Case of isovaleric acidaemia for cataract surgery: Anaesthetic implications

INTRODUCTION

Proteins are mobilised during exercise, fasting or dehydration from body stores and dietary sources. Out of 20 amino acids (AA), 12 are synthesised in the body from glycolysis and citric acid cycle. Glycine, gamma-aminobutyric acid act as neurotransmitters; and phenylalanine, tyrosine, tryptophan as hormone precursors, coenzymes and pigments.[1]

Isovaleric acidaemia (IVA) is an autosomal recessive disorder of AA leucine metabolism wherein enzyme deficiency causes isovaleric acid accumulation and toxicity.[2]

CASE REPORT

A 4-month-old 6 kg female child was scheduled for bilateral lensectomy for congenital cataract. She was delivered by caesarean section at term but developed respiratory distress and convulsions on the 4th day of life. She needed mechanical ventilation for 1 week and received peritoneal dialysis. She had been diagnosed earlier with IVA and was on formula feeds with carnitine and glycine supplements. Gas chromatography and mass spectrometric examination of urine showed massive elevation of isovalerylglycine. A month earlier, the parents had noticed opacities in both eyes and had sought treatment.

On examination, she was playful and normothermic, heart rate was 110/min, respiratory rate 26/min and systemic examination was normal. Her blood investigations revealed normal values of haemoglobin, platelets and haematocrit. Blood urea was 101 mg/dL, serum creatinine 0.8 mg/dL, serum Na^+/K^+, 148/6.8 mEq/L and bilirubin 8.8 mg/dL. Arterial blood gas analysis (ABG) values were obtained [Table 1] which showed metabolic acidosis. Patient was started on 10% dextrose 24 ml/h, intravenously with 8 hourly monitoring of ABG and blood sugar levels. She was scheduled for surgery on the 5th day after optimisation of acidaemia [Table 1].

After pre-oxygenation with 100% oxygen and premedication with injection glycopyrrolate 5 μg/kg, ondansetron 0.08 mg/kg, midazolam 0.03 mg/kg and pentazocine 0.3 mg/kg, intravenous (IV), the baby was induced with sevoflurane 2–4% in oxygen and trachea intubated with number 3.5 uncuffed polyvinyl chloride tube. Anaesthesia and relaxation were maintained with sevoflurane, atracurium 0.5 mg/kg bolus and top up doses. Electrocardiogram, oxygen saturation, non-invasive blood pressure, skin temperature and blood sugar levels were monitored intraoperatively. Trachea was extubated after thorough oropharyngeal suction and reversal with injection neostigmine 0.05 mg/kg and glycopyrrolate 8 μg/kg. The patient was monitored closely in the post-operative period. Blood sugar, ABG and electrolytes values done after 2 h were optimal [Table 1].

Table 1: Arterial blood gas analysis

Parameter	On admission	After optimisation	Post-operative
pH	7.3	7.4	7.45
pO_2 (mmHg)	155	160	144
pCO_2 (mmHg)	24	27	27
Hct	30	31	-
HCO_3^- (mEq/L)	13.9	21.3	21.3
Saturation (%)	98.1	99.1	99.3
Serum $Na^+/K^+/Cl^-$ (mEq/L)	139.6/5.8/90.1	141/3.5/92.2	141/3.5/92.2
BE	–3.7	–2.5	–3.7
Serum lactate	4.2	1.5	-
Serum ammonia	256	100	-
Anion gap	35.6	27.5	27.5
Blood sugar (mg/dL)	66	144	118

BE –Base excess; Hct – Haematocrit

DISCUSSION

Leucine undergoes oxidative decarboxylation and produces beta hydroxyisovaleric acid; its oxidation in the presence of enzyme isovaleryl CoA dehydrogenase forms beta methylcrotonyl CoA, CO_2 and water. Deficient production of enzyme results in accumulation of beta hydroxyisovaleric acid.[3]

Liver metabolism gets affected due to excess acid load. End products of carbohydrate, fat and protein metabolism, namely, pyruvate and lactate, ketoacids and acetoacetates continue to produce H^+, HCO_3^-, CO_2 and ammonia. During acidaemia, ammonia, CO_2 and water are in excess in peritubular capillaries and tubular cells of the kidney. Ammonia enters passively into the tubular fluid, reacts with H^+ to form ammonium. Unlike ammonia, ammonium cannot penetrate luminal membrane and is therefore

trapped within the tubules and excreted. Excretion of ammonium in urine eliminates H^+.[4]

IVA is known to be associated with accumulation of abnormal organic acids. Thrombocytopaenia and coagulopathy are associated with liver disease. Kidneys excrete excess urea and ammonium during acidosis. Peritoneal dialysis is needed to eliminate these factors and prevent the occurrence of cerebral oedema. In addition, anticoagulation therapy for dialysis poses risk for intracranial haemorrhage.[5]

Our patient had been diagnosed with IVA. Clinical manifestations of IVA include mental retardation, protein intolerance, metabolic ketoacidosis, ammonia intoxication and 'sweaty feet odour'. Symptoms are triggered by any minor illness; protein diet results in increased levels of isovaleric acid.

The 'acute form' is potentially life-threatening manifesting with acute neonatal coma. Recurrent episodes of vomiting, lethargy and developmental delay are consistent with 'chronic form'. Affected patients are at risk of episodes of acute acidosis and metabolic decompensation due to any stress including fasting for surgery. An asymptomatic third group with mild metabolic abnormalities has been identified through newborn screening of blood spots by tandem mass spectrometry.[6]

The acute form is associated with hyperammonemia, ketoacidosis and cardiomegaly leading to death. Early diagnosis and early initiation of therapy promote normal growth and less psychomotor anomalies.

Treatment[7] consists of prevention of metabolic acidosis by careful clinical observation during fasting or minor illness. Increased caloric intake with oral solutions containing simple sugars, leucine-free formula feeds, early hospitalisation for IV glucose administration and judicious use of parenteral amino acids (0.5 g/kg/day). Dietary proteins are restricted with a close watch to prevent muscle wasting and promote normal growth.

Glycine therapy helps excretion of IVA in the form of isovalerylglycine in urine. A dose of 150–250 mg/kg/day is reported to reduce the length and severity of symptoms during acute stress either parenterally or orally depending on severity of the symptoms.

Millington *et al.*[8] differentiated the dietary and endogenous sources of abnormal metabolism and the accurate contribution to toxicity in the disease. Turnover of endogenous proteins rather than diet was confirmed to produce toxic metabolites in IVA. Therefore, suppression of endogenous catabolism rather than dietary restriction was conclusively stated to be the more effective therapy.

Patients with IVA have feeding difficulties and vomiting leading to dehydration and acidosis with risk for aspiration. Prolonged fasting and surgical stress cause further decompensation. Such infants are always suspected to be hypothermic, hypo or hyperglycaemic and hypocalcaemic. Prolongation of drug actions and delayed recovery from anaesthesia is anticipated. Overall bone marrow depression and thrombocytopaenia make such patients likely for severe blood loss in cases of major surgical procedures. High likelihood of ventricular arrhythmias[9] demands judicious use of anaesthetic agents. Manoeuvres such as laryngoscopy, endotracheal tube placement and throat packing leading to usual minor abrasions can increase the protein load dangerously. We managed these anaesthetic challenges with meticulous pre-operative optimisation and cautiously planned anaesthetic. Patient was stabilised with IV supplementation of 10% dextrose and subjected to anaesthesia. Inhalation with sevoflurane prevented stress of crying. Atracurium used for neuromuscular blockade utilises pathways other than liver and kidneys for excretion. Post-operative analgesia was given with paracetamol suppository.

National Institute of Paediatrics states the importance of consanguinity and newborn screening. Dehydration, acidosis and abnormal urine odour signify metabolic disorders.[10]

CONCLUSION

Inborn errors of metabolism such as IVA can be managed with early diagnosis, specific treatment and early therapeutic intervention with appropriate measures.

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Conflicts of interest
There are no conflicts of interest.

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