

“Spleen Baby”: A Case Presentation of Pyruvate Kinase Deficiency in an Amish Neonate

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The purpose of this article is to educate nurses about pyruvate kinase deficiency, its prevalence, diagnosis, clinical manifestations, and nursing considerations when caring for an infant with this deficiency.

ABSTRACT

Pyruvate kinase deficiency (PKD) is an autosomal recessive trait in which there is a lack of the enzyme pyruvate kinase. Because of this lack of pyruvate kinase, red blood cells are broken down more freely, thereby causing hemolytic anemia. The degree to which the hemolysis occurs varies from mild-to-severe to life-threatening neonatal anemia and kernicterus necessitating an exchange transfusion. The purpose of this article is to introduce the reader to PKD through a case presentation of severe hyperbilirubinemia necessitating the need for an exchange transfusion. This article also includes the prevalence, clinical features and diagnosis, treatment, and nursing considerations in caring for this type of infant.

Keywords: pyruvate kinase deficiency; hyperbilirubinemia; exchange transfusion; infant

“WE CALL THEM SPLEEN BABIES.” This was the comment made by the Amish grandmother regarding her familiarity with pyruvate kinase deficiency (PKD) that had been diagnosed once again in her family, this time in her granddaughter. Despite being a medical facility located in the heart of Lancaster County, among the Old Order Amish and Mennonite populations, the Level III NICU at Women and Babies Hospital of Lancaster General Health had never admitted a neonate with such a high bilirubin level as it did with Baby Girl P, whose total bilirubin on admission was 35.4 mg/dL at 63 hours of age. If left untreated, such significant hyperbilirubinemia can result in acute bilirubin encephalopathy (ABE). This article outlines this infant's case of hyperbilirubinemia, as well as the discovery of PKD, and reviews clinical nursing considerations for the NICU team caring for this infant.

CASE PRESENTATION

Baby Girl P was born via spontaneous vaginal delivery at a local birthing center to

a G3P2 A+ Amish woman with an unknown group B streptococcus status. The prenatal course was uncomplicated with only a history of a yeast infection during the pregnancy. Baby Girl P was born at 39 and 0/7 weeks gestation and was average for gestational age with a birth weight of 3,900 g. Baby Girl P cried immediately after birth. Apgar scores were not recorded. Jaundice was noted at delivery. However, there is no documentation of a bilirubin level being drawn at the birthing center. From the time of birth until admission, normal activity was reported by the family. The mother was breastfeeding and noted that the infant did have an issue with the latch. The baby was being supplemented with formula but continued to feed poorly. No phenylketonuria was done prior to her admission to the NICU. Immediate family history was nonspecific for any medical issues. Two older siblings, ages 1 and 2 years, were healthy. Family history was significant for PKD in an uncle.

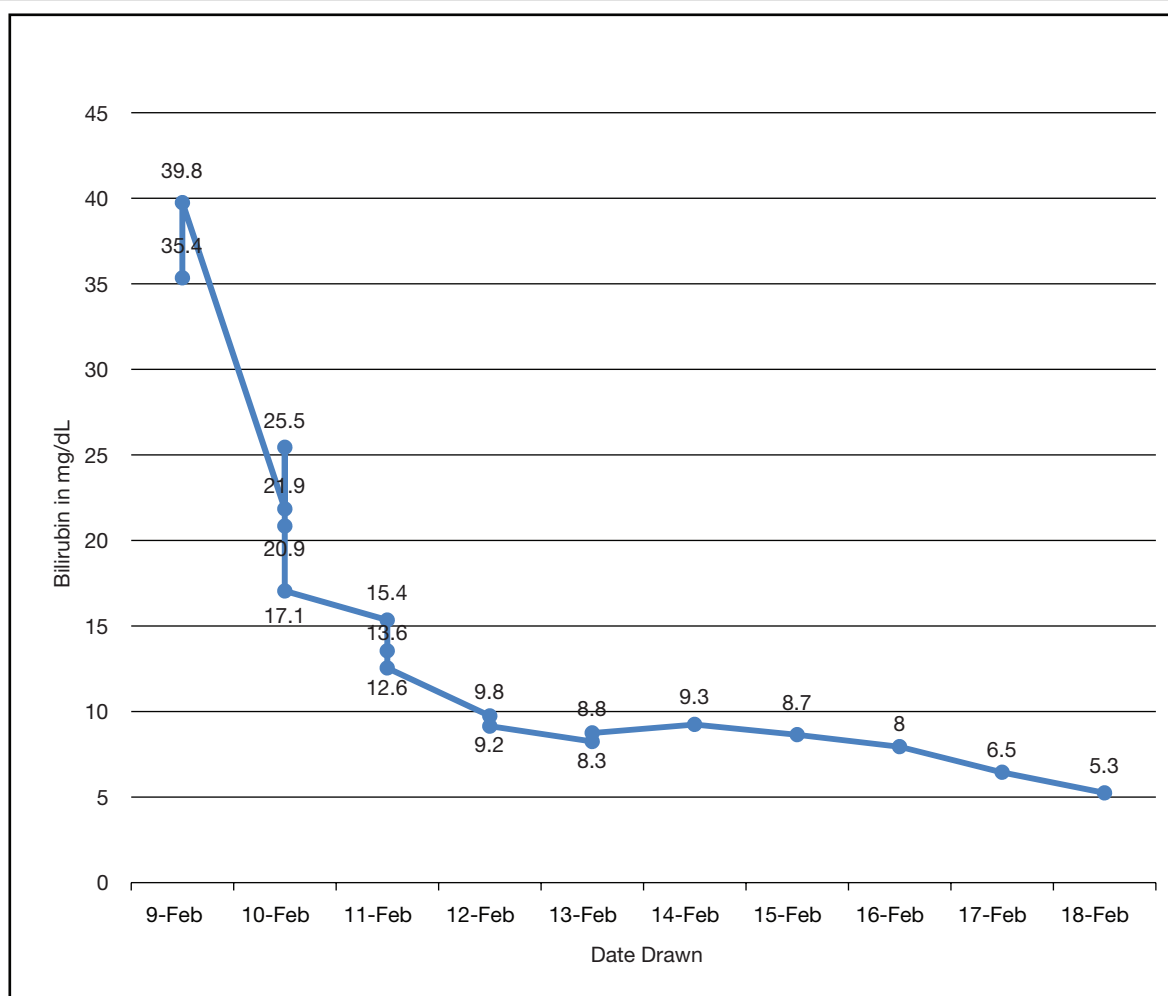
The infant was transported to the Level III NICU at approximately 63 hours of life because of worsening jaundice. Admission diagnosis ruled out sepsis and

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hyperbilirubinemia. Upon admission to the NICU, assessment findings noted shrill cry, poor skin turgor, poor feeding, lethargy, decreased urine output, and obvious jaundice. Infant was placed on nasal cannula 1 L flow at 25 percent oxygen because of mild respiratory distress. An umbilical venous catheter was successfully placed, and intravenous fluids were started at 185 mL/kg/day. Infant was NPO. Admission laboratory tests included blood culture, electrolytes, and calcium, which were normal, complete blood count (CBC), and a type and cross for blood typing. Initial CBC result once admitted to the NICU was as follows: white blood cell (WBC), 11.5; hemoglobin (Hgb), 19.9; hematocrit (Hct), 47.6; platelet count, 217,000; neutrophils, 54; lymphocytes, 23; monocytes, 15; eosinophils, 7; and nucleated red blood cells, 2. Further laboratory studies included a glucose-6-phosphate dehydrogenase (G6PD) of 14.9 (normal is 5.5–50.5 units/g of Hgb), and an alpha-antitrypsin of 129 (normal is 100–300 mg/dL). In addition to the CBC, a blood smear was performed, and the enzyme activity rate of the pyruvate kinase enzyme was tested. Baby

Girl P's enzyme level was low, thereby establishing the diagnosis of PKD. A bilirubin level drawn with the admission labs revealed a critical bilirubin level of 39.8 mg/dL. Direct bilirubin level was 1.2 mg/dL. Infant blood type was A+. Infant was prepared for an emergent exchange transfusion based on the admitting bilirubin level and noted admission assessment. Antibiotics were started, including ampicillin and cefotaxime, but no infectious disease process was noted. Laboratory results, physical examination, and clinical course as described to this point were all consistent with ABE. Blood culture was negative after 48 hours, and antibiotics were discontinued. Following the exchange transfusion, the bilirubin decreased to 21.9 mg/dL. The infant was placed under three phototherapy lights. The morning following the exchange, the bilirubin level increased to 25.5 mg/dL and a bili-blanket was added to help drive the bilirubin level down. Bilirubin levels were followed closely and drawn every six hours and slowly decreased over the next week (Figure 1). Baby Girl P developed seizures on Day 7 of life, which were attributed to ABE. A computed tomography scan

FIGURE 1 ■ Baby Girl P's trending bilirubin level during hospitalization.



was normal. An electroencephalogram (EEG) was also performed which showed diffuse cerebral dysfunction as well as epileptiform discharges, emanating independently from left to right hemisphere as well as subclinical electrographic seizures emanating from the frontotemporal region. Infant was given a loading dose of phenobarbital and maintenance dose thereafter. A repeat EEG on Day 10 of life revealed no further seizure activity. The nasal cannula and umbilical venous catheter were discontinued several days prior to discharge. Infant was discharged home on full breastfeeding, folic acid 1 mg, and phenobarbital daily. She will continue to be followed by child neurology and the Clinic for Special Children as her primary care physician. On the day of discharge, Baby Girl P's bilirubin was 5.3 mg/dL (see Figure 1 for her trends in bilirubin level during her hospitalization). Baby Girl P required only one double-volume (500 mL) exchange transfusion of packed red blood cells (PRBCs) on Day 1 of her hospitalization because of her elevated bilirubin level. There was no evidence of ongoing hemolysis, with decreasing Hct/Hgb values in her remaining days in the NICU.

PATHOPHYSIOLOGY OF HYPERBILIRUBINEMIA

Jaundice, or *icterus*, is a term used to describe a yellowish hue to the skin and sclera that is caused by excess bilirubin in the blood. Bilirubin is a waste product that remains in the bloodstream after iron is removed from the Hgb, which is released by the degradation of the red blood cell. One gram of Hgb yields 35 mg of bilirubin.¹ Bilirubin is the by-product of the breakdown of heme, the oxygen-carrying capability of the red blood cell.² Elevated bilirubin levels saturate the tissues, thereby giving the skin a yellow appearance.³ About 80–90 percent of bilirubin is produced during the breakdown of Hgb from red blood cells or ineffective erythropoiesis. The remaining 10–20 percent is resultant from the breakdown of other heme-containing proteins, such as cytochromes and catalase.⁴ Bilirubin is formed in two steps:

1. The enzyme heme oxygenase or HO, located in the liver, spleen, and all nucleated cells catalyzes the breakdown of heme, resulting in the formation of equimolar quantities of carbon monoxide (CO) and biliverdin.
2. Biliverdin is then converted by the enzyme biliverdin reductase.⁴

PREVALENCE

Pyruvate kinase is an enzyme within the body that affects the survival of red blood cells and was first identified by Valentine and colleagues in 1961.⁵ The PKD is the second most common cause of hereditary autosomal recessive hemolytic anemia. It is caused by enzyme aberration of the glycolytic pathway and is often associated with continuing anemia of varying severity; only G6PD, as it is commonly known, is more common.⁵ The prevalence of PKD is

estimated to be approximately 1 case per 20,000 live births in the United States, with a higher incidence among the Amish communities of Pennsylvania.^{6,7} Although the rationale for this is unclear, it may be related to race-related demographics.⁶

PATHOPHYSIOLOGY OF PYRUVATE KINASE DEFICIENCY

PKD is the most common cause of congenital nonspherocytic chronic anemia and is the result of an autosomal recessive erythrocyte enzyme defect.⁸ The mother and father are carriers and usually do not display any signs or symptoms of the deficiency.⁷ People with PKD have an alteration in the PKLR gene, which is present in the liver and in red blood cells. This gene provides instructions for producing pyruvate kinase, which is involved in glycolysis, the breakdown of glucose to produce energy. Specifically, pyruvate kinase is involved in the last step of the glycolytic pathway. In this step, a cluster of oxygen and phosphorus atoms (a phosphate group) is moved from the molecule phosphoenolpyruvate to adenosine diphosphate (ADP), resulting in the formation of pyruvate and adenosine triphosphate (ATP). The ATP is the erythrocyte's main energy source (Figure 2).⁹

A deficiency of pyruvate kinase in the blood causes the red blood cells to break down more easily as a result of dehydration at cellular level. Because of the unavailability of adequate ATP, all active processes in the red blood cell come to a halt. Sodium potassium ATPase pumps are the first to stop, and, because the cell membrane is more permeable to potassium than sodium, potassium leaks out. Intercellular fluid becomes hypertonic, and water moves down its concentration gradient out of the cells. Finally, cells shrink and die.¹⁰

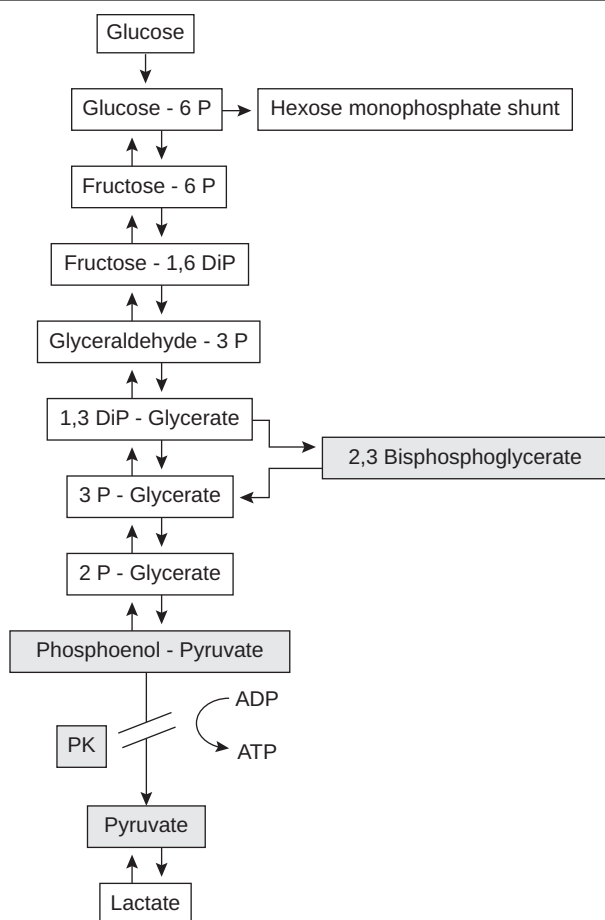
CLINICAL PRESENTATION

In PKD, the major characteristic as evidenced by our case study is hyperbilirubinemia at birth. In this case, the hyperbilirubinemia is caused by hemolysis of red blood cells.

In red blood cells, glycolysis is the only method available to produce energy. Without the proper amount of energy, the red blood cells do not function normally and have a shortened life span.¹¹ The breakdown of erythrocytes leads to the release of bilirubin and to the development of anemia. Anemia causes symptoms such as fatigue, pallor, shortness of breath, and tachycardia. A neonate with PKD may develop chronic hemolytic anemia. Hemolytic anemia develops when the red blood cells are destroyed and eliminated from the bloodstream in large numbers. In hemolytic anemia, the bone marrow cannot produce enough red blood cells to replace those being destroyed and meet the body's needs.¹² As erythrocytes are broken down, bilirubin production increases, leading to potentially critical hyperbilirubinemia.

The mechanism for hemolysis in PKD is not completely understood. Despite the fact that the defect in ATP generation contributes to hemolysis, it is not an adequate

FIGURE 2 ■ Glycolysis pathway.



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explanation because ATP deficiency is difficult to demonstrate in some of the affected patients.⁸ In addition, other disorders with more severe degrees of ATP deficiency are not associated with significant hemolysis.⁸ It has been purported that the mechanism of hemolysis in PKD is comparable to the yet-to-be-determined unexplained destruction of young red blood cells as described in individuals descending from high altitudes, a process termed *neocytolysis*.⁸ It is conceivable that the impaired mitochondrial autophagy (defined as the self-digestion of a cell through the action of enzymes originating in the same cell), leading to increased production of reactive oxygen species (ROS), may be involved; however, this remains speculation at this time.⁸ The ROS are chemically reactive molecules containing oxygen. Examples include oxygen ions and peroxides. The ROS form as a natural by-product of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis.¹³

The clinical severity of pyruvate kinase deficient hemolytic anemia varies from mild to severe; however, in more severe cases, a PRBC transfusion or splenectomy may be necessary. Most infants are diagnosed in infancy or early childhood and do not require medical intervention. In addition to jaundice, signs and symptoms in the neonate may include mild to severe normochromic and normocytic anemia, mild to moderate splenomegaly, reticulocytosis, failure to thrive, frontal bossing, and growth delay.¹⁰ In most of the severe cases, the neonate will die in utero with anemia. Newborns may require an exchange transfusion because of the elevated bilirubin level of the blood, but, afterward, the severity of the pyruvate kinase deficient hemolytic anemia is moderate.¹⁴ In some instances, diagnosis occurs in early adulthood. These adults display chronic hemolysis, jaundice, splenomegaly, or cholelithiasis and may be diagnosed when they are seen by their primary care physician for some other medical issue and evaluation.¹⁴

Diagnosis of PKD is suggested by family history, birth history, and events in the first days of life, as well as results of a CBC and differential, reticulocyte count, bilirubin level, and peripheral blood smear result.¹⁰

TREATMENT APPROACHES FOR CONSIDERATION

The treatment of PKD is primarily supportive in nature, when the disorder becomes evident, which may occur in early infancy or throughout childhood.⁸ Several treatment options are available for the patient diagnosed with PKD, which include but are not limited to the following:

- Intrauterine transfusion for severe anemia with hydrops fetalis
- Phototherapy and/or exchange transfusion for hyperbilirubinemia in the neonatal period
- Frequent red cell transfusions throughout infancy and early adulthood to treat anemia caused by the disease
- Splenectomy, which is only considered in cases of severe anemia; removal of the spleen does not eliminate hemolysis or improve mild anemia but can reduce severe anemia and decreases the need for blood transfusions, or, in some cases, can eliminate the need
- Folic acid supplementation; this B vitamin, normally found in foods such as dried beans, peas, lentils, oranges, whole-wheat products, liver, asparagus, beets, broccoli, brussels sprouts, and spinach, helps the body produce and maintain new cells and also helps prevent changes to DNA that may lead to cancer; folic acid is used to treat folic acid deficiency and certain types of anemia¹⁵
- Cell transplantation is a consideration, but success is limited⁸⁻¹⁰

Baby Girl P's elevated bilirubin level on admission necessitated an emergent exchange transfusion. This was accomplished several hours after admission to the NICU. She had a double-volume exchange done and was immediately placed

under triple phototherapy. Scheduled bilirubin levels were drawn to follow bilirubin trends. Phototherapy was used for the conversion of bilirubin molecules in the body into water-soluble isomers that can be excreted by the body.¹⁶ Breastfeeding was well established prior to her discharge, and she was prescribed folic acid supplementation daily.

NURSING CONSIDERATIONS

Nursing considerations for taking care of this type of patient are also primarily supportive. They include the following:

- Intravenous infusion as ordered
- Medications as ordered
- Phototherapy
- Laboratory draws as ordered

When caring for an infant with PKD, the most important goals for management include prevention of bilirubin-induced neurologic dysfunction (BIND) and ABE as well as the prevention of anemia. Nurses can follow laboratory results of a CBC and Hct, making sure those values are within an acceptable range for the patient.

Bilirubin-Induced Neurologic Dysfunction

Severe neonatal hyperbilirubinemia is defined as a serum bilirubin >25 mg/dL. It is associated with an increased risk of BIND, which occurs when bilirubin crosses the blood-brain barrier and binds to the brain tissue. At this threshold, unconjugated bilirubin can cause cell death by apoptosis and/or necrosis. BIND presents with a range of subtle neurologic findings and sequelae, which can manifest as disorders in vision, hearing, gait, speech, cognition, and language.¹⁷

Acute Bilirubin Encephalopathy

Major clinical signs and symptoms of ABE include the following:

Initial phase:

- Slight stupor (lethargic, sleepy), but arousable
- Slight hypotonia, paucity of movement
- Poor sucking, slightly high-pitched cry

Intermediate phase:

- Moderate stupor, irritability
- Tone variable, usually increased; some have retrocollis, opisthotonos
- Minimal feeding, high-pitched cry
- Febrile
- Jittery
- Difficult to console

Advanced phase:

- Deep stupor or coma
- Tone usually increased; some have retrocollis, opisthotonos
- No feeding
- Apnea
- Fever
- Seizures

- Inconsolable cry, or may be weak or absent
- Death because of respiratory failure or intractable seizures^{17,18}

Kernicterus

Kernicterus means *yellow kern*, a term indicating the most commonly affected region of the brain, and the kern is located in the nuclear region of the brain. The term refers to an anatomic diagnosis made at autopsy based on the characteristic pattern of staining that is found in babies who had an elevated bilirubin level before they died.¹⁹ In the past, kernicterus has been used interchangeably with both acute and chronic findings of bilirubin encephalopathy, but now BIND and ABE are the terms used to identify the clinical manifestations of hyperbilirubinemia, and kernicterus is used to identify an anatomic diagnosis (usually at autopsy).

PROGNOSIS

Usually, the prognosis of PKD is excellent if bilirubin levels do not lead to the development of ABE. The PKD has various morbidities. Some patients may present with mild, compensated, chronic hemolytic anemia that does not require medical intervention; others present with a severe hemolytic anemia that, in most cases, requires only transfusions during childhood. Morbidity and mortality are related to the severity of the disease and associated complications.¹⁰ During her hospitalization, Baby Girl P presented with signs and symptoms of acute brain encephalopathy from which she later recovered, indicating a reversal of ABE.

CONCLUSION

Based on research and gaining a better understanding of PKD, one can only assume that the comment made by Baby Girl P's grandmother about a "spleen baby" comes from her understanding of the disease process of PKD, its effect on the body, and its treatment. Maybe the uncle had his spleen removed. The comment was not further investigated, and the grandmother never offered a reason behind the designated title. The PKD is an inherited disorder that affects the red blood cells, thereby causing chronic hemolytic anemia. Complications associated with this anemia can range from mild to severe. Severe cases can be life threatening in infancy, requiring transfusions and close monitoring for survival. An exchange transfusion is indicated when the level of hyperbilirubinemia cannot be controlled with the use of phototherapy alone.²⁰ In a case where bilirubin is at a dangerous level, an exchange transfusion is warranted. Because of the therapies that are available today, exchange transfusions are rarely performed, but, on occasion, one may be done emergently. For the client diagnosed with PKD, the prognosis is excellent. It is important for NICU nurses caring for this type of patient to understand the underlying rationale for the hyperbilirubinemia such as PKD, as was presented in the

case study, or other underlying issues. Second, performing ongoing systemic assessments during the neonatal period for developing increasing bilirubin levels and treating appropriately is necessary as well to prevent hyperbilirubinemia and identifying potential complications of hyperbilirubinemia such as BIND and ABE. Third, jaundice in the newborn is a common occurrence. It is important to follow established hospital protocol for evaluating bilirubin levels in neonates as well as encouraging frequent breastfeeding with supplementation, if necessary, and phototherapy. Close follow-up with the primary care physician and treatment as indicated are essential in providing the best care possible for infants with an elevated bilirubin level.

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