Prevention of cerebral palsy in glutaric aciduria type 1 by dietary management

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Abstract

Aims—To study retrospectively the effects of treatment and the clinical outcome in 12 patients with glutaric aciduria type 1; and to compare the outcome in 6 patients diagnosed as a result of family screening with 6 patients who were diagnosed late after symptomatic presentation.

Setting—The National Centre for Inherited Metabolic Disorders, The Children's Hospital, Dublin, Ireland.

Result—Four of the 6 children detected on screening are developmentally normal, 1 died, and the remaining 1 has mild mental handicap. All 6 of the late diagnosed symptomatic group suffered dyskinetic cerebral palsy and 5 have died.

Conclusion—Experience of 50 patient treatment years has shown that early intensive management can alter the natural history of this rare disorder.

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Keywords: glutaric aciduria; dyskinetic cerebral palsy; dietary management

Glutaric aciduria type 1, an autosomal recessive inherited metabolic disorder, is an organic acidaemia and was first described by Goodman *et al* in 1975. A comprehensive overview of this condition has recently been published.¹ The condition results from a deficiency of the mitochondrial enzyme glutaryl-CoA dehydrogenase, which is essential in the degradation pathway of the amino acids lysine, hydroxylysine, and tryptophan.^{2 3}

Glutaric, 3-hydroxyglutaric, and glutaconic acids accumulate in the physiological body fluids and may be increased in the urine, particularly during acute illnesses. These acids can be detected by gas chromatography mass spectrometry in urine, cerebrospinal fluid, and serum.⁴⁻⁷ There is usually a decrease in serum carnitine concentrations, thought to be the result of excessive loss of glutarylcarnitine in the urine and impaired reabsorption of free carnitine.

The gene encoding the enzyme is localised on chromosome 19p13.2, and more than 40 mutations have been identified.^{8 9} Some patients are riboflavin responsive. Glutaric aciduria type 1 has a range of clinical presentations. Children can be asymptomatic or have macrocephaly. An acute encephalopathy, which occurs after minor illness or infections, is the most common presentation. Neurological signs, such as oral and facial dyskinesia, extrapyramidal signs, seizures, and motor and

speech delay might be present, although other intellectual functions are usually preserved.

Hypoglycaemia, acidosis, ketosis, and ketonuria can occur during illness or metabolic imbalance. Occasionally, child physical abuse has been suspected because of the presence of subdural effusions.^{10 11}

We present 12 children, six of whom were presymptomatic and were treated aggressively who, as a result, had a good outcome. This supports the hypothesis that early treatment can lead to a favourable neurological outcome.

Patients and methods

Twelve children were diagnosed with glutaric aciduria type 1 at the Children's Hospital, Dublin, Ireland—six were symptomatic on presentation and six were detected as a result of screening within the family because other siblings had been affected. Diagnoses were suspected clinically and abnormal organic acids were found in urine by capillary gas chromatography mass spectrometry. The condition was confirmed by enzyme assay of glutaryl-CoA dehydrogenase activity in cultured skin fibroblasts by measuring ¹⁴CO₂ released from (1,5-¹⁴C) glutaryl-CoA.^{12 13}

Approach to management

Management consisted of a dietary approach, as used in the aminoacidopathies, coupled with aggressive emergency management of conditions causing metabolic decompensation, including infections, immunisations, and surgery.

The basic diet consisted of a synthetic protein drink that is deficient in the amino acids lysine, hydroxylysine, and tryptophan. This was used with a limited intake of natural protein (ordinary food) which varied with growth, illness, etc. Energy intake was also adjusted according to the weight and presence of adverse factors, such as infection.

The total protein intake ranged from 1.5 to 3 g/kg body weight/day (range of natural protein, 0.5-2 g/kg/day; synthetic protein, 0.5-2 g/kg/day; tryptophan, 5-21 mg/kg/day). Riboflavin was given to ensure an adequate supply of the cofactor to the enzyme (none of our patients was riboflavin responsive). Because serum carnitine concentrations were found to be low, it was replaced orally or intravenously (100-200 mg/kg/day) and serum carnitine concentrations were monitored. The child's growth and head circumference were measured regularly. Serial cranial ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) were carried out.

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Table 1 Management of glutaric aciduria type 1

<i>Well patients</i>	
Synthetic protein (free from lysine, hydroxylysine, and tryptophan)	
Natural protein sufficient for growth	
Sufficient energy for growth and to avoid a catabolic state	
L carnitine: 100 mg/kg/day	
Monitoring of growth and development	
Regular annual cranial computed tomography and magnetic resonance imaging	
<i>Unwell patients: emergency protocol</i>	
Reduce natural protein (even stop it for a short period of 24–48 hours, then re-introduce it gradually as tolerated clinically and biochemically)	
Continue synthetic protein	
Increase energy intake via oral, nasogastric, intravenous routes by 20–100% more than the recommended daily allowance using carbohydrate (such as dextrose 20%) and fat (intralipid 20%)	
Double L carnitine intake to 200 mg/kg/day	
Monitor blood glucose, urea, electrolytes, liver function tests, blood gas, and vital signs	

During acute illness or subtle metabolic decompensation, as reflected by hepatomegaly, the emergency protocol was followed (table 1)—the intake of ordinary (natural) protein was reduced or stopped, but the synthetic protein continued. Using oral and intravenous glucose and lipids, the energy intake was increased by 20–50%. Large volumes of fluid were necessary to achieve the desired energy intake, and diuretics were used to avoid fluid overload. Approximately two thirds of the energy came from carbohydrate; soluble insulin was required intermittently to control hyperglycaemia. Electrolyte and fluid balance were monitored meticulously, with appropriate potassium and sodium supplementation. High dose L carnitine (200 mg/kg) was given intravenously. Natural protein was recommenced (usually after 24–48 hours) and increased gradually to prevent protein deficiency.

Clinical results

SYMPTOMATIC PATIENTS

Six patients were diagnosed after presentation with neurological signs such as dyskinesia and dystonia (table 2). Five had a preceding mild viral infection, such as gastroenteritis or respiratory tract infection, and one was suspected of non-accidental injury. In the latter, the cranial CT scan showed bilateral subdural collections, which were reported as possible non-accidental injury by a radiologist and neurosurgeon.

The age of presentation ranged from 3 to 9 months, but the diagnosis was delayed (6 to 24 months) because of various factors—for example, delay in organic acids results (one to 16 months) or lack of awareness of the condition. All patients had a head circumference above the 90th centile on presentation and they all had abnormal cranial scans, with cerebral atrophy and widening of intrahemispheric fissures.

The urine organic acids showed an abnormal increase in the excretion of glutaric and 3-hydroxyglutaric acids.

Outcome

Five patients in the symptomatic group have died. They were severely dyskinetic with reasonable preservation of intellect. One was found dead at 6 years of age, having been well an hour earlier. The others died after infection, which resulted in encephalopathy, hepatic failure, and/or renal failure. The sixth symptomatic patient, now a teenager, is moderately mentally retarded and has spastic quadriplegia.

PATIENTS DETECTED AS A RESULT OF FAMILY SCREENING

Six patients were diagnosed as a result of family screening, carried out because older siblings had been diagnosed previously. In these families, three other siblings had died before the diagnosis of glutaric aciduria type 1 was established. Deaths were attributed to “cot death” or “dyskinetic cerebral palsy”. There were also two stillborn infants.

Five of the six patients screened are still alive. Ages range from 3 to 9 years. Their ages at diagnosis ranged from 1 to 6 weeks. The birth weights ranged from 1700 to 4100 g. Two patients were preterm with intrauterine growth retardation. The diagnosis was suspected on urine organic acids analysis and was confirmed by skin fibroblast culture, which showed enzyme activity of less than 1% in all six patients.

Cerebral ultrasound, CT, and MRI

At birth, two of the screened group had abnormal ultrasound results: one had bilateral subependymal cysts and the other bilateral small cysts in the caudal nuclear region. At present, five have abnormal CT scans, with abnormalities consisting of widening of the sylvian fissure, and increases in intrahemispheric and extra-axial fluid (fig 1).

Outcome

Of the six screened patients, four are developing normally, although three of these have abnormal CT scans. One is borderline normal, and one died after a respiratory tract infection and failure to implement the emergency protocol quickly. She was neurodevelopmentally delayed but had a complex perinatal history and was preterm at 31 weeks' gestation; she was born by emergency Caesarian section for placenta previa and acute antepartum haemorrhage.

Table 2 Symptomatic patients: presentation and outcome

Patient	Age at presentation (months)	Age at diagnosis (months)	Clinical picture	Developmental age (months)			
				Motor and speech	Vision and hearing	Primary diagnosis	Outcome
1	6	18	Truncal hypotonia	<3	6	CP	Alive at 17 years; CP
2	4	13	Dystonia, dyskinesia	<3	4	CP	Died at 12 years
3	8	24	Dyskinesia, subdural fluid	<3	8	?NAI	Died at 11 years
4	9	11	Dyskinesia	<6	9	CP	Died at 4 years
5	6	7	Dyskinesia, hypotonia	<3	6	CP	Died at 10 months
6	12	13	Hemiparesis, seizures	<6	12	CP	Died at 3 years

CP, cerebral palsy; NAI, non-accidental injury.

Figure 1 Axial T2 weighted magnetic resonance imaging scan of a 4 year old boy with glutaric aciduria type 1 showing a large collection of fluid anterior to both temporal poles with lack of opercularisation of both sylvian fissures.

rhage; she had neonatal sepsis, rickets of prematurity, and bilateral cataracts treated by lensectomy.

Three of the four normal survivors are members of the traveller (Gypsy) community. Two of them are in the appropriate class in school (9 and 6 years old) and the third is younger and appropriate for age. Unfortunately, the standard scales of development are not appropriate for this group, who use their own dialect and vocabulary. Of the other two surviving children, one has normal development, whereas the other, aged 3 years, is functioning at 2 years 1 month using the same scale (born preterm at 32 weeks' gestation).

Discussion

Variable increases in concentrations of glutaric, 3-hydroxyglutaric, and glutaconic acids occur in the physiological fluids of the body in patients with glutaric aciduria type 1. The pathogenesis is poorly understood. Glutaric acid is probably neurotoxic and causes neurodegenerative changes. Some confirmed cases have escaped this toxic effect, even within the same family.¹⁴ It is not understood why 5% of affected but untreated individuals in the Amish population never develop neurological abnormalities.¹ No correlation has been established between genetic mutations and the severity of outcome. There is no helpful biochemical marker as in the aminoacidopathies. Hepatomegaly has been a useful clinical sign and is present early in metabolic decompensation.

Key messages

- Glutaric aciduria type 1 should be considered in the differential diagnosis of dystonic/dyskinetic cerebral palsy, macrocephaly, and non-accidental injury
- Siblings, older and younger, must be screened
- In presymptomatic patients, supplementation with L carnitine and intensive dietary treatment with aggressive emergency management results in a favourable outcome

There is a high mortality and morbidity in glutaric aciduria type 1. Patients can be asymptomatic and well, or have an acute handicapping encephalopathic episode after trivial infection. The incidence in Ireland is approximately one in 56 000 live births but could be higher, as a result of under diagnosis. Consanguinity is common in affected families.

Paediatricians must be aware of the subtle manifestations of the disorder. Glutaric aciduria type 1 is rare but should be considered in the differential diagnosis of dyskinetic cerebral palsy, macrocephaly, subdural haematoma, and an increase in intrahemispheric space. It might be advisable to review those already diagnosed as dyskinetic cerebral palsy and investigate them for glutaric aciduria type 1. This could prevent dyskinetic disorders in other siblings.

Abnormal urinary organic acids and acyl carnitine can provide the diagnosis in most cases. Enzyme assays of glutaryl-CoA dehydrogenase in lymphocytes or cultured fibroblasts are necessary to confirm or exclude the diagnosis in all instances.

Dietary management is the only currently available treatment and should be continued for life. Our data, incorporating experience of approximately 50 patient treatment years, indicate that early diagnosis and aggressive treatment lead to a favourable outcome, with prevention of major neurological sequelae.

Treatment aims to reduce the intake of natural protein and to suppress catabolism by providing a high energy intake when required. Large fluid volumes are needed in dyskinetic patients because of the excessive movement.¹⁴ Synthetic amino acid mixtures or foods that are deficient or low in lysine, hydroxylysine, and tryptophan are available. Low protein without synthetic supplement is used in some centres. Supplementation with L carnitine, and increasing the dose early during a metabolic crisis, is essential. Although we have not shown any vitamin responsiveness, riboflavin is added as a cofactor to encourage enzyme activity initially.¹⁵ During stress (acute infections, vaccinations, trauma, and poor feeding), the emergency protocol is instituted (table 1). Liver function tests (transaminases) and ammonia become abnormal up to 10 days after metabolic decompensation and might not become normal until much later. Parents are taught emergency management but hospital

admission for intravenous fluids is mandatory with any vomiting illness.

The only known normal patients in our population are those detected as a result of high risk family screening. Our finding that treatment has not reversed the neurological damage in symptomatic cases, but might prevent further injury to the brain, agrees with that of Baric *et al.*¹ Diet offers some hope for cases identified presymptomatically but the patient requires early aggressive meticulous management. The threat of handicap or death remains, and emergency management needs to be initiated with illness at all ages.

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- 1 Baric I, Zschocke J, Christensen E, *et al.* Diagnosis and management of glutaric aciduria type 1. *J Inher Metab Dis* 1998;**21**:326–40.
- 2 Goodman SI, Markey SP, Moe PG, Miles BS, Teng CC. Glutaric aciduria; a 'new' disorder of amino acid metabolism. *Biochemical Medicine* 1975;**12**:12–21.
- 3 Goodman SI, Kohlhoff JG. Glutaric aciduria; inherited deficiency of glutaryl-CoA dehydrogenase activity. *Biochemical Medicine* 1975;**13**:138–40.
- 4 Hoffman GF, Trefz FK, Barth PG, *et al.* Glutaryl-coenzyme A dehydrogenase deficiency; a distinct encephalopathy. *Pediatrics* 1991;**88**:1194–203.
- 5 Ribes A, Riudor E, Briones P, Christensen E, Campistol J, Millington DS. Significance of bound glutarate in the diagnosis of glutaric aciduria type 1. *J Inher Metab Dis* 1992;**15**:367–70.
- 6 Goodman SI, Freeman FE. Organic acidurias due to defects in lysine oxidation: 2-ketoadipic acidemia and glutaric acidemia. In Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic basis of inherited disease*. 7th ed. New York: McGraw-Hill, 1995:1451–60.
- 7 Morton DH, Bennett MJ, Seargeant LE, Nichter CA, Kelley RI. Glutaric aciduria type 1: a common cause of episodic encephalopathy and spastic paralysis in the Amish of Lancaster County, Pennsylvania. *Am J Med Genet* 1991;**41**:89–95.
- 8 Biery BJ, Stein DE, Morton H, Goodman SI. Gene structure and mutations of glutarylcoenzyme A dehydrogenase: impaired association of enzyme sub-units due to an A421V substitution causes glutaric aciduria type 1 in the Amish. *Am J Hum Genet* 1996;**59**:1006–12.
- 9 Aniskter Y, Shaag A, Joseph A, *et al.* Glutaric aciduria type 1 in the Aran and Jewish communities in Israel. *Am J Hum Genet* 1996;**59**:1012–18.
- 10 Osaka H, Kimura S, Nezu A, Yamazaki S, Saitoh K, Yamaguchi S. Chronic subdural haematoma as initial manifestation of glutaric aciduria type 1. *Brain Dev* 1993;**15**:125–7.
- 11 Drigo P, Burlina AB, Battistella PA. Subdural haematoma and glutaric aciduria type 1. *Brain Dev* 1993;**15**:460–61.
- 12 Christensen E, Jacob Brandt N. Studies on glutaryl-CoA dehydrogenase in leucocytes, fibroblasts and amniotic fluid cells. The normal enzyme and the mutant form in patients with glutaric aciduria. *Clin Chim Acta* 1978;**88**:267–76.
- 13 Christensen E. Improved assay of glutaryl-CoA dehydrogenase in cultured cells and liver: application to glutaric aciduria type 1. *Clin Chim Acta* 1983;**129**:91–7.
- 14 Hoffman GF, Athanassopoulos S, Burlina AB, *et al.* Clinical course, early diagnosis, treatment and prevention of disease in glutaryl-CoA dehydrogenase deficiency. *Neuropediatrics* 1996;**27**:115–23.
- 15 Lipkin PH, Roe CR, Goodman SI, Batshaw ML. A case of glutaric aciduria type 1: effect of riboflavin and carnitine. *J Pediatr* 1988;**12**:62–5.