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Severe Hypertriglyceridemia in an Infant with Red Cell Pyruvate Kinase Deficiency

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Severe hypertriglyceridemia has been observed in infants with β -thalassemia major, an association termed hypertriglyceridemia-thalassemia syndrome. The pathophysiological basis for this association has remained unclear. We describe 6-month-old American girl with red cell pyruvate kinase (PK) deficiency, failure to thrive, and marked hypertriglyceridemia ($=1500$ mg/dL). The hyperlipidemia resolved with hypertransfusion therapy. At age 18 months she underwent a splenectomy and has remained transfusion-independent with normal serum triglyceride levels. We suggest that severe hemolysis and chronic wasting are probably responsible for the hypertriglyceridemia seen in infants with thalassemia or PK deficiency.

Key words: Hemolytic anemia, Hyperlipidemia, Thalassemia.

Hypertriglyceridemia may be familial or acquired and may reflect increased hepatic

synthesis or decreased catabolism. A variety of diseases have been linked to secondary hypertriglyceridemia, including infection, renal insufficiency, and diabetic ketoacidosis. Hypertriglyceridemia may accompany acute, massive hemolysis(1). With the exception of infants with β -thalassemia major(2-5), however, there are no reports of hypertriglyceridemia associated with chronic hemolytic anemia. We describe an unusual case of severe hypertriglyceridemia in an infant with red cell pyruvate kinase (PK) deficiency and failure to thrive.

Case Report

A 6-month-old girl was referred to our hematology clinic for chronic anemia, jaundice, and poor growth. She was the 3.5 kg term product of a

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normal pregnancy. Jaundice, gall bladder microcalculi and a Coombs' negative, non-spherocytic hemolytic anemia (Hb 11.6 g/dL, reticulocyte count 24%) were noted in the newborn period, but no specific etiology was elucidated. She was exclusively breast fed. Her parents were of Northern/Central European ancestry, and there was no family history of anemia, hyperlipidemia, or consanguinity. Physical examination revealed a small infant who was unable to sit. Weight (6.3 kg) and length (61 cm) were both below the 5th centile for age and sex with a head circumference at the 75th centile. Skin examination revealed pallor and jaundice but no xanthomas. Frontal bossing, a systolic flow murmur, hepatomegaly, and splenomegaly were evident.

A complete blood count showed a WBC $12 \times 10^9/L$, Hb 5.5 g/dL, Hct 16.8%, MCV 115 fL, MCH 33.2 pg, MCHC 33.2 g/dL, reticulocyte count 37%, and platelet count $320 \times 10^9/L$. The peripheral blood smear revealed polychromasia and nucleated erythrocytes. The parents' blood counts and smears were normal. Direct and indirect Coombs' tests, hemoglobin electrophoresis, an osmotic fragility assay, and an isopropanol hemoglobin stability test were all normal. Erythrocyte PK activity was 1.8 IU/g Hb (normal >11.1 IU/g Hb). The diagnosis of PK deficiency was confirmed by sequence analysis of the PK-LR gene, which revealed homozygosity for the G1529A mutation. The serum was grossly lipemic, and the triglyceride level was 1485 mg/dL [normal for breast fed infants of this age is 150 mg/dL(6)]. A repeat fasting serum triglyceride was 1540 mg/dL, and the serum total cholesterol was 145 mg/dL. Other causes of secondary hypertriglyceridemia, including hypothyroidism and diabetes mellitus, were ruled out with appropriate testing. Neither the mother nor father had laboratory evidence of hyperlipidemia. Neither of the patient's two siblings had hypertriglyceridemia or PK deficiency.

The patient was begun on a chronic blood transfusion regimen. Her serum triglyceride level subsequently normalized, and her growth rate improved. At age 18 months, she underwent a laparoscopic splenectomy. She has remained transfusion-independent since that time with a baseline Hb of 8 g/dL (reticulocyte count 45%)

and normal serum cholesterol and triglyceride levels.

Discussion

PK deficiency is the most frequent enzymopathy of the glycolytic pathway causing hereditary non-spherocytic hemolytic anemia. The disease is inherited as an autosomal recessive trait. PK plays a critical role in red cell metabolism because it catalyzes one of the two steps of ATP production during glycolysis. The liver and red cell isoforms of PK are encoded by a single gene (PK-LR) using alternative promoters(7). More than a hundred different PK-LR mutations have been identified; most are missense mutations that encode unstable, rapidly degraded proteins(7). Although mutations in the PK-LR gene may affect both the liver and red cell isozymes, only red cell glycolysis is significantly impaired, because hepatocytes can replenish degraded PK through new synthesis whereas mature erythrocytes cannot.

The PK-LR mutation detected in our patient, G1529A, is the most common mutation among PK deficient individuals from the United States or Northern/Central Europe. This missense mutation results in an enzyme with lower thermostability and increased susceptibility to proteolysis. The residual red cell PK activity in patients homozygous for this mutation has been reported to be 10-25%, and the degree of hemolysis varies from moderate to severe in these individuals(7). It is presumed that environmental, epigenetic, or genetic factors apart from G1529A homozygosity contribute to the variability in the clinical manifestations.

A distinctive presenting feature of this case of PK deficiency was severe hypertriglyceridemia. Secondary hypertriglyceridemia is rarely observed in patients with chronic hemolytic anemia; the only reported cases have been young children with thalassemia major, an association known as hypertriglyceridemia-thalassemia syndrome(2-5). In several of these reports, serum triglyceride levels normalized following red cell transfusion therapy, as was the case in our patient with PK deficiency. Hypertransfusion therapy suppresses production of thalassemic or PK-deficient erythrocytes, thereby reducing the rate of hemolysis. We suggest that this decrease in erythrocyte turnover helps to ameliorate

hypertriglyceridemia. Malnutrition is another factor that may contribute to hypertriglyceridemia in infants with thalassemia or PK deficiency. Tumor necrosis factor- α (TNF- α), interferon- α , and other proinflammatory cytokines associated with wasting syndromes are known to elicit hypertriglyceridemia(8). TNF- α decreases adipose tissue lipoprotein lipase activity, and cytokine-driven hepatic very low density lipoprotein production is thought to contribute to the hypertriglyceridemia that accompanies infection(8). By decreasing energy expenditure on erythropoiesis, transfusion therapy serves to improve the nutritional status of infants with severe hemolytic anemia, which may reduce production of TNF- α and other cytokines that promote hyperlipidemia.

An association between hypertriglyceridemia and acute hemolysis is documented in the medical literature(1), although the pathological basis for this association remains obscure. Intriguingly, erythrocytes from patients with one type of acute hemolysis, Zieve syndrome (jaundice, hyperlipidemia, and transient hemolytic anemia due to alcohol abuse), exhibit acquired PK deficiency(9). PK thermostability is reduced in Zieve syndrome erythrocytes and resembles an oxidized form of the enzyme(10). It has been suggested that acetaldehyde, a metabolite of ethanol, may account for oxidation of PK in this clinical setting. The finding of hypertriglyceridemia in our patient with congenital PK deficiency lends credence to the notion that acquired PK deficiency contributes to the clinical features of Zieve syndrome.

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