Six months before she was seen by us, the referring physician started her on treatment with Sinemet-plus 125 mg (carbidopa 25 mg, levodopa 100 mg) four times a day with a dramatic initial benefit. Within a few months, however, she noticed wearing off problems with each dose lasting only three hours and the dose was increased to six Sinemet plus a day with one Sinemet CR (carbidopa 50 mg, levodopa 200 mg) at night.

The differential diagnosis in this patient was between dopa responsive dystonia and young onset Parkinson's disease. The initial presentation with what seemed to be a spastic paraparesis and the positive family history suggested dopa responsive dystonia. Later evaluation suggested the possibility of young onset Parkinson's disease as she had developed wearing off dose responses early after initiation of treatment with Sinemet.³ By contrast, patients with dopa responsive dystonia are known to have a sustained long term benefit without complications on small doses of levodopa. For purposes of prognosis and further management it was important to distinguish between the two conditions. This was achieved with ¹⁸F-dopa PET which showed significantly reduced tracer uptake in the putamen (averaged side to side, Ki values using an occipital reference; patient caudate = 0.0080 (0.0108 ± 0.0017), patient putamen = 0.0034 (0.0099 ± 0.0011)). These findings were suggestive of a diagnosis of young onset Parkinson's disease.^{3,4} With a diagnosis of young onset Parkinson's disease established the drug therapy was modified by giving her levodopa sparing drugs such as amantadine, dopamine agonists, and anticholinergic drugs to avoid the levodopa induced motor fluctuations for as long as possible.

This case shows the part functional imaging can play in selected cases and the prognostic and therapeutic implications made possible by this technique.

K P BHATIA
N TURJANSKI
D J BROOKS
C D MARSDEN

University Department of Clinical Neurology,
Institute of Neurology, Queen Square, and MRC
Cyclotron Unit, Hammersmith Hospital,
London UK

D THRUSH
Department of Neurology,
Derriford Hospital,
Plymouth, UK

Correspondence to: Professor C D Marsden,
Institute of Neurology, Queen Square, London
WC1N 3BG, UK.

- 1 Sawle GV. Imaging the head: functional imaging. *J Neurol Neurosurg Psychiatry* 1995; 58:132-144.
- 2 Sawle GV, Leenders KL, Brooks DJ, et al. Dopa-responsive dystonia: [18F]dopa positron emission tomography. *Ann Neurol* 1991; 30:24-30.
- 3 Snow BJ, Nygaard TG, Takahashi H, Calne DB. Positron emission tomographic studies of dopa responsive dystonia and early onset idiopathic parkinsonism. *Ann Neurol* 1993; 34:733-8.
- 4 Sawle GV, Morrish PK, Playford ED, Burn DJ, Brooks DJ. Young-onset parkinsonism: clues from [¹⁸F] dopa PET studies. *Neurology* 1994;44(suppl 2):A353-4.
- 5 Quinn N, Critchley P, Marsden CD. Young onset Parkinson's disease. *Mov Disord* 1987; 2:73-91.

Severe combined degeneration of the spinal cord after nitrous oxide anaesthesia in a vegetarian

Nitrous oxide has been extensively used as an anaesthetic agent and is regarded as an

ideal drug with few side effects. We report a female vegetarian who developed subacute combined degeneration of the spinal cord due to lack of vitamin B 12 one month after nitrous oxide anaesthesia.

A 50 year old white woman had become a vegetarian 10 years before admission. Over the past five years, she had increasingly restricted her diet to include only apples, nuts, and raw vegetables; intentionally avoiding legumes. Six weeks before admission she underwent surgery for a right hip fracture acquired while ice skating. Her pre-operative blood count showed a mild macrocytic anaemia with a packed cell volume of 33.8% (normal 37% to 47%), and a mean corpuscular volume of 101.2 (normal 80 to 93) fl. During combined anaesthesia with isoflurane, she was ventilated with 66% nitrous oxide for two hours. She continued her diet without any supplementation of vitamins or folate. Four weeks later, she rapidly developed increasing unsteadiness of gait and sensory impairment of her legs. Six weeks after anaesthesia, she was unable to walk and was readmitted to hospital. She showed normal mental status and cranial nerves. A spastic paraparesis of her legs, more pronounced on the right, was found with increased muscle reflexes and bilateral extensor plantar responses. She had severe impairment of position and vibration sense up to the iliac crest. Laboratory results showed a macrocytic anaemia with a packed cell volume of 28% and a mean corpuscular volume of 108.3 fl. Blood vitamin B 12 concentrations were decreased to 29.6 (normal 48-443) pmol/l with normal folate concentrations. Schilling test (part I) gave a normal result. Gastric biopsy ruled out atrophic gastritis. Electrophysiological testing showed normal brainstem auditory evoked potentials, prolonged latency of visual evoked potentials, absent tibial derived somatosensory evoked potentials, prolonged central motor conduction time, and mild reduction in peripheral motor and sensory nerve conduction velocity. Cervical and thoracic spinal cord MRI showed increased signal intensity within the dorsal columns on T2 weighted images. Brain MRI was normal. A diagnosis of subacute combined degeneration of the spinal cord secondary to vitamin B 12 deficiency was made and injections of cyanocobalamin were begun. After five months her clinical status was much improved. She was able to walk on crutches and had only mild spastic paraparesis of the legs, but still severe impairment in position and vibration sense. The tibial derived somatosensory evoked potentials continued to improve at one year after anaesthesia.

Vitamin B 12 deficiency in vegetarians is rare as only 5 µg of vitamin B 12 is needed per day and an adequate amount is usually available in legumes. Because our patient intentionally avoided legumes in her strictly vegetarian diet and her preoperative mean corpuscular volume was raised, it is likely that she had a pre-existing vitamin B 12 deficiency due to malnutrition. In patients with a vitamin B 12 malabsorption the course of subacute combined degeneration is mostly mild with only a minor neurological deficit six months after the onset of symptoms. As our patient had an interval of only two weeks between the beginning of paraesthesiae and being confined to a wheelchair a natural course of combined degeneration is highly unlikely.

Nitrous oxide is known to oxidise the cobalt (Co) atom of vitamin B 12 from an

active Co (I) to an inactive Co (II) or Co (III) state, which in turn reduces activity of cobalamin dependent enzymes. In particular, the methionine synthase methylcobalamin complex is rendered irreversibly inactive. In healthy subjects this side effect is well compensated for by large vitamin B 12 stores in the liver and bone marrow for up to 24 hours during nitrous oxide anaesthesia. For patients with a preexisting vitamin B 12 deficiency, even a short nitrous oxide anaesthesia may deplete the few remaining stores. Furthermore, the inactivation of methionine synthase by nitrous oxide may be more rapid in patients with low concentrations of vitamin B 12.

Only seven patients who developed combined degeneration after a short nitrous oxide anaesthesia have been reported so far.¹⁻⁶ They were five women and two men with an age range from 25 to 70 years. The duration of nitrous oxide application ranged from 90 minutes to 235 minutes and the elapsed time between anaesthesia and onset of symptoms was between 14 days and eight weeks. The cause of vitamin B 12 deficiency was resection of the terminal ileum for Crohn's disease in one patient, pernicious anaemia in four, and not stated in one. One patient had pernicious anaemia and was a vegetarian, but not a very strict one.⁵ To our knowledge this is the first case of vegetarianism alone leading to subacute combined degeneration of the spinal cord secondary to vitamin B 12 deficiency after short term nitrous oxide anaesthesia.

In summary, our patient shows that for strict vegetarians nitrous oxide might be a harmful anaesthetic and should draw the attention of physicians to the eating habits of their patients scheduled for anaesthesia.

MARTIN RÖSENER
JOHANNES DICHGANS

Eberhard-Karls-University, Department of Neurology,
Tübingen, Germany

Correspondence to: Dr Martin Rösener, Eberhard-Karls-University, Department of Neurology, Hoppe-Seyler-Strasse 3, 72076 Tübingen, Germany.

- 1 Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B 12 deficient subjects? *JAMA* 1986;255:1605-6.
- 2 Holloway KL, Alberico AM. Postoperative myeloneuropathy: a preventable complication in patients with B 12 deficiency. *J Neurosurg* 1990;72:732-6.
- 3 Flippo TS, Holder WD. Neurologic degeneration associated with nitrous oxide anesthesia in patients with vitamin B 12 deficiency. *Arch Surg* 1993;128:1391-5.
- 4 Timms SR, Curé JK, Kurent JE. Subacute combined degeneration of the spinal cord: MR findings. *AJNR Am J Neuroradiol* 1993; 14:1224-7.
- 5 McMorrow AM, Adams RJ, Rubenstein MN. Combined system disease after nitrous oxide anesthesia: a case report. *Neurology* 1995; 45:1224-5.
- 6 Kinsella LJ, Green R. "Anesthesia paresthetica": nitrous oxide-induced cobalamin deficiency. *Neurology* 1995;45:1608-10.

Homozygosity for Machado-Joseph disease gene enhances phenotypic severity

Machado-Joseph disease is an autosomal dominant ataxia originally described in Portuguese emigrants to Massachusetts and California, and now described worldwide.¹ Clinical phenotypes of Machado-Joseph disease vary widely, and have been considered to correlate with the age of onset; the younger the age of onset, the greater the extent of dystonia and pyramidal signs; the older the age of onset the more pronounced the cerebellar ataxia and peripheral neuropathy. Recently, the gene responsible for

Machado-Joseph disease was cloned,² and the degree of CAG expansion in the gene clearly correlated with the age of onset, as has been shown in other trinucleotide repeat diseases. Moreover, clinical phenotypes of Machado-Joseph disease type I, II, and III were also reversely correlated with the extent of CAG repeat expansion,³ suggesting that CAG repeat size is one determinant factor for the age of onset and clinical phenotypes of Machado-Joseph disease. Lang *et al*⁴ described a homozygous patient determined by genotyping of the members of the family, and suggested that the dose of the Machado-Joseph disease gene was an important determinant of the age of onset and clinical phenotype. In this report, we describe a family with Machado-Joseph disease, the propositus of which was homozygous for the Machado-Joseph disease gene with almost the same size of CAG expansion as his parents, but who exhibited a far younger age of onset with more severe and different phenotypes than his parents.

Patient 1 was a 42 year old Japanese man whose parents were cousins (figure, A; patient II:2). He first exhibited an unsteady gait at the age of 28, which caused lumbago and pain on the lateral side of his lower legs. Subsequently, slurred and dysarthric speech, a tendency to fall, and difficulty in climbing stairs also developed. Facial grimacing, which occurred particularly during speech and other volitional motion, was noticed. Neurological examination at the age of 31 showed a very unsteady wide based gait with generalised slow movement as well as slow, slurred speech. Fasciculations in the facial muscles and dystonic facial grimacing were present. Horizontal and upward vertical nystagmus was induced by lateral and upward gaze. Upward gaze was moderately impaired. Saccadic smooth pursuit and slow eye movement occurred. Bulging eyes were present. Muscle strength and size were generally well preserved. Deep tendon reflexes were generally hyperactive, being particularly pronounced in the patellar and achilles tendon reflexes, and Babinski's sign was seen on both sides. Muscle tone was increased, especially in the legs. Touch, pain, joint position, and vibration sense were not impaired. Dystonic posture was recognised in the hands and feet, particularly in volitional motion. Coordination of the limbs was impaired by the dystonic postures and cerebellar limb ataxia. Routine haematology, serum biochemistry, urinalysis, and protein and cell concentrations in the CSF were normal. Needle EMG examination showed mild denervation potentials with giant spikes and complex nerve-muscle units in the muscles examined. Motor nerve conduction and amplitude of the muscle action potentials were normal in the median and tibial nerves. Sensory nerve conduction and sensory nerve action potentials were also normal in the median and sural nerves. Cranial MRI showed atrophy of the cerebellar vermis and brain stem and dilatation of the fourth ventricle. By the age of 32, he was unable to walk alone and was confined to a wheelchair.

Patient 2 was a 66 year old man, the father of patient 1 (figure, A; patient II:15). At the age of 63, his speech was noticed to be slightly dysarthric by others, although he himself did not recognise it. He became aware of unusual leg fatigue after walking. His daily activities were not, however, impaired. Neurological examination at the age of 66 showed a somewhat wide based

A

B

and unsteady gait. Very mild truncal unsteadiness was also recognised. Saccadic smooth pursuit and fine horizontal nystagmus were seen in lateral gaze, and there was a limited upward gaze. Bulging eyes were not seen. His speech was mildly slurred and dysarthric. There was no fasciculation in the facial and bulbar musculatures, nor any dystonic or grimacing expression. Limb ataxia was not apparent, but there was a slight clumsiness in the hands and fingers during diadochokinetic movements. Muscle strength and size were normal, and deep tendon reflexes were all normal except Achilles tendon reflexes which were hypoactive on both sides. Babinski's sign was not seen. Muscle tone was generally hypotonic. Vibration sense was moderately impaired in the toes on both sides but other sensory modalities were normal. Routine haematology, biochemistry, and CSF examinations were all normal. Motor nerve conduction velocities and the amplitude of the compound muscle action potentials were normal, but distal motor latency was prolonged in the median and posterior tibial nerves. Sensory conduction studies were normal in the median and sural nerves. Atrophy of the cerebellar vermis and enlargement of the fourth ventricle were seen on cranial MRI.

Patient 3 was a 78 year old woman, the

(A) Pedigree of the family. Squares = males; circles = females; closed symbols = affected members; slashed symbols = deceased members. There is a consanguineous marriage between the parents of the homozygous patient. (B) Analysis of the CAG repeat size in the Machado-Joseph disease gene.

mother of patient 1 (figure, A; patient II:2). She had an unsteady gait when she was 65 years old. Subsequently, she could hardly walk without support. At 76 years of age, she became confined to a wheelchair after a fall with a fracture of the right femur. Slurred speech also developed. Neurological examination at the age of 78 showed that she could just manage to stand by assuming a wide based stance. She could not walk without support. There was saccadic pursuit eye movement, and lateral gaze evoked fine horizontal nystagmus and limited upward gaze. Bulging eyes were not present. Her speech was slightly slurred and ataxic. Facial muscles were normally preserved, and there was no contraction fasciculation. Very mild limb ataxia manifested as terminal oscillation of the fingers. Muscle strength was substantially preserved except for the leg with the bone fracture. Muscle tone was normotonic in the upper limbs and hypotonic in the lower limbs. Deep tendon reflexes were generally hypoactive, but Babinski's sign was present on both sides. There was a moderate decrease in light touch, vibration, and joint position sense at a level below both knees. There were no abnormal findings on routine biochemical, haematological and CSF examination. Motor conduction velocities of the median and posterior tibial nerves were fairly well preserved. Sensory nerve action potentials in the median and sural nerves were not elicitable. Cranial MRI showed atrophy of the cerebellar vermis and brain stem as well as dilatation of the fourth ventricle.

Genomic DNA was extracted from the leucocytes of these patients. MJ-N-(5'-TCGTGAAACAATGTATTTTCCT-TATG-3') and MJ-RN-(5'-GATGTGAAC-TCTGTCCTGAT-3') were used as primer pairs for polymerase chain reaction (PCR) analysis. Genomic DNA (200 ng) was used for 20 µl of PCR reaction and amplification and CAG repeat size analysis was carried out as previously described.^{2,3} The CAG repeat size of the father was 66 for the mutant allele, and 27 for the normal allele, and those for mother were 67 and 19 respectively (figure, B). However, patient 1 showed only one type of allele with 67 CAG repeat size, indicating that this patient had homozygous alleles for the Machado-Joseph disease gene (figure, B). The CAG repeat size was the same as his mother's and only one unit longer than the mutant allele of his father.

Patient 1 showed onset at the age of 28 with facial and limb dystonia, pyramidal signs, and cerebellar ataxia as well as bulging eyes and ophthalmoplegia. His father was 63 at disease onset and his mother 65. Moreover, their clinical manifestations were very mild compared with those of the son—namely, mild cerebellar signs and mild to moderate peripheral nerve involvement without bulging eyes. Cranial MRI, however, showed moderate to severe cerebellar and brain stem atrophy as well as an enlargement of the fourth ventricle. These abnormalities in the parents were unexpectedly large compared with the extent of their clinical manifestations. Slow progression of the disease process in the parents may have led to the expression of milder clinical manifestations than those of the son, despite a similar degree of MRI abnormalities.

Although the age of onset and clinical phenotypes were very different between the parents and their son, the CAG repeat size for the mutant allele was almost the same; 67 for the mother and son, 66 for the father. The age of disease onset for the son was significantly earlier than the expected 95% confidence regression lines on the correlation between the onset age and CAG repeat size.³ These findings strongly suggest that the differences in the age at onset and clinical phenotypes between the parents and son are due to the homozygosity of the Machado-Joseph disease gene in the son. The double dose of the gene in the homozygous son significantly enhanced the phenotypic severity of the disease. Patients with Machado-Joseph disease suspected to be homozygous^{1,4,5} were reported to develop an earlier age of onset and different clinical phenotypes than their parents. However, because the CAG repeat size is also a determinant factor for the age of onset and clinical phenotypes of patients with Machado-Joseph disease,^{2,3} the enhanced clinical severity in homozygous patients so far reported might have been attributed to the elongated CAG repeat size of the mutant allele. The almost identical CAG repeat size of the mutant allele of the Machado-Joseph disease gene in the homozygous son and his parents in this study clearly indicates that a double dose of the gene enhances clinical severity. This dose effect in increasing clinical severity has been described in the PMP-22 gene of Charcot-Marie-Tooth disease type 1a⁶ and in the PLP protein gene in Pelizaeus-Merzbacher disease.⁷

In conclusion, our results clearly indicate that a double dose of the Machado-Joseph disease gene is a determinant factor, in addition to the CAG repeat size of the gene, for the age of onset and clinical phenotypes.

Part of this work was supported by grants from the Ministry of Welfare and Health of Japan.

GEN SOBUE
MANABU DOYU
Department of Neurology, Nagoya University
School of Medicine, Nagoya, Japan
NAOKI NAKAO
NORIKO SHIMADA
TERUNORI MITSUMA
Division of Neurology,
Fourth Department of Internal Medicine,
Aichi Medical University, Nagakute, Aichi, Japan
HIROFUMI MARUYAMA
HIDESHI KAWAKAMI
SHIGENOBU NAKAMURA
Third Department of Internal Medicine,
Hiroshima University,
School of Medicine, Hiroshima, Japan

Correspondence to: Dr Gen Sobue, Department of Neurology, Nagoya University School of Medicine, Tsurumai-cho, Showa-ku 65, Nagoya 466 Japan.

- 1 Rosenberg RN, Nyhan WL, Coutinho P, Bay C. Joseph's disease: an autosomal dominant neurological disease in the Portuguese of the United States and the Azores islands. *Adv Neurol* 1978;21:33–57.
- 2 Kawaguchi Y, Okamoto T, Taniwaki M, et al. CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. *Nature Genet* 1994;8:221–8.
- 3 Maruyama H, Nakamura S, Matsuyama Z, et al. Molecular features of the CAG repeats and clinical manifestation of Machado-Joseph disease. *Hum Mol Genet* 1995;4: 807–12.
- 4 Lang AE, Rogaeva EA, Tsuda T, Hutterer J, St George-Hyslop P. Homozygous inheritance of the Machado-Joseph disease gene. *Ann Neurol* 1994;36:443–7.
- 5 Coutinho P, Guimaraes A, Scaravilli F. The pathology of Machado-Joseph disease. Report of a possible homozygous case. *Acta Neuropathol (Berl)* 1982;58:48–54.
- 6 Killian JM, Kloepper HW. Homozygous expression of a dominant gene for Charcot-Marie-Tooth neuropathy. *Ann Neurol* 1979; 5:515–22.
- 7 Ellis D, Malcolm S. Proteolipid protein gene dosage effect in Pelizaeus-Merzbacher disease. *Nature Genet* 1994;6:333–4.

Isolated body lateropulsion caused by a lesion of the cerebellar peduncles

Lateropulsion, or falling to one side, has been described in Wallenberg's syndrome. It also occurs with lesions of the vestibular end organ, vestibular nerve, brainstem, cerebellum, and basal ganglia. In these cases, body lateropulsion is only one of many manifestations. Lateropulsion rarely constitutes the sole symptom and sign of a neurological disorder. Isolated lateropulsion occurred in a patient in whom MRI showed an ipsilateral lesion in the cerebellar peduncle.

A 32 year old woman with no history of neurological disorder developed pronounced unsteadiness within a few hours. She was unable to stand or walk and fell to the left side. She had no vertigo, nausea, or vomiting and no difficulty with vision, hearing, speech, or individual limb functions. On the next day, neurological examination showed an immediate fall to the left when standing unsupported with opened eyes. She had no body oscillations but made an attempt to correct her gait by a wide based stance. She had no cerebellar dysmetria or hypotonia in the four limbs. Eye movements were full without nystagmus. There was no ocular lateropulsion even after eyelid closure. Pupil and cranial nerve examination were normal. There were no sensory and motor disturbances. Deep tendon reflexes were normal and there was no Babinski's sign. Two days later brain CT including contrast enhancement was normal. On the third day, a brain MRI showed a high signal adjacent to the fourth ventricle at the level of the pons on T2 weighted axial sequences. The lesion included both superior and inferior peduncles but not the middle cerebellar peduncle, the brainstem, or the cerebellum (figure). There was no other abnormality in the brainstem, cerebellum, or cerebrum. T1 weighted sequences with and without gadolinium injection were normal. Five days after the onset, caloric irrigation produced symmetric responses. A pure tone audiogram was normal. Brainstem auditory evoked potentials after stimulation of the left ear showed normal latencies of the different waves with a slight morphological instability of waves IV and V. They were normal on the right side. Visual and somesthetic evoked potentials were normal. Cerebrospinal fluid contained 5 cells/mm³, and 0.53 g/l protein with 15.8% IgG in an oligoclonal

T2 weighted axial MRI of the brain showing a high signal adjacent to the fourth ventricle at the level of the (A) lower and (B) middle pons.

pattern. As the CSF and MRI findings suggested an initial attack of multiple sclerosis, she was treated with steroids. She improved rapidly and was able to walk normally after 10 days. One year later brain MRI showed no abnormal signal intensity in the left cerebellar peduncles on either T1 or T2 weighted sequences. No further neurological deficit occurred during a two year follow up.

An isolated body lateropulsion is extremely rare. It has only been reported three times. In two patients, the lateropulsion was ipsilateral to a lesion located in the flocculo nodular lobe in one patient,¹ and probably in the reticular formation of the medulla oblongata in the other.² In the third patient, the side of the fall was contralateral to a lesion of the red nucleus or its environs.³ In our patient, body lateropulsion was the only symptom and sign. It was ipsilateral to a lesion, seen on brain MRI, adjacent to the fourth ventricle and corresponding to the topography of the superior and inferior cerebellar peduncles. The middle cerebellar peduncle, which is more lateral and not directly exposed to the cavity of the fourth ventricle, was spared. Experiments on animals support the hypothesis that the gait disturbance of our patient originated in the cerebellar peduncles. Although controversial, data suggest that unilateral section of the three cerebellar peduncles induces an ipsilateral body deviation.⁴ In monkeys, balance disorders have been seen after specific lesions of each peduncle. After lesion of the middle cerebellar peduncle, a truncal and an appendicular cerebellar ataxia occurred without reported body lateropulsion.⁵ Lesion of the superior cerebellar peduncle usually induced an ipsilateral appendicular ataxia but in at least one case a severe ipsilateral body deviation occurred that overshadowed the appendicular ataxia.⁶ Section of the inferior cerebellar peduncle