

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 treatment³ 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 "decuppering" 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 partial⁵ 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 "decuppering" 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

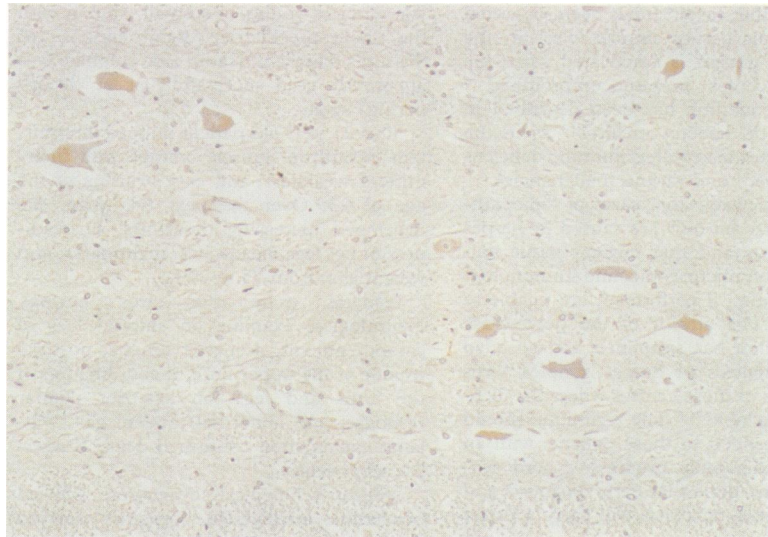


Figure 1 Immunostaining of normal spinal cord for androgen receptor (originally $\times 200$). There is dense immunoreactivity in the nuclei of the anterior horn cells of the cervical cord; immunoreactive materials are also present in the cytoplasm of some neurons.

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 by 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.

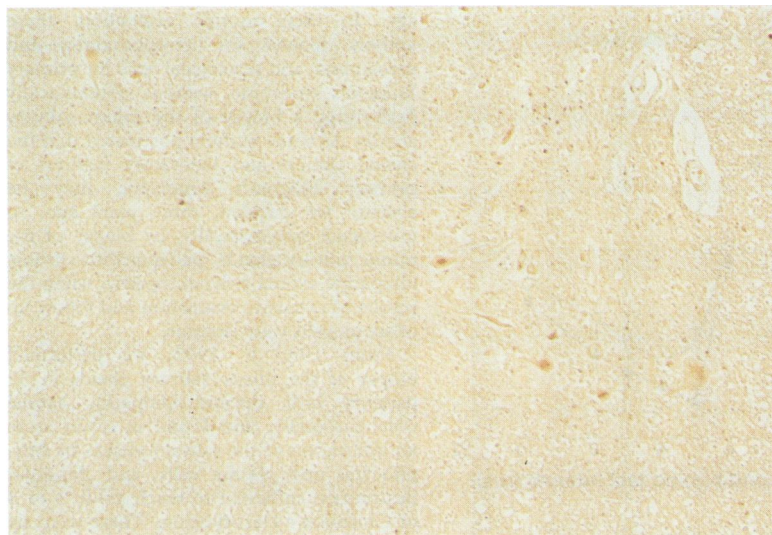
We analysed androgen receptors in the spinal cord and brain stem in necropsy samples from two brothers with spinal and bulbar muscular atrophy, four cases of sporadic amyotrophic lateral sclerosis, and four cases who died from causes other than diseases of the CNS. The analysis used immunohistochemical (avidine-biotin-peroxidase complex) methods with the anti-androgen receptor monoclonal antibody 5F4³ 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

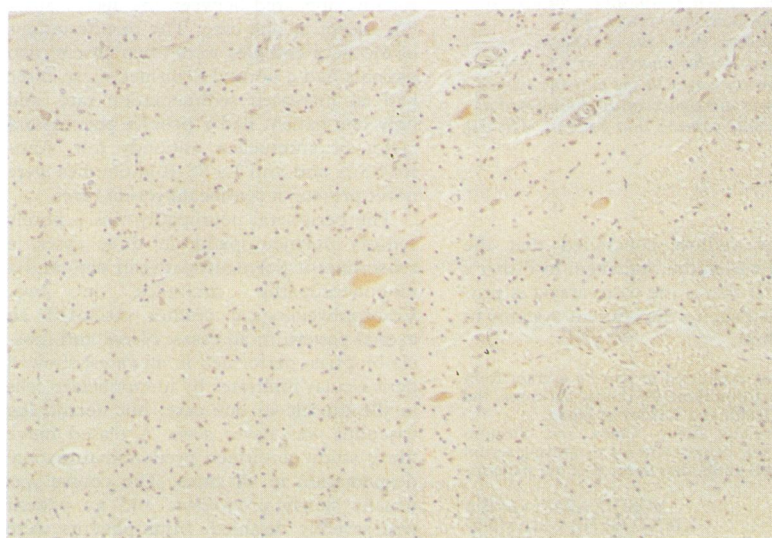
nerves III, IV, and VI. Neurons, other than motor neurons, were faintly stained. The atrophic neurons in the anterior horns of spinal cords and the XII cranial nerve nucleus in the two cases of spinal and bulbar muscular atrophy contained immunoreactive material. Although severely affected, the spinal 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-



(A)



(B)

Figure 2 Immunostaining of the anterior horn cells in X-linked spinal and bulbar muscular atrophy (A, case 2) and amyotrophic lateral sclerosis (B) with anti-androgen receptor antibody. Despite the pronounced decrease in anterior horn cells, the surviving cervical neurons contain androgen receptor antigens in both cases (originally $\times 200$).

ation has not been clarified. Igarashi *et al*⁵ have reported that the number of CAG repeats was significantly correlated with the severity and the age at onset of muscular weakness in patients with spinal and bulbar muscular atrophy. Although the interaction between androgen receptor function and the increased number of CAG repeats cannot be explained at present, it is likely that the slowly progressive neuronal degeneration in spinal and bulbar muscular atrophy is associated with the changes in androgen or other endocrine state due to dysfunction of other target organs affected by the increased CAG repeats, or is related to the alteration in transcriptional regulation by androgen receptor gene mutations.²

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Suppression of motor cortical excitability by electrical stimulation over the cerebellum in Fisher's syndrome

Electromyographic (EMG) responses evoked by transcranial magnetic stimulation of the motor cortex can be suppressed by electrical stimuli applied over the contralateral cerebellum.¹ Recently, we have investigated the pathophysiology of this suppression in patients with ataxia.² No suppression was provoked in patients with ataxia due to dysfunction of the cerebellum (degenerative ataxia or cerebrovascular disease) or the cerebellothalamocortical pathway (lesions of the superior cerebellar peduncle or the motor thalamus). By contrast, the amount of suppression was normal in patients with ataxia due to dysfunction of the afferent pathway to the cerebellum (lesions of the pontine nucleus), in those with sensory ataxia, and patients without ataxia. Recent studies of patients with unilateral focal cerebellar lesions with this method confirmed our results and suggested that this suppression effect is elicited when the cerebellar hemispheres and cerebellothalamocortical pathways are intact.³

In the present paper, we have studied cerebellar pathophysiology in patients with Fisher's syndrome by the same technique.

The experiments were done with the approval of the ethics committee of the University of Tokyo. The subjects were five patients with typical Fisher's syndrome. They all had a prodromal infection, ophthalmoplegia, hyporeflexia or areflexia, and ataxia. These signs recovered completely in all of them. Diagnosis was confirmed by the presence of increased serum anti-GQ1b IgG antibody in three patients.

The effect of electrical stimuli over the cerebellum on the contralateral motor cortical excitability was investigated with the methods previously described.^{1,2} Surface electromyographic (EMG) activity was recorded from the first dorsal interosseous muscle with surface cup electrodes. Signals were amplified with filters set at 100 Hz and 3 kHz, and recorded by a medical computer (DP-1100, NEC-San-Ei).

High voltage electrical stimuli over the cerebellum were given through two electrodes fixed with collodion on the incisura mastoidea on both sides. The intensity of stimulation was fixed at just under the threshold for activating the corticospinal tract at the level of the pyramidal decussation. At various times afterwards, magnetic stimuli were applied over the motor cortex with a Magstim 200 magnetic stimulator. A round coil 14 cm in external diameter was placed over the vertex. The intensity of stimulation was adjusted to produce a response of about 1mV peak to peak in the relaxed first dorsal interosseous muscle. All investigations were done on electrically silent muscles with subjects relaxed.

We used a randomised conditioning test design.^{1,2} Trials in which a test shock (magnetic stimulus over the motor cortex) was given alone were randomly intermixed with trials in which a conditioning shock (electrical stimulus over the cerebellum) was given before the test shock. Ten responses per condition were collected and averaged and their peak to peak amplitudes were measured. The peak to peak size of each single response under each condition was also measured so that we could compare statistically the size of control and conditioned