Cholestasis and Hepatic Failure in a Neonate: A Case Report of Severe Pyruvate Kinase Deficiency

François Olivier, MDa, Anna Wieckowska, MDb, Bruno Piedboeuf, MD, FRCPa, Fernando Alvarez, MD, FRCPc

abstract

Unexpected severe cholestasis is part of the presentation in some neonates with hemolytic anemia but is usually self-resolving. Here we report the case of a neonate with pyruvate kinase deficiency (PKD) who presented severe hemolytic anemia at birth, characterized by a rapidly progressive and severe cholestasis with normal γ-glutamyl transpeptidase level associated with hepatic failure. After an extensive investigation to rule out contributing conditions explaining the severity of this patient’s clinical presentation, PKD has remained the sole identified etiology. The patient abruptly died of sepsis at 3 months of age before a planned splenectomy and ongoing evaluation for liver transplantation. To the best of our knowledge, only a few similar cases of severe neonatal presentation of PKD complicated with severe hepatic failure and cholestasis have been reported.

Severe neonatal conjugated hyperbilirubinemia and anemia are common features in pyruvate kinase deficiency (PKD), but these aspects are usually not lethal.1–3 Severe cholestasis in newborns with red blood cell (RBC) hemolytic disease, such as iso-immunization, has also been reported but is usually self-resolving.4 Here we report a clinical case of PKD affected by severe cholestasis with normal γ-glutamyl transpeptidase (GGT) level and hepatic failure. After an extensive investigation to rule out contributing conditions explaining the severity of the patient’s clinical presentation, the diagnosis of PKD was retained as the sole possible explanation for the severe cholestasis with nonelevated GGT. To the best of our knowledge, only a few similar cases of severe neonatal presentation of PKD complicated with severe hepatic failure and cholestasis have been reported.

A 36-year-old woman gave birth to a term infant by elective cesarean delivery after an unremarkable pregnancy. The 3.4-kg boy was hypotonic and needed intubation at birth. A first blood count revealed anemia (hemoglobin 48 g/L) and thrombocytopenia (413 × 10⁹ platelets/L). Erythroblasts were elevated at 242/100 white blood cells. At 5 hours of life, lactate dehydrogenase reached 5411 U/L and conjugated bilirubin 57 µmol/L (45% of total bilirubin). The patient developed generalized edema over a few hours.

Before he received transfusions in his first hour of life, an extensive blood workup was done including pyruvate kinase (PK), hexokinase, and glucose-6-phosphate dehydrogenase enzyme, ToRCH serology, and hemoglobin electrophoresis. The child’s blood type was A positive, and the mother’s was O negative. The Coombs and Kleihauer tests were both slightly positive. The investigation eventually revealed low PK enzyme level (0.675 U/g Hb) and elevated hexokinase (0.881 U/g Hb) and glucose-6-phosphate dehydrogenase activity, ToRCH serology, and hemoglobin electrophoresis. The child’s blood type was A positive, and the mother’s was O negative. The Coombs and Kleihauer tests were both slightly positive. The investigation eventually revealed low PK enzyme level (0.675 U/g Hb) and elevated hexokinase (0.881 U/g Hb) and glucose-6-phosphate dehydrogenase activity, ToRCH serology, and hemoglobin electrophoresis.
enzymes levels (4263 U/g Hb), associated with elevated erythroblasts (242/100 white blood cells) and reticulocytosis (337.0 × 10⁹ reticulocytes). These findings were consistent with the diagnosis of PKD. Two pathogenic mutations in the PK-LR gene were found (ie, c.721G>T [p.Glu241*] and c.1195del [p.Ala399Leufs*20]). An exchange transfusion was performed at 12 hours of life, but the patient remained transfusion dependent for hemoglobin for many days. He rapidly developed important splenomegaly and hepatomegaly, associated with hepatic failure marked by asctes, coagulopathy, hypoalbuminemia, and severe cholestasis.

One of the main clinical features in this patient was the extremely severe cholestasis, with a normal GGT of 76 U/L. At 3 months of age, conjugated bilirubin reached 1009 µmol/L (ie, 59.4 mg/dL) and total bilirubin 1058 µmol/L (ie, 62.2 mg/dL). While he was in evaluation for liver transplantation and before a planned splenectomy, he abruptly died of sepsis. Over those 3 months, an additional extensive investigation was done to rule out other concomitant causes for the cholestasis and hepatic failure to explain the severity of the disease (for a summary of the conditions investigated, see Table 1). The liver biopsy showed the presence of bile deposits in the hepatocytes, bile ducts, and canaliculi associated with ductular proliferation and mild extramedullary hemopoiesis, which could be consistent with severe hemolysis secondary to PKD. Otherwise, it did not show features of conditions such as Alagille syndrome, steatosis, glycogenosis, α-1 antitrypsin deficiency, or ductopenia. MRI of the liver was negative for iron accumulation (alloimmune hepatitis of the newborn) and steatosis. Cholangio-MRI did not reveal obstruction of intrahepatic or extrahepatic bile ducts. Inborn errors of bile acid metabolism were not investigated. An autopsy was performed and did not reveal any other explanations for the cholestasis and hepatic failure. Overall, the only causative etiology explaining the clinical picture was PKD.

**DISCUSSION**

PKD is an enzymatic defect of the glycolytic pathway presenting with a variable degree of hemolytic anemia, ranging from fully compensated forms to severe neonatal anemia necessitating exchange transfusions. Hydrops fetalis and death in the neonatal period have been reported in rare cases of PKD. PK is an essential enzyme for the erythrocyte energetic metabolism, because maturation of the RBC is totally dependent on the adenosine triphosphate (ATP) generated by glycolysis, which maintains its integrity and function. ATP deficiency induces irreversible membrane injury, leading to premature erythrocyte destruction in the spleen and liver. It also reduces the erythrocyte capacity to protect itself against destruction from free radicals and oxidative stress.

Several hypotheses have been proposed to explain the cholestasis in severe hemolytic disorders such as intrauterine hemolysis, which might lead to persistent ductal obstruction after birth by blocking canaliculi and intrahepatic bile ducts with bile. Extramedullary hemopoiesis in the liver, secondary to hypoxia, would cause damage to intralobular canaliculi. Continued canalicular and small duct obstruction and intrahepatic cholestasis would contribute to hyperbilirubinemia and progressive liver disease.

Considering PKD itself, some hypotheses could explain this patient’s presentation. One of these is that lack of intracellular ATP, a major feature of PKD, and oxidative stress might have impaired ATP8B1 protein (FIC1) function and thus induced a downregulation of the Farnesoid X receptor, leading to downregulation of the bile salt exporting pump in the liver and upregulation of the apical sodium bile salt transporter in the intestine. Altogether, these molecular interactions result in a bile acid overload in hepatocytes and cholestasis without GGT elevation. ATP8B1 protein is part of a subfamily of P-type ATPs. The mutation of this gene has been ruled out in our case.

Mutations in the PKLR gene found in this patient are coding for liver (PK-L) and RBC (PK-R) isoenzymes. However, clinical symptoms are expected to be limited to RBCs, the hepatic enzyme activity usually being preserved in the hepatocytes or compensated by PK-M2 isoenzyme (dominant fetal form and most adult tissues). Persistent PK-M2 isoenzyme might explain the variability in anemia severity. The first mutation, 721G>T (p.Glu241*),
et al11 stated that clinical ineffective erythropoiesis.14 Zanella hemolysis with a very high degree of resulted in severe peripheral manifestations.13 Clinical studies also described to induce severe clinical disruptive mutations have been proposed to explain the severe anemia due to primary energy synthesis deficiency in hepatocytes (ATP dependent) and increase the susceptibility of the hepatocytes to insults. The resulting liver injury and clinical events during the course of the disease played a major role in the progressive cholestasis in this patient.

ABBREVIATIONS
ATP: adenosine triphosphate
GGT: γ-glutamyl transpeptidase
PK: pyruvate kinase
PKD: pyruvate kinase deficiency
RBC: red blood cell

REFERENCES
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