PRIMEVIEW

PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA

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For the Primer, visit doi:10.1038/nrdp.2017.28

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare haematological disorder named after its characteristic episodes of haemolysis, which are most conspicuous in the evening. PNH is caused by the clonal expansion of haematopoietic stem cells (HSCs) that carry somatic mutations in *PIGA*. *PIGA* encodes a protein that is essential for the biosynthesis of the glycosylphosphatidylinositol (GPI) anchor.

DIAGNOSIS

PNH can present with several haematological (such as anaemia, haemoglobinuria, thrombosis and bone marrow failure) and non-haematological (fatigue and smooth muscle dystonia) manifestations. Smooth muscle dystonia can lead to abdominal pain, oesophageal spasm, dysphagia (difficulty swallowing) and erectile dysfunction. Clinical diagnosis should be confirmed by standard laboratory tests (for example, complete blood count) and flow cytometry, which enables the identification and quantification of blood cell lineages that are deficient in GPI-anchored proteins.

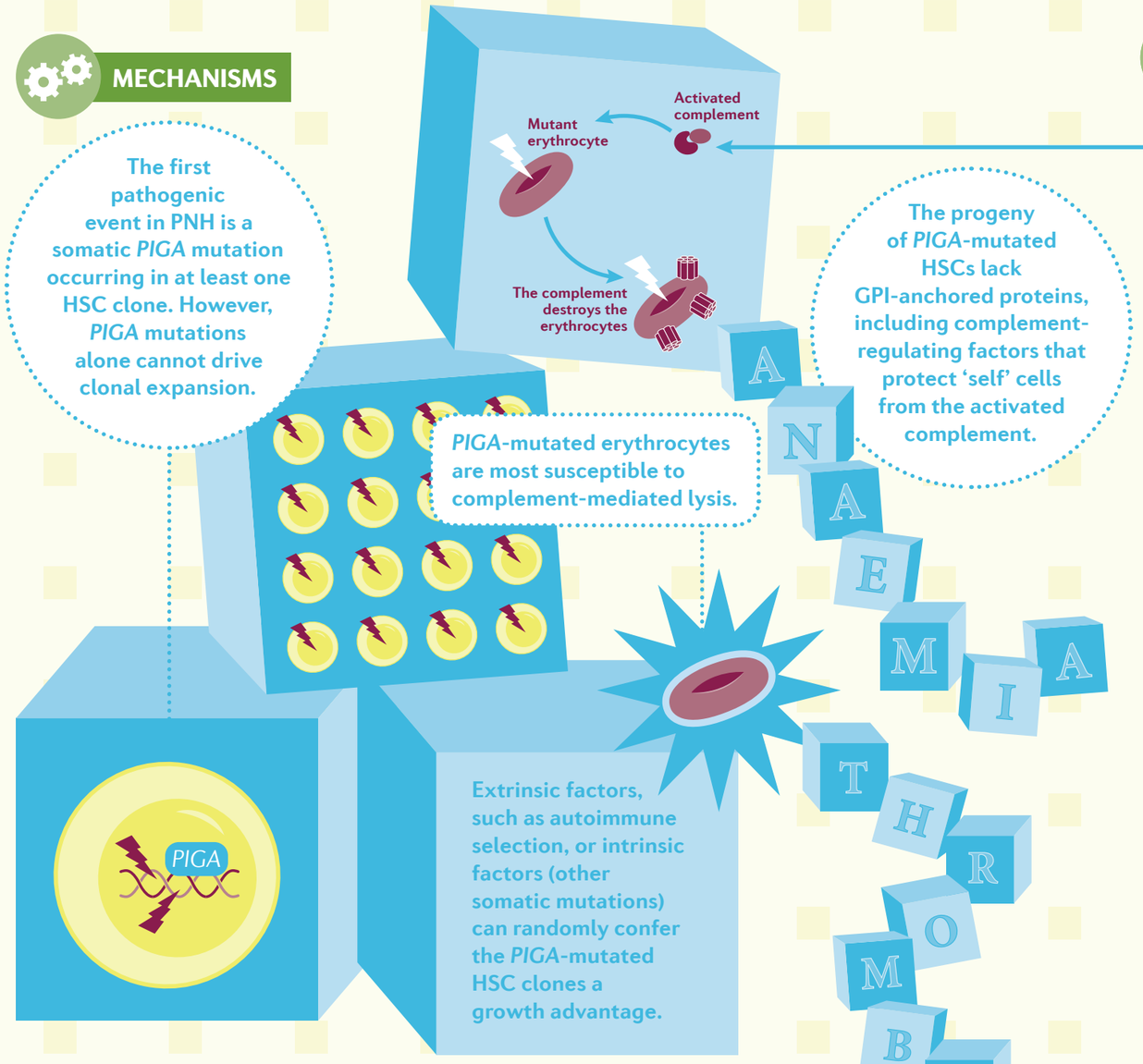
Haemoglobinuria (dark urine owing to the presence of free haemoglobin) is a hallmark of PNH

EPIDEMIOLOGY

The worldwide incidence of PNH is estimated at 1–1.5 cases per million individuals. Of the >1,600 patients with PNH enrolled in the International PNH Registry, 87.5% are of white ethnicity. PNH tends to first present at 30–59 years of age, and the clinical manifestations might vary in different ethnicities.

The median survival of patients with PNH was ~10–20 years before the introduction of complement inhibition therapy in the early 2000s

MECHANISMS



QUALITY OF LIFE

Although the main concerns of patients and physicians are the increased risks of end-organ damage and mortality, the non-fatal manifestations of PNH, in particular, severe fatigue and the need for frequent treatment, have substantial negative effects on patients. Complement inhibition treatment can improve quality of life; however, most patients still require lifelong fortnightly treatment administration.

MANAGEMENT

Bone marrow transplantation and complement inhibition therapy are the preferred disease-modifying strategies. Eculizumab is the only licensed therapy for PNH; owing to its efficacy in reducing complement-mediated haemolysis, it has replaced bone marrow transplantation as first-line therapy. However, patients receiving eculizumab are at increased risk of infections (in particular, from *Neisseria meningitidis*) and might still present with continued anaemia. Acute episodes of thrombosis or renal injury are also possible and require emergency care.

Eculizumab is a monoclonal antibody against complement C5, a factor involved in the final molecular steps of the complement activation pathway

OUTLOOK

The main goal in the development of novel complement inhibitors is designing compounds that are more effective, do not require intravascular administration or have a longer plasma half-life. An alternative therapeutic approach consists of developing inhibitors that target complement factors involved in the alternative pathway (which is always in a state of low-level activation) or in molecular steps upstream to C5 activation. Because this approach would confer an increased vulnerability to infections, its safety will need to be carefully evaluated.

Written by Lucia Brunello; designed by Laura Marshall

Article number: 17029; doi:10.1038/nrdp.2017.29; published online 18 May 2017