Pyruvate kinase deficiency (PKD) is the most common enzyme abnormality of the glycolytic pathway. As with other hereditary red cell defects, malarial resistance is found in patients with PKD.¹

**Pathogenesis**

Pyruvate kinase deficiency (PKD) is a defect in the Embden-Meyerhof pathway of anaerobic glycolysis. Pyruvate kinase (PK) catalyses the conversion of phosphoenolpyruvate to pyruvate. This is one of two glycolytic reactions in the red cell that produce adenosine triphosphate (ATP).

- The mismatch between the red cell’s energy requirements and its ATP-generating capacity damages the membrane irreversibly, distorting and dehydrating the cell and affecting the rigidity. As a damaged cell, it is destroyed prematurely by the spleen and liver.
- The low levels of ATP then have a sequential effect on intracellular electrolyte concentration as ATP powers the cation pump.
- Intermediates proximal to the PK defect influence erythrocyte function. Increases in 2,3-diphosphoglycerate (2,3-DPG) levels result in a right shift in the haemoglobin-oxygen dissociation curve. This means that affected individuals have an increased capacity to release oxygen into the tissues, enhancing oxygen delivery.²

**Epidemiology**

Pyruvate kinase deficiency (PKD) occurs worldwide but most cases have been reported in northern Europe, Japan and the USA. Many cases are found in the Amish population of Pennsylvania.

The prevalence is estimated at 51 cases per million by gene frequency studies but the observed prevalence in one northern England region was found to be 3.3 cases per million.³

**Risk factors**

- Family history consistent with autosomal recessive inheritance.⁴ More than 150 different causative mutations have been identified.²
- Although inheritance is clinically autosomal recessive, most affected individuals are compound heterozygous for two different mutant alleles.⁵
- Acquired PKD may occur as a result of acute leukaemia, pre-leukaemia or refractory sideroblastic anaemia.
- Chemotherapy may cause a more common and milder form of PKD.

**Presentation**
The resulting haemolytic anaemia may vary from a very mild, fully compensated form, to life-threatening neonatal anaemia requiring exchange transfusion. Milder forms may be unnoticed until some physiological stress is experienced, eg pregnancy or viral infection, later in life. Children may have signs of anaemia, growth delay and failure to thrive. The majority of cases are found during childhood, but some who are mildly affected may not be detected until late adulthood:
- Gallstones occasionally present in childhood, but usually after the first decade of life. There may be right upper quadrant tenderness and mild-to-moderate splenomegaly.
- Adults may have chronic leg ulcers.

Differential diagnosis

Other causes of haemolytic anaemia.

Investigations

- Haemoglobin concentration varies with severity of deficiency:
  - Anaemia is normochromic and macrocytic.
  - Reticulocyte count is increased by 5-15%.
  - Leukocyte and platelet counts may be slightly increased.
  - Blood film shows features of accelerated erythropoiesis, eg nucleated red blood cells. Erythrocyte lifespan is moderately-to-severely reduced.
  - Haemoglobin electrophoresis and red cell osmotic fragility are normal.

- Indirect hyperbilirubinaemia reflects the severity of the haemolytic process. Bilirubin levels of 100 μmol/L are not uncommon and may be much higher.
- The precise diagnosis depends on detecting the deficient enzyme. Measurement of the intermediate products in the pathway (2,3-DPG and glucose-6-phosphate) help confirm the diagnosis.

Management

This is usually supportive in mild-to-moderate cases:
- For neonates, therapy is focused on the treatment of anaemia and hyperbilirubinaemia.
- Red blood cell transfusion may be necessary if the haemoglobin value falls significantly.
- Some transfusion-dependent patients have benefited from splenectomy. This procedure may reduce anaemia (but does not improve mild anaemia), but haemolysis will continue.
- Bone marrow transplant has been successful.

Complications

- Gallstones and biliary tract obstruction may occur.
- Bacterial sepsis (post-splenectomy).
- Iron overload (from many transfusions).

Prognosis

Morbidity and mortality correlate with disease severity and are usually the result of complications.

Hydrops fetalis can occur but generally pregnancy outcomes are good, despite sometimes severe declines in haemoglobin during pregnancy.

Prevention
DNA analysis is limited because of the large number of possible gene mutations. It is of greater value when the mutation is known.

Prenatal enzyme testing is not useful because a large amount of fetal blood is required and the test has a high rate of false-negative results. [3]

Further reading & references

4. Pyruvate Kinase Deficiency, Online Mendelian Inheritance in Man (OMIM)

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