When the wrong pill can kill - The acute porphyrias
A group of severly underdiagnosed adult metabolic disorders

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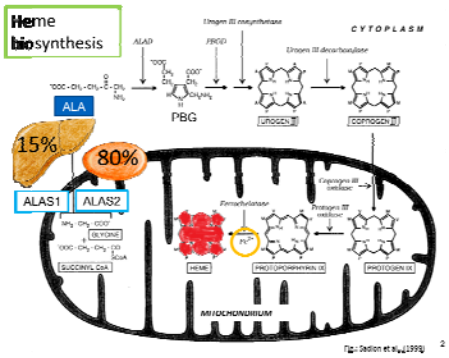
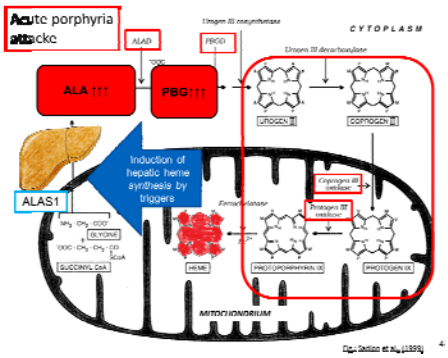
1 International Porphyria Patient Network (IPPN); www.ippn.info
2 Swiss Society for Porphyria (SGP); www.porphyria.ch
3 Berliner Leberring; http://www.porphyrie-leberring.de
4 EPP Austria: www.eppaustria.at
5 ProRaris - Allianz Seltener Krankheiten Schweiz; www.proraris.ch

Acute porphyrias are a group of genetic disorders, in which the wrong medication, stress, fasting, infections and other trigger factors like some endogenous and exogenous hormones may induce a potentially life-threatening metabolic crisis.





Heme biosynthesis:

- The red blood dye «heme» is build in eight enzymatic steps
- From simple precursors, cyclic molecules are formed, the «porphyrins»
- In the last step, an iron ion is bound to the last precursor to build the final product, heme
- While most heme is used in the red blood cells to build hemoglobin, around 15 % is used in the liver: Heme is used by liver enzymes to detoxify exogenous substances and to modify drugs, e.g. make them more water soluble for excretion or transform them into their active form.

The acute porphyrias:

- Four genetic defects affecting the heme biosynthesis in the liver cause the so-called «acute porphyrias».
- During biochemical reactions in the liver, heme is consumed. In the normal liver, the synthesis of heme is simply upregulated (by induction of the enzyme ALAS1). In case of mutations in the hepatic heme biosynthesis pathway, toxic precursors of heme accumulate and cause an acute porphyria attack:
- Typical symptoms of an acute porphyria attack are severe and excruciating abdominal pain. In addition, vomiting, obstipation, disorientation, paralysis, a low sodium concentration and death by respiratory arrest may occur.
- In two forms of acute porphyrias, in addition to acute crises skin blisters after sun exposure may also occur. In all acute porphyrias, the risk to develop liver cancer is markedly increased, and all patients with the mutation should be screened annually from the age of 50.

Diagnosis

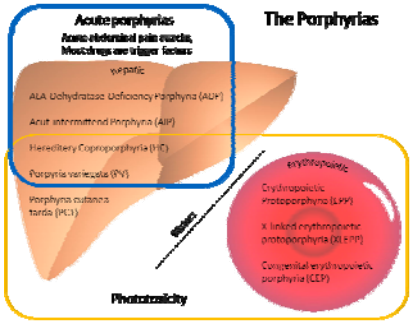
- During a crisis, the urine of the patients usually turns reddish-brown after exposure to light and oxygen. The urine is also the key to the right diagnosis: The substances “aminolevulinic acid” (ALA) and “porphobilinogen” (PBG) are excreted in the urine during the crisis in high concentrations (> 5 x upper reference limit). A positive test result performed in an experienced laboratory is a simple, cheap and specific proof for an acute porphyria crisis.
- The pain during the crises is caused by nerve damage and usually does not respond to pain medications other than opiates. The tests routinely performed in an emergency unit, like CT, MRI, ultrasound and laboratory tests on inflammation, do not show any abnormal features. Therefore the pain is often misdiagnosed as psychosomatic and the patient is sent home with some common pain medications – which are useless and can even aggravate the crisis.

Trigger factors and therapy

- In the acute porphyrias, the wrong medication, stress, fasting, infections and other trigger factors like some endogenous and exogenous hormones may induce the potentially life-threatening metabolic crisis. Lists with safe medications in acute porphyrias can be obtained by the national and European porphyria reference centers.
- In case of a crisis a preparation of heme is administered which effectively stops the acute attack. Currently, a new siRNA which targets ALAS1 in the liver is being tested in phase II/III clinical trials.

The porphyrias

- The acute porphyrias specifically affect the heme biosynthesis in the liver. Other defects in the same pathway cause the so called erythropoietic porphyrias which only affect the heme biosynthesis during maturation of the red blood cells and are characterized by severely painful phototoxic reactions.
- The two groups of porphyrias differ in nearly all aspects, in their diagnosis and therapeutic options and, most importantly, only patients with the acute porphyrias need to avoid the mentioned trigger factors and unsafe medications.



Literature:

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