ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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What Hematologists Need to Know About Acute Hepatic Porphyria

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H&O What is porphyria?

MB The porphyrias encompass a group of inherited metabolic disorders that result from a deficiency of one of the enzymes in the heme biosynthetic pathway. These are genetic disorders; they can be inherited in an autosomal dominant or recessive X-linked pattern; or they may be sporadic, as with porphyria cutanea tarda.

H&O How many types of porphyria exist?

MB There are 8 different kinds of porphyria. These may be classified as hepatic or erythropoietic based on the primary site of accumulation of porphyrins, but more commonly they are classified clinically as acute or cutaneous. The acute hepatic porphyrias include acute intermittent porphyria (the most common form), hereditary coproporphyria, and variegate porphyria, which are autosomal dominant in inheritance. Aminolevulinic acid dehydratase deficiency porphyria is autosomal recessive and very rare, with fewer than 10 cases reported worldwide.

The cutaneous porphyrias include porphyria cutanea tarda, which is the most common form; erythropoietic protoporphyria; X-linked protoporphyria; and congenital erythropoietic porphyria. These can present with blistering skin lesions or with nonblistering photosensitivity. Hereditary coproporphyria and variegate porphyria also can present with blistering skin lesions similar to those seen in porphyria cutanea tarda. Patients with cutaneous porphyria rarely present to hematologists, which is why I am focusing on the acute hepatic porphyrias.

H&O How common is acute hepatic porphyria?

MB Based on estimates from Western Europe, the combined prevalence of the acute hepatic porphyrias among the white population is approximately 1 in 200,000. These disorders are more common in certain parts of the world because of founder mutations. For example, the carrier frequency of acute intermittent porphyria is much higher in the Scandinavian countries, and variegate porphyria is much more common in South Africa.[1]

Even where the incidence is high, symptoms related to these disorders remain rare. In fact, most patients who inherit a genetic change do not manifest symptoms of the disorder—the disease remains latent in a vast majority of these patients. Based on studies from Europe, we have estimated that only about 10% of patients who have a mutation in one of these genes will actually present with symptoms. In fact, a more recent study using genomic and exomic databases suggests that having a mutation in one of these genes is much more common than we initially thought, making the penetrance of this disorder much lower.[2]

H&O Could you talk in more detail about the causes of acute hepatic porphyria?

MB As I mentioned, a genetic change leads to a deficiency in one of the enzymes in the heme biosynthetic pathway. Because these are almost always autosomal dominant disorders, patients have approximately half-normal enzyme

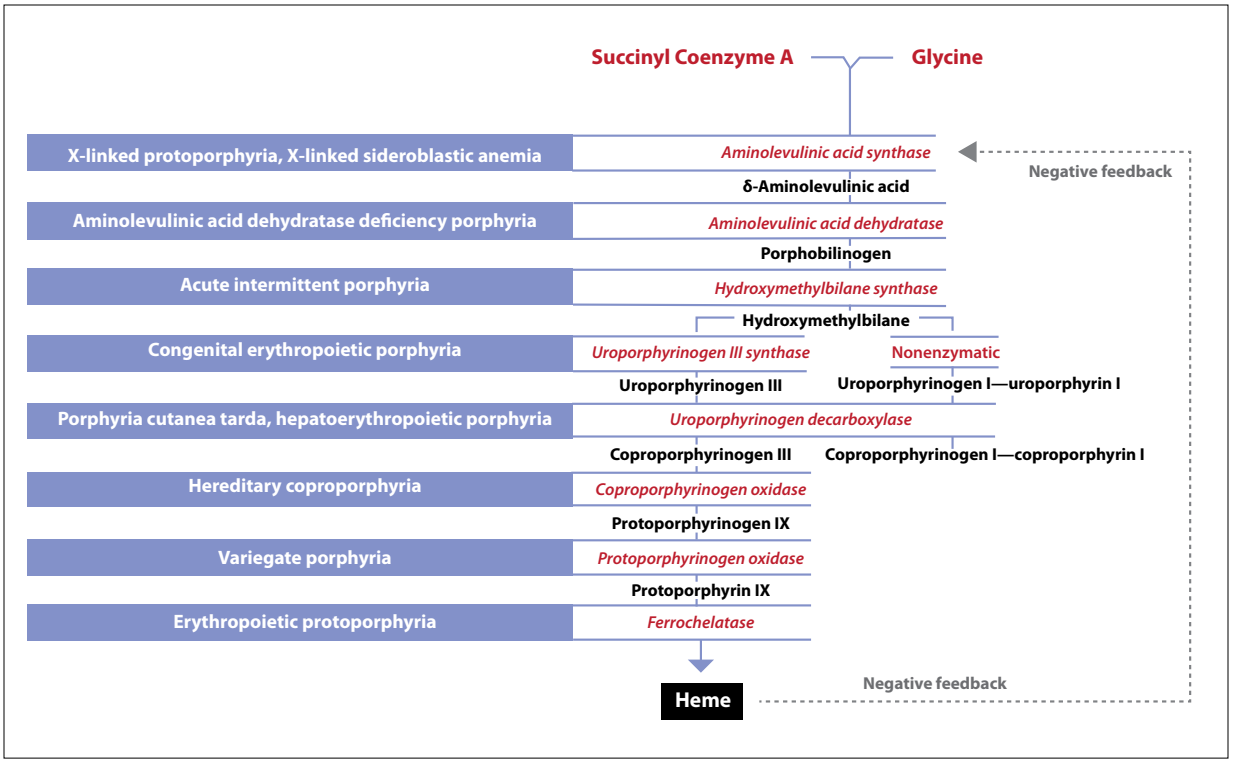

Figure. The heme biosynthetic pathway. Enzymes are in italics.

activity. Under normal circumstances, this is sufficient for heme synthesis. The presence of certain precipitating factors, however, can lead to symptomatic disease. The most common precipitating factors are drugs, fasting, hormonal changes, stress, and illness. Women are much more likely than men to manifest symptoms, presumably because of hormonal factors.

All of these factors markedly increase the demand for hepatic heme, and the decreased hepatic free heme induces the synthesis of δ-aminolevulinic acid synthase 1 (ALAS1)—the first enzyme in the heme biosynthetic pathway—by a negative feedback mechanism (Figure). Because of the approximately half-normal enzyme activity in these acute hepatic porphyrias, the marked overexpression of ALAS1 results in the increased production and subsequent accumulation of the neurotoxic porphyrin precursors, aminolevulinic acid (ALA) and urine porphobilinogen (PBG). These porphyrin precursors are thought to be neurotoxic and responsible for the multisystemic manifestations of this disorder.

H&O What is the prognosis for someone with acute porphyria?

MB The overall prognosis is good because specific treatment is available, but symptoms must be recognized and managed correctly. Delays in diagnosis and treatment may result in chronic complications that can be very debilitating for patients.

H&O What are the symptoms of porphyria, and what complications can occur?

MB One of the most common symptoms is acute abdominal pain that is poorly localized and very severe. Because the pain is neuropathic, it often is not accompanied by fever or leukocytosis. Patients also may experience nausea, vomiting, constipation, or pain in the chest or back. They also can have significant autonomic dysfunction, including tachycardia and hypertension. Patients also may develop paresis or acute motor neuropathy, and may experience changes in mental status, such as behavioral changes, agitation, or hallucinations. If patients do not receive appropriate treatment, there is a possibility that neuropathy could progress and even lead to respiratory paralysis. Recent reports have shown that during acute attacks, some patients develop posterior reversible encephalopathy syndrome, which can be diagnosed on magnetic resonance imaging of the brain and can give a clue to the diagnosis. One important thing to note is that no sign or symptom is universal, and presentations are often atypical.

Another important early sign of this disorder is hyponatremia. This is often seen when patients present with acute attacks, and can be one of the first clues leading to diagnosis. Hyponatremia presumably occurs because of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or because of loss of sodium in the gastrointestinal tract or kidneys. It is very important to monitor patients with hyponatremia because they can develop seizures.

Additional findings that can lead a physician to suspect porphyria include new-onset hypertension in a young patient, proximal muscle weakness, or dark or reddish-brown urine.[3]

H&O How is the disease diagnosed?

MB The most important diagnostic test for acute hepatic porphyria is PBG. This can be done on a spot sample of urine; there is no need to waste valuable time by collecting a 24-hour sample. If urine PBG is elevated, the patient has an acute hepatic porphyria. This is a highly sensitive test because urine PBG typically is elevated during an acute attack.

Second-line testing is available to determine the specific type of acute porphyria, although knowing the type is not necessary at the time of initial diagnosis because treatment for acute symptoms for all the forms is identical.

Genetic testing can be used as a confirmatory test for the diagnosis. Gene sequencing is available for all of the genes involved in acute hepatic porphyria. This is important not just to establish the diagnosis in the patient, but for testing family members.

We often see physicians ordering urine porphyrin levels instead of urine PBG in patients with suspected porphyria. Most of the referrals I receive are based on slight elevations in coproporphyrin levels on the urine porphyrin profile. Elevations in urine porphyrins are seen in a variety of conditions, however; this is a nonspecific test that should not be used to diagnose acute hepatic porphyrias. This is one of the most common causes of misdiagnosis in these patients.

H&O What type of testing should be done in family members after a diagnosis?

MB Once the genetic mutation has been identified in the patient, at-risk family members should be tested. Family members should receive targeted mutation analysis; they do not need their entire gene sequenced. Family testing is important because the vast majority of patients have latent disease, and identifying a genetic mutation provides an opportunity to counsel these patients about how to avoid the triggering factors that could precipitate acute attacks.

H&O Does porphyria often get confused with other diseases?

MB The most common presenting symptoms of this disorder—abdominal pain, nausea, and vomiting—are common, nonspecific symptoms. As you can imagine, this is a major reason why the disorder is often misdiagnosed and underdiagnosed. We often come across patients who have been misdiagnosed for many years. Some of the more common misdiagnoses are appendicitis and cholecystitis; other patients are told they have a urinary tract infection, colitis, or another common condition. Many patients actually have multiple surgeries before the diagnosis is established.

H&O What treatments are used for acute porphyria?

MB The most important step is to stabilize patients, and address symptoms such as nausea, vomiting, hypertension, and electrolyte imbalances such as hyponatremia. Patients also should be treated for their pain, which is severe—I would like to emphasize that many of these patients are undertreated for their pain. All patients need to have a careful history taken to identify what triggering factors might be involved. All offending drugs and other factors should be removed.

In the past, 10% dextrose solution was used as first-line treatment for these patients, but more recently we have switched to the use of intravenous hemin (Panhematin, Recordati Rare Diseases) for patients presenting to the hospital. This treatment is able to replenish the heme pool in the liver and represses the upregulation of hepatic ALAS1. Patients receive 3 to 4 mg/kg of hemin over 3 to 4 days.[3]

In the outpatient setting, patients should receive detailed counseling regarding precipitating factors for acute attacks. They also should be encouraged to maintain a healthy diet and avoid fasting. Although we do not recommend the concept of carbohydrate loading, which has appeared in the literature, some patients report a benefit from increasing carbohydrate intake if they are having symptoms.

For women who experience cyclic attacks that are related to their menstrual cycle, a gonadotropin-releasing hormone agonist such as leuprolide acetate (Lupron Depot, AbbVie) can be beneficial in some cases.

We are unable to identify a trigger in certain patients, and they continue to have recurrent attacks. Such patients can benefit from prophylactic administration of hemin

every 1 to 4 weeks as an outpatient. This typically is administered in a hematologist's office or outpatient infusion center.

H&O Is there a cure for acute hepatic porphyria?

MB Liver transplant can cure porphyria, but we use it only as a treatment of last resort because it has a very high morbidity rate. We typically reserve liver transplant for patients who are refractory to hemin therapy, are severely debilitated by attacks, and have a very poor quality of life.

H&O What kind of surveillance is required for patients after an acute attack?

MB These patients need ongoing follow-up and monitoring. They are at increased risk for hepatocellular carcinoma, so patients aged 50 years and older should receive annual screening using a combination of liver ultrasound and alpha-fetoprotein levels. They also are at high risk of developing renal insufficiency, so careful monitoring of renal function should be done. In a study from France, 59% of symptomatic patients developed chronic kidney disease.[4]

Women who are taking a gonadotropin-releasing hormone agonist will need additional monitoring by their gynecologist. Patients who are on chronic hemin therapy should have their ferritin monitored because they can develop iron overload.

H&O What are some of the recent studies that have shed additional light on acute hepatic porphyria?

MB One of the recent studies from our center that has greatly helped us understand the pathophysiology of acute intermittent porphyria was conducted on the explanted liver of a patient who had a liver transplant for this disease. The biochemical and other results from this study allowed us to confirm that ALAS1 mRNA is significantly increased in patients with acute attacks, and that ALA and PBG are the primary mediators of acute attacks. We had suspected this for many years, but this study offers much greater certainty.[5]

We also have seen results from several studies addressing an experimental therapy for acute porphyrias called ALN-AS1, which is currently in phase 1 clinical trials. ALN-AS1 is a small interfering RNA therapy that decreases the upregulation of ALAS1 mRNA. This subcutaneous agent has shown very promising initial results, along with sustained suppression of ALA and PBG. So this is an exciting time, and we hope that there will be a potential new therapy for patients with acute intermittent porphyria.[6]

Disclosures

Dr Balwani has participated in advisory boards for Recordati Rare Diseases and Alnylam.

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