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Short Communication

Very late-onset recurrent myelitis in a patient diagnosed with antiphospholipid syndrome: A puzzle of autoimmunity

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ABSTRACT

We describe the case of a man with a very-late onset neuromyelitis optica spectrum disorder syndrome (NMOSD) who was initially diagnosed as recurrent antiphospholipid syndrome-associated myelitis. This case illustrates that a puzzle of autoreactive antibodies can be detected in patients having neurological syndromes belonging to the NMOSD. Prompt identification and timely immunosuppression prevent relapses and the accumulation of irreversible disability.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) syndromes are autoimmune water channelopathies that predominantly target astrocytes or oligodendrocytes and are associated with anti-aquaporin-4 antibodies. Longitudinally extensive transverse myelitis (LETM) with MRI lesions spanning over 3 vertebral segments is one of major features of NMOSD, even more in elderly (Krumbholz et al., 2015). The average age at onset for NMO is usually between 30 and 40 years, although sporadic cases with age at onset higher than 50 (late-onset NMO) and 70 years (very late-onset NMO) were also reported (Pandit et al., 2015; Seok et al., 2017; Suchdev et al., 2017).

Recent studies have demonstrated that patients with NMOSD have an increased predisposition to develop antinuclear antibodies (ANA), such as anti-Ro, Sjogren's-syndrome-related antigen A and B, anti–-double stranded deoxyribonucleic acid and antiphospholipid antibodies, whose clinical and predicting value is only partly evaluated, especially in the very late-onset NMO population (Lavandier et al., 2019; Lee et al., 2019). Among the ANA-associated pathologies, antiphospholipid syndrome (APS) is a systemic autoimmune pro-thrombotic disorder associated with hypercoagulability. APS occur either in isolation (primary APS) or in the context of other systemic autoimmune disorders, such as systemic lupus erythematosus (secondary APS). The prevalence of antiphospholipid antibodies positivity in NMO patients is about 20% (Lee et al., 2019), but this figure might be different for the very late onset NMO, for whom such data are scarce.

Here, we describe an NMOSD patient with recurrent LETM who was initially diagnosed as APS-associated myelitis.

2. Case report

A 72-year-old right-handed Caucasian man with a medical history remarkable for ischemic cardiopathy and retinopathy, presented with progressive muscular weakness in the lower limbs accompanied by urinary retention and numbness in the superior thoracic region. Neurological examination revealed motor weakness and sensory loss to pinprick and light touch over the legs and superior thoracic region. Deep tendon reflexes were diminished over the lower extremities. The rest of his neurological examination was unremarkable. Cervico-dorsal spine MRI showed a longitudinally extensive cord lesion, extending from C7 to T2 level, whereas brain MRI was unremarkable. Laboratory workup including complete blood count with differential, C-reactive protein, fibrinogen, D-dimer and erythrocyte sedimentation rate was normal. Vitamin B12 and folate resulted within normal limits. A detailed immunological screening disclosed high titers of anti-β2-glycoprotein-I (aβ2GPI [IgG/M/A]) antibodies and the presence of anti-nuclear antibody (titre: 1:320). Sjogren's-syndrome-related antigen A and B, Scl-70, antineutrophil cytoplasmic, complement, immunoglobulins (including IgG4) and rheumatoid factor resulted within normal ranges. Viral testing (Hepatitis B, C virus, Immunodeficiency virus, Cytomegalovirus, Ebstein-Barr virus, Varicella Zoster virus) were also negative. Cerebrospinal fluid (CSF) analysis revealed normal white cell

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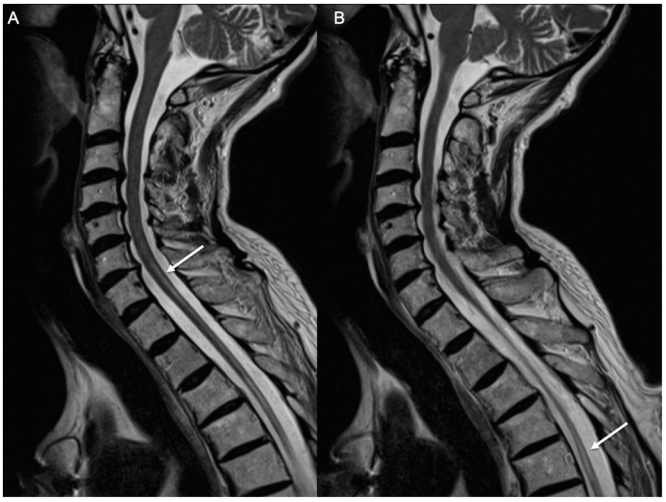

Fig. 1. T2-weighted images showing hyperintensity at C7 to T2 (A) and at T3 to T5 levels (B) as a result of recurrent LETM.

counts, glucose and proteins values. No atypical cells were detected. Blood and CSF cultures were negative. No isolated CSF oligoclonal bands were detected on the CSF. A high titre of aβ2GPI (IgG/M/A) antibodies was confirmed 12-weeks later.

The patient was diagnosed with APS-associated myelitis and treated with oral methylprednisolone (initially 1 g daily for 5 days; followed by decreasing dosage) and lifelong anticoagulation with warfarin (goal INR of 2–3). After treatment, the patient partially recovered the strength in lower limbs. Sensory symptoms completely disappeared. Follow-up cervico-dorsal MRI performed six months later reported a reduction of oedema surrounding lesion but no changes in length size.

At the age of 75, he had a second episode of myelitis manifesting as numbness in his legs and trunk up to the chest, imbalance, and urinary urgency. After further 2 years, he had a third episode of myelitis manifesting as worsening in weakness of the lower limbs. The search of serum NMO IgG level gave positive result. Paraneoplastic antibodies were also tested and resulted normal. Visual Evoked Potential showed increased latency and reduced amplitude in both eyes.

Last MRI performed at the age of 78 showed T2-weighted hyperintensities at C7 to T2 and at T3 to T5 as a result of recurrent LETM (Fig. 1 A–B). Patient was diagnosed with aquaporin 4 (AQP4)-IgG-seropositive NMOSD as the cause for his recurrent LETM according to the most recent diagnostic criteria for NMOSD (Wingerchuk et al., 2015), although he also met classification criteria for coexisting APS (Miyakis et al., 2006). Therapy with azathioprine (100 mg daily) was established. Warfarin was withdrawn. Patient has remained attack-free since then. His most recent neurological examination revealed moderate spastic weakness and severe vibratory loss in both lower extremities.

3. Discussion

This case illustrates that a puzzle of autoreactive antibodies can be detected in patients having neurological syndromes belonging to the NMOSD. Patients with recurrent LETM and antiphospholipid antibodies may be erroneously diagnosed as APS-associated myelitis if anti-AQP4 and anti-MOG antibodies are not investigated, especially when the age at onset is outside the average range for the disorder.

Anti-aquaporin-4 antibodies might also be detected in the context of other autoantibodies (Lee et al., 2019), but the biological role of such co-existence is still to be determined as well as the predictive value of such association on clinical course is still to be determined. Cross-sectional studies demonstrated the lack of association between anti-nucleus autoantibodies positivity and the disability burden in NMOSD patients (Park et al., 2015; Pittock et al., 2008), whereas longitudinal studies reported either a protective or neutral role of anti-nucleus autoantibodies for the NMO clinical course (Lee et al., 2019; Masuda et al., 2016). Also the biological role of such antibodies is still to be determined. One hypothesis suggests that autoantibodies other than anti-aquaporin-4 might lead to vascular damage, which will facilitate NMO-IgG to penetrate the blood brain barrier and damage central nervous system tissue (Jarius et al., 2011). However, the aforementioned findings for the biological and predictive roles were mostly drawn from studies including NMOSD patients with disease onset between 30 and 40 years old. It would be interesting to evaluate the clinical value of autoantibodies in patients with late and very-late onset of NMOSD. This search is hampered by the very low incidence of NMOSD starting after 50 years old and, by the even smaller incidence of the coexistence of autoantibodies in NMOSD elder patients.

Another important warning highlighted in the case presented is the need for AQP-4 and MOG IgG antibodies search in patients with LETM older than 50 years old even when other antibodies are detected. Although the clinical, laboratory and radiological picture might point toward NMOSD, the diagnosis is challenging when symptoms occurs later in life. Late onset NMOSD usually presents with a lower female to male ratio, more frequent initial motor impairment, more severe symptoms and reduced prevalence of brain MRI lesions when compared with early onset NMOSD (Zhang et al., 2017). However, beyond the clinical picture it might be always useful to consider NMOSD even in patients presenting stroke-like symptoms. Needless to say, NMOSD has a poor prognosis with mortality rate of 30% in 5 years. Nevertheless, an early diagnosis allows clinicians to introduce an early and appropriate treatment, ultimately resulting in a better outcome. Actually, while antithrombotic therapy represents the cornerstone of APS management, it is useless in modifying NMOSD disease course. Our case took advantage by the introduction of corticosteroids from its very first attack, even tough it was related to the antiphospholipid syndrome. This was witnessed by a reduction of oedema in the corresponding spinal MRI lesion. However, while corticosteroids are helpful in acute clinical and radiological disease activity, immunomodulatory drug such as azathioprine or rituximab are effective drugs in modifying NMODS long-term outcome.

In conclusion, our case highlights that the search for AQP-4 and MOG IgG antibodies is mandatory in LETM even tough other autoreactive antibodies are present and also in elder patients, since the therapeutic rebounds are considerable. Indeed, long-term immunosuppression is the standard therapy for NMOSD-associated LETM and should be initiated as soon as the diagnosis is achieved, in order to prevent relapses and the accumulation of irreversible disability.

Declation of Competing Interest

None.

Informed consent

The patient provided written informed consent for the publication.

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