Case report

Glutaric aciduria type 1 in a Kuwaiti infant

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Introduction

Glutaryl-coenzyme A (CoA) dehydrogenase deficiency (MIM 231670) is a recessively inherited neurometabolic disorder associated with encephalopathic crises and severe extra-pyramidal symptoms [*1*]. Macrocephaly, frontotemporal brain atrophy and acute encephalopathic episodes characterize it, with striatal necrosis followed by dystonia [*2*]. However, some patients develop motor disease without overt crisis and other biochemically affected individuals remain asymptomatic [*3–8*].

This is the first report of a Kuwaiti male infant with glutaric aciduria type 1 (GA-1). The clinical picture, the course of the disease, neuro-imaging findings and treatment are discussed.

Case report

F.A. is a Kuwaiti child, aged 3.5 years, who was admitted to hospital at the age of 10 months because of fever, cough and repeated vomiting of 1-week duration. After admission, he developed a series of short left-sided seizures followed a few days later by right-sided seizures. Phenobarbital therapy was started. The seizures continued for 5 days. Shortly after, he developed a left hemiplegia, and he was no longer able to sit or crawl and lost his words.

He is the sixth and youngest child to first-cousin phenotypically normal parents and has 5 healthy sisters. Pregnancy and delivery were normal. Birth weight was 3.6 kg. Macrocephaly was noted at birth, and his head circumference continued to grow parallel to the 98th centile. His development was said to be entirely normal until the age of 10 months. He sat alone at 7.5 months, was crawling and pulling to stand at 8 months and by 10 months he had 1 or 2 words. He was admitted to hospital at the age of 5 months with suspected meningitis excluded by cerebrospinal fluid (CSF) examination.

Examination after the acute episode at 10 months revealed a relatively healthy, mentally normal child, with weight 10 kg and head circumference 51.5 cm. His cranial nerves were normal on examination. He had a dystonia of the left side and left hemiparesis with increased muscle tone and exaggerated tendon reflexes on the same side. There were no abnormal neurological signs in the right limb. Examination of chest, heart, abdomen, skin and genitalia showed that all signs were within normal values. Fundus examination revealed no haemorrhage or other abnormalities. The following

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investigations were normal: plasma sodium, potassium, urea, creatinine, liver enzymes and glucose, haemoglobin, white blood cells and platelets, blood pH (7.36) and serum bicarbonate (21.2 nmol/L), prothrombin time, thrombin time and fibrinogen, and serum ammonia, lactic acid and amino acids. Activated partial thromboplastin time (APTT) was slightly increased at 42 seconds. Plasma ceruloplasmin was slightly elevated. CSF investigations were normal. However, urinary glutaric acid was 67 µmol/mol creatinine (normal < 14) and 3-hydroxy glutaric acid was 85 µmol/mol creatinine (normal range: traces). Glutarylcarnitine levels in urine were elevated and glutaryl-CoA dehydrogenase activity in cultured fibroblasts was low.

Computerized tomography (CT) and magnetic resonance imaging (MRI) scans of the head revealed severe frontotemporal atrophy and bilateral subdural haemorrhage (Figures 1 and 2).

His current therapy consists of carnitine 500 mg 6 hourly, with a low protein diet and carbohydrate drinks to be given during infections and sick days. He is also receiving regular physiotherapy. Phenobarbital was gradually discontinued 5 months after the acute episode. He is generally stable, fit-free, and showing mild improvement with left sided hemiparesis. The child is still alive at the time of writing this report.

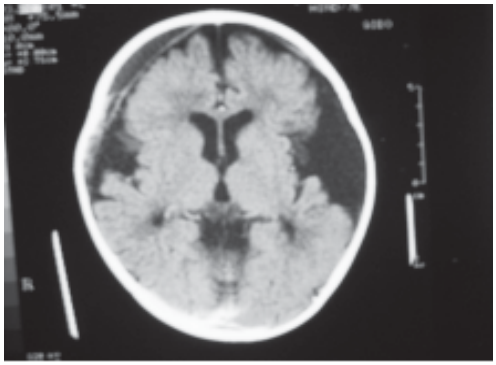

Figure 1 **Computerized tomography scans of the head shows severe fronto-temporal atrophy**

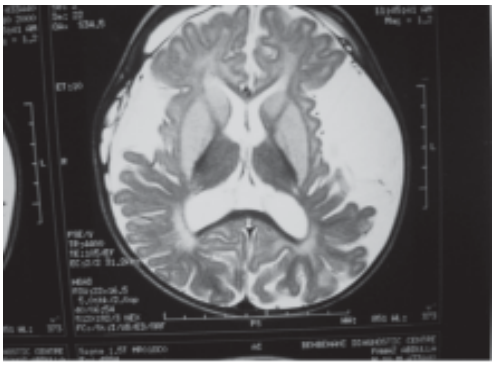

Figure 2 **Magnetic resonance imaging scans of the head shows fronto-temporal atrophy and bilateral subdural haemorrhage**

Discussion

Since the first description of GA-1 by Goodman et al. in 1975 [*9*], several reports have been added to the literature describing one of the more frequent inherited metabolic disorders [*10–12*]. GA-1 is an autosomal recessive disorder caused by deficiency of glutaryl-CoA dehydrogenase, a mitochondrial enzyme involved in the metabolism of lysine, hydroxylysine and tryptophan. The clinical picture typically shows varying degrees of muscular hypotonia, motor delay, dystonia, dysarthria and dyskinesia beginning acutely or gradually in the first few years of life, often in macrocephalic children [*7,13*].

It is difficult to estimate the incidence of GA-1, as the clinical presentation is variable. But the figure of 1:40 000 in Caucasians seems a reasonable approximation [*14–16*]. An incidence as high as 1:30 000 has been suggested [*16,17*]. The disease is particularly frequent in certain communities such as the Amish people in Pennsylvania (1:4000) and Saulteaux/Ojibway Indians in Canada [*1,13–15,18*]. Few patients have been recorded among Arab populations [*19*]. In Kuwait, its incidence has not been estimated so far. However, the frequency of metabolic disorders is common in Kuwait [*20*].

In the present report, the clinical picture, the course of the disease and the biochemical and radiological findings represent the classic presentation of GA-1. Both the onset and the clinical picture of the patient, who had a viral illness followed by encephalopathic crisis, have been considered common features. However, among 100 cases described worldwide, only 4 asymptomatic homozygotes for the disease have been described [*3,11,15*]. This variability in presentation sometimes necessitates a high index of suspicion for diagnosis. Page et al. [*21*] reported a case that presented in the neonatal period with seizures, while Superti-Furga and Hoffmann [*2*] emphasized that presentation may start between the early weeks and the 4th to 5th year of life when intercurrent illnesses, viral infections or gastroenteritis may trigger acute encephalopathy. The biochemical findings of the present case were highly diagnostic. The diagnosis of GA-1 is suggested by the findings of excess 3-hydroxyglutaric acid in the urine and this should be found on a urinary organic acid screen. Blood acylcarnitine profile has also been used as a more sensitive test. However, both tests may show negative results and a strong clinical suspicion is needed [*22*]. Recognition of the biochemical changes before the brain has been injured is essential for a satisfactory outcome. Diagnosis depends on the recognition of relatively non-specific physical findings such as hypotonia, irritability, macrocephaly and urine organic acid quantification [*13*]. The low activity of glutaryl-CoA dehydrogenase in cultured fibroblasts confirms the diagnosis of GA-1. In addition, the radiological finding of fronto-temporal atrophy is typically described in patients with GA-1 [*23*]. It has been suggested that the combination of wide CSF spaces anterior to the temporal lobe and low-density lesions in the basal ganglia are almost diagnostic of this condition [*24*]. In addition, the presence of subdural haemorrhage has been reported [*25*].

Glutaryl-CoA dehydrogenase is a multifunctional enzyme, which exists in the mitochondrial matrix as a homotetramer of 45-kD subunits. The human gene for glutaryl-CoA dehydrogenase has been cloned and mapped to the short arm of chromosome 19p13 [*26*]. More than 63 mutations have been identified so far in GA-1 families, but no one prevalent mutation was detected and little if any relationship between genotype and clinical phenotype could be recognized. The mutations were widely distributed through the gene, with the largest number in exon 10 [*27*]. Recessive inheritance of this disorder is confirmed.

In conclusion, this report is the first of GA-1 from Kuwait. The clinical, biochemical and radiological findings confirm the diagnosis. Our patient is now stable but has only minor improvement, which agrees with most of the reported cases in the literature. We hope that continued therapy with carnitine and low protein diet together with emergency regimen with carbohydrate drinks will at least prevent further deterioration and encephalopathic crisis. Coordinated research is needed to understand the

pathogenesis of the brain pathology, to define the role of dietary therapy and to explore the possibility of neonatal screening. Multi-centre studies are needed to establish the best method for diagnosis and the optimal therapy of this disorder.

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