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Original Research Paper

Neonatology

ISO-VALERIC ACIDEMIA - A CASE REPORT

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ABSTRACT Isovaleric acidemia (IVA) is a rare form of Inborn error of metabolism (IEM), an autosomal recessive disease of leucine metabolism due to deficiency of Isovaleryl Co A Dehydrogenase (IVD). We report this case in view of its rare incidence. Our case report emphasizes the importance of routine newborn screening, including the maximum possible IEMs. Our report also emphasizes the need for easy procurement and availability of special formula to address the IEMs, as time is the essence for management of these rare disorder.

KEYWORDS : Isovaleric academia, sweaty feet, IEM, Newborn Screening

INTRODUCTION

Isovaleric acidemia is an autosomal recessively inherited inborn error of metabolism, because of deficiency of Isovaleryl-Coenzyme A (CoA) dehydrogenase causing elevated plasma Isovaleric acid and urine Isovaleryl glycine levels[1]. Apart from the major clinical scenarios such as acute and chronic intermittent form, this condition may present as a continuous spectrum from asymptomatic presentation to life threatening scenario. A peculiar 'sweaty feet' odor is usually present in patient's sweat or other secretions due to accumulation of Isovaleric acid. We report one such rare case admitted in our Neonatal intensive care unit[2].

CASE REPORT

A late preterm male neonate was born to 24 years old third gravida mother. Mother gave a history of first trimester spontaneous abortion in the first pregnancy, and a history of early neonatal death on day 5 of life in the second pregnancy, which was attributed to sepsis. There is history of third-degree consanguinity. The pregnancy was complicated by oligohydramnios. In the index case, baby was an extramural, delivered at 34 weeks by spontaneous Preterm labor. Birth weight of the child was 1.8 kg (< 10th centile), length was 45 cm (10-50th centile) and head circumference was 31 cm (10-50th centile). Baby noted to have respiratory distress for which baby was shifted to our NICU at 3rd hour of life. At admission physical examination was normal with signs of respiratory distress in form of tachypnea, sub costal & intercostal retractions being present (Silverman Anderson Score - 4).

In view of mild respiratory distress, baby was started on Humidified high flow nasal canula (HHFNC), and Chest radiograph was s/o mild respiratory distress syndrome (RDS). As distress improved, baby was gradually weaned to room air at 32 HOL. Subsequently, baby was started on oral feeds. On DOL 5, baby developed respiratory distress for which baby was evaluated with sepsis screen and Chest X-ray, and restarted on HHFNC support. Complete blood picture revealed thrombocytopenia and leucopenia. In view of new onset tachypnea with leucopenia and thrombocytopenia, a blood culture was sent and baby was started on IV Antibiotics. A cardiac evaluation showed Mid-muscular VSD with left to right shunt. Clinically, there were no signs of Congestive Cardiac Failure. In view of serial blood gases showing metabolic acidosis, and history of previous sibling demise, parents were counselled for need for a neonatal metabolic screening (NBS – Newborn Screening). The NBS test was positive for Iso-valeric Acidemia. As blood culture was sterile and baby was hemodynamically stable, antibiotics were stopped. However, baby continued to have persistent and worsening leukopenia and thrombocytopenia.

3-Hydroxyadipic acid-3	78.13	NMT 597.47
3-Hydroxybutyric acid-2	648.09	NMT 25913.94
3-Hydroxyisovaleric acid-2	**3937.46**	**NMT 330.38**
3-Hydroxypropionic acid-2	166.17	NMT 473.32
4-Hydroxyphenylacetic acid-2	152.16	NMT 773.55
4-Hydroxyphenyllactic acid-3	38.47	NMT 2583.12
4-Hydroxyproline-3	83.19	NMT 750.91

REPORT- SUMMARY

Observations:
Increased excretion of 3-Hydroxyisovaleric acid, Isovalerylglycine and Methylsuccinic acid.

Interpretation:
The observed profile can be seen in case of Isovaleric acidemia.

Figure 1

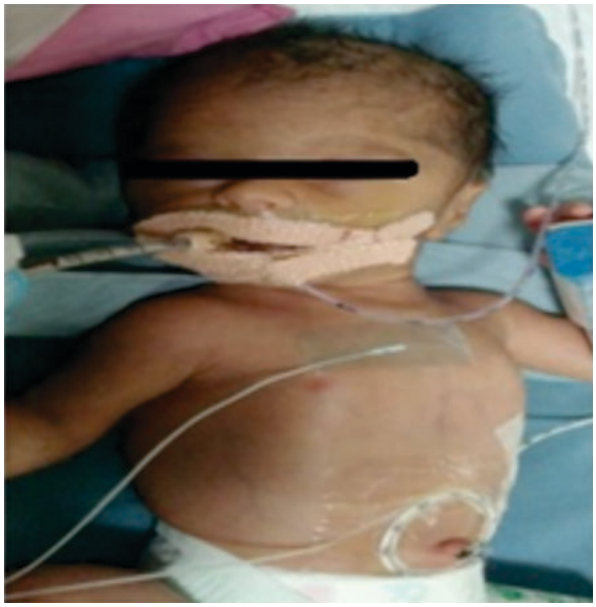

Figure 2

A geneticist was consulted, and as a part of further workup, urine for organic acids showed increased excretion of urine glycine conjugates, blood Ammonia level was 221mcg/dl and Serum Lactate was 6.2 mg/dl. Baby was continued on breast feeds, and preterm formula was with-held, in view of high protein content, till the special formula could be procured. Mutation analysis was pending for mutation in the IVD gene.

The baby was started on a special IVA free formula (which was outsourced) along with Glycine and Carnitine supplements, from Day 12 of life. Despite this, baby continued to have persistent pancytopenia and metabolic acidosis. Sepsis screen which was repeated periodically was negative. Baby characteristically had a peculiar odor emanating from the 2nd week of life, which could be described as "Sweaty feet".

On DOL -19, baby had one episode of seizure for which baby was started on an anticonvulsant (Injection Phenobarbitone), and basic metabolic workup was normal. EEG was s/o bilateral slowing. Lumbar puncture was deferred in view of persistent thrombocytopenia.

On DOL- 20, baby had an episode of prolonged apnea, for which baby was intubated and initiated on mechanical ventilation. A repeat sepsis screen sent was positive (CRP 88), hence repeat blood cultures were sent and antibiotics were restarted. In view of persistent pancytopenia baby was started on colony stimulating factor and anti-fungal. Blood culture showed growth of Pseudomonas and antibiotics were adjusted as per culture sensitivity pattern. However, general condition worsened and baby developed hypotension requiring vaso-pressor support. In v/o DIC, baby was given serial blood product transfusions, including PRBC, FFP and SDP. Despite all supportive treatment and broad spectrum antibiotics, baby continued to deteriorate and succumbed to refractory septic shock on day 27 of life

DISCUSSION

Isovaleric acidemia is an autosomal recessively inherited inborn error of metabolism, because of deficiency of Isovaleryl - Coenzyme A (CoA) dehydrogenase causing elevated plasma Isovaleric acid and urine Isovaleryl glycine levels. Isovaleric acidemia is a rare disorder with an incidence of 1:67,000 in India.

Isovaleric acidemia is a single gene disorder, caused by a mutation in the gene responsible for enzyme Isovaleryl - CoA dehydrogenase, causing deficient or absent activity of particular enzyme. This enzyme is responsible for utilization of Leucine, an amino acid, and its deficiency leads accumulation of metabolites in the blood that cause symptoms. Apart from the major clinical scenarios like acute and chronic intermittent forms, this condition may present as a continuous spectrum from asymptomatic presentation to life threatening scenario. A peculiar 'sweaty feet' odor is usually present in patient's sweat or other secretions due to accumulation of isovaleric acid. Development of aversion to protein-rich foods is noted in patients early in life.

Lethargy, poor feeding and vomiting are major acute symptoms presenting soon after birth which may progress to coma. Prolonged metabolic stress caused by this condition can cause neutropenia or pancytopenia. Hypothermia also noted in these patients. Resolution of this initial acute attack is typically followed up by chronic intermittent form of the disease.

Symptoms of chronic intermittent form are seen beyond infancy period. Failure to thrive, developmental delay, intellectual disability, seizures and spasticity are usually noted in affected patients. Early and rapid treatment of severe neonatal symptoms is usually associated with good outcome but total cure is not yet there. It is advised to start leucine free protein formula with additional L-Carnitine and Glycine supplementation to accelerate harmful metabolites excretion. Patients should remain in close follow up with a pediatrician and a geneticist who are well aware organic acidemia management. Growth and development monitoring should be done along with adequate dietary advice. Periodic monitoring for blood acid levels, blood counts, and electrolytes should be done. Treating physicians should monitor for other organ involvement like nervous system, liver, or other organs.

In our index case, the baby was started on Expressed breast milk and preterm formula from day 3, and formula feeds were with-held from day 7 only after the screening result was positive for IVA. In view of logistic issues, baby could be initiated on IVA free formula only from Day 12, as the formula had to be imported. Despite starting on the appropriate formula with Carnitine and Glycine supplementation, baby's general condition continued to worsen due to severe bacterial sepsis, possibly due to persistent pancytopenia, resistant to Colony stimulating factors. Baby's endogenous protein catabolism due to postnatal stress and sepsis could have precipitated the deterioration in health. As the demise of the previous sibling was also attributed to sepsis, it is possible that the sibling also could have had IVA deficiency.

Our case report emphasizes the importance of routine newborn screening, including the maximum possible IEMs. Most of the IEMs which present in the neonatal period can have a better outcome if appropriate dietary modifications and nutritional supplements are introduced at the earliest. It is possible that the incidence of this rare disorder is under-reported, as most centers in India do not test infants for a large panel of inherited metabolic disorders. It is important to make expanded panel of NBS universal and state sponsored, as many parents are not convinced to invest for IEM screening due to cost issues. Our report also emphasizes the need for easy procurement and availability of special formula to address the IEMs, as time is the essence for management of these rare disorders.

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