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Glutaric aciduria type 1: biochemical investigations and postmortem findings

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Abstract. Glutaric aciduria type 1 (GA1; deficiency of glutaryl – CoA dehydrogenase) was diagnosed in a 6.5-month-old female infant. Despite a good biochemical response to dietary reduction of lysine and tryptophan, there was no clinical response to diet nor to riboflavin therapy and her neurological condition deteriorated progressively until her death at 10.5 months. At postmortem examination only mild neuropathological abnormalities were found in contrast to previous reports of this condition. High levels of glutarate were found in liver, skeletal muscle, heart muscle and aqueous humor. Eye fluid which is readily available, may be a useful material for the postmortem diagnosis of this, and other organic acidurias when urine is not available.

Key words: Glutaric aciduria type 1 – Organic aciduria – Lysine – Tryptophan – Neurodegenerative disorders

Introduction

Glutaryl-CoA dehydrogenase deficiency or glutaric aciduria type 1 (GA1) is a rare inborn error of lysine and tryptophan metabolism known to present with dystonia and developmental regression [7].

Presentation is usually early in infancy and diagnosis has mostly been made in later childhood. This paper describes the complete course of such a child with new biochemical and postmortem data, and reviews the status of previously reported cases.

Case history

B-J.K. was a female infant (birth weight 2.6 kg) born to a primigravid, unmarried, known intravenous drug abuser following an uncomplicated pregnancy and delivery. Normal development progress is documented over the first 6 months of life. At 6.5 months of age she presented with a series of prolonged adversive occular attacks during which she was unresponsive and hypertonic. The results of initial emergency investigations (urea and electrolytes, calcium, glucose, blood gases, ammonia, blood film, CSF, EEG, and CT scan) were normal. Suspicion remained that these attacks had been precipitated by administered exogenous substances but results of a toxicology screen were normal.

Over the course of the next week the attacks became less frequent and she remained visually alert, but she assumed an opisthotonic posture with hypertonus fisting. At this time she had regressed in all developmental fields with poor head and trunk control, poor social response, no vocalisation and no response to sound.

Amino acid analysis of blood and urine gave consistently normal results. Organic acid screening performed at the time of admission showed a large peak of glutaric acid (vide infra)

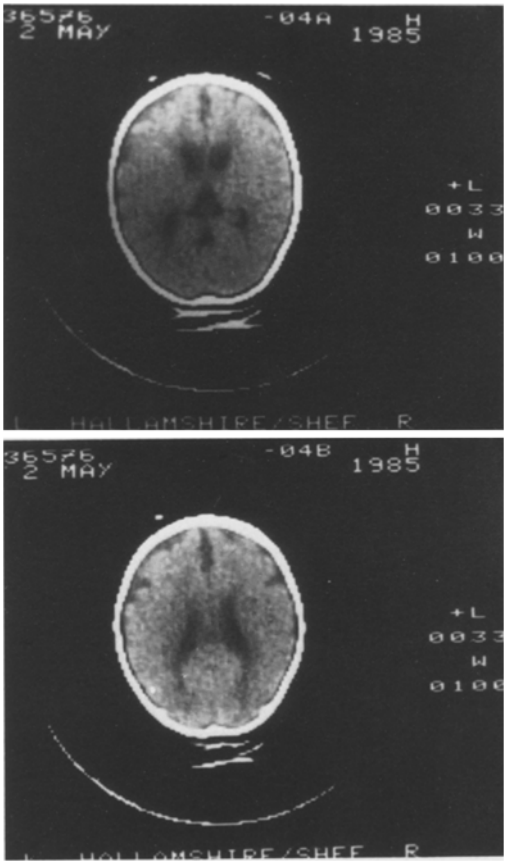

Fig. 1. CT scan of patient's brain prior to death showing the development of generalised widening of CSF spaces

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Abbreviation: GA1 = glutaric aciduria type 1

and the diagnosis of GA1 was confirmed on blood, urine and cultured fibroblast assay. Initial dietary control was attempted unsuccessfully with a low protein diet supplemented after 1 week with riboflavin (50 mg four times daily). Successful biochemical control (Fig. 2) was achieved with a low lysine and tryptophan diet using a lysine- and tryptophan-free amino acid mixture supplemented with formula feeds (0.5 g protein/kg), "Duocal" high fat calorific supplement, vitamin supplements and protein-free weaning foods. No clinical improvement was noted, indeed a progressive deterioration in neurological function occurred over the ensuing 3 months.

In view of this deterioration a therapeutic trial of the gamma amino butyric acid analogue Lioresal (2 mg/kg per 24 h) was commenced without effect. Further neurological deterioration occurred at 10 months of age with increasing athetoid movements, profound dystonia and opisthotonous, hypertonus on the right, marked facial grimacing and loss of temperature regulation.

A further CT scan (Fig. 1) demonstrated generalised widening of the CSF spaces and attenuation in the white matter indicating a generalised atrophic process. Death occurred at 10.5 months with an intercurrent bronchopneumonia.

Postmortem investigations revealed fatty infiltration of the liver, kidneys and heart. The brain showed only mild gyral atrophy with moderate fatty change in the caudate nucleus. There were no other significant features.

Materials and methods

Urine and plasma were stored at −20°C until analysed. Urine was collected as a series of random samples. Blood was collected into heparin and separated plasma was frozen within 30 min. Postmortem tissue and aqueous humor samples were obtained within 6 h of death and immediately frozen at −80°C until analysed. Organic acid analysis was carried out on all materials by gas chromatography-mass spectrometry (gc-ms) and trimethylsilyl derivatives after extraction into ethyl-acetate and ether [7]. An internal standard of stearic acid (50 mg/dl) was added to the urine and plasma. For analysis of aqueous humor and postmortem tissues an equal volume of deuterated glutaric acid (50 µmol/l) was used as an internal standard. The capacity of cultured fibroblasts to metabolise DL [6-C^{14}] lysine and [1-C^{14}] octanoate was examined using methods similar to those previously described [1].

Results

The urinary organic acid pattern showed a large excess of glutaric acid (0.5–5.0 mmol/mmol creatinine) and of 3-hydroxyglutaric acid (55–360 µmol/mmol creatinine). This is consistent with a diagnosis of GA1. Glutaconic acid, which has been reported in this disorder, was not detected in appreciable excess. There was no detectable release of CO_2 from [6-C^{14}] lysine by fibroblasts cultured from the patient [controls ($n = 5$): 2.79 ± 1.87 pmol CO_2/min per mg protein] but oxidation of [1-C^{14}] octanoate was normal. The biochemical response in terms of urine glutarate and 3-hydroxyglutarate levels is shown in Fig. 2. There was no response to riboflavin therapy or to protein restriction but a marked response to the synthetic low lysine and tryptophan diet. 3-hydroxyglutarate was not present in excess soon after initiating this therapy and

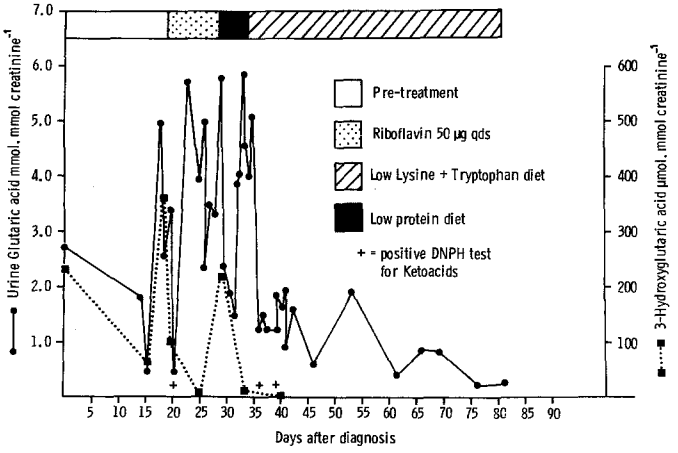

Fig. 2. Urinary metabolite output in response to the various treatment regimes initiated

Table 1. Glutarate levels in post-mortem material

Material	Patient	Control
Liver	401 nmol/g wet weight	26 nmol/g wet weight
Brain (frontal cortex)[a]	31 nmol/g wet weight	4 nmol/g wet weight
Cardiac muscle	441 nmol/g wet weight	10 nmol/g wet weight
Skeletal muscle	274 nmol/g wet weight	11 nmol/g wet weight
Aqueous humor	107 µmol/l	Less than 10 µmol/l

[a] Fixed in formalin: result may be spuriously low

the plasma glutarate fell from 255 µmol/l pretreatment to undetectable levels (less than 10 µmol/l). It was notable that there was a wide fluctuation in metabolite output emphasising the importance of not judging biochemical responsiveness with single results. An excess of glutaric acid was found in all postmortem material (Table 1). A urine sample collected postmortem demonstrated an excess of glutarate, 3-hydroxyglutarate, adipate and a mild ketonuria but no abnormality of amino acids. The aqueous humor glucose level was found to be low at 0.3 mmol/l (6 h postmortem).

Discussion

To date 12 previous cases of GA1 have been reported either in full or in abstract form [2, 3, 5, 6, 8, 11–15], with two postmortem investigations [9, 13]. A number of differences have emerged when compared to our patient, in particular the severity of the neuropathological changes. The changes reported by Goodman et al. [9] and Leibel et al. [13] included cerebral oedema and gross striatal degeneration, particularly in the putamen. In our patient the pattern was of a mild gyral atrophy. This differences may be related to the age of the subjects being studied, being 10 years in Goodman's patient, 3.5 years in Leibel's and less than 1 year in ours, suggesting a chronic deterioration in GA1. The fatty infiltration of liver, kidney and heart muscle is, however, a consistent finding.

The initial presentation of all reported cases of GA1 is similar but the clinical outcome demonstrates heterogeneity. Four patients are known to have died in late infancy/early

childhood following a progressive deterioration [6, 8, 13, 15]. A further five cases have been reported to be responsive to riboflavin, dietary restrictions, or Lioresal [2, 3, 5, 11] although many of these patients retained some symptoms of neurological damage. It has been suggested that these milder cases may possess a mutant form of the enzyme with high residual activity [4].

In the above case no residual activity was detected on fibroblast culture analysis, suggesting a severe form of GA1 and the reduction in metabolite output on a lysine and tryptophan-reduced diet did not correlate with a clinical improvement.

Neither metabolic acidosis nor hypoglycaemia were found in our patient either at diagnosis or during subsequent management, though both features have been recorded inconsistently in GA1. Hypoglycaemia may have been present at the time of death since the aqueous humor glucose level was very low shortly after death. Hypoglycaemia in GA1 may be related to inhibition of fatty acid oxidation by acyl-CoA accumulation within mitochondria [8] and in our case inhibition of fatty acid beta oxidation was indicated by the presence of adipate in excess of that expected for the mild degree of ketosis in the final urine sample.

The high levels of glutarate demonstrated in eye fluid have not previously been described in GA1. The postmortem diagnosis of this and perhaps other organic acid disorders could be aided by eye fluid investigation.

The prognosis for non-riboflavin responsive forms of GA1 is very poor and should be taken into account when counselling parents. Pre-natal diagnosis is possible [10] and should be made readily available.

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