

# GLUTARIC ACIDEMIA TYPE 1: FIRST SAUDI PATIENT DIAGNOSED BY TANDEM MASS SPECTROMETRY-BASED NEONATAL SCREENING

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Glutaric acidemia type 1 is an autosomal recessive disease caused by mutations in the glutaryl CoA dehydrogenase gene, leading to the deficiency of this enzyme.<sup>1</sup> As a result, the breakdown of L-lysine, L-hydroxy-lysine and L-tryptophan are interrupted. Approximately 80 cases of glutaric acidemia type 1 have been reported in the literature.<sup>2-4</sup> Its incidence appears to be 1 in 30,000 in Sweden,<sup>5</sup> but it is more common among heavily consanguineous communities, such as the Amish community in Pennsylvania,<sup>4</sup> and among Sauteaux/Ojibway Indians in Canada.<sup>3</sup> Although its incidence in the Kingdom is unknown, the medical records of the King Faisal Specialist Hospital and Research Centre contain 24 patients diagnosed to have the disease, of whom 18 are currently being followed. The clinical findings in three<sup>6</sup> and the neuroradiological findings in five of these patients have been published previously.<sup>7</sup>

As is the case elsewhere, the disease in Saudi Arabia causes acute neurodegeneration, following a metabolic stress between three and 10 months of age. This is characterized by acute onset of an extrapyramidal tract disease with dystonia and choreoathetosis. The disease is not included in the neonatal screening programs in the world, except for Saudi Arabia.<sup>8</sup> In other communities where it is encountered frequently, its presence in a neonate is detected by selective screening of the newborn of the families with a previously affected child.

This report is about the first Saudi newborn detected to have glutaric acidemia type 1 through normal neonatal screening. The patient is now 24 months of age and is doing fine with appropriate therapy. It is important to screen for this disease among Saudi neonates, since there is potential therapy.

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## Patient and Methods

The tandem mass spectrometry-based detection of type 1 glutaric acidemia has been reported in a previous study.<sup>8</sup> The urine gas chromatography (GC) mass spectrometry (MS) finding of glutaric and 3-hydroxyglutaric acidemia was made through conventional procedures.<sup>9</sup> The patient was a five-week-old infant, whose disease was detected by tandem mass spectrometry-based normal neonatal screening. When first encountered, the patient had no unusual physical findings, except for relative macrocephaly. His height and weight were at the 25th percentile and head circumference at the 95th percentile. Neurological examination indicated age-appropriate neurological development. He was treated with carnitine 200 mg/kg/day, riboflavin 100 mg/kg/day, baclofen 5 mg and diazepam 0.2 mg per day, in addition to low protein and a special formula restricted in lysine and tryptophan (Glutarex-2, Ross Company, Division of Abbott, Columbus, Ohio, USA). He was given IV carnitine, 200 mg/kg/day in four divided doses, and IV

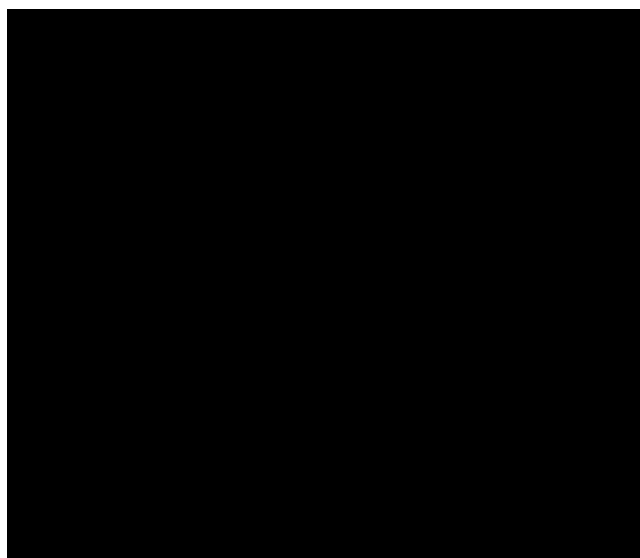


FIGURE 1. The appearance of the patient at two years of age.

FIGURE 2. Free and acylcarnitine profile obtained by ESI-MS/MS precursor ion scanning of  $m/z$  85 in blood spot (2A); in urine spot 2B (\*). Denotes deuterium-labeled internal standards. FC: free carnitine; C2: acetylcarnitine; C5DC: glutarylcarnitine; C14: tetradecanoylcarnitine; C16: hexadecanoylcarnitine; and C18: octadecanoyl-carnitine. The degree of unsaturation in fatty acylcarnitines are indicated as C16:1 and C18:1.

10% glucose when he experienced an intercurrent bacterial or viral infection.

The patient was next seen at 10 weeks of age, at which time he was found to have mild axial hypotonia and head lag. His next visit was at five months of age, when he had started to roll over and was babbling a lot, but with the macrocephaly unchanged. At nine months of age, his height and weight were at the 25th and head circumference was at the 75th percentile. He could transfer objects from one hand to the other, could stand with help and take a few steps holding onto things, and had a vocabulary of about six words. Neurologically, he had normal muscle tone, deep tendon reflexes and had developed primitive bipedal reflexes. He had no dystonia. He fell from his bed two weeks later, and developed bilateral subdural hematoma, more prominent on the right side. He had two generalized seizures at this time. The eye-ground examination indicated no retinal hemorrhages. In view of his stable condition, no neurosurgical intervention was advised. A neuropsychological assessment at 22 months of age indicated

him to be within normal limits in motor, verbal and social skills. At present he is 24 months old and his motor and psychological development are along normal lines (Figure 1).

The biochemical studies initially indicated elevated glutaryl carnitine in blood and urine (Figure 2), which was present in unchanged amounts at 10 months of age. The urine GC/MS studies at two months of age showed significantly elevated glutaric acid (194 mmol/mol creatinine, normal <2) and 3-hydroxyglutaric acid (42 mmol/mol creatinine, normal <3), in addition to other dicarboxylic acids, such as adipic and suberic acids.

Neurophysiological studies at two months of age, such as electroencephalogram, visual-evoked potentials, and

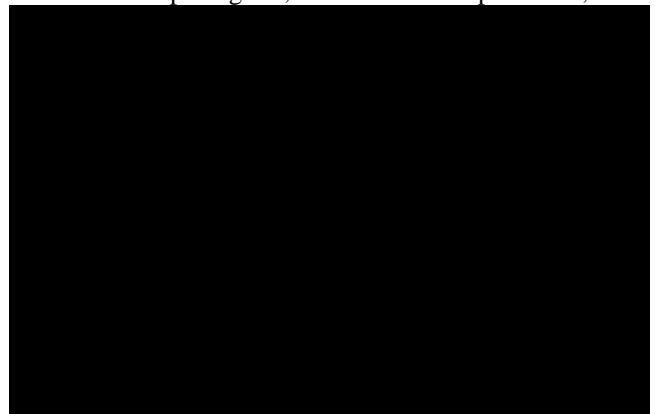


FIGURE 3A. Brain MRI at 5 weeks of age.

brain stem auditory-evoked response, were within normal limits. The neuroradiological studies included brain MRI and PET, using <sup>19</sup>fluoro-deoxyglucose (Figure 3). The initial MRI at five weeks of age was normal, except for widened opercula (Figure 3A). The basal ganglia were normal and there was no central white matter disease. A brain PET obtained at the same age was also within normal limits, with no loss of glucose uptake in basal ganglia (Figure 3B). A repeat brain MRI at the age of 9.5 months indicated bilateral subdural hematoma, more prominent on the right, unchanged opercular size and mildly increased size of the ventricular system. Finally, the last brain MRI at 13 months of age indicated the persistence of bilateral subdural hematomas, little or minimal effacement of cortical sulci on the right side, normal white matter and basal ganglia, with opercular size remaining the same.

### Results and Discussion

The case presented suggests that type 1 glutaric acidemia is a prenatal onset disease, as evidenced by the macrocephaly and by the pathognomonic brain MRI findings of the disease at birth. In a fetus in whom the disease was prenatally detected and an elective abortion performed, significant histologic abnormalities were found in the brain tissue.<sup>10</sup> Since the disease is potentially treatable, these observations raise the possibility of prenatal treatment of a diseased fetus by riboflavin and carnitine administration to the mother.

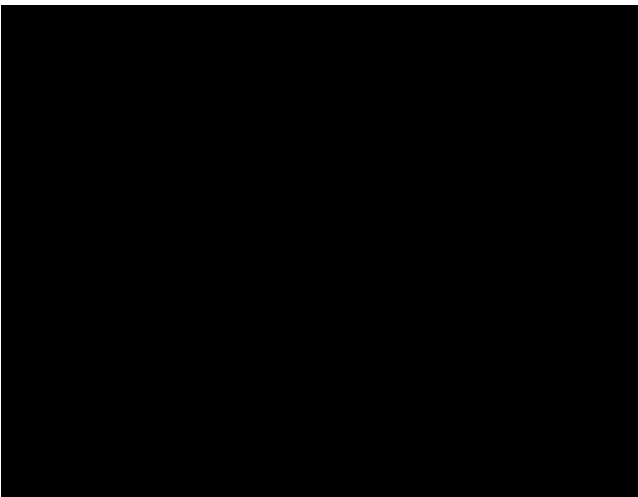


FIGURE 3B. PET-glucose at 5 weeks of age.

As a neonate, the patient in the present report showed the characteristic neuroradiological findings of widened or “bat-wing like” opercula<sup>7</sup> in the brain MRI (Figure 3A). Despite the significant involvement of the brain in the disease at birth, the PET-glucose (Figure 3B) indicated normal glucose uptake in the basal ganglia, particularly in the caudate heads. After prolonged therapy, the brain MRI remained unchanged, with no degeneration of the caudate heads and putamina, the usual findings in advanced glutaric aciduria type. These observations, as well as the absence of acute neurologic deterioration, indicate that glutaric acidemia in this patient was treatable.

The cause of acute neurodegeneration in type 1 glutaric acidemia is unknown. The accumulation of glutaric and 3-hydroxyglutaric acid in basal ganglia have been implicated in the inhibition of glutamic decarboxylase activity responsible for the synthesis of  $\gamma$ -amino butyric acid (GABA).<sup>11</sup> Glutamate toxicity has been considered to be due to repeated depolarization of glutamate receptors in basal ganglia.<sup>12</sup> In most patients with type 1 glutaric acidemia, the acute degeneration of basal ganglia occurs after a viral illness. This observation has led to the hypothesis of quinolinic acid toxicity as the cause of neural degeneration.<sup>13</sup> Glutaryl coenzyme A dehydrogenase, the defective enzyme in type 1 glutaric acidemia, is responsible for the breakdown of L-tryptophan, as well as L-lysine and its derivatives. A block in glutaryl coenzyme A dehydrogenase might shunt tryptophan catabolism to the alternate kynurenine pathway. When viral infections provoke the syntheses of  $\alpha$  and  $\beta$  interferons, a well-known effect of these compounds is to induce indolamine-2, 3-dioxygenase, which would then lead to the formation of quinolinic acid, a well-established neurotoxin.<sup>13</sup>

The patient developed acute subdural hematoma and seizures when he fell from a height of approximately three feet. Acute subdural hematoma is a known complication of the disease, and has been reported in patients with type 1 glutaric acidemia who suffered minor trauma to the skull.<sup>14,15</sup> The reason for this susceptibility is unknown, however, such subdural hematomas may not be of enough clinical significance to require any neurosurgical

intervention. In the present patient, seizures and some cortical gyral effacement was observed immediately after the trauma; however, he did not have a permanent neurologic sequel.

This report should emphasize the need for the inclusion of this disease in a potential nationwide neonatal screening program in the Kingdom. Type 1 glutaric acidemia may be a treatable disease and should be promptly and appropriately managed upon detection in a neonate, as described in the case history.

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