(a) Demonstration of haemorrhage by CT (without contrast) in the third ventricle, ambient, and quadrigeminal cistern. (b) Coronal section showed a pronounced haemorrhage in the third ventricle (arrow). In addition, small areas of haemorrhagic discoloration in cortical/subcortical regions secondary to agonal raised intracranial pressure are shown. (c) A necrotising haemorrhagic lesion in the floor of the fourth ventricle (arrow), small areas of haemorrhagic necrosis in cortical regions secondary to agonal raised intracranial pressure, and subarachnoid haemorrhage, especially in the basal cisterns and the leptomeninges of the cerebellar vermis secondary to intraventricular haemorrhage.

and cystectomy with construction of an ileal conduit were performed. Two and a half weeks before admission the patient developed a rectovaginal fistula; the rectum and sigmoid colon were resected and an end colostomy and another ileal conduit were constructed. Oesophagogastroscopy, performed because of vomiting four days before admission, showed candidiasis of the oesophagus. Neurological examination showed that the patient was disoriented in time, had a right sided abducens paresis, horizontal gaze evoked nystagmus to the left, and a vertical gaze evoked nystagmus upward. The tendon reflexes were normal. She had no paresis of the extremities, but slight dysmetria of the arms and legs. There were no sensory abnormalities. Routine laboratory tests were normal except for serum glucose (243 mg/dl), potassium (2.4

mmol/l), total bilirubin (1.59 mg/dl), γ -glutamyl transferase (73 U/l), and prothrombin time (1.37 international normalised ratio, normal values from 1.00 to 1.27). Examination of CSF one day after admission showed a raised CSF/serum albumin ratio (12.5), but a normal cell count (no malignant cells were detected) and glucose concentration; fluid was sterile on culture. Oligoclonal IgG bands were absent in the CSF. A cranial CT on admission as well as bilateral carotid angiography three days after admission were normal. Five days after admission her mental state deteriorated. She was intubated and transferred to the neurology intensive care unit. On admission there she was comatose without reaction to painful stimuli. Oculocephalic responses were absent. The isocoric pupils had slight bilateral reaction to light. Corneal reflexes were symmetrically present. An EEG showed diffuse slowing. She had hypotension requiring fluid administration, dopamine, and noradrenaline. She had a fever (39°C) and a raised C-reactive protein concentration (13.8 mg/dl); antibiotic treatment (imipenem plus erythromycin) was initiated. Repeat cranial CT was normal. Twenty four hours after admission at the intensive care unit she acutely developed bilateral dilated areactive pupils. Immediate CT showed severe intraventricular haemorrhage (figure, A). Coagulation studies (prothrombin time, partial thromboplastin time, platelet count) determined on the same day as well as the day before intraventricular haemorrhage were normal. The patient had no clinical signs of cutaneous or mucous bleeding. Despite immediate insertion of bilateral intraventricular drains the patient died 14 hours later.

At necropsy the brain weighed 1440 g and showed some arteriosclerosis of the great arteries at the base of the brain. An aneurysm was not found in the circle of Willis. Coronal sections showed pronounced haemorrhages at the walls of the third ventricle bilateral, which extended into the third ventricle, the aqueduct, and the floor of the fourth ventricle (figure, B, C). There was destruction of the mamillary bodies by haemorrhage. In addition to petechial haemorrhage, microscopy showed prominent and dilated capillaries, reactive astrocytes in the periventricular regions around the third and fourth ventricles and aqueduct, and mild neuronal loss.

The clinical diagnosis of Wernicke's encephalopathy is often overlooked¹ and was not suspected in our non-alcoholic patient during her lifetime. Her mental abnormalities had aroused clinical suspicion of carcinomatous meningitis, paraneoplastic disorder, cerebral vasculitis, or sinus thrombosis. A recent necropsy study showed that 80% of patients with the Wernicke-Korsakoff syndrome were not diagnosed during life (Harper *et al*, 1986, cited in Naidoo *et al*¹). Apart from patients with a history of chronic alcoholism, Wernicke's encephalopathy can be found in other medical settings—for example, malnutrition, prolonged intravenous feeding, cancer, gastric plication, and acquired immunodeficiency syndrome.^{1,2} The extensive abdominal surgery and vomiting before admission may have led to decreased food uptake and thiamine deficiency in our patient. Parenteral nutrition in the intensive care unit probably aggravated Wernicke's encephalopathy.

Neuropathological studies in patients with Wernicke's encephalopathy have shown symmetric lesions in the paraventricular regions of the thalamus and hypothalamus, in the mamillary bodies, periaqueductal region of the midbrain, floor of the fourth ventricle, and midline structures of the cerebellum.² Histologically, the acute lesions were found in and around blood vessels. Hypertrophic endothelial cells, demyelination, loss of neuropil, proliferation of astrocytic and microglial cells, and relative preservation of neurons have been reported in neuropathological studies. Periventricular haemorrhages, usually petechial in size, may be found in up to 20% of cases. Two patients were reported to have died of extensive haemorrhagic brainstem lesions detected on necropsy.³

Wernicke's encephalopathy remains a clinical diagnosis, because of the insensitivity of neuroimaging in this setting. Initial CT in our patient was normal. Haemorrhages due to Wernicke's encephalopathy detected on CT or MRI are seldom reported in the medical literature. In one report scattered haemorrhages in the thalami and posterior diencephalon in a patient with Wernicke-Korsakoff syndrome were shown by CT.⁴ In a case report a small haemorrhagic lesion adjacent to the body of the lateral ventricle was discovered on MRI.⁵ The severe intraventricular haemorrhage due to Wernicke's encephalopathy as seen in our patient raises the question of whether spontaneous bleeding of Wernicke's encephalopathy was accentuated by an associated coagulopathy. At the time of ventricular haemorrhage the data on clotting studies were normal. Moreover, the patient had not received antiplatelet agents.

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- 1 Naidoo DP, Bramdev A, Cooper K. Wernicke's encephalopathy and alcohol-related disease. *Postgrad Med J* 1991;67:978-81.
- 2 Victor M, Adams RD, Collins GH. *The Wernicke-Korsakoff syndrome and related disorders due to alcoholism and malnutrition*. 2nd ed. Philadelphia; Davis, 1989:1-117.
- 3 Harper C. Wernicke's encephalopathy: a more common disease than realised. A neuropathological study of 51 cases. *J Neurol Neurosurg Psychiatry* 1979;42:226-31.
- 4 Roche SW, Lane RJM, Wade JPH. Thalamic hemorrhages in Wernicke-Korsakoff syndrome demonstrated by computed tomography. *Ann Neurol* 1988;23:312.
- 5 Schroth G, Wichmann W, Valavanis A. Blood-brain barrier disruption in acute Wernicke encephalopathy: MR findings. *J Comput Assist Tomogr* 1991;15:1059-61.

Neuromyotonia in association with malignant hyperpyrexia

We report a case of neuromyotonia in a patient with malignant hyperpyrexia.

The patient, a 19 year old woman, has had several discrete episodes of muscular stiffness over her lifetime and several years of twitching in the hand and calf muscle. Episodes of calf muscle contracture and pain had occurred from the age of 5 with two severe episodes at the ages of 5 and 16.

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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- 1 Nelson TE, Flewelling EH. The malignant hyperthermia syndrome. *N Engl J Med* 1983; **309**:416–8.
- 2 Newsom-Davis J, Mills KR. Immunological associations of acquired neuromyotonia. *Brain* 1993; **116**:453–69.
- 3 Foster PS, Denborough MA. The effect of calcium channel antagonists and BAY K 8644 on calcium fluxes of malignant hyperthermia susceptible muscle. *Int J Biochem* 1993; **25**: 495–504.

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 59⁸ 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%; $\chi^2 = 0.97$, *P* = 0.32).

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.

Financial support from the Deutsche Forschungsgemeinschaft (DFG) and the Parkinson's Disease Society is gratefully acknowledged.

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- 1 Smith CAD, Cough AC, Leigh PN, Summers BA, Harding AE, Maraganore DM, et al. Debrisoquine hydroxylase gene polymorphism and susceptibility to Parkinson's disease. *Lancet* 1992; **339**:1375–7.
- 2 Armstrong M, Daly AK, Cholerton S, Bateman DN, Idle JR. Mutant debrisoquine hydroxylase genes in Parkinson's disease. *Lancet* 1992; **339**:1017–8.
- 3 Kurth MC, Kurth JH. Variant cytochrome P450 CYP2D6 allelic frequencies in Parkinson's disease. *Am J Med Genet* 1993; **48**:166–8.
- 4 Plante-Bordeneuve V, Bandmann O, Wenning G, Quinn NP, Daniel SE, Harding AE. CYP2D6 debrisoquine hydroxylase gene polymorphism in multiple system atrophy. *Mov Disord* 1995; **10**:277–8.
- 5 Armstrong M, Idle JR, Daly AK. A polymorphic cfo I site in exon 6 of the human cytochrome P450 CYP2D6 gene detected by the polymerase chain reaction. *Hum Genet* 1993; **91**:616–7.
- 6 Tsuneoka Y, Matsuo Y, Iwahashi K, Takeuchi H, Ichikawa Y, Hosokawa K, et al. A novel cytochrome P450IID6 mutant gene associated with Parkinson's disease. *J Biochem* 1993; **114**: 263–6.
- 7 Iwahashi K, Miyatake R, Tsuneoka Y, Matsuo Y, Ichikawa Y, Hosokawa K, et al. A novel cytochrome P-450IID6 (CYP2D6) mutant gene associated with multiple system atrophy. *J Neurol Neurosurg Psychiatry* 1995; **58**:263–4.
- 8 Quinn NP. Multiple system atrophy. In: Fahn S, Marsden CD, eds. *Movement disorders 3*. Oxford: Butterworths International Medical Reviews, 1994:262–81.

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