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Case report

Propionic acidemia mimicking diabetic ketoacidosis

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Abstract

Propionic acidemia manifesting with hyperglycemia is rare. Few cases have been reported mainly of the neonatal-onset form associated with high mortality. We report a 9-month-old Palestinian boy who manifested with coma, severe hyperglycemia and ketoacidosis mimicking diabetic ketoacidosis. Family history of unexplained infant deaths was helpful in reaching the correct diagnosis. In response to therapy, the patient regained consciousness without neurologic deficits and had normal examination. This is, to our knowledge, the first case report of late-onset propionic acidemia that had this presentation and survived.

Keywords: Coma; Propionic acidemia; Hyperglycemia; Ketosis; Diabetic ketoacidosis

1. Introduction

Propionic acidemia (PA) is an autosomal recessive disorder caused by a deficiency of propionyl-CoA carboxylase, which converts propionyl-CoA, derived from the catabolism of isoleucine, valine, methionine, threonine and odd-chain fatty acids, to methylmalonyl-CoA [1]. Most patients present in the neonatal period with refusal to feed, vomiting, hypotonia, lethargy and metabolic acidosis [1]. Early-onset PA patients may also present with sepsis resulting from immune deficiency, failure to thrive, pancreatitis, dystonia and seizures [1,2]. A late-onset form of PA carries an overall better prognosis; nevertheless, presentations of varying severity have been described ranging from acute life-threatening to intermittent, insidious or chronic symptoms. A few patients have presented later on in life with acute encephalopathy, episodic ketoacidosis or neurodevelopmental regression without ketosis or acidosis [3]. Hypoglycemia has been documented, in both forms of PA, during acute metabolic decompensation crises [2,4]. Hyperglycemia, however, is an unusual feature in these patients and has been associated with high mortality and worse outcome [5–9].

We describe an infant with PA whose initial presentation with acute respiratory distress, coma, severe hyperglycemia

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and metabolic ketoacidosis led to an initial misdiagnosis of diabetic ketoacidosis (DKA). Not only did the patient survive following therapy with intravenous insulin, L-carnitine and a special dietary formula, but he made a full neurologic recovery. To our knowledge, this is the first case of late-onset PA manifesting with severe hyperglycemia that survived with good neurologic outcome.

2. Case report

A 9-month-old Palestinian male is the subject of our report. He was born to consanguineous parents (double first cousins) after normal pregnancy and delivery and was breastfed exclusively until 6 months of age after which vegetables and fruits were introduced to his diet. The patient presented with rapid breathing and lethargy followed by vomiting that worsened over 2 days. His condition progressed to respiratory distress and coma prompting urgent hospitalization. He had no previous episodes of vomiting, lethargy, respiratory distress or seizures. There was a significant family history of sibling deaths in infancy after manifesting acutely with lethargy, flaccidity and difficulty breathing (Fig. 1). Physical examination showed an afebrile, comatose child (Glasgow coma scale of 3/15) in cardiorespiratory distress (heart rate 165/min and respiratory rate 80/min). Initial laboratory tests revealed severe metabolic acidosis (pH 6.99, HCO3 3 mmol/L, base excess −27), hyperglycemia (blood glucose 390 mg/dl), hemoglobin 10.8 g/dl, leucopenia (WBC 2900/mm^3, neutrophils 67%, lymphocytes 24%), platelets 260,000/mm^3 and calcium 7.5 mg/dl. Serum and urine ketones were positive and there was significant glucosuria. Liver and kidney function tests and other serum electrolytes were normal. Imaging studies (chest X-ray, abdominal ultrasound and brain CT scan) were all within normal. A preliminary diagnosis of DKA was made. Mechanical ventilation was initiated and intravenous (IV) fluids with sufficient concentrations of sodium, potassium and calcium were administered along with IV insulin infused at a rate of 0.1 units/kg per hour. As the blood glucose dropped below 300 mg/dl a few hours following admission, 5% dextrose was added to the IV fluids to deliver 4.5 mg glucose/kg per minute. Despite adequate oxygenation and tissue perfusion and correction of hyperglycemia and metabolic acidosis, the patient's condition failed to improve and his coma persisted. The lack of clinical response, in addition to the family history of sibling deaths during infancy, prompted a workup for an alternative diagnosis to DKA. Urine gas chromatography/mass spectrometry (GC/MS) analysis revealed increased excretion of 3-hydroxypropionic, 3-hydroxyvaleric, 3-oxovaleric acids and ketones and moderate excretion of tiglylglycine, propionylglycine and methylcitric acid. Plasma amino acids showed glycine concentration of 500 μmol/L (normal: 127–340 μmol/L). The diagnosis of PA was further confirmed by blood spot acylcarnitine analysis showing marked elevation of C3 carnitine and increased C3/C2 ratio. Serum biotinidase level was normal, as was serum ammonia and lactic acid. Hemoglobin A_{1C} was not performed.

Subsequently, insulin was discontinued and L-carnitine at a dose of 100 mg/kg per day along with a special dietary formula free of methionine, threonine, valine and isoleucine (XMTVI analogue) were given. The patient's general and neurologic status gradually improved and after the fourth day of hospitalization, he regained consciousness without residual neurologic deficits and had normal physical exam and laboratory tests (including blood gases, blood glucose and calcium). Following his hospital discharge, we monitored the patient closely in our outpatient metabolic clinic. He is currently 27 months of age and has achieved normal developmental milestones. His long-term management includes L-carnitine administration (100 mg/kg per day, orally), low-protein diet and XMTVI analogue. There have been no further episodes of hyperglycemia or acute metabolic decompensation.

3. Discussion

Propionic acidemia phenotype varies from severe early/neonatal-onset form with high mortality and poor outcome to milder forms with a later onset and varying presentations [3,10]. Despite this clinical heterogeneity, the course of PA and other organic acidemias is dominated by life-threatening episodes of metabolic decompensation [1,10]. These crises may be precipitous and cause irreversible damage, particularly neurologic deficits, if not managed aggressively [2]. Hypoglycemia has been described in patients with organic acidemia presenting in crisis. In a retrospective review, Henriquez et al. found hypoglycemia in 20–21% of PA patients in crisis, but did not find an association between hypoglycemia and the acid–base status or the mental status of these patients [2]. Hyperglycemia, on the other hand, is rare and has only been reported in a few PA patients in crisis. Lehner et al. reported a newborn with PA who had severe hyperglycemia and presented with hyperexcitability, drowsiness, vomiting and hypotonia. An autopsy revealed the presence of hypertrophic pyloric stenosis [5]. Another case report was of a female newborn with methylmalonic academia (MMA) associated with severe, insulin-resistant hyperglycemia. The patient died despite receiving insulin, peritoneal dialysis and mechanical ventilation. The authors suggested that another biochemical defect was probably responsible for the hyperglycemia and hypothesized that significant insulin resistance might be responsible for the glucose intolerance [7].

Two other newborns have also been reported- one suffering from acute neonatal-onset MMA while the other

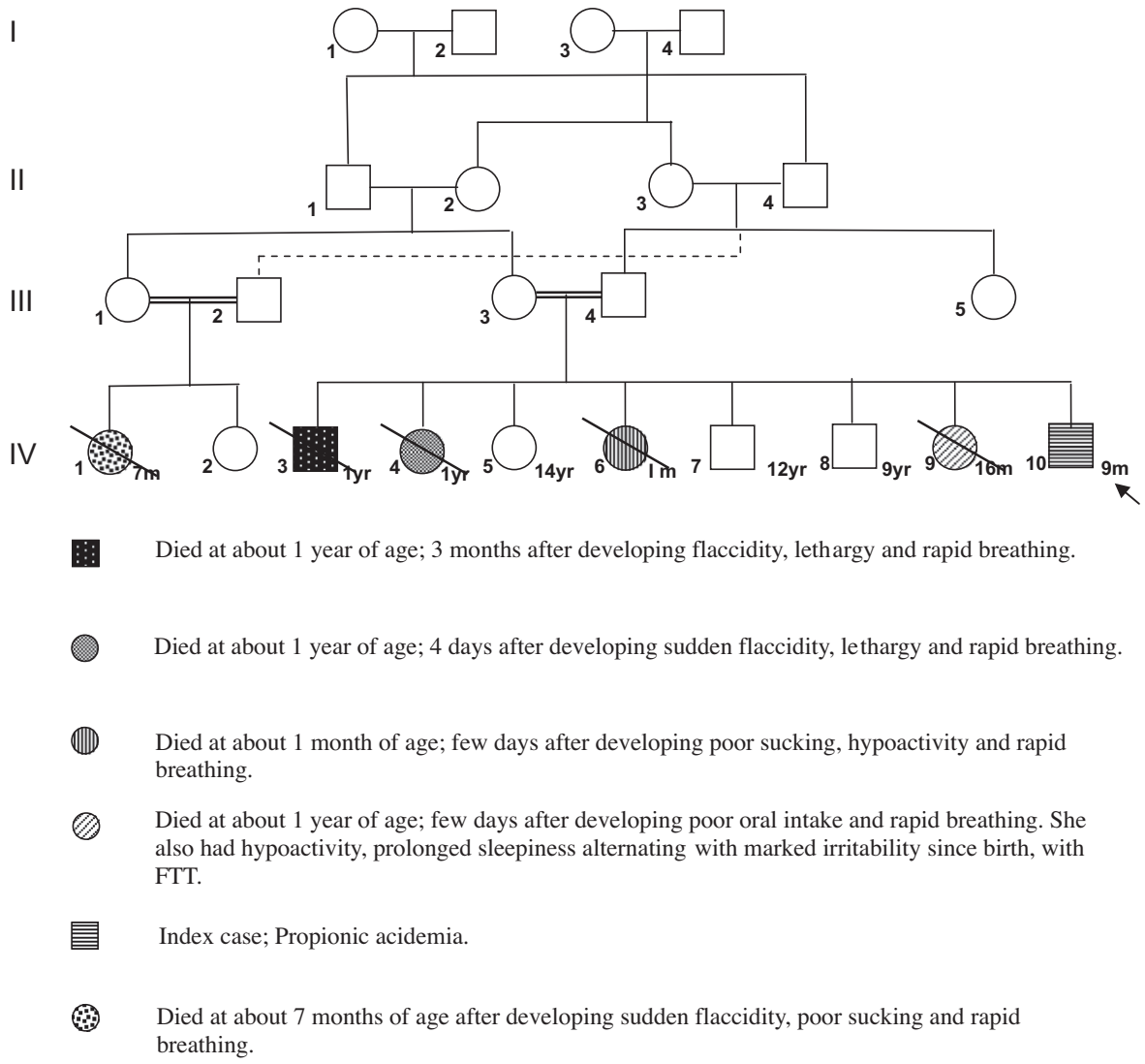

Fig. 1. Pedigree.

suffering from acute neonatal-onset PA- that presented acutely with dehydration, ketoacidosis and hyperammonemia. Both were found to have insulin-resistant hyperglycemia. The patient with MMA died while the patient with PA survived after strong reduction of IV glucose administration. It was hypothesized that such patients may have a transitory and reversible intolerance to high glucose concentrations and that a reduction of IV glucose administration can reduce some of the risks associated with persistent hyperglycemia [8]. Ciani et al. reported a case of late-onset MMA in a 12-year-old female who presented acutely with vomiting, fever, bronchopneumonia and coma associated with hyperglycemia, ketoacidosis and hyperammonemia. She was misdiagnosed as a case of insulin-dependent diabetes mellitus (IDDM) and died 3 days later despite receiving IV insulin [6].

Our patient's initial presentation at age 9 months with respiratory distress, progressive loss of consciousness, metabolic ketoacidosis and hyperglycemia led to a misdiagnosis of IDDM presenting as DKA. Only after poor clinical response to appropriate DKA management and review of suggestive family history was the correct diagnosis of PA considered and confirmed. The mechanism of hyperglycemia in the setting of organic acidemias remains poorly understood and possibly multifactorial. Unlike in previously described cases, the hyperglycemia in our patient was not insulin-resistant [6–8]. The two infants described by Filippi et al. received IV infusion of lipids which may have induced insulin resistance and accentuated their hyperglycemia [8]. Our patient did not receive IV lipids. In fact, the administration of intravenous insulin which led to reduction of blood glucose to normal values quickly after hospitalization along with use of L-carnitine and a special dietary formula may have contributed to his full recovery with such favorable outcome.

4. Conclusions

Although diabetes mellitus is the commonest cause of hyperglycemia and metabolic ketoacidosis, inborn errors of metabolism are complex multifaceted disorders that should be suspected especially when clinical deterioration occurs despite appropriate therapy. Family history of unexplained deaths should alert physicians to the possibility of an inborn error of metabolism. The nature of hyperglycemia during episodes of metabolic decompensation in patients with organic acidemia and its association with seriousness and mortality needs to be further investigated in future research.

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