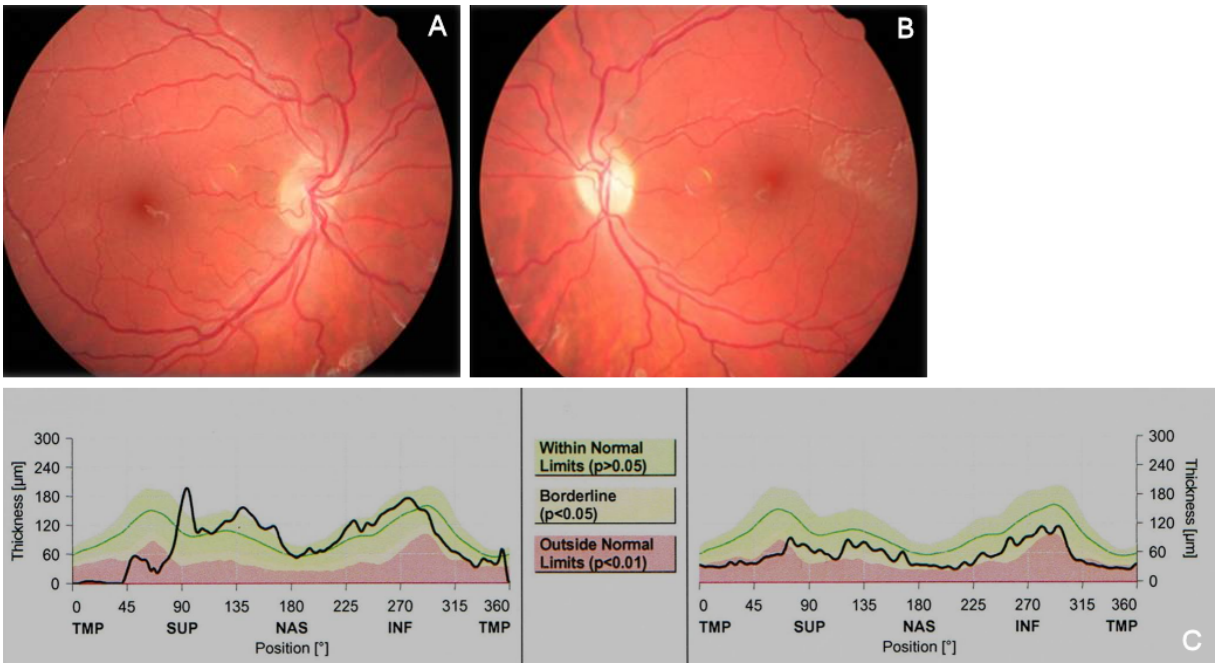

Figure 5: Four months later, the left eye showed a sectorial optical atrophy (A and B), confirmed by OCT (C).

Notes

Competing interests

The authors declare that they have no competing interests.

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