Glutaric aciduria type 1 in adulthood

Glutaric aciduria type 1 (GA-1) is an autosomal recessive disorder caused by deficiency of the mitochondrial enzyme glutaryl CoA dehydrogenase, which oxidises and carboxylates glutaryl CoA, an intermediate step in the metabolism of lysine and tryptophan. The onset of clinical manifestations is usually within the first year of life with an acute encephalopathic illness, often triggered by infection. A severe dystonic-dyskinetic syndrome appears in most patients, but others are less severely affected and asymptomatic cases have been described. It is a rare condition with only about 100 cases reported in the medical literature since its original description in 1975. However, it has been suggested that GA-1 is underdiagnosed and may exist undetected in populations of children and adults labelled as having cerebral palsy. We report a patient with GA-1 in whom the diagnosis was made at the age of 50 years when she was referred for reassessment of chronic neurological disability.

The patient, the product of a full term normal delivery and there were no problems in the neonatal period. Motor development was mildly delayed, and she did not start to walk until the age of 18 months when she was noted to drag her right leg. At the age of 7 years she was admitted to hospital with a "paralytic illness". She remained in hospital for four months and at the time of discharge required callipers to walk. Her manual dexterity was poor and her speech was slurred. These neurological disabilities subsequently remained stable. At the age of 12 a right subternal fusion was performed, and eight years later the left femur was shortened. She was able to complete her education at a normal school and then worked for 10 years in a factory before getting married. She was referred to us at the age of 50 because of increasing difficulty in walking caused by pain in the right ankle. There were no new neurological symptoms and no symptoms of autonomic dysfunction. She was being treated with a non-steroidal anti-inflammatory drug and was on hormone replacement therapy. She had not received any neuroleptic medication. Both her parents were caucasian and had died in their 80s. They had had no neurological illnesses, and there was no consanguinity. The patient has two siblings and three children of her own, all of whom are well with no neurological disorder.

Examination showed a severe dystarthis which made her speech very difficult to comprehend. Psychometric testing, however, showed her performance to be in the average range, with a verbal IQ of 104. The non-verbal part of the WAIS-R was not performed because of limited manual dexterity, but good average scores were achieved on the other part of non-verbal reasoning. There was a left exotropia, but the movements were otherwise normal. There was pronounced lingual dystonia and orofacial dyskinesia. Her right leg was hypoplastic and she used callipers and two sticks to walk. There

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was dystonic posturing and clawing of both hands. Power was reduced (grade 4) at the wrists 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 exten-
sor. There were no cerebellar or sensory signs. General examination was normal.

The following investigations were normal or negative: routine haematology and bio-
chemistry, 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 mmol/l; normal range: 40-138 mmol/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 tempo-
ral 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, mea-
sured by release of labelled CO₂ from [1-5,

\[ ^{14} \text{C}] \text{glutaryl CoA by cell homogenate, was undetectable in cultured skin fibroblasts (0-0}

\[ ^{0} \text{} \) 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 simultaneous controls) confirming a diagnosis of GA-1.

The dystonia and dyskinesia with severe dysarthria but relative preservation of cog-

tive function in this patient is typical of GA-1.\(^1\) In addition, the bitemporal enlargement of CSF spaces on MRI, although occasion-

ally 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.\(^3\) Our patient’s 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 lim-

ited, but as the neurological sequelae are typical of GA-1, it seems reasonable to attribute it to GA-1 rather than to imply 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 are left with residual disability 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.\(^4\) 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 demonstrat-
ing excretion of glutaryl acid and 3-hydroxyglutaric acid in urine. Glutaric acid is found in the urine in other metabolic disorders such as multiple acyl-CoA dehydro-
genase deficiency, but the presence of 3-

\[ ^{0} \text{hydroxyglutaric acid makes the diagnosis of GA-1 almost certain, as it has not been found in any other condition.\(^5\) However, during periods of neurological stability, which will invariably be the case in adults, exception might be made to this rule.\(^6\) 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,\(^7\) the presence of other features such as retinopathy, peripheral neuropa-thy, and dysmorphism help to distin-
guish 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 fibro-

blasts or blood lymphocytes.\(^8\) It is usually undetectable in homozygotes.

GA-1 is thought to be rare in adults, and there are almost certainly unrecognised cases among populations of adults with stab-

le neurological deficits acquired in child-

hood. 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 has been pointed out in a review by Sawle 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 [\[ ^{18} \text{F}\] dopa scan.\(^2\) The distinction between the two conditions is crucial with regard to therapy and prognos-

sis. Because of the problems associated with levodopa therapy in young patients with dystonia,\(^3\) 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 grandmother and a maternal aunt were said to have had a sim-

ilar tremor but further details were unknown. On examination she had parkin-

sonian features with an expressionless face, a 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.
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