LETTERS TO THE EDITOR

Chronic inflammatory demyelinating polyneuropathy during treatment with interferon-α

Interferon-α (IFN-α) is widely used for the treatment of chronic viral hepatitis. There have been some reports concerning the development of autoimmune diseases, particularly thyroid disease, in patients under treatment with IFN.[1] Disorders including autoimmune haemolytic anaemia, pernicious anaemia, thrombocytopenic purpura, systemic lupus erythematosus, Raynaud´s disease, parotiditis, and epididymitis have been reported. Some neurological problems have also been described[2]; although most such adverse events have involved the CNS, several cases of peripheral nervous system involvement have been reported—namely, axonal polyneuropathy,[3] neuralgic amyotrophy, multiple mononeuropathies, and myasthenia gravis.[4] On the other hand, some authors have reported that IFN-α may be an effective alternative therapy in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) who are refractory to conventional treatments.[5] Two trials using IFN-α and IFN-β on patients with CIDP are currently in progress. We describe one patient who developed CIDP during IFN-α treatment.

A 29 year old man who had hepatitis C for 2 years, was started on IFN-α treatment. He had the usual related flu-like syndrome during the first month of treatment. Previously he had had some migraine headache episodes, but no other medical problems. After 4 months of treatment, he progressively developed paraesthesias and weakness in both feet. When he came to our hospital 4 months later, his condition had worsened. Neurological examination disclosed tetraparesia (proximal and distal) with 4/5 strength (Medical Research Council scale), generalised areflexia, and hypoaesthesia both in his hands and feet. EMG data are summarised in the table. Prolonged distal motor latencies, slowed conduction velocities, temporal dispersion of the compound muscle action potentials (CMAPs), marked prolongation of F wave latencies, and a reduction of sensory and motor CMAPs in both arms and the right sural nerve were found. These findings were consistent with a demyelinating polyradiculoneuropathy with a mild axonal degeneration. The protein concentration in CSF was 208 mg/dl, there were no cells. Immunoelectrophoresis was normal, and antiganglioside antibodies (GM1, GD1a, GD1b, GT1b) were absent. Serum biochemical studies, including HIV antibody determination, were negative. We ruled out the presence of cryoglobulins. Although IFN-α was discontinued, the disease continued to worsen; the maximal neurological deficit was reached 5 months from onset. The patient was given prednisone (60 mg/day) and progressively improved. One year later he had no symptoms and showed areflexia only on neurological examination. A further EMG showed appreciable improvement.

This is the first report of CIDP development during treatment with IFN-α. CIDP is an immune mediated disorder that usually responds to plasma exchange, intravenous gammaglobulin, or corticosteroids, although occasionally the disease is refractory to these therapies. In the past, some authors have reported improvement in patients with CIDP who were receiving IFN-α.[5] The mechanism by which IFN induced improvement in these patients is uncertain, although it may be related to complex immunomodulating effects, possibly by reduction of proinflammatory cytokine concentrations (tumour necrosis factor and IFN-γ) which may have a role in the development of inflammatory demyelination.[5] The relation between IFN-α and CIDP in our patient is uncertain. Whether IFN-α was the cause of CIDP or whether their relation was only coincidental remains unknown. Nevertheless it seems clear that the treatment mentioned above did not prevent the development of this demyelinating disease with an immunological basis. IFN-α exerts complex immunomodulator effects, it can improve or worsen autoinmune diseases.

Although our findings could be coincidental, the data suggest caution, as IFN-α treatment might yield undesirable effects involving autoimmune phenomena.

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1 Burman P, Karlsson A, Oberg K, *et al*. Autoimmune thyroid disease in interferon-treated patients. *Lancet* 1985:ii;100–1.
2 Smedley H, Katrak M, Sikora K, *et al*. Neurological effects of recombinant human interferon. *BMJ* 1983:**286**;262–4.
3 Rutkove SB. An unusual axonal polyneuropathy induced by low-dose interferon α-2a. *Arch Neurol* 1997:**54**;907–8.
4 Batocchi AP, Evoli A, Servidei S, *et al*. Myasthenia gravis during interferon α therapy. *Neurology* 1995:**45**;382–3.
5 Gorson KC, Allam G, Somovic D, *et al*. Improvement following interferon-α 2A in chronic inflammatory demyelinating polyneuropathy. *Neurology* 1997:**48**;777–80.

Nerve conduction studies

	Distal latency (m/s)	*Conduction velocity (m/s)*	*Amplitude (μV (sensory) mV(motor))*
Sensory:			
Right median	3.1	50	4.2
Right ulnar	2.7	48	1.1
Left sural	2.8	41	8.5
Right sural	3	43	3.3
Motor:			
Right median	4.4	34	2.4
Left posterior tibial	10	39	0.8
Right common peroneal	7.9	38	3.6
F wave:	*Latency F-M*	*Incidence (n (%))*	
Right median	42.9	30 (100)	
Right ulnar	36.3	31 (60)	
Left posterior tibial	65.5	57 (70)	
Right common peroneal	63.7	57 (70)	

Posteroventral pallidotomy can ameliorate attacks of paroxysmal dystonia induced by exercise

Paroxysmal exercise induced dystonia is a rare disorder classified as one of the paroxysmal dyskinesias.[1 2] In this condition patients develop dystonia, mostly involving their feet, after prolonged exercise, usually walking or swimming.[1–3] Treatment response is poor to both antiepileptic drugs and drugs given for dystonia—for example, anticholinergic drugs, muscle relaxants, or acetazolamide.[3]

We recently noted the dramatic benefit of unilateral pallidotomy in completely abolishing attacks of paroxysmal exercise induced dystonia of the contralateral foot in one patient.

This 47 year old woman was followed up over 2 years for a 10 year history of attacks of dystonia affecting her right foot, induced by exercise. At onset the attacks were mild and were induced by walking long distances. During an attack her right foot would invert for a few minutes making it difficult for her to continue walking or stand. The attack would subside within 2–3 minutes on resting. Two years after onset the attacks subsided and she was attack free for 3–4 years. Four years ago the attacks returned and got progressively worse, increasing in frequency and intensity. Over the past 2 years she could have an attack on walking even 10–15 steps. The attacks in the past few years not only made her right foot to in turn as before but caused her to fall as the right leg would rise up in the air and flex at the knee and hip and there would be some involvement of the trunk causing her spine to twist to the left. Recently the toes of the left foot were also noted to curl up during attacks. She would never lose consciousness and the attacks would last 1–2 minutes and then subside. They never occurred in sleep. Interictally the neurological examination was normal although posturing of the right foot could be induced by repeated prolonged passive flexion-extension movements of the right ankle. More recently she also began to have occasional spontaneous attacks. Investigations including repeated MRI of the head and spine were normal as were tests for Wilson's disease and other causes of secondary dystonia. Examination of CSF gave normal results and disclosed no oligoclonal bands. The patient was negative for the common mitochondrial mutations. An EMG/nerve conduction study detected no evidence of a peripheral neuropathy and somatosensory evoked potentials were normal. Polymyography confirmed cocontraction of agonists and antagonist muscle pairs in the right leg during an attack supporting an organic basis for the dystonia. Surface EEG during an attack and interictally disclosed no abnormality. The patient was tried on a variety of treatments including baclofen, levodopa, benzexhol, tetrabenazine, and acetazolamide without benefit. Different antiepileptic drugs given individually or in combination (1g sodium

valproate with 1 g carbamazepine, and 2 m clonazepam a day) also did not help. The failure of the medical treatment and the frequency of up to 10 or more attacks a day made normal functioning impossible for the patient and therefore a surgical option was considered particularly as the attacks were mainly unilateral. With the consent of the patient a left posteroventral medial pallidotomy was carried out as in a previously described technique.[4] She made an uneventful recovery and had no neurological complications. Immediately after operation the attacks of exercise induced dystonia had ceased completely having occurred more than 10 times a day immediately before the operation even on walking 10–15 steps. At the end of 6 months follow up she had been attack free, apart from occasional minor spasms of her left foot on exercise, despite normal activities; anticonvulsant treatment was gradually being withdrawn.

This is the first example of the usefulness of pallidotomy in a patient with any form of paroxysmal dyskinesia. Pallidotomy and more recently pallidal stimulation are currently being used as surgical techniques for advanced Parkinson's disease in patients with complications of levodopa treatment.[5] These procedures are particularly helpful in abolishing the levodopa induced dyskinesias.[5] Pallidotomy has also been found beneficial in patients with generalised dystonia[6] and recently a unilateral pallidotomy was reported to produce bilateral benefit in one patient with tardive dyskinesia.[7]

Given the improvement in our patient a unilateral pallidotomy could be considered as a treatment option in patients with stereotyped paroxysmal attacks as occur in paroxysmal exercise induced dystonia and the other paroxysmal dyskinesias such as paroxysmal non-kinesigenic dyskinesias in which treatment is often unsatisfactory.[2] A bilateral procedure could be considered in patients with bilateral attacks such as patients with paroxysmal non-kinesigenic dyskinesias who are unresponsive to drug treatment as bilateral pallidotomy seems to improve patients with generalised dystonia.[6]

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1 Lance JW. Familial paroxysmal dystonic choreoathetosis and its differentiation from related syndromes. *Ann Neurol* 1977;ii:285–93.
2 Demirkirin M, Jankovic J. Paroxysmal dyskinesias: clinical features and classification. *Ann Neurol* 1995;**38**:571–9.
3 Bhatia KP, Soland VL, Bhatt MH, *et al*. Paroxysmal exercise-induced dystonia: eight new sporadic cases and a review of the literature. *Mov Disord* 1997;**12**:1007–12.
4 Laitinen LV. Pallidotomy for Parkinson's disease. *Neurosurg Clin N Am* 1995;**6**:105–12.
5 Lang AE, Lozano AM, Montgomery E, *et al*. Posteroventral medial pallidotomy in advanced Parkinson's disease. *N Engl J Med* 1997;**337**:1036–42.
6 Jankovic J, Ondo WO, Lai E, *et al*. Pallidotomy for dystonia [abstract]. *Ann Neurol* 1997;**42**:446.
7 Wang Y, Turnbull I, Calne S, *et al*. Pallidotomy for tardive dyskinesia. *Lancet* 1997;**349**:777–8.

Sudden appearence of invalidating dyskinesia-dystonia and off fluctuations after the introduction of levodopa in two dopaminomimetic drug naive patients with stage IV Parkinson's disease

Hyperkinesias (dystonia, dyskinesia) are, with fluctuating akinesias, the most debilitating disturbances appearing during the advanced course of Parkinson's disease.[1] The origin of these disturbances is controversial; as hyperkinesias are seen after long term treatment with levodopa or dopaminoagonist drugs many researchers think that these motor fluctuations could be prevented by dopaminomimetic drug restriction,[1] others think that hyperkinesias will appear anyway after enough years, independently of dopaminomimetic drug restriction—that is, the supersensitivity of striatal structures to external administration of dopaminomimetic drugs is an epiphenomenon of natural degeneration in Parkinson's disease.[2]

Ten years apart from one another we had the chance to observe two patients with Parkinson's disease with prevalent akinetic symptoms who came to us already in an advanced stage of Parkinson's disease, classified as stage IV according to the Hoehn and Yahr scale.[3] These patients had never been treated with dopaminomimetic agents (levodopa, dopaminoagonists), or amantadine or anticholinergic drugs, and both developed dyskinesias and motor fluctuations when levodopa was increased to the amounts commonly used in patients with stage III-IV Parkinson's disease treated for 6–10 years.

Patient 1 was a 76 year old man living in the inner mountainous part of central Italy. When he came to us he was incapable of rising from his bed; hypomimia, akinesia, flexed dystonic posture, and rigidity were rated 20 at motor examination with the unified Parkinson's disease rating scale (UPDRS),[4] modest 4–5 Hz tremor was present at the upper limbs, left and right intensity was rated 4 at the UPDRS, and utterances were feeble and incomprehensible. The total UPDRS score was 126 (SD 4).

It was possible to reconstruct his clinical history from relatives, and apparently his early stooped posture and akinetic disturbances had appeared at least 10 years before, but was considered to be due to severe arthrosis and was treated with salicilates. Brain MRI at admission was normal. Early treatment with 62.5 mg levodopa thrice daily+benserazide did not induce gastrointestinal intolerance but did not change his UPDRS score and was rapidly (4 days) increased to 250 mg levodopa four times daily+benserazide. Oromandibular dyskinesias, dystonic neck and trunk leftward rotations, and left leg dyskinesias were noticed 2 days after the 1g daily levodopa dosage was reached. Dystonic-dyskinetic movements appeared 20–30 minutes after the first (7 00 am) 250 mg levodopa+benserazide tablet, lasted through the day, and were painful, mostly in the afternoon.

His UPDRS scores were 72 (SD 3) from 8 00 am to 2 00 pm, 88 (SD 3) from 2 00 pm to 8 00 pm. Dyskinesia-dystonia scores were 11 (SD 2) from 8 00 am to 10 00 pm and 13 (SD 2) from 2 00 pm to 10 00 pm. Because dyskinetic-dystonic movements were not tolerated, the daily levodopa had to be reduced to 62.5 mg every 3 hours (total 375 mg/day). With this treatment UPDRS scores were 86 (SD 4); oromandibular dyskinesias and torsional dystonias were still present and rated 10 (SD 2). Bromocriptine up to 10 mg/day was not tolerated. During the next 2 years levodopa treatment could not be increased. His UPDRS scores was 89 at 2 weeks before his sudden death due to apparent cardiovascular complications with cardiac arrest. A postmortem examination showed anteroinferior myocardial infarction, and normal brain structures with depigmentation of the nigral structure. Mesencephalic structures were cut into horizontal 7 µm thick sections and stained with haematoxylin and eosin; three Lewy bodies were found in 109 identified pigmented cells and cell loss was about 86% compared with age matched controls and literature reports.[5]

Patient 2 was a 72 year old man from the same region of central Italy. He came to us akinetic and rigid, with a stooped posture and minor tremor of both upper limbs, and was confined to a wheelchair. Utterances were feeble and incomprehensible. His total UPDRS motor score was 93 for upper limbs, rest tremor was only 2. He had been incapable of walking during the past year, and spent his time on a chair, where he also slept. His relatives described the progressive deterioration in the past 10 years, from the stooped posture to progressive akinesia and language and walking deterioration. His disturbances were attributed to senescence-arthrosis, until comparison with other patients with Parkinson's disease living in the same region, prompted the neurological consultation. This patient was treated with increasing doses of levodopa+benserazide after a one week trial with 125 mg thrice daily had not changed his UPDRS score. A 1.5 g daily dose of levodopa (in 6 administrations) was reached in the next week. Oromandibular dyskinesias and leftward torsion dystonias appeared in the same week. He became able to walk unaided but tremor of the upper limbs was still present, at rest and during walking. His dyskinesias were uncomfortable, although not painful, and his stooped posture was only slightly modified (score 3 from 4). His UPDRS score during treatment was 57, tremor score was 4, and dyskinesia-dystonia score was 7 (SD 1). Treatment was then reduced to 500 mg levodopa+benserazide with 15 mg ropinirole (increasing in three weeks from 1.5 mg/day). With this treatment dyskinesias were reduced, UPDRS score for dyskinesias was 4 in the morning, 5 in the afternoon, and he was able to walk unaided in the morning. His UPDRS score was 65 (SD 4) in the morning and 79 (SD 2) in the afternoon. Brain MRI was normal.

In conclusion, both patients came to us with a levodopa responsive parkinsonism that had appeared, according to history reconstruction, at least 10 years before. Both could be considered at least in stage IV of the Hoehn and Yahr scale.[3] Both had never been treated with dopaminomimetic drugs or with other drugs currently used in the treatment of Parkinson's disease. In both patients dykinesias and dystonias, accompanied by motor fluctuations throughout the day, appeared in the first week. After that a levodopa dose able to modify the akinesia and rigidity scores was reached. Reduction of levodopa dosage in patient 2 and introduction of a dopaminoagonist improved dyskinesia but the total UPDRS score was higher than the score obtained with 1.5 g/day levodopa.

These findings favour the hypothesis suggesting that hyperkinetic fluctuations are not dependent on prolonged dopaminomimetic drug administration but on the natural

course of Parkinson's disease.[6] In favour of this viewpoint is the finding that MPTP exposed parkinsonian patients had severe loss of dopaminergic neurons and developed dyskinesias rapidly after starting levodopa therapy.[7] Caveats about this conclusion must be placed, relative to the fact that both patients had prominently akinetic disturbances, and thus prevalent tremorigenic parkinsonisms might have different courses with different occurrences of complications during levodopa treatment.

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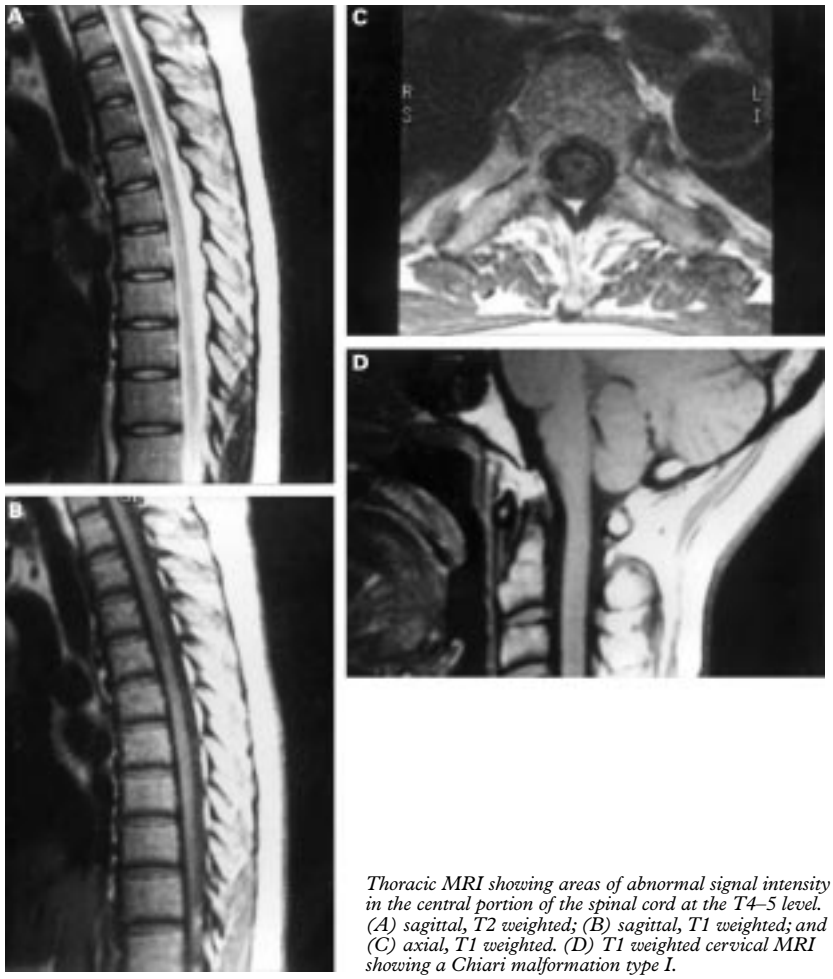
1 Stocchi F, Nordera G, Marsden CD. Strategies for treating patients with advanced Parkinson's disease with disastrous fluctuations and dyskinesias. *Clin Neuropharmacol* 1997;**20**:95–115.
2 Rajput AH, Fenton ME, Birdi S, *et al*. Is levodopa toxic to human substantia nigra? *Mov Disord* 1997;**12**:634–8.
3 Hoehn MM, Yahr MD. Parkinsonisms: onset, progression, and mortality: *Neurology* 1967;**17**: 427–42.
4 Fahn S, Elton RL, *et al*. Unified Parkinson's disease rating scale. In: Fahn S, Mardsen CD, Clane DB, *et al*. eds. *Recent developments in Parkinson's disease*. Vol 2. Florham Park; Macmillan Health Care Information, 1987:153–63, 293–304.
5 Gibb WRG, Lees AJ. Anatomy, pigmantation, ventral and dorsal subpopulations of the substantia nigra, and differential cell death in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1991;**54**:388–96.
6 Agid Y, Bonnet AM, Ruberg M, *et al*. Pathophysiology of levodopa induced abnormal involuntary movements. In: Casey D, Chase TN, Christensen VN, *et al*, eds. Dyskinesia-research and treatment. *Psychopharmacology (Berl)* 1985;(suppl 2):145–59.
7 Langstone JW, BallardP, Tetrud JW, *et al*. Chronic parkinsonism in humans due to a product of peperidine-analog synthesis. *Science* 1983;**219**:979–80.

Reversible hydromyelia in a synchronised swimmer with recurrent thoracic girdle pains

Synchronised swimming is considered a low injury competitive aquatic sport for all ages, although stress related symptoms such as knee or shoulder pain are common.[1] We report a case of recurrent thoracic girdle pains in a professional instructor of this sport due to reversible hydromyelia.

The patient was a 40 year old woman with 15 years experience as an instructor of synchronised swimming. She was in good health up to 15 December 1996 when she developed insidious left thoracic pains 2 days after an underwater exhibition performance that was longer and more strenuous than usual. The pains spontaneously disappeared over the next 10 days. On 6 February 1997, she again experienced similar thoracic girdle pains 2 days after prolonged lessons and a week later came to our hospital. The pain was dull and increased intermittently, in particular when she turned over in bed at night. On examination she was alert, afibrile, and normotensive. Neurological examination disclosed no abnormalities in her cranial nerve, motor, sensory, and autonomic functions. There was no nuchal rigidity. Routine laboratory findings for blood, urine and CSF were all normal. Bleeding and whole blood clotting times were normal. Tests for oligoclonal bands and myelin basic proteins of CSF were negative. Thoracic cord MRI detected areas of abnormal signal intensity (high in the T2 weighted and low in the T1 weighted images with no enhancement by Gd-DTPA) in the central portion of the spinal cord at the T4–5 level (figure A, B, C). The intensities were linear-elliptic in the sagittal plane, and small and round in the axial plane, indicative of hydromyelia (central canal dilatation). Myelography and MRI of the cervical and lumbar cord and of the brain showed no abnormalities except for a Chiari malformation type I (figure D). Only a recommendation not to strain or hold her breath was given, and the pains resolved spontaneously over the next 10 days. Two months later follow up MRI of the thoracic cord showed the absence of the initial abnormal finding.



Thoracic MRI showing areas of abnormal signal intensity in the central portion of the spinal cord at the T4–5 level. (A) sagittal, T2 weighted; (B) sagittal, T1 weighted; and (C) axial, T1 weighted. (D) T1 weighted cervical MRI showing a Chiari malformation type I.

Synchronised swimming requires flexibility, kinesthetic awareness, and aerobic conditioning. Few acute injuries occur in the participation of this sport, but overuse injuries such as knee pain associated with the eggbeater kick and shoulder pain associated with sculling are becoming more common.[1] Therefore the thoracic pain in our patient might have been wrongly diagnosed as having a musculoskeletal origin.

The combination of breath holding and the performance of compulsory figures, such as those that involve hyperextension of the spine, can markedly raise intrathoracic and intracranial pressures during prolonged underwater performances, and may cause dangerous hydromyelia (central canal dilatation) due to changes in the CSF dynamics, especially in those who have a Chiari malformation.[2] We have no idea why this hydromyelia developed at the upper thoracic level.

We conclude that synchronised swimming rules should not encourage prolonged underwater performances and unnatural compulsory figures, and that prior checks for risk factors such as a Chiari malformation should be made.

The lumbar puncture, myelography and follow up MRI were done at the Department of Neurology, the National Institute of Neuroscience Kohnodai Hospital, Ichikawa, Chiba. We thank Dr Takeshi Sato and his colleagues for their expert help.

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1 Weinberg SK. Medical aspects of synchronised swimming. *Clin Sport Med* 1986;**5**:159–67.
2 Williams B. On the pathogenesis of syringomyelia: A review. *J R Soc Med* 1980;**73**: 798–806.

Barium carbonate intoxication: an electrophysiological study

Barium carbonate is an uncommon poisoning agent in India. This whitish coloured powder is available over the shelf from the

chemists and is used mainly as a rodenticide (rat poison). We report an unusual case of barium carbonate poisoning. The nerve and muscle electrophysiological studies are reported for the first time in barium carbonate intoxication.

A 19 year old boy presented to a hospital emergency department with sudden onset tetraplegia. He was referred to our centre as a case of Guillian-Barré syndrome. The patient presented with tingling in the right upper arm, which was immediately followed by weakness in all four limbs. The weakness progressed and involved trunk muscles also within a few minutes. There was no history suggestive of bulbar or facial nerve involvement.

On examination, higher mental functions, cranial nerves, and sensory and cerebellar examination were normal. Examination of the motor system showed a power of 0/5 globally. No deep tendon reflex could be elicited. Surprisingly, with complete areflexic paralysis there was increased tone in the lower limbs. A diagnosis of Guillian-Barré syndrome was considered, but there were some pointers against this diagnosis. The onset and progression to complete tetraplegia was very rapid and the weakness started from the upper limbs followed by that of the lower limbs. Increased tone in the lower limbs was also not consistent with the diagnosis of Guillian-Barré syndrome.

Routine blood investigations at the time of admission, including serum electrolytes, were normal. Nerve conduction study showed normal distal latency of the compound muscle action potential and motor nerve conduction. Amplitude of the compound muscle action potential was low on proximal and distal stimulation. No conduction block, dispersion of compound muscle action potential, or F wave response was recordable. Sensory conduction studies on median and ulnar nerves at both sides of the body were normal for distal latency and amplitude of sensory nerve action potential. No H reflex was recordable on stimulation of posterior tibial nerves on both sides. The patient now disclosed that he had accidentally consumed barium carbonate (15 g) on the day before admission. He ingested barium salt by mistaking it for dieting food given to him by a slimming centre. Ingestion was followed immediately by profuse vomiting. One hour later, the patient had watery diarrhoea. Four hours later he was taken to hospital where his stomach was washed out with magnesium sulphate solution. Blood investigations repeated 8 hours after admission showed normal blood counts, blood gas analysis, and renal and liver function tests. Serum potassium was 2.8 m mol/l and sodium was 140 mmol/l. An ECG showed prominent U waves. Based on available history and investigations, a diagnosis of barium carbonate induced hypokalemic periodic paralysis was considered. The patient was moved to the intensive care unit and monitored for arrhythmias. He was started on intravenous potassium. On day 2, the patient had completely recovered clinically (power 5/5). Serum potassium was normal. Nerve conduction studies were performed as on day 1 with similar results except that the amplitude of compound muscle action potentials were in the normal range. The F waves and H-reflexes were still unrecordable. Electromyography was carried out with concentric needles in the biceps, deltoid, and quadriceps. It showed no abnormal insertional or spontaneous activity and motor unit action potentials were normal in amplitude and duration. The recruitment pattern was reduced. Visual evoked potential, EEG, and brain stem evoked potential were all normal. Nerve conduction velocity and EMG were repeated on day 7 and were normal in all aspects.

Most patients with barium intoxication have gastrointestinal and cardiac involvement with tetraplegia. Barium carbonate is a rare cause of hypokalaemic periodic paralysis.[1] Diarrhoea and arrhythmias are due to direct stimulatory action of barium ions on smooth and cardiac muscles.[2] Heart failure and hypertension may occur in a few cases. Barium blocks the potassium channels and thus potassium efflux from the muscle is reduced whereas the sodium-potassium pump is intact. This causes increased potassium in the muscle and decreased resting membrane potential.[3] Barium acts mainly at the neuromuscular junction by this mechanism.[4] The fatal dose of barium carbonate is 0.8 g and death occurs within 2–12 hours.[4]

There is only one report of an EMG study done in four patients with paralysis because of barium carbonate poisoning. It was done within 1 week of admission and did not show any abnormality.[4] In our case nerve conduction velocity studies and EMG were done on the first day and were sequentially repeated. Interpreting the nerve conduction velocity studies of day 1—namely, low amplitude of compound muscle action potentials— would indicate axonal neuropathy but similar findings can be found in profound muscle weakness because of neuromuscular junction blockade or myopathy. Loss of F waves and H reflexes on day 1 can be explained by the presence of lower amplitudes of compound muscle action potentials on distal nerve stimulation. Loss of F waves and H reflexes with normal distal nerve conduction velocity is suggestive of proximal demyelination or dysfunction at the spinal cord level. Loss of H reflexes and the F response has not been reported previously in patients with hypokalaemic periodic paralysis. As H reflex latency depends on several factors including the central delay in the cord involving conduction, synaptic transmission, and activation of anterior horn cells, any of these processes might be involved in barium carbonate poisoning. The exact mechanism for their absence is still unclear. These responses reverted back to normal on day 7. The concentric needle EMG study on the second day showed a reduced recruitment pattern which is found in neuropathies but has also been reported in hypokalaemic periodic paralysis.[5]

In most cases of barium ingestion the recovery from weakness occurs rapidly and uneventfully.[4] Oral magnesium sulphate or sodium sulphate precipitate barium in the gut and thus reduce absorption. Large amounts of intravenous potassium are needed to restore the pump electrogenesis and to displace barium from potassium channels.[1] Hypertension caused by barium cannot be reversed by this treatment. Haemodialysis is a useful therapeutic adjuvant in severe barium carbonate poisoning. Ventilatory support may be required due to respiratory muscle involvement.[4]

In summary, this is the first electrophysiological study done on day 1 in a case of barium carbonate poisoning with paralysis. Previously involvement of neuromuscular junctions has been considered as a cause for weakness. In our study, we found that barium acted at more than one level—that is, muscles, proximal segments of the reflex arc, and probably γ efferents as the tone was increased.

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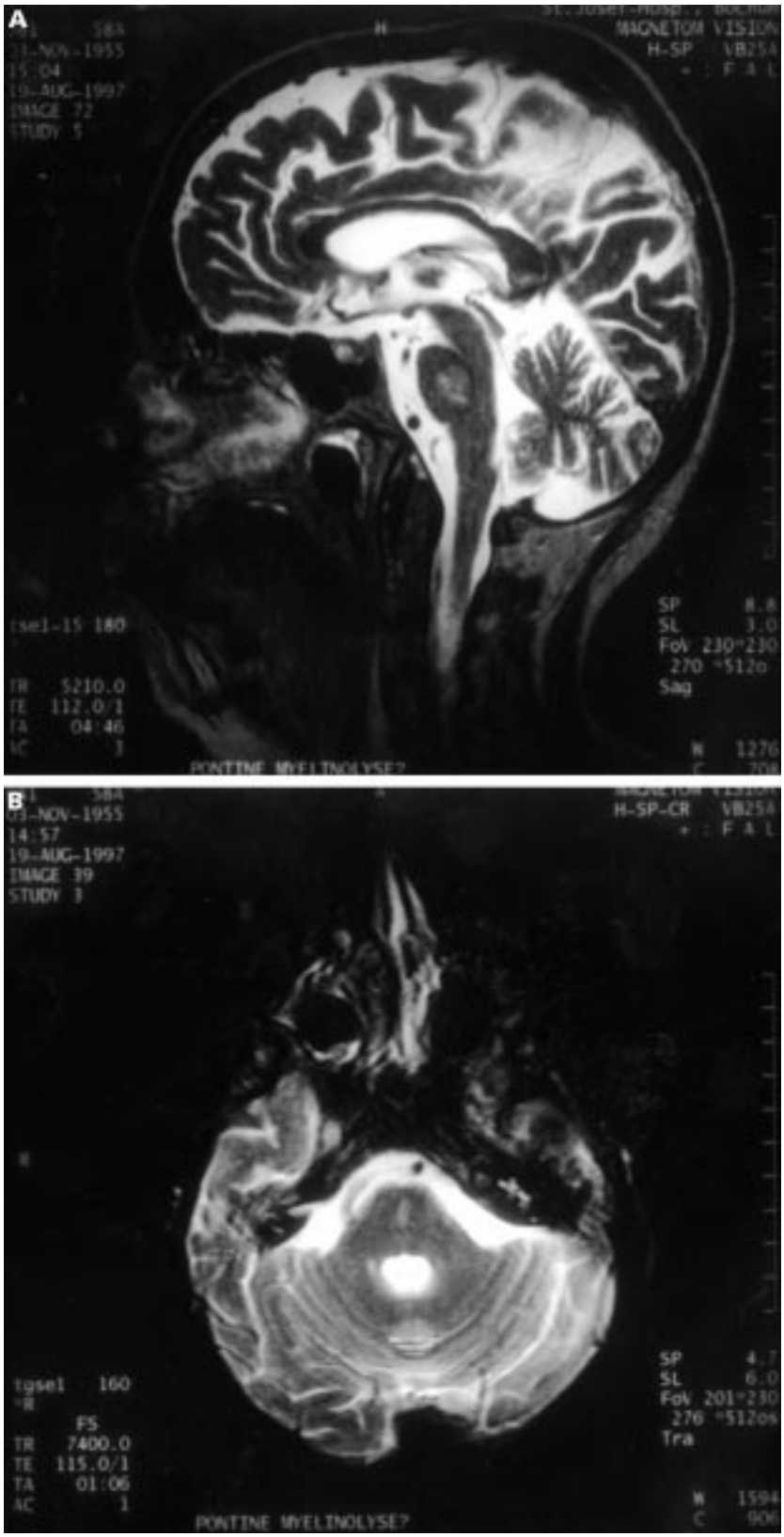
1 Stedwell RE, Allen KM, Binder LS. Hypokalemic paralysis: review of etiologies, pathophysiology, presentation and therapy. *Am J Emerg Med* 1992;**10**:143–8.
2 Gosselin RE, Smith RP, Hodge HC, *et al .Clinical toxicology of commercial products*, *5th ed*. Baltimore: Williams and Wilkins, 1984:**3**;61–2.
3 Layzer RB . Periodic paralysis and the sodium-potassium pump. *Ann Neurol* 1982;**11**:5437–52.
4 Agarwal AK, Ahlawat SK, Gupta S, *et al*. Hypokalemic paralysis secondary to acute barium carbonate toxicity. *Trop Doct* 1995:**25**: 101–3.
5 Clinical aspect of electromyography. In: Amnoff MJ, ed. *Electromyography in clinical practice. Electrodiagnostic aspect of neuromusclar disease*. 2nd ed. New York: Churchill Livingstone, 1987:73–101.

Central pontine myelinolysis causes bilateral loss of deep sensitivity and pseudochoreoathetosis

Central pontine myelinolysis is characterised as symmetric and selective destruction of myelin sheath of the basis pontis. Central pontine myelinolysis often results from rapid increase of serum sodium after hyponatraemia. Patients with central pontine myelinolysis often show symptoms such as conscious disturbances, tetraparesis, and pseudobulbar palsy.[1–3] We present a case of central pontine myelinolysis due to compensation of hyponatraemia, resulting in acute onset of pseudochoreoathetosis and sensory disturbances.

A 39 year old woman was submitted to a department of internal medicine of another hospital due to a long history of alcoholism, resulting in bad general condition accompanied by severe anaemia, toxic gastritis, and acute pancreatitis. She was alert without any mental disturbances. Laboratory data disclosed metabolic acidosis and hyponatraemia of 126 mmol/l. She received bicarbonate and physiological saline intravenously to compensate for the metabolic disturbances. Serum sodium increased to 136 mmol/l within 3 days. On the third day she suddenly developed severe choreoathetotic movements. Therefore she was transfered to our department of neurology. On the day of submission to our department she remained alert, but she had difficulties in swallowing and speaking. Examination of the cranial nerves showed bilateral ptosis and a dissociated nystagmus on the left side. We also found weakened corneal and pharyngeal reflexes. There was a general reduction of deep tendon reflexes and muscle tone. Muscle strength was normal. Involuntary movements were absent but angle positioning during movements was choreoathetotic. She was unaware of the position of her limbs with closed eyes. We instructed her to watch her limbs and she was then able to reach her nose with the finger. When investigating her sensitivity we found a complete loss of touching, vibration, and position sense in all limbs. Pinprick sensation was unremarkable in the upper limbs, whereas testing of the legs caused a painful burning sensation. Thermal sensation and



T2 weighted MRI (A) sagittal, and (B) axial scan after acute onset of pseudochoreoathetosis: high signal in the central part of the pons.

sensitivity of her face were normal. We excluded tabes dorsalis and vitamin B12 deficiency by laboratory tests. Cranial CT was normal. T2 weighted MRI showed a hyperintense lesion within the pons but no extrapontine myelinolysis (figure). Within 4 weeks the subject's symptoms had nearly disappeared. Only a slight reduction of the vibration sense in all limbs persisted. Control MRI after 4 weeks disclosed an unchanged size of the patient's pontine lesion. At that time nerve conduction velocities and somatosensory evoked potentials, which, due to technical reasons, were only performed after the patient's recovery, were normal.

To our knowledge this is the first reported case of central pontine myelinolysis associated with acute onset of movement disorder and isolated affection of propioceptive sensitivity.[1] The appearance of parkinsonism, dystonia, or choreoathetosis in the course of central pontine myelinolysis are often looked on as symptoms of additional manifestation of extrapontine myelinolysis. The association with manifestation of central pontine myelinolysis remained speculative in some cases of delayed onset of movement disorders after central pontine myelinolysis.[1] By contrast our patient showed an acute onset of pseudochoreoathetosis after manifestation of central pontine myelinolysis and MRI imaging in our subject disclosed no signs of extrapontine myelinolysis.

Our patient additionally showed an isolated loss of propioceptive sensation. Disturbances of sensation are described as less severe symptoms of central pontine myelinolysis. Silver *et al*[2] described an association of sensory ataxia and affection of vibration and position sense, but with reduced pinprick sensation.[2] This case may imply a further extension of the pontine lesion or a possible extrapontine lesion, not detectable on MRI.[2] Defebre *et al* reported two cases of central pontine myelinolysis with isolated affection of deep sensation.[3] Isolated affection of the medial lemniscus of the brain stem or thalamic infarction may cause sensory ataxia and disturbances of deep sensitivity resulting in choreoathetotic movements.[4 5] Therefore, we speculate that our patient's pontine lesion caused sensory ataxia and subsequent pseudochoreoathetosis, because the movement disturbances appeared without delay after the onset of sensory defects. Moreover, the loss of propioceptive sensitivity with spared thermal and pain sensation implies an isolated alteration of the medial lemniscus by sparing the spinothalamic tract.[4] This finding suggests a lesion with a pontine site. We found no extrapyramidal lesion by MRI in our patient. In conclusion we hypothesise that the pontine lesion itself may be a possible cause of our patient's pseudochoreoathetotic movements.

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1 Tison FX, Ferrer X, Julien J. Delayed onset movement disorders as a complication of central pontine myelinolysis. *Mov Disord* 1991;**6**:171–3.
2 Silver NC, Barker GJ, MacManus DG, *et al*. Decreased magnetisation transfer ratio due to demyelination: a case of central pontine myelinolysis. *J Neurol Neurosurg Psychiatry* 1996;**61**:208–9.
3 Defebvre L, Rogelet P, Destée A, *et al*. Regressive dystonia and cerebellar ataxia: two unusual symptoms in central pontine myelinolysis. *J Neurol* 1995;**242**:450–4.
4 Roh JK, Lee YS. Bilateral medial medullary infarction manifested as sensory ataxia: a case report and review of the literature. *J Korean Med Sci* 1996;**11**:193–6.
5 Lee MS, KimDY, Kim JT, *et al*. Abrupt onset of transient pseudochoreoathetosis associated with proprioceptive sensory loss as a result of a thalamic infarction. *Mov Disord* 1998;**13**:184–6.

Successful treatment of peripheral paraneoplastic neurological syndromes in small cell cancer

Immune mediated paraneoplastic neurological syndromes often become manifest before the underlying malignancy is detected. As a rule, these syndromes do not improve with antineoplastic treatment.[1] We report on a case of a patient with small cell cancer with peripheral neurological syndromes that responded favourably to combination chemotherapy.

At the time of admission the patient, a 66 year old woman, had had a combination of peripheral neurological symptoms for 3 months: (*a*) muscle weakness and muscle pain of the legs so that she could not walk unattended; (*b*) a numbness of both legs from the foot to the middle of the thigh; (*c*) dryness of the eyes and mouth; and (*d*) severe constipation.

Clinical examination showed a load dependent, proximally accentuated symmetric muscle weakness and hypoaesthesia of the legs. The patient was unable to stand or walk without support. The deep tendon reflexes of the arms were decreased on both sides and leg reflexes could not be elicited. No pathological reflexes were detectable. Analysis of CSF yielded normal values for protein content, cell number, and glucose. Besides a slightly increased erythrocyte sedimentation rate (35 mm in the first hour), standard laboratory values showed no abnormalities. Abdominal auscultation and CT were unrevealing.

Electrophysiological investigation (somatosensory evoked potentials of the tibial and median nerves, EMG, and electroneurography) showed delayed latencies and a reduced amplitude of P40 (tibial SEP), N10, and N13 potentials (median SEP) and polyphasic muscle action potentials. Nerve conductance velocities were on the border of the normal range for the motor peroneal and tibial nerves as well as for the sensory sural nerve. Stimulation of the ulnar nerve with 20 Hz yielded an increment of 60%. Besides a polyneuropathy syndrome, the results of the electrophysiological examinations suggested Lambert-Eaton myasthenic syndrome.

Computed tomography showed a small metastasis of an undetectable primary tumour in a mediastinal para-aortal lymph node, which was immediately resected and histologically identified to be small cell cancer.

As an autoimmune paraneoplastic origin of the neurological symptoms, particularly Lambert-Eaton myasthenic syndrome, was suspected, we measured autoantibodies against presynaptic voltage gated calcium channels by immunoprecipitating ^{125}I-conotoxin binding proteins. The antivoltage gated calcium channel titre of 105 pM was positive, although not extremely so. The titre of antinuclear antibodies was 1:960; most of them were identified as anti-Scl-70. High titre (1:6000) antineuronal antibodies were seen on immunofluorescence of fresh frozen sections of rat cerebellum. Anti-Hu appeared as a prominent band in a western blot of recombinant Hu protein.

As treatment with 3,4-diaminopyridine (10 mg every 4 hours) improved the muscle weakness but had no effect on constipation and the sensory disorder, these symptoms were thought to indicate anti-Hu syndrome. Four cycles of chemotherapy (ACO-I scheme), however, improved all neurological syndromes. Muscle pain and leg hypoaesthesia disappeared, and muscle strength was fully restored so that the patient was able to walk unattended for long distances. The features of Lambert-Eaton myasthenic syndrome were also no longer detectable by EMG. Constipation was alleviated. All types of autoantibodies declined considerably. The antinuclear antibodies titre was reduced to 1:32; immunoprecipitation for antivoltage gated calcium channel antibodies yielded 22.7 pM, which is within the normal range. Antineuronal antibodies were barely detected on sections of rat cerebellum at a serum dilution of 1:32. The anti-Hu signal was also clearly reduced on a western blot. The clinical, physiological, and laboratory findings before and after chemotherapy—that is, six months after admission—are summarised in the table. Combination chemotherapy brought about a considerable and unexpected improvement of two peripheral neurological syndromes (Lambert-Eaton myasthenic syndrome and anti-Hu syndrome with gastrointestinal pseudo-obstruction, muscle pain, and sensory deficits) and a concomitant decrease in autoantibody titres in a patient with small cell cancer.

The results of treatment for paraneoplastic neurological syndromes are still discouraging, despite widespread use of chemotherapy combining antineoplastic and immunosuppressive activity. The reasons for the frequent failures may be irreversible loss of neurons due to autoimmune attack and the differential susceptibility of autoreactive B and T cells inside and outside the blood-brain barrier to the infusion of immunosuppressive drugs. Autoimmune paraneoplastic syndromes involving the CNS are probably caused by intrathecal autoreactive lymphocytes, which may be less accessible to inhibiting drugs than immune cells outside the blood-brain barrier. This hypothesis is supported by the case presented here and by reports of the differential response of central and peripheral syndromes to treatment.[2 3]

By contrast with the refractory central syndromes, tumour treatment for Lambert-Eaton myasthenic syndrome has been shown to have beneficial effects in many patients. In at least two cases, a differential response to immunotherapy of peripheral and central syndromes was found in the same patients.[2 3] In one case,[2] a patient with paraneoplastic Lambert-Eaton myasthenic syndrome and subacute cerebellar degeneration due to an initially undetected small cell lung cancer, chemotherapy had a beneficial effect on Lambert-Eaton myasthenic syndrome, but not on subacute cerebellar degeneration. In the second case,[3] the same combination of peripheral syndromes was caused by a non-Hodgkin's lymphoma. Immunosuppression improved neuromuscular, but not cerebellar symptoms.

Paraneoplastic autoantibodies seem to arise from immunological cross reactions between tumour antigens and normal target proteins. They may take part in the immune response to malignancies, or simply be an epiphenomenon of an immune process triggered by the neoplasm.[4] The prognosis of patients who mount a humoral antitumour response is usually better than that of patients without response.[5] The immune process characterised by production of paraneoplastic autoantibodies, however, is a two edged sword. The neurological disorders often associated with some paraneoplastic autoantibodies are so severe that they require immediate treatment, even before a tumour is detected. In such cases, immunosuppressive treatments bear the risk of supporting tumour growth by inhibiting the ongoing immune attack against the neoplasm without interfering with the metabolism of the malignant cells. Therefore, all efforts should be directed at identifying the underlying malignancy. As soon as the presence of a tumour is confirmed, chemotherapy should be initiated to control its growth and to suppress autoantibody production, at least outside the CNS.

Table 1 Clinical, electrophysiological, and immunological variables before and after chemotherapy in a patient with small cell cancer

	Time of admission	*3 Months after chemotherapy*
Tumour diameter	3 cm	Not detected
Titre of ANAs	1:960	1:32
IgG titre on rat cerebellum	1:6000	1:32
Anti-Hu	Band in western blot	Declined
Pseudo-obstruction	Present	Absent
Ability to walk unattended	No	Yes
Numbness of legs	Present	Absent
Antibodies against VGCC	105 pM	22.7 pM
Electromyography at 20 Hz	Increment 60%	No increment

ANA=antinuclear antibody; VGCC=voltage gated calcium channel.

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1 Voltz RD, Posner JB, Dalmau J, *et al*. Paraneoplastic encephalomyelitis: an update of the effects of the anti-Hu immune response on the nervous system and tumour. *J Neurol Neurosurg Psychiatry* 1997;**63**:133–6.
2 Blumenfeld AM, Recht LD, Chad DA. Coexistence of Lambert-Eaton myasthenic syndrome and subacute cerebellar degeneration: differential effects of treatment. *Neurology* 1991;**41**: 1682–5.

3 Goldstein JM, Waxman SG, Vollmer TL. Subacute cerebellar degeneration and Lambert-Eaton myasthenic syndrome associated with antibodies to voltage-gated calcium channels: differential effect of immunosuppressive therapy on central and peripheral defects. *J Neurol Neurosurg Psychiatry* 1994;**57**:1138–9.
4 Drlicek M, Bianchi G, Bogliun G, *et al*. Antibodies of the anti-Yo and anti-Ri type in the absence of paraneoplastic neurological syndromes: a long-term survey of ovarian cancer patients. *J Neurol* 1997;**244**:85–9.
5 Winter SF, Sekido Y, Minna JD, *et al*. Antibodies against autologous tumor cell proteins in patients with small-cell lung cancer: association with improved survival. *J Natl Cancer Inst* 1993;**85**:2012–8.

A preliminary investigation of laterality in Parkinson's disease and susceptibility to psychosis

Cerebral disease with more prominent left sided cerebral involvement may be more closely associated with psychotic phenomena; a comprehensive review of cerebral laterality in relation to psychosis has suggested that a special, although unclear, pathophysiology may be at work.[1]

A review of patients with treated Parkinson's disease found an overall incidence of psychiatric side effects of 20% (range 10–50) in 908 patients treated in major studies.[2] Psychoses—that is, hallucinations and delusions—occurred with a frequency of 4% and were more likely to occur with concurrent dementia, increasing age and use of higher dose of levodopa. It is assumed that the main precipitant of psychotic phenomena in Parkinson's disease is dopaminergic excess secondary to treatment. Cognitive impairment, which has been reported to occur in as many as 29% of patients with Parkinson's disease, associated with increased age and older age at onset, may also increase vulnerability to psychosis.

Asymmetry in Parkinson's disease is said to remain unchanged over time,[3] and patients with unilateral onset of Parkinson's disease manifestations have greater degeneration of the contralateral substantia nigra at postmortem examination.[4] If predominantly left sided pathology increases the vulnerability to psychotic phenomena then initial right sided predominance of parkinsonian symptoms and signs might be a predictor of increased vulnerability. If initial right sided symptom predominance did indeed predict the subsequent development of psychotic phenomena (independent of cognitive decline, age, and medication) this might be clinically useful in identifying a patient subgroup in whom particular care is required in titrating medication.

A retrospective review of all case notes of patients with Parkinson's disease, identified by their presence on the specialist Parkinson's disease nurse register in a district general hospital, was carried out (*a*) to evaluate the presence of psychotic symptoms using a checklist, (*b*) to record asymmetry of parkinsonism both currently and at onset, and (*c*) to record handedness. Psychotic symptoms (delusions and hallucinations) were only noted when they occurred outside an acute confusional state. All patients had been diagnosed by one of two consultant neurologists. The level of medication, both current and while having psychotic symptoms, cognitive assessment, number of years of illness, and demographic variables were also recorded. Patients who had had a psychotic episode were compared with the remainder with respect to asymmetry of symptoms at onset of illness, age, duration of illness, medication levels and demographic variables. This was repeated with a subgroup of patients with no cognitive deficit. Logistic regression analysis (forward stepwise) was carried out with psychosis as the dependent variable.

The case notes of 100 patients were reviewed. There were 51 men and 49 women in the sample. Fifty one patients were right handed, four were left handed, and in 45 handedness was unknown. Dementia was noted in 30 patients, with "memory difficulties" recorded in a further eight. Hallucinations were recorded in 28 patients and delusions in six. The patients with hallucinations or delusions were classified as the psychosis group (n=30), and those with dementia and memory difficulties as the cognitively impaired group (n=38), for analysis. Details of illness, for the whole sample and separated into psychotic and non-psychotic subgroup, side of onset, and the demographic data, are shown in the table.

Patients' characteristics and the presence of psychosis

	Total sample	*Psychosis*		*p Value*
		Yes	*No*	
Patients (n)	100	30	70	
Age (y):				
Mean	71	71.8	71	NS
SD	6.8	4.5	7.5	
Age at onset:				
Mean	64	61.6	64.7	NS
SD	8.9	8.2	9.1	
Duration of illness (y):				
Mean	7	10	6.3	<0.02
SD	5.7	7.1	4.6	
Dose of levodopa (mg/day):				
Mean	455	506	433	NS
SD	353	320	367	
Dose of selegeline (mg/day):				
Mean	3.8	2.8	4.1	NS
SD	5.7	4.3	6.1	
Side of onset total (n=100):				
Right	43	16	27	NS
Left	45	9	36	
Side of onset cognitively unimpaired (n=62):				
Right	25	7	18	<0.03
Left	32	2	30	
EPS at onset (n=95):				
Tremor	55	13	42	NS
Rigidity	19	4	15	
Akinesia	21	10	11	

Comparison of side of onset with presence of psychosis disclosed more patients with right sided onset of parkinsonian symptoms having psychotic symptoms, although this was not significant (χ^2=3.0, df=1 p<0.09; table). Presence of psychosis was significantly associated with presence of cognitive decline. Eighteen out of 38 in the cognitively impaired group were psychotic by comparison with 12 out of 62 in the cognitively intact group (χ^2=13.5, df=1, p<0.003). Presence of psychosis was also associated with duration of illness (*t* test=2.69, df=36, p<0.02). There were no significant differences between the psychotic symptom group and the other patient groups in age, age at onset of symptoms, and dosage of current medication. Comparative dosage of levodopa and selegiline are shown in the table. Benzhexol, bromocriptine, pergolide, and orphenadrine were taken by 10, 14, 13, and seven patients respectively, and showed no differences between the groups. Furthermore there were no significant differences in the dose of current medication and the dose noted when undergoing a psychotic episode.

Cognitive decline was associated with increasing age but was not related to age of onset or dosage of medication. When patients with cognitive decline (n=38) were removed from the analysis, right sided onset of symptoms was significantly related to the presence of psychosis (χ^2=5.0, df=1, p<0.03) in the remainder. In this subsample there were no significant differences between left and right side onset for age, duration of illness, or dosage of different medication.

Logistic regression analysis of the total sample, with psychosis as the dependent variable, confirmed the association between psychosis and cognitive decline (*t*=3.89, p<0.003) and increased duration of illness (*t*=2.64, p<0.02). There were no other significant contributing variables, although side of onset was the strongest associated variable remaining (*t*=1.69, p<0.09). However, when the logistic regression was repeated with the subsample without cognitive decline, right sided onset was the only variable significantly associated with psychotic symptoms (*t*=2.30, p<0.03).

Our results show only a trend, in the sample as a whole, linking right sided symptoms at onset and the subsequent development of psychosis; perhaps unsurprising in view of the confounding effect of cognitive impairment. In the cognitively intact subsample there was a significant association with right sided onset of symptoms of Parkinson's disease. This suggests that damage to left hemispheric structures involved in Parkinson's disease is associated with a predisposition to psychosis. Our results do not support an iatrogenic dopaminergic excess as a cause of psychosis; this may be because of subsequent dosage adjustment, or the explanation may lie in asymmetric upregulation of dopaminergic receptors and supersensitivity to dopaminergic therapy at equivalent doses of medication.

The limitations of using retrospective data are well recognised and the possibility of mild cognitive dysfunction not being detected in the cognitively intact group needs to be recognised. However, this preliminary study provides support for our a priori hypothesis that right sided predominance of neurological deficit at the onset of Parkinson's disease predicts the subsequent development of psychosis.

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1 Flor-Henry P. *Cerebral basis of psychopathology*. Bristol: John Wright, 1983.
2 Goodwin FK. Psychiatric side effects of levodopa in man. *JAMA* 1971;**218**:1915–20.
3 Lee CS, Schulzer M, Mak E, *et al.* Patterns of asymmetry do not change over the course of idiopathic Parkinson's disease. *Neurology* 1995; **45**:435–9.
4 Kempster PA, Gibb WR, Stern GM, *et al.* Assymetry of substantia nigra neuronal loss in Parkinson's disease and it's relevance to the mechanism of levodopa related motor functions. *J Neurol Neurosurg Psychiatry* 1989;**52**: 72–6.

Cerebral venous sinus thrombosis associated with 20210A mutation of the prothrombin gene

Predisposing factors can be identified in up to 80% of patients who develop cerebral venous thombosis (CVT).[1] In many patients risk factors are acquired but 10 to 15% of patients may have inherited tendencies to thrombosis. Deficiencies of protein C, protein S, or antithrombin are reported in large series. The recently identified factor V Leiden mutation (FVR506Q) giving rise to activated protein C resistance is one of the most prevalent genetic mutations currently identified (10% to 15% of the white population),[2] and it is now known to be an important risk factor for cerebral venous thrombosis.[3–6] All of these thrombophilic tendencies, and particularly the factor V Leiden mutation, are compounded by other factors such as the oral contraceptive pill, pregnancy, pueperium, or immobility.

Prothrombin is a precursor of the serine protease thrombin and is a key enzyme in the process of haemostasis. Recently, a single nucleotide substitution (G to A) at position 20210 in the 3' untranslated region of the gene encoding prothrombin has been identified.[7] Its heterozygous state, 20210A, is a risk factor for the development of deep vein thromboses,[7 8] and it has recently been implicated in the development of superior sagittal sinus thrombosis in a woman taking the oral contraceptive pill.[9] We report the development of extensive cerebral venous thrombosis in a patient, without other risk factors, who was found to be heterozygous for this newly identified genetic mutation.

A 46 year old man had headaches for 2 weeks which became acutely worse and were associated with vomiting and dizziness. His conscious level fluctuated but was progressively deteriorating. He had a generalised tonic-clonic seizure and a history of a spontaneous deep vein thrombosis. There was no family history of thromboses.

He was obtunded with bilateral papilloedema. There were no focal signs except for a right extensor plantar. Unenhanced brain CT was normal but a lumbar puncture disclosed a pressure of 34 cm of CSF with 28 000 red blood cells, 40 white blood cells/mm^3 and a protein concentration of 1.5 g/l with normal glucose. A repeat brain CT with contrast showed diffuse swelling in the posterior fossa, with supratentorial and infratentorial haemorrhages and high attenuation around many of the venous sinuses. Brain MRI disclosed extensive thrombosis of the superior sagittal sinus, the straight sinus, and both transverse and sigmoid sinuses. There was haemorrhage in the left cerebellar hemisphere and haemorrhagic infarcts in the left parietal and both cerebellar hemispheres.

Results of thrombophilia screening

Test	*Result*	*Laboratory normal range*
Prothrombin gene (20210A) mutation	Heterozygous	
Factor V Leiden mutation	Negative	
Antithrombin III activity (%)	70	80–155
Antithrombin III (4 months later) (%)	85	80–155
Protein C activity (%)	66	65–165
Protein S free antigen (%)	79	70–115
Protein S total antigen (%)	87	65–115
Activated protein C resistance ratio	3.05	>2.3
IgG anticardiolipin antibodies (GPL U/ml)	4.1	0.0–14.1
IgM anticardiolipin antibodies (MPL U/ml)	1.3	0.0–1.6 MPL U/ml
Russell's viper venom test ratio	1.16	0.9–1.1
50/50 Russell's viper venom ratio	1.01	0.9–1.1
Platelet neutralisation ratio	1.16	
Correction (%)	0.0	0.0–12

Full blood count and biochemistry were normal. The erythrocyte sedimentation rate was 24 mm in the first hour and C reactive protein was 24.1 mg/l (normal<8). Autoantibodies including antinuclear antibodies were negative. Treponemal pallidum haemagglutination test and rapid plasmin reagin tests were negative. The prothrombin time and activated partial thromboplastin time were normal. A thrombophilia screen was performed 24 hours after starting heparin (table). Initial antithrombin activity was reduced at 70% but was normal when repeated 4 months after the initial presentation; however, the patient was found to be heterozygous for the 20210A prothrombin gene mutation. This was identified using the polymerase chain reaction (PCR) of exon 14 and the 3'-untranslated region of the prothrombin gene, followed by restriction digestion by Hind III. The mutant allele then appeared as an extra DNA fragment on agarose gel electrophoresis. The presence of the 20210A allele was subsequently confirmed by DNA sequencing.

He was treated with intravenous heparin (APTT ratio 2 to 3) with the gradual introduction of warfarin which he will continue for life. His condition gradually improved; he had mild residual pyramidal signs, but no significant disability, and no further seizures.

The substitution of G to A at position 20210 of the prothrombin gene is a recently recognised risk factor for venous thrombosis. It has been found in 18% of selected patients with a family history of venous thrombosis, 6% to 7% of unselected patients with deep vein thrombosis, but only 1% to 2% of controls,[7 8] making it the second most common hereditary thrombophilia after the factor V Leiden mutation.[2] Prothrombin is encoded by a 21 kb gene located on chromosome 11p11 to q12. Patients with the mutation (20210A) have higher plasma prothrombin concentrations than controls with the normal genotype (20210G), suggesting that hypercoaguability is due to hyperactivity of the common coagulation pathway resulting in increased thrombin production.[7]

Our patient had reduced antithrombin concentrations at 70% on initial testing. Thrombotic tendencies arise when concentrations are less than 60% of normal. The initial concentration was probably secondary to the acute thrombosis or treatment with heparin. Repeat testing after 4 months showed normal concentrations, hence we think that antithrombin deficiency is unlikely to be implicated in this patient's CVT. There were no other risk factors for venous thrombosis in our patient, unlike the recently reported patient with sagittal sinus thrombosis, who was taking the oral contraceptive pill.[9]

Activated protein C resistance due to the factor V Leiden mutation is the most common hereditary thrombophilia associated with CVT,[3–6] although in most cases it is also associated with an acquired prothrombotic tendency,[3] such as the oral contraceptive pill. In a recent study of 40 patients with CVT, Activated protein C resistance with the Leiden mutation was found in four patients, protein C deficiency in one, and protein S deficiency in another.[3] Isolated hereditary thrombophilias as a cause of CVT seem to be rare in the absence of other factors, with only the patient with protein S deficiency in the series of Deschiens *et al*[3] and other occasional cases[4 5] having no other predisposing factor.

The identification of an inherited thrombophilia in a patient with CVT should not, therefore, preclude a search for other provoking factors. To the list of inherited thrombophilias should now be added the newly identified 20210A prothrombin gene mutation.

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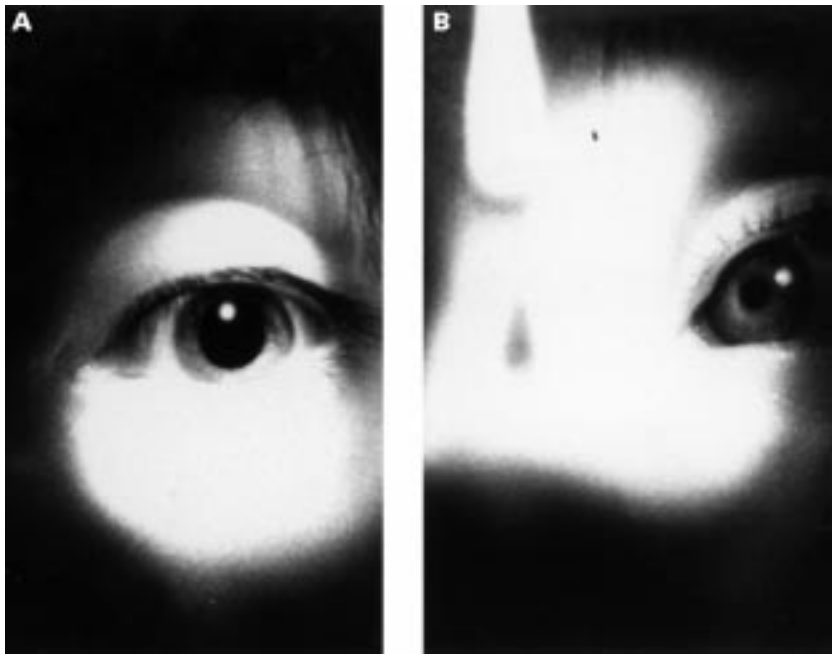
1 Bousser M-G, Ross Russell R. *Cerebral venous thrombosis*. London: WB Saunders, 1997.
2 Dahlback B, Hillarp A, Rosen S, *et al.* Resistance to activated protein C, the FV:Q506 allele, and venous thrombosis. *Ann Haematol* 1996;**72**:166–76.
3 Deschiens M, Conard J, Horrellou M, *et al.* Coagulation studies, factor V Leiden and anticardioloipin antibodies in 40 cases of cerebral venous thrombosis. *Stroke* 1996;**27**:1724–30.
4 Dulli DA, Luzzio CC, Williams EC, *et al.* Cerebral venous thrombosis and activated protein C resistance [comments]. *Stroke* 1996;**27**: 1731–3.

5 Martinelli I, Land G, Merati G, *et al*. Factor V gene mutation is a risk factor for cerebral venous thrombosis. *Thromb Haemost* 1996;**75**: 393–4.
6 Zuba M, Toulon P, Marnet L, *et al*. Factor V Leiden mutation in cerebral venous thrombosis. *Stroke* 1996;**27**:1721–3.
7 Poort SR, Rosendaal FR, Reitsma PH, *et al*. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996;**88**:3698–703.
8 Hillarp A, Zoller B, Svensson P, *et al*. The 20210A allele of the prothrombin gene is a common risk factor among Swedish outpatients with verified deep vein thrombosis. *Thromb Haemost* 1997;**78**:900–2.
9 Bloem BR, van Putten MJAM, van der Meer FJM, *et al*. Superior sagittal sinus thrombosis in a patient heterozygous for the novel 20210A allele of the prothrombin gene. *Thromb Haemost* 1998;**79**:235.

Pseudo-Argyll Robertson pupil of patients with spinocerebellar ataxia type 1 (SCA1)

A pseudo-Argyll Robertson pupil is a neurological sign indicating a normal near reflex but the absence of a light reflex (light-near dissociation), a lack of miosis, and pupil irregularity. It has been reported in patients with diabetes mellitus, multiple sclerosis, Wernicke's encephalopathy, sarcoidosis, tumours, and haemorrhage.[1] Although the appearance of pseudo-Argyll Robertson pupil is very similar to Holmes-Adie pupil, the first is distinguishable from the second by the location of lesions and pharmacological response. The responsible lesion in pseudo-Argyll Robertson pupil is in the central region, whereas that of Holmes-Adie pupil is peripheral. Dilute pilocarpine constricts the pupils of patients with Holmes-Adie pupil, but it is not effective in patients with pseudo-Argyll Robertson pupil. We present a patient with spinocerebellar ataxia type 1 (SCA1) and her asymptomatic younger brother who both exhibited pseudo-Argyll Robertson pupil.

Patient 1 was a 21 year old woman who complained of gait instability in 1996. Thereafter, she noticed difficulties in speech and in the fine movement of her hands. Her mother had had gait disturbance since her 20s and died of pneumonia at the age of 35. The condition of our patient deteriorated gradually, and she was admitted to our hospital in April, 1997. Neurological examination showed bilateral mydriasis (7.0 mm in diameter) and light-near dissociation (figure). Although the light reflex was absent, the near reflex was normal. The extraocular movements were saccadic and the upper gaze of both eyes was slightly limited. Optokinetic nystagmus was absent. Her tongue showed atrophy and fasciculation. The distal muscles of the limbs were slightly weak, although muscle tone was normal. The deep tendon reflexes were augmented in her upper and lower limbs. Babinski's and Chaddock's signs were positive on both sides. The sensory system was normal. Her speech was ataxic; slight limb ataxia was detected in the limbs; and her gait was wide based and ataxic. Blood and urine laboratory findings were normal. Her pupils reacted to 1% pilocarpine, but not to 0.2% pilocarpine. Brain MRI showed remarkable atrophy of the cerebellum and a slight atrophy of the pontine tegmentum. ^{99m}Technetium-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) SPECT disclosed a hypoperfusion of the cerebellar vermis, pons, and basal ganglia.



Light-near dissociation in the left eye of the sister. (A) The light reflex was absent. (B) A steady gaze on the marker in front of her nose induced the convergence and accomodation reflexes.

Patient 2 was a 20 year old man, the brother of patient 1. He consulted our clinic for examination, although he had not experienced any neurological problems. He received dialysis three times a week because he had renal failure due to pyelonephritis. On examination, he presented pupillary abnormalities which were similar to those of patient 1 (mydriasis; 6.5 mm, light-near dissociation). Although the light reflex was absent, the near reflex was normal. His upward gaze was slightly limited. Fasciculation was noted on his tongue. The distal portion of the upper limbs was slightly weak and the deep tendon reflexes in the limbs were slightly accentuated. Babinski's sign was positive in both feet, although there were no signs of spastic or ataxic movement in his limbs and in his gait. Their father showed no abnormalities on neurological examination.

Blood was collected for molecular studies with informed consent from both patients and their father. Total DNA was extracted by the phenol/chloroform method from peripheral blood leucocytes. To detect CAG expansion in the SCA1 region, we performed a polymerase chain reaction (PCR) with Rep-2 (5' CAACATGGGCAGTCTGAG 3') and Rep-1 (5' AACTGGAAATGTGGGCGTAC 3') according to Orr *et al*.[2] The products of PCR were separated by electrophoresis (2% agarose) with ethidium bromide staining. Patients 1 and 2 showed the CAG repeat expansion in the SCA1 gene. A sequencing analysis for patient 1 indicated a CAG repeat number of 60/27 (Dr Igarashi, Niigata University).

Pupillary reactions are divided into light reflexes and near reflexes. The light reflex pathway reaches the Edinger-Westphal nucleus through the pretectal nucleus . The near reflex consists of both the convergence reflex and the accommodation reflex. Their pathways are different from that of the light reflex until they reach the Edinger-Westphal nucleus. Therefore, it may be that the lesion for light-near dissociation is located between the pretectal nucleus and the Edinger-Westphal nucleus. Although the pupillary diameter is reduced in the Argyll Robertson pupil, mydriasis was seen in our patients. A patient with similar pupillary abnormalities (pseudo-Argyll Robertson pupil) has been reported by Olsen *et al*.[3] The causative disorder of the patient reported by Olsen *et al*[3] was congenital oculomotor paralysis. They attributed the pupillary abnormalities to the aberrant regeneration of the oculomotor nerve. In Holmes-Adie pupil, the reaction to a parasympathomimetic agent (0.2% pilocarpine) can usually be confirmed. Our patient 1, however, did not respond to 0.2% pilocarpine. Therefore, there was no denervation supersensitivity in the post-ganglionic parasympathetic nerve fibre after the ciliary ganglion. The most plausible explanation for the mydriasis in our patients is the dysfunction of the preganglionic parasympathetic nerve fibre connecting the ciliary ganglion and the Edinger-Westphal nucleus. It is conceivable that the near reflex is maintained through a different pathway. Dacso *et al*[4] have divided the Edinger-Westphal nucleus into the rostral and caudal portion, with the rostral portion relating to the light reflex and the caudal portion relating to the near reflex.

Patients with SCA1 present mydriasis and occasionally the absence of a light reflex.[4] However, light-near dissociation has not been reported in any of these patients. Gilman *et al*[5] have reported a postmortem case of SCA1 in which they found neuronal loss and a marked gliosis of the periaqueductal grey matter as well as a neuronal loss of the Edinger-Westphal nucleus. These pathological changes may cause light-near dissociation. Future detailed examinations of the pupillary abnormalities in SCA1 patients are eagerly anticipated.

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1 Dacso CC, Bortz DL. Significance of the Argyll Robertson pupil in clinical medicine. *Am J Med* 1989;**86**:199–202.
2 Orr HT, Chung MY, Banfi S, *et al*. Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. *Nat Genet* 1993; **4**:221–6.
3 Olsen T, Jakobsen J. Abnormal pupillary function in third nerve regeneration (the pseudo-Argyll Robertson pupil). A case report. *Acta Ophthalmol Scand Suppl* 1984;**62**:163–7.
4 Abe T, Abe K, Aoki M, *et al*. Ocular changes in patients with spinocerebellar degeneration and repeated trinucleotide expansion of spinocerebellar ataxia type 1 gene. *Arch Ophthalmol* 1997;**115**:231–6.
5 Gilman S, Sima AAF, Junck L, *et al*. Spinocerebellar ataxia type 1 with multiple system degeneration and glial cytoplasmic inclusions. *Ann Neurol* 1996;**39**:241–55.

"Non-neuroleptic malignant" syndrome

We report on a patient with the clinical and biochemical features of the so-called neuroleptic malignant syndrome, occurring more than a decade after her last exposure to phenothiazines, but while taking the cyclopyrrolone zopiclone. We consider possible mechanisms underpinning the development of this clinical syndrome in the light of these findings and current models of basal ganglia dysfunction.

A 62 year old woman was found collapsed at home. On admission to hospital she was alert, eye opening and moving limbs spontaneously, but her affect was flat and she was unable to give any account of herself. She was pyrexial (38.9°C) and clinically dehydrated with a pulse rate of 110/min and a blood pressure of 90/60 mm Hg. She was mute and akinetic with a jaw tremor, but there was no muscle tenderness. There was profound axial and limb rigidity with opisthotonos, making it impossible to assess power. Psychiatric review found no evidence for a catatonic psychotic state. She was rehydrated with IV crystalloids, but on the day after admission had an episode of tachycardia (pulse rate 140/min) and profound hypotension (BP unrecordable) which responded to IV colloids. After this, she was noted to be less rousable, and her level of consciousness continued to fluctuate between alert and unrousable for the next three days.

Through relatives, friends, and her previous medical notes, a history of alcohol dependence came to light, dating back to 1984; she had been admitted on at least three occasions in the past for alcohol detoxification, but continued to indulge in occasional binges and was on long term nitrazepam (10 mg nightly) because of difficulty sleeping. However, there was no history of recent binge drinking, or of attempted withdrawal from benzodiazepine. Also, in 1984 the patient had presented with paranoid delusions and auditory hallucinations which were thought to be due to a psychosis secondary to alcohol withdrawal; brain CT at this time was normal. She was then seen by a psychiatrist and the diagnosis was revised to schizophrenia; she was treated initially with trifluoperazine (5 mg twice daily).

for less than 1 month, then with pimozide (6 mg daily) and procyclidine (5 mg thrice daily) for 5 months at which time medications were stopped. She was next seen in 1996 when she was admitted with an acute confusional state which was thought to be alcohol related. Brain CT was again normal, and an EEG showed diffuse beta activity consistent with her benzodiazepine use. At the time of discharge she was taking zopiclone (7.5 mg nightly) in addition to nitrazepam, but no neuroleptic medication was used.

At the time of her acute admission, investigations disclosed a mild neutrophil leucocytosis (10.1×10^9/l), hypernatraemia (152 mmol/l), hypoalbuminaemia (22 g/l), and raised erythrocyte sedimentation rate (90 mm/h) and C-reactive protein (157 mg/l). Creatine kinase was raised (maximum 978 U/l, first measured 7 days after presentation; normal<190 U/l; 100% MM isoenzyme) as was lactate dehydrogenase (maximum 839 U/l, normal<450 U/l). Cultures of blood, urine, faeces, and CSF were negative. Brain CT was normal; MRI showed widespread ischaemic changes in the cerebral deep white matter but the basal ganglia were spared and no lesions were visible in the brainstem. Analysis of CSF showed a moderately raised protein (0.57 g/l) but was normal in all other respects; CSF polymerase chain reaction was negative for various infectious agents (herpes simplex virus, varicella zoster virus, adenovirus, enterovirus, mumps, Mycoplasma). Toxicology screen was negative for phenothiazines and enquiries with both her consultant psychiatrist and general practitioner afforded no evidence for recent neuroleptic prescription. Before the availability of this information, a working diagnosis of neuroleptic malignant syndrome had been made, based on the presence of the appropriate clinical features.[1] Despite appropriate medical management, the rigidity had persisted for 10 days and therefore, as soon as the diagnosis of neuroleptic malignant syndrome was considered, the patient was treated with bromocriptine, initially 1 mg twice daily rising to a maximum of 2.5 mg twice daily. Over the first three days on this regime, the rigidity improved dramatically, tone returning to normal. Neurological examination at this time was normal; particularly, there were no abnormal brainstem signs, although there was some evidence of mild cognitive impairment.

The neuroleptic malignant syndrome, first named by Delay and Deniker,[2] is characterised by hyperpyrexia, hypertonus, fluctuating level of consciousness, and autonomic disturbances; the presence of these features is thought to be essential to establish the diagnosis.[1] Most cases have been associated with neuroleptic use, although levodopa withdrawal may also precipitate a similar state. Loss of dopaminergic drive in the basal ganglia has been suggested as a common feature in both of these situations. Similar phenomena, labelled as acute lethal catatonia or fatal catatonia, were reported in the pre-neuroleptic era.[3] Hence, current neuroleptic use is not an absolute requirement for the occurrence of this clinical syndrome, as also shown in the reported case. It remains possible that medication may act as a trigger for some independent process, for which concurrent organic brain disease is recognised to be a predisposing factor.[1] Perhaps previous neuroleptic use may also sensitise the basal ganglia in some way to the development of these features.

Could zopiclone have contributed to the pathogenesis of the syndrome? At first sight this would seem unlikely; It is a cyclopyrrolone with a pharmacological profile similar to that of short acting benzodiazepines, its actions mediated through increased GABA activity in the brain. Hence, it has muscle relaxant effects, as well as sedative, anxiolytic, and anticonvulsant properties.[4] However, GABA is an important neurotransmitter in the basal ganglia, present in striatopallidal, striatonigral, pallidothalamic, pallidosubthalamic, and nigrothalamic fibres. In movement disorders, it has been postulated that within the basal ganglia-thalamocortical motor circuit there are two separate projection systems from the putamen: a direct pathway of GABA/Substance P neurons to motor portions of the internal segment of the globus pallidus and substantia nigra pars reticulata, providing positive feedback to precentral motor fields; and an indirect pathway of GABA/enkephalinergic neurons influencing basal ganglia output through a sequence of connections involving the external segment of the globus pallidus and the subthalamic nucleus, providing a negative feedback to precentral cortex.[5] Shifts in the balance of activity within these pathways may alter globus pallidus/substantia nigra pars reticulata output and hence result in hypokinesia or hyperkinesia; for example, hypokinesia is thought to result from increased pallidothalamic inhibition and enhanced conduction in the indirect pathway, whereas reduced conduction through the direct pathway, secondary to reduced pallidothalamic inhibition, results in hyperkinesia.[5] For this model, it is of note that a selective loss of indirect pathway GABA/enkephalin neurons is found in Huntington's disease,[6] and that GABAmimetics (progabide) have been reported to iron out on-off fluctuations in Parkinson's disease.[7] Hence, in the light of this model, we suggest that our patient may have had increased brain GABA activity as a result of zopiclone (with or without nitrazepam) treatment, resulting in increased pallidothalamic inhibition and enhanced conduction in the indirect pathway, and thus producing profound hypokinesia in the absence of recent neuroleptic treatment.

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1 Guzé BH, Baxter LR. Neuroleptic malignant syndrome. *N Engl J Med* 1985;**313**:163–6.
2 Delay J, Deniker P. Drug-induced extrapyramidal syndromes. In: Vinken PJ, Bruyn GW, eds. *Handbook of clinical neurology.* Vol 6. *Diseases of the basal ganglia*. Amsterdam: North-Holland, 1968:248–66.
3 Stauder KH. Die todliche katatonia. *Archiv fur Psychiatrie und Nervenkrankheiten* 1934;**102**: 614–34.
4 Goa KL, Heel RC. Zopiclone: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy as a hypnotic. *Drugs* 1986;**32**:48–65.
5 DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 1990;**13**:281–5.
6 Reiner A, Albin RL, Anderson KD, *et al*. Differential loss of striatal projection neurons in Huntington disease. *Proc Natl Acad Sci USA* 1988;**85**:5733–7.
7 Bergmann KJ, Limongi JCP, Lowe YH, *et al*. Potentiation of the dopa effect in parkinsonism by a direct GABA receptor agonist. *Lancet* 1984;i:559.

CORRESPONDENCE

Corpora amylacea in hippocampal sclerosis

I read with pleasure the short report of Van Paesschen *et al*.[1] This finding perhaps may raise some interest again in corpora amylacea as well as in the pathology of temporal lobe epilepsy. As I studied corpora amylacea for about 25 years I call the attention of the authors to the first—but important—finding of Ramsey who published in her article in 1965[2] a case of a 35 year old man who had intractable temporal lobe epilepsy. Surgical intervention was performed with temporal lobe resection including 3 cm of hippocampus. The pathologist's report stated that the tissue seemed histologically normal except for a few areas of pyknosis and shrinkage of neurons and a decrease in the number of neurons in the hippocampus. The presence of corpora amylacea without gliosis was noted and was especially prominent in the hippocampus. The diagnosis was "mild presenile cortical atrophy of the temporal lobe with corpora amylacea in the hippocampus."

I studied the occurrence of corpora amylacea in 1407 cases of various diseases with special reference to the so called predilection sites of corpora amylacea, and I sometimes found large numbers of corpora amylacea in the hippocampal area and other regions with and without special pathology, even in young people. The conditions which favour the development of corpora amylacea vary greatly (aging, chronic vascular—hypoxic—diseases, ALS, multiple sclerosis, dementias, etc) as well as various pathogenetic mechanisms promoting formation, which included chronic hypoxia, neuronal degeneration, external hydrocephalus—as a consequence of local cortical atrophy—diabetes mellitus, and other processes which induce stress states expressed by strong HSP 60 positivity in our investigations (see[3–7] for appropriate references). So the corpora amylacea formation really is an epiphenomenon in different diseases, as Van Paesschen *et al* state.

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1 Van Paesschen W, Révész T, Duncan JS. Corpora amylacea in hippocampal sclerosis. *J Neurol Neurosurg Psychiatry* 1997;**63**:513–15.
2 Ramsey HJ. Ultrastructure of corpora amylacea. *J Neuropathol Exp Neurol* 1965;**24**:25–39.
3 Leel-Ossy L. The origin and the pathological significance of the corpus amylaceum. *Acta Neuropathologica (Berl)* Suppl II, 1981:396–99.
4 Leel-Ossy L. The structure and the pathological significance of the corpus amylaceum. (Hung.) In: Leel-Ossy L, ed. *Selected chapters in neuropsychiatry*. Budapest: Statistics Publishing Co, 1989:189–202.
5 Leel-Ossy L. Pathological significance and characteristics of corpus amylaceum. *Neuropathology (Japan)* 1991;**11**:105–14.
6 Leel-Ossy L. The occurrence of corpus amylaceum (polyglucosan body) in diabetes mellitus. *Neuropathology (Japan)* 1995;**15**:108–11.
7 Leel-Ossy L. Statistical evaluation and pathological significance of the incidence of corpus anylaceum. *Clinical Neuroscience (Hung)* 1997; **50**:90–102.

Secondary hyperkalaemic paralysis

In their report describing a case of hyperkalaemic paralysis associated with renal failure and use of spironolactone, Evers *et al*[1] provide an illustration of the results obtained from conduction studies performed on the patient's median sensory nerve. Utilising the calibration markers, the average amplitude of the sensory action potential (SAP) measures 10.6 μV before haemodialysis and 27.2 μV afterward. However, these measurements are recorded in table 1 as being 20.0 μV and 24.0 μV, respectively.

An increase in SAP amplitude after normalisation of serum potassium concentration would offer additional support the authors' suggestion that the pathological process causing weakness in secondary hyperkalaemic paralysis probably originates at the level of nerve rather than muscle.

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1 Evers S, Engelien A, Karsch V, *et al*. Secondary hyperkalaemic paralysis. *J Neurol Neurosurg Psychiatry* 1998;**64**:249–52.

Evers replies:

The figures in table 1 were indeed incorrect and the correct figures from the original data are 8 μV before haemodialysis and 24 μV after haemodialysis.

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Traumatic distal femoral neuropathy

We read with interest the recent report by Padua *et al*[1] on a body building champion with an isolated mononeuropathy of a distal branch of the femoral nerve, having recently seen a similar patient, with a different cause.

A 39 year old sports physiologist underwent a resting muscle biopsy using the Bergstrom technique, for research purposes. He had previously undergone eight of these biopsies on the other leg without adverse effect, and this biopsy was performed by an experienced operator. Under lignocaine anaesthesia the biopsy needle was inserted. As manual suction was applied followed immediately by closing the biopsy needle, the subject had an intense feeling of cramp (that had not been noticed with previous biopsies). The site of the biopsy was 5 cm lateral to the midpoint between the patella and the anterior superior iliac spine. Over subsequent months wasting of the distal lateral vastus lateralis muscle was noted. An EMG 3 months after injury showed increased insertional activity, fibrillation potentials, and positive sharp waves with no activation of motor unit potentials in the distal fibres of the vastus lateralis muscle. A further EMG 6 months after the biopsy showed evidence of reinnervation.

In our patient, the distal mononeuropathy was traumatic, and clearly related to the needle biopsy. A distal motor branch of the femoral nerve as identified in the anatomical studies of Padua *et al*[1] was traumatised by the biopsy. It does raise the possibility of an alternative mechanism for the patient of Padua *et al* which was not considered in the article, and can be difficult to verify by clinical history alone. The use of anabolic steroids is very prevalent among body builders with the lateral thigh being a common site of administration. Direct injection could have traumatised the nerve, and may also explain the lack of any improvement with time. It is also noted in the illustration of the unaffected leg, that a small dimple is present in the skin at a site where the distal motor branch may be vulnerable, although this is significantly more distal than the biopsy site in our patient. This may, however, be an indicator of previous injections to the lateral thigh.

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1 Padua L, D'Aloya E, LoMonaco M, *et al*. Mononeuropathy of a distal branch of the femoral nerve in a body building champion. *J Neurol Neurosurg Psychiatry* 1997;**63**:669–71.

The authors reply:

We are grateful for the response of Silbert *et al*. In our paper[1] we described an isolated mononeuropathy of a distal branch of the femoral nerve and hypothesised that stretching and compression of the nerve had probably occurred during strenuous exercise.

We agree with the possibility of a traumatic nerve lesion due to needle injection and we have knowledge of some cases of this kind of nerve injury in body builders, but in the case reported in the article, we specifically asked the patient if drug injections had been carried out in the thigh. He replied that he had never used this kind of drug administration. Moreover, our patient did not refer to any pain in the thigh, whereas in the case of Silbert *et al* an "intense cramp" was felt by the subject. Concerning the figure, detailed clinical examination of both thighs had been performed and no suspected "dumping" was seen. We think that the effect in the figure could rather be due to the hypertrophy of a nearby muscle and as noted it is distal to the site of the femoral nerve branch.

For these reasons, the hypothesis of needle injury was not considered in the article, but we agree that in the case of nerve lesion in body builders, a needle injury (for anabolic drug injection) must always be suspected.

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BOOK REVIEWS

Radiosurgery. Volume Two. Edited by DOUGLAS KONDZIOLKA. (Pp 268, Sw Fr 258). Published by S Karger AG, Switzerland, 1998. ISBN 3-8055-6547-X.

It has sometimes been said, perhaps unfairly, that radiosurgery has been a treatment looking for a successful application. This volume, the second in the series on radiosurgery, attempts, in some parts more successfully than others, to refute that suggestion. The technique was first established by Lexsell, using a collimated cobalt source ("the gamma knife"). In the United Kingdom, the Stereotactic Radiosurgery Centre in Sheffield has been treating patients since 1985. The published results for treatment of arteriovenous malformations have been good and its place in the non-operative management of cerebral arteriovenous malformations is now secure. Radiosurgery has now become the treatment of choice for appropriately sized and located malformations. However, increasingly refined techniques of endarterial obliteration for vascular lesions have also been developing apace in parallel, and it seems likely that the combined use of both techniques will in future make it increasingly rare for us to have to undertake surgery for these often demanding lesions.

The main drawback of the "gamma knife" technique of radiosurgery has been the enormous capital outlay required for the equipment. In the United Kingdom there is only one machine and this has perhaps inhibited a wider application of the technique in the management of intracranial malignancy. The greater availability of machines in the United States, and the commercial pressures to retain the appropriate return on investment, has led to a wider range of applications in the United States and the results of some of these are published in this book. The development of fractionated stereotactic radiotherapy using relocatable stereotactic frame and a linear accelerator has shown that it is possible to achieve good results with this technique and some of these are also published here. In the United Kingdom we are beginning to identify a much wider range of applications for this technique and, in the not too distant future, we should expect a whole range of reports of its use in malignant brain tumours, recurrences, melanomas, and other metastatic lesions. However, for the moment the literature is rather sparse and it remains to be seen whether the technique in future will also become the treatment of choice for these rather dismal conditions.

The place of radiotherapy in general, and stereotactic techniques in particular, for benign lesions, such as acoustic neuromas and meningiomas, in my view remains uncertain despite some rather encouraging results published here. At this stage it is perhaps sensible to proceed with caution until the long term effects are clearer. With regard to the future, the rapid advances in imaging techniques using MRI, the various new variants of CT, and the PET machine, offer the tantalising possibility of being able to identify both the anatomical and functional pathology to be targeted for treatment. With the merging of these exciting new technologies it may at last be possible to make some real progress in improving the outcomes for CNS tumours.

DAVID HARDY

Handbook of Neurologic Rating Scales. Edited by ROBERT M HERNDON (Pp 276, US$125). Published by Demos Vermande, New York, 1997. ISBN 1-888799-07-2.

This well produced book joins a small group of books which actually show some of the measures now used in clinical research. There are many, many measures, and each book can only show a selection. This book would be helpful to anyone who is interested in learning about measures of disease severity and outcome, although it might not be the best in any particular circumstance.

Everyone should read the introduction to this book, written by Dr Herndon. It is full of common sense. It also emphasises the most important point of all, and I repeat it here: ".. the most important question in designing or choosing a scale is how well it is suited to the task at hand in terms of validity, efficiency, sensitivity and specificity ... ". If only every researcher would read, remember, and act on this one statement then neurological research would advance greatly.

The book is then primarily structured around diseases. This is useful to anyone interested in a specific disease, but means that many non-specific areas of measurement are not covered. The chapters cover most of the common and important neurological diseases: multiple sclerosis; amyotrophic lateral sclerosis; head injury; stroke; movement disorders including Parkinson's disease; epilepsy; and dementia. Many of the chapters follow a similar layout, but there are exceptions. Most seem to be written by people who have direct experience of the scales, and indeed there is much original and useful data relating to the assessment of progression in motor neuron disease in that chapter. There are two more general chapters. The first covers paediatric developmental scales, and I think that this is the only similar book to cover this area. The second covers the measurement of the outcome from rehabilitation. The best chapters are those covering multiple sclerosis, amyotrophic lateral sclerosis, movement disorders, and dementia. The chapter on stroke is much less comprehensive, and contains some errors in references (for example, to the Hamrin ctivity Index), and the chapter on head injury stands out as containing much less useful information.

The book gives considerable useful information about many of the scales mentioned, and certainly would help anyone who was unfamiliar with the field. The references are reasonable, although sometimes inaccurate and quite often statements are made without reference, which can be irritating especially as references do exist to support most statements. Overall this book is good, and complements the other books available well. It will be especially helpful to those interested in the current "hot" diseases, multiple sclerosis, amyotrophic lateral sclerosis, and Parkinson's disease.

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