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## CASE REPORT

# Devic's syndrome and primary APS: a new immunological overlap

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Neuromyelitis optica (NMO or Devic's syndrome) is a rare autoimmune disease, previously considered a multiple sclerosis variant. The most important laboratory and clinical features are optic myelitis and transverse myelitis, associated with neuromyelitis optica-IgG antibody (NMO-IgG) positivity. Subsequent to this immunological test being available, different groups have described the not-so-rare comorbidity of neuromyelitis optica with other systemic autoimmune diseases, systemic lupus erythematosus with secondary anti-phospholipid syndrome (APS) in particular. We describe a patient meeting both the classification criteria for primary APS and the new diagnostic criteria for neuromyelitis optica. It's important to diagnose NMO syndrome as both optic neuritis and transverse myelitis were also considered neurological complications of antiphospholipid syndrome. NMO-IgG is a new and fundamental test to decide if immunosuppressant therapy is warranted for such patients. *Lupus* (2010) 0, 1–3.

**Key words:** antiphospholipid syndrome; Hughes syndrome; neuropsychiatric lupus; systemic lupus erythematosus; neuromyelitis optica; Devic's syndrome

### Case presentation

A 50-year-old white man was admitted to the hospital because of sudden loss of sensation and weakness of the lower limbs. His past medical history was remarkable for deep vein thrombosis when he was 20 years old and ischemic stroke in the left hemisphere, with residual right hemiparesis, when he was 45 years old. Lupus anticoagulant, anticardiolipin and anti-B2GPI antibodies were persistently highly positive. As anti-nuclear (ANA), extractable nuclear antigen (ENA) and anti-DNA antibodies were not detected and as he had no symptoms of connective tissue diseases, primary antiphospholipid syndrome (APS) was diagnosed, at which time warfarin therapy was started with an international normalized ratio (INR) target of 2.5–3.5. One year later he developed left optic neuritis, with no radiological or cerebro-spinal fluid findings suggestive of multiple sclerosis. High dose

glucocorticoids were administered with gradual recovery of visual acuity.

He was well until the age of 50, after which he complained of sudden abdominal numbness, under the D10–D12 level, which progressively extended to the lower limbs. After a few hours he was unable to stand or walk. On arrival at the hospital he had bilateral leg weakness (Medical Research Council scale 2/5 left leg and 3/5 right leg). Babinsky sign was bilaterally positive. He subsequently developed bowel and urinary retention, which required laxative therapy and a bladder catheter insertion. No new visual deficit was reported. Magnetic resonance imaging (MRI) showed T2 hyperintense signal with swelling involving the spinal cord from T6 to L1 level (Figure 1). A transverse myelitis was diagnosed and the patient was treated with high dose intravenous methylprednisolone (1 gr/die for 7 days), with gradual although incomplete recovery of neurological symptoms. A second MRI, performed 10 days after corticosteroidal therapy, showed a significant reduction of the spinal inflammation to T8–T11 segments (Figure 2). As he was diagnosed as having an APS-associated transverse myelitis, warfarin therapy was titrated to target an INR of 3.0–4.0. Subsequent to discharge from the hospital, he was regularly followed at our center. After a thorough review of his medical history, considering the previous

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**Figure 1** Pre-therapy MRI findings: sagittal acquisitions on spinal cord, T2-weighted (left) and T1-weighted with Gadolinium contrast medium (right) images. On the T2-weighted image, a long (from T6 to L1 level) intramedullary hyperintense area (white arrows), due to edema, is well visible. The same hyperintense finding on the enhanced T1-weighted image (white arrows) is attributable to the interruption of blood-brain barrier due to inflammation.



**Figure 2** Post 1 week therapy MRI findings: sagittal acquisitions on spinal cord T2-weighted (left) and T1-weighted with Gadolinium contrast medium (right) images. Significant decrease of the pre-therapy findings on both T2- and T1-weighted images (white arrows), due to diminished inflammatory edema and to blood-brain barrier restoration.

optic neuritis episode associated with the recent transverse myelitis attack, we decided to test the patient's serum for NMO-IgG antibody. After the latter positive result, neuromyelitis-optica associated to primary APS was diagnosed and azathioprine (2 mg/kg/day) was started.

## Discussion

Neuromyelitis optica (NMO or Devic's syndrome) is a rare autoimmune disease, previously considered a variant of multiple sclerosis, which differs from pathogenesis and more aggressive clinical course.<sup>1</sup> New criteria, recently developed to correctly diagnosis the disease, include: neurological findings (optic neuritis and transverse myelitis), MRI pattern (lesions distribution not meeting multiple sclerosis criteria and longitudinal extensive transverse myelitis (LETM) involving more than three contiguous vertebra) and, most importantly, serological positivity for neuromyelitis optica-IgG antibody (NMO-IgG).<sup>2</sup> As T2 images show spinal cord edema and T1 images with gadolinium contrast well document blood-spinal cord barrier damage, MRI is the preferred imaging technique to detect transverse myelitis. Soon after the NMO-IgG test was available, different authors have described the association between neuromyelitis optica and other autoimmune diseases, systemic lupus erythematosus with secondary antiphospholipid syndrome in particular.<sup>3-6</sup> NMO-IgG is indeed considered the most important diagnostic tool. Considering its high specificity (94%) and sensitivity (76%), it was initially developed to differentiate neuromyelitis optica from multiple sclerosis.<sup>7</sup> Transverse myelitis or optical neuritis can occur simultaneously or more often at different times, as shown by our patient who developed myelitis four years after the previous optic neuritis attack.

Knowledge of the disease is hence required in a rheumatological setting, as optic neuritis and transverse myelitis have been linked to the wide spectrum of APS-central nervous system (CNS) involvement creating differential diagnosis problems if NMO-Ig is not tested.<sup>8-9</sup> To our knowledge this is the first case of neuromyelitis associated with a confirmed isolated primary APS. Until recently antiphospholipid syndrome was reported to be associated with both optic neuritis and transverse myelitis, but we cannot rule out that for some of these cases the diagnosis of NMO was missed, as the NMO-IgG test was not available in the past. However NMO-Ig positivity remains strongly associated with antiphospholipid antibodies and to explain this phenomena we

propose a two hit model, in which the APS antibodies determine endothelial dysfunction and blood barrier damage (first hit), therefore permitting NMO-IgG to pass into the CNS and to start inflammation in target tissue (second hit).<sup>10</sup> If we start to consider NMO as a new distinct but possibly associated autoimmune disease, in the future it will be necessary to differentiate APS patients who need titration of anticoagulant therapy from patients who need to start immunosuppressive drugs (azathioprine, plasmapheresis or rituximab for the most resistant cases) such as the patient we describe in this case report.

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