A newborn infant with generalized glutathione synthetase deficiency

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Pyroglutamic aciduria (5-oxoprolinuria) is a rare autosomal recessive disorder caused by either glutathione synthetase deficiency (GSSD) or 5-oxoprolinase deficiency. The severe form of the disease, generalized GSSD, is characterized by acute metabolic acidosis, usually present in the neonatal period with hemolytic anemia and progressive encephalopathy.

We report a female infant who had a severe metabolic acidosis with high anion gap, hemolytic anemia, and hyperbilirubinemia. High level of 5-oxoproline was detected in her urine and a diagnosis of generalized GSSD was made. She died of severe metabolic acidosis and sepsis at the age of six weeks.

Key words: glutathione synthetase deficiency, newborn.

Pyroglutamic aciduria (5-oxoprolinuria) is a rare autosomal recessive disorder caused by either glutathione synthetase deficiency (GSSD) or 5-oxoprolinase deficiency. 5-oxoprolinase deficient patients have normal acid-base status and do not have hemolytic anemia[1].

Glutathione synthetase deficiency has two clinical forms: generalized and erythrocyte GSSD. The former is severe with clinical features of severe metabolic acidosis, hemolytic anemia, hyperbilirubinemia, neurologic disabilities and sepsis[1,2]. It has been described in 40 patients from 35 families[2]. Here we report a newborn infant with generalized GSSD.

Case Report

The baby was admitted to our newborn intensive care unit for evaluating metabolic disease when she was four days old. She was born after a term pregnancy to a healthy mother, G3P1. Her parents were second-degree cousins. They had one healthy son; the second child had died at 17 days due to sepsis and metabolic acidosis.

Our case was normal at birth and was fed mother's milk. On the 3rd day of life she became tachypneic. A severe metabolic acidosis was detected and she was referred to our hospital. On admission her weight was 2720 g (10-25 p), length 49 cm (50 p), and head circumference 35 cm (75-90 p). Vital signs were as follows: temperature: 36.4°C, heart rate: 137/min, respiratory rate: 68/min and blood pressure: 80/36 mm Hg. She was lethargic and tachypneic. The remainder of the physical examination was unremarkable. She had a severe metabolic acidosis (pH: 6.9, base excess –25 mmol/L, anionic gap 32) without lactic acidosis (lactic acid: 27 mg/dl) or ketoacidosis. Urine and blood metabolic screening, plasma amino acid chromatography, renal function tests and eye examination were normal. She had a hemolytic anemia with progressive direct hyperbilirubinemia (17.8/8.2 g/dl). She required several packed blood transfusions. Glucose-6-phosphate dehydrogenase (G6PD) activity was within normal limits. The urine gas chromatography/mass spectrometry showed massive excretion of pyroglutamic acid. The laboratory findings of the patient are given in Table I. She was treated with intravenous sodium bicarbonate solution to overcome her metabolic acidosis. Nevertheless, she maintained a variable degree of metabolic acidosis. During the second week of hospitalization she developed sepsis and died when she was 41 days old. Parents did not give permission for autopsy.

Table I. Laboratory Findings of the Patient with Generalized Glutathione Synthetase Deficiency

Blood gases	pH: 6.9, PCO_2: 43 mmHg, PO_2: 78 mmHg, base excess -25 mmol/L, HCO_3: 3 mmol/L
Complete blood count	Hb: 5.3 g/dl, Htc: 18%, WBC: 14,000/mm^3, platelets: 207,000/mm^3 peripheral smear: significant anisopoikilocytosis
Anionic gap	32
Total/direct bilirubin	17.8/8.2 g/dl
Plasma amino acid chromatography	Normal
Urine metabolic screening	Normal
Blood metabolic screening	Normal
Pyroglutamic acid excretion in urine	3 times excretion of pyroglutamic acid of normal (normal internal standard: 130 mmol/molcre)
G6PD activity	Normal
Lactic acid	27 mg/dl

G6PD: glucose-6-phosphate dhydrogenase.

Discussion

Glutathione is a tripeptide containing glutamic acid, cysteine and glycine. The cysteinyl moiety of glutathione provides the reactive thiol group that is responsible for detoxification of reactive electrophiles and peroxides[3]. Glutathione normally regulates its own biosynthesis by inhibiting γ-glutamylcysteine synthetase, the enzyme catalyzing the first step in the γ-glutamyl cycle. When glutathione concentration is reduced, γ-glutamylcysteine formation increases and this dipeptide is converted to 5-oxoproline in the plasma; some of the 5-oxoproline is excreted in urine. As it is a highly acidic compound it causes metabolic acidosis[1,2].

Clinically there are two different forms of GSSD. The severe form of the disease, generalized GSSD, is characterized by decreased cellular levels of glutathione, severe metabolic acidosis, massive urinary excretion of 5-oxoproline, elevated levels of 5-oxoproline in blood and cerebrospinal fluid (CSF), increased rate of hemolysis, central nervous system symptoms and granulocyte dysfunction. The milder form is associated with low levels of erythrocyte glutathione and compensated hemolytic disease and does not lead to 5-oxoprolinuria[1,2,4,5]. GSSD is inherited as autosomal recessive trait.

Clinical signs usually first appear during the neonatal period. After the neonatal period, the condition is usually stabilized but may deteriorate during an infection due to severe acidosis or electrolyte imbalance. Five of 40 patients reported in the literature died in the neonatal period due to severe acidosis and infection[1,2]. Patients have progressive central nervous system damage including mental retardation, ataxia, spasticity and seizures. As it has a variable phenotype, it is difficult to predict the outcome in patients. Increased susceptibility to bacterial infections due to defective granulocyte function was reported in two patients with GSSD[6].

The present case had a severe metabolic acidosis with a high anionic gap, hemolytic anemia, hyperbilirubinemia, and high levels of 5-oxoprolinuria. Thus she was diagnosed with generalized GSSD. She was the product of a cousin marriage and a sister had most likely died of the same metabolic disease.

The generalized form is postulated to be due to mutations affecting the catalytic properties of the enzyme whereas the erythrocyte form of

glutathione synthetase (GSS) deficiency is postulated to be due to a mutation primarily affecting the stability of the enzyme[2]. GSS gene exists in chromosome 20q11.2[7]. Eighteen different mutations have been identified in 17 patients[1]. We could not perform a mutation analysis in this patient.

Pyroglutamic aciduria may also be due to secondary causes such as acetaminophen, antibiotic therapy or vigabatrin use[1,8-11]. Sepsis appears to be associated with hepatic glutathione pool reduction and may cause pyroglutamic aciduria[12].

Diagnosis is usually made clinically and there is massive excretion of L-5-oxoproline (up to 1 g/kg/day) in urine. Decreased activity of GSS can be demonstrated in erythrocytes, leukocytes and cultured fibroblasts. Parents show intermediate levels of GSS. Prenatal diagnosis of GSSD is possible by analyzing 5-oxoproline in amniotic fluid, or by enzyme analysis in cultured amniocytes or chorionic villi samples[2].

Treatment involves correction of metabolic acidosis initially by parenteral compounds followed by oral maintenance, antibiotic treatment if there is an infection, and supportive care. In the neonatal period it is important especially to prevent hyperbilirubinemia in order to protect the brain from kernicterus. Anemia often needs to be treated with blood transfusion. As there is increased sensitivity to oxidative stress, such anti-oxidative agents as vitamin E, C, and N-acetylcysteine have been used[13-15]. Drugs avoided in G6PD deficiency should also be restricted in GSSD. Oral administration of glutathione analogues have been shown to increase glutathione concentration in leukocytes and plasma with no effect on 5-oxoproline excretion in urine[13-14]. High doses of α-tocopherol may improve erythrocyte survival in GSS deficient patients[15]. Predicting the prognosis is difficult. It depends on the type of mutation, severity of acidosis, associated bacterial infections and the quality of supportive therapy.

In conclusion, pyroglutamic aciduria (5-oxoprolinuria) should be considered in a newborn with severe metabolic acidosis, hemolytic anemia, hyperbilirubinemia and neurologic deterioration. Excessive urinary 5-oxoproline excretion must be investigated to confirm the clinical diagnosis. Prenatal diagnosis is available and should be offered to parents.

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