Pyruvate Kinase Deficiency & Hemolytic Anemia
Objectives

- Pyruvate Kinase in normal metabolism
- Pyruvate Kinase deficiency
- Hemolytic anemia in relation to PKD

- Symptoms
- Clinical signs
- Diagnosis
- Medical care and Treatment
- Prognosis and Complications
Pyruvate Kinase in normal metabolism

Glycolysis
Pyruvate kinase enzyme *isozymes* in the human body:

- **M1**: skeletal muscle and brain
- **M2**: most fetal and adult tissues
- **L**: works in the liver
- **R**: works in the red blood cells
In Erythrocytes

Erythroid precursors use the PK-M2 isoenzyme

Mature RBCS

the PK-R isoenzyme replaces the PK-M2 enzyme
Pyruvate Kinase Deficiency

PKD is part of a group of disorders called hereditary nonspherocytic hemolytic anemias. Mutation occurs in PKLR gene which is located on chromosome 1, on the q arm in region 21 (1q21). This leads to deficiency of the enzyme:

• completely in homozygous mutations

• partially in heterozygous mutations (carriers)
Hemolytic anemia

Hemolytic Anemia means:
The bone marrow is unable to compensate premature destruction of red blood cells

Causes could be:
- Infection
- Certain medications
- Autoimmune disorders
- Inherited disorders

Classified by the location of the defect:
- In the red blood cell itself (intrinsic factor)
- Outside the red blood cell (extrinsic factor)
Hemolytic anemia in relation to PKD

Immature reticulocytes can use phosphorylation pathway to produce ATP

- Mature erythrocytes do not have mitochondria
- Depend on glycolysis for energy

But this ability is diminished when the reticulocytes are exposed to hypoxia or when they mature to adult red cells

In PKD, the amount of ATP produced is not matching the energy requirements
Hemolytic anemia in relation to PKD

Low ATP

disturbs the cation gradient across the membrane

causes loss of potassium and water

causes cell dehydration, contraction, and crenation

premature destruction of the RBC
Symptoms

The severity is widely variable

-Mild form of PKD
  May appear to have no symptoms at all.

- Severe form of PKD

Symptoms include:

  Chills    Fatigue

  Earlier in life symptoms tend to be detected

  Pallor, dark urine and enlarged spleen
Clinical signs

Biochemical findings of hemolytic anemia in addition to PK deficiency, are

- Elevated indirect bilirubin levels
- Elevated Hapatoglobin
- Hemoglobin in the urine
- Hemosiderin in the urine
- Increased urine and fecal urobilinogen
- Elevated total reticulocyte count
- Low red blood cell count
- Elevated serum LDH
Diagnosis of PKD

1- measuring the amount of pyruvate kinase in red blood cells

2- If there is a family history, mutation analysis could be done to determine carrier status of an individual.

PK level in most PKD patients is 5-25% of the normal value.

(Normal Pyruvate kinase level range from 2 to 8.8 U/g of hemoglobin).

Carriers of PKD also can have less pyruvate kinase in their red blood cells, approximately 40-60% of the normal value.

3 - Direct measurement of the red cell life span by isotopic tagging techniques shows a decreased life span.

Overlap between the normal range and the ranges seen with carriers of PKD.
Medical care and Treatment

In the severe cases

✓ multiple blood transfusions may be required

✓ spleen may be removed (spleenectomy)
Prognosis and Complications

- Early intervention and treatment of symptoms frequently improves the individual's health.

- Without treatment, individuals may experience severe complications that may become lethal.

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