Case Report

A Rare Case of Inborn Error of Metabolism - Isovaleric Acidemia

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Abstract

Isovaleric Acidemia (IVA) is an autosomal recessive inborn error of leucine metabolism caused by a deficiency of the mitochondrial enzyme isovaleryl-CoA dehydrogenase (IVD) resulting in the accumulation of derivatives of isovaleryl-CoA. Early diagnosis and treatment with a protein restricted diet and supplementation with carnitine and glycine are effective in promoting normal development in severely affected individual. We report a case of 1.5 years old child with Isovaleric Acidemia with intact neurological outcome.

Key words

Isovaleric Acidemia, Isovaleryl-CoA dehydrogenase, GC-MS urine, Lucine free special diet.

Introduction

Isovaleric Acidemia (IVA) is an autosomal recessive inborn error of leucine metabolism cause by a deficiency of the mitochondrial enzyme isovaleryl-CoA dehydrogenase (IVD) resulting in the accumulation of derivatives of isovaleryl-CoA including free Isovaleric acid and 4 - hydroxyisovaleric acid [1] that can be toxic and can cause serious health problems. The use of gas chromatography/ mass spectrometry (GC-MS) ultimately became the mainstay of the identification and routine clinical diagnosis of a new class of inborn errors of metabolism resulting in the abnormal accumulation of organic acids in urine, and it remains a valuable tool for biochemical geneticists today [2]. After introduction of special diet for IVA significant reduction of Isovaleric Acid level in Urine is seen and significant weight gain documented on follow up.

Case report

A Full Term, Female infant, delivered by normal vaginal delivery to 3rd degree consanguinity

parents without any significant antenatal history. Baby birth weight was 3.2 kg, cried immediately after birth hence baby was shifted to mother side. Baby was brought to hospital on 4th day of life (DOL) with lethargy, poor feeding, 2 episodes of seizure and respiratory distress. Baby previous sibling died with similar presentation at 4th DOL. Baby was intubated and ventilated for 24 hours. Routine investigations were sent which was normal. Septic Screen was negative and Blood gas was s/o metabolic acidosis. HCO_3 correction was given. Initial IEM work up was done which was s/o high plasma ammonia (1004 µmol/L) and ketoacidosis. Peritoneal Dialysis was done for 48 hours & Ammonia level was reduced (58 µmol/L). Urine and Plasma assessment for amino acids were sent with suspecting IEM and GC-MS of urine showed grossly elevated Isovalerylglycine suggestive of Isovaleric Acidemia (**Figure - 1**) (**Table – 1**). Special diet by powder formula specific for Isovaleric Acidemia (Pristine Balance Metanutrition – provides 15 gms protein/100 gms powder) (**Figure - 2**) and Oral Glycine (250 mg/kg/day) powder with Carnitine (100-300 mg/kg/day) was started. Baby tolerated feed well and was discharged on special diet. After 1 month of special diet for IVA there was significant reduction of Isovaleric Acid level in Urine. Significant weight gain documented on follow up. At present 18 months of age her growth and development is appropriate for age. She is following up with Bayley Scales of Infant Development III for growth and development assessment.

Long term treatment

- Low- protein high calorie diet. Small calculated amount of EBM may be given with watch on urine ketones and blood anion gap.
- Special formula for IVA (without Leucine) in the dose of 1.5 g protein/kg/ day
- Glycine powder (250 mg/kg/day) to continue for life long.
- Monitor HCO_3 (should be at least > 20 mmol/L)

Figure - 1: GC-MS of urine shows grossly elevated Isovalerylglycine s/o Isovaleric Acidemia.

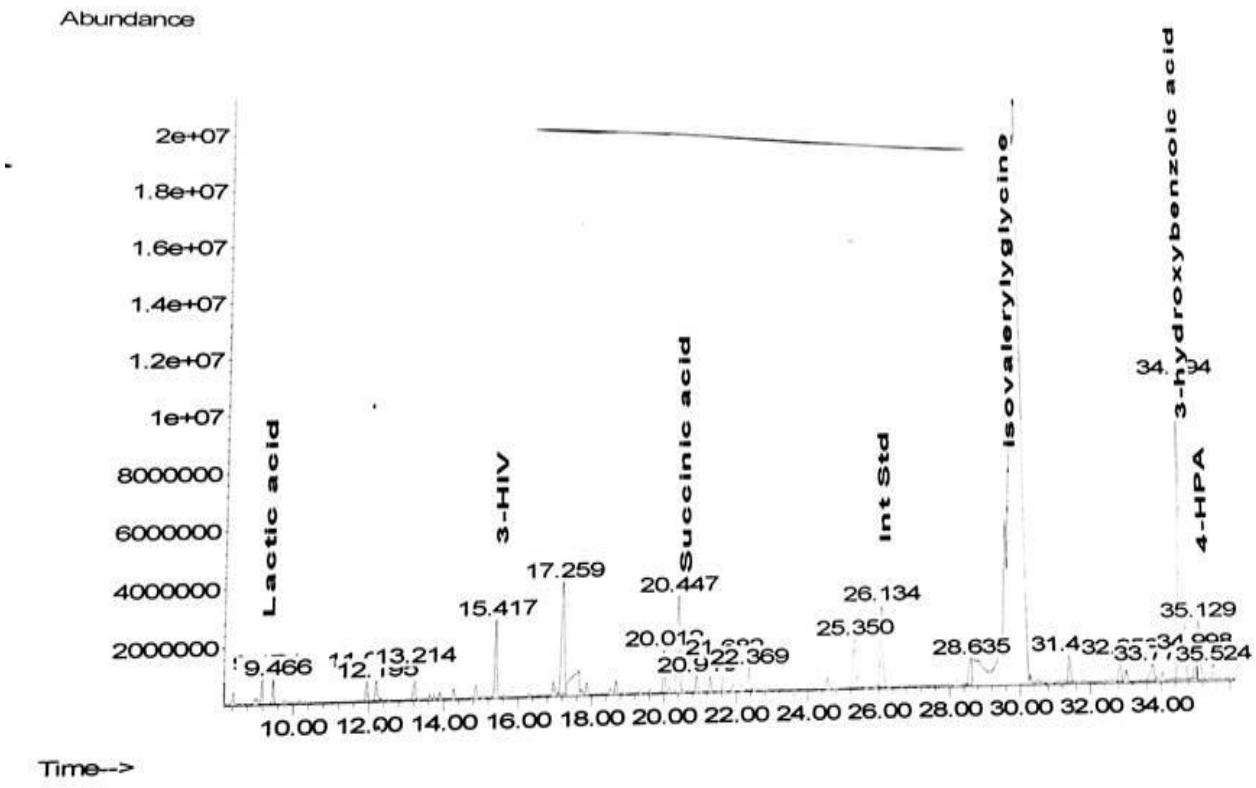

Table - 1: Significantly elevated C5 and C5/C2, suggestive of Isovaleric acidemia.

	Acyl Carnitines	Values	**Cut-offs**	Ratios	Values	**Cut-Offs**
1	C 2	6.91	**25.0**	C3/C0		**0.20**
2	C 3	0.16	**6.00***	C3/C2		**0.20**
3	C 3DC	0.23	**0.30***	C3/C16		**3.50**
4	C 4	0.10	**1.30***	C4/C2		**0.10**
5	C 4-OH	0.30	**0.65***	C4/C3		**0.70**
6	C 4DC	0.05	**0.63**			
7	**C 5**	**47.37**	**0.70***	**C5/C2**	**6.85**	**0.05**
8	C 5-OH	0.04	**0.90***	C5-OH/C2		**0.04**
9	C 5:1	0.01	**0.25***	C5:1/C2		**0.20**
10	C 5 DC	0.02	**0.35***	C5DC/C2		**0.02**
11	C 6	0.04	**0.45***	C5DC / C12		
12	C6 OH	0.02	**0.35**			
13	C 8	0.02	**0.45***	C8/C2		**0.03**
14	C 10	0.04	**0.45***	C10:1/C2		
15	C 10: 1	0.05	**0.30***			
16	C 10: 2	0.04	**0.15***			
17	C 12	0.08	**0.50**			
18	C 14	0.03	**0.80***	C14/C2		**0.03**
19	C 14: 1	0.01	**0.60***	C14:1/C16		**0.30**
20	C14 : 2	0.01	**0.15**			
21	C 16	1.58	**7.50***			
22	C 16-OH	0.01	**0.15***	C16-OH/C2		**0.01**
23	C 18	0.48	**2.50***	C18 :1/C2		**0.15**
24	C 18-OH	0.01	**0.10***			
25	C 18: 1	0.55	**3.50***	C18-OH/C2		**0.10**
26	C 18: 1-OH	0.01	**0.16**	C18:1OH/C2		**0.01**

Figure - 2: Special diet for Isovaleric Acidemia.

Discussion

Isovaleric Acidemia (IVA) is an autosomal recessive inborn error of leucine metabolism and can cause significant mortality and morbidity [3]. It was the first organic acidemia recognized in humans. Incidence is approximately 1:67,000 in India. A 2011 review of 176 cases found that diagnosis made early in life (within a few days of birth) were associated with more severe disease and a mortality of 33%. Children diagnosed later, and who had milder symptoms, showed a lower mortality rate of ~3% [4]. Patient with IVA shows typical sweaty feet odor, unlike other organic acidemias, the urine has no odor since the unconjugated isovaleric acid responsible for the odor is not excreted in urine in appreciable quantity [5, 6]. Initially, two phenotypes with either an acute neonatal or a chronic intermittent presentation were described. More recently, a third group of individuals with mild biochemical abnormalities who can be asymptomatic have been identified through newborn screening of

blood spots by tandem mass spectrometry. Secondary hyperammonemia is presumed to be due to inhibition of N-acetylglutamate synthetase by isovaleryl-CoA and/or intracellular depletion of acetyl-CoA leading to reduced N-acetylglutamate synthesis and impairment of the urea cycl [7]. Pancytopenia as well as isolated neutropenia and thrombocytopenia can occur due to bone marrow suppression [8]. If patient is not treated on time then patient may progress to coma and death due to cerebral edema or cerebral hemorrhage [9]. In our case patient was diagnosed very early and appropriate treatment was started on time so neurologically as well as physically patient is doing well till date. Regarding routine follow up visits, there is no established laboratory marker for monitoring therapeutic control or disease state. Weight gain, growth and development should be age-appropriate and thus, body measurements are key parameters to follow on a routine basis. Specifically, protein malnutrition must be avoided if the patient is protein restricted.

Conclusion

Isovaleric Acidemia is a rare autosomal recessive disorder. Early diagnosis of Inborn error of metabolism (I.E.M) by newborn screening and urine GC-MS with Specific protein restricted diet can rescue the infant with I.E.M. Infant presenting with lethargy, poor feeding and seizure is not always sepsis, meningitis etc. but it can be I.E.M. Hyperammonia can be treated with early Peritoneal dialysis. Prospective long term follow-up of newborns identified with IVA and clinical trials of carnitine and glycine therapy will be critical to optimization of outcome in these patients.

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