Libyan International Medical University

Faculty of Basic Medical Science

Paroxysmal Nocturnal Hemoglobinuria

Student name: Salma Samir

Student number: 1199

Group: B2

Date of submission: 13.4.2018

Abstract:
Paroxysmal Nocturnal Hemoglobinuria originates from mutant genes in stem cells of bone marrow that differentiate to different types of blood cells.Hemolytic anemia, bone marrow failure and thrombophilia is Clinical triad typical for PNH. The management depend on patient case.

Introduction:

Paroxysmal Nocturnal Hemoglobinuria is a very rare disease occurs in 1 every million worldwide. It hard to differentiate its symptoms from other overlapping conditions, and takes long time to be properly diagnosed.It is mainly caused by mutation in genes that code anchoring proteins on different blood cells types. The different symptoms mainly depends on intravascular hemolysis. The management aimed to correct the anemia and to prevent life-threatening conditions as thrombi and intravascular clotting.

Discussion:

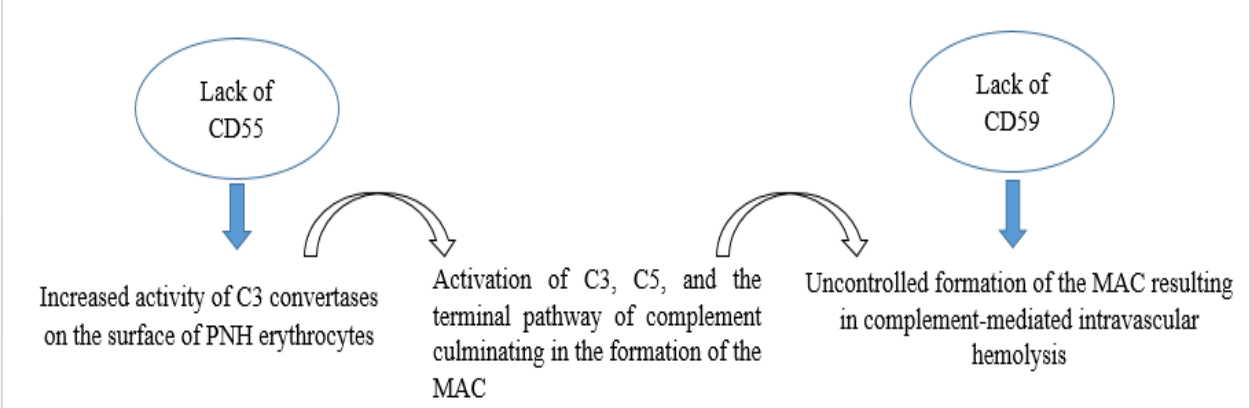
A deficiency of decay-accelerating factor (DAF) on the surface of blood cell precursors, leading to an increased activation of the alternative pathway of complement, characterised generally by Hemoglobinuria, iron-deficiency anemia, thrompoctyopenia, & generalized fatigue.

It is rare acquired bone marrow failure results from **colony-forming unit-granulocyte, erythrocyte, monocyte, megakaryocyte (CFU-GEMM)** disorder that give rise to all the mature blood elements.

Cell that has PIG-A mutation results in severe deficiency or absence for glycosylphosphatidylinositol GPI There are >12 GPI-anchored proteins (GPI-APs) on hematopoietic cells, including blood group antigens, adhesion molecules, and complement regulatory proteins. The deficiency of complement inhibitory proteins CD55 and CD59 accounts for most of the clinical manifestations of PNH.

CD59 is a glycoprotein that directly interacts with the membrane attack complex (MAC) to prevent lytic pore formation by blocking the aggregation of C9.

CD55, a glycoprotein, functions to accelerate the rate of destruction of membrane-bound C3 convertase.



Opsonized erythrocytes by C3d are cleared and destroyed by cells of the reticuloendothelial system.

Mutation causes:

1. PIGA is on the X chromosome >> X linked disease.
2. Acquired PNH resulted from aplastic anemia >> PNH stem cells have a conditional survival advantage in the setting of an autoimmune attack that targets the bone marrow.
3. PIGA mutations in MDS are transient and also arise from colony-forming cells rather than hematopoietic stem cells.

Some inherited CD59 deficiency also present with relapsing immune-mediated peripheral neuropathy. Differ from PNH, that the CD59 is deficient in all cells in the body rather than blood cells only.

Classification of PNH:

1. Classical PNH, which includes hemolytic and thrombotic patients.
2. PNH in the context of other primary bone marrow disorders.
3. Subclinical PNH, in which patients have small PNH clones but no clinical or laboratory evidence of hemolysis or thrombosis.

Clinical manifestation:

Intravascular hemolysis: hallmarked by "Elevated reticulocyte count and serum LDH level with a low serum haptoglobin level in the absence of hepatosplenomegaly" leads to:

1. Dark urine during the night because the lower oxygen concentration in the blood during sleep increases the susceptibility of the red cells to lyse,with partial clearing during the day. This dark urine may be confused with other causes of hematuria.
2. Iron deficiency anemia

Increased level of free hemoglobin lowers the NO level contributes to:

3. Deregulation of smooth muscle tone >> Smooth muscle dystonia & abdominal pain.
4. Platelet activation >> Thrombosis cause of mortality in PNH. Venous thrombosis is more common than arterial.
5. Increased risk of chronic kidney disease, caused by microvascular thrombosis and accumulation of iron deposits.

Treatment:

There is no specific treatment, Iron can be given for the anemia, and alsoEculizumab can be given. Eculizumab is a humanized monoclonal antibody that blocks the formation of the MAC and in doing so compensates for the CD59 deficiency of PNH patients. The drug is highly effective in stopping intravascular hemolysis, eliminating or decreasing the need for red cell transfusions, improving quality of life, and reducing the risk of thrombosis, the leading cause of mortality from PNH. It has also been shown to improve renal function and to reduce prothrombotic and proinflammatory markers in PNH patients. Eculizumab does not alleviate bone marrow failure, For Patients with ongoing bone marrow failure from aplastic anemia these patients. In sver cases the only treatment and management is bone marrow transplantation especially in young patients.

Conclusion:

Uncontrolled activation of alternative pathway of complement system is the leading cause of different symptoms in Paroxysmal Nocturnal Hemoglobinuria. The appropriate treatment for PNH depends on the severity of symptoms in each case. Complement inhibitors appears to improve quality of life for mild to moderate PNH patients. Bone marrow transplantation is the only curative therapy available for PNH.

References:

1. Michael hill. (2018). Hopkinsmedicineorg. Retrieved 5 March, 2018, from https://www.hopkinsmedicine.org/kimmel_cancer_center/types_cancer/paroxysmal_nocturnal_hemoglobinuria_PNH.html.
2. Nihgov. (2018). PubMed Central (PMC). Retrieved 5 March, 2018, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5379214/.
3. Nihgov. (2018). Nihgov. Retrieved 5 March, 2018, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4215311/.