Porphyrias: a challenge for diagnostic assessment and treatment

by Dr. Aasne Aarsand and Dr. Sverre Sandberg

Porphyrias are relatively rare hereditary diseases, caused by defects in the pathway of haem synthesis. Symptoms such as abdominal pain, pareses and photosensitivity are easily confused with those found in a number of other diseases, so diagnostic assessment, follow-up and treatment can be difficult.

Sunlight is directly or indirectly responsible for maintaining all forms of life on earth. Plants absorb sunlight and utilise this energy to make carbohydrates from simple inorganic compounds including carbon dioxide during the process of photosynthesis. Oxygen, necessary for all forms of higher life, is produced. A central factor in the process of photosynthesis is a porphyrin-containing molecule, namely chlorophyll. Another molecule with a porphyrin ring, haem, is also found in some eukaryotic cells. Haem is involved in different structures concerned with the transport and storage of oxygen (haemoglobin and myoglobin), and is an essential component of the enzymes catalase and peroxidase that protect cells against toxic oxygen derivatives. Haem also takes part in the respiratory chain (mitochondrial cytochromes), thus contributing to the consumption of oxygen, the production of carbon dioxide and the completion of the cycle.

Porphyrias are a group of mostly hereditary disorders caused by enzymatic defects in the haem synthesis pathway [Figure 1]. The name porphyria refers to the accumulation and excretion of porphyrins and porphyrin precursors seen in the different diseases. Porphyria comes from the Greek porphyrus, meaning purple, and refers to the reddish colour of the urine often seen with porphyria patients. Porphyrias are called imitator diseases because the patient’s symptoms resemble those found in many other diseases. Patients with porphyria exhibit symptoms such as abdominal pain, pareses, psychiatric symptoms, bullae and vesicles in areas exposed to light, and increased photosensitivity.

Classification

The porphyrias can be classified as either hepatic or erythropoietic porphyrias, with those found in a number of other diseases, so diagnostic assessment, follow-up and treatment can be difficult.

Table 1. Classification of the porphyrias.

<table>
<thead>
<tr>
<th>Hepatic porphyrias</th>
<th>Erythropoietic porphyrias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute intermittent porphyria</td>
<td>Erythropoietic porphyria (Günther’s disease)</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Erythropoietic protoporphria</td>
</tr>
<tr>
<td>Porphyria variegata</td>
<td>Hereditary coproporphyria</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of acute intermittent porphyria.

<table>
<thead>
<tr>
<th>Suspected if:</th>
<th>Repeated unexplained episodes of abdominal pain, paresis, or psychiatric symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic tests</td>
<td>ALA, PBG and total porphyrins in urine Porphyrins in faeces Plasm a porphyrins</td>
</tr>
<tr>
<td>Follow-up tests</td>
<td>PBG-deaminase DNA examination</td>
</tr>
<tr>
<td>Treatment</td>
<td>Increased intake of carbohydrates Possibly i.v. administration of glucose Haematin (e.g. Norensang)</td>
</tr>
<tr>
<td>Objective of treatment</td>
<td>Remove symptoms Reduce the excretion of ALA, PBG and porphyrins in urine</td>
</tr>
<tr>
<td>Follow-up (every one or two years)</td>
<td>Excretion of porphyrin Ultrasonography of liver in patients &gt; 55 years Alpha-feto protein in patients &gt; 55 years BP Kidney function</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Avoid alcohol, medicinal products that trigger attacks, stress, fasting. See <a href="http://www.porphyrria-europe.com">http://www.porphyrria-europe.com</a></td>
</tr>
</tbody>
</table>
Porphyria cutanea tarda (PCT) Worldwide, this is perhaps the most common of all the porphyrias [Table 3]. The accumulation of porphyrins in PCT results from a deficiency of the hepatic form of uroporphyrinogen decarboxylase (UROD), resulting in an overproduction of especially uroporphyrin and heptaporphyrin. The surplus porphyrins are mostly formed in the liver, but are accumulated in the skin where exposure to sunlight causes the cutaneous symptoms. PCT can be divided into four different types, the two most common being familial and sporadic PCT. The familial type is an autosomal disorder with low penetrance caused by mutations in the UROD gene and is characterised by low UROD activity in all cells, whereas the sporadic type only shows reduced UROD activity in the liver. Both forms are associated with liver cell damage and iron overload and are primarily provoked by alcohol, hepatitis and/or the use of oestrogens. There is also an association with mutations in the haemochromatosis gene. The symptoms are vesiculobullous eruptions on sun-exposed skin areas, in addition to hyperpigmentation and hypertrichosis. The skin symptoms of patients with hereditary coproporphyria or porphyria variegate are identical to those of PCT. It is therefore important that treatment should not start until it has been established which type of porphyria is present, as the medication used in PCT may trigger attacks of the other two types of porphyria. The diagnosis of PCT is made by demonstrating a typical pattern of porphyrins in urine and faeces. In order to diagnose the familial form, uroporphyrinogen decarboxylase activity should be measured and the UROD-gene sequenced. Treatment consists of removing iron by phlebotomy, increasing the output of porphyrins by giving chloroquine, or both removing iron and giving chloroquine.

Erythropoietic protoporphyria (EPP) Erythropoietic protoporphyria is characterised by increased free protoporphyrin in erythrocytes and is caused by reduced activity of the final enzyme in the haem synthesis pathway, ferrochelatase, which incorporates iron into protoporphyrin. EPP is considered to be an autosomal dominant disorder with low penetrance, and in order for symptoms to develop, co-inheritance of a low expression allele or another mutation are required. The typical pattern of porphyrins in urine and faeces is primarily based on a high excretion of coproporphyrin, which gives the skin a slight yellowish brown tinge, increases tolerance for sunlight. The most serious complication of EPP is liver damage which is caused by protoporphyrin accumulating in the hepatocytes. Liver failure occurs in approximately 2% of EPP patients.

Variegate porphyria (VP) and hereditary coproporphyria (HCP) Variegate porphyria and hereditary coproporphyria both show acute and cutaneous symptoms. The acute symptoms and cutaneous symptoms cannot be differentiated from porphyria cutanea tarda. Patients with VP mostly suffer from cutaneous symptoms whereas approximately 90% of HCP patients have acute attacks. HCP is the most rare of the acute porphyrrias. Variegate porphyria is particularly common in South Africa where it can be traced back to a Dutchman who immigrated in 1680. The diagnosis of VP is based on the demonstration of a characteristic fluorescence spectrum with an emission peak at about 624-7 nm. In addition the excretion of faecal protoporphyrin is increased and in the acute stage the level of ALA and PBG in urine is high. The diagnosis of HCP is primarily based on a high excretion of coproporphyrin in faeces and reversal of the coproporphyrin I/III isomer ratio. The treatment regimen is the same as in AIP for acute attacks of both HCP and VP. However, the effect of haematin is poorly documented. The treatment of cutaneous symptoms is primarily the avoidance of exposure to the sun. Chloroquine may trigger attacks and should not be used.

Erythropoietic porphyria Erythropoietic porphyria or Günther’s disease, is inherited as an autosomal recessive trait and is characterised by extreme photosensitivity from early childhood, which may lead to mutilating lesions on the nose and fingers. The disease is caused by a defect in uroporphyrinogen III cosynthase; porphyria cutanea tarda (defect in uroporphyrinogen decarboxylase), hereditary coproporphyria (defect in coproporphyrinogen oxidase), porphyria variegate (defect in protoporphyrinogen oxidase), and erythropoietic protoporphyria (defect in ferrochelatase).

General information about the diagnostic assessment of porphyrias The diagnostic assessment of porphyria can be difficult.
The clinical symptoms are non-specific, but patients who have had repeated unexplained episodes of abdominal pain, pareses, epilepsy or psychiatric symptoms, as well as those with photosensitivity should be investigated for porphyria. The classical finding in patients with pronounced porphyria is the excretion of red to reddish brown urine. In some cases, the urine may not become reddish brown until it has been left standing for a time, preferably exposed to light. The urine can be examined using simple qualitative tests, but it is important to realise that these tests may often give false positive or false negative results. In most cases, therefore, it is advisable to examine urine, faeces and blood using quantitative tests. Test material sent to the laboratory should always be accompanied by clinical information, where special emphasis is put on stating the patient’s symptoms, when the symptoms arise (in relation to certain medicinal products, stress, hunger, alcohol, etc.), and whether there are known cases of porphyria in the family.

The European Porphyria Initiative (EPI) is an organisation whose aim is to present an up-to-date approach to the understanding of porphyria, focussing in particular on the prevention and treatment of acute attacks. It also provides information and support to families affected by porphyria, and supports and encourages medical research. It is possible to find up-to-date information of porphyria and links to national porphyria centres on the EPI web page (http://www.porphyria-europe.com)

Further reading

The authors
Aasne Karine Aarsand, MD
Sverre Sandberg, MD
National Porphyria Centre
Laboratory of Clinical Biochemistry
Haukeland University Hospital
N-5021 Bergen, Norway