CONNECTIVE TISSUE DISEASE MIMICKING MULTIPLE SCLEROSIS

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Abstract:
Systemic lupus erythematosus, primary Sjögren's syndrome and systemic sclerosis may be associated with acute transverse myelitis and chronic relapsing neurological syndromes mimicking multiple sclerosis in the same individuals and/or their relatives. We now present three cases which suggest that there is a wide spectrum of connective tissue disorders mimicking multiple sclerosis and acute disseminated encephalomyelitis. These cases demonstrate that the diagnosis of multiple sclerosis should be kept under constant review by searching for the development of connective tissue disorders in the patients or their relatives. (Aust NZ J Med 1989; 19: 469-472.)

Key words: Multiple sclerosis, systemic lupus erythematosus, Sjögren's syndrome, connective tissue disease.

Clinical syndromes mimicking multiple sclerosis, a primary demyelinating disease of the central nervous system (CNS), have been reported to occur in association with several connective tissue diseases, namely systemic lupus erythematosus (SLE),[1] primary Sjögren's syndrome,[2] and rarely systemic sclerosis.[3] There have also been occasional reports of the occurrence of multiple sclerosis in first degree relatives of patients with SLE[4,5] or systemic sclerosis.[3,6] In addition to causing a chronic relapsing CNS disease mimicking multiple sclerosis, SLE may present with an acute monophasic CNS disorder such as acute transverse myelitis.[7] Here we report the cases of two women, diagnosed as having multiple sclerosis, who were later found to have connective tissue disorders. We also report one patient with SLE who presented with a clinical syndrome mimicking acute disseminated encephalomyelitis, a primary demyelinating disease of the CNS. These cases illustrate the overlap between the clinical features of connective tissue diseases and primary demyelinating diseases of the CNS.

CASE REPORTS

Case 1

A 51-year-old woman presented in January 1987 with weakness in the legs, unsteadiness of gait, tingling of both lower limbs extending up to the waist level on the trunk, and blurring of vision in the right eye with pain on eye movement. Her neurological problems had commenced in 1964 when she developed transverse myelitis followed two weeks later by right optic neuritis. She was treated with ACTH and made a good recovery. In the 1960s she also had six first trimester miscarriages, recurrent polyarthritis and grittiness of the eyes. The LE cell preparation was found to be positive. A diagnosis of SLE was made in 1969 and she was treated with corticosteroids. In 1970 she experienced an episode of left leg weakness which improved after an increase in the dose of corticosteroids. She developed left optic neuritis in 1973 and right optic neuritis in 1974. On each occasion improvement occurred after increasing the dose of corticosteroids. In 1975 she developed tingling in the right leg spreading up to the right waist followed several days later by a bilateral shingles rash and pain at waist level. These symptoms resolved over several weeks. In 1979 she experienced recurrent transient episodes of a burning right facial pain precipitated by touching the face or by a breeze blowing on the face. The episodes ceased after the corticosteroid dose was increased. In 1983 the anti-double-stranded-DNA antibody level was 63 units (normal <20). In 1984 she developed numbness in the right leg and right trunk to waist level several days after a fall. The corticosteroid dose was increased, and the numbness resolved over several weeks. She also had an episode of right optic neuritis in 1984. In January 1987 she developed a urinary tract infection followed several days later by weakness in both legs, unsteadiness of gait, tingling of both lower limbs extending up to waist level on the trunk, blurring of vision in the right eye and pain on right eye movement. Her sister has a history of arthritis, anosmia, ageusia, dry eyes and sensory disturbance in the lower limbs. Her mother had arthritis, dry eyes and recurrent miscarriages.

On examination at the time of admission in January 1987 the visual acuity was 6/6 in each eye. Colour vision testing with

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Ishihara plates was normal in each eye. She had a right afferent pupillary defect and the right optic disc was pale. The cranial nerves were otherwise normal. Examination of the upper limbs was normal. She had a paraparesis with normal deep tendon reflexes and extensor plantar responses. Light touch sensation was reduced below the T9 level bilaterally and vibration sense was reduced in the lower limbs. During the first 48 hours after admission the visual acuity in the right eye declined to 6/9 and colour vision was severely reduced to the extent that with the right eye she correctly read only the first of the Ishihara plates. Schirmer's test was positive in the left eye (4 mm at 5 minutes) and borderline in the right eye (8 mm at 5 minutes). A rose bengal dye test was negative. The antinuclear antibody (ANA) titre was 1:2560 and the anti-double-stranded-DNA antibody level was at the upper limit of normal at 19 units. The level of anticardiolipin antibodies was not assessed at the time of admission but ten months later was 15 units (normal <25). Cerebrospinal fluid studies, including electrophoresis, were normal. Biopsy of the minor salivary glands was normal. The P100 latency of the visual evoked potential was prolonged for the right eye (138 ms) and normal for the left eye (110 ms). Peripheral nerve conduction studies were normal.

Her daily oral dose of prednisone was increased from 20 mg to 60 mg and her vision and gait gradually improved. The prednisone was gradually reduced to a maintenance level of 25 mg on alternate days. The clinical and laboratory features of this case and of the subsequent ones are summarised in Table 1.

TABLE 1
Clinical and Laboratory Features in Three Patients with Central Nervous System and Connective Tissue Disease

Case	Myelopathy	Optic neuropathy	Facial sensory disturbance	Course of neurological illness	Symptoms of Sjögren's syndrome	Other clinical features of connective tissue disease	First trimester miscarriages	Highest ANA titre	Highest anti-double-stranded-DNA antibody level (units) (normal <20)	Anti-cardiolipin titre (units) (normal <25)	Family history
1	+	+	Facial pain	Chronic relapsing	+	Polyarthritis	6	1:2560	63	15	Sister with arthritis, anosmia, ageusia, dry eyes and sensory disturbance in lower limbs. Mother with arthritis, dry eyes and recurrent miscarriages.
2	+	+	Facial numbness	Chronic relapsing	+ Punctate keratitis	Polyarthritis Malar rash Photosensitivity Raynaud's phenomenon Pleuritic pain Oral ulcers	13	1:40	21	Not tested	Sister, mother, mother's brother with similar symptoms. Daughter with polyarthritis and photosensitivity.
3	+	–	Facial sensory loss	Acute monophasic	–	Polyarthritis Alopecia Malar rash	5	1:640	23	>100	—

Case 2

A 39-year-old woman was referred for assessment in March 1986. She had a history of recurrent polyarthritis, photosensitivity, pleuritic chest pain, and erythematous rashes (on the face, arms and trunk) beginning in childhood. Her neurological problems commenced in 1961 when she developed weakness in the legs lasting for three months. In 1966 she had an episode of paralysis of the left upper limb lasting for six weeks. At about this time she began to experience xerophthalmia, xerostomia and recurrent parotid gland enlargement. From 1966 onwards she experienced recurrent episodes of numbness in the territory of the third division of the left or right trigeminal nerve. The episodes occurred about twice each year and lasted 1-2 weeks. Since 1966 she also had had recurrent episodes of blurring of vision in the left or right eye associated with pain in the respective eye. On some occasions both eyes had been affected simultaneously. Each episode lasted about one month. She also experienced episodes of transient flashes of a red colour in either eye (not precipitated by eye movement) and episodes of severe painful spasms in the buttocks and lower limbs associated with weakness and numbness in the lower limbs. The latter episodes lasted for several days on each occasion. She also experienced recurrent vertigo, diplopia, urgency incontinence of urine, Raynaud's phenomenon and oral ulceration. In 1985 ophthalmological examination revealed punctate keratitis and a poor tear film. In early adulthood she had 13 first trimester miscarriages. She also had food allergy managed with an elimination diet and had the carcinoid syndrome treated successfully with cyproheptadine. Her sister, mother and mother's brother experienced symptoms similar to hers. She has a 16-year-old daughter with polyarthritis and photosensitivity.

On examination in 1986 the visual acuity was 6/12 in the left eye and 6/18 in the right eye. There were no scotomata but there was a bitemporal lower quadrantic restriction of her visual fields. The optic discs were normal. Pain sensation was absent over the entire face and scalp but the corneal reflexes were intact. The cranial nerves were otherwise normal. Power was normal in the upper limbs but reduced in the hip flexors. There was ataxia of both upper and lower limbs. The deep tendon reflexes were

normal in the upper limbs. The knee jerks and right ankle jerk were depressed while the left ankle jerk was increased. The plantar responses were extensor. Light touch sensation was normal on the trunk and limbs but pain sensation was absent in all dermatomes except T1-T3 and T9 bilaterally. Joint position sense and vibration sense were normal in the upper limbs. Vibration sense was reduced in the lower limbs and joint position sense was severely impaired in the toes bilaterally. Two point discrimination was reduced in the digits of both hands. She had a positive Romberg's sign and was ataxic on tandem gait.

Anti-nuclear antibodies were not elevated and the anti-double-stranded-DNA antibody level was 18 units. Antibodies to extractable nuclear antigens (including SSA and SSB) were not detected. Cerebrospinal fluid examination, including electrophoresis, was normal. The visual evoked potentials were normal (P100 latency 105 ms for each eye). Peripheral nerve conduction studies were normal. She was treated with a maintenance oral dose of 18 mg prednisolone on alternate days.

Case 3

A 21-year-old woman developed bloody diarrhea followed one week later by fever, myalgia, lethargy, vomiting, diplopia and weakness of the lower limbs in August 1987. She had a history of five first trimester miscarriages in the previous four years. On specific questioning it was determined that she had a five year history of recurrent arthritis affecting the hands, knees and ankles and experienced excessive hair loss from the scalp. She was admitted to her local hospital and found to have bilateral lateral rectus palsies, paralysis of the left lower limb, severe weakness of the right lower limb and a sensory level at L2. There was tenderness over both shoulders, the left wrist and the right first and second proximal interphalangeal joints and left first proximal interphalangeal joint of the hands. A malar rash was present. A myelogram was normal. The ESR was 112 mm/h and the ANA titre was elevated (1:640) with a homogeneous pattern. A CT head scan was normal. Cerebrospinal fluid examination revealed 1 leukocyte/cmm and a protein of 0.81 g/l. Over the next few days she developed difficulty swallowing, sensory impairment in the second and third divisions of both trigeminal nerves, left facial weakness, difficulty breathing, mild bilateral upper limb weakness, extensor plantar responses and incontinence of urine. She required mechanical ventilation for several days. She gradually improved but still experienced urgency incontinence of urine and faeces and required a walking stick. She was admitted to the Royal Brisbane Hospital in June 1988 for re-evaluation.

On examination the cranial nerves were normal. She had a spastic paraparesis with generalised hyperreflexia in the upper and lower limbs and extensor plantar responses. Sensory examination was normal. General physical examination was normal. The ANA titre was 1:160 with a homogeneous pattern. Anti-double-stranded-DNA antibodies were elevated (23 units). The lupus anticoagulant was present and the APTT was prolonged to 57 seconds (normal range 28-43). The anticardiolipin antibody level was >100 units. The serum C3 and C4 components of complement were normal. The ESR was 72 mm/h. Cerebrospinal fluid examination was normal. Visual evoked potentials, brainstem auditory evoked responses and a CT head scan were normal. Magnetic resonance imaging of the brain and T8-L4 spinal cord was normal. She is being treated with baclofen and aspirin.

DISCUSSION

We have reported the cases of two women with a relapsing remitting neurological disorder affecting the spinal cord and optic nerves mimicking multiple sclerosis. The first patient had had recurrent first trimester miscarriages and later developed polyarthritis and the serological features of SLE; the second developed Sjögren's syndrome and many of the clinical features of SLE without definite serological evidence of the latter. She also had multiple first trimester miscarriages. The third patient had a monophasic disorder of the spinal cord and brainstem superimposed on a history of polyarthritis and recurrent first trimester miscarriages; her neurological syndrome closely resembled that of acute disseminated encephalomyelitis but it later became clear that it was due to SLE.

In each case the neurological illness was the major medical presentation, and the original diagnosis was either multiple sclerosis (Cases 1 and 2) or acute disseminated encephalomyelitis (Case 3). Cases 1 and 2 met the positive criteria for the diagnosis of clinically definite multiple sclerosis, as they had clinical evidence of CNS white matter lesions disseminated in time and place.[8] However, the diagnosis of clinically definite multiple sclerosis also requires that there is no better explanation of the neurological condition. Initially no other cause of neurological disease was evident but it later became apparent that Cases 1 and 2 had clinical features of connective tissue disorders which could explain the neurological syndromes. Case 1 had polyarthritis, elevated anti-double-stranded-DNA antibodies and an elevated ANA titre, which together with a neurological disorder fulfil the mandatory 4 criteria required by the American Rheumatism Association (ARA) for the diagnosis of SLE; however, these criteria define a neurological disorder as either seizures or psychosis, neither of which our patient had.[9] Case 2 had prominent clinical features of Sjögren's syndrome (symptomatic xerophthalmia, keratoconjunctivitis sicca, symptomatic xerostomia and recurrent parotid gland enlargement) and also had features which met the ARA criteria for SLE (malar rash, photosensitivity, oral ulcers, arthritis and serositis) even though she did not have definite serological evidence of SLE. Because the criteria for SLE were fulfilled, her Sjögren's syndrome must be labelled as secondary rather than primary. Neurological syndromes like those of cases 1 and 2 have been reported in association with SLE[1] and primary Sjögren's syndrome.[2] Optic neuritis, which occurred in both our cases, has also been reported in patients with elevated antinuclear and/or anticardiolipin antibodies without overt clinical signs of connective tissue disease.[10] In Case 3 the association between the neurological disease and the connective tissue disease was recognised early. She had a malar rash, polyarthritis, elevated anti-double-stranded-DNA antibodies and an elevated ANA titre, which thus met the ARA criteria for a diagnosis of SLE.

All three of our patients also had recurrent miscarriages, which together with neurological disease, recurrent thrombosis and thrombocytopenia are features of the anticardiolipin syndrome.[11] This syndrome was originally described in patients with SLE but it is now known that it may also occur without SLE. None of our cases had peripheral venous thrombosis or thrombocytopenia. Anticardiolipin antibodies were elevated in Case 3; they were not tested for in Case 2 and were normal in Case 1, albeit at a clinically quiescent stage.

The two patients with the multiple sclerosis-like syndrome shared the following features: (1) myelopathy, optic neuropathy and facial numbness or pain and (2) a benign course, with a tendency for recurrence to be limited to the same regions of the nervous system and with a lack of progression. Because of the small number of patients it is not possible to determine whether these stereotyped presentations are fortuitous or whether they reflect a genuine deviation from the usual diversity and progression of multiple sclerosis. The facial pain and numbness may have been due to involvement of the trigeminal sensory pathway within the CNS; alternatively these symptoms could have been due to a trigeminal sensory neuropathy as has been reported to occur in connective tissue disorders.[12] Neither of our patients with the multiple sclerosis-like syndrome had cerebrospinal fluid abnormalities, although Alexander *et al.*,[2] found oligoclonal bands and an elevated IgG index in the cerebrospinal fluids of their patients with primary Sjögren's syndrome and CNS involvement. Magnetic resonance imaging of the brain was not performed in Cases 1 and 2, but features typical of multiple sclerosis have been reported in patients with connective tissue disease and CNS involvement.[2]

It is unknown whether the CNS disease in our patients is due to ischemia due to small vessel involvement by the connective tissue disease, thrombosis related to anticardiolipin antibodies, or primary demyelination. Primary demyelination, if it occurs, might be due to vasculitis or myelin-targeted autoimmune disease (arising from the genetic background of defective immune regulation that led to the connective tissue disorder).

In conclusion, these cases emphasise the overlap between the neurological syndromes produced by connective tissue disorders and primary demyelinating disorders. As the clinical diagnosis of multiple sclerosis requires the exclusion of other causes of a similar syndrome, this diagnosis should be constantly reviewed by searching for the development of connective tissue disorders in the patients or their relatives. Symptoms of connective tissue disease may be intermittent and easily overlooked in patients diagnosed as having multiple sclerosis. ■

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References

1. Fulford KWM, Catterall RD, Delhanty JJ, Doniach D, Kremer M. A collagen disorder of the nervous system presenting as multiple sclerosis. Brain 1972; 95: 373-86.
2. Alexander EL, Malinow K, Lejewski JE, Jerdan MS, Provost TT, Alexander GE. Primary Sjögren's syndrome with central nervous system disease mimicking multiple sclerosis. Ann Intern Med 1986; 104: 323-30.
3. Trostle DC, Helfrich D, Medsger Jr TA. Systemic sclerosis (scleroderma) and multiple sclerosis. Arthritis Rheum 1986; 29: 124-7.
4. Holmes FF, Stubbs DW, Larsen WE. Systemic lupus erythematosus and multiple sclerosis in identical twins. Arch Intern Med 1967; 119: 302-4.
5. Sloan JB, Berk MA, Gebel HM, Fretzin DF. Multiple sclerosis and systemic lupus erythematosus: occurrence in two generations of the same family. Arch Intern Med 1987; 147: 1317-20.
6. Reveille JD, Wilson RW, Provost TT, Bias WB, Arnett FC. Primary Sjögren's syndrome and other autoimmune diseases in families: prevalence and immunogenetic studies in six kindreds. Ann Intern Med 1984; 101: 748-56.
7. Al-Husaini A, Jamal GA. Myelopathy as the main presenting feature of systemic lupus erythematosus. Eur Neurol 1985; 24: 94-106.
8. Poser CM, Paty DW, Scheinberg L *et al.* New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13: 227-31.
9. Tan EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271-7.
10. Kupersmith MJ, Burde RM, Warren FA, Klingele TG, Frohman LP, Mitnick H. Autoimmune optic neuropathy: evaluation and treatment. J Neurol Neurosurg Psychiatry 1988; 51: 1381-6.
11. Hughes GRV, Harris NN, Gharavi AE. The anticardiolipin syndrome. J Rheumatol 1986; 13: 486-9.
12. Lecky BRF, Hughes RAC, Murray NMF. Trigeminal sensory neuropathy: a study of 22 cases. Brain 1987; 110: 1463-85.