

Paroxysmal Nocturnal Hemoglobinuria

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[Abstract](#)

[Keywords](#)

[Disease name and synonym](#)

[Definition and Differential Diagnosis](#)

[Etiology](#)

[Clinical Description](#)

[Diagnostic Methods](#)

[Epidemiology](#)

[Management](#)

[References](#)

Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal disorder of the bone marrow characterized by the lack (total or partial) of all proteins normally attached to the cell membrane by the glycosylphosphatidylinositol (GPI) anchor. This cellular defect arises in a hematopoietic stem cell and is due to a somatic mutation of the PIG-A gene, encoding a protein needed for the biosynthesis of the anchor GPI. The variable clinical manifestations are intravascular hemolytic anemia, venous thrombosis (particularly within the abdomen), and cytopenia due to deficient bone marrow production of blood cells. The diagnosis is definitively established by demonstrating the deficiency of GPI-anchored proteins on blood cells, using monoclonal antibodies and flow cytometry. The genesis of the mutation is usually unknown; the disorder often arises in the setting of aplastic anemia. PNH is a rare disorder with a minimum prevalence estimated to 1-1.5 cases per million. Treatment is primarily symptomatic (transfusion, erythropoietin, glucocorticoids, anticoagulation) or includes, in severe cases, bone marrow transplantation. Techniques for the suppression of complement activation with monoclonal antibodies are currently under development and appear to be very promising.

Keywords

Paroxysmal nocturnal hemoglobinuria (PNH), clonal disorder, bone marrow, glycosylphosphatidylinositol (GPI) anchor, hemolytic anemia, venous thrombosis, cytopenia

Disease name and synonym

- Paroxysmal nocturnal hemoglobinuria (PNH)
- Marchiafava-Micheli syndrome

Definition and Differential Diagnosis

PNH is a clonal disorder of bone marrow characterized by blood cells lacking membrane proteins that are normally attached by the glycosylphosphatidylinositol (GPI) anchor (e.g. CD55, CD59, etc.) (Rosse, 1997). In the

strictest definition, the deficiency, partial or complete, of two such proteins on two hematopoietic cell lines (e.g. red blood cells, granulocytes) should be demonstrated (Richards, *et al.*, 2000). All patients have evidence of intravascular hemolysis; many have isolated or multiple cytopenias and/or a history of thrombosis.

Differential diagnosis

PNH is most frequently confused with [autoimmune hemolytic anemia](#) but the direct

antiglobulin test is always negative in the former disorder. PHN may be confused with congenital hemolytic anemias but rarely occurs in childhood. It often occurs in the setting of bone marrow hypo- or aplasia.

Etiology

PNH is caused by a somatic mutation arising in a hematopoietic stem cell in the *PIG-A* gene, whose product is necessary for the initial step of the biosynthesis of the GPI anchor (Takeda *et al.*, 1993). Etiology of these acquired *PIG-A* gene mutations is unknown. The mutation usually completely abrogates the production of the GPI anchor, resulting in cells completely lacking the anchored proteins (PNH III cells); in some cases, small amounts of the anchor are made, resulting in cells with small amounts of the anchored proteins (PNH II cells). The progeny of a single such abnormal cell occurs as a clone varying from 1-2% to nearly 100% of the cells of the blood. It is not clear why the clone is able to expand in the bone marrow, but this clonal expansion is thought to be related to coincident immune suppression of the marrow. All patients with PNH have laboratory or clinical evidence of marrow hypoplasia (e.g. inability to grow marrow *in vitro* despite a cellular or even hypercellular bone marrow, thrombocytopenia or granulocytopenia, a history of aplastic anemia) (Rosse, 1997).

Clinical Description

The clinical symptoms of PNH result from the intravascular hemolysis, unusual venous thromboses and bone marrow hypoplasia (Rosse, 1997). The intravascular hemolysis is due to the activation of complement as the abnormal red blood cells lack proteins that normally down-regulate its effects (decay accelerating factor (DAF, CD55) and CD59 (membrane inhibitor of reactive lysis, protectin, etc.)). The severity and occurrence of hemolysis (manifested as increased reticulocyte count, hemoglobinemia, and hemosiderinuria with or without hemoglobinuria) varies greatly depending upon the proportion of abnormal cells, their abnormality, and the activation of complement. Characteristically, hemolysis occurs at night, leading to hemoglobinuria seen in the morning but clearing during the day; this is often not seen if the amount of hemolysis is insufficient to produce hemoglobinuria. Hemolytic paroxysms may occur without apparent cause or may be brought on by concurrent infections, particularly gastrointestinal viral ones. Acute renal failure may occur (Mooraki *et al.*, 1998), especially in dehydrated patients, but is rare. About 10% of patients with PNH suffer from

renal failure, often late in their disease (Clark *et al.*, 1981, Nishimura *et al.*, 2004). Hemolytic episodes may be accompanied by marked esophageal spasm. Most men with PNH have erectile dysfunction (impotence).

The thromboses that occur in PNH are often intra-abdominal, particularly in the hepatic and portal veins (Nishimura *et al.*, 2004; Socie *et al.*, 1996). They may occur in the cerebral veins, in the veins of the extremities and in unusual sites as well. About 20% of patients present with evidence of thrombosis. Thrombosis, particularly intra-abdominal, is a serious negative prognostic sign.

The degree of bone marrow suppression may vary greatly from minimal to that seen in aplastic anemia (Dacie *et al.*, 1961). Granulocytopenia and thrombocytopenia, seen in about 70% of patients is due to hypoproduction since the circulating survival of these cells, in the absence of splenic enlargement, is normal. From 5 to 30 % of patients recovering from aplastic anemia have blood cells diagnostic of PNH (Nissen *et al.*, 1999).

Rarely, patients with PNH acquire acute leukemia (Harris *et al.*, 1999); the phenotype is nearly always granulocytic and the leukemic cells almost always lack the GPI-anchored proteins.

Diagnostic Methods

The diagnosis is definitively established by demonstrating the deficiency of GPI-anchored proteins on blood cells, as described above (Hall *et al.*, 1996; Richards *et al.*, 2000) using monoclonal antibodies to these proteins and flow cytometry. Methods demonstrating the susceptibility of the red blood cells to the hemolytic action of complement (the Ham's or acidified serum lysis test, sucrose lysis test, etc.) are less reliable, being neither as sensitive nor as specific as flow cytometry.

Epidemiology

PNH is a rare disorder with a minimum prevalence estimated to 1-1.5 cases per million.

PNH has the same general epidemiology as aplastic anemia (e.g. in Thailand the coincidence has been clearly shown) (Issaragrisil *et al.*, 1999). Both are most common in young adults with a later secondary increase in the 7th decade (Socie *et al.*, 1996, Nishimura *et al.* 2004, Hillmen *et al.*, 1995). The diagnosis is made often in East Asian countries but it is not certain that the incidence is greater in that region (Issaragrisil *et al.*, 1999). The occurrence of thrombosis is clearly lower in these populations (5-10% vs. 30-40%

in European and European-descended populations).

Management

In the past, management of the anemia PNH has been largely symptomatic: iron replacement, folate replacement, and transfusion (Meyers and Parker, 2003). Prednisone (20-40 mg every other day) is helpful in some patients with relatively severe hemolysis. Treatment with a humanized monoclonal antibody against the fifth component of complement is currently under development and appears to be very promising (Hillmen *et al*, 2004). Patients with esophageal spasm may find relief with sublingual nitroglycerine.

Thrombosis is treated with anticoagulation (heparin or lovenox acutely, coumadin for maintenance) and, acutely, with fibrinolysis. The efficacy of coumadin in prophylaxis has been demonstrated (Hall *et al*, 2003).

Bone marrow hypoplasia may be treated, as in aplastic anemia, with antithymocyte serum and cyclosporine (Rosenfeld *et al*, 1995). Androgens and large doses of glucocorticoids are of little value.

PNH may be cured by bone marrow transplantation, preferably from an HLA-identical sibling (Kawahara *et al*, 1992, Raiola *et al*, 2000). This is indicated in patients with severe bone marrow hypoplasia or serious thrombosis.

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