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Case Report

Transverse myelitis: a complication of systemic lupus erythematosus that is associated with the antiphospholipid syndrome

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We report a case of a patient with Systemic Lupus Erythematosus (SLE) complicated by the antiphospholipid syndrome and recurrent episodes of transverse myelitis. Transverse myelitis is a rare complication of SLE and most cases are associated with the presence of an antiphospholipid antibody (APA). The pathogenic mechanism of transverse myelitis in this condition may result from a vasculitic process. However, the association with an APA suggests a thrombotic causation, hence consideration should be given to anticoagulant therapy in addition to established immunosuppressive treatment. This case also illustrates the value of recently developed enzyme linked immunosorbent assays for measuring anticardiolipin antibodies over previous methods available in Belfast particularly those employing the VDRL cardiolipin as antigen.

CASE REPORT. A 58 year old Caucasian woman presented to the Rheumatology Unit with a 3 day history of progressive weakness and numbness in her legs, vague lower back pain and urinary incontinence. A diagnosis of systemic lupus erythematosus (SLE) had been made twelve years previously on the basis of arthritis, pleurisy, a "butterfly" facial rash and a positive antinuclear antibody. She described three similar episodes requiring hospital admission during the previous three years. On each occasion she had received oral corticosteroids, with gradual, albeit incomplete, improvement in her clinical condition. Examination showed severe weakness of the left lower limb and moderate weakness on the right in a pyramidal pattern. There was a sensory level to pinprick sensation below T8 on the right side and impaired posterior column sensation on the left. Deep tendon reflexes were increased in the lower limbs with bilateral extensor plantar responses. The cranial nerves and upper limbs were normal. These signs suggested an incomplete spinal cord lesion in the region of T8.

Initial investigations were as follows:

ESR 45mm/hr (Westergren); Full blood picture normal; C-reactive protein (CRP) 6mg/1 (normal range < 1 Omg/l); Renal function normal; Antinuclear antibody IgG 160, IgM 80; antinucleolar antibody IgG 320, IgM negative; antibody to double stranded DNA 6.6 (normal range 0-Smg/l); antibodies to Ro, La and Sm were all positive; pANCA 80, anti-myeloperoxidase antibodies negative; immunoglobulins, C3, C4 and CH50 were all within the normal range with no circulating immune complexes detected. Antibody to anticardiolipin (VDRL Antigen) was negative on repeated testing. The ELISA test for anticardiolipin (aCL) was, retrospectively performed on 7 serum samples stored during the previous 2 years, with aCL IgG elevated on 2 of these occasions at levels of 24.2 and 32.7 GPL units/mL (normal range < 23) and aCL IgM elevated on one occasion at a level of 13.5 MPL units/mL (normal range <11). Visual and sensory

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evoked responses were all normal. Magnetic resonance imaging (MRI) of the dorsal spine and brain showedno spinal abnormalitybutmultifocal cerebral infarctions were reported as being suggestive of vasculitis. Cerebrospinal fluid examination revealed only amoderately increased protein level (0.64mg/1) with remaining parameters being normal. CT myelogram performed during a previous hospital admission was normal. Echocardiogram showed no evidence of endocarditis. A diagnosis of recurrent transverse myelitis complicating SLE was made and treatment was commenced with pulsed intravenous cyclophosphamide (350mg) and methylprednisolone (SOOmg) on every sixth day. Her subsequent inpatient course was complicated by recurrent urinary tract infections, necessitating a change in her immunosuppressive regime from cyclophosphamide to methotrexate. There was little improvement in her condition on either drug and a course of intravenous immunoglobulin was therefore introduced with some benefit. Prior to discharge she was commenced on maintenance oral therapy with cyclophosphamide lOOmg/day and prednisolone 15mg/day.

Nine weeks from her initial presentation she developed a deep venous thrombosis in her left leg despite routine heparin prophylaxis of 12,500 IU given daily by subcutaneous injection, following which she was commenced on long term warfarin therapy maintaining the international normalised ratio (INR) at a level greater than 3.0. Eleven months after initial presentation to our unit she had grade 3/5 power of the right hip flexors and grade 4/5 power on the left. She continued to have regular outpatient physiotherapy.

DISCUSSION

Neuropsychiatric manifestations of SLE occur in up to 50% of patients, ranking only second to renal complications as the leading cause of death in SLE.[1] Transverse myelitis is uncommon, occurring in less than 1% of patients and is generally associated with a poor prognosis.[2] The myelopathy usually presents acutely with paraethesia in the legs, ascending to the thorax within 24-48 hours. Other consistent features include paraplegia, back pain and loss of sphincter control.[3] In SLE the occurrence of transverse myelitis is strongly associated with the presence of elevated levels of antiphospholipid antibody (APA). In one large study 12 patients with SLE found to have transverse myelitis were all positive for anticardiolipin antibody.[4] It is of note that patients with the clinically similar Jamaican myelopathy frequently have chronic false positive tests for syphilis.[5] The diagnosis of transverse myelitis was initially made on clinical grounds aided by serological tests and imaging modalities primarily aimed at excluding other pathology. The value of CSF examination is controversial but abnormalities reported include elevated protein, pleocytosis, low C4, low glucose, altered immunoglobulin concentration and immune complexes.[6] MRI is the procedure of choice for detecting lesions of the spinal cord and several case reports have shown abnormal signals at the level of the patients' tranverse myelitis. This suggests it may have an additional role in the diagnosis of transverse myelitis and in monitoring the response to treatment.[2,7]

The antiphospholipid syndrome (APS) was initially described in SLE patients as a triad of venous or arterial thrombosis, recurrent foetal loss and thrombocytopenia associated with the presence of an antiphospholipid antibody[8] (Table 1). Since the original description further clinical manifestations have been found to correlate with elevated antiphospholipid antibody levels in SLE [9] (Table 2). It has also become clear that 'primary' antiphospholipid syndrome can also occur in the absence of clinical or serological evidence of SLE.[10]

There are three main ways of detecting APA in serum or plasma.[11] The first consists of serological tests used in the diagnosis of syphilis, as the antigenic material used in the VDRL test contains the anionic phospholipid cardiolipin. This performs poorly in screening for APS and was negative on several occasions in our patient. The second is the lupus anticoagulant test (LA) which is detected as a paradoxical prolongation of the partial thromboplastin time that cannot be corrected by the addition of normal human plasma in vitro. It has been shown to be mediated by antibodies which bind to anionic phospholipids.

The LA test was not determined in our patient as prophylactic heparin had been commenced from the time of admission and the test would therefore have been invalid. Finally, an enzyme linked immunosorbent assay (ELISA) has been developed to measure anticardiolipin antibody levels (aCL) directed against the cardiolipin diphosphatidyl glycerol from calf heart. This has

TABLE 1

Original Diagnostic Criteria For The Antiphospholipid Syndrome (after GRV Hughes et al Reference 8)

Clinical Features	*Laboratory*
Venous thrombosis	1gG aCL (elevated levels)
Arterial thrombosis	1gM aCL (elevated levels)
Recurrent foetal loss	Positive LA test
Thrombocytopenia	

Patients with the syndrome required at least one clinical plus one laboratory finding during their disease. The laboratory test must be positive on at least two occasions.

several benefits in that it can be used on banked frozen sera, anticoagulants do not affect results and identification and quantification of different aCL isotypes is possible. The ELISA is more sensitive at detecting aCL, thus manyregard it as the most clinically useful screening test. However, the LA test appears to be more specific for predicting clinical features other than transverse myelitis which has not been formally tested. Unfortunately, the ELISA test was not available in Belfast during this patient' s initial presentation and the elevated aCL was detected on banked frozen sera 2 years later. Sera from 94 healthy blood donors have been tested by the Sigma immunoassay currently used in Belfast; the mean + 2 SD (standard deviation) values obtained were 12 + 10.6 GPL units/mL for IgG and 5 + 5.6 MPL units/mL for IgM. The frequency of aCL positivity in SLE patients ranges from 17-61%.[11] In a series of 95 Irish patients it was found to be 44%.[12]

The pathogenic mechanisms underlying transverse myelitis are unknown, although vasculitis and ischaemia have been described at postmortemexamination.[6,13] The almost universal finding of antiphospholipid antibodies in such patients can be interpreted in different ways; for instance APA might simply result from inflammatory vascular damage. There is, however, good evidence that they contribute directly to a procoagulant state[5] so that vascular occlusive myelitis secondary to thrombosis must be considered. Finally direct interaction between APA and spinal cord phospholipids in the presence of a co-factor, a B-2 glycoprotein I has been postulated.[5, 14] In our patient, vasculitis should not be assumed on the basis of the cerebral MRI findings, since similar appearances have been reported in primary APA syndrome[9] and in addition she had no clinical features to suggest widespread lupus vasculitis.

The treatment regimes available include high dose steroids and immunosuppressive agents, which suppress the autoimmune response and inflammation involved in the vasculitic process. The value of isolated cases reported as showing improvement with plasma exchange and hydroxychloroquine have yet to be validated. In summary, this case emphasises the need to test for antiphospholipid antibodies, ideally by all three methods, in all patients presenting with transverse myelitis whether known to have SLE or not. As antibody levels vary with time and disease activity repeated measurements are advised.[9] While consensus has yet to be reached on some aspects of treatment in the APS it is accepted that those individuals with elevated APA and a history of previous thrombosis require long term anticoagulation with warfarin.[14, 15] Recent evidence suggests that maintenance of the INR at greater than 3.0 is required for secondary prevention of thrombosis in this condition.[16]

While continuation of traditional treatment regimes for transverse myelitis are appropriate the presence of an elevated APA should alert the clinician to the possible thrombotic mechanism, and the need for the prompt initiation of adequate anticoagulation.

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TABLE II

Clinical Manifestations in SLE and Anticardiolipin Status. (after Alarcon-Segovia et al Reference 9)

Clinical manifestation	*Number of patients with*	*% with positive aCL*
Liovedo reticularis	162	62
Thrombocytopenia	88	66
Recurrent foetal loss	43	60
Venous thrombosis	36	83
Haemolytic anaemia	25	72
Arterial occlusion	16	62
Leg ulcer	15	87
Pulmonary hypertension	5	80
Transverse myelitis	4	100

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