Paroxysmal nocturnal haemoglobinuria

Synonyms: Marchiafava-Micheli anaemia

What is paroxysmal nocturnal haemoglobinuria?[1]

There are three features of paroxysmal nocturnal haemoglobinuria (PNH) that are most uncommon together and the finding of them all is pathognomonic:

- There is an acquired haemolytic anaemia due to the susceptibility of the erythrocyte membrane to the haemolytic action of complement.
- There are thromboses in large vessels, such as hepatic, abdominal, cerebral and subdermal veins.
- There is deficient haematopoiesis that may be mild or severe and cause a pancytopenia with aplastic anaemia.

Pathogenesis[1]

PNH is caused by somatic mutations in the PIGA gene (which encodes phosphatidylinositol N-acetylglucosaminyltransferase subunit A) in one or more haematopoietic stem cell clones.

The gene product of PIGA is required for the biosynthesis of glycosylphosphatidylinositol (GPI) anchors, and PIGA mutations lead to a deficiency of GPI-anchored proteins, such as complement decay-accelerating factor (also known as CD55) and CD59 glycoprotein (CD59), which are both complement inhibitors.

Clinical manifestations of PNH occur when a HSC clone carrying somatic PIGA mutations acquires a growth advantage and differentiates, generating mature blood cells that are deficient of GPI-anchored proteins.

The loss of CD55 and CD59 renders PNH erythrocytes susceptible to intravascular haemolysis, which can lead to thrombosis and to much of the morbidity and mortality of PNH.

Paroxysmal is an incorrect description as haemolysis actually occurs all day but the more concentrated urine at night makes it appear darker and the haemoglobinuria is more obvious. In PNH there is a marked deficiency or absence of the complement regulatory proteins CD55 and CD59.[2]

How common is paroxysmal nocturnal haemoglobinuria? (Epidemiology)

This is a haematopoietic stem cell mutation defect of the PIGA gene in the X chromosome[3] .

- It is not familial and sex distribution is equal.
- It is rare but may be slightly less rare in Southeast Asian communities.

The affected stem cell clone passes the gene to all its descendants (red cells, white cells and platelets) producing a haematological mosaic. The proportion of erythrocytes derived from this stem cell determines the severity of the disease.

Paroxysmal nocturnal haemoglobinuria symptoms (Presentation)[1]

PNH can present anywhere from early childhood to very late in life. In childhood and adolescence the features are more orientated towards the aplastic anaemia. The natural history of PNH is very variable, ranging from mild to life-threatening.

Paroxysmal nocturnal haemoglobinuria is characterised by complement-mediated intravascular haemolysis, severe thrombophilia and bone marrow failure:[4]

- Haemolytic anaemia. This is the most common form of presentation. There is haemoglobinuria that is often mistaken for haematuria. The urine is dark brown in colour, especially the first of the morning.

- **Thrombosis**. This is usually in veins rather than arteries and tends to affect hepatic, abdominal, cerebral and subdermal veins. The exact presentation will depend upon the veins involved - eg, Budd-Chiari syndrome, abdominal, or cerebral vein thrombosis. A 2015 review found that females with PNH were notably more likely than males to have a cerebral vein thrombosis.[5] Thrombosis of dermal veins can cause raised, painful and red nodules in the skin over large areas, like the entire back. It subsides within a few weeks but occasionally necrosis requires skin grafts.
- **Deficient haematopoiesis**. This will produce symptoms of anaemia-like shortness of breath on exertion and fatigue. Neutropenia and thrombocytopenia may allow infection and purpura.

Other symptoms are related to **smooth muscle dysfunction** and include oesophageal spasms that occur in the morning and resolve in the day. Males often have erectile dysfunction.

Examination

Physical signs will depend upon the systems involved:

- Anaemia will cause pallor.
- Infections may produce fever and purpura may be apparent.
- The Budd-Chiari syndrome will produce hepatomegaly and ascites. There may be splenomegaly too.
- Ischaemia of the gut produces absent bowel sounds.
- Cerebral vein thrombosis can produce papilloedema and other neurological signs.
- Red, painful nodules may occur in the skin.

Investigations

- Dipstick urine tests for blood will be positive but microscopy will not show red blood cells. This is the difference between haematuria and haemoglobinuria.

- FBC will show varying degrees of anaemia, usually of a normochromic, normocytic picture, although high cell turnover can produce folate deficiency and a picture of macrocytosis. White cells and platelets may be reduced. The reticulocyte response may be high or low depending upon whether the picture is predominantly one of haemolytic anaemia or aplastic anaemia.
- LDH is elevated with haemolysis and haptoglobin low or absent.
- Bone marrow examination will differentiate an erythroid and hyperplastic marrow during the haemolytic phase or a hypoplastic marrow in the aplastic phase.
- Leukocytes have a low alkaline phosphatase score as in chronic myeloid leukaemia.

Specific tests

- Flow cytometry: blood test to detect CD59 (MIRL), a glycoprotein, and CD55 (DAF) in regulation of complement action. Absence or reduced expression of both CD59 and CD55 on PNH red blood cells is diagnostic.[6]

Radiology

- MRI with contrast can demonstrate saggital vein thrombosis.
- Venography can show thrombosis of major veins.
- MRI, ultrasound or technetium ^{99m}Tc colloid scan of the liver and spleen may demonstrate hypoperfusion.

Differential diagnosis

- Paroxysmal cold haemoglobinuria.
- Other haemolytic anaemias.
- Ischaemic bowel disease.

The combination of haemolytic anaemia, aplastic anaemia and thrombosis is diagnostic but not all three features may be immediately apparent.

Paroxysmal nocturnal haemoglobinuria treatment and management

Anti-C5 monoclonal antibodies (eg, eculizumab or ravulizumab) have revolutionised treatment, resulting in control of intravascular haemolysis and thromboembolic risk, with improved long-term survival. Novel strategies of complement inhibition are emerging.[4]

General measures

Blood transfusion may be required but leukocyte depletion is necessary to reduce antibody formation aggravating haemolysis. There is a risk of meningococcal infection and so meningococcal vaccination is essential.

Pharmacological

Eculizumab[7]

- This is a humanised monoclonal antibody that binds and prevents activation of complement C5 and the subsequent formation of the cytolytic membrane attack complex of complement. It is administered by infusion under expert guidance.
- It reduces intravascular haemolysis and haemoglobinuria, stabilises haemoglobin concentration and reduces the need for transfusion.
- Long-term safety and efficacy of eculizumab have been shown in studies. Survival for those treated with eculizumab was not different from that of a sex-matched and age-matched control group from the general population.[8]
- It has been shown to improve quality of life in patients with PNH.[9] [10]
- A 2014 Cochrane review concurred with the findings above but concluded that the use of eculizumab for patients with PNH could neither be supported or rejected and recommended further, high-quality studies.[11]

Although chronic treatment with eculizumab increases the risk of infections with *Neisseria meningitides*, the drug is generally safe and well tolerated.

However, as is the case with other drugs developed for treatment of ultra-orphan diseases, eculizumab is expensive and treatment must continue indefinitely because C5 inhibition does not affect the process that underlies PNH.

Moreover, due to the heterogeneous nature of the disease, treatment with eculizumab is not appropriate for all patients with PNH.

Ravulizumab [12]
Ravulizumab is recommended by the National Institute for Health and Care Excellence (NICE) as an option for treating paroxysmal nocturnal haemoglobinuria in adults with haemolysis with clinical symptoms suggesting high disease activity, or whose disease is clinically stable after having eculizumab for at least 6 months.

Pegcetacoplan [13]
Pegcetacoplan is a proximal complement pathway inhibitor that primarily prevents extravascular haemolysis. [14]

NICE recommends that pegcetacoplan can be considered for treating paroxysmal nocturnal haemoglobinuria in adults who have anaemia after at least three months of treatment with a C5 inhibitor

Anticoagulation

- For patients who are not treated with eculizumab, consideration of primary anticoagulation prophylaxis should be given to reduce the risk of thrombosis if there is no contra-indication.
- Management of acute thrombotic events requires immediate full anticoagulation (having excluded significant contra-indications) - beginning with heparin - and starting eculizumab. Subsequent anticoagulation with vitamin K antagonists should be maintained long-term. [15]
- Pregnancy with PNH requires careful management.

Prednisolone

- This successfully reduces haemolysis in about 70% of cases.

- The dose for adults is 20-40 mg daily during periods of haemolysis, reduced to that dose on alternate days at other times.
- However, long-term toxicity of corticosteroids significantly limits their attractiveness as a treatment.

Bone marrow transplantation

Allogeneic bone marrow transplantation can cure classic PNH but treatment-related toxicity is a major problem.[16]

Prognosis

This depends upon severity of symptoms and complications. The abnormal clone responsible for the disease may die out but this usually takes at least five years and may take 15-20 years. Acute infection can reactivate the clone.

Thromboembolism is the most common cause of death in patients with PNH: the condition accounts for approximately 40-67% of deaths of which the cause is known.[15]

Further reading

- Brodsky RA; How I treat paroxysmal nocturnal hemoglobinuria. Blood. 2021 Mar 11;137(10):1304-1309. doi: 10.1182/blood.2019003812.
- Colden MA, Kumar S, Munkhbileg B, et al; Insights Into the Emergence of Paroxysmal Nocturnal Hemoglobinuria. Front Immunol. 2022 Jan 28;12:830172. doi: 10.3389/fimmu.2021.830172. eCollection 2021.

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