

# Neonatal Hyperbilirubinemia Caused By Pyruvate Kinase Deficiency

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**Abstract:** We report an infant with neonatal hyperbilirubinemia due to pyruvate kinase deficiency. The initial approach involved rapid evaluation, phototherapy, and close monitoring of serum bilirubin levels. Follow-up included maintenance on folic acid, monitoring blood counts, and educating the parents about the course of pyruvate kinase deficiency, especially aplastic crisis. We suggest that the informed

family practitioner can manage neonatal hyperbilirubinemia and pyruvate kinase deficiency with referrals at critical times to pediatric or surgical specialists. The practitioner must be able to recognize quickly the need for exchange transfusion for severe jaundice and for blood transfusions or splenectomy when significant anemia or aplastic crisis occurs. (J Am Bd Fam Pract 1988; 1:288-90.)

Pyruvate kinase deficiency is an uncommon hemolytic cause of neonatal jaundice. Hemolysis can be caused by isoimmunization, hemoglobinopathies, and defects of red blood cell membranes and enzymes. After glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency is the second most frequent cause of red blood cell enzyme deficiency in North America. Red blood cells metabolize greater than 90 percent of their glucose by means of the Embden-Meyerhof pathway. Pyruvate kinase deficiency interrupts this energy source and commits red blood cells to increased catabolism by the reticuloendothelial system (hemolysis). The neonate is then presented with an increased bilirubin load that results in a high frequency of significant and possibly life-threatening jaundice.

Pyruvate kinase deficiency is an autosomal recessive trait that occurs worldwide among many ethnic groups, but most frequently in those of northeastern European stock.<sup>1</sup> It is also common among the Amish in southeastern Pennsylvania.<sup>2</sup> Our report describes an infant whose father was Hispanic and whose mother had a German surname. There are 0.24 percent pyruvate kinase deficiency carriers in Spain, but the frequency has not been well established in most other ethnic groups.<sup>3</sup>

## Case Report

A 3266 g term female infant was delivered vaginally to a 28-year-old gravida 2, para 1, white mar-

ried woman. Less than 12 hours later, the newborn was jaundiced, and total bilirubin level was 10.8 mg/dL (184.68  $\mu\text{mol/L}$ ). The mother and neonate were blood type O, Rh positive, and the newborn was Coombs negative with hematocrit, 61.9 percent (capillary); reticulocyte count, 17.3 percent; and mean corpuscular volume, 119  $\text{mm}^3$  (119 fL) (normal range, 110–128). Phototherapy was begun immediately, and a repeat bilirubin level approximately 6 hours later was 11.0 mg/dL (188.1  $\mu\text{mol/L}$ ). The following day, the reticulocyte count was 19.7 percent. The pathologist's review of the peripheral smear showed macrocytosis without evidence of spherocytosis, elliptocytosis, or fragmented cells.

A hemolytic work-up yielded the following results: hemoglobin electrophoresis, normal; glucose-6-phosphate dehydrogenase level, high at 6.2 U/10 billion cells (normal range, 1.5–4.5); and osmotic fragility, normal at 24 and 48 hours. The initial pyruvate kinase level was reported as "absent" on qualitative testing, suggesting the diagnosis of pyruvate kinase deficiency.

The bilirubin level peaked at 11.7 mg/dL (200.07  $\mu\text{mol/L}$ ) on the third postpartum day and was 8.5 mg/dL (145.35  $\mu\text{mol/L}$ ) on the fourth postpartum day. Phototherapy was discontinued, and the bilirubin level continued to decline to 5.25 mg/dL (89.78  $\mu\text{mol/L}$ ) on the sixth postpartum day. Serial tests of hemoglobin and hematocrit continued to drop to a low of 16.7 g/dL (167 g/L) and 49.5 percent, respectively, on the sixth postpartum day, when the infant was discharged. A second qualitative pyruvate kinase level to verify the original measure was reported as "present." Table 1 shows the results of quanti-

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**Table 1.** Quantitative Pyruvate Kinase Levels of the Patient and Family Members.

Family Member	Result (in Eu/gm)*	Consistent with
Control	2.1	Normal, Homozygote
Mother	1.0	PK Deficiency, Heterozygote
Father	1.5	PK Deficiency, Heterozygote
Sister	1.7	PK Deficiency, Heterozygote
Patient	0.4	PK Deficiency, Homozygote

\*Normal 1.8–3.6 Eu/gm hemoglobin.

tative pyruvate kinase measures of the patient and other family members that were used to resolve the conflicting findings of the qualitative tests. These data verified the neonate's homozygous status and established the diagnosis of pyruvate kinase deficiency.

The serum bilirubin level was 2.5 mg/dL (42.75  $\mu$ mol/L) on the eighth postpartum day. The infant was maintained on a regimen of 1 milligram of folic acid by mouth daily. The mother was informed of the signs and symptoms of aplastic crisis and the prognosis. Serial hemoglobin and hematocrit levels were stable at approximately 11 g/dL (110 g/L) and 32 percent, respectively, during the next 6 months of follow-up.

### Comment

Clinical jaundice in the neonate less than 24 hours old mandates rapid evaluation to determine cause and the potential need for exchange transfusion. Table 2 defines other criteria that require investigation. The initial evaluation must include a history and physical examination and those laboratory tests listed in Table 3. In this case, a significantly elevated reticulocyte count suggested hemolysis. Exchange transfusion must be considered when the total serum bilirubin level is 10 mg/dL (171  $\mu$ mol/L) at 24 hours, 15 mg/dL (256.5  $\mu$ mol/L) at 48 hours, or 20 mg/dL (342  $\mu$ mol/L) at any age. Anemia or a rise in the serum bilirubin level by more than 0.5 mg/dL/hour (8.55  $\mu$ mol/L/hour) suggests brisk hemolysis that requires exchange transfusion.

Exchange transfusion was not elected in this case because the rate of rise of the bilirubin level clearly

reached a plateau. Physicians must be cautious and measure bilirubin levels frequently to verify such a plateau. When exchange transfusion is indicated, reliance on phototherapy may delay inappropriately the decision for such definitive therapy.

There are several periods of time when intervention may be required in the management of pyruvate kinase deficiency. During the neonatal period, phototherapy or exchange transfusion may be necessary to control hyperbilirubinemia. The neonate should also be given folic acid, 1 milligram daily by mouth to sustain hematopoiesis.<sup>6</sup> Hemoglobin and hematocrit should be monitored. Parents should be educated about the variability of prognosis, which ranges from mild, asymptomatic chronic anemia to life-threatening anemia. The clinical course cannot be predicted easily because of variable degrees of compensation<sup>1</sup> and because the course does not correlate well with enzymatic activity.<sup>7</sup>

During the first 6 months of life, severe anemia may require repeated transfusions. The physician and parents should discuss warning signs of aplastic crisis, including pallor and fatigue in conjunction with a viral illness. During childhood years, most patients tolerate the chronic anemia well, although some may require transfusion occasionally. The increased tolerance for anemia is due to increased 2,3 diphosphoglycerate, which reduces the affinity of hemoglobin for oxygen and produces a favorable shift in the oxygen-hemoglobin dissociation curve and increased tissue unloading of oxygen. Evaluation for transfusions should be made on the basis of evidence for cardiac decompensation. The child should be continued on folic acid at the same dose that is prescribed for infants.<sup>6</sup> Splenectomy may eventually become necessary to decrease red blood cell breakdown. After childhood, pyruvate kinase deficiency compli-

**Table 2.** Criteria That Necessitate Investigation of Neonatal Jaundice.<sup>4,5</sup>

Clinical jaundice in the first 24 hours of life
Total serum bilirubin level greater than 12 mg/dL (205.2 $\mu$ mol/L) in bottle-fed or 15 mg/dL (256.5 $\mu$ mol/L) in breast-fed infants
Total serum bilirubin level rising by more than 5 mg/dL/day (85.5 $\mu$ mol/L/day)
Direct serum bilirubin level greater than 1.5 mg/dL (25.65 $\mu$ mol/L)
Clinical jaundice longer than 1 week in full-term or 2 weeks in premature infants

**Table 3.** *Basic Laboratory Investigation for Suspected Pathological Neonatal Jaundice.*

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Fractionated bilirubin
Hemoglobin or hematocrit
Reticulocyte count
Peripheral blood smear for red cell morphology
Blood type, Rh (mother and infant)
Direct Coombs test

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cates pregnancy as a result of increased hemolysis due to an unknown mechanism.<sup>8</sup> As with any chronic hemolytic process, pyruvate kinase deficiency may predispose to early gallbladder disease.<sup>7</sup>

### Conclusion

This case report has illustrated the approach, management, and follow-up of a patient with early-onset neonatal jaundice due to pyruvate kinase deficiency. The essentials, in this instance, included assessing and controlling hyperbilirubinemia in the neonatal period, maintenance on folic acid, monitoring hematocrit, and educating parents. Consultations for exchange transfusion for hyperbilirubinemia and later for transfusion or splenectomy for anemia may be required. While most jaundiced neonates are not in jeopardy from hyperbilirubinemia, family physicians who are

aware of the rarer, more serious, and treatable causes such as pyruvate kinase deficiency can manage them accurately and expeditiously.

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