Isovaleric acidemia in a neonate presenting as sepsis and diabetic ketoacidosis: A case report

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ABSTRACT

Isovaleric acidemia (IVA), an inborn error of leucine catabolism resulting in the accumulation of derivatives of isovaleryl-CoA that leads to hyperammonemia and ketoacidosis. IVA is clinically characterized by lethargy, vomiting, and a distinctive smell of "sweaty feet." We report the case of a 10-day-old male neonate who presented with acute encephalopathy, hyperglycemia, increased anion gap metabolic acidosis, ketosis, and features of sepsis. After the management of acute metabolic decompensation, he was successfully treated with dietary restriction of leucine and L-carnitine supplementation. This case is of interest because of the rarity of presentation, early detection, and prompt implementation of the treatment with satisfactory outcomes.

Key words: *Diabetic ketoacidosis, Inborn errors of metabolism, Isovaleric acidemia, Sepsis*

Inborn errors of metabolism (IEMs) are among over 500 heterogeneous disorders resulting from an enzyme deficiency in metabolic pathways, leading to high childhood non-infectious morbidity and mortality, if undiagnosed. Overall birth prevalence of IEM has been estimated at 50.9/100,000 live births worldwide [1]. Isovaleric acidemia (IVA) is an autosomal recessive deficiency of isovaleryl-CoA dehydrogenase (IVD), a vital enzyme for leucine metabolism that results in the accumulation of toxic metabolites including N-isovaleryl glycine, isovaleric acid, 3-hydroxyisovaleric acid, methylsuccinic acid, and 4-hydroxyisovaleric acid [2].

In India, the overall estimated incidence of IVA is 1:67,000 per live births [3]. The main diagnostic dilemma is when a baby presents with features of sepsis or diabetic ketoacidosis (DKA) but actually has an inborn error of metabolism. The typical body smell without any smell in urine, which persists even after repeated cleaning, indicating toward the inborn error of metabolism. A high index of suspicion is required when assessing a baby with an atypical presentation for diagnosis from day 1 of the presentation.

CASE REPORT

A male baby, born of non-consanguineous marriage at 39 weeks of gestation to a 33-year-old primigravida by cesarean section with a birth weight of 3250 g, was on exclusive breastfeeding and presented on day 10 of life with symptoms of poor feeding, lethargy, respiratory distress, and reduced urine output. There was no significant maternal morbidity and no known previous miscarriage, intrauterine death, or other suggestive history of note.

On examination, the baby had pallor that was dehydrated and tachypneic with chest retractions and weight loss of 470 g (14.5%). There was a foul-smelling discharge from the umbilicus, hepatomegaly, and a general odor resembling that of "sweaty feet." A provisional diagnosis of sepsis was made and IV antibiotics were started with ampicillin and netilmicin.

There was initial hyperglycemia up to 400 mg/dl with ketonuria and increased anion gap metabolic acidosis that required insulin infusion for 24 h. The sepsis screen showed leukopenia up to 1800/μL and thrombocytopenia up to <10,000/μL and required platelet transfusion. Umbilical swab culture grew of *Escherichia coli and Staphylococcus haemolyticus.* The cerebrospinal fluid analysis showed raised protein with low sugar. Ammonia levels were raised up to 400 μmol/L. Liver function tests were essentially normal except raised gamma-glutamyl transpeptidase up to 720 units. Urine and blood were sent for the metabolic screen. Gas chromatography–mass spectrometry of baby's urine tested positive for isovaleryl glycerine 1 (IVG1) suggesting IVA (Fig. 1).

Leucine free formula specific for IVA (Pristine Balance Metanutrition – provides 12.5 g protein and 493 kcal/100 g powder) and L-carnitine was started. This leads to the improvement of his general condition including cytopenia. The child was readmitted with acute metabolic decompensation triggered by acute gastroenteritis which improved with treatment. Till the last follow-up at 3 months of age, he was tolerating well with this formula and asymptomatic.

DISCUSSION

Since first being described, the clinical course of IVA still remains mostly anecdotal. Three distinct phenotypes are now described;

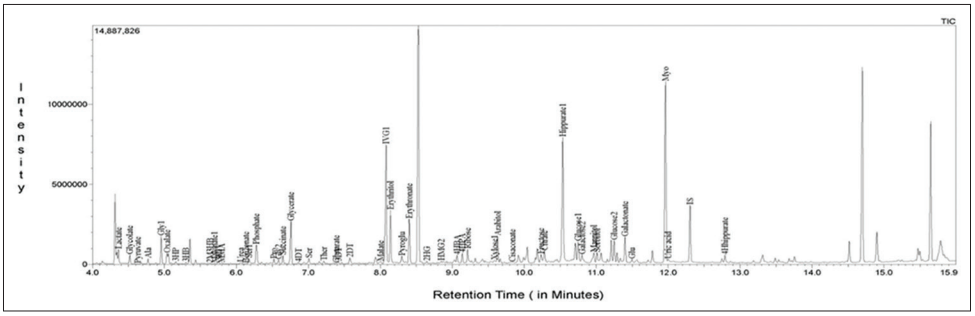

Figure 1: Total ion chromatogram of urinary metabolites by gas chromatography/mass spectrometry

acute neonatal, chronic intermittent acidotic episodes with developmental delay, and clinically asymptomatic form detected by neonatal screening only [4]. The neonatal form has required intensive therapy as it presents as fulminant metabolic acidosis and/or coma, leading to mortality of up to 33%. Early diagnosis is defined as detection within 5 weeks of age and intelligence quotient is inversely proportional to the age of diagnosis [4].

The above-mentioned case presented at day 10 of life with fulminant metabolic acidosis and encephalopathy which improved with restriction of diet. Our initial differential diagnoses were sepsis, DKA, acute kidney injury, and other inborn error of metabolism. Mustafa *et al.* reported IVA in a 2-year-old female patient presented with DKA, but the pathophysiology of hyperglycemia has not yet been identified. A general characteristic odor similar to "sweaty feet" or "rancid cheese" has been described due to the accumulation of unconjugated isovaleric acid which is not to excrete through urine, thus urine remains odorless [5].

Kellehe *et al.* reported severe pancytopenia in two infants with IVA which could be the toxic effect of organic acids on hematopoietic cells and secondary hemophagocytic syndrome [6]. In our patient, neutropenia and profound thrombocytopenia were observed. Complications such as recurrent pancreatitis, cerebellar hemorrhage, transtentorial herniation, focal gray, and white matter degeneration are rarely reported [7]. In our case, the patient was diagnosed very early and appropriate treatment was started on time so neurologically as well as physically patient is doing well till the last follow-up.

Urine levels of isovaleryl glycerine and 3-hydroxyvaleric acid are diagnostic. Confirmation by mutation analysis of the IVD gene has revealed the following mutations: c.457–3_2CA>GG, c.1199A>G (p.Y371C), c.281C>G (p.A65G), c.358G>A (p.G91R), and c.827T>C (p.L247P) [8]. Prenatal diagnosis in high-risk pregnancies involves stable isotope dilution analysis of isovaleryl glycine in amniotic fluid, and parallel *in vitro* assays using amniocytes have confirmed its high predictive value [9]. Dietary protein restriction has been found to be less effective than reducing endogenous protein breakdown [10]. Yudkoff *et al*. and Roe *et al*. reported that glycine and L-carnitine supplementation help in eliminating the toxic metabolite rapidly, which forms non-toxic isovaleryl glycine and isovaleryl carnitine, respectively [11,12].

CONCLUSION

This is a case of acute neonatal presentation of IVA, masquerading as sepsis, and diabetes ketoacidosis, former well-known triggers of a catabolic state. The present case report illustrates that organic acidemias should be kept in mind as a differential diagnosis when the patient presents with a distinct smell, late-onset sepsis, cytopenia, and features of DKA.

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