Porphyrias
# Case Discussion - Monday 27/3/2017

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Porphyridins are cyclic molecules formed by the linkage of four pyrrole rings through methenyl bridges. Three structural features of these molecules are relevant to understanding their medical significance.

1. Side chains: Different porphyrins vary in the nature of the side chains that are attached to each of the four pyrrole rings. For example, uroporphyrin contains acetate (-CH2-COO-) and propionate (-CH2-CH2-COO"), side chains, whereas coproporphyrin is substituted with methyl (-CH3) and propionate groups.
Porphyrsins contain four pyrrole rings (A, B, C, and D) joined through methenyl bridges.

Porphyrsins contain side chains attached to each of the four pyrrole rings. In type I porphyrsins, the side chains are arranged symmetrically, that is, for uroporphyrin I, A (acetate) alternates with propionate (P) around the tetrapyrrole ring.

Acetate (A) and propionate (P) are reversed in ring D of uroporphyrin III compared with uroporphyrin I. Only type III porphyrsins are physiologically important in humans.

Figure 21.2
Structures of uroporphyrin I and uroporphyrin III. [Note: A = acetate and P = propionate.]
The side chains of porphyrins can be ordered around the tetrapyrrole nucleus in four different ways, designated by Roman numerals I to IV. Only type III porphyrins, which contain an asymmetric substitution on ring D are physiologically important in humans. [Note: in congenital erythropoietic porphyria, type I porphyrins, which contain a symmetric arrangement of substituents are synthesized in appreciable quantities.
Porphyrinogens

Porphyrin precursors exist in the chemically reduced form called porphyrinogens. In contrast to the porphyrins, which are colored, the porphyrinogens, such as uroporphyrinogen, are colorless. Porphyrinogens serve as intermediates between porphobilinogen and protoporphyrin in the biosynthesis of heme.
Porphyrias are caused by inherited (or occasionally acquired) defects in heme synthesis, resulting in the accumulation and increased excretion of porphyrins or porphyrin precursors. With the exception of congenital erythropoietic porphyria, which is a genetically recessive disease, all porphyrias are inherited as autosomal dominant disorders. The mutations that cause the porphyrias are heterogenous (not all are at the same DNA locus), and nearly every affected family has its own mutation. Each porphyria results in the accumulation of a unique pattern of intermediates caused by the deficiency of an enzyme in the heme synthetic pathway.
Clinical manifestations

The porphyrias are classified as **erythropoietic** or **hepatic**, depending on whether the enzyme deficiency occurs in the erythropoietic cells of the bone marrow or in the liver. Hepatic porphyrias can be further classified as acute or chronic.
Individuals with an enzyme defect leading to the accumulation of tetrapyrrole Intermediates show **photosensitivity**—that is, skin itches and burns \((\textit{pruritis})\) when exposed to visible light.

[Note: These symptoms are thought to be a result of the porphyrin-mediated formation of superoxide radicals from oxygen. These reactive oxygen species can oxidatively damage membranes, and cause the release of destructive enzymes from lysosomes. Destruction of cellular components leads to the photosensitivity].
Porphyria cutanea tarda, the most common porphyria, is a chronic disease of the liver and erythroid tissues. The disease is associated with a deficiency in uroporphyrinogen decarboxylase, but clinical expression of the enzyme deficiency is influenced by various factors such as:

a. hepatic iron overload,
b. exposure to sunlight, and
c. the presence of hepatitis B or C, or
d. HIV infections.

Clinical onset is typically during the fourth or fifth decade of life. Porphyrin accumulation leads to cutaneous symptoms, and urine that is red to brown in natural light, and pink to red in fluorescent light.
Figure 21.5
Skin eruptions in a patient with porphyria cutanea tarda.

Figure 21.6
Urine from a patient with porphyria cutanea tarda (right) and from a patient with normal porphyrin excretion (left).
Acute hepatic porphyrias (acute intermittent porphyria, hereditary coproporphyria, and varigate porphyria) are characterized by acute attacks of gastrointestinal, neurologic/psychiatric, and cardiovascular symptoms. Porphyrias leading to accumulation of ALA and porphobilinogens, such as acute intermittent porphyria, cause abdominal pain and neuropsychiatric disturbances. Symptoms of the acute hepatic porphyrias are often precipitated by administration of drugs such as barbiturates and ethanol, which induce the synthesis of the heme-containing cytochrome P450 microsomal drug oxidation system. This further decreases the amount of available heme, which, in turn, promotes the increased synthesis of ALA synthase.
Erythropoietic porphyrias

The erythropoietic porphyrias (congenital erythropoietic porphyria and erythropoietic protoporphyria) are characterized by skin rashes and blisters that appear in early childhood. The diseases are complicated by: cholestatic liver cirrhosis and progressive hepatic failure.
One common feature of the porphyrias is a decreased synthesis of heme. In the liver, heme normally functions as a repressor of *ALA synthase*. Therefore, the absence of this end product results in an increase in the synthesis of *ALA synthase* (derepression). This causes an increased synthesis of intermediates that occur prior to the genetic block. The accumulation of these toxic intermediates is the major pathophysiology of the porphyrias.
Treatment

During acute porphyria attacks, patients require medical support, particularly treatment for pain and vomiting. The severity of symptoms of the porphyrias can be diminished by:

1. intravenous injection of **hemin** which decreases the synthesis of ALA synthase.
2. Avoidance of sunlight and
3. Ingestion of β-carotene (a free-radical scavenger) are also helpful.
LEAD POISONING
- Ferrochelatase and ALA dehydrase are particularly sensitive to inhibition by lead.
- Coproporphyrin III and ALA accumulate in urine.

ACUTE INTERMITTENT PORPHYRIA
- An acute disease caused by a deficiency in hydroxymethylbilane synthase.
- Porphobilinogen and δ-aminolevulinic acid accumulate in the urine.
- Urine darkens on exposure to light and air.
- Patients are NOT photosensitive.
**PORPHYRIA CUTANEA TARDA**
- A chronic disease caused by a deficiency in *uroporphyrinogen decarboxylase*.
- Uroporphyrin accumulates in the urine.
- It is the most common porphyria.
- Patients are photosensitive.

**CONGENITAL ERYTHROPOIETIC PORPHYRIA**
- This disease is caused by a deficiency in *uroporphyrinogen III synthase*.
- Uroporphyrinogen I and coproporphyrinogen I accumulate in the urine.
- Patients are photosensitive.

Diagram:
- δ-Aminolevulinic acid → Porphobilinogen → Hydroxymethylbilane (enzyme bound) → Uroporphyrinogen III → Uroporphyrin III → Coproporphyrinogen III → Coproporphyrin III
**ERYTHROPOIETIC PROTOPORPHYRIA**
- The disease is due to a deficiency in ferrochelatase.
- Protoporphyrin accumulates in erythrocytes, bone marrow, and plasma.
- Patients are photosensitive.

**VARIGATE PORPHYRIA**
- An acute disease caused by a deficiency in protoporphyrinogen oxidase.
- Protoporphyrinogen IX and other intermediates prior to the block accumulate in the urine.
- Patients are photosensitive.

**HEREDITARY COPROPORPHYRIA**
- An acute disease caused by a deficiency in coproporphyrinogen oxidase.
- Coproporphyrinogen III and other intermediates prior to the block accumulate in the urine.
- Patients are photosensitive.