A Novel Presentation of Multiple Cranial Neuropathies in Systemic Sclerosis

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Neurological manifestations of systemic sclerosis are rare. Here we present a case of a 45-year-old woman who presented with sequential cranial neuropathies due to vasculitis associated with systemic sclerosis. This case is novel because ophthalmoplegia in systemic sclerosis is unreported. The various neurological manifestations of systemic sclerosis and the rationale for therapy are discussed.

Case report

In December 2009, a 45-year-old woman with a five-year history of anti-Scl-70 positive limited systemic sclerosis developed headaches and then diplopia during a course of iloprost in an attempt to rescue a necrotic digit on her left hand. Over the preceding three months she had lost weight, was constitutionally unwell and had received two successful courses of iloprost for blue discolouration of a digit. This time her digit had become necrotic, and she received iloprost again. On the day of her second dose she developed a gradual onset right sided headache and photophobia, and after a few hours, diplopia. Despite the infusion being terminated, symptoms persisted and by day three she noticed ptosis and examination revealed a complete third and a partial sixth nerve palsy. Involvement of the pupil was not documented. By day seven she had developed slurred speech and felt unsteady. Examination now revealed a left twelfth nerve palsy and dysarthria, with no other neurological signs. The patient was apyrexial throughout, had ankle oedema, but a normal jugular venous pressure.

Her prior disease manifestations included scleroderma, Raynaud's phenomenon, mild pulmonary fibrosis, pulmonary hypertension, treated with nifedipine, and joint pain. She also suffered from hypertension and asthma. She took nifedipine, clopidogrel, seretide, strontium, lansoprazole, candesartan, dosulepin, folic acid, gabapentin, and morphine sulphate tablets. She had never smoked, and had a brother with ulcerative colitis.

The differential diagnosis for rapid sequential cranial neuropathies in this setting includes vasculitis, sarcoid, forms of acute inflammatory demyelinating polyneuropathy, malignant meningitis, and infection.

MR brain venography and then repeat MR with diffusion weighted, FLAIR and contrast images revealed no evidence of infarct, thrombosis or space occupying lesion. CSF was acellular with raised protein, 1.33g/L(<0.4g/L), 4.63mmol/L glucose (no paired sample taken), normal cytology, negative bacterial culture, and negative PCR for enterovirus, herpes-simplex and varicella-zoster viruses. MR angiography of her thoracic aorta, left subclavian and axillary artery was normal. A CT of chest, abdomen and pelvis showed no malignancy. Carotid doppler studies showed no significant stenosis. Blood tests showed a CRP of 16mg/L (<10mg/L) on day 1 and ESR of 120mm/h (3-9mm/hr) on day 11, ANA raised at 5.3 U (0-0.9), Scl-70 (topoisomerase I) positive. There was a mildly positive CMV IgM of 66 iu/ml (0-20 iu/ml), and slightly reduced Protein S at 49 u/dL (>63), both of which were probably insignificant. ANCA, FBC, including eosinophils, anti-cardiolipin IgG and IgM, complement, cryoglobulins, Hu, Yo, Ri antibodies, immunoglobulins and protein electrophoresis, B12, protein C, AT/hep ratio, APC sensitivity ratio, DRVVT, silica clotting time, factor V Leiden, Factor II (G20210A), hepatitis A, B and C serology, and urine dipstick were normal or negative. Transthoracic echocardiogram revealed mild left ventricular hypertrophy. Pulmonary function tests showed FEV1 2.49 (110%), TLC 4.62 (107%), FVC 2.92 (110%), TLCO 71.5% (81% in September 2008).

Without evidence of active infection or malignancy, the presence of an acute-phase response with connective tissue disease suggested a probable small vessel vasculitis of the cranial nerves secondary to systemic sclerosis as the diagnosis. There was no affected nerve available to biopsy safely. The patient was treated with three pulses of 1g methylprednisolone, and oral prednisolone taper, followed by ten pulses of intravenous 15mg/kg cyclophosphamide over six months, and azathioprine. She also received therapeutic enoxaparin for the two weeks of her admission, and then maintained with dual anti-platelet therapy: aspirin and clopidogrel. Her symptoms rapidly improved and at six months review she had no symptoms or signs. The improvement with steroids made other differential diagnoses including malignancy much less likely. At one year follow up she remains well on prednisolone 15mg od and azathioprine 50mg od. She had developed some sensory symptoms in her hands but nerve conduction studies and EMG at 14 months were normal.

Discussion:

The main differential diagnosis in our patient was a malignant or infective meningitis, and a limitation of our case was the lack of histology. Obtaining a relevant tissue sample in our patient was judged to be too risky, and she started to improve shortly after immunosuppressive therapy was started, supporting the diagnosis of vasculitis.

Systemic sclerosis is rare with an incidence of 2-23 per million persons per year (F:M 3-14:1). There are limited and diffuse (rapidly progressive) forms.[1] These forms are distinct from localised craniofacial scleroderma (morphea) which is associated with linear scleroderma en coup de sabre, manifesting with seizures and/or progressive hemiatrophy.[2] The pathology of systemic sclerosis is one of early microvascular damage, mononuclear-cell infiltrates, and slowly developing fibrosis.[1] Systemic sclerosis has well described central and peripheral neurological complications, which are rare. Cerebrovascular disease occurs and can usually be attributable to cardiac, renal disease or carotid stenosis rather than a CNS vasculitis. Cranial neuropathy associated with systemic sclerosis is rare. When seen, it is usually insidious and causes a trigeminal neuropathy.[3] Reports of other cranial nerves being affected are scarce but can be found in the case series by Teasdall et al (1980) which reported 10 patients with insidious trigeminal neuropathy. Some of these patients had multiple-cranial nerve palsies: facial nerve (five patients), chorda tympani (two patients), vestibulochochlear nerve, (two patients), glossopharyngeal nerve (one patient) and, like our patient, hypoglossal nerve (one patient).[4] A sub-clinical sensory axonal peripheral neuropathy has also been reported by Schady et al in up to 50% of 29 systemic sclerosis patients. Subsequently, it has been proposed that the progressive microangiopathy and a direct effect of fibrosis might affect the vasa-nervorum and account for these findings.[3]

There are no good randomised controlled trials of immunotherapy in vasculitic neuropathy of any type, though some retrospective evidence of early relapse in patients treated with steroids alone compared to those treated with cyclophosphamide.[5-7] In ANCA-associated vasculitis involving the kidneys there is evidence that azathioprine is as effective as cyclophosphamide for remission maintenance.[8] Cyclophosphamide has modest effect on scleroderma lung disease compared to placebo in one RCT.[9]

In conclusion, though rare, vasculitis is a complication of systemic sclerosis and should be considered early in such presentations. Aggressive and early immunotherapy can mitigate the course of the disease and minimise damage. ◆

Key Points:

- Systemic sclerosis can cause a small vessel vasculitis of the cranial nerves, though mimics of this such as malignancy and infection should be sought and reasonably excluded prior to aggressive immunotherapy.
- Early recognition of cranial nerve vasculitis can mitigate the course of the disease and minimise damage.

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