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Review article

Pathogenesis and clinical features of the acute hepatic porphyrias (AHPs)

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ABSTRACT

The acute hepatic porphyrias include four disorders: acute intermittent porphyria [AIP], hereditary coproporphyria [HCP], variegate porphyria [VP], and the rare porphyria due to severe deficiency of ALA dehydratase [ADP]. In the USA, AIP is the most severe and most often symptomatic. AIP, HCP, and VP are due to autosomal dominant genetic abnormalities, in which missense, nonsense, or other mutations of genes of normal hepatic heme biosynthesis, in concert with other environmental, nutritional, hormonal and genetic factors, may lead to a critical deficiency of heme, the end-product of the pathway, in a small but critical 'regulatory pool' within hepatocytes. This deficiency leads to de-repression of the first and normally rate-controlling enzyme of the heme synthetic pathway, delta- or 5-aminolevulinic acid [ALA] synthase-1, and thus to marked up-regulation of this key enzyme and to marked hepatic overproduction of ALA. In addition, except for ADP, there is marked overproduction as well of porphobilinogen [PBG], the intermediate immediately downstream of ALA in the synthetic chain, and, especially in HCP and VP, also porphyrinogens and porphyrins farther down the pathway. The major clinical features of the acute porphyrias are attacks of severe neuropathic-type pain. Pain is felt first and foremost in the abdomen but may also occur in the back, chest, and extremities. Attacks are more common in women than in men [ratio of about 4:1], often accompanied by nausea, vomiting, constipation, tachycardia, and arterial hypertension. Hyponatremia may also occur. Some patients also describe chronic symptoms of pain, anxiety, insomnia, and others.

1. Overview

The acute hepatic porphyrias include 5-aminolevulinic acid (ALA) dehydratase deficient porphyria (ADP), acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP). The genetic abnormalities that underlie these disorders cause deficiencies in one of the enzymes of normal heme synthesis [Fig. 1]. [for recent reviews, see 1–3] The enzymatic deficiencies in the acute porphyrias are as follows: ADP, severe homozygous or compound heterozygous deficiency of ALA dehydratase [also known as PBG synthase], the second enzyme in the pathway of heme biosynthesis; AIP, partial heterozygous deficiency in hydroxymethyl bilane synthase [HMBS, also known as PBG deaminase], the third enzyme in the pathway; HCP, partial heterozygous deficiency in coproporphyrinogen oxidase [CPOX], the sixth enzyme in the pathway; and VP, partial heterozygous deficiency in protoporphyrinogen oxidase [PPOX], the seventh enzyme in the pathway. Rarely, patients present with more severe compound heterozygous or severe homozygous deficiencies of the latter three enzymes. Such deficiencies are likely usually embryo lethal. Newborns or infants who are born alive with such defects are severely affected with developmental delay, failure to thrive, and usually do not survive into adulthood.

2. Prevalence and penetrance

The acute porphyrias have generally been considered to be rare, with prevalences estimated as ~ 5/100,000 in most countries and regions of the world. [for reviews, see [1–3]]. Due to founder effects, the prevalence in some regions, such as northern Scandinavia, is appreciably higher [4]. However, more recent population-based studies have indicated that enzymatic deficiency of HMBS is ~1/1700 among Europeans [5,6] and that disease-causing mutations may be as frequent as ~6/1000 among Caucasians [7]. Thus, the penetrance of clinical disease is now estimated to be only ~1%.

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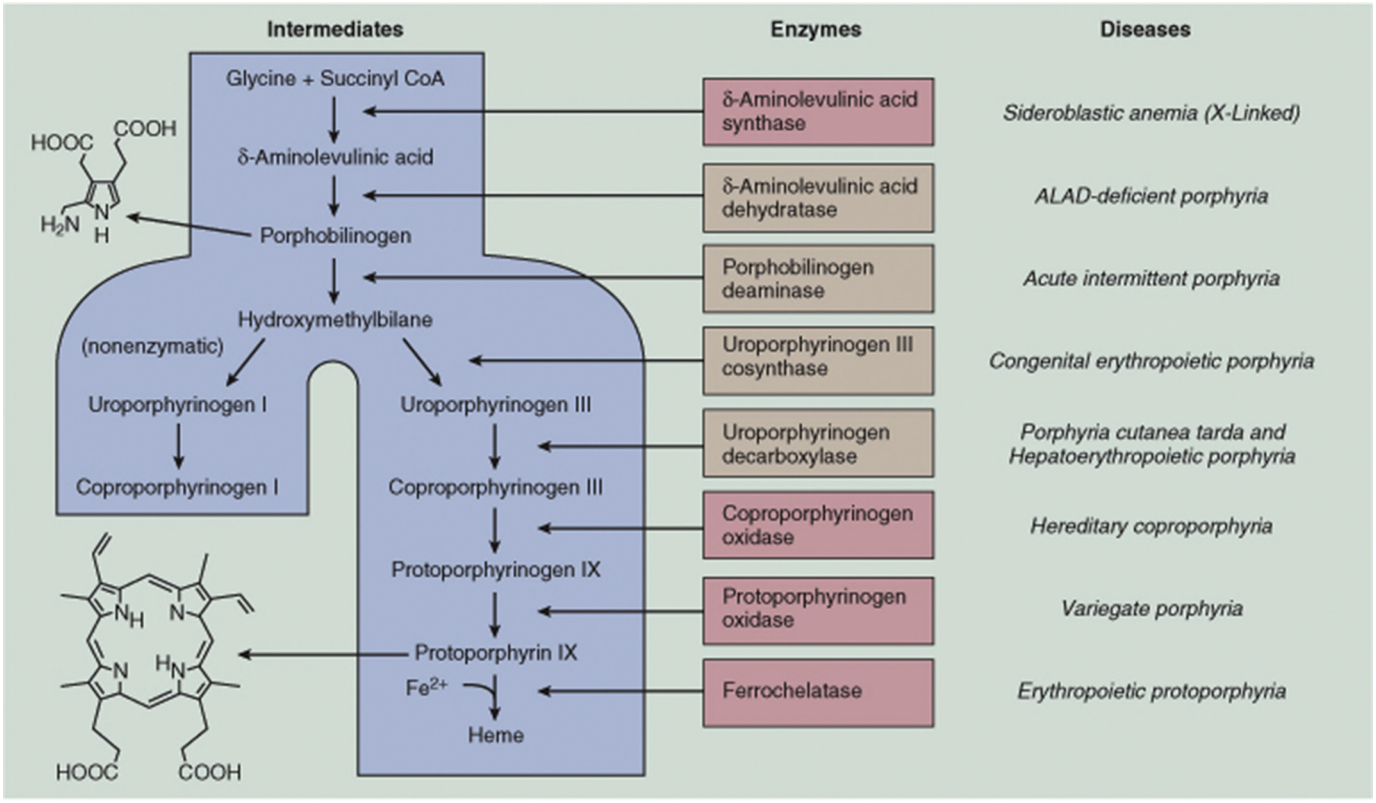

Fig. 1. Summary of the heme synthetic pathway and sites of defects in the porphyrias.

In a similar vein, due to a founder effect that has been traced back to 1688, with the arrival into Cape Town of Dutch settlers, there are now thousands of persons of Dutch-Afrikaner descent with VP in South Africa. Fortunately, most persons with the founder mutation [p. R59W of the PPOX gene] remain asymptomatic or suffer only one or two acute attacks throughout their lives.

3. Pathogenesis and pathophysiology of AHP

In the rare form of ADP, due to severe deficiency of ALA dehydratase [compound heterozygous or homozygous deficiency with < 10% of normal activity], all affected persons have severe disease, with onset early in life. However, for the most part, acute hepatic porphyrias are caused by ~50%, heterozygous defects in HMBS, CPOX, or PPOX [Fig. 1], and additional genetic or acquired factors are required for development of the disease phenotype. This serves to emphasize the key role played by other factors in pathogenesis, such as excess alcohol and/or smoking, porphyrogenic drugs and chemicals, starvation or severe fasting, intercurrent infection, physical and/or emotional stress and exhaustion, *etc.* [Table 1]. In addition, other genetic factors/variations outside the heme synthetic pathway, are probably also important in pathogenesis, such as genetic variation in peptide transporter 2 [PEPT2], which, *inter alia,* facilitates the transport of ALA across biological membranes and which has been implicated as a factor in modulating the severity of neurotoxicity or nephrotoxicity of ALA [8–11].

The genetic defects in the primary genes of heme synthesis, combined with diverse additional nutritional, environmental, and other genetic factors may lead to uncontrolled up-regulation of hepatic ALA synthase-1 [ALAS1], which is the biochemical hall mark and *sine qua non* for all forms of biochemically and clinically active acute porphyrias. Up-regulation of ALAS1, in combination with down-stream defects in normal heme synthesis, leads to overproduction and toxic accumulations of porphyrins and their precursors, ALA and PBG. It is likely that the neurovisceral symptoms and signs are cause mainly by ALA [1–3]. The overproduction of porphyrins in HCP and especially in VP may cause chronic blistering photo-sensitive skin rashes.

Table 1
Risk factors and triggering factors for acute porphyric attacks.

Drugs and chemicals	
Alcohol	Barbiturates
Smoking	Carbamazepines
Estrogens	Hydantoins ≈
Sulfonamides	Progestagens
Other inducers of hepatic cytochrome(s) P-450 + ALA synthase-1	
Luteal phase of menstrual cycle	
Pregnancy and the post-partum period	
Fasting/starvation/post gastric bypass	
Stress/exhaustion	
Infection	
Surgery/anesthesia	

Chemicals and medications that up-regulate ALAS1 and cytochromes P-450, excess alcohol use, regular tobacco use, and fasting/crash dieting, are among precipitating factors of the acute porphyrias [1–3,12–15] [Table 1].

There has been much interest regarding the pathogenesis of the neurovisceral symptoms of the acute hepatic porphyrias. We and others have reviewed theories of pathogenesis and advanced two as being of greatest importance: 1) cellular heme deficiency causing a deficiency in hemoproteins in neuronal cells, and 2) ALA being neurotoxic at the levels seen during acute porphyric attacks [16]. The triggering factors, such as alcohol excess, smoking, drugs, fasting/starvation likely act by both directly to up-regulate ALAS1 mRNA and indirectly to increase heme demand and deplete the regulatory heme pool [Fig. 2].

When precipitating factors are avoided, the ~50% reduced enzyme

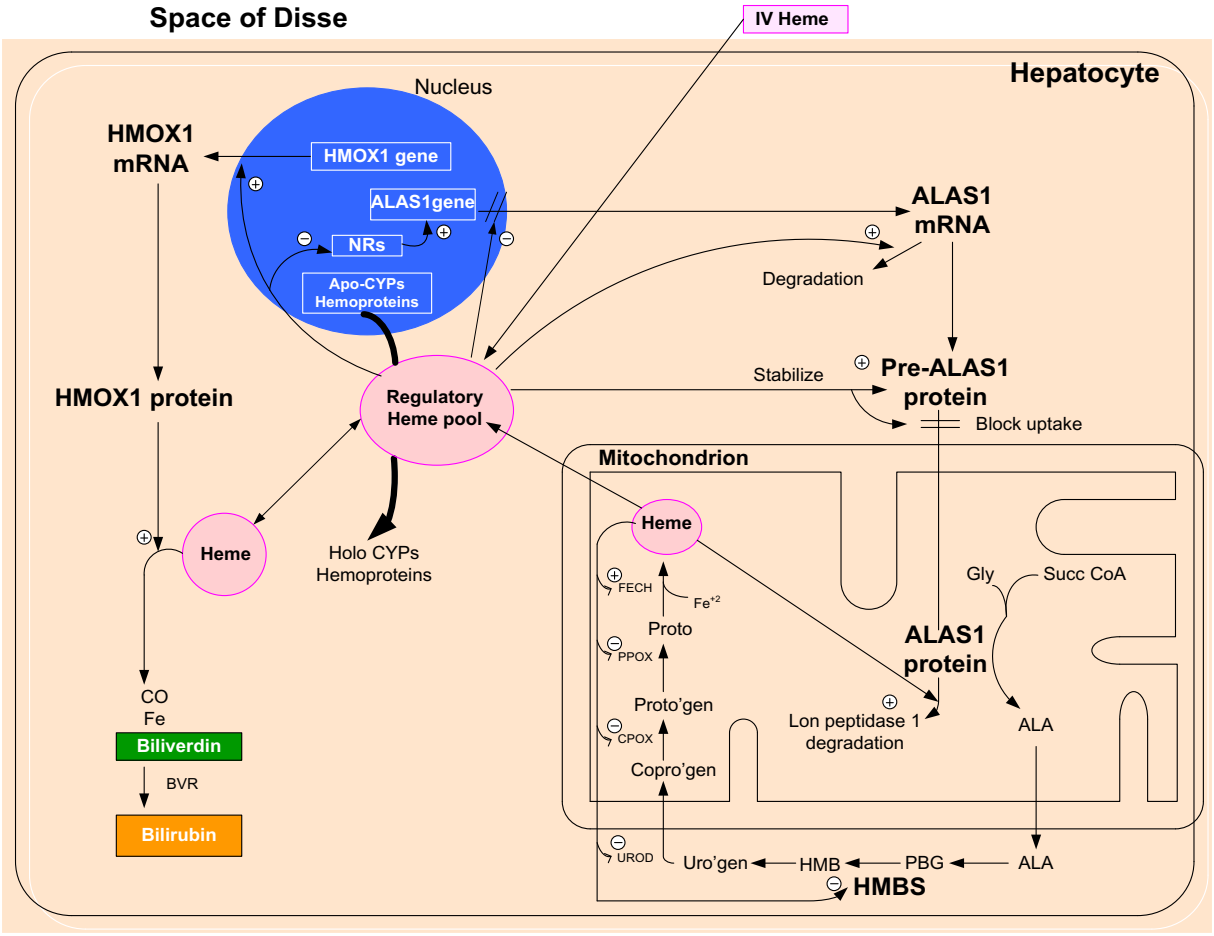

Fig. 2. The regulatory heme pool and key roles of heme in regulation of expression of hepatic ALA synthase-1.
Key roles are played by ALA Synthase-1 [ALAS1], heme oxygenase-1 [HMOX1], nuclear receptors [NRs], and hydroxymethylbilane [HMB] synthase [HMBS]. Heme itself down-regulates several steps in the synthetic pathway, especially ALAS1, as shown in the figure, by down-regulating transcription (minus sign, −), up-regulating mRNA breakdown (plus sign, +), blocking uptake into mitochondria (−), and increasing Lon peptidase 1 breakdown of the mature mitochondrial enzyme (+). Heme up-regulates HMOX1 (+), mainly by increasing its transcription through binding to Bach1, a b-zip protein that binds DNA, and a tonic repressor of HMOX1. HMBS is present in relatively low amounts, compared to other enzymes in the biosynthetic pathway down-stream of ALAS1, and HMBS becomes rate-controlling for heme synthesis when ALAS1 is induced. 50% deficiency of HMBS, the defect in acute intermittent porphyria (AIP), can lead to critical deficiency of heme and uncontrolled induction of ALAS1. Such induction may also occur, albeit less often and less severely, when there are inherited or acquired defects in coproporphyrinogen oxidase (CPOX) or protoporphyrinogen oxidase (PPOX). Heme administered intravenously is taken up by hepatocytes, and can replete heme pools rapidly and transiently down-regulate ALAS1 and correct the defects caused by HMBS, CPOX, or PPOX deficiency.
[Other abbreviations: BVR, biliverdin reductase; CO, carbon monoxide; Copro'gen, coproporphyrinogen III; Gly, glycine; PBG, porphobilinogen; Proto'gen, proto-porphyrinogen IX; Succ CoA, succinyl coenzyme A; UROD, uroporphyrinogen decarboxylase; Uro'gen, uroporphyrinogen]

activity of HMBS adequately supplies hepatic heme to maintain normal functional status. However, after onset of menarche in young women and puberty in young men, with their attendant increases in sex hormones, especially estrogen and progesterone in women, the demand for heme is increased. This, in turn, leads to de-repression of hepatic ALAS1 and to uncontrolled overproduction of ALA and, except for ADP, also PBG. In addition, certain medications/drugs, such as barbiturates, carbamazepines, and hydantoins and several others, can also up-regulate ALAS1 gene expression in a more direct way, by binding to transcription factors that interact with 5′-promoter region of the ALAS1 gene [2]. Some drugs may act as suicide substrates for the heme of CYPs or other hepatic hemoproteins, leading to relative heme depletion. This ultimately results in a buildup of the heme precursors ALA and PBG due to the deficiency of HMBS. The key role of heme in regulation of expression of hepatic ALAS1 and its therapeutic role in treatment of acute porphyric attacks are summarized in Fig. 2.

3.1. ALA as the chief neurotoxin

ALA, PBG, and other hepatic heme precursors are able to cross the blood brain barrier [1,2,14]. Thus, these heme precursors can exert neurotoxic and other effects throughout the central, as well as the peripheral and autonomic, nervous system. ALA is structurally similar to gamma-amino butyric acid [GABA] and has the potential to bind to GABA receptors. ALA serves as a partial agonist, but also antagonist to the more potent neuro-inhibitory effects of GABA, the major inhibitory neurotransmitter in the mammalian central nervous system. High levels of ALA also increase oxidative stress and influence glutamate and other neurotransmitters. Neurological symptoms and signs of acute porphyric attacks, such as delirium, confusion, and seizures, are probably secondary to these mechanisms. In all acute porphyrias, as well as in acute lead poisoning and hereditary tyrosinemia type 1, there are similar symptoms and signs and elevations in plasma and urine ALA levels, which reinforces the notion that it is a major pathogenic factor [17]. The body of evidence that incriminates ALA, in preference to PBG, is particularly strong in light of the similar clinical manifestations in acute

lead poisoning and tyrosinemia, in which there are not increases in PBG, but rather only in ALA. In acute lead poisoning, the increase in ALA is due to the profound inhibition of ALA dehydratase produced by excess lead, whereas, in hereditary tyrosinemia type I, it is caused by accumulation of 4, 6 dioxoheptanoic acid [also known as succinyl acetone], which is a nearly irreversible inhibitor of ALAD, and which binds its active site with very high affinity [2,17].

Among several hypotheses that have been suggested to play a role in pathogenesis of AHP is that there is partial deficiency of heme in the nervous system [16]. There is scant, if any direct evidence for such deficiency, due to difficulties in measuring levels of total heme and critical heme pools and hemoproteins in human subjects. Heme given intravenously is likely able to gain access to the cells of the peripheral nervous system, but not the central nervous system, as heme does not cross the normal blood-brain barrier.

4. Homozygous forms of AHP

Such forms, fortunately, are very rare. It seems likely that homozygous or compound heterozygous forms of AIP, HCP or VP are usually embryo lethal so that affected infants are still-born or die shortly after birth. However, a few have been described, and the clinical features have been of severe affections of the nervous system with developmental delay and evidence of mental retardation manifest at early ages [18–20]. Few such children have survived into adulthood. The treatment of such children has generally been supportive and, it seems, not of much benefit. One boy with this severe form in the UK was treated briefly with IV heme, but without evidence of clinical benefit. [P Stein, pers. commun]. The parents of this child were not related and harbored different mutations in exon 10 of the HMBS gene [20]. Currently in the USA, we are aware of two such children, one of whom underwent intravenous heme therapy, with a sizable, albeit only partial, decrease in levels of urinary ALA and PBG, for about two months prior to his undergoing a liver transplant. The clinical course post-transplant has been rocky, with need for frequent readmissions to hospital for difficulties in feeding and nutrition, organ rejection, continuing seizure activity, developmental delay, and hypotonia. He also has continued to overproduce and over excrete ALA and PBG, although with ~ 50% decrease compared with values prior to liver transplant [N Dixon, *et al*—unpublished observations]. Whether and to what extent the liver transplant will prove beneficial in ameliorating the clinical features of disease remain to be determined over the coming months and years. The other child also has severe developmental delay and has not shown apparent benefit from intravenous heme therapy [RJ Desnick, pers. commun].

5. Clinical manifestations of AHP

5.1. Typical presentation: clinical vignette

A 22-year-old woman, with history of anxiety, presented to the emergency department [ED] of an outside hospital with recurrence of gradually worsening crampy lower abdominal pain that had been present for the past 18 h. Her abdominal pain had been gradual in onset. It had started about 15 days after the onset of her last menstrual flow, *i.e.*, during the luteal phase of her menstrual cycle. Her menstrual periods had begun at age 12, and she described them as always having been very painful, especially during the first day or two of menstrual flow. She had tried a variety of treatments over the prior several years, particularly ibuprofen and acetaminophen, with little relief. In addition to abdominal pain, she also had noted fatigue, weakness, and difficulty with concentration for several days. In the prior six months, she had presented twice to her local ED with similar symptoms. During one prior ED visit, she had been thought, perhaps, to have acute appendicitis, despite only low grade fever [$T = 38^{o}$ C] and mildly elevated WBC count [12,500/uL], and negative abdominal CT scan. She had undergone laparoscopic exploration of the abdomen with appendectomy. The resected appendix was not acutely or severely inflamed, and the pathologic description was 'mild chronic appendicitis.' Her symptoms recurred six weeks after the surgery.

The patient had been actively attempting to lose weight for the preceding 4 months. She was taking an oral contraceptive, which she had been taking for 3 years. She denied having started new medications or herbals or dietary supplements. She had also been recently referred to a general surgeon for consideration of a cholecystectomy because of her recurrent abdominal pain, despite the lack of gall stones. She reported that, during episodes of recurrent pain, she developed nausea, anorexia, darkening of urine color and worsening of constipation, which, for her, was a chronic problem.

In the emergency room, height was 59 in.; weight 180 lbs., BMI 36.4, temperature 99.5° F, BP 170/110 mmHg, HR 107 beats/min, RR 18 breaths/min. She was apprehensive, oriented to person and place but not to time, and lethargic. She was slow to respond to questions. She was writhing in pain and often screaming out requesting relief. The cardiopulmonary exam was normal. The abdomen was soft, non-distended. Bowel sounds were absent. Deep palpation did not elicit complaints of increased pain, nor any voluntary guarding. A neurological exam revealed no focal deficits, but there was generalized mild weakness and hyporeflexia. Plantar responses were flexor.

Laboratory studies revealed serum sodium = 128 mEq/L, serum potassium = 3.5 mEq/L, chloride = 100 mEq/L, HCO3 = 28 mEq/L. Blood sugar = 95 mg/dL; BUN = 33 mg/dL; creatinine = 1.0 mg/dL. Urinalysis revealed scant bacteria, occasional WBC and RBC [< 5/hpf], trace protein, and positive ketones. Urinary glucose was not detected. Serum ALT = 30, AST = 40; AP'ase = 85 IU/L [all normal]. Serum albumin, total protein, bilirubin, lipase and amylase were normal, and a serum *H. pylori* antibody was non-reactive. A contrast-enhanced CT scan of the abdomen and pelvis was normal, except for much retained stool in the colon. The findings were like those of three previous CT scans.

She was treated with intravenous 5% dextrose and 0.45% saline and hydromorphone, with only partial and incomplete improvement in her symptoms. After 6 h in the ED, she was witnessed by the staff to have a generalized grand-mal seizure, and she was given intravenous diazepam and intramuscular magnesium sulfate.

She was admitted for additional observation. A contrast-enhanced CT scan of the head did not show focal abnormalities. In light of her gender, young age, recurrent abdominal pain, hyponatremia, and seizure, a random urine was sent for PBG, ALA, and creatinine, and she was treated as though she had an acute porphyria with narcotic analgesics, phenothiazines, ondansetron, propranolol, and IV dextrose, 300 g/d. Barbiturates, hydantoins, and sulfonamides were expressly avoided. After 5 days, urinary PBG was reported as 95 mg/g creatinine [reference range 0–4] and ALA as 55 mg/g creatinine [reference range 0–7]. A diagnosis of acute hepatic porphyria, felt most likely to be AIP, was made; and, in addition to the above treatment, she was treated with intravenous heme in the form of Panhematin [Recordati Rare Chemicals], 4 mg/kg/d for 4 days, with rapid improvement in her symptoms. The Panhematin was reconstituted in human serum albumin [21,22] and was administered by way of peripherally inserted central venous catheter into a high flow, large bore vein, to decrease likelihood of development of thrombosis or thrombophlebitis.

Blood was obtained for genetic testing of *HMBS*, *CPOX*, and *PPOX* [the acute porphyria battery]. The results, reported three weeks later, showed p. R167Q, a known disease-causing mutation in *HMBS* and no mutations detected in *CPOX* or *PPOX*, confirming the clinical diagnosis of AIP.

5.2. Typical features of acute attacks

These are well exemplified by the clinical vignette just presented. Most patients are women in the 2nd through 5th decades of life. They

typically give histories of recurrent and severe abdominal pain, with a prodrome of feeling unwell and of increasing anxiety, and feelings of generalized weakness. Often, there is loss of appetite, decreased oral intake, nausea, and vomiting. These factors lead to negative calorie and energy balance and to a gradual escalation of pain, often with extension also to the back, the chest, and the proximal extremities. A vicious cycle or 'snowball' effect ensues, with mild symptoms becoming moderate and then severe over the course of hours to days. The pain of acute porphyric attacks lasts for many hours to days, especially if not promptly treated with high doses of narcotic analgesics and intravenous heme, which, as recently summarized [1–3], is clearly the treatment of choice for all except mild attacks.

5.2.1. Cardinal symptoms

Among patients who are ill enough to require visits to the emergency department or to urgent care, nearly all complain first and foremost of severe, searing, stabbing abdominal pain, usually in the lower abdomen with severe constipation in about 55%, nausea and vomiting in about 50%, and paresthesias and dysesthesias, indicative of neuropathic pain, in about 60% [1–3,13].

5.2.2. Cardinal signs

Include tachycardia [80%], dark urine [75%], peripheral motor deficits [70%], defects in cranial nerve functions [55%]. Less frequent, but still present in many are confusion, delirium, hallucinations, systemic arterial hypertension, absent deep tendon reflexes, peripheral sensory deficits. Seizures, often associated with severe hyponatremia, occur in about 20%, urinary bladder retention in 15%, and coma in ~ 10%. Fever with no source of infection found occurs in ~10% as well [1–3,13,23].

The clinical characteristics of an acute porphyric attack are similar for each of the acute porphyrias, but are typically more severe in ADP and AIP [1–3]. In VP and, rarely, in HCP there may also be cutaneous manifestations with blisters and fluid-filled bullae on sun-exposed areas of the skin, especially the backs of the hands and forearms, the face, neck, and ears.

5.2.3. Neurological features

The acute porphyrias exhibit effects on the autonomic, central and peripheral nervous systems. Peripheral neuropathy is a mostly motor neuron process due to axonal degeneration [16]. Patients may progress to quadriparesis and respiratory failure. When the central nervous system is involved, patients may present with irritability, insomnia, anxiety, paranoia, hallucinations, and psychoses [1–3]. Major motor seizures occur in up to 20% of acute porphyric attacks [1–3,23], often in association with marked hyponatremia, as in the patient described above. The hyponatremia is associated with increases in anti-diuretic hormone [ADH] and have often been ascribed to the syndrome of inappropriate anti-diuretic hormone [ADH] secretion [SIADH]. However, when total and effective circulating blood volumes have been measured in patients with AIP, even in the absence of acute attacks, they have been found to be significantly decreased [24]. Thus, because, by definition, SIADH requires the presence of normal or increased effective circulating volume, it is contentious whether the increase in ADH seen in acute porphyric attacks is 'inappropriate' or appropriate. In any event, the finding of hyponatremia [serum $Na^+ < 130$ mEq/L] in the setting of acute severe pain should raise suspicion of AHP. Treatment with anticonvulsants can be challenging as many of the commonly used anti-convulsants [barbiturates, carbamazepines, hydantoins, valproate, etc] cause up-regulation of ALAS1 and can precipitate and/or worsen acute porphyric attacks [1–3,23].

5.2.4. Psychiatric features

During acute attacks, patients often report confusion, 'brain fog', difficulty in mental concentration, anxiety, and dread. Patients with frequent and recurrent attacks [three of more per year], often report chronic anxiety, depression, trouble sleeping, and diverse other psychiatric symptoms. Increased risks of schizophrenia and bipolar disorder have also been associated with AIP, especially in Sweden, in which AIP is highly prevalent. In 1993, Sanders *et al* described an association between genetic variations of the PBG deaminase [aka HMBS] gene and schizophrenia [25]. Results of another Swedish study showed that individuals with AIP had a fourfold excess risk of being diagnosed with schizophrenia or bipolar disorder, compared to a non-porphyric control population [26]. This study also reported an increased risk of schizophrenia and bipolar disorder in first-degree relatives of individuals with AIP.

5.2.5. Chronic symptoms

It has been recognized for many years that patients who have experienced acute porphyric attacks, especially those with ADP or AIP, often exhibit chronic and ongoing symptoms, as well. Indeed, in a recent observational study of 110 patients with AHP, mostly women with AIP [27], 65% or more reported chronic symptoms continuing between acute attacks, accompanied by marked decrements in health-related quality of life. Thirty-nine percent of such patients self-reported moderate to severe chronic pain; 28% reported anxiety and/or depression; 25% reported limitations in performing usual activities of daily living; and 17% trouble with walking and normal mobility. Trouble sleeping was another common complaint. Of note, only 30% reported working full-time and only 50% reported living independently at home without special care. Among those working, 85% reported unplanned absences from work due to AHP, with the median number of days of work missed annually being 20. These emerging insights serve to emphasize the human and economic toll that AHP exacts on those who suffer from these diseases and on their families. Reduced quality-of-life in AIP has been described by others, as well [28,29].

5.2.6. Natural history

As already mentioned, fortunately, the clinical penetrance of acute porphyric attacks is low. Thus, most patients with disease-causing mutations experience no or only a few acute attacks during their lifetimes. Yet, a few patients experience repeated attacks and/or have severe and chronic symptoms. In some of the latter, triggering events such as excess alcohol, smoking, bariatric surgery or other severe weight loss, and xenobiotics can be identified, but in many the triggering events remain unknown and in need of further elucidation.

6. Summary: important diagnostic clues and key testing

In summary, the possibility of an acute hepatic porphyria should be considered especially in women of child-bearing potential [in the 2nd through 5th decades of life] who present more than once with severe abdominal pain that remains of uncertain cause after common diagnoses have been excluded. Helpful signs, but too often overlooked, include tachycardia and/or systemic arterial hypertension and hyponatremia during the acute attacks. The patients, when asked, also often describe passing dark reddish-brown urine during attacks. All such patients should have at least one test for urinary ALA, PBG and creatinine performed during or shortly after one of these acute attacks. If the urinary ALA or PBG/creatinine is not at least 4-fold elevated above the reference range, the diagnosis of acute hepatic porphyria as explanation for the symptoms has been excluded with a very high degree of confidence [> 99%]. Although the prevalence of disease-causing mutations (~1/1700 among Caucasians from western Europe) is higher than previously believed, the clinical penetrance of AHP is low. Nevertheless, patients with a severe clinical phenotype experience recurrent acute attacks. Better treatment of such patients constitutes an unmet medical need. A promising new therapy is RNAi down-regulation of ALAS1 [1,30], a treatment that is in phase 3 clinical study and that has shown benefit and safety.

Competing interests/author disclosures

Within the past three years, Dr. Bonkovsky has served as consultant to Alnylam Pharma, Blue Pharma, Mitsubishi-Tanabe Pharma, Moderna, Recordati Rare Chemicals, and Stoke Pharma. He has received funding for clinical studies on the porphyrias from Alnylam, Gilead Pharma, and Mitsubishi- Tanabe Pharma. He also serves as a member of the Medical and Scientific Advisory boards of the American Porphyria Foundation [Bethesda, MD] and the Iron Disorders Institute [Greenville, SC].

Within the past three years, Dr. Dixon reports no competing interests.

Within the past three years, Dr. Rudnick has served as an investigator for clinical studies on the porphyrias from Alnylam, Gilead Pharma, and Mitsubishi-Tanabe Pharma.

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