Outcome and clinical spectrum in patients with Isovaleric acidemiaFrom India and Pakistan.

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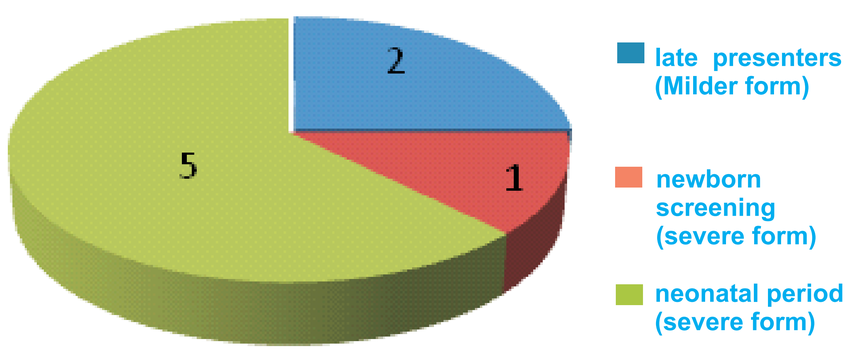
Introduction : Isovaleric acidemia (IVA) (OMIM# 243500) is known as one of the "classical" organic acidemias / acidurias. It is caused by a genetic deficiency of Isovaleryl - CoA dehydrogenase (IVD) catalyzing the third step in Leucine catabolism. The enzyme defect results in the accumulation of derivatives of Isovaleryl - CoA including free Isovaleric acid and 3 - hydroxyisovaleric acid[1]. The incidence of IVA is 1 in 67,000 live births[2].

Objective : To investigate the outcome and clinical spectrum of IVA Patients in India and Pakistan.

Materials & Methods : We performed retrospective analysis of 8 IVA patients from the year Jan 2006 - June 2014. Metabolites of isovaleryl CoA were screened using GC - MS of Urine and TMS of blood. Plasma amino acids levels were monitored using UHPLC (Agilent Technologies 1260 Infinity). Other parameters like total serum protein, serum alkaline phosphatase activity and serum creatinine levels were monitored.

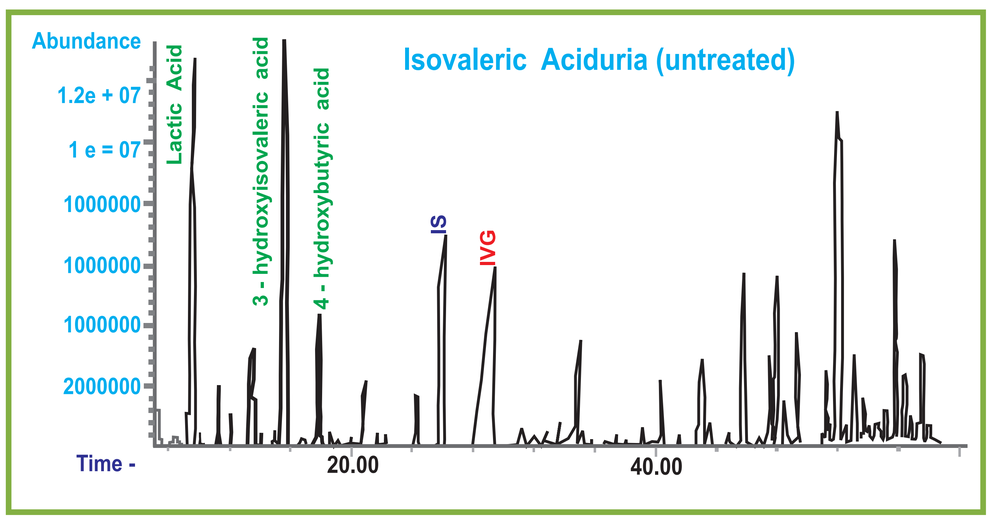
According to mean age of presentation we categorised these 8 patients into **1.** Early Presenters (neonatal period - before 2 months) **2.** Late Presenters (after 2 months) **3.** Patients identified through newborn screening.

Number of children and their age of presenatation



Result : We studied 8 patients with IVA from India (n=7) and Pakistan (n=1). Of these (n=5) presented within neonatal period, (n=2) presented late and (n=1) was detected by new born screening. The most common symptoms observed in our cohort were lethargy, vomiting, convulsions, poor weight and dysmorphic features.

Forms	Number of patients	Freeee carnitine (µmol/L)	Isovalerylcarnitine (µmol/L)
Early Presenters	5	11.67+ 6 .4	6.40 + 2.92
Late presenters	2	27.63 + 3.33	8.25 + 5.42



Discussion : IVA is an autosomal recessive disorder of Leucine catabolism and can cause significant morbidity and mortality[3]. In this study we have performed retrospective analysis for 8 patients with IVA. Of the total 5 patients that presented in neonatal period, 3 patients expired and 2 patients were lost for follow up.

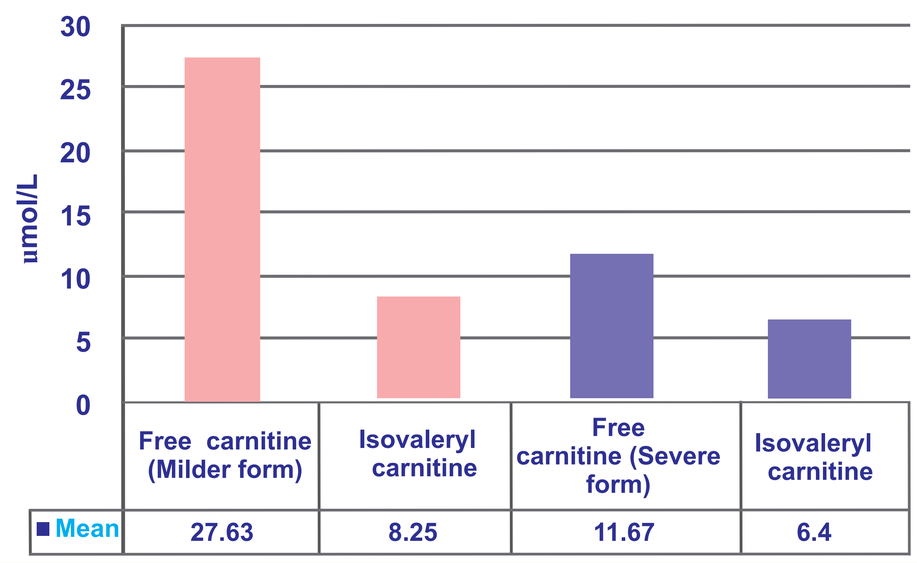
- Two pateints, who survived, were late presenters having mild form. They initially had Hyperammonia and elevated ketones. Now they have reduced ammonia levels and ketones. They are on protein restricted diet along with carnitine and glycine supplementation. Other neurological symptoms have reduced but they have poor scholastic performance.
- The patient that was diagnosed through NBS is doing well. She is asymptomatic. She receives special diet, carnitine and glycine.
- Patients presented within neonatal period expired as they were having severe form of the disease.

Retrospective analysis of this data shows that patients with milder form survive and with the help of proper treatment and diet they can be managed well.

Newborn screening using TMS is reliable method for screening of IVA which can be easily confirmed using GC-MS of urine. Patient diagnosed through NBS has a better outcome.

However from the observed data it can be seen that severe form (neonatal presenters) of this disease is fatal.

Levels of Free carnitine and isovaleryl carnitine in milder and severe form



Conclusion : From the total number of patients observed, the mortality rate was 37.5% whereas the survival rate was 62.5%. However in India and Pakistan NBS is still not available which leads to high morbidity and mortality. Special diets are not easily available in India and are also very difficult to procure and expensive for an average Indian.

References:

1. Grünert SC, Wendel U, Lindner M, Leichsenring M, K Otfried Schwab KO, Vockley J, Lehnert W, and Ensenauer R. Clinicaland neurocognitive outcome in symptomatic Isovaleric Acidemia. Orphanet J Rare Dis, 2012 : 7 : 9.

2. Ensenauer R, Fingerhut R, Maier EM, Polantez R, Olgemoller B, Roschinger W, Muntau A. Newborn screening for Isovaleric acidemia using tandem mass spectrometry : Data from 1.6 million newborns. Clinical chemistry, 2011 : 57 (4) ; 623 - 626.

3. Vockley J, Ensenauer R. Isovaleric acidemia : new aspects of genetic and phenotypic heterogeneity. Am J Med Genet, 2006 : 142C(2); 95 - 103.

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