Antiphospholipid Antibodies in Multiple Sclerosis: The Chicken or Egg Paradox

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ABSTRACT

We present the case of an adult gentleman with features of both multiple sclerosis and antiphospholipid antibody (aPL) syndrome. Whether this antibody is involved in the primary disease pathogenesis or it only signifies the dysregulation of humoral immune response is being debated and concluded through this case report.

Keywords: Multiple sclerosis, Antiphospholipid antibodies, IgG, IgM, Pathogenesis

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CASE REPORT

A significant proportion of patients with multiple sclerosis (MS) have co-existent presence of autoreactive antibodies.[1] Antiphospholipid antibodies (aPL) comprise a notable half of this pool, with estimated prevalence ranging from 2% to 88% in patients with multiple sclerosis.[2] The classical criteria for diagnosis of antiphospholipid antibody syndrome (APS) might or might not be fulfilled in such cases. APS and aPL-positive MS may have similar clinical presentation, yet the criteria for diagnosis and management are different and definitive diagnosis is challenging. These elevated antibody titres have previously been described only in relapsing remitting and secondary progressive type of multiple sclerosis, but not in primary progressive multiple sclerosis. The chicken or egg paradox, whether the antibody is involved in primary disease pathogenesis or whether it only signifies the dysregulation of humoral immune response has to be looked into.

A 51-year-old male, with no prior co-morbidities, presented with 2-year duration of insidious onset, gradually progressive gait difficulty in the form of stiffness of bilateral lower limbs, imbalance on walking and tripping episodes. Around one year into the illness, he also started to notice strained quality of speech and occasional choking episodes with liquids. 6 months later, he also started to experience mild dexterity impairment of both hands. There is history of bladder disturbances in the form of urgency and frequency. On examination, he had spastic dysarthria, grade 2 spasticity of all four limbs, normal power and exaggerated deep tendon reflexes along with bilateral extensor plantar response. Release reflexes were also present. Sensory examination was within normal limits and he had spastic gait. On evaluation, his MRI brain with spine showed multiple T2/ FLAIR hyperintensities in subcortical, periventricular white matter of bilateral frontal, temporal and parietal lobes along with short segment eccentric lesions of dorsal spinal cord with no evidence of contrast enhancement **(Figure 1).** CSF analysis was normal including normal protein levels and IgG levels with absence of oligoclonal bands.

The patient satisfies the criteria for primary progressive multiple sclerosis as per McDonald's criteria 2017.[3] However, before labelling as multiple sclerosis, complete workup for secondary causes were done. He was extensively evaluated for other paraneoplastic etiology with tumour markers, antineuronal antigen panel and CECT chest and abdomen which was negative except for

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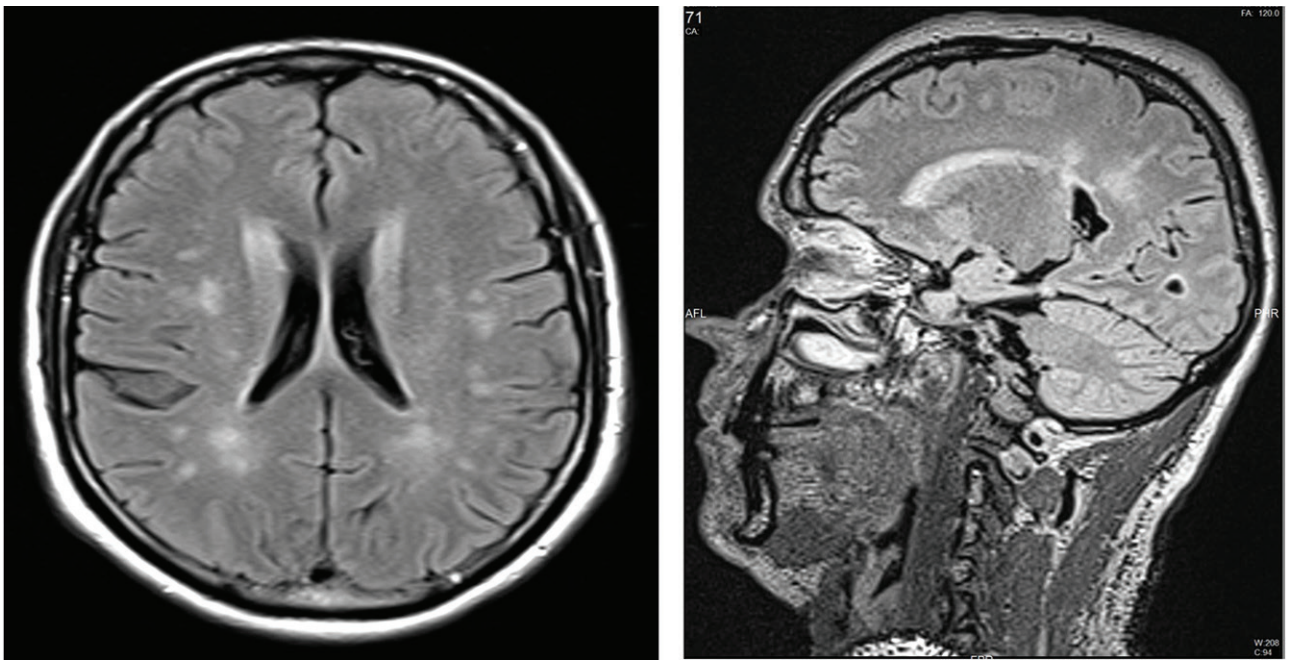

Figure 1. **(a) Axial and (b) Sagittal T2 FLAIR images showing subcortical and periventricular hyperintense lesions**

mildly elevated titre of Anti SOX 1 antibodies (Titre of 33- normal value within 0-7), which has not been described yet to cause a progressive spastic syndrome.[4] Electromyography and nerve conduction study done with the suspicion of anterior horn cell involvement was negative. His vasculitic workup was positive for IgM APLA antibody with an elevated titre of 55.3 MPL-U/mL (Normal value within 5 MPL- U/mL) and was negative for the rest of antibodies including ANA, C-ANCA, P- ANCA, anti dsDNA. The complete APLA panel sent was also negative including IgG APLA antibodies, IgG and IgM anticardiolipin antibodies, Ig and IgM anticardiolipin antibodies and lupus anticoagulant levels. He was treated with pulse dose of intravenous steroids followed by oral steroids, with which there was no significant improvement. He is planned for further immunomodulation on follow-up.

MS is a chronic inflammatory disease of the central nervous system that is characterised by demyelination and concomitant axonal and neuronal degeneration. Around 85% of the patients with MS present with a relapsing remitting course or further evolve to have secondary progression. The remaining 10-15% of patients have a gradual neurological deterioration from onset, termed primary progressive MS. The pathogenesis behind the progression of primary and secondary MS is not fully understood but is proposed to involve neurodegenerative processes driven by dysfunction of the innate immune system and B cells.[5]

The presence of one or more autoreactive antibodies were observed in around 69% of patients with multiple sclerosis of which one half was constituted by APLA antibodies, predominantly of the IgM subtype.[1] Another significant finding from similar studies was a much higher frequency of APLA positive test results for MS patients in exacerbation compared to remission, which suggests aPL as a marker of CNS injury.[6] This may be due to immune-mediated B-cell reaction[1], where molecular mimicry of aPL-target antigens with myelin, myelin-related proteins and brain phospholipids leads to cross reactivity, prothrombotic states and induced vasospasm.

There is no clear distinction between MS and APS mimicking MS, however there are certain features that can be used to distinguish between the two groups. The absence of associated clinical features suggestive of APS, lupus anticoagulant, and prothrombin time elevation in majority of MS patients with positive APLA suggests that these patients are distinct from primary or secondary APS.[1] Along with these features, there are radiological findings that can be used to differentiate between these two entities. Lesions in APS tend to maintain shape and size on repeat scanning, have lower total lesion volumes, are predominantly subcortical instead of periventricular, do not show the typical ovoid shape nor predilection for the corpus callosum, may affect the putamen, and are less associated to a reduction in brain parenchymal fraction.[7] Cerebrospinal fluid (CSF) analysis with a normal cell count and absence of oligoclonal bands is in favour of APS.[8] Another neurophysiological test ruled as suf-

ficient to discriminate MS from APS diagnosis is the Visual Evoked Potential (VEP) test.[9]

As far as treatment aspect is considered, APS is recognized as a severe but potentially treatable condition, considering also the neurological complications. However, no standard treatment is available yet for the aPL-associated neurologic manifestations not included in the APS classification criteria, and the effects of immunosuppressive and anti-inflammatory agents, usually used in MS, is unknown in these patients.[10] Despite MS being an incurable neuroinflammatory and neurodegenerative disease, a prompt and adequate treatment, focused on control of MS relapses, partially ameliorates accumulation of physical and neurological disability in the long-term. The presence of aPL antibodies in MS may herald a misdiagnosis of APS or the co-existence with APS, implying the establishment of anticoagulant therapy and the improvement of the prognosis for the individual patient.

END NOTE

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