Methylmalonic Acidemia with the Unusual Complication of Severe Hyperglycemia

Roger L. Boeckx and Jocelyn M. Hicks

We describe a case of neonatal methylmalonic acidemia with the unusual complication of severe, insulin-resistant hyperglycemia. Methylmalonic acidemia, an inherited metabolic disease affecting the catabolism of propionic acid, is manifested by persistent metabolic acidosis, urinary excretion of large amounts of methylmalonic acid, and occasionally by hypoglycemia. Severe and persistent metabolic acidosis and hyperglycemia, despite large doses of insulin, were observed in this infant, who excreted large amounts of methylmalonic acid. The diagnosis of methylmalonic acidemia was confirmed by gas chromatography–mass spectroscopy, but the patient died before the defect in glucose tolerance could be delineated. We hypothesize that, in addition to the methylmalonic acidemia, the patient may have had an insulin-receptor defect, which was manifested as an inappropriate response to endogenous and exogenous insulin.

Additional Keyphrases: heritable disorders • newborns • pediatric chemistry • insulin resistance

Methylmalonic acidemia (MMA) refers to a group of disorders involving deranged propionate catabolism. Two of these disorders are due to altered apoenzymes, three are related to altered bioynthesis of cobalamin coenzymes (1). Many of the patients presenting with the type of MMA related to defective adenosylcobalamin synthesis will respond to large doses of cyanocobalamin or hydroxycobalamin, but the apoenzyme defects are unresponsive to this type of therapy. Defects in either methylmalonyl-CoA racemase (EC 5.1.99.1) or S-methylmalonyl-CoA mutase (EC 5.4.99.2) will result in MMA (Figure 1).

Oberholzer et al. (2) and Stokke et al. (3) first described the cobalamin unresponsive type of MMA in 1967; shortly thereafter, Rosenberg et al. (4) and Lindblad et al. (5) described vitamin B12-responsive MMA.

Yet another type of MMA, in which discriminated sulfur amino acid metabolism is a feature, was described by Mudd et al. (6) in 1969. In this type of MMA, defective synthesis of both adenosyl cobalamin and methyl cobalamin results in decreased activities of methylmalonyl-CoA mutase and tetrahydrofolate synthetase (EC 2.1.1.13) and is manifested by combined MMA and homocystinuria. The clinical features of MMA, regardless of etiology, are quite similar, but the disorder related to defective synthesis of both adenosyl cobalamin and methylcobalamin differs. Before the age of one year, patients present with severe and recurrent metabolic acidosis; ketoacidosis is invariably present, and hyperglycemia is a common finding. Inconsistently, hypoglycemia is present (1). There are recurrent bacterial or viral infections in half the patients. Osteoporosis and transient neutropenia and thrombocytopenia are frequently seen. Death is often due to uncontrollable acidosis or overwhelming infection. Methylmalonic acid concentrations in plasma as great as 340 mg/L have been reported, and children with MMA may excrete as much as 5 g of methylmalonic acid in 24 h (1).

In the Massachusetts Metabolic Disorders Screening Program (7) an incidence of 1:48 000 was observed for MMA. In that study, nine infants with MMA were investigated, of whom six had a cobalamin synthesis defect. The other three patients had a defect in methylmalonyl-CoA mutase.

Here we describe a case of vitamin B12-unresponsive MMA with the unusual complication of severely insulin-unresponsive hyperglycemia.

Case Report

The patient was a white girl born to a 13-year-old mother. The family history indicated consanguinity, the infant's father being also her maternal grandfather. There was no prenatal care, and the infant was born at home. The birth weight was reportedly 2770 g. The infant was hospitalized on the third day after birth for dehydration, low birth weight, and lethargy. She was fed with nasogastric feedings and discharged five days later to the care of foster parents.

At three weeks of age, five days before the second hospital admission, the infant had an episode of projectile vomiting, and subsequently began to feed poorly. Recurrent vomiting, coarse and rapid respirations, and pallor prompted the foster mother to bring the child back to the hospital.

At the time of this second admission, the infant weighed

**Fig. 1. Metabolism of methylmalonic acid**

Step 1 involves methylmalonyl-CoA racemase; 2, methylmalonyl-CoA mutase; 3, cobalt/adenosyl transferase (EC 2.5.1.17); 4, adenosylcobalamin reductase (EC 1.6.99.8); 5, cobalt/adenosyl transferase (EC 1.6.99.9); 6, uptake and internalization of transcobalamin II-bound cobalamin (TCII-Cbl); CblII, CblI, and Cbl are cobalamins with respective cobalt valences of 3+, 2+, and 1+; AdoCbl is adenosylcobalamin. Defects at steps 3, 4, and 5 are responsive to pharmacological doses of cobalamin, but defects at steps 1, 2, and 6 are not. A defect at step 6 would result in a disorder manifest by both methylmalonic acidemia and homocystinuria. Modified from Rosenberg (1).
2380 g and was thin, lethargic, dehydrated, tachypneic, and acutely ill.

Biochemical results obtained shortly after admission indicated a profound metabolic acidosis: pH 7.32, pCO2 8.7 kPa, P50 1.3 kPa, bicarbonate 5.0 mmol/L, and base excess −17.6 mmol/L. Serum sodium concentration was 143 mmol/L; potassium, 3.8 mmol/L; chloride, 98 mmol/L; and total CO2 12.0 mmol/L. A diagnosis of sepsis was considered. Blood and cerebrospinal fluid specimens were cultured and treatment with chloramphenicol (20 mg/kg body weight per day) and gentamicin (7.5 mg/kg per day) was begun. The acidosis was treated with repeated doses of sodium bicarbonate, but the base deficit persisted.

The patient was hypocalcemic (serum total calcium 50 mg/L). Therapy was begun with an intravenous solution of glucose (100 g/L), sodium chloride (11.4 mmol/L), potassium chloride (14.0 mmol/L), and calcium gluconate (220 mg/L) at the rate of 18 mL/h. The serum calcium concentration continued to decline, and frequent doses of calcium gluconate were required. Glucose, as measured by a glucose-specific method (8), increased to 3470 mg/L on the first day of this admission and significant ketonuria and hematuria were observed. No glucosuria was evident, however.

The hyperammonemia (ammonia nitrogen 1.84 mg/L), persistent metabolic acidosis, ketonuria, and history of consanguinity prompted an investigation for metabolic disease. A spot test for methylmalonic acid in urine (9) was strongly positive. Results for all other metabolic screening tests (10) were within normal limits. Analysis for urinary organic acids by gas chromatography–mass spectrometry showed a high excretion of 3-hydroxybutyric acid, methylmalonic acid, 3-hydroxyvaleric acid, and 3-keto-n-valeric acid, confirming a diagnosis of methylmalonic acidemia. Quantitative analysis for amino acids in the plasma showed increased glutamic acid, (513 μmol/L; normal, 20–100 μmol/L) but the concentration of glycine was within normal limits (155 μmol/L; normal, 100–300 μmol/L), as was that of all other amino acids. Values for lactic acid (84 mg/L; normal, 50–200 mg/L) and pyruvic acid (4.2 mg/L; normal, 3.0–9.0 mg/L) were also within normal limits.

On the third day after admission, the infant continued to be pale and lethargic, and began to have frequent seizures and periods of apnea. She received two loading doses of phenobarbital (10 mg/kg body weight, 12 h apart) and thereafter was maintained on 4 mg/kg per day, resulting in a phenobarbital concentration in serum of 34 mg/L. Because seizure activity continued, phenytoin was added at 8 mg/kg per day, producing a phenytoin concentration in serum of 12 mg/L. Because of continuing periods of apnea, the patient was placed in a respirator, in an oxygen-rich (250 mL/L) atmosphere.

When the hyperglycemia worsened (Figure 2), therapy with insulin was begun on the fourth day. The plasma C-peptide concentration at this time was 30 μg/L (normal 1.5–9.0 μg/L), indicating adequate endogenous insulin release. Ketonuria continued, and the β-hydroxybutyrate concentration increased to 450 mg/L (normal, 7–21 mg/L).

Administration of vitamin B12 (1 mg/day) produced no improvement in the metabolic acidosis. Plasma ammonia nitrogen concentration increased to 4.65 mg/L, and peritoneal dialysis was begun. The patient underwent a total of 110 cycles of peritoneal dialysis, involving a total of 9.4 L of dialysis fluid, during the next 85 h. At the end of this period, on respirator support, the patient’s serum pH was 7.24, pCO2 was 4.4 kPa, Po2 was 12.4 kPa, bicarbonate was 14.3 mmol/L, and base excess was −11.9 mmol/L. Blood ammonia nitrogen had decreased to 59 μg/L.

By the end of the fifth day after admission, the patient showed little spontaneous movement and responded only to painful stimuli. On the sixth day, she was comatose, displaying frequent seizure activity despite therapy with anticonvulsants, and had decreased urine output. On the morning of the eighth day she died.

Blood and tissues removed at autopsy were cultured; results were positive for Candida parapsilosis. No other findings, other than those ascribed to the agonal events immediately preceding death, were identified.

Discussion

Metabolic disease must always be considered as a possible diagnosis when an infant presents with a severe metabolic acidosis accompanied by an increased anion gap. In this particular case the infant presented with a severe metabolic acidosis and an anion gap of 37 mmol/L. Diabetic ketoacidosis and lactic acidosis should be considered as causes of the anion gap. Blood lactic acid and pyruvic acid concentration were normal, but ketonuria and increased β-hydroxybutyric acid concentration in blood were present. Considered with the hyperglycemia, these findings might point to diabetic ketoacidosis; however, the patient was able to secrete endogenous insulin in response to the increased glucose concentration in her blood.

The biochemical diagnosis of methylmalonic acidemia accounts for the metabolic acidosis and the ketoacidosis but does not explain the hyperglycemia. In fact, hypoglycemia has been described in some of these patients (1). Therefore, another biochemical defect was probably responsible for the hyperglycemia in this patient. For example, significant insulin resistance might be responsible for the glucose intolerance, and has been described in patients with obesity, insulin antibodies, Cushing’s syndrome, lipo-atrophic diabetes, ataxia telangiectasia, Prader–Willi syndrome, acanthosis nigricans, Werner’s syndrome, and several other disease states (11).

Another interesting and unexplained finding in this patient is the absence of glucosuria in the presence of the severe hyperglycemia. Despite good renal function and appropriate urine output, glucosuria was not observed until the glucose concentration in plasma exceeded 10 g/L.

Unfortunately, this patient died before further studies of the glucose intolerance, insulin resistance, and absence of glucosuria could be undertaken. The complexity of this case
of methylmalonic acidemia reminds us that inborn errors of metabolism are often complex and multifaceted disorders.

We thank Dr. Stephen Goodman (Department of Pediatrics, University of Colorado) for the gas chromatography-mass spectrometry of urine.

References