Porphyria: The Neglected Diagnosis

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Porphyria is a neglected diagnosis even among experienced physicians. For most physicians, porphyrias are considered complicated diseases and too rare to commit to memory. However, the prevalence of some types of porphyria may be higher than is generally assumed [1].

Porphyrias are a group of rare metabolic disorders, either inherited or acquired, along the heme biosynthetic pathway [1-3]. Each type of porphyria is the result of a specific deficiency in one of the enzymes involved in the pathway and, accordingly, is characterized by a specific pattern of accumulation of heme precursors and typical clinical manifestations [1,2].

The diseases have been grouped as acute hepatic porphyrias or photocutaneous porphyrias. The acute forms are due to hepatic overproduction of the porphyrin precursors: delta aminolevulinic acid and porphobilinogen. Symptoms are caused by injury, primarily to the nervous system. The photocutaneous form is due to overproduction of photosensitizing porphyrins by the liver or bone marrow, depending on the type of porphyria [1].

Acute intermittent porphyria (AIP) is caused by a partial deficiency of the third enzyme of heme synthesis: porphobilinogen deaminase. It is an autosomal dominant condition that occurs globally. The prevalence of mutations in Western populations is approximately 1 carrier per 2000 individuals [4,5]. However, acute attacks occur in less than 10% of the at-risk population, which may indicate environmental influences [6,7].

The typical patient with an attack of AIP is a previously healthy young woman who has had several days of severe fatigue and an inability to concentrate [1,8] followed by progressively worsening abdominal pain, nausea, vomiting, and subtle neurologic signs such weakness, dysesthesia, and altered affect. Analgesic agents, including opioids, provide little or no relief. Some patients have recurrent visits to the emergency department with the same symptoms and a non-diagnostic evaluation [9]. In some patients, tachycardia and elevated systolic blood pressure are noted.

An abdominal examination is unexpectedly benign. The lack of objective findings and a poor response to analgesics often create an initial impression of psychosomatic pain or drug addiction. Laboratory evaluations are normal, apart from a minor elevation of liver enzyme levels and a low serum sodium level. The serum sodium level may decrease precipitously after administration of intravenous glucose in water [1,10]. The color of freshly voided urine in patients with AIP may be unremarkable, although the term porphyria implies purplish urine. Voided urine, exposed to light at ambient temperature, will slowly turn dark through formation of uroporphyrin-like pigments (porphobilin).

Seizures occur in approximately 20% of acute attacks [1,11]. The triad of seizures, abdominal pain, and hyponatremia in a young woman is highly suggestive of acute porphyria. Approximately 80–90% of acute attacks occur in women of reproductive age [1,12]. They are unusual before menarche and after menopause. Certain medications, including oral contraceptives, may trigger attacks. Acute attacks also occur with caloric deprivation related to intercurrent illness, peri-surgical fasting, crash dieting, or bariatric surgery [1,13,14].

A review of the patient's medications should be conducted to determine whether any are considered to be risky in patients with porphyria. Initial management includes the administration of fluids, antiemetic agents, analgesic agents, and, if indicated, anti-seizure medication. Currently, the only specific treatment for an acute attack is intravenous heme. Alternatives to intravenous heme are being developed. One approach is the use of gene therapy in which the normal hydroxymethylbilane synthase gene is delivered to hepatocytes in a viral vector [15]. At present, liver transplantation is the only remedy for recurring attacks with a poor response to heme and neurologic progression [16]. Before the 1980s, mortality among patients with acute attacks of porphyria was approximately 25%. With early diagnosis and specific treatment, the outlook has improved [17,18].

In this issue of the *Israel Medical Association Journal* (*IMAJ*), Khoury and colleagues [19] described a typical patient with AIP. The young patient presented with severe epigastric abdominal pain and later developed severe hyponatremia. The clinical presentation of epigastric pain, hyponatremia, and gastroparesis in combination with high clinical suspicion and knowledge of the associated manifestations enabled the clinical staff to make the diagnosis rapidly. The urine was exposed to the sun light, and its color changed from light yellow to dark orange color, which is highly suspicious for porphyria. Subsequently, the diagnosis of porphyria was confirmed by the presence of porphobilinogen in the urine.

Severe attacks of AIP can be life-threatening and early diagnosis and treatment can be potentially lifesaving. The rapid diagnosis and the specific treatment with intravenous glucose in addition to hemin prevented serious complications.

Although the clinical symptoms in a young female patient are typical for AIP, the diagnosis is missed in most cases during the initial presentation. Since early diagnosis is critical for administering specific treatment early and for preventing serious complications including mortality, a high clinical suspicion is needed.

The diagnosis is challenging since epigastric abdominal pain is frequent, which is one of the most common symptoms to be referred to the emergency department. In most cases these symptoms are due to peptic ulcer disease [19].

Indeed, the suspicion must be raised if the pain is severe and no improvement is seen with opioids, especially if the symptoms are combined with hyponatremia and neurologic symptoms [Figure 1].

Elevated porphobilinogen levels in urine or plasma are specific for acute porphyria. The test can be performed in a random sample with the result normalized per gram of urine creatinine. A 24-hour collection is not required.

Patients having their first attacks of AIP often present to an emergency department, where rare diseases generally are not considered. Moreover, a test to detect porphobilinogen in urine is rarely available in real time. Until the 1990s, rapid methods for measuring porphobilinogen in urine were available in many emergency departments. These tests were qualitative only and subject to false positive results. Today, the only route to a confirmed diagnosis is a routine quantitative porphobilinogen test, which has a turnaround time of 4 to 10 days at commercial reference laboratories. This method often means a substantial delay in diagnosis, which can be costly in terms of misdirected medical care, progressive neurologic loss, respiratory paralysis, and even death [1].

As in the case reported by Khoury's group [19], exposing the urine to sunlight and finding that its color changes from light yellow to dark orange in color, can attribute to rapid diagnosis.

CONCLUSIONS

Porphyrias are a heterogeneous group of diseases that can present in different ways. Diagnosis of porphyrias can be missed for a long time. Awareness of porphyria in patients with acute neurovisceral attacks or cutaneous symptoms may lead to an accurate diagnosis and prompt treatment, which might be lifesaving [2].

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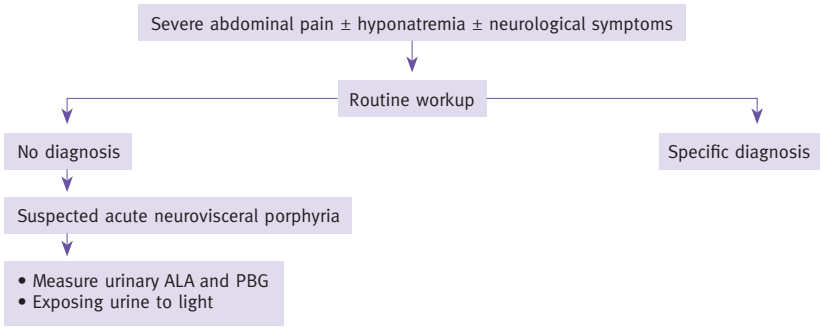
Figure 1. Algorithm for diagnosis of acute porphyria



ALA = aminolevulinic acid, PBG = porphobilinogen