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Student Case Study #4: Small Steps, Big Energy Crisis

Case Background:
A 3-year-old male named Patrick is brought into the emergency room by his parents. They report increased fatigue, yellowing eyes, and dark-colored urine over the past two days. They say that Patrick had recently recovered from a mild viral infection but now he becomes unusually lethargic and pale during play. On examination Patrick appears pale and jaundiced and his spleen is palpable. His vitals are all within normal limits except for tachycardia (elevated heart rate) consistent with compensatory anemia. You decide to perform a variety of tests of which the results are below.

Laboratory Results:

	Upon Admission	Normal Range
RBC panel	3300000/μL	4500000/μL
Hemoglobin	9.2 g/dL	11.5-13.5g/dL
Hematocrit	28%	34-40%
Reticulocyte Count	5.5%	0.5%-2.5%
Peripheral Blood Smear	Presence of Burr cells	Normal RBC Morphology
Creatine Kinase Levels	1,350 U/L	22 - 198 U/L
Urinalysis	Myoglobin Present	No Myoglobin Present

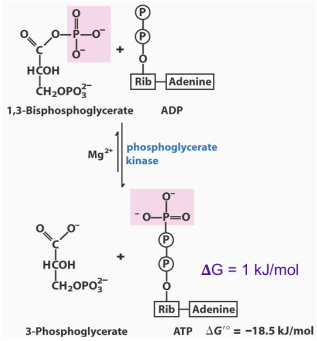
Vocabulary:
- Burr Cells - mature deformed RBCs
- Reticulocyte Count - measures % of immature RBCs in blood
- Hematocrit - measures % of RBCs in blood to look for anemia

Discussion Question 1:
1. What is notable about the test results and what might they suggest is happening biochemically?
    - Low RBC count, hemoglobin, and hematocrit indicating anemia
    - High reticulocyte count shows bone marrow response to anemia by making new red blood cells to replace lost ones

- Burr cells present suggest structure of RBCs are affected due to ATP depletion resulting in membrane abnormalities
- Elevated creatine kinase levels and myoglobin in the urine indicates rhabdomyolysis
- Combined these results indicate that the patient has a defect in glycolysis resulting in decreased ATP production

Noticing the trend in anemia and muscle damage you decide to run additional testing to look for any abnormalities in the glycolysis pathway. The results show a decrease in PGK1 activity. You confirm your suspicion of a PGK1 deficiency with genetic testing that shows a mutation on the gene that encodes for the PGK1 enzyme.

Biochemistry:



Phosphoglycerate kinase (PGK) catalyzes the conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate while producing ATP from ADP. If this enzyme is ineffective the ATP production at this step is interrupted and reduced, the upstream intermediates like 1,3-BPG and glyceraldehyde-3-phosphate accumulate, and the downstream intermediates are severely decreased in output.

A PGK1 defect is a genetic disorder caused by mutations in the PGK1 gene, leading to a deficiency in the phosphoglycerate kinase 1 enzyme, which is crucial for energy production. This can result in a range of symptoms including chronic hemolytic anemia (shortage of red blood cells), muscle weakness and cramping (myopathy), and neurological problems like intellectual disability, seizures, and parkinsonism.

Discussion Questions 2 & 3:

2. Why might it be that red blood cells and muscles are especially affected in this condition?
    - Phosphoglycerate kinase enzyme is crucial for converting 1,3-diphosphoglycerate into ATP, when it is deficient the body cannot efficiently produce ATP leading to muscle cell damage or death.
    - Because less ATP is available, cells that rely heavily on glycolysis for energy such as RBCs and muscle cells are especially affected.
    - RBCs rely entirely on glycolysis for ATP because they don't have mitochondria so lack of ATP triggers a chain of failures in their pumps resulting in improper ion balance and cell volume. Sodium and calcium builds up inside the cell and as a result water is driven in by osmosis causing the cells to swell becoming fragile and prone to bursting
    - Loss of ion control in muscle cells causes a similar effect to RBCs

3. How might you treat a patient with this condition? Is there a cure?
    - Not really but you can…
    - Avoidance of triggers like exercise, fasting, and infections
    - Hydration and rest during episodes of rhabdomyolysis (destruction of muscle cells)
    - Blood transfusions in cases of severe anemia
    - Splenectomy may reduce severe hemolysis in some patients
    - mRNA-based replacement is under review

References:

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