Understanding the Porphyrias

A breakdown of heme synthesis causes widespread symptoms of porphyria, an unusual comorbid disease in primary immunodeficiencies.

By Cynthia Perry

MANY PATIENTS WITH a primary immunodeficiency (PI) and other diseases treated with immune globulin have comorbidities. These diseases may be caused by the PI, or it may cause the PI or be entirely unrelated. In addition, many of these diseases are accompanied by nonspecific and overlapping symptoms. One of the most unusual of these diseases is porphyria, which unlike many other diseases, can often be confirmed by a genetic diagnosis.

Porphyria is a group of diseases that cause the body to incorrectly produce heme due to specific enzymatic defects. Heme is the substance that gives blood its red color. It is required to transport oxygen in the body and is essential for all cells. Most heme comes from the bone marrow and the liver, and it is used throughout the body, but especially for red blood cell hemoglobinization (when red blood cells begin producing a lot of haemoglobin inside them).[1] Heme is produced in an eight-enzyme step process. Enzyme activity is diminished in the heme synthesis steps for all but one of the porphyrias, X-linked protoporphyria (XLP), in which enzyme activity is increased.[1]

In porphyria, cells fail to completely metabolize porphyrins and porphyrin precursors into heme. When these heme precursors build up in the body, they cause illness. Depending on the type of porphyria and enzymatic defect, these chemicals may collect in the liver or the bone marrow.[3]

Hepatic porphyrias are those in which there is an accumulation of heme precursors in the liver. Most of these result in porphyrias with acute attacks thought to be caused by neurotoxic effects of the heme precursors.[2] In erythropoietic porphyrias, heme precursors first accumulate in the bone marrow and red blood cells. The symptoms of porphyrias, which primarily have skin manifestations, are caused by the buildup of photosensitizing porphyrins in the skin.[4]

Acute Hepatic Porphyrias

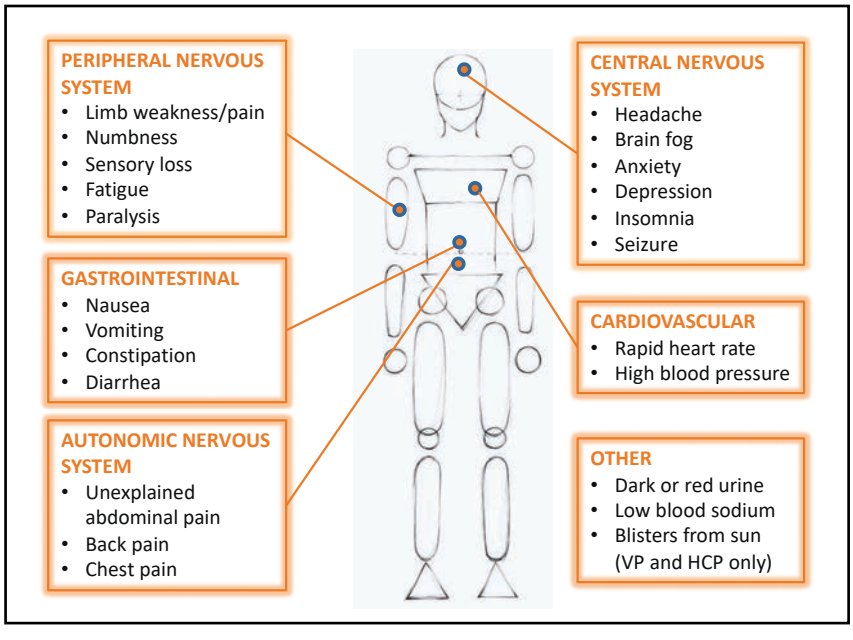
The hepatic porphyrias that manifest with acute attacks are:

- Acute intermittent porphyria (AIP)
- Aminolevulinic acid dehydratase deficiency (ALAD) porphyria (ADP)
- Hereditary coproporphyria (HCP)
- Variegate porphyria (VP)

Enzyme activity in the heme synthesis pathway is reduced to about 50 percent of normal in AIP, HCP and VP, and is less than 50 percent in ADP.[2] Symptom onset of these porphyrias is rare before puberty. Since hormones trigger acute attacks, approximately 80 percent of those who suffer from symptomatic acute hepatic porphyrias are women.[5]

All four acute porphyrias present with indistinguishable symptoms during acute attacks that typically start with

Figure: Acute Hepatic Porphyria Symptoms[5]



brain fog, insomnia and fatigue, and they can progress over hours or days to more severe symptoms. Without early and appropriate intervention, acute attacks can last for months and can cause life-threatening complications, including respiratory failure, seizures, chronic kidney failure, liver damage and coma.[6]

Symptoms of acute attacks are nonspecific and affect the entire body (Figure):[6]

- Widespread pain: Attacks can include severe abdominal pain, chest pain, pain in the neck, lower back, buttocks, arms or legs.
- Gastrointestinal: Nausea, vomiting, constipation or diarrhea are common symptoms during attacks.
- Urological: Patients can present with dark (reddish or brownish) urine and sometimes urinary retention during attacks.
- Neurological and psychological: Symptoms of acute attacks can include headache, anxiety, irritability and depression, psychosis, seizures and coma.
- Peripheral nervous system: Numbness and tingling, muscle weakness and sometimes difficulty breathing can occur during attacks.
- Cardiovascular: Rapid heart rate, high blood pressure and cardiac arrhythmia can also occur.
- Solid organs: Over time, patients can develop liver or kidney damage from an accumulation of toxins in these organs.

The acute symptoms of HCP and VP are identical to other acute porphyrias. However, with HCP, blistering skin lesions and fragile skin may occur with or apart from acute attacks. VP can also manifest with skin symptoms identical to those seen in porphyria cutanea tarda (PCT), which is explained below. Sometimes, skin manifestations are the only symptom of VP.[2]

Many of the triggers of an acute porphyria attack act by increasing the body's demand for heme, as is the case in metabolizing certain medications. With porphyria, the production of heme is limited, porphyrin precursors in the body increase, the offending medication is not metabolized properly, and an acute attack ensues.[6]

Triggers for the acute porphyrias include (but aren't limited to):[5]

- Alcohol
- Smoking
- Certain drugs, especially P450 pathway drugs
- Stress
- Dieting and fasting
- Hormonal fluctuations
- Exposure to sunlight (in the forms with cutaneous symptoms)

Acute porphyria attacks may require hospitalization to stabilize the patient. Treatments can include:[4]

- IV hemin
- Pain medications
- Nutrition and hydration
- Hypertonic saline to correct hyponatremia (low sodium)

Frequent acute attacks may be decreased by suppressing ovulation in women and avoiding porphyrogenic (nitrogen-containing) drugs.

Cutaneous Erythropoietic Porphyrias

When the heme synthesis process breaks down in the cutaneous erythropoietic porphyrias, excess heme precursors accumulate in the skin, causing photosensitivity. The cutaneous erythropoietic porphyrias are:

- Congenital erythropoietic porphyria (CEP)
- Erythropoietic protoporphyria (EPP)
- X-linked protoporphyria (XLP)

Symptoms in all the cutaneous porphyrias include severe pain, itching, burning, swelling, edema and redness of the skin after exposure to light — sometimes as soon as a few minutes after exposure. Most symptoms subside within 48 hours, but pain and discoloration may last longer. The skin may eventually take on a leathery appearance after repeated exposure to sun.[2]

Symptoms unique to each disease include:[6]

- CEP: Skin reactions can also include blistering and fragile skin. Patients can exhibit red or dark urine and anemia and may have an enlarged spleen. They can also have skeletal changes such as bone loss and calcification. Some affected individuals may lose nails, lips or parts of the ears, nose and fingers.
- EPP: Skin blistering isn't common, but patients may develop mild anemia, gallstones and liver damage; some may even have liver failure.
- XLP: This disease doesn't involve blistering of the skin, but it can involve anemia. Patients with XLP can also develop gallstones and/or liver disease, including liver failure.

All cutaneous porphyrias cause photosensitivity to sunlight; patients may also be sensitive to some indoor lights such as fluorescents.[6]

The most effective treatments for the cutaneous erythropoietic porphyrias include avoiding sunlight and wearing protective clothing. And, increasing skin pigmentation with afamelanotide can increase sunlight tolerance.[2]

Cutaneous Hepatic Porphyrias

The cutaneous forms of porphyria that are also hepatic are:

- Porphyria cutanea tarda (PCT)
- Hepatoerythropoietic porphyria (HEP)

PCT is the only form of porphyria that can develop in the absence of genetic mutation; it is the most common type of porphyria. In PCT, uroporphyrinogen decarboxylase (UROD) deficiency and iron accumulation in the liver play a role in the disease process.[4] HEP also stems from a UROD deficiency, but this type of porphyria is very rare.[6]

With PCT, patients may experience photosensitivity, including blistering of the skin and extremely fragile skin, excessive hair growth, especially on the face, and small skin bumps with a white head, especially on the backs of the hands. Patients may also develop liver abnormalities, including iron accumulations, fatty liver, inflammation and scarring of the portal vein.[6]

In HEP, symptoms usually start within the first two years of life. Patients experience skin symptoms identical to PCT. They may also have anemia from premature destruction of red blood cells. Anemia associated with HEP may be mild or severe. If the anemia is severe, it can cause fatigue, pale skin, irregular heartbeat, chest pain, dizziness and abnormally cold hands and feet. Some patients may have an enlarged liver and/or spleen.[6]

Sun exposure triggers both HEP and PCT. In addition, there are other triggers for PCT, including alcohol and smoking.[1]

Treatments for the cutaneous hepatic porphyrias include avoiding sunlight and wearing protective clothing. Also, increasing skin pigmentation with afamelanotide can increase sunlight tolerance.[6]

Patients with PCT who suffer from iron accumulation in the liver can have blood extracted on a regular basis to reduce their blood iron levels. Patients with HEP and anemia may need iron supplements or blood transfusions.[2,6]

Testing for the Porphyrias

Clinical tests for the various porphyrias depend on the suspected type of porphyria. Since there are overlapping symptoms in many of the porphyria types, panels are often used to rule in or out variants of the disease. The tests typically run for the porphyrias look for elevated levels of aminolevulinic acid (ALA), coproporphyrin (COPRO), porphobilinogen (PBG), protoporphyrin and/or uroporphyrin (URO) in the urine, blood and/or stool.

Hyponatremia (low blood sodium) often occurs in the acute porphyrias. Liver enzymes (alanine transaminase and aspartate transaminase) may also be slightly elevated in hepatic forms of porphyria, while other liver function tests remain normal.

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Genetic testing is available for all types of porphyria discussed in this article.[7] The tests may not detect all genetic defects, and thus won't detect all cases of porphyria. However, genetic testing can confirm clinical diagnoses in many cases. It can also be useful to screen family members of affected individuals to see if they are carriers of porphyria — either affected or unaffected; unaffected carriers can pass the disease on to their offspring. The results of genetic tests should always be discussed with a geneticist or a trained genetics counselor.

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