LETTERS TO THE EDITOR

Retrospective diagnosis of fatal herpes simplex myelitis by immunocytochemistry and polymerase chain reaction

There have been few reports of herpes simplex producing a myelopathy. This may stem from difficulty in identifying the virus responsible for an acute myelitis. With the polymerase chain reaction, it is possible to selectively amplify small amounts of viral DNA within a CSF sample and thus identify the viral genome. This method has recently been used to identify cases of herpes simplex encephalitis from samples taken early during the course of the infection.

To our knowledge, this is the first reported case of herpes simplex myelitis identified at postmortem using this technique.

A 38 year old woman presented to the neurology unit with proximal muscle weakness in the upper limbs. She had mild learning difficulties and had delayed motor milestones after birth hypoxia. Six months earlier she was found to have maturity onset diabetes mellitus, which was controlled by diet alone. This was followed by a mild exogenous depression that was treated with a tricyclic antidepressant with some benefit.

Two weeks before admission, her mother had noticed weakness around the patient’s shoulders, which had developed acutely. There were no features of sensory disturbance. Lower limb and bladder function were normal. General medical examination was unremarkable and the only abnormality in the cranial nerves was horizontal gaze evoked nystagmus. There was pronounced bilateral wasting and weakness (MRC grade 2) of all muscle groups about the shoulders and arms. Forearm and intrinsic hand muscles were weak (grade 4) but not wasted. All upper limb reflexes were normal. Deep tendon reflexes all were absent despite reinforcement. In view of her mental subnormality, it was impossible to test sensation and coordination. Tone, power, and reflexes were normal in the lower limbs and the plantar responses were flexor. Over the next three weeks, power in the upper limbs continued to deteriorate and weakness developed in her legs. Examination then showed grade 1 weakness of proximal upper limb musculature, grade 4 bilateral weakness of hip flexion, abnormally brisk lower limb reflexes, and flexor plantar responses.

Haematological and biochemical analysis were normal, including creatine kinase and thyroid function tests. A random blood sugar was 8.2 mmol l⁻¹. Electromyography of the left supraspinatus, biceps, deltoid, and triceps showed severe denervation. Distal motor and sensory nerve conduction studies were normal in the upper limbs but latencies from Erb’s point to the supraspinatus, biceps, and triceps were minimally prolonged in keeping with anterior horn cell loss. Latencies of F waves were prolonged in both ulnar nerves. Motor and sensory nerve conduction velocities were reduced in the lower limbs in keeping with a mild diabetic neuropathy. Myelography demonstrated a normal spinal cord enlargement in the cervical region and no evidence of an extrinsic compressive lesion. The procedure was difficult to perform in view of her poor cooperation so CSF was not available. Eight days later, while awaiting cerebral MRI, she had a respiratory arrest and died despite resuscitative measures.

Postmortem examination showed a localised myelitis between C2 and T1 involving both the grey and white matter. This consisted of perivascular lymphocytic cuffing, neuronal loss, and astrocytosis in the ventral and dorsal horns. Myelin swelling, foamy macrophages, and gliosis occurred in the dorsal columns. Foci of haemorrhage were seen in the dorsal horn and columns. Lymphocytic infiltration was present in the meninges, dorsal and ventral roots, and the brachial plexus. Immunoperoxidase staining with a standard indirect method for herpes simplex virus type 1 antibody (polyclonal; Dako Co) showed positive staining of some endothelial cells, glia, and neurons (fig 1). As well as these changes of myelitis there was bilateral hippocampal scarring consistent with perinatal hypoxia, along with recent diffuse hypoxia secondary to the respiratory arrest.

For the polymerase chain reaction on spinal cord (C4 level) DNA was extracted from 10 × 5 mm paraffin sections by incubation in an SDS digestion buffer containing proteinase K at 37°C for five days followed by phenol–chloroform extraction and ethanol precipitation as described previously. Extracted DNA (6 ng) was amplified by nested polymerase chain reaction with primer sequences selected from the glycoprotein D gene of herpes simplex virus type 1. The DNA was amplified in a 50 μl reaction mixture containing 50 pmol of each outer primer, HSV 1-1 and HSV 1-2; 10 mM Tris HCl (pH 9.0); 50 mM KCl; 2 mM MgCl₂; 0.1% Triton-X100; 200 μM each dNTP and 1/5 units of SuperTaq Tag DNA polymerase (HT Biotechnology, Cambridge). Amplification was carried out at 94°C for five minutes, 55°C for 30 seconds and 72°C for one minute for one cycle followed by 94°C for one minute, 55°C for 30 seconds, and 72°C for one minute for 24 cycles with an MJ Research programmable thermal cycler (Genetic Research Instrumentation Ltd, Essex). One μl of this reaction product was added to a second reaction mixture as described but containing 50 pmol of each inner primer HSV 1-3 and HSV 1-4 and the reaction mixture was subjected to the same thermal cycling as described. The amplified product was analysed by electrophoresis on a 2% agarose gel stained with ethidium bromide. The presence of a 137 bp product indicated successful amplification of HSV (fig 2).

There are few reported cases of herpes simplex myelitis in the literature. Most present with a fatal ascending myelopathy, although the availability of necropsy data may have led to reporting bias towards more severe cases. The thoracolumbar region of the spinal cord was primarily affected in most cases in the initial stages of the illness. The striking flaccid upper limb weakness in the present patient is unusual. Rapid progression occurs over a matter of days until large areas of the cord and eventually the respiratory centres are involved. Herpes simplex virus myelitis has been fatal in most of the reported cases, although recovery has occurred in patients treated with intravenous acyclovir.

The histological changes within the spinal cord in this case were surprisingly localised between C2 and T1 but otherwise the appearances were comparable with previous reports of herpes simplex virus myelitis. The finding of herpes simplex virus antigen within the cord along with viral DNA strongly suggests that this was the responsible agent rather than a dormant virus from a previous infection.

The route of entry of herpes simplex virus is unknown in the present patient. Recent genital herpes has preceded myelitis.

Figure 1 Neurons (straight arrows), endothelial cell (curved arrows), and glia (arrowheads) showing immunostaining for HSV 1 (Immunoperoxidase, originally × 377).

Figure 2 Agarose gel stained with ethidium bromide. Lane 1 shows 132 bp ladder (size reference standard). Lane 5 is a positive control (known herpes simplex encephalitis). Lane 6 is a negative control. Lane 2 is test sample showing positive bands of expected size for herpes simplex virus type 1.
in several other cases. It has been suggested that dormant herpes simplex virus in the dorsal root ganglia is reactivated when the patient becomes immunocompromised. Thus the condition has been described in patients with AIDS. In the present case, the acquired immune deficiency syndrome, and various malignancies. It is conceivable that cases of "idiopathic" transverse myelitis are caused by herpes simplex virus and that current tissue culture, electron microscopic, and immunological techniques, if performed, are unable to detect it. The advent of the polymerase chain reaction has simplified and speeded up the diagnosis of herpes simplex virus encephalitis in those centres where the technique is available. The technique should now be extended to those patients with an undiagnosed rapidly progressive cord syndrome in the hope that early diagnosis and treatment with acyclovir will carry a better prognosis.

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We report a young, acutely ill woman with the neuropsychiatric manifestations of Wilson's disease in whom zinc sulphate was apparently used successfully as a "decoppering" agent. This 27 year old patient noticed intermittent dysarthria, muscle cramps with intermit- ment weakness, and easy bruising at the age of 23. Over the next two years she developed increasing dysarthria, unsteadiness of her legs, headaches, nightmares, and weight gain from 75 to 99 kg.

General examination was normal. Neurological examination showed loss of smooth pursuit, a spastic tongue, postural tremor of the upper limb, incoordination of the arms and legs, an extensor plantar response, and abnormal tandem gait. Slit-lamp examination confirmed dense Kayser-Fleischer rings.

Neuropsychological evaluation showed borderline intelligence, impaired delayed recall of both verbal and visual material, and impaired cognitive flexibility.

Laboratory investigations showed thrombocytopenia (platelets 89 x 109/l; normal: 164-432). The liver enzymes, urea, and electrolytes were normal. Serum copper concentration was 4 µmol/l (N: 12-25), as in the previous investigations, and serum ceruloplasmin concentration 0-05 g/l (0-15-0-6), and urinary copper excretion 3-5 µmol/24 h (N: 0-24-0-79). A serological screen for connective tissue disease including the anti-DNA antibodies was negative.

Magnetic resonance imaging of the brain was performed on a 0-5 Tesla scanner with spin echo sequences. The first study showed increased signal intensity lesions on the T2 weighted images (T2WI (TR 2300; TE 105) bilaterally in the putamen, brainstem, cerebellum and the subcortical white matter. A new lesion developed increasing dysarthria, dysmetria, and ataxia.

Wilson's disease: neurological and magnetic resonance imaging improvement on zinc treatment

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Figure 1 Axial T2 weighted (TR 2300; TE 105) MRI. (A) Bilateral hyperintense lesions in the thalamus, striatum, and pallidum (arrows); (B) After 16 months on zinc sulphate treatment the lesions have largely resolved (arrows).

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This patient with a neurological presenta- tion of Wilson's disease was initially treated with penicillamine but effectively received less than three months of interrupted treatment due to gastrointestinal intolerance and neuropsychiatric deterioration. We assessed the second as most likely due to the copper redistribution effect of penicillamine. A drug induced lupus-like syndrome seemed unlikely.

Although copper is deposited throughout the CNS morphological changes are localised to the basal ganglia, deep cortical