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CASE REPORT

Transient Insulin Resistance in Propionic Acidaemia

Knowing is half the battle

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ABSTRACT: Propionic acidaemia (PPA) is a disorder of amino acid and odd-chain fatty acid metabolism. Hypoglycaemia is a more commonly described finding rather than hyperglycaemia during metabolic decompensation of PPA. There is a high mortality rate in patients with organic acidaemias having severe insulin-resistant hyperglycaemia. We report a nine-month-old boy with PPA who was admitted to tertiary care hospital in Muscat, Oman, in 2018 with metabolic decompensation, persistent hyperglycaemia and transient insulin resistance. Hyperglycaemia did not respond to high insulin infusion. Plasma glucose only improved when glucose infusion rate (GIR) reached 7 mg/kg/min. The patient has full recovery and was discharged, with follow up plan. It is important to balance the GIR to achieve the targeted insulin level, beyond which the risks of hyperglycaemia start to outweigh the potential anabolic benefits of additional insulin secretion. Timely clinical attention should be given to achieve adequate caloric delivery through alternative sources other than high GIR to permit better glycaemic control, especially when insulin-resistant hyperglycaemia is present.

Keywords: Propionic Acidaemia; Insulin Resistance; Infant; Case Report; Oman.

Propionic acidaemia (PPA) is caused by genetic mutations which affect amino acid and odd-chain fatty acid metabolism due to the deficiency of propionyl-CoA carboxylase resulting in the defective conversion of propionyl-CoA to methylmalonyl-CoA. The disorder is inherited in an autosomal recessive manner and its incidence varies across the world. While the estimated incidence in the USA is approximately 1 in 105,000 to 1 in 130,000 it is as high as 1 in 20,000 in some Middle Eastern countries.[1–4] Most patients with classic PPA present, in the first few days of life, with progressive encephalopathy. Even patients who are stabilised with protein restriction, carnitine supplementation and decontamination of gut bacterial flora are at risk of recurrent metabolic crisis.[5] These are usually characterised by a variable combination of metabolic acidosis, elevated anion gap, hyperammonemia and ketosis.[6] Even patients with a stable condition are at risk of developing complications that include developmental delay, intellectual disability, seizures, basal ganglia hyperintensities, autistic features, deafness, optic atrophy, cardiomyopathy and long QTc abnormalities.[7,8]

Hypoglycaemia is a commonly described finding during metabolic decompensation of organic acidaemias, but hyperglycaemia has been rarely described in a patient with PPA as is seen in the current case.[9,10] There is also a paucity of studies addressing the pathophysiology of disease and clinical correlates for this complication.[9]

Case Report

This case report describes a nine-month-old boy known to have PPA. He was diagnosed at birth through screening, as his elder brother had already been diagnosed with the same disease. The diagnosis was confirmed genetically following elevated propionylcarnitine in dried blood spots. He presented to the Emergency Department of a tertiary care hospital in Muscat, Oman, in 2018 with a three-day history of poor oral intake and lethargy. No history of fever, vomiting, loose motion or contact with a sick person was reported by the family. He was admitted with breathlessness and altered sensorium. On initial assessment, he was found to be drowsy and had acidotic breathing, weak peripheral pulses and delayed capillary refill without fever. Investigations revealed severe metabolic acidosis, mild lactic acidosis, elevated anion gap and hyperammonaemia. Initially, plasma glucose was normal with significant ketonuria. Other than hypernatremia, electrolytes were in the normal range [Table 1].

The patient was admitted to paediatric intensive care unit due to his depressed sensorium, severe metabolic crisis and respiratory distress that necessitated mechanical ventilation. Fluid resuscitation was given in the form of normal saline bolus 20 mL/kg followed by double maintenance of intravenous (IV) dextrose 10% and 0.9% sodium chloride solution. He was given IV carnitine at a dose of 300 mg/kg/day. In addition, IV glucose infusion was started with a glucose infusion

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Table 1: Initial blood investigation results of a nine-month-old boy with propionic acidaemia

Test	Patient's results	Reference range
Arterial blood gas		
pH	7.11	7.35–7.45
PCO_2 in mmol/L	21	35–48
HCO_3 in mmol/L	8	23–30
BE in mmol/L	-24.3	-2 to +2
Lactate in mmol/L	2	0.5–1.6
Anion gap in mmol/L	40	5–13
Serum ammonia in mcg/dL	173	30–50
Serum electrolyte		
Sodium in mmol/L	160	135–145
Potassium in mmol/L	4	3.5–6.1
Chloride in mmol/L	103	98–107
Renal function		
Urea in mmol/L	5	2.1–7.1
Creatinine in µmol/L	23	15–31
Bone profile		
Calcium in mmol/L	2.42	2.17–2.55
Phosphate in mmol/L	1.8	1.16–2.1
Alkaline phosphatase in units/L	240	0–280
Liver function		
ALT in IU/L	40	14–59
AST in IU/L	30	15–35
Protein in g/L	65	64–82
Albumin in g/L	40	38–54

PCO_2 = partial pressure of carbon dioxide; HCO_3 = bicarbonate; BE = base excess; ALT = alanine aminotransferase; IU = international unit; AST = aspartate aminotransferase.

rate (GIR) of 8 mg/kg/min, which was then increased to 12 mg/kg/min after four hours of admission. IV lipids was started at a dose of 2 g/kg/day. These measures were aimed at delivering a caloric intake of 120–150 kcal/kg/day to promote anabolism. Metabolic acidosis was aggressively managed with IV sodium bicarbonate bolus at a dose of 1 mmol/kg followed by continuous bicarbonate infusion titrated to blood gas at a rate that did not exceed 1.5 mmol/kg/hour. Hyperammonaemia was additionally treated with IV ammonia scavenger therapy with IV sodium benzoate at a dose of 250 mg/kg and sodium phenylbutyrate at a dose of 250 mg/kg, both delivered as loading and maintenance doses. The initial repeat ammonia level was 123 mcg/dL; a loading dose of carglumic acid (100 mg/kg) was administered followed by maintenance doses of 25 mg/kg/dose every six hours.

The patient's plasma glucose was significantly elevated outside the upper limit of detection in the glucometer that was used. Insulin therapy was started early for the anticipated hyperglycaemia with an initial dose of 0.1 IU/kg/hr; this dose was later increased in the first six hours to 0.4 IU/kg/hr for persistent uncontrolled hyperglycaemia. GIR was kept in the range of 8–10 mg/kg/min (5^{th}–11^{th} hours after admission) as a measure of attempted suppression of catabolism as per the protocol of the treatment of metabolic crisis.[11,12] Urine dipstick showed significant glucosuria and ketonuria with associated polyuria (urine output of 8.6 mL/kg/hr). With persistent ketones in the urine, feeding was not started and GIR remained high. The patient's plasma glucose remained very high despite escalating insulin infusion dose reaching 1.4 IU/kg/hr in the following six hours. Associated severe electrolyte disturbances including hypokalaemia, hypocalcaemia, hypophosphataemia and hypomagnesaemia were recorded. IV correction was given for all these disturbances, with persistent severe hypokalaemia being a prominent side effect of the high dose of insulin infusion.

The child remained critically sick on mechanical ventilation. His acidosis improved with continuous IV infusion of bicarbonate leading to discontinuation after normal pH was maintained. It was only after 18 hours subsequent to his admission with this severe condition that his urine dipstick was negative for ketones; nasogastric feeding was started to provide protein at 1 g/kg/day. His plasma glucose recorded high readings (>20 mmol/L) for more than 10 hours notwithstanding the escalation of the dose of insulin infusion. The plasma glucose reading decreased only after gradually and cautiously minimising the GIR after 12 hours of admission given the concern about catabolism inducing further metabolic decompensation in this child with PPA. The patient has full recovery and was discharged with a follow-up plan. Guardian consent was obtained for publication purposes.

Discussion

PPA, organic aciduria, is considered a major health burden in the Arab world due to high rates of consanguinity.[13] Both hypoglycaemia and hyperglycaemia could be part of the initial presentation of organic aciduria, including PPA. Lehnert et al. reported the first observation of the unexplained bouts of hyperglycaemia in a patient with PPA.[14] The literature review showed a high mortality rate in patients with organic acidaemias who presented with

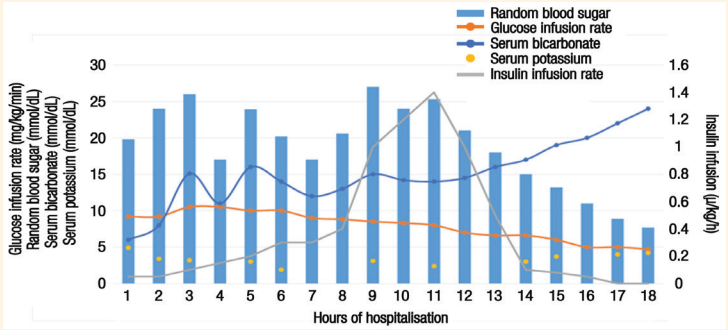

Figure 1: Metabolic profile during glucose and insulin administration of a nine-month-old boy with propionic acidaemia.

severe insulin-resistant hyperglycaemia. In conjunction with encephalopathy, hyperammonaemia and severe metabolic acidosis, hyperglycaemia may be a marker of more serious metabolic decompensation.[15,16] It should be noted that the clinical presentation of PPA can be misdiagnosed as diabetic ketoacidosis.[15,16]

Although hyperglycaemia, including insulin-resistant hyperglycaemia, has been reported in patients with different organic acidaemia (including isovaleric acidaemia, methylmalonic acidaemia and PPA), the underlying mechanism remains largely unknown and it is presumed to be multifactorial. Reduced muscle and hepatic uptake of glucose, coupled with IV lipid-related fatty-acid-induced insulin resistance, are postulated to be the underlying mechanisms.[10] Lipotoxicity and hyperglycaemia will cause hyperactivation of protein phosphatase 2A, which leads to reduced phosphorylation of insulin receptors (IR) and insulin receptor substrate (IRS).[17] Mitochondrial dysfunction causes the same effect through activation of serine/threonine-specific kinases. Hyperinsulinaemia hyperactivates PH domain and leucine rich repeat protein phosphatase 1 and growth factor receptor-bound protein 14, which decreases Akt serine 473 phosphorylation competition for IRS binding to IR.[17] The notable improvement in glycaemic control with reduction of GIR may clinically support this possibility.

As was seen in the current case, plasma glucose started to improve when the rate of glucose infusion of 7 mg/kg/min was reached. Plasma glucose gradually decreased to 10 mmol/L when insulin infusion stopped. The first negative urine dipstick for glucosuria was done when the GIR dropped to 5–6 mg/kg/min, and at that time, the insulin infusion rate was at 0.4 IU/kg/hr [Figure 1]. Although most metabolic emergency protocols recommend high GIR to bring in more insulin secretion that may promote anabolism, there is no evidence to suggest that patients receiving exogenous insulin to combat hyperglycaemia recover faster or quickly achieve positive nitrogen balance compared to patients relying on their endogenous insulin secretion to combat hyperglycaemia that may accompany high GIR. The long-term risk of diabetes and pancreatic exhaustion caused by repeated exposure to high GIR with a recurrent metabolic crisis is a matter of concern. Unfortunately, this has not been followed in patients with metabolic disorders.

Conclusion

An important challenge that needs to be addressed is achieving a balanced GIR, which is considered to be enough to achieve the targeted insulin level beyond which risks of hyperglycaemia start to outweigh potential anabolic benefits of additional insulin secretion. Given the few case reports published so far, insulin-resistant hyperglycaemia in the context of metabolic decompensation associated with organic aciduria, seems to be a poor prognostic factor. Timely clinical attention should be provided to achieve adequate caloric delivery through alternative sources instead of through high GIR to permit better glycaemic control, especially when insulin-resistant hyperglycaemia is present.

AUTHORS' CONTRIBUTION

MAN drafted the introduction. MAN and KA drafted the discussion and references. MR drafted the case presentation. KA revised the case presentation with management. MAN edited the manuscript. All authors approved the final version of the manuscript.

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