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Case Report and Follow up of a Neonate with Isovaleric Acidemia at a Tertiary Care Centre

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Abstract
We report a case of neonate who was clinically normal at birth and was on direct breast feeds. Evaluation was done in view of abnormal odour of urine and previous 2 sibling deaths. Baby developed symptoms in the form of vomiting and lethargy on day 7 of life. Baby had associated late onset sepsis & was treated with antibiotics. Initial baseline workup for IEM showed hyperammonia & ketoacidosis. Tandem Mass Spectrometry was suggestive of Isovaleric academia & was started on specialized formula feeds (Leucine free diet). Baby was also continued on quantified amounts of breast feeds. Baby tolerated feeds well & was discharged with leucine free diet & carnitine supplementation which promotes normal development of infant. Baby was also continued with quantified amount of mother's milk (30 ml/kg/day). Serial monitoring of growth parameters was done which was appropriate for age and serum aminoacid levels were monitored which was normal.

Keywords: *inborn error of metabolism, isovaleric acidemia , sweaty feet odour , leucine free diet.*

Introduction

The burden of non-communicable diseases including Inborn errors of metabolism (IEM) are increasing as communicable diseases are coming down. As increase in diagnostic modality and health care facilities, more metabolic conditions are being recognized in symptomatic cases and advances in the diagnosis & treatment of IEM have improved the prognosis for many of these conditions. The exact incidence of IEM's in India is not known. The prevalence of IEM in India is 1 in 2497 newborns & in Andhra Pradesh 1 in 1000 newborns.[1]

Isovaleric acidemia/aciduria (IVA) is an autosomal recessive disorder, one of the major organic acidurias due to a genetic deficiency of isovaleryl-CoA dehydrogenase (IVD) enzyme which catalyses the third step in leucine

catabolism. IVA is clinically diagnosed with features of vomiting, lethargy and an unusual urinary sweaty feet odour, biochemically it is characterized by accumulation of isovaleryl-CoA derivatives like isovaleryl carnitine and isovaleryl glycine that are associated with hyperammonemia and metabolic acidosis. IVA can be diagnosed with newborn screening tests by tandem mass spectrometry and urine gas chromatography mass spectrometry.

Figure: 1

Case Presentation

A 2660 grams full term male baby born to a **3 degree consanguineous** parents was delivered to multigravida mother by LSCS in view of precious pregnancy at 38 weeks + 4 days with history of **previous 2 siblings** deaths with uneventful antenatal history. Baby had normal APGAR scores at birth. Baby was initially on Direct breast feeds, metabolic screening was done on day 2 of life in view of previous sibling deaths and baby urine smells **sweaty feet odour**, routine investigations was done which was normal. Thyroid profile normal. Child was lethargic & had vomitings on day 7th of life and septic screen was done suspecting late onset of sepsis which was positive, antibiotics given for 7 days and stopped once blood culture showed no growth and blood gas reveals **metabolic acidosis**. Initial IEM work up done which revealed hyperammonemia & ketoacidosis. Tandem mass spectrometry and urine Gas Chromatography Mass Spectrometry revealed **ISOVALERIC ACIDEMIA** with **increased levels of ISOVARERYLCARNITINE (fig: 3) and ISOVARERYLGLYCINE (fig: 4) respectively**. Baby was given biotin, arginine and sodium benzoate supplimentents for hyperammonemia till it normalized. Specialized formula (Leucine free diet, figure: 2) specific for IVA with carnitine (100mg/kg/day) was started & baby tolerated feeds well & was discharged with leucine free diet by special formula & carnitine supplementation which promotes normal development of infant. Baby was also started on **quantified amount (30ml/kg/day) of mother's milk & serial monitoring of serum aminoacid levels were monitored & was normal on follow up**. At present baby was 3 months 7 days old on specialized formula (Leucine free diet) & on quantified amount of mother's milk. Attained partial head control & social smile, cooing present, weight gain present i.e, growth and development is appropriate for age as per Denver Development Screening test (DDST) scale.

Figure: 2

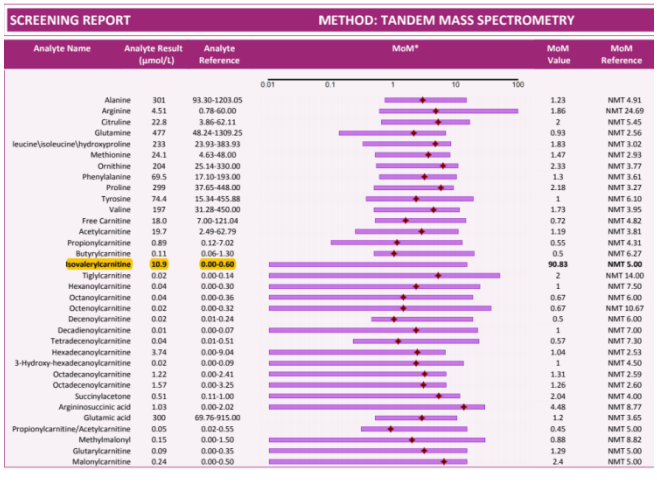

Figure: 3

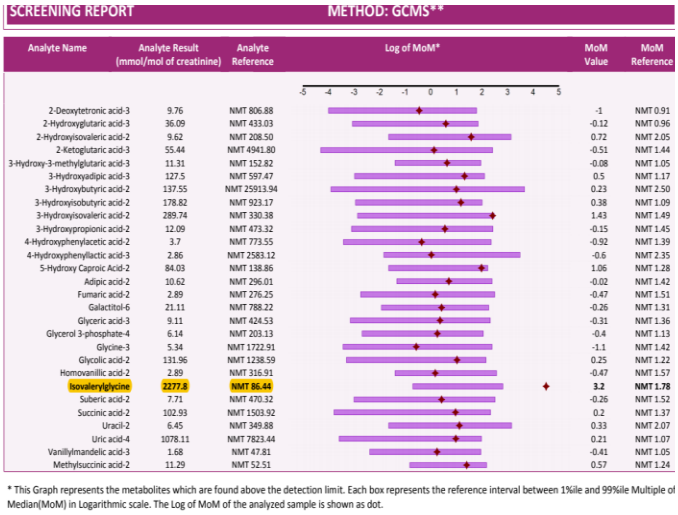

Figure: 4

Discussion

Isovaleric academia has an incidence of 1 in 67,000 in India.[2] .Deficiency of IVD results in an accumulation of derivatives of isovaleryl-coenzyme A, such as isovaleric acid, 3-hydroxyisovaleric acid, 4-hydroxyisovaleric isovaleryl carnitine and isovaleryl glycine which is toxic to the central nervous system[3]. The pathogenesis of IVA is still not fully well established.[4]Two clinical phenotypes have been observed in unscreened patients. they may become symptomatic within the first days or weeks of life, presenting with poor feeding or vomiting and severe metabolic acidosis accompanied by neurological signs including lethargy, potentially progressing to coma or death[5].

Alternatively, patients may present later in childhood with acute acidotic episodes often triggered by catabolic stress such as intercurrent illness[6].Besides, a third distinct phenotype of IVA has been identified by newborn screening[7]. If diagnosed antenatally (undetectable or minimum levels of Isovaleryl dehydrogenase in amniotic cells or increased levels of isovaleryl glycine in amniotic fluid) can be confirmed at the earliest in the neonate & treatment can be started early for better neurological outcome.

IVA was first reported by Tanaka., et al.,[8] who described the sibling with recurrent episodes of vomiting and lethargy and an unusual odor of "sweaty feet", in whom a high urinary excretion of isovaleryl glycine and other metabolites of isovaleryl-CoA were detected using gas chromatography (GC) and mass spectrometry (MS).

Leucine is an essential amino acid; it plays an important role in the regulation of metabolism, promotes global protein synthesis by signalling an increase in translation[9] Leucine promotes insulin release and inhibits autophagic protein degradation. Over restriction will lead to anorexia, triglyceride lipolysis, weight loss, and amino acid imbalance[10]. The IVA E-IMD guidelines[11] recommend that natural protein intake should be restricted to reduce the isovaleric acid burden but ought to supply at least the safe levels of protein intake advocated by WHO/FAO/UNU 2007 [12]. There is limited published IVA patient outcome data that describes dietary management in depth. The prescription of median natural protein intake was below safe levels of protein intake when centres were giving LFAA (leucine free amino acid). Overall, there may be 'over restriction' of natural protein and unnecessary use of LFAA creating a diet that is burdensome and expensive[13].

Generally, long term treatment with carnitine, glycine and a low protein diet (with or without LFAA) & high protein / high luicine containing foods like meat, poultry, egg, pulses, nuts should be kept to the minimum as advised by the dietician appears to lead to relative metabolic stability, particularly after the early childhood years.

Conclusion

Isovaleric acidemia has a good prognosis if the condition has been diagnosed and treatment initiated with specialized formula as early as possible. Growth and development on follow up will be better with earlier initiation of treatment. Quantified amount (30ml/kg/day) of mother's milk should be started in neonates with isovaleric academia to meet median total protein intake. Serial monitoring of serum amino acid levels is essential on follow up. Long term follow up is

needed for the infant for neurological, nutritional, growth and development assessment.

What is already known
Isovaleric academia is a rare IEM presenting in newborn period & early diagnosis & treatment with specialized formula has good outcome.
Whats New
Quantified amounts of breast feeding of infants with isovaleric acidemia is feasible with close monitoring of growth, development & serial monitoring of aminoacids, organic acids & ammonia to maintain median total protein intake as advised by WHO/FAO/UNU 2007 and to decrease burden and expense on specialized formula (Leucine free diet).

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