Pyruvate kinase deficiency is an inherited metabolic disorder characterized by a deficiency in the enzyme "pyruvate kinase" causing hemolytic anemia. It is more severe in early presentation, and it has no sex predilection. The majority of the cases occur because of genetic mutation while some may be caused by diseases such as leukemia and refractory sideroblastic anemia. PKD presents with severe anemia, lethargy, fatigue, failure to thrive and associated complications such as heart failure and liver failure. Diagnosis of the disease is mainly done by blood studies that show normocytic normochromic anemia with increased reticulocytes without blood loss. The treatment modalities are mainly conservative involving blood transfusion, folic acid supplements and chelation of deposited iron.

Definition

Pyruvate kinase deficiency is an inherited metabolic disorder of the enzyme “pyruvate kinase” that causes enzyme-deficient hemolytic anemia by affecting the survival of red blood cells. Inheritance is mainly via autosomal recessive pattern, but autosomal dominant patterns have also been seen.

Epidemiology of Pyruvate Kinase Deficiency

Pyruvate kinase deficiency has a worldwide distribution, although it is more prevalent in Northern Europe, Japan and China. The global incidence is around five cases per population of one million. In the United States, the incidence is 1 in 20 000, and
most cases are identified via prenatal genetic screening. The estimated prevalence of the
disease is 51 per million population. The frequency of the disease is higher among the
Pennsylvania Amish and Romani communities.

The disease mainly affects children but may also be evident in adolescents and adults.
Diagnosis is mostly conducted during childhood after the child suffers symptomatic
anemia. Neonatal and intrauterine occurrences are associated with severe disease and
high mortality rates.

The disease has no sex predilection.

**Classification and Etiology of Pyruvate Kinase Deficiency**

Pyruvate kinase deficiency can either be genetic or acquired, a factor that gives the
classification of the disease into:

**Hereditary variant**

Hallmark is the presence of genetic mutations in the PK gene that encodes pyruvate
kinase isoenzymes. Chromosome 15q22 encodes the muscular M1 and M2 isoenzymes,
while the gene encoding isoenzymes L and R is in chromosome 1q21.

**Acquired pyruvate kinase deficiency**

It’s observed in the setting of medical conditions such as leukemia and refractory
sideroblastic anemia or after chemotherapy.

The disease can also be classified based on the severity of the anemia into:

1. **Mild**
2. **Moderate**
3. **Severe pyruvate kinase deficiency**

**Pathophysiology of Pyruvate Kinase Deficiency**

Deficiency in pyruvate kinase may be secondary to a genetic mutation or may present
from an acquired cause. The pyruvate kinase enzyme is **required for conversion of
phosphoenolpyruvate into pyruvate and ATP**. This is the final step in the Embden-
Meyerhof pathway which supplies erythrocytes with energy and ATP for cell membrane
stability.

Lack of this enzyme, therefore, hinders the completion of the reaction with the effect
being:

- Increase in the level of dangerous precursors;
- Decrease in a number of products such as pyruvate, ATP and lactate.

The cell responds by seeking alternative sources of energy, since the primary pathway
has been compromised, and **immediately activates the oxidative phosphorylation
pathway**. This is, however, a temporary measure. In periods of hypoxia, such as stressful
situations or during infections, the pathway is similarly compromised.

The effects of a decrease in ATP are felt before the body initiates any response. ATP is
needed in maintaining membrane stability. Its deficiency will lead to **uncontrolled loss of water and potassium out of the cell.** This causes shrinkage, dehydration of the cell and eventually death of the cell. Destruction of multiple red blood cells is countered with an increase in the oxygen carrying capacity to avoid development of symptoms. This is achieved by increasing the 2,3-DPG content of existing erythrocytes.

Continued destruction of red blood cells leads to **anemia that manifests as easy fatigability**, lethargy and other symptoms. Absorption of the resultant hemoglobin leads to hemochromatosis and eventually liver failure and death, especially in neonates.

**Clinical Features of Pyruvate Kinase Deficiency**

Presentation of the symptoms can be highly variable. The condition can present as **different levels of severity depending upon A) heterozygous or homozygous status** and B) the genes affecting specific isoenzymes. If it’s more severe, death tends to occur in utero.

Most of the affected neonates are diagnosed at birth. Very few only present the condition later, during times of stress such as acute infections.

**Symptoms**

- Family history says one parent may be suffering from a similar disease.
- Generalized delay in growth or failure to thrive.
- Fatigue and lethargy due to anemia.
- History of multiple transfusions indicates symptomatic treatment of anemia that doesn’t resolve.

**Signs**

**General signs:**

- Frontal bossing
- Pallor due to secondary anemia. Mild to severe chronic hemolytic anemia with an excess of young red blood cells (reticulocytosis) usually occurs.
- Fever
- In infants, failure to thrive (not gaining weight and growing as expected) causes symmetrical growth delay.
- Musculoskeletal dysfunction
- Weakness
- Hypotonia

**Gastrointestinal system signs:**

- GI dysfunction
- Splenomegaly
- Gallstones
- Jaundice

**Neurological signs**

- Kernicterus — neurologic condition affecting the brain

**Cardiovascular signs**
Tachycardia

Diagnostic Workup for Pyruvate Kinase Deficiency

The diagnostic investigations include:

- Complete blood count (CBC):
  - It indicates normocytic normochromic anemia with no history of blood loss.
  - The reticulocyte count is typically elevated.

Peripheral smear:

- It is obtained from the blood and confirms the finding of normocytic normochromic anemia; reticulocytes can be seen.
- Direct enzyme assays should be carried out to demonstrate pyruvate kinase deficiency in erythrocytes.
- Genetic testing shows mutations in the various pyruvate kinase genes.

Important investigations to rule out differential diagnosis include:

- Coombs test to rule out immune hemolysis that is common in neonates and would have a similar presentation.
- Serum bilirubin studies should be done to rule out gallbladder abnormalities. The test results indicate a rise in indirect bilirubin with no pathologies of the biliary system.

PK enzyme activity testing should be considered if any of the following are present:

- Congenital, chronic, non-spherocytic hemolytic anemia without evidence of immune mediated hemolysis, hemoglobin abnormality, or glucose-6-phosphate dehydrogenase deficiency.
- The child is transfusion dependent since birth without an obvious cause.
- Unexplained severe neonatal hyperbilirubinemia.
- An elevated reticulocytes cell count after splenectomy.
- Family history of PK deficiency.

When to perform molecular PK-LR analysis:

- Molecular PK-LR analysis is the confirmatory test of PK deficiency.
- It should be performed in any patient with a low or low-normal PK activity that is associated with increased activity of other red-blood-cell enzymes.
- It should be also performed in any patient who is transfusion-dependent and who had a PK enzyme activity test that was revealed to be normal.
- Finally, it is recommended in any patient with documented low PK activity in the absence of family history of PK deficiency.

Differential Diagnosis of Pyruvate Kinase Deficiency

| Glucose-6-phosphatase deficiency | An enzymatic disorder in close association with PKD which lacks hemolysis after exposure to oxidants. It involves the glutathione pathway. |
Neonatal jaundice

The common presentation of jaundice. It can be distinguished by the lack of biliary system abnormalities in PKD and morphological changes of blood cells.

Immune hemolysis

It's considered in a neonate with jaundice and anemia. Coombs test is positive.

Hereditary spherocytosis

Appreciated cause of severe hemolysis. The presence of spherocytes and a positive osmotic fragility test.

Glutathione synthase deficiency

A disease of the glutathione pathway and thus lacks hemolysis after exposure to oxidants.

### Treatment of Pyruvate Kinase Deficiency

Treatment is predominantly supportive as the available curative measures have a very high risk that outweighs the benefit of attempting them.

The most important step is to control the associated anemia and its complications. **This can be done by:**

#### Simple transfusion

Transfusion with packed red blood cells is done in children and adolescents, although the intervention is associated with dangerous side effects in neonates.

Severe anemia causing fetal hydrops in utero may be rescued via intrauterine transfusion.

#### Supplemental folic acid and vitamins

The increased hematopoiesis is detrimental to the existing reserve of folic acid and other vitamins needed for this process. Thus supplemental folic acid and vitamins help to maintain the production of erythrocytes.

#### Chelation therapy

These patients have a high turnover rate of iron from erythrocytes. The high hemolytic rate coupled with multiple massive transfusions leads to hemochromatosis. Therefore, chelation therapy is important to remove the excess iron and prevent the long-term hemochromatosis complications.

#### Phototherapy

It should be administered to neonates with hyperbilirubinemia and jaundice to avoid adverse effects of brain damage.

#### Splenectomy

In cases where the above interventions are not successful, then splenectomy is the next step of management. It reduces hemolysis and the excessive red blood cell destruction but does not cure the disease. Therefore, it is reserved for patients with severe anemia and/or symptomatic spleen enlargement. After splenectomy, the hemoglobin level rises by 1-3 g/dl.

#### Complications

Although splenectomy causes improvement in the symptoms and the overall condition
due to decreased red blood cell hemolysis, it should be delayed for as long as possible
due to the fatal complications that set in once it’s done, such as increased susceptibility
to capsulated infection such as pneumococcal infections.

**Suitable age**

Splenectomy should be done when the child is at least 3 years old since beyond this age
pneumococcal infections are not so common as compared to before this age.

**Preparation**

Preparation and care for splenectomy involve administration of preoperative antibiotics
and postoperative penicillin for 2 or 3 years after the procedure.

Moreover, several vaccines must be administered before the procedure, i.e.,
pneumococcal vaccine and Influenza Type B vaccine.

Advancements in the management of these children include attempts to cure the disease
that has been successful although the risk associated with some is greater than the
benefit. They include:

- Gene therapy
- Administration of pyruvate kinase stimulating drugs
- Allogeneic stem cell transplantation. Stem cell transplant is reserved for
  patients who may not benefit from splenectomy.

**Complications of Pyruvate Kinase Deficiency**

Iron overload is seen due to the high hemolytic rate and multiple transfusions.
Accumulation of iron in the liver may lead to liver cirrhosis and failure.

Infections, mostly pneumococcal infections, are common after splenectomy. Viral
infections are associated with blood transfusion.

**Severe anemia**

Acute stress factors can cause sudden worsening of anemia, e.g., viral infections
especially parvovirus B19), because of transient decrease in production of RBCs (i.e.,
aplastic crisis).

Heart failure could result from sudden and severe anemia or because of ischemia to the
heart.

Cholecystolithiasis is common in children with severe anemia, usually in the early years.

A common risk shared by all diseases requiring repeated blood transfusions is contracting
certain infections (e.g., HIV, HCV) that are not well detected.

**Course and Prognosis for Pyruvate Kinase Deficiency**

Morbidity in children and infants with pyruvate kinase deficiency is usually the result of:

- **Severe anemia**
- **Hyperbilirubinemia**
- Development of gallstones
- Infections post splenectomy such as pneumococcal diseases

Morbidity may also be seen with adverse effects associated with the management of these conditions. The severity varies with age, and it is more severe in the very young. Pyruvate kinase deficiency is associated with intra-uterine deaths due to liver failure.

References


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