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CASE REPORT

Defect of Cobalamin Intracellular Metabolism Presenting as Diabetic Ketoacidosis: A Rare Manifestation

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Abstract Hypoglycemia is the usual feature of commonly occurring organic acidemias. Organic acidemias manifesting as hyperglycemia or diabetic ketoacidosis are rare and only a few cases have been reported. We report a 13-month-old boy who presented with vomiting, dehydration, coma, hyperglycemia, high anion gap metabolic acidosis and ketosis, mimicking diabetic ketoacidosis (DKA). Treatment with parenteral fluid, electrolytes, and insulin infusion resulted in an improvement in hyperglycemia, but persistence of metabolic acidosis and lack of improvement of neurologic status led us to suspect an organic acidemia. Urinary organic acid analysis revealed increased methylmalonic acid levels. In addition, hyperhomocysteinemia and homocystinuria were also noted in presence of normal vitamin B_{12} levels. This confirmed the diagnosis of cobalamin metabolism defect leading to combined methylmalonic aciduria and homocystinuria. There was some improvement in neurologic status and metabolic parameters after treatment with low-protein diet, vitamin B_{12}, folic acid, and L-carnitine, but he ultimately succumbed to polymicrobial nosocomial sepsis. The entire MMACHC gene of the patient was sequenced and no mutations were identified. This is probably the first case report of cobalamin intracellular metabolism defect (CblC/CblD/CblF/CblJ or ABCD4) presenting as diabetic ketoacidosis.

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Introduction

Metabolic acidosis and ketosis are the hallmark features of organic acidemias. Hypoglycemia is frequently associated with acute episodes of decompensation in most commonly encountered organic aciduria like methylmalonic aciduria, propionic aciduria, isovaleric aciduria, multiple carboxylase deficiency, and 3-oxothiolase deficiency. Hypoglycemia is possibly due to inhibition of gluconeogenesis through various mechanisms: inhibition of malate shuttle by methylmalonic acid and inhibition of pyruvate carboxylase by methylmalonyl-CoA, inhibition of multiple enzymes by propionyl-CoA and accumulation of organic acid-CoA esters through acylcarnitine formation (Worthen et al. 1994). However, metabolic acidosis and ketosis with hyperglycemia is a rare feature of methylmalonic aciduria (Guven et al. 2012), propionic aciduria (Dweikat et al. 2011), and biotinidase deficiency (Hou 2004). We present a presumed case of cobalamin metabolism defect presenting as diabetic ketoacidosis (DKA).

Derivatives of cobalamin (vitamin B_{12}) are required for activity of two enzymes. Adenosylcobalamin (AdoCbl) is required for activity of mitochondrial enzyme methylmalonyl CoA mutase (MUT) which converts methylmalonyl-CoA to succinyl-CoA, and methylcobalamin (MeCbl) is required for activity of cytoplasmic enzyme methionine synthase (MS) that catalyzes methylation of homocysteine to form methionine (Froese and Gravel 2010; Watkins and Rosenblatt 2011). Deficiency in cobalamin or impaired absorption of cobalamin can result in accumulation of methylmalonic acid and homocysteine in blood and serum homocysteine and urine homocystine. Inborn errors affecting cobalamin absorption (inherited intrinsic factor deficiency, Imerslund–Gräsbeck syndrome) and transport (transcobalamin deficiency) have been described

(Watkins and Rosenblatt 2011). A series of inborn errors of intracellular cobalamin metabolism, designated as cblA, cblB, cblC, cblD, cblE, cblF, cblG, and cblJ, have been differentiated by complementation analysis (Fowler et al. 2008; Coelho et al. 2012; Kim et al. 2012). These can give rise to isolated methylmalonic acidemia (cblA, cblB, cblD variant 2), isolated hyperhomocysteinemia (cblD variant 1, cblE, cblG), or combined methylmalonic acidemia and hyperhomocysteinemia (cblC, cblD, cblF, cblJ). Transcobalamin II deficiency and transcobalamin receptor deficiency have also been described with inborn errors of cobalamin absorption and metabolism, but it is not clear that they have any consistent clinical phenotype (Watkins and Rosenblatt 2011).

All these disorders are inherited as autosomal recessive traits. The genes underlying each of these disorders have been identified (Froese and Gravel 2010; Watkins and Rosenblatt 2011). Approximately 400 patients have been described with cblC, making it the most common disorder of intracellular vitamin B_{12} metabolism (Lerner-Ellis et al. 2009). The gene responsible for the cblC group is MMACHC (Lerner-Ellis et al. 2006). More than 50 different disease-causing mutations have been identified (Lerner-Ellis et al. 2009). It was recognized that cblF represents a defect in the export of cobalamin out of the lysosome into the cytosol (Rosenblatt et al. 1985). The gene responsible for cblF was very recently cloned and found to correspond to LMBRD1, which encodes the lysosomal membrane protein LMBD1 (Rutsch et al. 2009). The gene responsible for cblD is MMADHC (Coelho et al. 2008).

Combined methylmalonic acidemia and homocysteinemia can present with a wide spectrum of clinical manifestations ranging from intrauterine period to late infantile and also in adults. Here, we describe a patient with a form of combined methylmalonic aciduria and homocystinuria who presented with diabetic ketoacidosis. To the best of our knowledge, this is the first case of a combined cobalamin metabolism defect, most possibly due to cblC or cblD or cblF or cblJ deficiency, who presented clinically with diabetic ketoacidosis (DKA). Physicians should be aware of these diverse clinical presentations in order to provide an early diagnosis and to guide management of affected individuals and to screen other family members.

Case Report

A 13-month-old boy presented with a short history of fever, cough, vomiting, deep sighing breathing, and lethargy. His condition soon deteriorated to respiratory distress and coma requiring hospitalization in the pediatric emergency. He was the first child born to a non-consanguineous couple, delivered normally with a birth weight of 2,700 g, and had no adverse perinatal events. The child had no previous history of episodes of vomiting, seizures, lethargy, respiratory distress that required hospitalization, polyuria, polydipsia, or abnormal weight loss. He was developmentally normal for age. The past medical history was unremarkable; he was on mixed vegetarian and nonvegetarian diet with daily calorie and protein deficit of 200 Kcal and 5 g, respectively; and he was not on any vitamin supplements prior to this illness. Physical examination on admission showed an afebrile and comatose child with a Glasgow Coma Scale (GCS) of 7/15. His pulse rate was 150 beats/min, respiration was deep and sighing (Kussmaul respiration) with rate of 34/min, and blood pressure of 100/64 mm Hg. His weight, length, and head circumference was 8 kg (3rd percentile), 76 cm (75th percentile), and 46 cm (70th percentile) for age, respectively. The initial laboratory tests showed hyperglycemia (random blood glucose – 284 mg/dL), metabolic acidosis (pH – 7.09, bicarbonate – 8 mmol/L, and base excess – 20 mmol/L), high anion gap (AG – 29 mmol/L), and presence of ketones and glucose in urine. His hemoglobin was 10.2 g/dL, total leukocyte count 16,000/mm^3 (neutrophils 70%, lymphocytes 30%), platelets 1, 56, 000/mm^3, and calcium 9.5 mg/dL. Liver and renal function tests and other serum electrolytes were normal as were chest X-ray and abdominal ultrasound. No focus of sepsis was found. Based on clinical presentation and investigations, a provisional diagnosis of diabetic ketoacidosis was made. The child was intubated for low a GCS and mechanical ventilation was initiated. Intravenous (IV) fluids with recommended concentration of electrolytes were started along with insulin infusion at a rate of 0.1 unit per kg per hour (Milwaueke regimen protocol of the unit). With this therapy, there was improvement in hyperglycemia within 24 h. Despite the adequate oxygenation and tissue perfusion and correction of hyperglycemia, the metabolic acidosis, anion gap, and clinical condition failed to improve and his coma persisted. The lack of clinical response and persisting metabolic acidosis prompted us to investigate for an alternative diagnosis. An inborn error of metabolism, most likely an organic acidemia, was suspected and screening tests were sent. The child was found to have hyperammonemia [181μmol/L; normal <74 μmol/L] and elevated lactate [5.4 mmol/L; normal <1.5mmol/L]. High performance liquid chromatography (HPLC) showed increased plasma homocysteine concentration [40.1 μmol/L; normal range: 5–15 μmol/L], low methionine [5.6 μmol/L; normal range: 15–54 μmol/L], normal glycine [140 μmol/L; normal range: 100–300 μmol/L], and increased excretion of homocystine in urine [16.4 mmol/mol creatinine; normal range: 0.2–4 mmol/mol creatinine]. Urine gas chromatography–mass spectrometry (GCMS) analysis revealed increased excretion of methylmalonic acid

[141mmol/mol creatinine; normal: <9 mmol/mol creatinine]. Both vitamin B_{12} [455 pg/mL; normal range: 200–900 pg/mL] and folate levels (14 ng/mL) were normal. The diagnosis of methylmalonic aciduria with homocystinuria was made. Subsequently, insulin was discontinued and the baby was started on L-carnitine, pyridoxine, vitamin B_{12}, and folic acid along with a low-protein diet. After the fifth day of hospitalization, the general condition and neurologic status gradually improved along with some improvement in biochemical parameters: random blood glucose – 178 mg/dL; pH – 7.25; bicarbonate – 16 mmol/L; AG – 18 mmol/L; plasma ammonia – 94 μmol/L; and lactate – 2.2 mmol/L. He remained admitted in the hospital for 10 days and succumbed to polymicrobial sepsis (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*), in presence of multiple risk factors such as long hospital stay, presence of invasive lines, and mechanical ventilation. Since the glucose intolerance improved with insulin (for short duration) and metabolic therapy, further evaluation for type 1 diabetes mellitus was not undertaken. Sequencing of the entire MMACHC gene of the patient revealed no mutations, while sequencing of MMACHC gene of parents was not done (planned on follow-up).

Discussion

Many disorders of inborn errors of metabolism (IEMs) lead to hypoglycemia and ketoacidosis, including methylmalonic acidemia, propionic acidemia, isovaleric acidemia, maple syrup urine disease, congenital lactic acidosis, defects of gluconeogenesis and glycogen synthesis, and ketolytic defects (Henriquez et al. 1994; Worthen et al. 1994; Marles and Casiro 1998; Ozand 2000). Inborn errors of metabolism must always be considered as a possible diagnosis when an infant presents with a severe metabolic acidosis accompanied by an increased anion gap. When we consider severe metabolic acidosis with hyperglycemia and ketosis, DKA is always highest on the list of diagnosis. However, in case of lack of improvement in the clinical or metabolic profile even after appropriate therapy, one should always have a high index of suspicion for IEMs, and further investigational workup should be done.

Our patient was admitted with severe metabolic acidosis precipitated by an acute febrile illness. Severe ketoacidosis and hyperammonemia are typical features of acute forms of aminoacidopathies, including MMA, that typically present in the first weeks of life with complaints of poor feeding and lethargy, progressing to coma. The older infants or children may present with lethargy, seizures, muscular hypotonia, and hypoglycemia during an episode of metabolic decompensation that is often associated with an intercurrent illness (Guven et al. 2012). Although hyperglycemia is an unusual presentation for MMA, Boeckx and Hicks for the first time in 1982 reported a newborn female with severe and persistent metabolic acidosis and hyperglycemia resistant to large doses of insulin, who excreted large amounts of methylmalonic acid in urine, but the patient died before any further investigations (Boeckx and Hicks 1982). Mathew et al. also reported a newborn girl with transient diabetes mellitus in association with MMA. She died at the age of 6 months (Mathew and Hamdan 1988). Filippi et al. reported a newborn suffering from acute neonatal-onset MMA who presented acutely with dehydration, ketoacidosis, hyperammonemia, and insulin-resistant hyperglycemia (Filippi et al. 2009). Ciani et al. reported a case of late-onset cbl-B 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 (Ciani et al. 2000).Two of the most recent cases of diagnosed MMA presenting as DKA include a 13-month-old female child (Guven et al. 2012) and a 14-month-old male child who presented with fever, vomiting, acute generalized dystonia, and lethargy (Imen et al. 2012). Investigations showed hyperglycemia, lactic acidosis, and hyperammonemia. Urinary organic acid analysis showed accumulation of methylmalonic acid, tiglylglycine, and methyl citrate which led to the diagnosis of MMA. He survived the metabolic crises (Imen et al. 2012). All these case reports concluded that hyperglycemia was a rare manifestation of MMA and could be a marker for worse prognosis (Table 1).

The index patient presented at 13 months of age with respiratory distress, progressive loss of consciousness, hyperglycemia, and metabolic ketoacidosis, mimicking DKA. Only after poor clinical response to appropriate management, the diagnosis of organic acidemia was considered and confirmed by appropriate tests. The administration of intravenous insulin and fluids led to improvement in blood glucose. Further evaluation revealed elevated levels of methylmalonic acid and homocystine in urine as well as raised homocysteine in the plasma. A defect in the intracellular metabolism of cobalamin could explain this combined metabolic abnormality in the index child. A low-protein diet, L-carnitine, pyridoxine, vitamin B_{12}, and folic acid could have contributed to some recovery in our patient though he later on succumbed to nosocomial sepsis. Although we were unable to pursue a complete evaluation for a cobalamin disorder, which should include obtaining a skin biopsy for fibroblast cellular biochemical studies and the procurement of patient and parental DNA for mutation studies (Fowler et al. 2008), our limited

Table 1 Summary of reported cases of methylmalonic acidemia that presented with hyperglycemia/diabetic ketoacidosis along with details of index case

S. No.	Reported patients	Age at onset, sex	Clinical features	Laboratory features[a]	Outcome
1	**Index patient**	13 months, male	Fever, cough, vomiting, dehydration, coma	Hyperglycemia, HAGMA, ketosis, elevated ammonia and lactate, methylmalonic aciduria, hyperhomocysteinemia, and homocystinuria	Died
2	**Boeckx et al. 1982**	3 weeks, female	Recurrent episodes of projectile vomiting, poor feeding, rapid respirations, and pallor	Hyperglycemia which was insulin resistant, HAGMA, ketonuria, hematuria, hypocalcemia, increased excretion of 3-hydroxybutyric acid, methylmalonic acid, 3-hydroxyvaleric acid, and 3-keto-n-valeric acid in urine	Died
3	**Mathew et al. 1986**	11 days, female	Poor feeding, drowsiness, rapid breathing, dehydration	Transient hyperglycemia, HAGMA, ketonemia, ketonuria, hypocalcemia, pancytopenia, high urine MMA	Died at 6 months
4	**Abramowicz et al.** 1994	Shortly after birth, female	Small for gestation age	Persisting hyperglycemia, acidosis, high urine methylmalonic acid, isodiosomy of chromosome 6, and agenesis of pancreatic beta cells (postmortem examination)	Died on day 16
5	**Federica et al. 2000**	12 years, female	Fever, vomiting, bronchopneumonia, coma	Hyperglycemia, ketosis, HAGMA, hyperammonemia, lactic acidosis, large amount of lactic acid, MMA, and methylcitric acid in aqueous humor (postmortem)	Died
6	**Filippi et al.** 2009	Newborn, male	Dehydration	Insulin-resistant hyperglycemia, ketoacidosis, hyperammonemia, high urine MMA	Died
7	**Guven et al. 2011**	13 months, female	Polyuria, polydipsia, weight loss, dehydration, acidotic breathing, lethargy, vomiting, loss of sensorium	Hyperglycemia, HAGMA, ketosis, hyperammonemia, high lactic acid, high excretion of MMA in urine	Survived
8	**Imen et al.** 2012	13 months, male	Fever, lethargy, vomiting, acute generalized dystonia	Hyperglycemia, lactic acidosis, hyperammonemia, increased urinary MMA, tiglylglycine, and methylcitrate	Survived

HAGMA high anion gap metabolic acidosis, *MMA* methylmalonic acid, *GCMS* gas chromatography–mass spectrometry

[a] None of the reported patients except the index case had hyperhomocysteinemia or homocystinuria

evaluation suggests the patient did not have cblC deficiency, but did appear to have a distinct inborn error of cobalamin metabolism.

After internalization, vitamin B_{12} enters a metabolic cascade to generate Mecbl in the cytsol and Adocbl in the mitochondria. At least eight different defects in the intracellular metabolism of cobalamin have been identified (Watkins and Rosenblatt 2011). These are designated cblA to cblJ (except cblH) (Fowler et al. 2008; Coelho et al. 2012; Kim et al. 2012). Defects of cblA, cblB, and cblD (variant II) cause MMA only. The cblE and cblG defect result in homocystinuria without MMA. In patients with cblC or cblD or cblF or cblJ defects, synthesis of both adenosylcobalamin and methylcobalamin is impaired, causing hyperhomocysteinemia in addition to MMA (Watkins and Rosenblatt 2011). Clinicians should be aware of diverse clinical presentations of combined methylmalonic aciduria and homocystinuria in order to provide an early diagnosis and to guide management of affected individuals. The workup in all patients with suspected cobalamin IEMs should include a skin biopsy for cellular biochemical studies and collection of parental samples for future genomic studies (after the proper consent) (Fowler et al. 2008). Unfortunately, we were unable to perform these tests before our patient expired, which are must for proper evaluation of cobalamin IEMs.

Isolated MMA masquerading as DKA or in combination with hyperglycemia has been reported in literature (Boeckx and Hicks 1982; Mathew and Hamdan 1988; Abramowicz et al. 1994; Ciani et al. 2000; Filippi et al. 2009; Guven et al. 2012; Imen et al. 2012) (Table 1). The mechanism of hyperglycemia in the setting of organic acidemias remains poorly understood and is possibly multifactorial. Unlike in previously described cases, the hyperglycemia in our patient was not insulin resistant (Boeckx and Hicks 1982; Ciani et al. 2000; Filippi et al. 2009). Other rare but possible differential diagnoses to be considered in an acute presentation with severe metabolic acidosis presenting with hyperglycemia instead of hypoglycemia includes other IEMs, e.g., fructose-1,6-diphosphatase enzyme deficiency

(Paksu et al. 2011) and also mitochondrial disorder such as Kearns–Sayre syndrome (Bachynski et al. 1986). The cobalamin intracellular metabolism defect [possibly cblC, cblD, cblF, and cblJ] presenting as DKA has not been described previously.

Conclusion

The unusual presentation in the index patient of cobalamin metabolism defect as DKA reminds us of the wide clinical spectrum of IEMs. Though diabetes mellitus is the commonest cause of hyperglycemia and metabolic ketoacidosis, IEMs should be suspected, especially when clinical deterioration occurs despite appropriate therapy. The etiology and impact of hyperglycemia on morbidity and mortality in patients with cobalamin metabolism defects need further evaluation.

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Conflicts of Interest

None

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None

Take-Home Message

Inborn errors of cobalamin metabolism can present with hyperglycemia and ketoacidosis, mimicking classical diabetic ketoacidosis. Testing for metabolic disorders in new onset diabetes patients should be considered, especially when response to traditional therapy is incomplete.

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