LETTERS TO THE EDITOR

Progressive systemic sclerosis with CNS vasculitis and cyclosporin A therapy

Progressive systemic sclerosis is a multi-system disorder characterised by inflammatory, vascular and fibrotic changes of skin and a variety of internal organs. Most reports describing neurological complications of PSS have focused on damage to the peripheral nervous system. CNS dysfunctions are rare and are thought to result from uraemia, hypoxaemia, and severe hypertension. This is the first trial of cyclosporin A (CyA) in a patient with CNS vasculitis secondary to PSS.

A 67 year old woman was admitted with difficulty in walking and with speech. She had been in good health until December 1985, when she noted that her hands turned white in a cold environment. Subsequently, she developed a nonproductive cough. In February 1986 she experienced occasional dizziness. In July 1990 she began to walk with a waddle.

On admission, her blood pressure, pulse, body temperature, and respiration were normal. The skin of her face was so taut that she was unable to open her mouth fully; her lips were thin and shortened. She had telangiectasis on the chest. Auscultation of the chest disclosed fine crackles on the lower fields of both lungs. The skin of her fingers and hands was firm and thickened and tightly bound to underlying subcutaneous tissue. The skin changes spread from her hands to the chest. Calcinosis cutis was not found. Raynaud's phenomenon could be induced by cold stimuli.

She had dysarthria; left hemiparesis with slight rigidity and spasticity; and mild incoordination. Deep tendon reflexes were normal and pathological reflexes were absent.

The ESR, blood count, and biochemical tests, were normal. The C-reactive protein was negative; rheumatoid factor positive; antinuclear antibody present in a 1:320 dilution; anti-Scl-70 antibody (antiscleroderma antibody) was positive in a 1:16 dilution. Electrocardiogram showed first-degree atrioventricular block with a prolonged PR

interval of 0.24 second. Pulmonary function tests revealed a slightly restrictive ventilatory defect; the ratio of FEV1/FVC was 0.96 and the ratio of FVC observed/FVC predicted was 0.73. Cold water (10°C) immersion test on the skin of the hand showed a delay in regaining the initial temperature, which was compatible with Raynaud's phenomenon. CSF was normal. Radiograph of the chest showed fine fibrotic strands in the lower portions of both lungs. Barium-meal revealed a dilated oesophagus with decreased peristalsis. MRI scan of the head disclosed ischaemic lesions in the right occipital region, the right middle cerebellar peduncle, and the basilar part of the pons. Digital subtraction angiogram (DSA) showed localised severe stenosis and post-stenotic dilation, a "string of beads" appearance, from the distal end of the right vertebral to the proximal portion of the basilar arteries (fig). There was no definite stenosis in other arteries. Skin biopsy specimen showed proliferation of thickened collagen fibres in the dermis.

Based on these findings, we diagnosed PSS, following the scleroderma criteria of the American Rheumatism Association, and we attributed the abnormal angiogram findings to vasculitis. Treatment was started with CyA 8 mg/kg a day. Two months later, urinalysis disclosed an increase in urinary β_2 -microglobulin, a sign of renal damage caused by CyA. Immediately the dose was reduced to 6 mg/kg, and during the next month it was reduced by 1 mg/kg every week, to 3 mg/kg.

Though the abnormal findings of serological tests were not improved, during this period the urinary β_2 -microglobulin returned to normal. The patient's nonproductive cough subsided and Raynaud's phenomenon did not occur. The skin involvement gradually diminished, and the abnormal ECG findings and pulmonary function tests improved: PR interval, 0.20 second; FVC observed/FVC predicted ratio, 0.8. The neurological symptoms that resulted from multiple CNS infarction remained stable. Cold water immersion test showed a normal recovery to the initial temperature.

One year after the beginning of CyA treatment, the patient takes 150 mg/day (3 mg/kg/day) of CyA, her hands and fingers are still slightly firm and thick, but autoantibodies, including anti-Scl-70 antibody, have normalised, except for a positive ANA in a 1:160 dilution.

The classical "string of beads" appearance on the angiogram is characteristic of vasculitis, but may be present in infection and arteriosclerosis. There have been three reports about PSS with CNS vasculitis.¹⁻³ In all the cases the authors diagnosed PSS based on angiograms, and in Lee's report, post mortem examination disclosed mononuclear cell infiltration into the left internal carotid artery.¹

Recently, some researchers have emphasised the importance of vascular involvement in the pathogenesis of PSS, and have suggested that it was probably the initial event preceding abnormal fibrosis. Why our patient had CNS vasculitis without systemic vasculitis is unclear. We assume that there are unknown differences in antigenicity between arteries of the CNS and other organ systems.

Effective drug therapy in PSS has not been established. D-penicillamine has been reported to reduce skin thickening, but it

does not change the clinical course of PSS. Corticosteroids are considered to aggravate symptoms of PSS. Some investigators have reported that CyA was effective against PSS.^{4,5} Our first trial of CyA in PSS with CNS vasculitis appeared dramatically successful.

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Ocular myasthenia: diagnostic value of single fibre EMG in the orbicularis oculi muscle

When myasthenia gravis is restricted to ocular muscles it can present a difficult diagnosis. Firstly, the response to Tensilon iv can be negative or ambiguous; secondly, repetitive nerve stimulation and titration of serum anti-acetylcholine receptor antibodies (anti-AChR abs) often give negative results.¹ Chronic progressive external ophthalmoplegia (CPEO) must be distinguished. Single fibre electromyography (EMG) has proved the most sensitive diagnostic test in patients with myasthenia gravis.² However, increased jitter and impulse blocking can also be found in nerve and muscle diseases^{3,4} and abnormal findings have been reported in some patients with chronic progressive external ophthalmoplegia.^{5,6}

In this study, we verified the diagnostic sensitivity of single fibre EMG of the orbicularis oculi muscle in patients with ocular myasthenia gravis and its usefulness in the distinction from chronic progressive external ophthalmoplegia.

We studied 14 patients with purely ocular myasthenia and 8 patients affected with chronic progressive external ophthalmoplegia. There were 7 male and 7 female patients with myasthenia gravis, aged 13-61, mean (SD) 41.4 (18.3), with duration of disease ranging from 1-40 years, mean (SD) 7 (10.1). The diagnosis of ocular myasthenia was based on history and clinical signs together with at least one of these features: unequivocal improvement after intravenous edrophonium; presence of serum antibodies to AChR; decremental response to repetitive nerve stimulation. Thirteen patients showed fluctuating ptosis and/or diplopia, while in one case, with long-standing disease, clear fluctuations were not evident. Twelve patients improved

Figure Digital subtraction angiogram shows localised stenosis and post-stenotic dilation. There was no definite stenosis in other arteries.

considerably on the Tensilon test, six had detectable anti-AChR abs, five showed decremental pattern on RNS performed on proximal muscles (deltoid and biceps brachii). In the patient without fluctuations of clinical signs, in whom the Tensilon test was negative, the diagnosis of myasthenia gravis was confirmed by the presence of serum anti-AChR abs. Muscle biopsy performed in this patient as well in another case with no detectable anti-AChR abs, showed normal findings. All patients had a follow up period of at least two years and alternative diagnoses were excluded.

Eight patients had chronic progressive external ophthalmoplegia, 3 males and 5 females, aged 35–71, mean (SD) 56 (14.9) with duration of disease ranging from 1.5–17 years mean (SD) 5.3 (5.1). All patients had clinical weakness restricted to ocular muscles and five complained of mild fluctuations of ptosis. In this group, serum anti-AChR ab titration and repetitive nerve stimulation gave negative results, while the response to the Tensilon test was negative in four cases and equivocal (minimal improvement of ptosis) in the other four. The diagnosis of chronic progressive external ophthalmoplegia was confirmed by the presence of typical ragged red fibres on muscle biopsy in all cases.

Single fibre EMG was performed in the orbicularis oculi muscle during slight voluntary contraction. A single fibre EMG electrode (Medelec SF 25) was inserted in the inferior and lateral portion of the muscle and recordings were made on a Medelec Mistro electromyograph. For each muscle tested, 20 action potential pairs were analysed and the overall mean jitter as mean consecutive difference (MCD), the percentage of potential pairs with prolonged jitter and the percentage of potential pairs with blocking were evaluated. In agreement with other authors,⁷ we considered a jitter study pathological when either a value for mean MCD was above the 95% upper limit for age or a jitter was above the 95% upper limit for potential pairs in more than 10% of pairs. The reference values for these parameters, in different age groups, were derived from literature data.⁷

Single fibre EMG studies were performed, at least 48 hours after discontinuing therapy, on patients with myasthenia.

Results of the single fibre EMG in the orbicularis oculi muscle were pathological in 13 of 14 patients (93%) with purely ocular myasthenia gravis. Eleven patients showed abnormal mean jitter and more than 10% potential pairs had prolonged jitter (in 8 patients blocking was recorded); two patients had mean MCD below the 95% upper limit and respectively 20% and 40% potential pairs with prolonged jitter.

In all patients with chronic progressive external ophthalmoplegia, single fibre EMG studies showed values within the normal limits. The mean jitter did not exceed 25 μ sec. Only one patient had 5% of potential pairs with prolonged jitter and no blocking was recorded.

In patients with ocular myasthenia gravis, the positivity rate with single fibre EMG was higher than with the Tensilon test (86%), RNS (36%) or anti-AChR abs (43%).

Serum anti-AChR abs, which are present in more than 90% of patients with generalised myasthenia gravis, are detectable in a much lower percentage of patients with the

ocular form of the disease. Single fibre EMG has proved the most sensitive technique in detecting the neuromuscular transmission defect in ocular myasthenia gravis, especially when facial muscles are tested. The orbicularis oculi muscle shows abnormal results more often than the frontalis muscle.^{6,8} Unfortunately, single fibre EMG abnormalities can also be seen in primary neuropathic and myopathic disorders as a result of abnormal conduction of the impulse in degenerating or reinnervating nerve terminals and newly formed endplates.^{3,4} In CPEO patients, Krendel and Sanders described increased jitter and blocking in facial (frontalis) and in arm muscles⁶ and a primary defect of neuromuscular transmission has been suggested in this condition.⁵ In our study, single fibre EMG performed in the orbicularis oculi muscle revealed a neuromuscular transmission defect in 93% of patients with purely ocular myasthenia gravis and so demonstrated a diagnostic capacity significantly higher than the Tensilon test, repetitive nerve stimulation or anti-AChR ab titration. Also, in our experience, the sensitivity of single fibre EMG is higher in facial muscles, particularly in the orbicularis oculi, than in the extensor digitorum communis muscle.

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Soluble interleukin-2 Receptor levels in serum of patients with demyelinating polyneuropathy associated with monoclonal gammopathy

Monoclonal gammopathies, especially monoclonal gammopathy of uncertain significance (MGUS) with IgM M-components, are associated with demyelinating polyneuropathy (PN). In approximately 50% of these patients, the IgM M-component reacts with myelin associated glycoprotein (MAG) or other subcomponents of

myelin and a pathogenetic role of the M-component has been proposed. However, other mechanisms, besides the M-component acting as antibody, may be operating. In vitro studies have shown that monoclonal antibodies against MAG in a patient with monoclonal gammopathy were subject to T-cell regulation,¹ but the role of a T-cell mediated immune response has not been further investigated.

Interleukin-2 (IL-2), which is synthesised by antigen or mitogen activated T lymphocytes, plays an essential role in triggering T-lymphocyte proliferation, T-cell differentiation, and surface expression of IL-2 receptors (IL-2R) on T-cells. It also induces maturation and proliferation of B-lymphocytes. Surface bound IL-2 has a rapid turnover. Therefore the measurement of soluble (s) IL-2R in serum is preferable as a means to evaluate T-cell activation. Elevated serum levels of sIL-2R have been demonstrated in several autoimmune disease states, for example, multiple sclerosis², and the Guillain-Barré syndrome.³

We analysed sIL-2R levels in serum as a measure of T-cell activation in 19 patients (12 men and 7 women, age 43–85 years, mean age 68) with monoclonal gammopathy (15 with MGUS and 4 with Waldenström's macroglobulinaemia; 17 of IgM- and 2 of IgG-isotype) and demyelinating PN. Seventeen of these patients had anti-MAG and/or anti-peripheral nerve myelin (PNM) antibodies. Sera from 19 patients (13 men and 6 women, age 43–80 years, mean age 66) with monoclonal gammopathy (15 with MGUS and 4 with multiple myeloma; 13 of IgG-, 2 of IgM-, 2 of IgA-isotype, and 2 with light chain proteinuria) without PN and without antibodies against MAG or PNM, and sera from 15 healthy individuals (9 men and 6 women, age 47–80 years, mean age 66) without monoclonal gammopathy served as controls. Antibodies against MAG and PNM were analysed by enzyme linked immunosorbent assays (ELISA) essentially as described previously.^{3,4} In 15 patients with monoclonal gammopathy and PN, 2 serum samples or more were obtained during or shortly after tapering off the immunosuppressive treatment. Serum samples were stored at –70°C, and thawed only once. Serum sIL-2R levels were measured using a commercial ELISA kit (Cellfree, T Cell Diagnostics, Inc, Cambridge, MA) according to instructions from the manufacturer. Values exceeding the mean value +2SD (> 919 U/ml) of 50 blood donors were considered pathological (manufacturers information).

Seven of 19 patients with M-component associated PN had increased sIL-2R levels in the first serum sample, compared with 2 of 19 M-component patients without PN ($p = 0.06$ according to Fisher's exact test, one-tail) and 1 of 15 healthy controls ($p < 0.05$ according to Fisher's exact test, one-tail) (fig). At the time of the sample 4 patients with M-component associated PN and 4 M-component patients without PN were receiving immunosuppressive treatment. One of 4 treated patients with M-component associated PN had elevated serum sIL-2R levels and 6 of 15 untreated patients had elevated serum sIL-2R levels.

In 15 patients with M-component associated PN, subsequent serum samples were taken during or shortly after tapering off the immunosuppressive treatment. Seven of