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PAROXYMAL NOCTURNAL HEMOGLOBINURIA-A REVIEW

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ABSTRACT

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare life-threatening and debilitating disorder of haematopoiesis. It is characterised by the clinical triad of Coombs-negative acquired extracorpuscular haemolytic anaemia, thrombophilia and bone marrow failure. The sequelae of intravascular haemolysis drastically affect the quality of life of patients. Cytopenia and in particular thrombophilia can cause life-threatening complications. Thromboembolic events are the major cause of deat. The only curative treatment for PNH is allogeneic stem cell transplantation from a related or unrelated stem cell donor. Recent reports demonstrated favourable outcomes. Other treatments were generally supportive in nature. Recently, eculizumab, a humanised monoclonal antibody that inhibits complement factor C5, was approved. It is a targeted, disease-modifying treatment of PNH.

Key words: Monoclonal antibody, Thrombophilia, Haemoglobinuria.

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INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, chronic, debilitating disorder that most frequently presents in early adulthood and usually continuous throughout the life of the patient. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired, life-threatening disease of the blood. The disease is characterized by destruction of red blood cells (hemolytic anemia), blood clots (thrombosis), and impaired bone marrow function (not making enough of the three blood components). PNH affects 1-1.5 persons per million of the population and is primarily a disease of younger adults [1]. The median age of diagnosis is 35-40 years of age, with occasional cases diagnosed in childhood or adolescence. PNH is closely related to aplastic anemia. In fact, up to 30% of newly diagnosed cases of PNH evolve from aplastic anemia. Similarly, the risk of developing PNH after treatment for aplastic anemia with immunosuppressive therapy (anti-thymocyte globulin and cyclosporine) is approximately 20-30%. The median survival after diagnosis is 10 years; however, some patients can survive for decades with only minor symptoms. PNH results in the death of approximately 50% of affected individuals due to thrombotic complications and, until recently, had no specific therapy [2-4].

AFFECTED POPULATIONS

PNH is believed to affect males and females in equal numbers, although some studies show a slight female preponderance. The prevalence is estimated to be between 0.5-1.5 per million people in the general population. The disorder has been described in many racial groups and has been identified in all areas of the world. The disorder may occur with greater frequency in individuals of Southeast Asia or the Far East who experience greater rates of aplastic anemia. The disorder can affect any age group. The median age at diagnosis is during the 30s.

Causes

- PNH is genetic.
- Two factors are necessary for the development of PNH: an acquired somatic mutation of the PIGA gene, which affects one or more hematopoietic stem cells creating defective "PNH" blood cells, and a process that leads to the multiplication and expansion of these defective stem cells. Most likely, PNH arises in the setting of autoimmune bone

- marrow failure, as occurs in most cases of acquired aplastic anemia [5].
- These cells don't have proteins that shield them from immune system.
- Some doctors believe PNH is related to weak bone marrow. People with a certain type of anemia, called aplastic anemia, are more likely to get PNH.
- The reverse is also true: People with PNH are more likely to get aplastic anemia, though not everyone does. In this condition, bone marrow stops making new blood cells.

PATHOPHYSIOLOGY

PNH occurs when mutations of a gene called PIG-A occur in a bone marrow stem cell. Stem cells give rise to all the mature blood elements including red blood cells , which carry oxygen to our tissues; white blood cells , which fight infection; and platelets, which are involved in forming blood clots.

In PNH, the affected stem cell passes the PIG-A mutation to all cells derived from the abnormal stem cell. Cells harboring PIG-A mutations are deficient in a class of proteins called GPI-anchored proteins. Certain GPI-anchored proteins protect red blood cells from destruction, some are involved in blood clotting, and others are involved in fighting infection. The majority of PNH-related issues, including destruction of red blood cells (hemolytic anemia), blood clots (thrombosis), and infection, result from a deficiency of these proteins. The genetic defect responsible for causing PNH has been identified. Knowledge of the genetic defect will allow researchers to study the disease in a manner that was not previously possible, and may give insight for developing more effective therapies [6].

DIAGNOSTIC TEST

Laboratory Studies

The tests involved in establishing the diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) demonstrate the presence of red blood cells (RBCs) that are exceptionally sensitive to the hemolytic action of complement. These tests include the following:-

- Flow cytometry
- Acidified serum lysis and Ham test
- Complement lysis sensitivity test
- Sugar water or sucrose lysis test

Most laboratories no longer perform the Ham test or the sugar water test.

Flow Cytometry

The use of flow cytometry in PNH differs from many applications in that the diagnosis depends upon demonstrating the absence of relevant antigens. In this context, it is important that at least two GPI-linked antigens are studied to exclude rare congenital deficiencies of single antigens (CD55 and CD59) and polymorphism with individual antigens (CD16), which render them undetectable by some monoclonal antibody clones.

Standard and high-sensitivity flow cytometric procedures for detecting PNH cells are now available. For routine analysis and diagnosis of suspected PNH, the standard test is sufficient. This test can detect 1% or more PNH cells, bu; most laboratories report only 10% or more as a positive result. High-sensitivity analysis (in which as little as 0.01% PNH cells can be detected) may be helpful in aplastic anemia patients, who may eventually develop PNH, and possibly in those with hypoplastic myelodysplasia syndrome (MDS), to predict responses to immunosuppressive therapy [7].

Fluorescent Aerolysin

A more accurate alternative reagent for PNH screening and PNH clone measuresment is the bacterial toxin aerolysin, which binds to RBCs via GPI anchor and initiates hemolysis. A modified, nonhemolytic form of a fluorescently labeled molecule has been developed that can detect PNH cells to a level of 0.5% (fluorescently labeled inactive toxin aerolysin [FLAER] binding of peripheral blood granulocytes). The advantage of this assay is that it can detect the clone in all hematopoietic cell lineages in one assay [8].

Immmunotyping

Peripheral blood is the most suitable specimen for immunephenotyping for PNH, and it is important to screen both RBCs and granulocytes, because RBC transfusions are common among these patients and granulocytes may not be present in severe hypoplastic anemia patients.

Studies have shown that the size of the PNH clone correlates with the risk for venous thrombosis. Patients with less than 50% PNH granulocytes seldom develop thrombosis, whereas patients with larger clone sizes appear to be at great risk and will require anticoagulation.

Acidified Serum Lysis And Ham Test

If performed properly, acidified serum lysis and the Ham test (from Thomas Hale Ham) are reliable ways to diagnose PNH (see image below). Dr. Ham demonstrated that the RBCs in PNH were lysed by complement when normal serum was acidified or activated by alloantibodies.

The Ham test (acidified serum lysis) establishes the diagnosis of paroxysmal nocturnal hemoglobinuria (PNH), demonstrating a characteristic abnormality of PNH red blood cells by acidified fresh normal serum. Here is a PNH patient's (Pt) red blood cells lysed by normal serum at room temperature (RT) and at 37°C compared with normal red cells (no hemolysis) (control [C]). Heated serum at 56°C inactivates complement and prevents hemolysis in PNH cells.

Complement Lysis Sensitivity Test

The complement lysis sensitivity test is a more precise method for diagnosing PNH. RBCs are sensitized with a potent lytic anti-I antigen and hemolyzed with limiting amounts of normal serum as a source of complement. This demonstrates three groups of RBCs in patients with PNH, including the following:

- PNH I cells are normal in sensitivity to complement
- PNH II cells are moderately more sensitive to complement than normal cells
- PNH III cells are markedly sensitive to complement, requiring one fifteenth to one twentieth of the amount of complement for an equal degree of lysis; this group of cells is increased in patients with more severe PNH, and it is associated with a mean life span of 10-15 days [9].

Sugar Water Or Sucrose Lysis Test:

The sugar water or sucrose lysis test uses the ionic strength of serum that is reduced by adding an iso-osmotic solution of sucrose, which then activates the classic complement pathway, and complement-sensitive cells are lysed. This test is less specific but more sensitive for PNH than the Ham test, because some RBCs hemolyze from autoimmune hemolytic anemias, leukemia, and aplastic anemia to a minor degree. Although the tests are inexpensive and simple to perform, they are more labor intensive and less sensitive due to the short half-life of circulating PNH RBCs [10].

Other tests to demonstrate intravascular hemolysis include the following:

- Elevated serum lactate dehydrogenase (LDH)
- Elevated reticulocyte count
- Low-to-absent serum haptoglobin
- Hemoglobinuria and hemosiderinuria – The presence of hemolysis may be intermittent and can be missed easily, depending on when the tests are performed

Imaging Studies

Thromboses of major veins are best evaluated by radiographic means. Investigate hepatic vein thrombosis with a routine technetium-99m (^{99m} Tc) colloid scan of the liver and spleen. This study often reveals diminished function in all portions of the liver except the caudate lobe, which is spared because it is drained by the inferior vena cava rather than the hepatic vein. A magnetic resonance imaging (MRI) study or ultrasonogram can demonstrate the cessation of flow through the hepatic vein or by injection or use of a dye to demonstrate a thrombus in the vein. MRI with contrast may demonstrate sagittal vein thrombosis.

Urinalysis

Urinalysis is the physical, chemical, and microscopic examination of urine. It involves a number of tests to detect and measure various compounds that pass through the urine.

Hemosiderinuria

(syn. haemosiderinuria), "brown urine", occurs with chronic intravascular hemolysis, in which hemoglobin is released from RBCs into the bloodstream in excess of the binding capacity of haptoglobin. (Haptoglobin binds circulating hemoglobin and reduces renal excretion of hemoglobin, preventing tubular injury.) The excess hemoglobin is filtered by the kidney and reabsorbed in the proximal convoluted tubule, where the iron portion is removed and stored in ferritin or hemosiderin. The tubule cells of the proximal tubule slough off with the hemosiderin and are excreted into the urine, producing a "brownish" color. It is usually seen 3-4 days after the onset of hemolytic conditions.

Other Tests

PIG-A gene mutation analysis is still limited to research laboratories and, although very specific, is still not diagnostic for paroxysmal nocturnal hemoglobinuria (PNH)

RELATED DISORDERS

Symptoms of the following disorders can be similar to those of PNH. Comparisons may be useful for a differential diagnosis.

- PNH and acquired aplastic anemia are closely related disorders,
- Myelodysplastic syndrome (myelodysplasia) is a rare group of blood disorders that occur as a result of improper development of blood cells within the bone marrow. The three main types of blood cells (i.e., red blood cells, white blood cells and platelets) are affected.
- Rarely, individuals with PNH may develop leukemia, which is a form of cancer affecting the bone marrow and blood. It is characterized by the uncontrolled accumulation of immature blood cells. Acute forms of leukemia may result in low levels of red and white blood cells and platelets (pancytopenia) or in a high white blood cell count (leukocytosis) with low levels of red cells and platelets.
- Paroxysmal cold hemoglobinuria is a rare autoimmune hemolytic disorder characterized by the premature destruction of healthy red blood cells (hemolysis) minutes to hours after exposure to cold.
- Budd-Chiari syndrome is a rare disorder characterized by narrowing and obstruction (occlusion) of the veins of the liver (hepatic veins). In individuals with PNH, blood clots (thromboses) block the hepatic veins.

SIGNS AND SYMPTOMS

Skin: Red, painful, or swollen area
Arm or Leg: Sore, warm, and swollen limb
Stomach : Pain and Ulcers and bleeding

Brain : Bad headache with or without vomiting, Seizures & Trouble moving.
Lung: Trouble breathing, Sharp chest pain, Coughing up blood(Heamoptosis) & Sweating

TREATMENT

Most treatments for PNH aim to ease symptoms and prevent problems. Treatment will depend o how severe symptoms and disease are.
If their is only a few symptoms from anemia, then one may need:

- Folic acid to help bone marrow make more normal blood cells
- Iron supplements to make more red blood cells

Other treatments include

- Blood transfusions. These help treat anemia, the most common PNH problem.
- Blood thinners . These medicines make your blood less likely to clot.
- Eculizumab (Soliris). The only drug approved to treat PNH, it prevents the breakdown of red blood cells. This can improve anemia, lower or stop the need for blood transfusions, and reduce blood clots
- Hematopoietic stem cell transplantation: Hematopoietic stem cell transplantation (HSCT) using allogeneic donors is the only curative therapy for PNH.

Life Style Modification

Healthy diet : Body absorbs iron better when you get it with vitamin C. Try combos like iron-fortified cereal with strawberries or spinach salad with orange slices.

Keep a diary of symptoms: It is important that all symptoms are openly discussed at every meeting with the healthcare team; coping mechanisms and lifestyle adaptations to symptoms, such as fatigue, may mask the disease severity or deterioration.

Pregnancy: For women with PNH, pregnancy can be risky for both the mother and the child. Women who have PNH and are hoping to become pregnant should speak to their specialist PNH team to discuss the best options to reduce the risk of complications during pregnancy. Close communication between the obstetric team and the haematology team is key to a safe mother and baby.

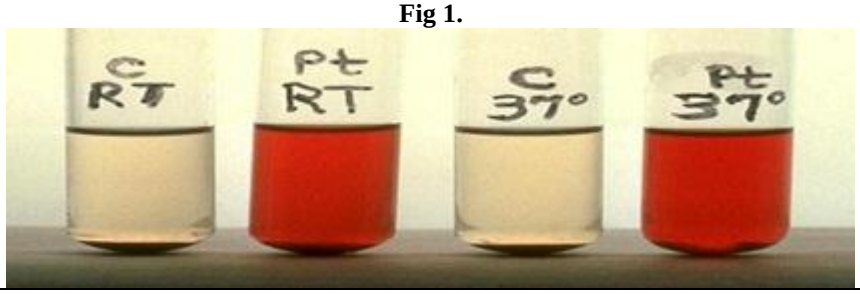
Contraception: For people with PNH, the safest methods of contraception are either the progest eroneimplanted coil or condoms. The combined oral contraceptive pill should be avoided because it can result in an increased risk of developing a blood clot. Patients should discuss contraception with their healthcare team, who will be able to provide more information and advice.

Surgery: Surgery can pose a number of risks for people with PNH. It can increase activity of the complement system, which causes haemolysis. In this context, surgery can increase the risk of blood clots and can cause serious bleeding in people with a low platelet count (which can occur in PNH). People with PNH who require surgery should speak to their specialist PNH doctor to ensure that any special measures can be put in place.

Complementary therapies

Complementary therapies are those used alongside traditional medical treatments, such as counselling, aromatherapy, massage therapy, meditation and visualisation techniques. They are often used to promote physical and emotional wellbeing, and may help to improve quality of life, reduce stress and anxiety, improve sleep patterns and relieve some symptoms. Healthcare teams will be able to offer advice on therapies that may be safe and appropriate for an individual.

Fig 1.



CONCLUSION

The name of the disorder is a descriptive term for the clinical consequence of red blood cell (RBC) breakdown with release of hemoglobin into the urine, which manifests most prominently as dark-colored urine in the morning (see image below).The major advances in the management of PNH during the last year and, in particular, will discuss new results of eculizumab, treatment of thrombosis and stem cell transplantation. Given the new advances there is hope for improved survival of these patients.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with theethical standards of the institutional research committee and with the 1964Helsinki declaration and its later amendments or

comparable ethicalstandards. This article does not contain any studies with animals performed by any of the authors.

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Nil

CONFLICT OF INTEREST

No interest

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