in several other cases.[6] It has been suggested that dormant herpes simplex virus in the dorsal root ganglia is reactivated when the patient becomes immunocompromised.[4 8] Thus the condition has been described in patients with diabetes mellitus[4 8] as in the present case, the acquired immune deficiency syndrome,[2 3] and various malignancies.[7]

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.[5] 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.[9-11] 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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Wilson's disease: neurological and magnetic resonance imaging improvement on zinc treatment

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 intermittent 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 thrombocytopaenia (platelets 89 × 109/l; normal (N): 164–432). The liver enzymes, urea, and electrolytes were normal. Serum copper concentration was 4 μmol/l (N: 12–25), caeruloplasmin concentration 0·05 g/l (N: 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, basis pontis, and pontine tegmentum. One year later the lesions had progressed to involve the thalamus, striatum, pallidum, substantia nigra, midbrain, and medullary tegmentum (figure).

A trans-jugular liver biopsy confirmed the diagnosis of Wilson's disease with the presence of hepatic cirrhosis and copper associated protein. The patient was started on 500 mg D-penicillamine daily in divided doses and a copper deficient diet.

Within a month the patient's tremor increased and her husband noticed a change in personality and a deterioration in her personal hygiene. Despite a reduction in penicillamine dosage, the deterioration continued with increasing nightmares, hyperphagia (body weight 120 kg), and mood disturbances. The patient admitted poor compliance due to gastrointestinal intolerance and subjective generalised pruritis although no rash was ever noted.

The penicillamine was stopped and reintroduced after a week at a lower dose (125 mg daily) under prednisone cover. She soon reverted to non-compliance and was readmitted two months later in a delirious, confused state. She was grossly obese from hyperphagia (179 kg), drooled from the mouth, and exhibited general motor restlessness and head titubation. Coordination had deteriorated and the patient exhibited cogwheeling in the arms.

The laboratory investigations were unchanged apart from an anti-DNA antibody test which was now positive (19 μg DNA bound/ml serum; N = 0–10). The rest of the lupus profile was negative.

Zinc sulphate treatment was initiated at 1320 mg daily in divided doses. Three months later her handwriting, speech, and

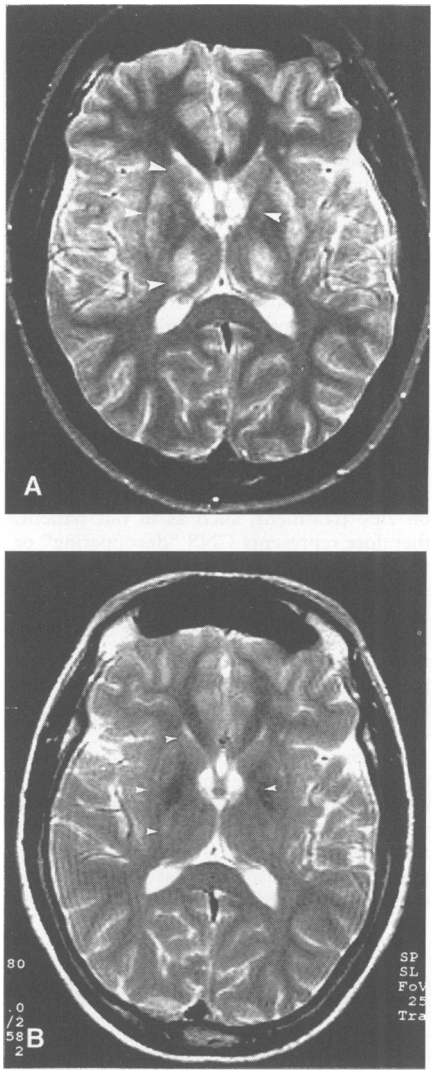

Figure 1 Axial T2 weighted (TR 2300: TE 105) MRI. (A) Bilateral hyperintense lesions in the thalamus, striatum, and pallidum (arrows); (B) After 16 months on zinc sulphate treatment the lesions have largely resolved (arrows).

tremor had improved. She weighed 102 kg and was eating a normal diet. Sixteen months after the zinc sulphate was instituted the patient had improved dramatically. She appeared well groomed and weighed 70 kg. Her speech, cognitive functioning, and flexibility had improved and at retest her performance IQ was 14 points higher than previously. The only neurological abnormality was a slight intention tremor and dysdiadochokinesis in her left arm. A repeat MRI study showed almost complete resolution of all the lesions in the brain and brainstem. The zinc sulphate dose was reduced to 660 mg daily.

This patient with a neurological presentation 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

layers, cerebellum, and brainstem.[1] Findings from MRI in Wilson's disease have been well documented and our patient displayed all the typical features.[2 3] Particularly, T2WI hyperintense lesions in the basal ganglia in Wilson's disease are thought to reflect oedema, necrosis, or cystic changes.

Regression of T2WI signal alteration on follow up brain MRIs have been documented in several patients with Wilson's disease on chelation treatment (D-penicillamine and trientine) and after liver transplantation.[2-4] We report virtual complete resolution of these abnormalities, however, on zinc sulphate treatment.

Changes in MRI appropriate to clinical worsening or improvement on chelation treatment[3] suggest copper redistribution either into or out of the CNS. It is uncertain whether brain MRI that has improved on zinc treatment, such as in our patient, therefore represents CNS "decoppering" or the detoxification of copper with consequent cellular recovery after the metabolic insult.

Our patient's improvement provides further evidence that acutely ill neurological patients can be treated successfully with zinc sulphate resulting in partial[5] or almost complete recovery, as in our patient. Furthermore, the dramatic clinical and radiological recovery that our patient exhibited on zinc treatment makes it reasonable to presume that increased faecal copper loss is not the only beneficial effect of zinc in patients with Wilson's disease and that zinc may be an effective "decoppering" agent.

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Expression of androgen receptor in X-linked spinal and bulbar muscular atrophy and amyotrophic lateral sclerosis

Androgen has a variety of effects on many target organs as well as mediating sex differentiation and development, and is known to play an important part in motor neuron growth, development, and regeneration. Although the aetiological basis of motor neuron diseases may be multifactorial, the hypothesis that amyotrophic lateral sclerosis might be due to the loss of androgen receptors has been proposed.[1] Furthermore, androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy have recently been reported.[2] Among a variety of motor neuron diseases, spinal and bulbar muscular atrophy is characterised byt X-linked inheritance, adult onset, and slowly progressive spinal and motor neuron degeneration as well as a frequent association with gynaecomastia and reduced fertility, suggesting an abnormality of androgen receptors.

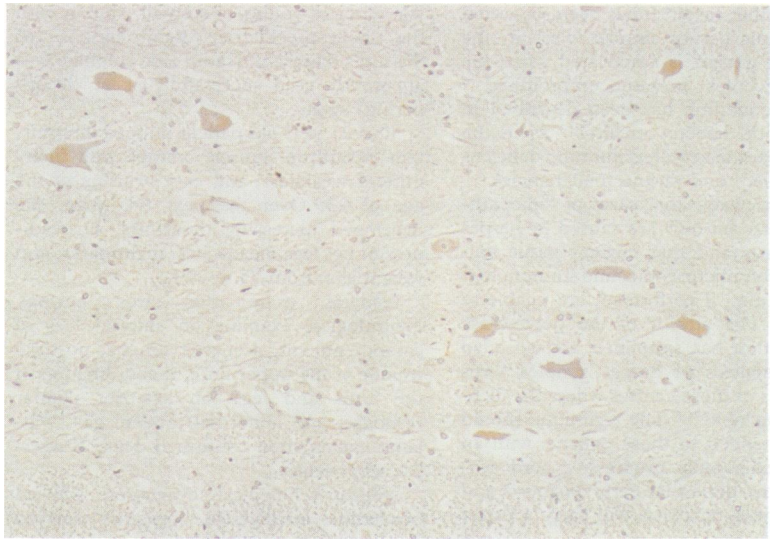

Figure 1 Immunostaining of normal spinal cord for androgen receptor (originally × 200). There is dense immunoreactivity in the nuclei of the anterior horn cells of the cervical cord; immunoreactive materials are also present in the cytoplasm of some neurons.

We analysed androgen receptors in the spinal cord and brain stem in necropsy samples from two brothers with spinal and bulbar muscular atrophy, four cases of sporadic amyotrophic lateral sclerosis, and four cases who died from causes other than diseases of the CNS. The analysis used immunohistochemical (avidine-biotin-peroxidase complex) methods with the anti-androgen receptor monoclonal antibody 5F4[3] to identify hormone binding sites. The necropsies were performed within three hours of death. The detailed clinical and endocrine findings and pathological features of the two patients with spinal and bulbar muscular atrophy associated with gynaecomastia and testicular atrophy were described (cases 1 and 2) by Nagashima *et al.*[4] The full clinical courses of case 1 (a 65 year old man) and case 2 (a 62 year old man) were about 45 years and 20 years respectively. The four cases of sporadic amyotrophic lateral sclerosis were confirmed on the basis of characteristic clinical, electrophysiological, and pathological features. There was no family history of any neurological disease in these patients.

In normal spinal cords, most motor neurons were immunopositive for androgen receptor. Dense immunoreactivity was found mainly in the nuclei of the anterior horn cells (fig 1), but immunoreactive material was also present in the cytoplasm of some neurons. Some neurons in the substantia gelatinosa, nucleus proprius, substantia intermedia, and central grey contained androgen receptor positive material. Androgen receptor protein expression was also found in the neurons of cranial nerves III, IV, and VI. Neurons, other than motor neurons, were faintly stained. The atrophic neurons in the anterior horns of spinal cords and the XII cranial nerve nucleus in the two cases of spinal and bulbar muscular atrophy contained immunoreactive material. Although severely affected, the spinal motor neurons were positively stained with the androgen receptor antibody in case 2 (fig 2A). In amyotrophic lateral sclerosis, the anterior horn cells of the spinal cords were much reduced; nevertheless, the remaining motor neurons contained androgen receptor, microscopically shown to be in the cell nuclei (fig 2B).

Thus in spinal and bulbar muscular atrophy and amyotrophic lateral sclerosis, androgen receptor positive neurons were found in the anterior horns throughout the spinal cords and also in the Onufrowicz nucleus.

At present, there is a paucity of information about the pathogenesis of amyotrophic lateral sclerosis. The hypothesis that amyotrophic lateral sclerosis may be due to the loss of androgen receptors has been proposed.[1] This is suggested by the male to female ratio in amyotrophic lateral sclerosis, the age of onset, and the sparing of neurons of cranial nerves III, IV, and VI that coincidentally lack androgen receptors. In our study, however, androgen receptor proteins were expressed in the neurons of cranial nerves III, IV, and VI and in the Onufrowicz nucleus. Furthermore, La Spada *et al*[2] have recently detected an increased number of CAG repeats in the first exon of the androgen receptor gene in patients with spinal and bulbar muscular atrophy. Our study suggests that an androgen receptor abnormality, at least in terms of the binding sites, is not the major cause of motor neuron death in amyotrophic lateral sclerosis and spinal and bulbar muscular atrophy, because even severely affected motor neurons in these diseases produce androgen receptor protein. From some experimental studies, it is suggested that androgens play an important part in motor neuron growth, development, and regeneration. Nevertheless, the association between gene mutations and motor neuron degener-