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Glutaric Aciduria Type I Presenting with Hypoglycaemia

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We present a child with glutaryl CoA-dehydrogenase deficiency (type I glutaric aciduria) who presented with bilateral subdural hydromas, and progressive choreoathetosis and dysarthria. The diagnosis was made when she was investigated for hypoglycaemia at the age of 3.5 years. Temporary adrenocortical insufficiency was also noted. Three years after diagnosis the adrenal insufficiency and hypoglycaemia have resolved and treatment with riboflavin and 'lioresal', a GABA analogue, has prevented any further neurological deterioration.

Very large amounts of glutaric acid have been detected in the urine of patients with two clearly defined syndromes. Glutaric aciduria type I (McKusick 23167) as first described by Goodman and his colleagues (1975) presents with progressive choreoathetosis, hyperkinesia and dysarthria, and is due to glutaryl CoA-dehydrogenase deficiency, an inborn error of lysine and tryptophan metabolism (Stokke *et al.*, 1975; Gregerson *et al.*, 1977; Whelan *et al.*, 1979; Kyllerman and Steen, 1977). The condition first reported by Przyrembel and his colleagues (1976), which they named glutaric aciduria type II is characterized by massive acidosis and hypoglycaemia. The condition usually presents in the newborn period, although mild cases presenting later have been described (Dusheiko *et al.*, 1979). This disease is caused by deficiency of several acyl-CoA dehydrogenases (Goodman *et al.*, 1980).

Whereas in type II glutaric aciduria hypoglycaemia may be the only presenting feature (Dusheiko *et al.*, 1979), it is unusual for patients with type I to have significant hypoglycaemia. We report a child with proven glutaryl CoA-dehydrogenase deficiency who presented with hypoglycaemia. In addition we present evidence to support the observations of Brandt *et al.* (1979) that treatment with riboflavin and lioresal, a GABA analogue, may be effective in this condition.

CASE REPORT

N.B. is the third child of unrelated Bengali parents. She was born weighing 2.9 kg in Bangladesh after an uneventful pregnancy and delivery. At the age of 15 months she presented with a 3 month history of recurrent irritability and vomiting. Her head circumference was above the 90th centile and a CAT scan demonstrated bilateral subdural hydromas which contained sterile xanthochromic fluid. There was no history of injury, accidental or non-accidental. The episodes of drowsiness, vomiting and convulsions continued and further surgery was carried out with the temporary insertion of subdural peritoneal shunts.

Around the time of these neurosurgical procedures she was given several short courses of dexamethasone. She was also given 6 months treatment with INAH because she was a tuberculosis contact, showing intradermal skin test conversion.

After the surgery at the age of 2 years her general health remained good, but signs of spasticity were noted. By the age of 3.25 years she had developed, in addition, truncal ataxia and involuntary choreiform movements. Her motor development had regressed in that she was no longer standing or sitting without support. Non-motor skills were less severely affected and were only delayed by 0.5 years.

At age 3.5 years she was brought to the casualty department, having been found unrousable by the parents in the morning. She was hypoglycaemic (blood glucose <0.5 mmol/l) with ketonuria. She had been unwell with a mild upper respiratory tract infection for a few days.

Apart from the hypoglycaemia, initial investigations including arterial pH and bicarbonate were normal. The CAT scan showed some increase in the size of the ventricular system, with residual effusions over both temporal lobes but no signs of raised intracranial pressure.

ANALYTICAL METHODS

Insulin, cortisol and growth hormone were assayed by standard radioimmunoassay, glucose by glucose oxidase, lactate by the specific dehydrogenase methods. Amino acids were measured quantitatively.

Identification and quantitation of glutaric acid and 3-hydroxyglutaric acid were performed by gas–liquid chromatography after ether extraction as trimethylsilyl derivatives with undecanedioc acid as an internal standard. The identity of all metabolites was confirmed by mass spectrometry (Mr G. Lynes, Queen Elizabeth Hospital, Hackney).

Fibroblasts were cultured from a skin biopsy and assayed for glutaryl CoA-dehydrogenase activity by incubation with [^{14}C]glutaric acid and detection of liberated $^{14}CO_2$ by Dr Christensen, Copenhagen (Gregerson *et al.*, 1977).

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RESULTS

Endocrine investigations

Hypoglycaemia occurred consistently after periods of fasting greater than 8–12 h. Plasma ketones were appropriately elevated in fasting specimens and suppressed normally after a glucose load. Fasting blood lactate concentrations were normal, as were the glucose response and lactate concentrations during a standard glucagon test. There was no evidence of hyperinsulinism.

The growth hormone response during an insulin tolerance test was normal (>30 mU/l) but cortisol concentrations remained low throughout (<165 nmol/l). Midnight and 8.0 a.m. cortisol concentrations (110 and 220 nmol/l) were within the normal range but the concentration only rose to 480 nmol/l after 'Synacthen'. Similarly the rise in 11-deoxycortisol during a short metyrapone test was abnormal (Koplberg *et al.*, 1972). Other tests of pituitary function (TRH and GnRH) were normal. Adrenal antibodies were not detected and no adrenal masses or calcification were evident on abdominal ultrasound.

Metabolic investigations

Plasma and urinary amino acids were normal in fasting and non-fasting specimens. Urine samples at the time of presentation, and consistently thereafter, contained large amounts of glutaric and 3-hydroxyglutaric acid (Table 1). No other important metabolites were detected. Glutaconic acid was not found even after a protein load (2 g/kg), but this was probably due to the use of ether extraction (Stokke *et al.*, 1975). A deficiency of glutaryl CoA-dehydrogenase activity was confirmed in cultured skin fibroblasts (Table 2).

Effects of treatment

In view of the low cortisol concentrations during the insulin tolerance and Synacthen tests, cortisol replacement therapy was begun (hydrocortisone 20 mg/M^2/day). In addition the patient was started on a low protein diet (2 g/kg/day) and riboflavin (100 mg daily) which resulted in a small but not consistent reduction in the quantities of metabolites detected in the urine (Table 1). Lioresal, a GABA analogue, was later added in a dose of 2 mg/kg/day (Brandt *et al.*, 1979).

Table 1 Raised urinary excretion of glutaric and 3-hydroxyglutaric acids

Patient N.B.	*Metabolite*	
	Glutaric acid (mg/g creatinine)	*3-Hydroxyglutaric acid* (mg/g creatinine)
At diagnosis	1967–3360	148–303
After treatment*		
2 weeks	1327–1780	50–169
3 months	920	
1 year	1600	
2.5 years	2600	

* Treatment – Riboflavin (100 mg daily), a low protein diet (2g/kg/day) and lioresal 2 mg/kg/day

Table 2 Enzyme deficiency in cultured fibroblasts

Patient N.B.	*Fibroblast glutaryl CoA-dehydrogenase activity* (μmol CO_2/h/g protein)
	0
Control 1	5.9
Control 2	7.8

Three months after the diagnosis was made, while the patient was on cortisol replacement therapy, hypoglycaemia still occurred after periods of fast greater than 8 h. Synacthen response was subnormal.

One and a half years after diagnosis, hypoglycaemia still occurred during fasting, but there had been some improvement in her neurological condition. She was beginning to walk with support, speech was improving and there had been no intellectual deterioration.

Two and a half years after diagnosis, cortisol responsiveness to Synacthen had returned, and she was taken off hydrocortisone therapy. Hypoglycaemia did not occur even after a fast of 18 h. Her neurological condition had remained static during the previous 6 months spent in Bangladesh during which time drug compliance had been poor and physiotherapy lacking.

DISCUSSION

The child reported has proven glutaryl CoA-dehydrogenase deficiency and like other children with type I glutaric aciduria she developed progressive choreoathetosis, hyperkinesia and dysarthria (Goodman *et al.*, 1975; Stokke *et al.*, 1975; Gregerson *et al.*, 1977; Whelan *et al.*, 1979; Kyllerman and Steen, 1977). But in other ways, her presentation with subdural hydromas, hypoglycaemia and transient adrenocorticol insufficiency has been unusual. The response to treatment in this patient provides support for the observations of Brandt *et al.* (1979), that lioresal and riboflavin may be effective in preventing further progression of the neurological disease. The effects of treatment may be principally within the central nervous system for there was very little alteration in the urinary excretion of metabolites.

The transient adrenocorticol insufficiency is difficult to explain. There was no other evidence of pituitary dysfunction. Adrenal suppression can occur after dexamethasone therapy and may persist for many months (Editorial, 1980). Tuberculosis may cause adrenal disease but then it is unusual for it to resolve spontaneously after two years. Finally, however unlikely, we cannot exclude the possibility that the metabolic defect might have affected cortisol synthesis in some way.

It seems unlikely that the hypoglycaemia was entirely due to adrenocortical insufficiency as it still occurred after satisfactory cortisol replacement therapy. However, *in vitro* glutaryl CoA is an inhibitor of mitochondrial uptake of malate, which is a rate-limiting step in gluconeogenesis (Tanaka and Kerley, 1975) and

an accumulation of glutaryl CoA could further impair gluconeogenesis. Hypoglycaemia, although not a common feature of type I glutaric aciduria, has been reported.

The improvement in tolerance to fasting could be due not only to the apparent resolution of the adrenal disorder but also to improvement in the glutaric aciduria with diet and riboflavin.

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