Some of the episodes may have been associated with fever. A third severe episode occurred at the age of 19 two weeks after normal vaginal delivery of a healthy child. She developed rapid onset of spasms affecting her legs and arms which progressed so that she had difficulty breathing and swallowing. She was also vomiting. Examination showed a temperature of 42°C with tachycardia and tachypnoea and generalised muscular spasm. Her creatine kinase was raised at 740 IU/l and investigation for an infective source including blood cultures was negative. A chest radiograph was normal and autoantibodies were negative. She responded well to treatment with intravenous dantrolene within one week and had no permanent neurological sequelae. Further admissions to a general medical unit occurred two weeks after starting phenytoin, with rash, fever and generalised muscle stiffness, and two months later just after starting trimethoprim for a urinary infection, with rash and muscle stiffness only. No further episodes have since occurred during treatment with carbamazepine. In addition to the episodes of fever and muscle stiffness she has several years of twitching of the hand and calf muscles. No muscle spasm due to exertion or cold was described. Neurological examination showed hypertrophy of both calves and continuous twitching of the calves and forearms. Two sisters and her parents had no neuromuscular symptoms; none had ever received a general anaesthetic.

Sensory and motor nerve conduction studies and EMG were performed. The sensory (superficial peroneal and median) and motor (posterior tibial and median) distal latencies and conduction velocities were normal. The sensory nerve action potential amplitudes were normal as were the compound muscle action potential (CMAP) amplitudes recorded from the abductor pollicis brevis and abductor hallucis. The CMAP waveforms were followed by after discharges lasting for up to 50 seconds, which made accurate estimation of F wave latencies impossible. Concentric needle EMG of tibialis anterior and medial gastrocnemius showed repetitive spontaneous discharges of motor unit potentials at all sites sampled. This activity occurred irregularly in rhythmical 0·5–1·5 second bursts at high rates (50–200/s).

This patient has electrophysiologically established spontaneous and stimulus induced neuromyotonia without neuropathy with episodes of hyperpyrexia consistent with malignant hyperthermia.[1] Patients with neuromyotonia may have increased sweating and feel unwell but we think that malignant hyperthermia has not previously been described. The underlying deficit in neuromyotonia is likely to lie in the nerve cell membrane, and some patients may have potassium channel abnormalities.[2] Malignant hyperthermia has been associated with muscle membrane disorders, and abnormalities in muscle ion channels have been described.[3] We suggest an anomalous ion channel common to muscle and nerve as a possible mechanism for the association in this patient.

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Arg296 to Cys296 polymorphism in exon 6 of cytochrome *P*-450-2D6 (CYP2D6) is not associated with multiple system atrophy

An allelic association between mutant alleles of the cytochrome *P*-450-2D6 (CYP2D6) and Parkinson's disease has been shown by several groups[1–3]. The analysed mutations lie in exon 4 and 5 of the CYP2D6 gene, homozygotes showing the poor metaboliser phenotype. Analysis of these mutant alleles among patients with multiple system atrophy showed no difference in the frequency of these alleles from that in control subjects.[4]

A further polymorphism causing an amino acid change from Arg296 to Cys296 at the *HhaI* site in exon 6 of the CYP2D6 gene has been described.[5,6] The frequency of this polymorphism, which is not associated with the poor metaboliser phenotype,[5] was 26% among normal white subjects,[5] but only 9% in Japanese control subjects.[6] Recently, an association with the Arg296 to Cys296 polymorphism was suggested in a small series of 10 Japanese patients with multiple system atrophy and it was suggested that this polymorphism may be a useful marker for susceptibility to this disease.[7]

We examined the frequency of this polymorphism in a larger series of 74 white patients with multiple system atrophy. The diagnosis was clinical in 59[8] and pathologically established in a further 15, in whom frozen brain samples were analysed. The method for the detection of the polymorphism has been described elsewhere.[6] Our results show a similar frequency of the mutant allele (48 of 148 total alleles) among the patients with multiple system atrophy to the published frequency among white control subjects (32% *v* 26%; $\chi^2 = 0{\cdot}97$, $P = 0{\cdot}32$).

We conclude that, at least in white subjects, the *HhaI* polymorphism in exon 6 of the CYP2D6 gene is not associated with multiple system atrophy and is therefore not a useful marker for susceptibility to multiple system atrophy.

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Ataxic hemiparesis with bilateral leg ataxia from pontine infarct

Ataxic hemiparesis is a syndrome characterised by weakness and cerebellar-like ataxia on the same side of the body.[1] A lesion resulting in ataxic hemiparesis must involve both the corticospinal fibres and the afferent or efferent cerebellar fibres in locations where the tracts are in close proximity. The afferent and efferent cerebellar fibres form a loop extending from the cerebral cortex through the pons and middle cerebellar peduncle to the cerebellar cortex and then extending from the dentate nucleus through the superior cerebellar peduncle, red nucleus, and thalamus back to the cerebral cortex. Ataxic hemiparesis has been associated with lesions in the corona radiata, thalamus, midbrain, and pons. Fisher and Cole first reported that a paramedian infarct of the basis pontis located at the junction of the upper one third of the pons with the lower two thirds could produce a contralateral ataxic hemiparesis.[1] One of the major questions concerning pontine ataxic hemiparesis is why the limb ataxia is seen only contralateral to the lesion and not bilaterally.[1,2] The corticopontine fibres terminate by synapsing with the pontine nuclei and most fibres then cross the midline to enter the contralateral middle cerebellar peduncle. A basis pontis infarct might thus be expected to produce bilateral limb ataxia because it would involve ipsilateral pontine nuclei and corticopontine fibres as well as pontocerebellar fibres that have crossed from the contralateral side. We report a case of a mid-pontine paramedian infarct with caudolateral extension resulting in ataxic hemiparesis with bilateral leg ataxia.

An 80 year old white man with a history of coronary artery disease suddenly noticed left sided weakness. On examination, he had

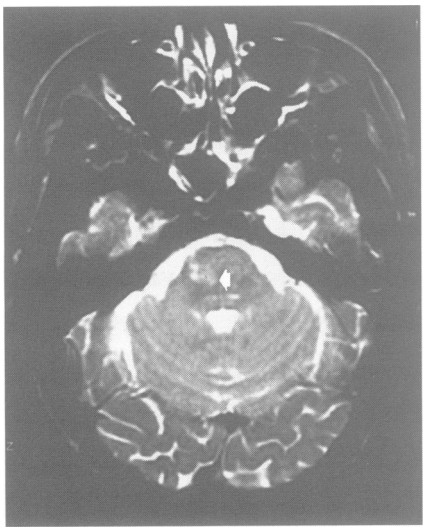

Figure 1 Axial T2 weighted MRI of mid-pons showing infarct in the right lateral basis pontis extending medially.

a blood pressure of 120/72. He had a left central facial weakness and a mild left hemiparesis affecting the arm and leg equally. Incoordination of the left upper extremity was present on finger to nose testing and bilateral heel-knee-shin ataxia was present, worse on the left. The muscle stretch reflexes were normal and the plantar reflexes were flexor bilaterally. Brain MRI disclosed an area of increased signal intensity involving both the paramedian mid-pons and extending laterally in the caudal third of the pons (fig 1).

It is unclear why patients with ataxic hemiparesis usually have ataxia contralateral to the lesion rather than bilateral limb ataxia. It has been suggested that the pontine nuclei are more vulnerable to ischaemia than the transverse pontocerebellar fibres crossing from the contralateral side but there is no histological evidence for this.[3] Huang and Chang[2] suggested that the crossing transverse pontocerebellar fibres take an oblique downward course to the contralateral middle cerebellar peduncle and in this way a more rostrally placed pontine lesion may involve only the corticopontine fibres and pontine nuclei ipsilaterally, but miss the more caudally placed crossing pontocerebellar fibres. A more caudolateral lesion would be expected to give rise to ipsilateral ataxia (fig 2). Our case supports this suggestion, as the lesion extended more laterally and caudally than previously described pontine infarcts associated with ataxic hemiparesis. The more caudolateral part of the infarct in our patient may have damaged the crossed pontocerebellar fibres and have resulted in the leg ataxia ipsilateral to the infarct, whereas the more medial and rostral part may have given a contralateral ataxic hemiparesis (fig 2). This suggestion is supported by Fisher's report of a lower lateral pontine infarct[4] and Fisher and Tapia's report of a lateral medullary infarct extending into the lower lateral pons.[5] Both these infarcts gave rise to ataxia only ipsilateral to the lesion.

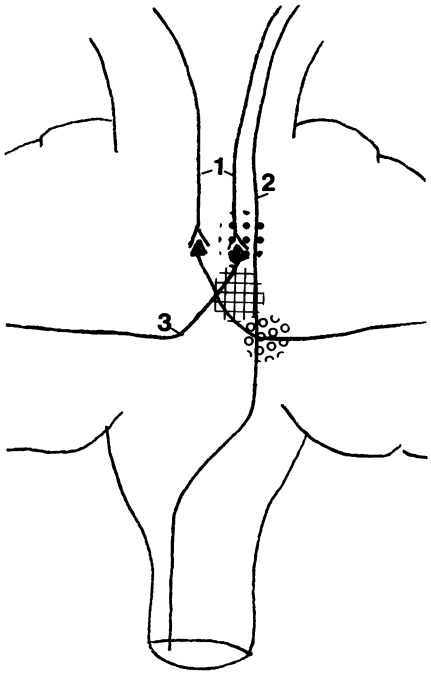

Figure 2 Diagram of coronal section through brainstem showing corticopontine fibres (1), corticospinal tract (2), and pontocerebellar fibres (3). The site of a pontine lesion causing ataxic hemiparesis as described by Fisher[1] is shown in bold dots, the site of a lesion causing ipsilateral ataxia[4] is shown in open dots, and the site of the lesion in our patient is shown in cross hatching.

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Autoimmune chronic active hepatitis and polymyositis in a patient with myasthenia gravis and thymoma

Myasthenia gravis is known to occur with other autoimmune disease. It is rarely associated with polymyositis,[1] and very exceptionally with autoimmune chronic active hepatitis.[2] We describe a patient with generalised myasthenia gravis, cortical thymoma, polymyositis, and autoimmune chronic active hepatitis.

A 25 year old Chinese woman presented with intermittent weakness of the limbs for one month with no diplopia, speech disturbance, or bulbar symptoms. She had mild ptosis of her left eye which increased progressively with maintained upward gaze, and proximal limb muscle weakness. The rest of the examination was normal. She had a positive edrophonium test, and serum antiacetylcholine receptor and antistriated muscle antibody titres. Chest radiography disclosed a mediastinal mass which was subsequently confirmed by CT to be a thymoma measuring 4·2 cm (anteroposterior) × 3·1 cm (width) in the left lobe of the thymus. Serial serum muscle enzymes were raised. A repetitive stimulation test on three muscles showed a more than 15% decrement with postexercise exhaustion. An EMG showed abundant fibrillations, positive sharp waves and insertional irritability, and short, small polyphasic motor units. Biopsy of her deltoid muscle showed perivascular infiltration of lymphocytes with phagocytosis and variable numbers of angulated atrophic fibres.

Incidentally she was found to have hepatitis. During the initial stay in hospital, a liver function test gave albumin 45 g/l, globulin 37 g/l, alkaline phosphatase 106 U/l, bilirubin 21 umol/l, alanine aminotransferase 1158 U/l, and aspartate aminotransferase 943 U/l. Viral markers of hepatitis A, B, and C were all negative, whereas antinuclear factor and antismooth muscle antibody were positive. Her HLA antigens were A33, B17, and DR3. Liver biopsy showed a picture of active chronic hepatitis with enlarged portal tracts and a pronounced mononuclear cell infiltrate which spilt across the limiting plate. There were foci of piecemeal necroses and the hepatocytes often displayed ballooning degeneration. Staining for hepatitis B was negative.

Her muscle weakness responded promptly but not completely to pyridostigmine (60 mg four times daily), and after the liver biopsy, she was treated with prednisolone (55 mg daily) and azathioprine (50 mg) daily. Three weeks after, she developed ophthalmic herpes, which was treated with acyclovir.

She continued to improve both in muscle power and liver function. Two months after treatment with prednisolone and azathioprine, the liver enzymes were considerably decreased—alanine aminotransferase 39 U/l and aspartate aminotransferase 38 U/l. Thymectomy was then performed and the postoperative course was uneventful. Histology confirmed that the thymoma was encapsulated, non-invasive, and of cortical type.

This is the first report of the combination of generalised myasthenia gravis with thymoma, polymyositis, and autoimmune chronic active hepatitis. Fifty per cent of patients with chronic active hepatitis will die of liver failure within five years if no treatment is given. Although the prognosis can be considerably improved with steroid and azathioprine treatment, most patients develop cirrhosis.[3]

The susceptibility of the patient to generalised myasthenia gravis, autoimmune chronic active hepatitis, and polymyositis seems to be related to HLA DR3.[4] There is probably an interplay of genetic and environmental factors in the occurrence of these diseases. Interestingly, the association of polymyositis and HLA DR3 is claimed to be related to the coexistent presence of antibodies to histidyl tRNA synthetase (Jo-1).[5] In this regard the appearance of such autoantibodies in polymyositis is reported to be most uncommon[4] and was absent in the patient reported herein. Despite the coexistence of the diseases, a good response was obtained with steroid combined with azathioprine and thymectomy.

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