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Case Report

Obstetrics and Gynaecology Section

Isovaleric Acidemia as a Rare Cause for Bad Obstetric History

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ABSTRACT

Isovaleric acidemia is an inborn error of metabolism, inherited as an autosomal recessive disorder, caused by deficiency of isovaleryl-Coenzyme A (CoA) dehydrogenase, leading to elevated plasma isovaleric acid and urine isovalerylglycine levels. Isovaleric acidemia is an unusual disorder with an incidence of 1:67,000 in India. Parents of the child are assumed to be carriers and the offsprings have a one in four (25%) chance of inheriting the disorder. The present article reports a 33-year-old, Gravida 3 Para 2 Live 0 (G3P2L0) at 38 week + 1 day, with previous two Lower Segment Caesarean Surgery (LSCS) and two neonatal deaths, who delivered a term boy baby with incidental finding of isovaleric acidemia at birth. Isovaleric acidemia could sometimes be a rare case for bad obstetric history and should be considered while evaluating a patient. Also, it is now possible to diagnose the condition by early prenatal tests and even before pregnancy by Preimplantation Genetic Diagnosis (PIGD) and by taking necessary steps.

Keywords: Inborn error of metabolism, Neonatal death, Pregnancy loss

CASE REPORT

A 33-year-old, G3P2L0, previous two LSCS and two neonatal deaths, visited the Obstetric and Gynaecology Outpatient Department for antenatal check-ups from 33 weeks onwards. She had regular cycles, married for seven years with history of 3rd degree consanguinity. Her first pregnancy was terminated at 34 weeks of gestation. Later, she delivered a live, preterm girl by emergency LSCS in view of Preterm Premature Rupture of Membranes (PPROM). The baby died after one week of birth. She delivered next child, an alive, term girl, by elective repeat LSCS after an interpregnancy period of five years. The child died within two weeks of life. However, the cause of death was unknown. But both newborns had symptoms of vomiting and features suggestive of failure to thrive.

All routine antenatal investigations were done and found to be normal but the blood sugar was found to be elevated (184 mg/dL). Patient was diagnosed with gestational diabetes mellitus and was started on diet plan and oral hypoglycaemic drugs (tablet metformin 500 mg BD). Steroid prophylaxis (Two doses of injection betamethasone 12 mg given Intramuscular i.m.) was given and patient was taken up for elective repeat LSCS at 38 weeks. A healthy boy baby was extracted by vertex, weighing 2.66 kg.

In view of previous two neonatal deaths with no known cause, the child was kept in Newborn Intensive Care Unit (NICU), for observation. On day 2 of life, Tandem Mass Spectrometry (TMS) and Urine Gas Chromatography Mass Spectrometry (GCMS) were advised. While awaiting results, serum ammonia, Liver Function Test (LFT), Renal Function Test (RFT), serum electrolytes were analysed which showed increasing trends in ammonia levels from 207 to 245 µg/L the next day. The child was found to be lethargic. He developed subtle seizures and sweaty feet odour. He was kept nil per oral and started on i.v. fluids. Meanwhile, TMS and Urine GCMS showed isovaleric acidemia [Table/Fig-1,2].

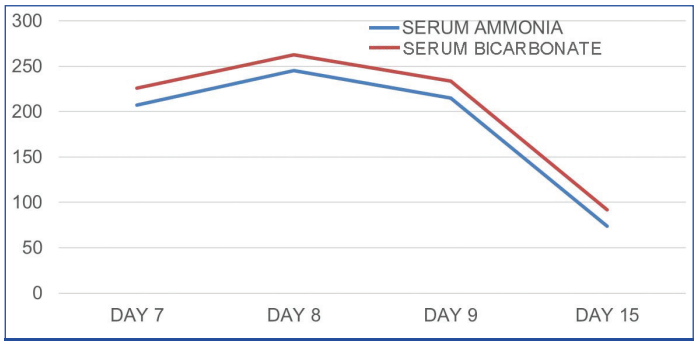
Screening test	Tandem mass spectrometry	
Analyte name	**Reference value (µmol/L)**	**Result**
Alanine	93.30-1203.05	301
Arginine	0.78-60.00	4.51
Citruline	3.86-62.11	22.8
Glutamine	48.24-1309.25	477
Leucine/Isoleucine/Hydroxyproline	23.93-383.93	233
Methionine	4.63-48.00	24.1
Ornithine	25.14-330.00	204
Phenylalanine	17.10-193.00	69.5
Proline	37.65-448.00	299
Tyrosine	15.34-455.88	74.4
Valine	31.28-450.00	197
Free carnitine	7.00-121.04	18.0
Acetylcarnitine	2.49-62.79	19.7
Propionylcarnitine	0.12-7.02	0.89
Butyrylcarnitine	0.06-1.30	0.11
Isovalerylcarnitine	0.00-0.60	10.9
Tiglylcarnitine	0.00-0.14	0.02
Hexanoylcarnitine	0.00-0.30	0.04
Octanoylcarnitine	0.00-0.36	0.04
Octenoylcarnitine	0.00-0.32	0.02
Decanoylcarnitine	0.01-0.24	0.02
Decadienoylcarnitine	0.00-0.07	0.01
Tetradeconoylcarnitine	0.01-0.51	0.04
Hexadecanoylcarnitine	0.00-9.04	3.74
3-Hydroxy hexadecanoylcarnitine	0.00-0.09	0.02
Octadeconoylcarnitine	0.00-2.41	1.22
Succinylacetone	0.11-1.00	0.51
Arginosuccinic acid	0.00-2.02	1.03
Glutamic acid	69.76-915.00	300
Acetylcarnitine	0.02-0.55	0.05
Methylmalonyl	0.00-1.50	0.15
Glutarylcarnitine	0.00-0.35	0.09
Malonylcarnitine	0.00-0.50	0.24
Malonylcarnitine	0.00-0.50	0.24

[Table/Fig-1]: Table showing the Tandem Mass Spectrometry (TMS) report of the child at day 4 of life.

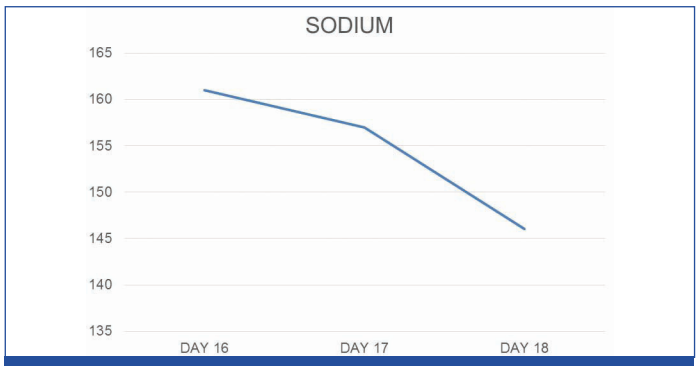
Screening test	GCMS	
Analyte name	Reference value (µmol/L of creatinine)	Result
2-Deoxytetronic acid-3	NMT806.88	9.76
2-Hydroxyglutaric acid-3	NMT433.03	36.09
2-Hydroxyisovaleric acid-2	NMT208.50	9.62
2-Ketoglutaric acid-3	NMT4941.80	55.44
3-Hydroxy-3-methylglutaric acid-3	NMT152.82	11.31
3-Hydroxyadipic acid-3	NMT597.47	127.5
3-Hydroxybutyric acid-2	NMT25913.94	137.55
3-Hydroxyisobutyric acid-2	NMT923.17	178.82
3-Hydroxyisovaleric acid-2	NMT330.38	289.74
3-Hydroxypropionic acid-2	NMT473.32	12.09
4-Hydroxyphenylacetic acid-2	NMT773.55	3.7
4-Hydroxyphenyllactic acid-2	NMT2583.12	2.86
5-Hydroxy caproic acid-2	NMT138.86	84.03
Adipic acid-2	NMT296.01	10.62
Fumaric acid-2	NMT276.25	2.89
Galactitol-6	NMT788.22	21.11
Glyceric acid	NMT424.53	9.11
Glycerol-3-phosphate-4	NMT203.13	6.14
Glycine-3	NMT1722.91	5.34
Glycolic acid-2	NMT1238.59	131.96
Homovanillic acid-2	NMT316.91	2.89
Isovalerylglycine	NMT86.44	2277.8
Suberic acid-2	NMT470.32	7.71
Succinic acid-2	NMT1503.92	102.93
Uracil-2	NMT349.88	6.45
Uric acid-4	NMT7823.44	1078.11
Vanillylmandelic acid-3	NMT47.81	1.68
Methylsuccinic acid-2	NMT52.51	11.29

[Table/Fig-2]: Table showing the urine GCMS report of the child at day 4 of life. NMT: Not more than

The child was started on carnitine, sodium benzoate, calcium biotin and L-arginine supplements. He improved and slowly started on leucine-free formula feeds [Table/Fig-3,4]. On day 15 of life, the child became lethargic with sunken eyes and failed to gain weight (2.45 kg). Sepsis screen showed C-reactive Protein (CRP) positive and hypernatremia. Newborn was started with i.v. fluids and antibiotics (Inj. Piptaz). The general condition of the child had improved. He was active and alert, with good tone and neonatal reflexes. No further episodes of seizures were noted. Ultrasonography (USG) cranium was normal. Fundus examination was normal. A 2 Dimensional Echocardiogra (2D ECHO) showed a small ostium secundum atrial septal defect. On day 20 of life, he was partly on leucine-free formula feeds and direct breast feeds.



[Table/Fig-3]: Shows the trends in serum ammonia and bicarbonate levels of the newborn.



[Table/Fig-4]: Shows the trends in serum sodium levels of the newborn.

The baby tolerated the feeds well and was discharged on day 24 of life. The parents were explained about the danger signs such as fast breathing, lethargy, poor feeding, change in temperature, in the event of which, they were advised to bring the child to the hospital immediately. The child is on regular follow-up and is one year and three months of age at present, healthy and is on leucine-free regular feeds and special formula feeds.

DISCUSSION

Women with history of two or more consecutive pregnancy loss are categorised high-risk and require detailed evaluation. The incidence of bad obstetric history among the general population is about 1-2% [1]. Bad Obstetric History (BOH) includes previous two or more consecutive spontaneous abortions, history of intrauterine foetal death, severe intrauterine growth retardation, stillbirth, early neonatal death, and congenital anomalies. The causes of BOH may be multifactorial including genetic, hormonal, abnormal maternal immune response, structural anomalies and maternal infection [2]. On evaluation, the contributing factor can be identified in about 40 to 50% of the cases [1].

There are more than 500 inherited point defects in metabolism identified at present [3]. The incidence of these diseases individually are rare, they collectively account for a significant proportion of neonatal morbidity and mortality. Diagnosis is important not only for treatment but also for genetic counselling and antenatal diagnosis in subsequent pregnancies. Isovaleric acidemia is an inborn error of leucine metabolism, caused by deficiency of isovaleryl-CoA dehydrogenase. It is an organic acidemia which can have a number of metabolic as well as neurological manifestations. The child may have normal development with minimal retardation [4]. Two forms of isovaleric acidemia have been identified- acute and chronic. The acute form ranges from metabolic acidosis to seizures and death in the early neonatal period, while the latter is a more severe form but with asymptomatic intervening periods [5].

Budd M et al., way back in 1967, observed an aberrant odour resembling sweaty feet with revulsion to protein leading to acidosis and coma. The peculiar smell was found to be due to isovaleric acid, an intermediary of leucine [6]. Sidbury J et al., observed that children of a second degree consanguinity died within one week of life due to convulsions, dehydration, and an unusual urinary odour like that of sweaty feet. Postmortem examination showed: hypoplastic marrow, scattered haemorrhages of viscera, and terminal septicaemia. The deviant odour was the result of butyric and hexanoic acids. They stated that it is an inborn error of short-chain fatty acid metabolism. These cases are considered to have been instances of isovaleric academia [7].

Inborn errors of metabolism should be considered in the diagnosis of any sick neonate along with common acquired causes such as sepsis, hypoxic ischaemic encephalopathy and congenital infections. The long-term mainstay treatment modality is dietary modification. Special diets without leucine are expensive and available in the west but not in India. Diet low in the particular aminoacid (leucine in this case) can be adviced in low resource setup. Every attempt has to be made to reach the diagnosis of inborn error of metabolism to

aid parents to plan future pregnancy [8]. If this child fails to thrive, further evaluation in terms of counselling, prenatal diagnosis, PIGD followed by Artificial Reproductive Technique (ART) may be done, thereby preventing further pregnancy losses or neonatal deaths [9]. Premarital screening to identify the carrier status can also be done in case of consanguinous marriage.

According to Kleijer W et al., the optimal strategy for early, rapid and reliable prenatal diagnosis of isovaleric acidemia is by the measurement of metabolites in amniotic fluid (Isovalerylglycine {IVG}) and by monitoring the leucine catabolic pathway in chorionic villi (10 to 12 weeks) or amniotic fluid cells (14 to 16 weeks) [10].

CONCLUSION(S)

Recent advances in newborn screening tests have made the timely diagnosis and treatment of isovaleric acidemia feasible. However, there is not enough evidence to ascertain the course of the condition. The probability of milder forms developing severe metabolic derangements remains unclear. In recent times, newborn screening programmes have been implemented, focusing on diagnosis of isovaleric acidemia. In conclusion, the difficulty to identify the underlying cause for Bad Obstetric History (BOH) requires rigorous diagnostic investigations, thus reducing the incidence of recurrent pregnancy losses and improving the outcome of subsequent pregnancies. Timely diagnosis and evaluation is required to initiate prophylactic therapy in such cases.

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