

Presentation and follow up of a newborn with glutaric aciduria type 1

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Glutaric aciduria type 1 (GA-1) is an autosomal recessive disease due to deficiency of glutaryl-CoA dehydrogenase (GCDH)¹. GCDH gene is located on chromosome 19p13.2^{2,3}. GA-1 is characterized by accumulation of glutaric acid, 3-hydroxyglutaric acid, glutaconic acid and glutaryl carnitine which are detectable in body fluids and tissues by gas chromatography-mass spectrometry (GC-MS) or electrospray-ionization tandem mass spectrometry^{4,5}.

Case report

An eleven day old baby girl, born of a third degree consanguineous marriage (first cousins) presented with poor feeding, decreased urine output and weight loss. Baby was born at term with a birth weight of 3.75kg and was on breast feeds. At admission, baby's weight was 2.5kg, with more than 30% weight loss. She was irritable with poor perfusion and severe dehydration with well-preserved reflexes. There was no organomegaly.

Investigations revealed very high serum sodium levels (164mEq/L) and normal potassium and glucose levels. Blood gas showed high anion gap metabolic acidosis, with normal ammonia levels and no ketosis. Sepsis work up was negative and 17 hydroxy progesterone levels were normal. In view of the high anion gap metabolic acidosis and consanguinity, tandem mass spectrometry and urine organic acid profile by GC-MS were done and turned out to be positive for GA-1.

Genetic test showed a homozygous missense

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variation in the exon 6 of glutaryl-CoA dehydrogenase (GCDH) gene (Chr 19:13004408; T>C: Depth 99x) that results in amino acid substitution of threonine for methionine at codon 149 (p.Met149Thr). Magnetic resonance imaging (MRI) of brain at 3 months of life showed widened bilateral sylvian fissures, bilateral T2W hyperintensities in the globus pallidus and volume loss of bilateral temporal lobes (Figure 1)



Figure 1: MRI of brain showing widened sylvian fissure and temporal lobe atrophy

Hypernatraemia and acidosis were corrected. Empirical intravenous antibiotics were given till cultures came back sterile. Baby was stabilized, lactation re-established and she started gaining weight.

Further management included medical nutrition therapy with low lysine diet along with breast feeds. Daily lysine intake was calculated and kept below the recommended level⁶. Predominantly lysine free formula (from Pristine Organics) along with breast feeds was given till 6 months. After 6 months, low lysine containing foods such as rice, sago pearls, banana, semolina, vegetables (like carrot, potato tomato) and fruits (like guava, apple, banana, papaya) were encouraged^{6,7}. Ready to use low lysine containing rice based powder (Naturice) and low protein multipurpose flour were also used. Foods with high lysine content like egg, fish, meat, milk, pulses etc. were strictly avoided. Baby was supplemented with carnitine at 100mg/kg/day and

riboflavin at 200mg/ day. Written emergency management protocols were given to parents. Intercurrent infections were managed promptly to prevent recurrence of metabolic crisis. Later on, an older cousin of this baby, with dystonia was investigated and diagnosed to have GA-1 after this index case was identified.

Now baby is 2 years old with normal growth parameters. Due to strict adherence to the medical nutrition therapy and regular follow up by parents, there were no further episodes of metabolic crisis. Although we started low lysine diet early, she had already developed basal ganglia injury. She developed dystonia for which she was started on tetrabenazine. Her neurological symptoms are not progressing. She has motor development delay (DQ- 60%) and other domains of development correspond with age.

Discussion

Infants affected with GA-1 can have normal development up to 2 years of age. However, macrocephaly frequently precedes onset of neurologic manifestations¹. In contrast to other organic acidurias, GA-1 rarely presents in the neonatal period⁸. Untreated, approximately 90% of children with GA-1 will develop neurological disease associated with ketoacidosis, hyperammonaemia, hypoglycaemia and encephalopathy following gastroenteritis, intercurrent infection, immunisation or surgical intervention. Dystonia is the predominant extrapyramidal symptom, frequently superimposed on axial hypotonia^{9,10}. Treatment includes:

1. Medical nutrition therapy-lysine free low tryptophan diet
2. L-carnitine 100mg/kg/day
3. Riboflavin 200-300mg/day
4. Intensified emergency therapy during episodes of intercurrent illness.

Emergency therapy should begin promptly and aggressively during febrile illness, surgery and immunization. Natural protein is stopped for 24-48 hours and oral maltodextran solution or IV glucose is given according to the general condition of patient. This has markedly reduced the frequency of acute encephalopathy in patients who are diagnosed early⁶.

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