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Glutaric aciduria type 1: An underdiagnosed cause of encephalopathy and dystonia–dyskinesia syndrome in children

SEP HAUSER and H PETERS

The Murdoch Institute, Royal Children's Hospital, Parkville, Melbourne, Victoria, Australia

Abstract: Two cases of glutaric aciduria type 1 (GA 1) are presented. GA 1 is probably underdiagnosed and misdiagnosed, and may explain a proportion of cases of extrapyramidal and 'postencephalitic' cerebral palsy. Most cases of GA 1 present with a severe dystonic–dyskinetic syndrome following an acute encephalopathy. Asymptomatic cases have also been described, complicating genetic counselling and prenatal diagnosis.

We raise awareness of GA 1 and stress that if clinically suspected, immediate institution of therapy may reduce late morbidity. Moreover, if recognised in the presymptomatic stage, early institution of treatment may prevent the onset of neurological symptoms. GA 1 is an inborn error of lysine and tryptophan catabolism, caused by deficiency of the enzyme, glutaryl coenzyme-A dehydrogenase. Urine organic acid analyses may be negative. Blood acylcarnitine profile has recently been employed as a more sensitive test but was negative in both our patients. Enzyme assay remains the definitive diagnostic test.

Key words: encephalopathy; glutaric aciduria type 1; inborn errors of metabolism.

CASE REPORTS

Case 1

An 18-month-old girl first presented at 10 months of age with acute encephalopathy and focal seizures, following a 3-day coryzal illness associated with vomiting. She was the third child of nonconsanguineous Albanian parents. The pregnancy and neonatal period were uncomplicated and her development was normal. On examination she was drowsy but there were no focal central nervous system signs. Support in intensive care was required. Extensive investigation including glucose, ammonia, lactate, cultures of blood, urine and cerebrospinal fluid (CSF), and urine amino and organic acid profiles were normal. A magnetic resonance imaging scan demonstrated bilateral increase in signal intensity in the basal ganglia. Over the period of a week she showed gradual improvement but residual left-sided weakness and abnormal right-sided tone and choreiform movements were noticed. Acute loss of developmental milestones was evident, in particular she was no longer able to sit without support or crawl. She was no longer able to vocalise. With ongoing intensive physiotherapy and occupational therapy she made slow improvement in her physical abilities.

She presented at 14 months of age with right lower lobe pneumonia. Increased lethargy and irritability were present, with striking dystonia and opisthotonic posturing. CT scan of the brain demonstrated persistent changes within the basal ganglia. In addition there was evidence of cerebral atrophy predominantly involving the temporal lobes bilaterally. Urine amino and organic acid analyses were again normal. The diagnosis of Glutaric aciduria type 1 (GA 1) was suspected based on the clinical presentation. Retrospective analysis of urine collected between these two clinical episodes was analysed for organic acids and this demonstrated slightly raised glutaric acid. Acylcarnitine profile following carnitine supplementation was normal (Dr S Kahler, Duke University, North Carolina, USA). Subsequent enzyme assay of glutaryl-CoA dehydrogenase activity in skin fibroblasts (Dr E Christensen, Denmark) demonstrated reduced activity (0.63 micromoles/h/g^{-1} protein, *vs* 5.0 $\pm$ 1.6 micromoles/h/g^{-1} in control cells).

She was commenced on riboflavin (50 mg day^{-1}) and carnitine (300 mg three times a day) in addition to a low lysine and tryptophan diet. Following the second episode she remained irritable with marked dystonia and sweatiness, particularly when distressed. Despite her severe movement disorder she is alert, interested and responsive. However, she remains significantly delayed in all areas of development. In particular she is unable to sit unsupported and is unable to crawl. She has no purposeful language. Her dystonia has been difficult to control, and she developed vascular compromise in her left arm related to severe muscle spasm. Because of a temporal association with the commencement of baclofen this drug was ceased and significant improvement in symptoms has subsequently occurred with the commencement of diazepam.

At the time of diagnosis her mother was pregnant. Prenatal diagnosis was pursued and the fetus was found to be unaffected on enzyme assay.

Case 2

A 2-year-old boy first presented at 15 months of age with an acute onset of encephalopathy, choreoathetosis and dystonia

Correspondence: Dr SEP Hauser, The Murdoch Institute, 10th floor, Royal Children's Hospital, Flemington Road, Parkville 3052, Melbourne, Australia.

SEP Hauser, MBBS, FRACP, Metabolic Fellow. H Peters, MBBS, Metabolic Fellow.

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following an episode of acute gastroenteritis. This was associated with loss of developmental milestones to a 4–6 month level over a 48-hour period. There were no perinatal problems and his development prior to this illness was normal. He was the first child of nonconsanguineous Australian parents. Extensive investigation including glucose, ammonia, lactate, cultures of blood, urine and CSF, and urine organic acid analysis were normal. A MRI scan of the brain revealed symmetrical, generalised increase in signal intensity in the caudate nuclei and putamina with sparing of the thalamus and globus pallidi.

There was some developmental progress after this initial illness. He presented at 2 years of age with further developmental regression, worsening dystonia and choreoathetosis, and irritability following a further episode of gastroenteritis. His head circumference was normal and there were no focal central nervous system signs or evidence of raised intracranial pressure. Despite the severe movement disorder, he remained alert and responsive.

GA 1 was suspected based on the clinical presentation. Repeat urinary organic analysis was normal. Acylcarnitine profiles prior to and after loading with carnitine were normal (Dr S Kahler, Duke University, North Carolina, USA). Subsequent enzyme assay of glutaryl-CoA dehydrogenase activity in skin fibroblasts (Dr E Christensen, University of Copenhagen, Denmark) demonstrated reduced activity (0.60 micromoles/h/g^{-1} protein, *vs* 5.0 $\pm$ 1.6 micromoles/h/g^{-1} in control cells).

He was commenced on a low lysine and tryptophan diet with riboflavin (100 mg day^{-1}) and carnitine (330 mg three times a day) supplementation. He was also treated with diazepam and baclofen to control the movement disorder. On review shortly after hospital discharge he has persistent choreoathetosis and dystonia, but is alert and responsive. He has significant global developmental delay with marked delay in motor skills, partly attributable to his dyskinesia-dystonia. He is babbling, but has not attained any purposeful speech.

At the time of diagnosis his mother was 12 weeks pregnant. The family did not wish to pursue prenatal diagnosis.

DISCUSSION

We describe two children with normal development who suffered an acute loss of developmental milestones following an acute encephalopathy. Both children were left with a severe dystonic-dyskinetic movement disorder with relative preservation of intellect. In both families the mother was pregnant at the time of diagnosis, and because this condition is inherited in an autosomal recessive manner, rapid diagnosis was important.

GA 1 has a presymptomatic stage and diagnosis and institution of treatment at this time may prevent the onset of neurological symptoms.[1] Presymptomatic clinical manifestations are subtle and include macrocephaly, hypotonia, motor delay and irritability. Macrocephaly is present in up to 70% of patients, but is nonspecific.[1] Abnormalities on neuroimaging in the presymptomatic phase are frequent, often impressive, but again nonspecific. These include fronto-temporal atrophy, delayed myelination, diffuse white matter abnormalities,[2] chronic subdural effusions/haematomas,[3,4] and bilateral arachnoid cysts.[5] Without recognition of this condition in its prodromal stage $\approx$75% of symptomatic patients proceed to an acute devastating encephalopathy with residual dyskinesis and dystonia. The remaining 25% have gradual progression of developmental delay from birth. Development of extrapyramidal symptoms appears to coincide with irreversible necrosis of the striatum of the basal ganglia.

GA 1 was first described by Goodman *et al.*[6] and is caused by a deficiency of mitochondrial glutaryl-CoA dehydrogenase. This enzyme is responsible for the oxidation and decarboxylation of glutaryl-CoA, an intermediate compound in the catabolism of the essential amino acids, lysine and tryptophan. The incidence is unknown outside Sweden where it occurs in $\approx$1 in 30 000 of the population.[7] It is likely that some cases remain undiagnosed or misdiagnosed. Glutaric acid, 3-hydroxyglutaric acid or glutaconic acid, produced in excess in this condition are toxic to neuronal cells, particularly the striatum of the basal ganglia.[8] The pathogenic mechanism is not known but inhibition of the enzyme glutamic acid decarboxylase with concurrent deficiency of gamma-aminobutyric acid (GABA) has been proposed.[9] Reduced levels of GABA in cerebrospinal fluid[10] and corpus striatum[11,12] have been found.

There are a number of difficulties in making the diagnosis of GA 1. Glutaric acid is often excreted intermittently in the urine and multiple urine samples may be necessary before it is detected. In addition glutarylcarnitine, a carnitine conjugate of glutaric acid, may not be present in blood. Acylcarnitine profile has previously been stated to be a highly sensitive method for the detection of GA 1,[13] however, in both our patients glutarylcarnitine was not present on tandem mass spectrometry even after carnitine loading. Thus when clinical suspicion of this diagnosis is strong, the diagnosis must be confirmed by direct enzyme assay on cultured skin fibroblasts. With the increasing availability of tandem mass spectrometry in Australia, acylcarnitine analysis on newborn screening cards may soon be a reality, leading to diagnosis of the majority of infants with GA 1 in the neonatal period.

Strategies for the treatment of GA 1 are controversial. The role of dietary therapy is not clear, although there is some evidence that it halts further deterioration in the neurological condition.[14] A formal randomised clinical trial would be necessary to evaluate this. L-carnitine appears to be an effective agent, albeit nonspecific, in treating this condition as deterioration of neurological status on carnitine withdrawal has been reported.[1] L-carnitine conjugates with glutaric acid and is excreted in the urine.[15] The roles of riboflavin, the cofactor for the enzyme, and of baclofen and vigabatrin, are less certain and variable effects have been observed.[16–19] Because basal ganglia damage is irreversible, diagnosis and treatment needs to be instituted in the presymptomatic stage.[20] Vigorous treatment during acute catabolic illnesses with a high calorie intake and carnitine supplementation may arrest the progression of the neurological symptoms although the vast majority of those surviving the acute encephalopathic event are left with severe disability.[1,20]

A further confounding issue in this condition is the significance of low enzyme activity in asymptomatic siblings of affected patients. Because the enzyme defect is inherited in an autosomal recessive manner, Hoffman studied siblings of affected patients to see if they had intermediate levels of enzyme activity. Surprisingly a number of them were found to have the same level of enzyme activity as their siblings yet without symptoms. All asymptomatic patients had abnormalities on neuroimaging. They were treated aggressively during intercurrent infections with a high calorie source, carnitine and riboflavin and virtually all remained asymptomatic. The question remains as to whether

these children would have remained asymptomatic without treatment, or whether they were in the presymptomatic stage. Case reports have also documented asymptomatic or only mildly affected cases.[16,21,22] This has implications for prenatal testing, which is now available[23] as low enzyme activity does not necessarily imply clinical disease.

CONCLUSIONS

Glutaric aciduria is an uncommon disorder but almost certainly underdiagnosed. Description of the clinical manifestations of GA 1 is reminiscent of the extrapyramidal type of cerebral palsy and may account for a proportion of cases of 'post encephalitic' cerebral palsy. A high index of suspicion should be kept for this condition as early recognition and rapid institution of treatment can prevent development of neurological symptoms. The role of dietary therapy is uncertain but vigorous treatment during acute catabolic illnesses may prevent further neurological deterioration. Diagnosis is difficult as early manifestations are subtle and urine and blood testing may be negative. Definitive diagnosis requires direct enzyme assay. Patients have been described with low enzyme activity in the range of disease, but without symptoms. This has important implications for prenatal diagnosis and counselling: low enzyme activity does not necessarily imply that clinical manifestations will develop. Siblings of newly diagnosed cases should have enzyme testing to see if they are in a presymptomatic stage.

We recommend that all children with macrocephaly and developmental delay, and children with extrapyramidal or 'post encephalitic' cerebral palsy have urine examined for glutaric acid and other metabolites of lysine metabolism. If clinical suspicion for GA 1 is strong, further investigations should be performed despite a negative urinary organic acid test. These should include an acylcarnitine profile after carnitine loading, and direct enzyme assay.

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