was dystonic posturing and clawing of both hands. Power was reduced (grade 4) at the wrist and in the hands, worse on the right. The right leg was flaccid, and there was no movement at the right ankle. Power was reduced (grade 4) proximally in both legs. The right ankle jerk was absent, but all the other tendon reflexes were brisk. The right plantar response was absent, the left extensor. There were no cerebellar or sensory signs. General examination was normal.

The following investigations were normal or negative: routine haematology and biochemistry, serum copper and caeruloplasmin, serum and urinary amino acids, syphilis serology, antinuclear factor, lupus anticoagulant, and anticardiolipin antibody. Constituents of CSF were normal including lactate (1.15 mmol/l; normal range: 0.5–1.8 mmol/l), and pyruvate (83 μ mol/l; normal range: 40–138 μ mol/l). Motor and sensory nerve conduction velocities and amplitudes were within normal limits.

Brain MRI showed large CSF spaces around the anterior portions of both temporal lobes (figure). There was also a mild degree of generalised cortical atrophy and focal areas of signal abnormality in the white matter of both cerebral hemispheres. A trace of glutaric acid was present in the urine, with a small peak of 3-hydroxyglutaric acid. Glutaryl CoA dehydrogenase activity, measured by release of labelled CO₂ from [1,5-¹⁴C]glutaryl CoA by cell homogenate, was undetectable in cultured skin fibroblasts (0.0 and 0.0 compared with 12.9, 13.9, 19.6, 20.1, 12.5 and 12.7 pmol/mg protein/min in simultaneous controls) and was <1% of normal in blood lymphocytes (0.06 and 0.02 compared with 11.3 and 10.8 pmol/mg protein/min in a simultaneous control) confirming a diagnosis of GA-1.

The dystonia and dyskinesia with severe dysarthria but relative preservation of cognitive function in this patient is typical of GA-1.² In addition, the bitemporal enlargement of CSF spaces on MRI, although occasionally reported in other conditions, is strongly suggestive of GA-1. No other cause was identified for this patient's neurological disorder.

Most patients with GA-1 present in the first year of life with acute metabolic decompensation and encephalopathy. A recent

review of reported cases suggests that 97% of those surviving an acute encephalopathic onset are left with severe disabilities.² Our patient presented with delayed walking and dragging the right leg. Up to 25% of cases may present insidiously and there is some evidence that the prognosis in this group is better with only 64% being left with severe disability.² It is rare for new neurological deficits to develop after the age of 3 years, and after this age any residual disability remains static.⁴ Our patient is unusual in that, after a gradual onset, there was further deterioration in neurological function at the age of 7. The details of that episode are limited, but as the neurological sequelae are typical of GA-1, it seems reasonable to attribute it to GA-1 rather than to implicate a second disease process. From the age of 7 until 50, her neurological state remained stable. The current decline in mobility was thought to be related to degenerative joint disease rather than neurological deterioration.

The proportion of cases diagnosed in infancy that will survive into adulthood is, as yet, unknown given that GA-1 was first described only 20 years ago. At the age of 50 years, our patient is the oldest documented case with GA-1. Four other clinically affected patients with GA-1, in whom the diagnosis was made after the age of 18 (aged 19, 23, 28, and 37), have been reported.^{3,4} It is likely that there are other unrecognised cases of GA-1, born before the condition was first described, who have survived into adulthood.

The diagnosis of GA-1 in clinically suspected cases is usually made by demonstrating excretion of glutaric acid and 3-hydroxyglutaric acid in urine. Glutaric acid is found in the urine in other metabolic disorders such as multiple acyl-CoA dehydrogenase deficiency, but the presence of 3-hydroxyglutaric acid makes the diagnosis of GA-1 almost certain, as it has not been found in any other condition.¹ However, during periods of neurological stability, which will invariably be the case in adults, excretion may be low or undetectable.² Neuroradiological findings (enlarged frontotemporal CSF spaces and signal abnormalities in cerebral white matter and, in severe cases, in the basal ganglia) may also suggest a diagnosis of GA-1, but they are not specific. Similar abnormalities are seen in the basal ganglia in the mitochondrial encephalopathies and in Leigh's syndrome. Although dystonia may be prominent in Leigh's syndrome,⁵ the presence of other features such as retinopathy, peripheral neuropathy, and dysmorphism help to distinguish it from GA-1. In addition, enlarged frontotemporal CSF spaces are not found in Leigh's syndrome. To confirm a diagnosis of GA-1, glutaryl CoA dehydrogenase activity must be measured in cultured skin fibroblasts or blood lymphocytes.³ It is usually undetectable in homozygotes.

GA-1 is thought to be rare in adults, but there are almost certainly unrecognised cases among populations of adults with stable neurological deficits acquired in childhood. This report illustrates the clinical and neuroradiological findings that may be seen in adults and extends the clinical range of GA-1.

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The usefulness of functional imaging in movement disorders: an illustrative case

The clinical utility of functional imaging for movement disorders is limited but as pointed out in a review by Sawle¹ it can be a valuable tool in the subset of patients where a diagnosis of dopa responsive dystonia versus young onset Parkinson's disease is suspected. These two conditions can be clearly differentiated by a [¹⁸F]-dopa scan.^{2–4} The distinction between the two conditions is crucial with regard to therapy and prognosis. Because of the problems associated with levodopa therapy in young onset Parkinson's disease,⁵ an early diagnosis is helpful so that alternate treatment, such as the use of agonists, can be initiated keeping levodopa in reserve for as long as possible to delay the emergence of motor fluctuations and dyskinesias. We report an illustrative case.

This 26 year old woman had normal birth and milestones. She first noticed problems at the age of 11 years when she began to walk on the outside of her feet with knock knees. At the age of 12 she developed a tremor of both arms and occasionally of her legs. As she was thought to have a spastic paraparesis, a myelogram was performed which was normal as was examination of the CSF. She had only a mild deterioration between the ages of 12 to 25 years, but then the tremor and her gait markedly worsened over a year. Her maternal grandfather and a maternal aunt were said to have had a similar tremor but further details were unknown. On examination she had parkinsonian features with an expressionless face, stooped posture, pronounced bradykinesia, and rigidity. Her tendon reflexes were very brisk but the plantar responses were flexor. The rest of the neurological examination disclosed no other abnormality. Routine and special investigations including blood counts, serum biochemistry, and tests to exclude Wilson's disease were all normal. Head CT was normal.

1.5 T MRI. T2 weighted axial image showing enlarged anterior temporal CSF spaces.

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.

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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.

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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