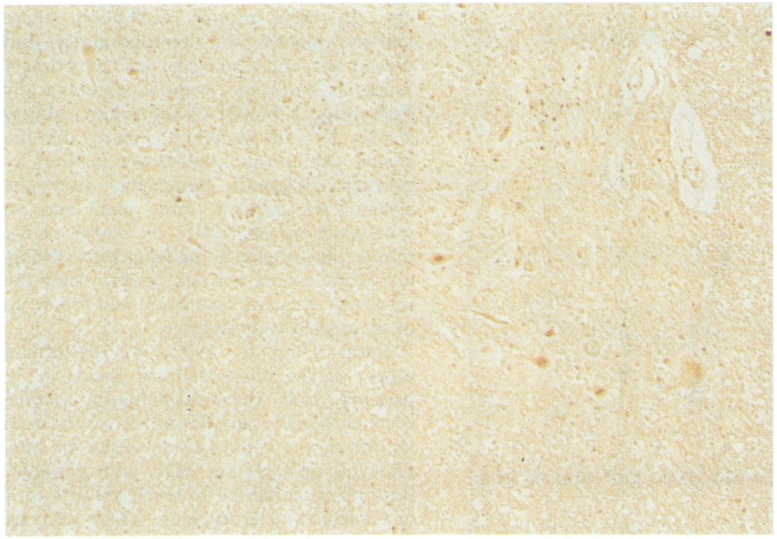
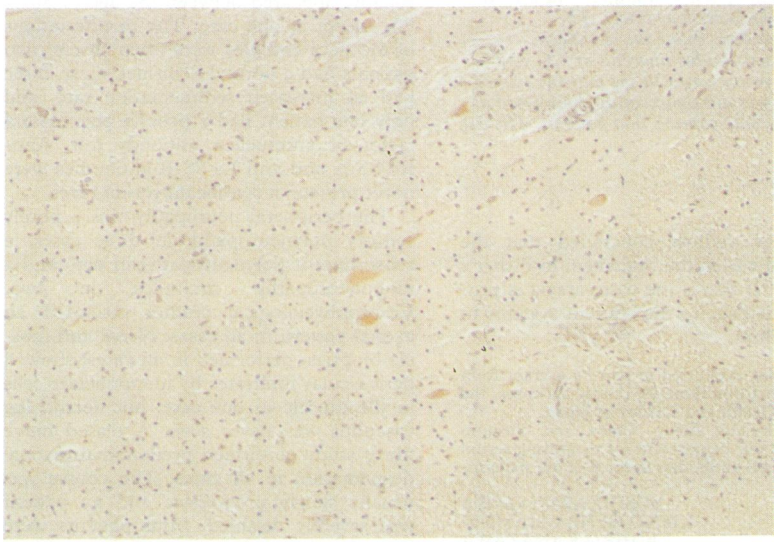


(A)



(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 × 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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1 Weiner LP. Possible role of androgen receptors in amyotrophic lateral sclerosis: a hypothesis. *Arch Neurol* 1980;37:129–31.
2 La Spada AR, Wilson JD, Lubahn DB, Harding AE, Fischbeck KH. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. *Nature* 1991;352:77–9.
3 Demura T, Kuzumaki N, Oda A, Fujita H, Ishibashi T, Koyanagi T. Establishment and characterization of monoclonal antibody against androgen receptor. *J Steroid Biochem* 1989;33:845–51.
4 Nagashima T, Seko K, Hirose K, *et al*. Familial bulbo-spinal muscular atrophy associated with testicular atrophy and sensory neuropathy (Kennedy-Alter-Sung syndrome): autopsy case report of two brothers. *J Neurol Sci* 1988;87:141–52.
5 Igarashi S, Tanno Y, Onodera O, *et al*. Strong correlation between the number of CAG repeats in androgen receptor genes and the clinical onset of features of spinal and bulbar muscular atrophy. *Neurology* 1992;42:2300–2.

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]

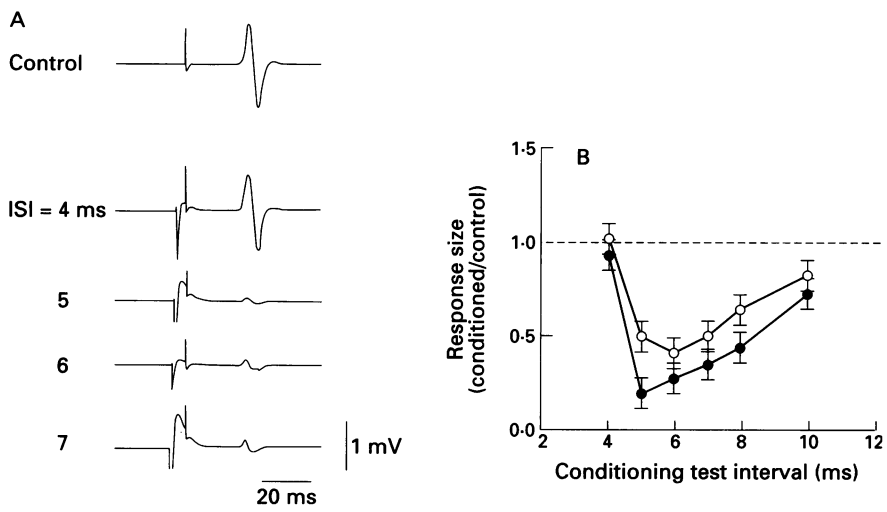
In the present paper, we have studied cerebellar pathophysiology in patients with Fisher's syndrome by the same technique.

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



(A) typical responses in a patient with Fisher's syndrome. The first trace shows that the test magnetic stimulus over the motor cortex elicits a response of about 1·6 mV in peak to peak amplitude in the relaxed first dorsal interosseous muscle. Responses to the test stimulus given 4,5,6, and 7 ms after a conditioning electrical stimulus over the cerebellum are shown in the lower four traces. The conditioning stimulus has no effect on the response size when given 4 ms before the test shock. Responses are significantly smaller than the control response at interstimulus intervals of 5,6, and 7 ms. (B) Average (SEM) time course of suppressive effect on the motor cortex in the patients (closed circles) and normal subjects (open circles). The conditioned responses are significantly diminished at conditioning test intervals of 5,6, and 7 ms ($p < 0·01$) in both normal controls and patients. The two time courses are not significantly different ($p > 0·5$, ANOVA).

responses by unpaired Student's *t* test. The time course of the effect was made from the data of several blocks of trials. The average time courses for all the patients were compared with the normal values described elsewhere[2] by analysis of variance (ANOVA).

Traces in the figure (A) are typical responses in a patient with Fisher's syndrome. The test magnetic stimulus elicited a response of above 1·6 mV in peak to peak amplitude (first trace). The conditioning electrical stimuli significantly ($p < 0·01$) reduced the size of EMG responses to the test shock at interstimulus intervals of 5,6, and 7 ms (third to fifth traces). The size was not significantly ($p > 0·05$) affected by the conditioning stimuli when they were given 4 ms beforehand (second trace).

The figure (B) shows the average time course of suppression for all the patients with the average time course for normal controls. There were no significant differences between the two ($p > 0·05$, ANOVA).

Clinical features of our patients were all typical of Fisher's syndrome. Electrical stimuli over the cerebellum evoked a normal amount of suppression of motor cortical excitability in all patients. A comparison of these results with previous results obtained from patients with ataxia due to various disorders,[2 3] suggests that the efferent pathway from the cerebellar cortex to cerebellar nuclei, thalamus, and cerebral cortex is intact in patients with Fisher's syndrome. We conclude that ataxia in these patients is due either to an abnormality of the sensory afferent input to the cerebellum, or to abnormal processing of this input within the cerebellum.

Our conclusion is consistent with previous postulates that ataxia in Fisher's syndrome is due to dysfunction of the peripheral nervous system.[4] If some special components of proprioceptive sensation are disturbed, ataxia is a kind of sensory ataxia in our pathophysiological classification. Some other authors concluded that the main lesion was in the brainstem in Fisher's syndrome.[5] If this is the case, ataxia is produced by damage to the afferent systems to the cerebellum.

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1 Ugawa Y, Day BL, Rothwell JC, Thompson PD, Merton PA, Marsden CD. Modulation of motor cortical excitability by electrical stimulation over the cerebellum in man. *J Physiol (Lond)* 1991;441:57–72.
2 Ugawa Y, Genba-Shimizu K, Rothwell JC, Iwata M, Kanazawa I. Suppression of motor cortical excitability by electrical stimulation over the cerebellum in ataxia. *Ann Neurol* 1994 (in press).
3 Di Lazzaro V, Molinari M, Restuccia D, Leggio MG, Nardone R, Fogli D, Tonali P. Cerebro-cerebellar interactions in man: neurophysiological studies in patients with focal cerebellar lesions. *Electroencephalogr Clin Neurophysiol* 1994;93:27–34.
4 Ropper AH, Shahani BT. Proposed mechanism of ataxia in Fisher's syndrome. *Arch Neurol* 1983;40:537–8.
5 Meienberg O. Lesion site in Fisher's syndrome. *Arch Neurol* 1984;41:250–1.

Primary Sjögren's syndrome in chronic polyneuropathy presenting in middle or old age

Notermans *et al*[1] studied chronic idiopathic polyneuropathy presenting in middle or old age. In their routine evaluation, these authors looked for xerophthalmia and xerostomia, and serological tests for primary Sjögren's syndrome, without systematically performing a biopsy of the minor salivary glands. As some authors postulated that the classic clinical and laboratory features of primary Sjögren's syndrome may be absent,[2] we decided, three years ago, to investigate systematically, by biopsy of the minor salivary glands, patients with chronic idiopathic axonal polyneuropathy, when the results of extensive evaluation and follow up of six months were negative.

From 1990 to 1993, we performed biopsy of the minor salivary glands in 32 patients with chronic idiopathic axonal polyneuropathy, and found in seven cases an infiltration of the salivary glands by lymphocytes and plasma cells, and glandular destruction sufficient to reach grade 3 or 4 of Chisholm's classification. There were six women and one man, aged 56 to 80 (mean 65·8). The symptoms of the peripheral neuropathy appeared between the age of 50 to 70, except in one case. The manifestations of the sicca complex were often absent: two patients had a normal Schirmer's test, three had an increased sedimentation rate, and only one patient had a positive rheumatoid factor or antinuclear antibody test. Anti-Ro/SS-A and anti-La/SS-B antibodies were never present at significant serum titres.

The peripheral neuropathy was a purely sensory polyneuropathy in three cases, a sensorimotor polyneuropathy in two, and a mononeuropathy multiplex in two. Electrophysiological studies disclosed an axonal pattern in all cases. Nerve and muscle biopsies, performed in all cases, showed perivascular infiltrates by mononuclear cells in the muscle in one case, but necrotising vasculitis was never seen. A teased nerve fibres study confirmed predominant axonal degeneration in all cases. The course was usually slowly progressive and no patient was severely disabled. Four patients were treated with either steroids or plasma exchanges without clear improvement of the peripheral neuropathy.

There is no rule to date for performing a biopsy of the minor salivary glands in patients with chronic polyneuropathy of unknown cause, despite extensive evaluation. Primary Sjögren's syndrome is known to primarily affect middle aged women.[2 3] Predominantly sensory polyneuropathies seem to be more frequent than mononeuropathy multiplex.[3] Sensory neuropathies have been reported by other authors,[4] but seem to be rare. In addition, cerebral involvement, perhaps asymptomatic, may be present in some cases.[5] Griffin *et al* recommended biopsy of the minor salivary glands when Schirmer's test is considered positive. For most authors, two of the classic features (keratoconjunctivitis, xerostomia, and arthritis) are required to establish the diagnosis of primary Sjögren's syndrome,[3] but extraglandular involvement may overshadow the sicca syndrome or occur in the absence of glandular dysfunction.[2] On the other hand, biopsy of the minor salivary glands is a simple outpatient procedure that may provide an accurate diagnosis, even in the absence of clinical evidence of primary Sjögren's syndrome. We did not find side effects of this procedure in our series.

In conclusion, we suggest that appropriate evaluation of patients with chronic