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Opinion Article

Pyruvate Kinase Deficiency and its Related Disorders in Children and Adults

Demetriou Valois*

Department of Health Science, Ain Shams University,Cairo, Egypt

INTRODUCTION

In the early 1960s, the glycolytic pathway abnormality known as Pyruvate Kinase Deficiency (PKD), the most prevalent cause of congenital hemolytic anaemia, was initially identified. After Selwyn and Dacie first identified the connection between glycolysis and hemolytic anaemia in the 1950s, de Gruchy and colleagues reported a number of patients with nonspherocytic hemolytic anaemia whose hemolysis could be cured by Adenosine Triphosphate (ATP), but not by glucose. Pyruvate Kinase (PK) insufficiency was shortly after identified as the underlying molecular cause of this anaemia by Valentine, Tanaka, and their associates.

Red cell ATP is mostly produced by glycolysis in healthy Red Blood Cells (RBCs). Phosphoenolpyruvate is converted to pyruvate by PK, which causes the synthesis of ATP. RBCs have a lifespan of 100 to 120 days, during which time ATP is crucial for preserving their structural and functional integrity. Pyruvate Kinase (PK) enzyme activity that is abnormal or defective leads to insufficient ATP synthesis, loss of membrane flexibility, cellular dehydration, and early death of RBCs in the spleen or liver. Reticulocytes, which need high amounts of ATP, switch from oxidative phosphorylation to glycolysis in the hypoxic spleen, making them more vulnerable to dehydration and damage. The hemoglobin-oxygen dissociation curve shifts to the right due to the accumulation of 2,3-diphosphoglycerate (2,3-DPG), an upstream product of the glycolytic process, when PK activity is inadequate.

Related disorders of pyruvate kinase deficiency

The symptoms of the subsequent conditions can resemble of pyruvate kinase deficiency. For a differential diagnosis, comparisons could be helpful.

Acquired hemolytic anemias

Autoimmune hemolytic anaemia: When a person's immune system damage, distroy their own red blood cells is called autoimmune haemolytic anaemia. A type of acquired hemolytic anaemia, results chronic hemolysis, thrombosis (blot clots), an elevated risk of infections, and bone marrow failure are all symptoms of Paroxysmal Nocturnal Hemoglobinuria (PNH), a clonal illness of hematopoietic stem cells.

Microangiopathic hemolytic anaemia: which includes conditions like thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and disseminated intravascular coagulation, is characterised by mechanical destruction of RBCs. Infections are linked to some of these illnesses. Direct red cell death can occur as a result of illnesses and drugs. Hemolysis may also be triggered by shear inside blood vessels.

Congenital hemolytic anemias

Red cell membrane defects: Hereditary spherocytosis and hereditary ellipocytosis, genetic diseases of the red cell membrane (outer shell), cause the red cell to have an oval or sphere shape rather than a disc-like form. The red cells in the spleen are more likely to fragment due to these aberrant forms.

Red cell permeability defects: Hereditary xerocytosis and associated illnesses are hemolytic syndromes brought on by aberrant water content within the red cells, which results in red cell permeability problems.

Hemoglobin disorders: Sickle cell disease and thalassemia are examples of hereditary haemoglobin abnormalities. Chronic hemolysis is a consequence of sickle cell disease, which can also be linked to periods of discomfort, an elevated risk of infection and stroke, and other issues.

Problems in the glycolytic route or a similar pathway are the root cause of enzyme deficiencies. The identification of gene alterations and the confirmation of decreased enzyme activity serve as the foundation for the diagnosis of each of these diseases. The most prevalent red cell enzyme defect is glucose-6-phosphate dehydrogenase (G6PD) insufficiency, which is a hereditary metabolic condition brought on by G6PD deficiency. Most frequently, fava bean consumption or specific drugs will cause G6PD insufficiency, which is an episodic illness.

Symptoms management in children and adults

The median haemoglobin value in nontransfused, nonsplenectomized children is 9 g/dL (range, 6-12.5). In 90% of

Correspondence to: Demetriou Valois, Department of Health Science, Ain Shams University,Cairo, Egypt, E-mail: valoisdementriou@yahoo.com

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patients, splenectomy reduces the need for transfusions, partially improves hemolytic anaemia, and raises haemoglobin levels to a median of 1.6 g/dL. After splenectomy, there is a paradoxical rise in the number of reticulocytes. Even while lactate dehydrogenase is often in the normal range, a slight rise in it occasionally occurs, especially during episodes of enhanced hemolysis. Splenomegaly is common (80%-85%), and some patients with associated mild thrombocytopenia, leukopenia, and/or increased transfusion needs may also exhibit mild hypersplenism.

CONCLUSIONS

PKD is a chronic hemolytic anaemia that lasts a lifetime and has a wide range of signs and symptoms. Monitoring is crucial because there is a high possibility that complications will develop over the course of a patient's lifetime. Transfusions, splenectomy, and chelation therapy are currently included in supportive care. Gene therapy and PK activators are two cutting-edge disease-directed strategies that could change patients' clinical phenotypes in the future. Careful consideration is required to choose the best management techniques for individual patients given the potential future therapy options for PKD.