:: Paroxysmal Nocturnal Haemoglobinuria

- This document is a translation of the French recommendations drafted by Prof. Gérard Socié, reviewed and published by Orphanet in 2008.
- Some of the procedures mentioned, particularly drug treatments, may not be validated in the country where you practice.

Synonyms:
Marchiafava -Micheli disease, PNH, NPH

Definition:
Paroxysmal nocturnal haemoglobinuria is a rare disease characterised by the combination to **varying degrees of a medullary aplastic pancytopaenia, Coombs negative haemolytic anaemia** and a propensity to develop thromboses especially of the **Budd-Chiari syndrome** type or **cerebral venous thromboses**. It is diagnosed by flow cytometry. It is a clonal disease of haemopoetic stem cells caused by a somatic mutation of the *PIG A* gene.

Further information:
See the Orphanet abstract

Pre-hospital emergency care recommendations
Call for a patient suffering from paroxysmal nocturnal haemoglobinuria

Synonyms

- Marchiafava–Micheli disease, PNH

Aetiology

- genetic mutation of *PIG A* gene in haemopoetic stem cells causing, to varying degrees, pancytopaenia, haemolytic anaemia, thrombosis.

Special risks in an emergency

- cerebral venous thrombosis
- acute haemolysis, acute renal insufficiency
- abdominal pain
- Budd-Chiari syndrome (sub-hepatic venous thromboses): abdominal pain; hepatic autolysis, ascites
- severe infections (meningococcus spp.) in patients treated with eculizumab

Frequently used long term treatments

- anti-coagulants
- eculizumab (SOLIRIS®): complement inhibiting antibodies
- stem cell transplants

Complications

- varying clinical signs: abdominal, neurological...
- abdominal surgical diagnoses to be considered

Specific medical care prior to hospitalisation

- symptomatic treatment
- analgesics (level 2 or 3)
- risk of haemolytic crisis with general anaesthetic in patients under treatment with eculizumab
- possible hyperthermia and its cause have to be treated in parallel

Recommendations for hospital emergency departments

Emergency situations

Various problems can occur in PHN patients in an emergency and are related to the polymorphism of the disease's symptoms. It is necessary to recognise:

- symptoms that can **mimic acute surgical conditions.**
- **real emergencies** requiring treatment (Budd Chiari syndrome, renal insufficiency, cerebral venous thrombosis).
- the **specific problems of PNH patients who have received a transplant** which need the same therapeutic measures used for any patient who has received a transplant of haemopoetic stem cells
- A new **treatment by complement fraction C5 inhibiting antibodies** that has been recently introduced **may** eventually **result in a specific management problem** in patients suffering from PNH

1. Abdominal pain crisis

Faced with a **severe abdominal pain** in patients with PNH, the possibility of **an abdominal pain crisis must be considered**. PNH abdominal pain crises have an uncertain aetiology but are probably caused by mesenteric micro-thromboses. Abdominal pain may also be a sign of **Budd-Chiari syndrome** or a **haemolytic crisis** (see below).

- **Immediate diagnostic measures:**
  - Use all normal means to **eliminate acute surgical disorders** especially appendicitis, peritonitis and biliary colic.
  - The difficulty of diagnosing Budd-Chiari syndrome is discussed below.
- **Immediate therapeutic measures:**
  - **Simple analgesics** with or without **spasmolytics**.
  - **Morphine is used for intense pain (>7/10)** with normal precautions **and after ensuring that all abdominal surgical differential diagnoses have been eliminated**.

2. Budd-Chiari syndrome

Budd-Chiari syndrome must be considered as a differential diagnoses in patients **abdominal pain accompanied by a severe hepatic autolysis**. In addition to the abdominal pain, the symptoms include an **ascites syndrome**.

- **Immediate diagnostic measures:**
  - Emergency abdominal ultrasound
- **Immediate therapeutic measures:**
  - No treatment needs to be started in casualty prior to transfer **except** in rare cases of **shock**
  - Hospitalise in an **intensive care unit**

3. Cerebral venous thrombosis

When faced with **severe unusual and resistant headaches** in a patient suffering from PNH with or without localisation, a cerebral venous thrombosis must always be considered.

- **Immediate diagnostic measures:**
  - **Angio-MRI** as soon as possible
- **Immediate therapeutic measures:**
  - No treatment needs to be started in casualty prior to transfer **except** management of **coma**
  - Hospitalise in an **intensive care unit**

4. Haemolytic crisis and acute renal insufficiency

Renal insufficiency must be considered for every case of **severe haemolytic crisis**, which is often associated with **febricula** and **abdominal pain**.

- **Immediate diagnostic measures:**
  - blood biochemistry
  - urea and creatinine levels
  - electrocardiogram (hyperkalaemia)
- **Immediate therapeutic measures:**
  - Hospitalise in an **intensive care unit**

5. Special case of patients treated with Eculizumab (Soliris®)

This antibody inhibits complement and **patients are therefore likely to develop serious meningococcus spp. infections**. They will all been vaccinated against meningococcus spp. but must always be given oral penicillin prophylaxis.

- **Emergency diagnostic measures:**
  - Any fever that occurs in these patients must **always raise the suspicion of meningococcus infection (ENT entry point)**
  - **perform emergency blood cultures and a lumbar puncture if there is any doubt.**
  - Any symptoms of ***purpura fulminans*** requires **transfer to intensive care**
- **Emergency therapeutic measures:**
  - Hospitalise in a service intensive care unit

Orientation

- Where: hospitals with **both haematology and intensive care units**.
- When: **as soon as possible**, given the disease's rarity.

Drug interactions

- No specific medical contra-indication. No drug is recognised as triggering haemolytic crises

Anesthesia

- Caution is recommended with general anaesthesia **if the patient is receiving Eculizumab** (new drug that prevents complement activation in the disease's haemolytic forms). In practice, the still limited data suggest **a risk of serious haemolytic crisis after general anaesthesia.**

Preventive measures

- Take the patient's temperature to check for infection
- Evaluate the risk factors for a thrombo-embolic event
- Undertake haematology investigations and evaluate the need for a transfusion
- Localise and evaluate any pain
- Contact the patient's haematologist or general practitioner if in any doubt.

Additional therapeutic measures and hospitalisation

- Monitor for infection starting in **catheterised patients.**
- **In patients receiving complement inhibitor (Soliris®)** follow the recommended antibiotic regime and, in the event of abdominal pain, check the date of the next perfusion
- **In patients receiving anticoagulants,** do not stop them without specialist advice except in the event of an anticoagulant accident where the normal protocol should be used
- **In the event of severe vomiting**: IV anti-emetic
- **In the event of pain** (usually abdominal pain): type II analgesics

Organ donation

- The disease does not allow organ donation to be considered given the potential damage to renal and hepatic functions.

Documentary resources

- Peffault de Latour R., Socié G. L'hémoglobinurie paroxystique nocturne. Encyclopédie Orphanet. Avril 2007 www.orpha.net/data/patho/Pro/fr/HemoglobinurieParoxystiqueNocturne-FRfrPro21v01.pdf
- Peffault de Latour R, Mary JY, Salanoubat C, Terriou L, Etienne G, Mohty M, Roth S, de Guibert S, Maury S, Cahn JY, Socie G. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. Blood. 2008 Jun 5.

These guidelines have been prepared in collaboration with Professor Gérard Socié of the Medullary Aplasias Reference Centre, the Association HPN-France, and Dr. Gilles Bagou SAMU-69, Lyon

These guidelines have been translated thanks to the financial support of Alexion. ALEXION

Latest update: September 12th 2008