Paroxysmal Nocturnal Hemoglobinuria (PNH)

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, chronic, life-threatening, hemolytic anemia caused by an acquired intrinsic defect in the cell membrane of RBCs, WBCs and platelets. It is a clonal stem cell defect disease caused by complement-mediated destruction of these cells. It presents with a triad of Coombs-negative hemolytic anemia, pancytopenia, and venous thrombosis.

PLAY PICMONIC

Pathophysiology

Defective PIG-A Gene

Defective PIG with Apple

RBCs in patients with PNH are either missing or have a mutated phosphatidylinositol glycan class A (PIG-A) gene, resulting in a mutated PIG-A protein. Without PIG-A, important proteins cannot connect to the cell The PIG-A gene codes for a protein that ultimately results in the production of a GPI anchor.

Deficiency of DAF (Decay Accelerating Factor CD55)

Deficient DAF-Daffy with CD55 guns

Decay accelerating factor (DAF) is a glycosylphosphatidylinositol (GPI) anchored protein to RBC's that is also known as CD55. The decreased expression of DAF (CD55) leads to an inability to adequately protect RBC's from hemolysis because of increased activation of C3. C3 accumulation on RBC's opsonizes them for destruction.

Symptoms

Dark Urine in the Morning

Dark Urine with Morning-sun

Also termed “cola-colored” urine. Breathing slowly at night causes retention of carbon dioxide. This slight increase in CO2 during sleep leads to respiratory acidosis which enhances complement attachment to RBCs, neutrophils and platelets leading to hemolysis and thrombosis formation.

Intravascular Hemolysis

Hemolysing-rbc

Intravascular complement-mediated lysis or destruction of RBCs, neutrophils and platelets can lead to pancytopenia, aplastic anemia, or acute leukemia. These patients are coombs negative.

Thrombosis

Thrombosis in vessel

Formation of small blood clots are formed within veins. This is the most common cause of death.

Diagnosis

Decreased CD55 and CD59

Down-arrow CD 55 guns and 59 gun and hook

Flow cytometry will show a decrease in CD55 (Decay Accelerating Factor) and CD59 on RBCs and granulocytes. For RBCs, the lack of CD55 and CD59, which are both GPI-linked, leads to the inability to inhibit complement and therefore lysis of RBCs. The Ham's test (acidified serum lysis) and Sugar water test (sucrose lysis test) are abandoned diagnostic tests that are no longer used as diagnostic tools.

Treatment

RBC Transfusion

Blood Transfusion

Severe anemia in patients with hemolytic disease are often administered transfusions including RBC's at a hemoglobin less than 7 g/dL. Washed RBC transfusions to reduce ABO incompatibilities and reactions are not required in patients with PNH.

Eculizumab

Eco-lizard-mob

A humanized monoclonal antibody that is a terminal complement inhibitor. Eculizumab specifically binds to the complement protein C5 and inhibits its cleavage to C5a and C5b. Inhibiting cleavage of C5 prevents the generation of the terminal complement complex C5b-9 and therefore prevents the cell from being lysed. The -li- in eculizumab indicates that this drug targets part of the immune system, -zu- indicates that it is humanized, and the ending -mab indicates this is a monoclonal antibody.

Bone Marrow Transplant is Curative

Bone Arrow Transplant

Allogenic (from same species) bone marrow transplant is the only known cure. Bone marrow transplant is offered to patients with severe disease (life-threatening thrombosis and/or very low blood counts) because the procedure has a 15-20% chance of death.