Current Neurology and Neuroscience Reports (2020) 20:56
https://doi.org/10.1007/s11910-020-01078-8

AUTONOMIC DYSFUNCTION (L.H. WEIMER, SECTION EDITOR)

# Porphyric Neuropathy: Pathophysiology, Diagnosis, and Updated Management

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Accepted: 29 September 2020


## Abstract

**Purpose of Review** To review the peripheral neurological complications of the acute hepatic porphyrias, as well as the latest advances in their pathophysiology and management.

**Recent Findings** The diagnosis of porphyric neuropathy remains challenging as varying neuropathic patterns are encountered depending on disease stage, including a non-length-dependent distribution pattern. The major pathophysiologic mechanism is δ-aminolevulinic acid (ALA)–induced neurotoxicity. The less restrictive blood-nerve barrier in the autonomic ganglia and myenteric plexus may explain the frequency of dysautonomic manifestations. Recently, a prophylactic small interfering RNA (siRNA)-based therapy that reduces hepatic ALA Synthase-1 mRNA was approved for patients with recurrent neuro-visceral attacks.

**Summary** Neurologists should appreciate the varying patterns of porphyric neuropathy. As with most toxin-induced axonopathies, long-term outcomes depend on early diagnosis and treatment. While the short-term clinical and biochemical benefits of siRNA-based therapy are known, its long-term effects on motor recovery, chronic pain, and dysautonomic manifestations are yet to be determined.

**Keywords** ALA · Dysautonomia · Hemin · Neuropathy · Porphyria · Small interfering RNA

## Introduction

Porphyrias are a group of eight disorders, each resulting from a specific enzymatic defect in the heme biosynthesis pathway, with the resultant accumulation of heme biosynthetic intermediates (Fig. 1) [2, 3]. The four acute hepatic porphyrias (AHPs) are due to hepatic overproduction of the porphyrin precursors, δ-aminolevulinic acid (ALA), and porphobilinogen (PBG). Their symptoms primarily involve the central and peripheral nervous system [4]. They include acute intermittent porphyria (AIP), the most common, variegate porphyria (VP), and hereditary coproporphyria (HCP) which are less frequent and often have photosensitive cutaneous lesions (Table 1) [4–7]. ALA-dehydratase deficiency porphyria (ADP) is extremely rare with ≤ 12 reported cases [8, 9]. AIP, VP, and HCP are autosomal dominant disorders, while ADP is autosomal recessive [10]. The Human Gene Mutation Database [11] presently lists > 400 variants in the hydroxymethylbilane synthase (*HMBS*) gene causing AIP. Pathogenic mutations in the protoporphyrinogen oxidase (*PPOX*) and coproporphyrinogen oxidase (*CPOX*) genes cause VP and HCP, respectively. There is no significant genotype-phenotype association and penetrance is low [12]. The objective of this review is to discuss the peripheral neurologic complications of the AHPs focusing on the diagnosis, pathophysiology, and recent advances in management.

This article is part of the Topical Collection on *Autonomic Dysfunction*

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## Epidemiology

Estimates of prevalence vary widely, based on geographical region, and do not always distinguish between the

Published online: 07 October 2020

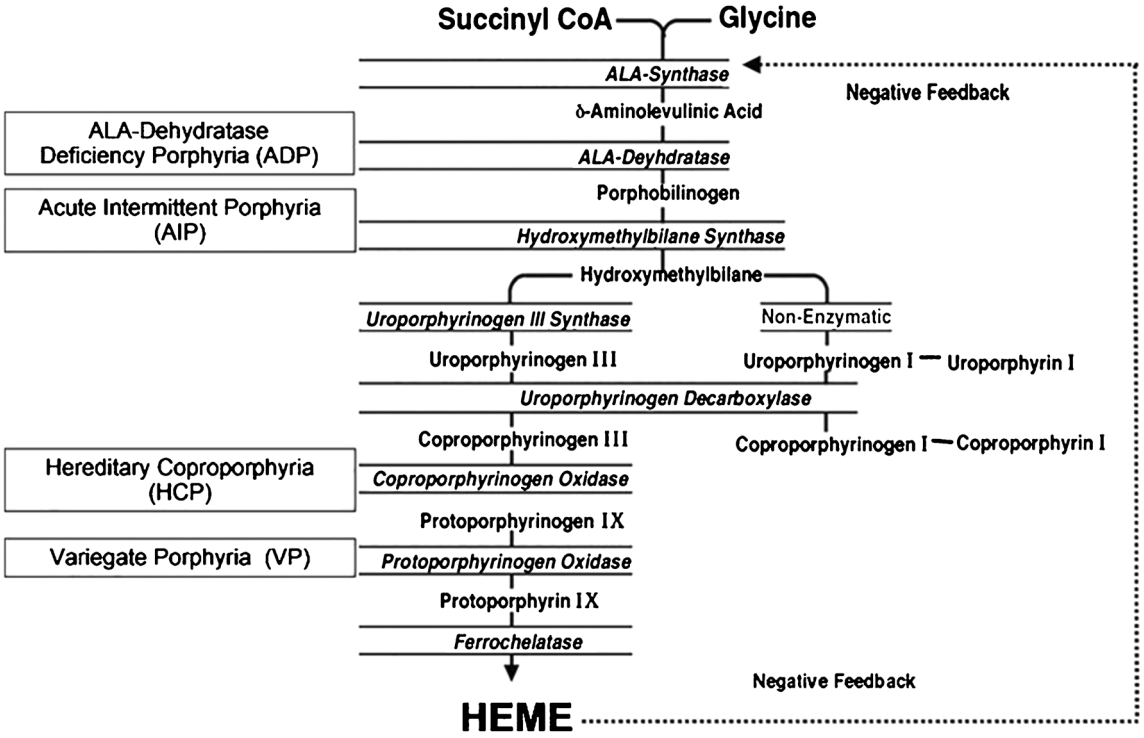


**Fig. 1** Heme biosynthetic pathway highlighting the specific enzymatic defects in the different acute hepatic porphyrias. Courtesy of Balwani et al., with permission [1]

symptomatic and latent cases (having the mutation but no symptoms). Although the prevalence of Caucasian individuals with heterozygous pathogenic *HMBS* mutations was estimated to be ~ 1:1700 [13], the acute attacks occur in only ~ 1%, reflecting the importance of environmental exposure(s) and genetic modifiers [14, 15]. The prevalence of neuropathy

**Table 1** Epidemiology and clinical characteristics of the acute hepatic porphyrias (AHPs)

| | | Acute intermittent porphyria | Hereditary coproporphyria | Variegate porphyria | ALAD deficiency porphyria |
|---|---|---|---|---|---|
| Mode of inheritance | | AD | AD | AD | AR |
| Deficient enzyme | | Hydroxy-methylbilane synthase | Copro-porphyrinogen oxidase | Proto-porphyrinogen oxidase | ALA dehydratase |
| Enzymatic activity | | ~ 50% | ~ 50% | ~ 50% | ~ 5% |
| Defective gene | | *HMBS* | *CPOX* | *PPOX* | *ALAD* |
| Estimated prevalence | | 5–10:100,000* | 0.5:100,000[†] | 0.5:100,000[‖] | Very rare[§] |
| Symptoms | Neuro-visceral | +++ | ++ | ++ | +++ |
| | Cutaneous | - | + | ++ | - |
| Urine during attacks | ALA | +++ | ++ | ++ | +++ |
| | PBG | +++ | ++ | ++ | NL |
| | Coproporphyrin III | - | ++ | + | - |
| Total fecal porphyrins | | NL | ++# | ++[‡] | NL |

*AD*, autosomal dominant; *ALA*, δ-aminolevulinic acid; *AR*, autosomal recessive; *NL*, normal, *PBG*, porphobilinogen

*Gene carrier frequency is 1/1700

[†] Gene carrier frequency is not known

[‖] Prevalence is 3/1000 in South Africa due to founder effect in the population of Dutch origin

[§] Only 12 reported cases worldwide

[#] Mainly coproporphryin III

[‡] Protoporphryin IX > Coproporphyrin III

in heterozygous AHP patients remains unknown, especially in latent heterozygotes. Rough estimates, based on reports from clinically symptomatic patients, suggest that 10–40% develop neuropathy. Moreover, the percentage of latent cases who may have mild neuropathic manifestations is unknown [16].

## Clinical Presentation

### During Attacks

About 90% of acute attacks occur in women during the luteal phase of menstrual cycle [3, 12]. The attack typically starts with "brain fog" for a few days [17], followed by worsening, poorly localized, severe abdominal pain, nausea, and vomiting [3•]. Review of the patient's prior medical records typically reveals recurrent visits to the emergency department (ED) for these manifestations and non-informative diagnostic workups [18]. Diagnosis can be delayed for 15 years [12]. General examination is mostly normal except for tachycardia, elevated systolic blood pressure (BP), and perhaps an abdominal scar from previous surgical exploration. The lack of objective findings and the poor response to pain medications, including opioids, frequently raise the suspicion of a somatization disorder and/or drug seeking behavior [3•].

The peripheral neuropathy occurs within 4 weeks of onset of the abdominal pain in > 80% of patients [16, 19, 20]. Motor predominant neuropathy is most common, presenting as a diffuse symmetric, proximal more than distal, muscle weakness [19, 21, 22]. The weakness may begin unilaterally and then extend bilaterally [16]. In one AIP cohort, 50% of patients presented with onset in the upper extremities, and 80% had proximal arm weakness. One-third of the patients had onset in the legs where weakness was mainly proximal. In the remaining, weakness occurred simultaneously in the arms and legs [22]. Generalized areflexia with preserved ankle jerks is present in half of the patients [19]. Positive sensory symptoms (pain, hyperesthesia, or hyperalgesia) are uncommon, typically in a proximal "bathing suit" distribution [16, 19]. Sensory loss is rare, occurring in a glove-and-stocking or patchy proximal distribution [22]. The non-length-dependent distribution of porphyric neuropathy should alert ED physicians and the consultant neurologists to an alternative etiology other than the common diabetic, metabolic, or toxic neuropathies. Cranial neuropathies, mainly affecting the III, VI, IX, and X cranial nerves, develop in 35–35% of cases [19, 22, 23].

Dysautonomic manifestations include abdominal pain, the most common symptom in acute attacks (83–100%) [23, 24]. Patients may report a few days of alternating constipation and diarrhea, and atonic bladder may occur [22, 23, 25]. Autonomic cardiovascular manifestations include systolic hypertension, orthostatic hypotension [22], and tachycardia [26], likely due to cardio-vagal neuropathy and/or reaction to visceral pain [23].

Respiratory failure, perhaps due to phrenic neuropathy, was common in earlier studies [19, 21, 22, 27], but is now rarely seen. Nowadays, family members with latent AIP are diagnosed by genetic testing of a symptomatic relative and counseled on avoiding attack precipitating factors. Acute episodes can be treated proactively, preventing progression to a more extensive motor neuropathy [28]. The most common presentations of acute attacks now are a combination of abdominal pain, mild cognitive symptoms, autonomic dysfunction, and motor predominant neuropathy [23, 29]. Frequent severe attacks with insufficient time for neuronal recovery occur in 3–5% of symptomatic AIP cases [15, 30].

### Between Attacks

Chronic porphyric neuropathy presents with a different pattern of distribution with a distal sensorimotor polyneuropathy [31]. When motor neuropathy is significant during an attack, weakness recovers slowly taking up to 1 year for near-complete resolution, leaving patients with residual foot or wrist drops [3•]. After repeated attacks, cumulative deficits occur leading to permanent atrophy, especially in the distal muscles [16]. Chronic neuropathic, myalgic, lower-back, or abdominal pains are present in ~ 65% of AHP patients with recurrent acute attacks [24••]. One study found that half of patients were on opioid analgesics between attacks [32]. It is often challenging to distinguish flares of chronic pain from acute attacks based on clinical assessment without biochemical studies. Disturbance of thermal perception was also reported in AIP patients [33, 34]. Cardiovagal impairment persisted between attacks [35], leading to resting tachycardia, palpitations, and exaggerated tachycardic responses to stand-up or head-up tilt table (HUT) tests. The prominent autonomic and sensory symptoms imply the presence of a small fiber neuropathy (SFN) in these patients [36].

## Diagnostic Workup

### Biochemical and Genetic Testing

A markedly elevated urine PBG level is diagnostic of a porphyric attack. The test is performed on a spot urine sample with the PBG normalized per gram of urinary creatinine; a 24-h collection is not required. The upper limit of normal is 2 mg/g of creatinine and the level increases at least 10-fold in an acute attack [4, 37]. The sample must be protected from prolonged light exposure by covering the container with tinfoil [38]. PBG remains stable in the dark at 4 °C for 48 h, and least a month at − 20 °C. The turnaround time is often 4–10 days at commercial reference laboratories, potentially resulting in diagnostic delay, misdirected medical care, and

progressive neurologic deficits [3]. Urinary PBG decreases between attacks, but may remain increased for years, without symptoms, in most AIP patients [39, 40], typically increasing again during a recurrent attack. Urinary ALA is always increased during acute attacks and remains elevated in ~ 62% of AIP cases in remission [41]. Those "chronic high excretor" patients likely develop more nerve damage with age.

Mutation analysis is the most reliable method to confirm the biochemical diagnosis and determine the specific type of AHP. Erythrocyte enzyme assays are not reliable for diagnosing AIP due to overlap of low-normal and the high heterozygote ranges and since certain AIP-causing mutations show normal erythroid HMBS activity. They are not available for HCP or VP. To summarize, AHPs should be diagnosed in symptomatic patients by markedly elevated urinary PBG, followed by mutation analysis of the three dominant AHP-causing genes.

## Electrodiagnostic Testing

### During Attacks

Electrodiagnostic testing in the acute stage aids diagnosis of porphyric neuropathy and rules out other possibilities. The neuropathy is predominantly axonal motor [7, 31, 42–45]. Sensory studies are often normal when performed on the same nerves pointing to nerve root pathology [45, 46]. The axonal motor involvement is manifested by low compound muscle action potential (CMAP) amplitudes mainly in the radial and peroneal nerves [45–47]. The distal latencies are sometimes prolonged, but within a range that could be accounted for by loss of the fastest conducting axons [16]. A few studies reported occasional primary demyelinating changes without evidence of significant axonal involvement in one nerve, which is insufficient to establish a diagnosis of primary demyelinating polyneuropathy [44]. There are, additionally, a few case reports describing the occurrence of a primarily demyelinating neuropathy during attacks [23, 34, 43], based on significantly slowed motor conduction velocities or prolonged F-waves, temporal dispersions, or conduction blocks.

Needle electromyography shows evidence of widespread acute/subacute denervation in the form of fibrillations and positive sharp waves, particularly in proximal muscles, further emphasizing nerve root involvement [16, 45, 48]. Reduced recruitment of normal motor unit potentials (MUPs) is present early during attacks [45]. The possibility of reduced activation should always be considered given the pain and confusion experienced during attacks.

### Between Attacks

Electrodiagnostic testing aids in following the neuropathy and predicting recovery when performed after an acute attack. While the encephalopathy and acute autonomic symptoms resolve quickly after starting treatment, resolution of the neuropathy from an electrophysiologic standpoint is slower and depends on the severity and extent of axonal degeneration. Recovery usually takes months, often with incomplete normalization of the CMAP amplitudes [31]. Electromyography performed during this stage demonstrates reinnervation, as evidenced by reduced recruitment and high-amplitude, long-duration, polyphasic MUPs. Residual small fibrillation potentials are often limited to distal muscles, denoting incomplete reinnervation [31, 45]. Note that in some electrodiagnostic reports, case ascertainment was made based on clinical manifestations and biochemical testing, as confirmatory genetic testing was not yet available [42–44]. Moreover, older electrodiagnostic studies did not correlate the severity of the electrodiagnostic findings with disease duration or the number of previous attacks.

## Autonomic Function Testing

Although autonomic dysfunction is the major presentation of acute attacks, its pathophysiologic mechanisms are unknown. Laiwah et al. [35] reported that both cardio-sympathetic and cardio-vagal functions were affected during acute attacks, with the latter persisting during remissions. The sympathetic function testing that they used included BP responses to sustained isometric handgrip and stand-up. BP responses to the Valsalva maneuver (VM) or HUT were not assessed. The handgrip test was shortened from 5 min to 15 s in some patients due to motor weakness and poor endurance. The cardio-vagal parameters assessed included heart rate responses to deep breathing (HRDB), VM, and stand-up. The Valsalva ratio was normal in AIP patients in remission, whereas HRDB remained significantly reduced. This discrepancy was ascribed to the small number of patients; however, it may simply have been due to the higher sensitivity of HRDB [35]. Again, it should be noted that patients in this study were included based solely on clinical and biochemical diagnoses, as genetic testing was not yet available.

Another study used frequency domain spectral analysis of heart rate variability (HRV) to assess cardio-sympathetic and cardio-vagal functions in a genetically confirmed Swedish AIP cohort [49]. They compared low-frequency (LF) bands (0.04–0.15 Hz) after HUT in patients and healthy controls as a measure of cardio-sympathetic function. To study cardio-vagal function, they analyzed high-frequency bands (0.15–0.4 Hz) during controlled breathing (12 breaths/min) and LF bands during controlled breathing (six breaths/min). They found decreased LF band power during deep breathing at six breaths/min compared with controls. Such difference did not occur during the HUT test. They interpreted these findings as evidence of cardio-vagal impairment [49]. The use of HRV frequency domain analyses to assess autonomic function,

while sensitive, is an indirect method that reflects the balance between sympathetic and vagal influences on heart rate [50]. Moreover, an international task force on HRV recommended LF analysis as a measure of cardio-sympathetic rather than cardio-vagal control [51]. More direct testing of cardio-sympathetic functions using blood pressure responses to VM or HUT was not performed.

### Histopathologic Studies

The most consistently reported pathologic findings in porphyric neuropathy are axonal loss and Wallerian degeneration [48]. Similar pathologic changes were reported in the femoral nerve of the *HMBS* (−/−) mice at 6 months of age, occurring with only 2-fold increased ALA levels [52]. Patchy areas of grouped demyelination, observed in association with axonal degeneration, are likely secondary to the primary axonopathy. Pure sensory nerves are often spared. However, none of these changes are specific to porphyric neuropathy [48]. Given the lack of specificity and the motor predominance in porphyric neuropathy, a sural nerve biopsy is unnecessary, unless required to rule out another diagnosis, e.g., vasculitic neuropathy.

Skin punch biopsy helps to confirm a diagnosis of SFN, in cases presenting with non-radicular positive sensory symptoms, when sensory NCS are normal [53]. A few case reports described pathologic evidence of SFN in AIP [33, 34]. Serial skin punch biopsies performed on a patient during and for up to 3 months after an attack demonstrated reduced intraepidermal nerve fiber density, at day 48 from onset which did not improve by day 92 despite initiation of muscle strength recovery, again emphasizing the potential role for SFN in the chronic pain reported by AIP patients [33].

## Differential Diagnosis

The acute onset polyradiculoneuropathy and autonomic involvement point to acute inflammatory demyelinating polyradiculoneuropathy (AIDP) or Guillain-Barre syndrome as a differential diagnosis of acute porphyric neuropathy [54]. As AIDP is usually monophasic, recurrent attacks favor porphyric neuropathy [45]. Unlike AIDP, ankle jerks may be preserved during AIP attacks [16]. The severe diffuse abdominal pain during attacks further distinguishes porphyric neuropathy [23]. The lower abdominal pain infrequently reported in AIDP is mostly radicular, originating from the lower thoracic and lumbar spine. Electrophysiologic evidence of axonal loss favors porphyric neuropathy, although axonal variants of Guillain-Barre Syndrome occur [54]. Routine cerebrospinal fluid analysis in AIP is normal and cyto-albuminologic dissociation does not occur [19, 43].

Other diseases presenting with an acute axonal neuropathy should be included in the differential diagnosis. Vasculitic neuropathy is usually asymmetric at onset, presenting as mononeuritis multiplex with substantial sensory involvement. Laboratory testing of inflammatory markers is helpful if positive, but nerve biopsy may be required for definitive diagnosis [55]. The combination of encephalopathy, abdominal pain, and axonal neuropathy raises suspicion for toxic neuropathies, particularly inorganic arsenic or lead-induced neuropathies. Inorganic arsenic acute neurotoxicity often presents after 1–2 weeks of severe abdominal pain, nausea, vomiting, and diarrhea. However, this neuropathy, now rarely encountered in developed countries, is often length-dependent, sensory-predominant, and painful [56].

Historically, it has been important to consider lead neuropathy in the differential diagnosis of AHP neuropathy. Lead poisoning is associated with inhibition of ALA-dehydratase and ferrochelatase, resulting in elevated urinary excretion of ALA and protoporphyrins [57]. Today, lead intoxication is rare; however, it should be considered in economically disadvantaged communities, and particularly in children with calcium deficiency or sickle cell disease. The diagnosis is ruled out by a normal blood lead level [58]. The biochemical pattern of elevated urine ALA with normal PBG levels is also seen in patients with ADP or hereditary tyrosinemia type-1 [9, 59, 60]. In the latter, succinylacetone accumulation, like lead, inhibits ALA-dehydratase. Patients develop recurrent acute painful neuropathy and respiratory dysfunction [59].

## Pathophysiology

The pathophysiologic mechanism of porphyric neuropathy remains unclear [61]. Most of the current hypotheses were proposed to explain the central nervous system involvement, but are also likely relevant to the neuropathy [62]. The dominant theory is that of ALA-induced, rather than, PBG-induced neurotoxicity. ALA is elevated in all four AHPs, whereas PBG is not elevated in ADP. Other disorders associated with excess production of ALA, but not PBG (hereditary tyrosinemia type-1 and lead poisoning), have similar clinical presentation to AIP [59, 63]. The liver is the primary source of the accumulated ALA in AHP patients, and liver transplantation in severe AIP patients rapidly decreases ALA and PBG, and halts the recurrence of acute attacks, providing evidence for a harmful effect of excess liver-derived ALA on neurons [64, 65]. Notably, "domino" liver transplants from AIP donors with recurrent attacks resulted in acute attacks in non-porphyric recipients [66]. In addition, the beneficial effects of heme infusions that decrease the ALA and PBG levels via a negative feedback mechanism, and more recently, hepatic delivery of a small interfering RNA (siRNA) that markedly decreases ALA production by silencing ALA synthase-1

(ALAS1) expression markedly reduces attack frequency [67]. These findings provide evidence that delivery of excess ALA to neurons underlies the AHP neuropathology.

**Why Would ALA Excess Result in Neuropathy?** One hypothesis is that ALA is structurally similar to the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and appears to competitively bind to GABA receptors [68]. Elevated ALA levels are also pro-oxidative in vitro and are associated with increased formation of reactive oxygen species (ROS) in neural tissue [69]. ROS induced by ALA exposure damage Schwann cells, inhibiting myelination in vitro [70]. Note that ALA per se is commonly used in in vitro studies of cell lines with intact heme biosynthesis pathways to stimulate protoporphyrin and heme synthesis [71], and it is likely heme or one of its biosynthetic intermediates, protoporphyrin IX, increases ROS in response to ALA exposure. Excess ALA can cause mitochondrial and nuclear DNA damage in cell lines [72] and the addition of ALA to AIP neurons appears to cause mitochondrial impairment and decreased ATP production [73]. Fast axonal transport is highly dependent on ATP availability, especially during repolarization [16].

Studies of the AIP mouse model (T1/T2, ~30% enzyme activity) offer parallels with the human AIP neuropathy. These mice develop chronic severe axonal motor neuropathy, due to loss of large nerve fibers (60% and 90% loss at 6 and 17 months, respectively, vs controls), without primary demyelination [62]. As also seen in AIP patients, there was ongoing re-innervation of murine muscles, as evidenced by reduced recruitment and polyphasic MUPs.

**Why Do Acute Episodes Predominantly Affect the Autonomic and Peripheral Nerves?** The blood-nerve barrier (BNB) is considered the most restrictive microvascular barrier after the blood-brain barrier (BBB) [74•]. While intraperitoneal injection of ALA (10 mg/kg) in normal mice led to significantly less ALA concentrations in the CSF (1% of plasma levels), the levels in tissue surrounding the tibial nerve were much higher, 30% [62]. BNB is less restrictive in nerve roots and autonomic ganglia [74•]: consistent with earlier autopsy studies demonstrating central chromatolysis in anterior horn cells, likely due to axonal dying-back [75] and in autonomic ganglia [76]. Additionally, ALA has a direct spasmodic effect in rat jejunum [77], where the BNB is also less restrictive [78]. The known ALA transporters, PEPT1 (SLC15A1) and PEPT2 (SLC15A2), were not found in the BNB transcriptome, yet a different transporter was, SLC36A1 [74, 79].

Remarkably, the neuropathy in the AIP mouse model occurred in the absence of pharmacologically induced attacks, with plasma ALA levels chronically between 1- and 3-fold that of controls, raising the possibility that the chronic axonal neuropathy may result from a mild chronic ALA excess [62]. The T1/T2 mice do not develop obvious autonomic or sensory symptoms with induced attacks, suggesting confounding factors mitigating the autonomic and sensory pathology, perhaps related to differences in murine vs human pathology [62].

In summary, the dominant theory for the neurotoxicity of AIP relates to ALA excess produced by the liver, through interference with GABA receptor function, induction of ROS (perhaps through increasing heme synthesis), and/or mitochondrial dysfunction. Chronically, this results in axonal degeneration, while acute increases in ALA production predominantly affect the autonomic system, likely related to the deficient BNB in autonomic ganglia and myenteric plexus. While parenteral heme therapy ameliorates AIP attacks, this relates to its rapid reduction of hepatic ALA production, and heme does not cross the BBB [80].

## Treatment

ALAS catalyzes the rate-limiting step in heme biosynthesis pathway [3•]. Its ubiquitous isoform, ALAS1, is tightly regulated by hepatocyte heme content in a negative feedback loop [81]. It is also upregulated during fasting, due to its regulation via the glucose-sensitive peroxisome proliferator-activated receptor gamma coactivator-1 [82]. ALAS1 thus serves as a target of various therapeutic interventions during and between attacks [83].

### During Attacks

1. Supportive and symptomatic treatment:

Initial management of acute attacks includes discontinuing any potential precipitants and symptomatic management. Review of the patient's medications for those that could have precipitated the attack is mandatory [29]. The American Porphyria Foundation and the Sweden Porphyria Center provide searchable databases that classify medications by safety. In patients with seizures, which can occur in up to 20%, the consultant neurologist must avoid commonly used antiepileptic medications deemed unsafe in porphyria patients (Table 2). Abdominal pain is typically severe, and opiates are usually needed at scheduled intervals or via a patient-controlled analgesia pump [3, 29]. Prochlorperazine are ondansetron safe options for nausea and vomiting [84]. Beta blockers are commonly used for tachycardia/tachyarrhythmia and hypertensive crises [85]. Checking serum CK is needed to screen for rhabdomyolysis [86]. Bulbar weakness, respiratory insufficiency, and arrhythmias are indications for intensive care admission [29].

2. IV glucose:

The rationale of using IV glucose during mild attacks, i.e., mild pain without weakness, seizures, or hyponatremia [60], is

**Table 2** Safety profiles of commonly prescribed neurologic medications

| | Safe | Probably safe* | Probably unsafe | Unsafe† |
|---|---|---|---|---|
| Anti-epileptic drugs | | | | |
| Carbamazepine | | | | + |
| Clonazepam | | | | + |
| Ethosuximide | | | + | |
| Felbamate | | | | + |
| Lacosamide | | + | | |
| Lamotrigine | | + | | |
| Levetiracetam | + | | | |
| Oxycarbamazepine | | | | + |
| Phenobarbital | | | | + |
| Phenytoin | | | | + |
| Valproic acid | | | | + |
| Zonisamide | | | + | |
| Neuropathic pain drugs | | | | |
| Amitriptyline | + | | | |
| Duloxetine | | + | | |
| Gabapentin | + | | | |
| Opioids | + | | | |
| Pregabalin | + | | | |
| Topiramate | | | + | |
| Muscle relaxants | | | | |
| Baclofen | | + | | |
| Carisoprodol | | | | + |
| Cyclobenzaprine | | | + | |
| Others‖ | | | | |
| Meclizine | + | | | |
| Pramipexole | + | | | |
| Primidone | | | | + |
| Ropinirole | | + | | |

*Should be used with caution

† Used only in urgent and short term indications when a less risky alternative is unavailable

‖ Information on more drugs is available on http://porphyriadrugs.com/, www.porphyriafoundation.com, and www.drugs-porphyria.org/index.php

to downregulate ALAS1 activity. A daily dose of 300 g of 10% dextrose is infused over 24 h [60]. Syndrome of inappropriate antidiuretic hormone secretion and hyponatremia is common (25–60%), and sodium levels should be monitored regularly [29]. It should be slowly corrected (12 mmol/L/24 h) to avoid central pontine myelinolysis [87].

3. Hemin infusion:

Hemin suppresses ALAS1 activity and inhibits the production of heme precursors during attacks [88]. The available preparations are lyophilized heme (Panhematin, Recordati Rare Diseases, NJ) in the USA and heme arginate (Normosang, Orphan Europe, Berkshire, UK) in Europe [29]. Panhematin is available as powder that is reconstituted immediately before use with water or human albumin. The dose is 3–4 mg/kg, daily infused over a 40-min period for ≥ 3 days. Markedly decreased urine PBG levels typically occur after 2–3 doses, with the pain and nausea resolving within 4 days [3•]. Motor weakness often persists, but should not progress [20]. Side effects include phlebitis that can be avoided by mixing the powder with human albumin rather than water, and accessing a central or a large peripheral vein [89]. Panhematin may cause platelet aggregation with a transient decrease in platelet count and may also prolong the prothrombin time [90], without bleeding tendency. Hepatic iron overload may also occur with chronic administration [91]. Patients are usually discharged when narcotics are no longer needed, and oral caloric intake is adequate [3•].

## Between Attacks

1. Prophylactic hemin infusions:

Weekly, biweekly, or monthly IV hemin infusions have been used to reduce the frequency of recurrent attacks in severe cases [12, 37, 84]. A UK audit of 22 patients with severe recurrent attacks showed that patients received 1–8 heme arginate infusions per month. Reduction in pain severity was achieved in 67%, but 55% continued to have repeated hospital admissions due to disease worsening, tachyphylaxis, or development of chronic pain syndrome. Complications included vascular access problems, iron overload, and difficulty withdrawing treatment [32].

2. Liver transplantation:

Liver transplantation has been regarded as a heroic, but curative treatment for patients with severe recurrent attacks where medical management was unsuccessful or where complications, e.g., poor vascular access, precluded infusions [64, 65]. Liver transplantation led to rapid normalization of porphyrinogens' levels, cessation of attack recurrence, and improvement in chronic pain [92]. However, the motor deficit incurred during earlier attacks persisted [93]. The burden of illness and side effects of conservative treatment must be weighed against the risks of surgery and life-long immunosuppression [64, 93, 94]. The recent introduction of effective prophylactic therapies has greatly reduced the need for liver transplant in AHP patients (see below).

3. Replacement therapies:

A trial of HMBS enzyme replacement was unsuccessful. Although intravenous infusion of a recombinant human

HMBS enzyme preparation lowered plasma PBG levels, the plasma ALA levels remained elevated and there was no effect on patients' acute symptoms, likely because the HMBS was infused in insufficient quantities to mitigate the hepatic production of ALA [95••]. In another strategy, the *HMBS* gene was delivered to hepatocytes using an adenoviral vector, with encouraging data in the AIP mouse model [96]. However, a phase-1 clinical trial in patients with frequent attacks demonstrated no reduction in plasma or urine ALA or PBG levels, with only trends towards fewer hospitalizations and prophylactic hemin infusions [97].

4. siRNA silencing of ALAS1:

Givosiran, an siRNA molecule directed against hepatic ALAS1, was FDA approved, based on a 6-month randomized double-blinded placebo-controlled phase-3 study followed by a 30-month open-label extension in adults with AHP [98••]. Givosiran is conjugated with *N*-acetylgalactosamine to facilitate hepatocyte targeting. A phase-1 study demonstrated that one dose reduced ALAS1 expression within 24 h. The effect was significant and sustained, remaining within the target range for 1 month [99]. When given at a dose of 2.5 mg/kg monthly by subcutaneous injection to AHP patients with chronically elevated PBG and ALA levels, it led to 74% and 77% reduction in the mean annual attack rate and annualized number of days of IV hemin use, respectively. The daily worst pain score was significantly lower in the givosiran group compared with placebo. Adverse reactions included elevated liver enzymes (15%), impaired renal function (15%), and mild injection site-related reactions (25%) [98••].

5. Chronic pain management:

Pain treatment options include safe antiepileptic and antidepressant agents like gabapentin [100], pregabalin, amitriptyline, and duloxetine (Table 2). These should be tried before resorting to less safe options or long-term use of opiates [29, 84]. Prophylactic hemin infusions or subcutaneous administration of givosiran may help improve severe chronic pain [12, 84].

6. General prophylactic measures:

Other measures include patient education on the known precipitating factors, specifically alcohol intake, fasting or dieting, and use of high-risk medications; educating primary care physician and local neurologists on the available safe medication lists; and OBGYN consultation on using GnRH analogues to prevent catamenial attacks [3, 29, 84]. Medical care of these patients is complex, and they should be monitored for the development of chronic liver disease, renal failure, hyponatremia, and hypertension. The Porphyrias Consortium published more detailed recommendations regarding the long-term management and follow-up of AHP patients [1]. Note that genetic testing of first-degree family members is important after the diagnosis is confirmed in the symptomatic index case as biochemical testing of asymptomatic relatives is usually normal [83]. Latent AIP heterozygotes should be counseled to avoid precipitating factors.

## Conclusion

The diagnosis of AHP is challenging due to the variable clinical presentation and similarities with other neurological conditions that neurologists and ED physicians encounter more frequently, e.g., AIDP or somatization disorders. Moreover, the clinical picture of the porphyric neuropathy depends on the disease course (single versus recurrent attacks) at the time of presentation and hence, varying patterns of neuropathy are seen, particularly non-length-dependent polyradiculoneuropathy. Neurologists should be aware of the updated management of porphyric neuropathy as, left untreated, the burden of neurological disability increases with each attack. Similar to most toxin- and drug-induced axonopathies, long-term outcomes critically depend on early diagnosis, timely intervention, and the avoidance of precipitating factors.

Large gaps in our knowledge of the pathophysiology of porphyric neuropathy remain, with most evidence supporting ALA-induced neurotoxicity. The majority of the earlier electrophysiologic reports included cases that were not genetically confirmed and did not correlate the severity of axonal injury with disease duration or the number of previous attacks. The reasons why AHP patients present predominantly with dysautonomic manifestations (both acute and chronic) also remain unknown. We propose that the autonomic nervous system is primarily affected in regions where the BNB is less restrictive (i.e., the autonomic ganglia and myenteric plexus). Even the pathogenesis of the chronic pain that occurs between attacks is still unclear, and the potential pathophysiological role of SFN needs further study. Until recently, treatment options included supportive measures and IV hemin infusions. The introduction of siRNA approach appears to be a significant therapeutic advance in AHP, based on its ease of use, the absence of intravenous access-related side effects, and the sustained clinical benefit with monthly dosing. While siRNA treatment decreases the frequency of attacks and the need for heme infusions, its long-term effects on motor recovery, chronic pain, and dysautonomic manifestations remain to be determined.

**Acknowledgments** The authors thank Dr. Peter H. King, Professor of Neurology, The University of Alabama at Birmingham, for the critical revision of the manuscript.

## Compliance with Ethical Standards

**Conflict of Interest** Dr. Kazamel received consulting fees from Akcea Therapeutics.

Dr. Desnick is a consultant for Alnylam Pharmaceuticals and Recordati Rare Diseases. He has received grants from both entities. He receives royalties for a licensed patent to Alnylam Pharmaceuticals.

Dr. Quigley received consulting fees from Alnylam Pharmaceuticals.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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