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Understanding Hepatic Porphyrias: Symptoms, Treatments, and Unmet Needs

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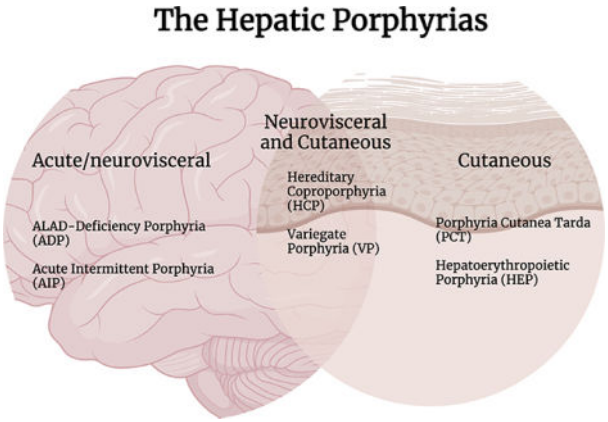
Abstract

Hepatic porphyrias are a group of metabolic disorders that are characterized by overproduction and accumulation of porphyrin precursors in the liver. These porphyrins cause neurologic symptoms as well as cutaneous photosensitivity, and in some cases patients can experience life-threatening acute neurovisceral attacks. This review describes the acute hepatic porphyrias in detail, including acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria, as well as the hepatic porphyrias with cutaneous manifestations such as porphyria cutanea tarda and hepatoerythropoietic porphyria. Each section will cover disease prevalence, clinical manifestations, and current therapies, including strategies to manage symptoms. Finally, we review new and emerging treatment modalities, including gene therapy through use of adeno-associated vectors and chaperone therapies such as lipid nanoparticle and siRNA-based therapeutics.

Graphical Abstract



Lay summary:

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Conflict of Interest

Kari Nejak-Bowen is a consultant for Surrozen, Inc.

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Porphyrias are rare genetic disorders in which buildup of toxic by-products of heme synthesis, called porphyrins, accumulate in the body. Depending on the enzyme defect, these porphyrins can cause complications ranging from light sensitivity to life-threatening neurological attacks. Here we describe in detail each of the hepatic poprhyrias, or porphyrias that primarily affect the liver. We also outline the current medical therapies to manage symptoms and reduce the severity of acute attacks, and discuss future treatments on the horizon.

Keywords

acute intermittent porphyria; hereditary coproporphyria; variegate porphyria; porphyria cutanea tarda; hepatoerythropoietic porphyria

Introduction

Poprhyria is an inherited genetic disorder caused by defects in heme biosynthesis that result in accumulation of precursors called porphyrins. Each type of porphyria is the result of a specific abnormality in one of the eight enzymes responsible for heme biosynthesis, and are classified as either hepatic or erythropoietic.[1,2] The acute hepatic porphyrias are characterized by overproduction and accumulation of porphyrin precursors in the liver; in erythropoietic porphyrias, accumulation of porphyrins occurs in bone marrow erythroid cells and liver.[3,4] In a previous review, we described the common mutations and enzymatic defects that cause porphyria, focusing specifically on the hepatic porphyrias.[5] In this review, we aim to provide an extensive analysis of the porphyrias with hepatic manifestation and highlight barriers to treatment. For more details on the specific mutations and DNA variations that cause the hepatic porphyrias, we have collated a list of searchable databases that provide information on porphyria-related genes and genetic phenotypes. This reference supplement also provides lists of drugs that are safe or unsafe for porphyria patient use, as well as information on diagnosis, management, and treatment guidance for patients (see Supplement 1).

Overview of Heme Biosynthesis

Heme is an iron molecule contained within a tetrapyrrole ring, and is produced primarily in bone marrow and liver.[6] It is an essential co-factor for heme-containing proteins such as hemoglobin, myoglobin, peroxidases, respiratory cytochromes, and cytochrome P450 enzymes, and its unique properties allow it to function as both an electron carrier and a catalyst for redox reactions.[6] Heme is synthesized in eight enzymatic steps that are carried out in both the mitochondria and the cytoplasm.[7] The first and rate-limiting step occurs in the mitochondria and combines glycine and succinyl Co-A to form δ-aminolevulinate acid (ALA). This reaction is catalyzed by ALA-synthase (ALAS), which exists in two isoforms: ALAS1, which is expressed ubiquitously, and ALAS2, which is expressed only in erythroid precursors.[8] ALA then exits the mitochondria, where ALA-dehydratase (ALAD) forms porphobilinogen (PBG) by catalyzing the condensation of two ALA molecules.[9] The next enzyme, hydroxymethylbilane synthase (HMBS), catalyzes the formation of hydroxymethylbilane (HMB) from four molecules of PBG.[10] HMB is then converted

to uroporphyrinogen III, an asymmetrical pyrrole ring, by uroporphyrinogen synthase (UROS), and then to coproporphyrinogen III by uroporphyrinogen decarboxylase (UROD).[11] Coproporphyrinogen III is transported back into the mitochondria and is decarboxylated by coproporphyrinogen oxidase (CPOX) to form protoporphyrinogen-IX, which is oxidized by protoporphyrinogen oxidase (PPOX) to protoporphyrin-IX (PP-IX)[2,9]. Finally, PP-IX is metallated by ferrochelatase (FC), the last enzyme in the pathway, to form iron containing heme[8,12]. ALAS1 is negatively regulated by heme, which represses *ALAS1* transcription.[13] Thus, depletion of the regulatory 'free' heme pool activates ALAS1. Heme levels can also be regulated by the rate of catabolism, which is controlled by heme oxygenase 1 (HO-1), the enzyme responsible breaking down heme into biliverdin, carbon monoxide, and iron.[14]

Hepatic Porphyria(s) with Acute Manifestations

ALAD-Deficiency Porphyria (ADP)

δ-aminolevulinic acid dehydratase porphyria (ADP) (OMIM 125270) also known as "Doss Porphyria" and the rarest of all porphyrias, is a genetic disease triggered by a severe insufficiency of the enzyme δ-aminolevulinic acid dehydratase (ALAD) (Figure 1A).[15–17] To date, all six documented cases have been in male patients, with symptoms manifestating at age 14.[18,19]

ADP is a homozygous disease with severe neurological symptoms attributed to the accumulation of the toxic porphyrin precursor δ-aminolevulinate acid (ALA) and the subsequent deficiency of porphobilinogen. Besides a defective gene, precipitating factors like alcohol, certain drugs, physical and psychological stress, infection, reduced caloric intake, dehydration, and the use of estrogen and progesterone are recognized triggers of acute attacks in ADP patients.[15] In several instances the symptoms are exacerbated by drugs which induce cytochrome P450 (CYP) enzymes, leading to subsequent induction of δ-aminolevulinate synthase 1 (ALAS1), the first and rate-limiting enzyme in heme biosynthesis.[20] Under normal conditions, the activity of ALAD is present in excess and a partial deficiency of the enzyme (~50%) is not associated with disturbances of heme synthesis. The normal abundance of this enzyme offers an explanation as to why heterozygotes with ~50% of normal ALAD activity remain asymptomatic.[19,21]

Prevalence & Penetrance: To date, only eight cases of ADP have been diagnosed, of which two were identified at birth, one at age 7, 4 at the ages of 12–15, and one at age 63.[20] ADP is highly heterogenous at the molecular level, with 14 mutations in *Alad* identified in the eight patients with the disease.[18,20,22] Reports based on a small population analysis revealed that the prevalence of individuals with 50% of normal ALAD activity, caused by one aberrant ALAD allele, is 2% in the normal asymptotic population, indicating that most instances of compound heterozygosity in ALAD produces spontaneous abortions. The frequency of heterozygotes among the normal population in Sweden was estimated to be ~2%.[19]

Clinical Manifestations: ADP is more severe than the other acute porphyrias.[15,20] Patients with ADP have clinical symptoms typical of acute hepatic porphyria (AHP), usually

intense cycles of neurovisceral or acute attacks that may last for days or weeks. Although the symptoms of ADP are generally neurological and gastrointestinal, these also vary between patient populations.[16,23] Neuropsychiatric symptoms present as psychological changes, possible psychosis, diminished peripheral neuropathy that results in tingling in the hands and feet, burning pain, sensitivity to touch, and lack of coordination.[16,23] Additional neurological symptoms include disorientation, delirium, agitation, anxiety, restlessness, hysteria, hallucination, apathy, altered consciousness, depression, and phobias.[20] Of the eight patients with confirmed diagnosis, six displayed motor dysfunction.[20] Advanced patients may experience a partial or complete loss of the ability to use voluntary muscles. Tachycardia, hypertension, seizures, respiratory impairment, severe abdominal cramping, vomiting, and constipation are also associated with acute attacks related to ADP.[16,20,23] Although liver disease is not a complication, ADP can also have a significant erythropoietic component that may cause cutaneous symptoms in early childhood and can be complicated by cholestatic liver cirrhosis and progressive hepatic failure.[20]

Clinical Diagnosis: Presence of the trio of abdominal pain, peripheral neuropathy and neuropsychiatric symptoms should raise concern and prompt consideration and investigation for acute porphyria.[20,24] Other diseases, like lead poisoning can also mimic ADP; lead is a potent inhibitor of ALAD and can produce similar symptoms and biochemical anomalies as ADP including increased urinary ALA. Hereditary tyrosinemia type 1 also produces symptoms similar to ADP, since succinyl-acetone, another potent inhibitor of ALAD, is found in high quantities in the blood and urine of patients.[19,20] Differential diagnosis has also been recommended in other toxic states where ALAD activity is suppressed such as zinc deficiency, smoking, alcoholism, diabetes mellitus and chronic renal insufficiency.[19]

Treatment/Therapies: Treatment with hemin proved effective in four young male patients; however glucose loading was ineffective, as was liver transplantation.[19] Prophylaxis in the form of deterrence and patient education are highly encouraged. Patients are counseled to avoid precipitants of acute attacks including alcohol and tobacco. Education on the inheritance patterns and risk for future generations is also extremely important, as is providing patients with the information that available treatment is currently only for acute attacks. Healthcare providers are encouraged to give patients a list of medications that are safe or unsafe, help them recognize symptoms of acute attacks, and provide instructions to seek emergency care in the case of abdominal pain.[20]

Acute Intermittent Porphyria (AIP)

AIP (OMIM #176000), also the most prevalent type of acute porphyria, is a metabolic disorder precipitated by mutations in the hydroxymethylbilane synthase *(HMBS)* gene that result in overproduction of porphyrin precursors ALA and porphobilinogen (PBG) (Figure 1B).[25,26] AIP is classified as either overt (a heterozygote who was previously or is currently symptomatic) or latent (a heterozygote who has never displayed symptoms).[27] Acute attacks can be provoked by exposure to drugs that induce heme biosynthesis in the liver, as well as certain drugs that induce the cytochrome P450 detoxification system, excessive alcohol consumption, caloric restriction, stress, infection, certain hormonal

factors, and increased production of hepatic ALAS1 in addition to other environmental factors.[7]

Prevalence & Penetrance: Although AIP occurs in all ethnic groups, specific clusters have been identified due to a founder effect in some northern European countries. The prevalence of AIP in Europe is estimated to be 1—2/100,000 individuals[28], ~5/100,000 in the United States[19], 2.4/100,000 in Finland, [29] 1/132,000 in France,[30] and 1 /1500 in northern Sweden.[7] In Sweden, the incidence and prevalence of AIP are four times higher than in other parts of Europe due to a founder effect centered in Lapland.[31] The United Kingdom also displays high incidence of *HMBS* mutations at 1/500, with incomplete penetrance and prevalence of symptomatic disease at 1–2/100,000.[19] The penetrance of this disorder is low, at roughly about 1% of all AIP heterozygotes.[32] A cohort of families (French Reference Porphyria Center) revealed an estimated disease penetrance in affected families at 22.9%.[33] Exome variant server data estimates prevalence in the general population at 1:1299; in France prevalence is estimated at 0.5%-1%, with penetrance attributed to a consequence of both environmental and genetic factors.[33] The monogenicity of this disease further suggests that genetic or environmental factors play a role in predisposing heterozygotes to acute attacks.[32]

Clinical Manifestations: Although most people with genetic defects in *HMBS* remain asymptomatic, AIP is accompanied by occasional neuropsychiatric crises associated with accumulation of ALA and PBG, which are released into the circulation from the liver.[7,21,23,25,34] The course of acute attacks is variable within and between individuals, and the visceral, peripheral, autonomic and central nervous system may be affected, leading to a range of findings that although often intermittent may be life threatening.[35] Due to hormonal influences, AIP is more likely to manifest after puberty and is more prevalent in women; affected women may develop monthly attacks due to hormonal changes in the luteal phase of their menstrual cycles.[32] Although affected individuals may recover from acute attacks within days, recovery from severe attacks with no intervention may take weeks or months. Additionally, although attacks are typically caused by either endogenous or exogenous factors, individuals can also have acute attacks without the involvement of precipitating factors.[35]

Symptoms associated with acute episodes include fluctuating combinations of severe abdominal pain, vomiting, nausea, gastrointestinal motility disorders, hyponatremia, hypertension, tachycardia, and bladder dysfunction, possibly due to autonomic neuropathy.[36] Cutaneous features are absent.[35,37] Peripheral neuropathy consists of muscle weakness of the legs and arms, and can progress to respiratory muscles. Mental changes are present in up to 30% of symptomatic individuals but are rarely the dominant feature. These changes include insomnia, anxiety, depression, hallucinations, confusion, paranoia, amnesia, and altered consciousness ranging from somnolence to coma.[35] Central nervous system signs may include delirium, weakness with progress to quadriplegia, cortical blindness and even coma. About 5% of patients may develop seizures, with partial seizures being the most common subtype.[37,38]

Clinically manifest or latent persons with disease are at increased risk for developing hepatocellular carcinoma (HCC), typically after age 54.[39] AIP in women over the age of 60 is associated with a 160-fold increased risk of hepatocellular carcinoma, and a 37-fold increased risk in men.[40] Renal dysfunction is apparent in approximately 70% of individuals with recurrent attacks and may be due to chronic renal exposure to elevated concentrations of ALA and PBG or genetic variation in ALA transporter PEP2.[35,41] In fact, one study consisting of 415 *HMBS* deficient patients (French Porphyria Center) identified 59% of AIP patients as comorbid for chronic kidney disease, with AIP classified as an independent factor for chronic tubulointerstitial nephritis. Other chronic and pathological complications include muscle denervation[19] and systemic arterial hypertension.[37]

Treatment/Therapies: Hematin infusions are particularly effective, as they replenish the hepatic heme pool, downregulate ALAS1, and reduce the excretion of urinary PBG and ALA.[35,42–44] Strict avoidance is recommended for inducers of acute attacks e.g., alcohol, infections, and high-risk porphyrinogen drugs.[35] The Norwegian Porphyria Centre and International Porphyria Network provide and continuously update a list of medications not recommended for use in porphyria patients.

Caloric deprivation triggers acute attacks in AIP that is attenuated by nutritional supplementation with an intake of carbohydrates administered enterally or parenterally.[42] Patients also often suffer from dehydration due to a combination of poor oral intake, vomiting, and increased fluid loss, which is treated by replacement of sodium and fluid deficits.[35,42] Agitation and anxiety are treated with chlorpromazine and pain is mitigated with meperidine. Propranolol is also useful in patients suffering from anxiety and agitation.[42] Ovulatory suppressant, androgens, oral contraceptives, and oophorectomy may be indicated in women with recurrent menstrual cycle-related acute neurovisceral attacks.[35,42] Other supportive treatments include effective analgesia for pain relief, ondansetron and other analogues to combat nausea and vomiting, and beta blockers for hypertension.[35]

Givosiran (Givlaari™), an ALAS1-directed siRNA therapeutic, has recently been approved for the treatment of adults with AIP. Givosiran treatment reduces the expression of ALAS1 within 24 hours and this reduction is retained for at least one month.[45] Studies have also shown the Givosiran also facilitates a sustained decrease in urinary ALA and PBG.[46] Liver transplantation is another treatment option for severe AIP.[35,47] Combined liver and kidney transplantation has also been successful and recommended for individuals with renal complications.[48]

Homozygous Dominant Acute Intermittent Porphyria (HD-AIP)

HD-AIP is a rare condition due to biallelic *HMBS* loss-of-function mutations. HD-AIP can be distinguished from heterozygous AIP as patients have <4% residual HMBS activity and constitutively elevated levels of urinary ALA and PBG. Clinically, HD-AIP patients are characterized by infantile onset of severe and chronic neurological impairment, including early-onset ataxia, psychomotor retardation, and nystagmus. Affected individuals fails to thrive and typically die in early childhood. Cerebrospinal fluid samples taken from a 2.5-year-old HD-AIP child with severe neurological impairment was found to have normal ALA

levels but over 250-fold normal PBG levels, suggesting that PBG is potentially neurotoxic. There are currently no reports of acute attacks in HD-AIP patients,[49] and therapies like hemin and RNAi that diminish hepatic ALAS1 levels are likely to fail as treatments for this disease. Furthermore, liver-targeted gene therapy and transplantation are unlikely to be beneficial as they do not address the elevated porphyrin precursor levels in the central nervous system.[49]

Hereditary Coproporphyria (HCP)

Perturbation of the enzyme coproporphyrinogen oxygenase (CPOX) generates an acute form of hepatic porphyria known as HCP (OMIM #121300) (Figure 2A).[7] Of the three autosomal dominant acute porphyrias, HCP is the most uncommon. [40] Although pathogenic enzyme variants occur equally in males and females, acute attacks appear more frequently in women, predominantly between the ages of 16 and 45 which are the years of active ovulation.[40] The hallmark biochemical feature of HCP is elevated porphyrins, most notably coproporphyrinogen II and uroporphyrinogen, in the urine and feces of affected individuals.[40,50]

Prevalence: The incidence of HCP is 0.2/10,000,000 per year.[51] The penetrance of *CPOX* pathogenic variants is unknown, as acute attacks are rare in comparison to AIP, suggesting that clinical disease only manifests in a small number of heterozygotes.[40] A study investigating a family with HCP found that of 14 members diagnosed with disease only 1 expressed clinical manifestations.[40,52] A recent study investigating seven cases of HCP from a single family with a novel mutation found evidence contrasting current literature including a notably high disease penetrance, high rate of severe, recurrent attacks, and a high incidence of venous-thromboembolism, a phenomenon not known to be associated with acute porphyria.[53]

Clinical Manifestation: HCP is associated with neurovisceral symptoms i.e., acute attacks, severe abdominal pain, motor neuropathy and more rarely psychiatric symptoms, similar to AIP and VP.[50] It is classified as both an acute (hepatic) porphyria (with neurologic manifestations that occurs as discrete, severe episodes) and a chronic (cutaneous) porphyria with long-standing photosensitivity[40]

Acute Attacks: As with other hepatic porphyrias, acute attacks are nonspecific and are characterized by low-grade abdominal pain that gradually intensifies over several days, accompanied by nausea and vomiting. Deep and aching pain, not localized to joints or muscle groups but predominantly to the back or extremities, has been identified in a minority of affected individuals. [40,50]

Neurological Manifestations: As with VP, undiagnosed, untreated, or improperly treated acute attacks may progress to motor neuropathy, which appears between several days to a few weeks after the onset of symptoms. Neuropathy usually starts as proximal weakness in the arms and legs, progressing to distal weakness in the hands and feet. Certain individuals display motor neuropathy that affects the nerves associated with the respiratory muscles and diaphragm leading to ventilator support. Acute attacks usually start

with seizures that are generally the cause of hospitalization. Acute attacks also commonly involve the autonomic nervous system manifesting as tachycardia and constipation.[40,50]

Kidney and Liver Disease: Chronic liver and kidney involvement frequently accompany AHP. Patients with repeat acute attacks have a higher risk of developing HCC. However, the risk of hepatic and renal complications may be less in HCP than in AIP, possibly because ALA and PBG are minimally elevated in individuals with disease heterozygosity.[40]

Chronic cutaneous manifestations: Cutaneous complications may also occur in persons with HCP and chronic liver disease. Coproporphyrinogen is removed from the plasma via the liver and bile; however, in chronic liver damage bile transport processes or formation may be impaired allowing coproporphyrin to accumulate in the plasma, resulting in photosensitivity.[40] Specifically, uroporphyrinogen and coproporphyrinogen result in bullae and fragility in light-exposed skin.[40] It has been reported that 20% of patients experiencing acute attacks also experience photosensitivity.[40] The hands and face, which are often exposed to the sun, are most affected and are prone to scarring, erosion, and disfigurement. Hypertrichosis, hyper-, and hypopigmentation may also occur in sun-exposed skin. High levels of circulating porphyrins promote brown and reddish discoloration of teeth due to the deposition of porphyrins in the enamel layer of the developing tooth. Anemia is a common symptom due to hemolysis and can fluctuate from mild to severe. Other symptoms associated with acute attacks include mental confusion, cardiovascular symptoms, and respiratory symptoms. The attacks are characterized by low grade pain that gradually intensifies over a period of days. Nausea and vomiting typically accompany the pain, which occurs predominantly in the back or extremities. [40] Respiratory inadequacies may affect some patients due to loss of innervation of the diaphragm and muscles involved in respiration. [40]

Treatment/Therapies: Heme arginate is a well-established treatment for HCP. Monthly heme arginate infusions significantly reduce the frequency of attacks, alleviate cutaneous blistering and erosions, and normalize urinary excretion of PBG. In fact, treatment withdrawal triggered a rapid return of clinical symptoms.[50,54] Furthermore, heme arginate has been demonstrated as an effective maintenance therapy for patients with HCP, and can significantly improve quality of life.[40,50]

Givosiran is indicated for use in AHP and may reduce or prevent the development of neurologic symptoms in persons with HCP; however, this remains to be determined with long-term studies.[40] In a phase 3 trial of Givosiran, only one individual with HCP was included in the study, although reports indicate clinical response.[55] Other strategies include glucose administration to reverse fasting state, dextrose rehydration for hyponatremia, and anti-seizure medications.[40]

Management Strategies: Omission of precipitating factors or circumstances commonly associated with acute attacks are highly recommended.[40] Further prophylactic measures include avoiding sunlight, wearing protective clothing and use of topical sunscreens, and annual surveillance of liver and kidney functions.[40]

Variegate Porphyria (VP)

Also known as South African genetic porphyria, VP (OMIM#176200) is an autosomal dominant hepatic disorder of porphyrin metabolism with a high penetrance clinically characterized by attacks of neurologic dysfunctions, photo-cutaneous lesions, or both (Figure 2B).[25,56] VP is the result of decreased activity of protoporphyrinogen oxidase (PPOX), an enzyme responsible for the seventh step in the biosynthesis of protoporphyrin IX (PPIX).[57] The majority of individuals who inherit the gene for VP remain asymptomatic throughout life, especially when known precipitants are avoided.[58–60] Only a minority of people with the enzyme defect develop clinical manifestations. Symptoms vary dramatically between individuals but typically begin in adulthood; cases reported in infancy or early childhood are rare.[61]

Prevalence: Variegate porphyria is much higher in the South African population than anywhere else probably due to a founder effect; three individuals per 1,000 are heterozygous for the PPOX pathogenic variant.[62] Meanwhile, the prevalence in Europe is estimated at 3.2:1,000,000, half that of AIP.[51]

Clinical manifestations: Abdominal pain is reported in 100% of VP patients and is often accompanied by vomiting, constipation, hypertension, and tachycardia, which are all frequent features of the early phase of the acute attack.[58] Other common manifestations are back, chest, and extremities pain; anxiety, seizures, and motor neuropathy that may progress to quadriparesis and respiratory paralysis. Acute neurovisceral symptoms may be severe and potentially fatal.[63]

VP is both an acute and cutaneous porphyria and presents with chronic blistering skin lesions (cutaneous porphyria) and severe intermittent neurovisceral symptoms (acute porphyria). However, most common manifestations begin with adult-onset cutaneous blistering lesions on areas exposed to the sun, particularly the hands and face.[63] As in HCP, acute photosensitivity that results in the formation of massive bullae occurs when VP is accompanied by liver disease or biliary obstruction due to increased concentration of circulating porphyrins that are excreted from feces and urine.[58]

Earlier reports indicate that only 14% of patients display simultaneous skin symptoms and acute attacks, while 27% of these patients have acute attacks and about 70% or less have skin symptoms.[64] The acute episodes associated with VP are similar to AIP and can also display photo-cutaneous manifestations resembling those observed in PCT.[65]

Treatment: There is currently no recognized treatment that is effective for VP. Cutaneous manifestations are best managed by avoiding exposure to sunlight and wearing protective clothing.[63] Gonadotropin-releasing hormone analogs can be used to avert recurrent premenstrual attacks in women.[66,67] Progestins, alcohol, anticonvulsants, barbiturates, griseofulvin and sulfonamide antibiotics should be avoided. [63] Narcotic analgesics can be used for pain and other applicable medications for nausea, vomiting, agitation and hallucinations. The phase 3 trial of Givosiran included two patients with VP that responded to treatment with reduced levels of ALA and PBG.[55]

Preventative strategies: VP is an important risk factor for development of HCC.[63,68] Liver surveillance twice a year beginning after age 50 is recommended in patients who have persistent elevation in porphyrin accumulation as this may aid in early detection of HCC.

Hepatic Porphyrias with Cutaneous Manifestations

Porphyria Cutanea Tarda; PCT

PCT (OMIM #176100) is the most common type of human porphyria. The disease is the result of an intrahepatic deficiency of the fifth and final cytoplasmic enzyme of the heme biosynthesis pathway, uroporphyrinogen decarboxylase (UROD) (Figure 3A). The National Organization for Rare Disorders reports disease development after age 30. No ethnic or gender preferences have been associated with PCT, but due to greater susceptibility factors PCT appears to exhibit a preference for men.[69,70]

In the mid-nineties, de Verneuil et al., subdivided porphyria cutanea into two categories: the sporadic type (or Type I (OMIM 176090)), which occurs in mostly male adults with no detectable family cases;[71,72] and the familial type (or Type II (OMIM #176100)), which occurs in women and children, with several cases of PCT type II detected in the same family.[71] Upwards of 80% of PCT cases are sporadic. The National Organization for Rare Disorders estimates that the prevalence of both PCT variants is approximately 1:10,000–25,000 individuals in the general population.

Susceptibility factors: Mild to moderate iron overload alongside amplified serum ferritin levels and hepatic siderosis reportedly occurs in 90% of disease cases.[69,73,74] Iron overload can also be caused by mutations in the hemochromatosis gene (*HFE*).[74] Hereditary hemochromatosis is a disease that affects iron metabolism triggering iron accumulation in organs such as liver. Patients with PCT express more mutations in the *HFE* gene than the general population.[69,74] Data from several large studies indicate that the *HFE* mutation is present in almost 73% of cases.[69] Another study found 64.9% of PCT patients carried at least one HFE mutated allele.[75] Other factors that can increase iron levels include HCV infection, alcohol, and increased absorption of iron.[69]

Heavy alcohol use (>40g/day) is recorded in almost 90% of PCT cases,[69] and is more prevalent in males.[75] Alcohol consumption exacerbates PCT by inhibiting the activity of ALAD, UROD, CPOX and ferrochelatase, while enhancing the activity of ALAS and HMBS thereby promoting accumulation of porphyrin. While the correlation between the effects of alcohol on ALAS and clinical expression of PCT is yet to be elucidated, chronic alcoholics are known to suffer from suppression of erythropoiesis and increased dietary iron absorption.[76,77] Alcohol is also thought to contribute to increased iron absorption, alcohol induced oxidative stress, and downregulation of hepcidin.[69]

Smoking can induce earlier onset of PCT Type I and is therefore a risk factor.[78] Mechanisms of smoking mediating the development of PCT remain unclear, but increased oxidative stress and induction of hepatic cytochrome P450 enzymes are thought to contribute to disease pathology.[69]

Infections with Hepatitis C Virus (HCV), and comorbid HCV and Human Immunodeficiency Virus (HIV) infections are associated with development of PCT.[79] HCV is the most common PCT-related viral infection, and although associated with both subtypes, it is observed more frequently in PCT Type I and Type II. [45,76,80] A large study of 152 patients with PCT indicated that HCV infection is the most prevalent risk factor, especially in men.[75] Although mechanisms are unclear, there is some indication that HCV-induced reactive oxygen species can trigger disease manifestations by fostering reduced hepcidin levels and promoting hepatic iron accumulation.[81] Chronic HCV infection also lessens glutathione in hepatocytes, decreasing their ability to reduce oxidized porphyrins and causing their accumulation.[76] It is noteworthy that HCV-infected persons develop PCT at an earlier age than those without the virus. *HFE* mutations also cause iron overload that further promote hepatocellular injury and fibrosis in patients with HCV.[76]

Estrogens have been identified as precipitating factors for women with Type 2 PCT.[75,79] Reports indicate use of oral contraceptives, hormone replacement therapy, and use of tamoxifen for breast cancer to be associated with PCT.[69,82,83] Diethylstilbestrol, a synthetic nonsteroidal estrogen, also induces hepatic ALAS, though there is currently no clear understanding of the accompanying increased porphyrin excretion in PCT patients.[76] Estrogen as a treatment for prostate cancer has also been identified as a risk factor in men.[84] Administration of estrogens via transdermal route is safe and recommended for at-risk women previously treated for PCT.[83]

Hepatic siderosis,[6,83] systemic lupus erythematosus,[85] end-stage renal disease on hemodialysis,[86] diabetes mellitus,[87] and hematologic malignancies[88] are all associated with the development of PCT,[69,76] as is exposure to toxins such as polychlorinated biphenyls, hexachlorobenzene, and other polyhalogenated hydrocarbons that significantly induce cytochrome P450 enzymes.[89]

Current Treatment/Therapies: Presently, there are no effective treatments that restore UROD enzyme levels in individuals with familial PCT.[89] Reduction of hepatic iron content is the general recommendation, and patients with PCT comorbid for HCV have favorable outcomes after phlebotomy due to iron reduction.[76,89–91] Iron chelation therapy i.e., deferasirox or deferoxamine may be considered when phlebotomy is contraindicated, and low iron diet may be beneficial if the latter fails.[89] Furthermore, use of antiviral therapy may benefit patients with chronic HCV infections and reduce risk of progressing to HCC.[76] Preventative measures for affected persons include avoiding all susceptibility factors.

Hepatoerythropoietic Porphyria (HEP)

HEP (OMIM #176100) is the homozygous and autosomal recessive form of familial PCT (Figure 3B).[92] HEP is a severe form of cutaneous porphyria that occurs early in infancy and is clinically similar to congenital erythropoietic porphyria (EP). UROD enzyme activity in HEP patients has been recorded as between 5% to 10% of normal.[93] The exact incidence or prevalence of HEP in the general population is unknown, as fewer than 100 individuals have been reported in the literature. However, the frequency of HEP can be inferred based on that of PCT which occurs as 1 in 20,000 individuals.[94]

Clinical Diagnosis: Repeated sun exposure promotes the development of recurrent blisters and erosions, with secondary infections that may result in severe scarring, sclerodermatous change, and deformities of the hand.[95] Sclerodactyly, osteolysis and shortening of the phalanges, and progressive joint deformities can occur as well.[95,96] Non-cutaneous manifestations are unusual; however anemia and hepatosplenomegaly may be present.[93,95,96] No increased risk for HCC has been documented in HEP.[94] Because the disease occurs so rarely, ascertaining additional risk factors has proven difficult. However, avoidance of identified susceptibility factors (reviewed in PCT) has been suggested.[94]

In contrast to VP, a disease characterized by neurological abnormalities, these are not typical in HEP.[95] Nevertheless, developmental delay and seizures have been reported.[92]

Prophylaxis and Management Strategies: No clinical practice guidelines have been published for HEP.[94] As with most porphyrias, treatment is largely symptomatic.[96] Reports indicate that although helpful in PCT, phlebotomy is generally ineffective.[95,96] Current treatment recommendations resemble those for familial PCT.[94]

Challenges to diagnosis, treatment, and management of porphyria

Because porphyrias are rare diseases, they are often difficult to diagnose and treat. Porphyria is not typically part of a differential diagnosis, and for patients presenting to emergency departments with pain or acute attacks, the priority is placed on stabilizing the patient rather than identifying the underlying cause.[97,98] Laboratory screening tests used to confirm a diagnosis may also be unreliable.[99] Complicating matters, concentrations of urinary PBG and ALA are often normal between acute attacks, and the turnaround time for results is 1–2 weeks, since testing is only performed at large reference centers .[100] Because the disease can mimic other conditions and symptoms are variable, misdiagnosis is also common.[98] One study found diagnosis of porphyria was delayed by a mean of 15 years from onset of symptoms,[101] yet timely diagnosis is essential since untreated attacks can progress and lead to permanent neurological damage or life-threatening complications.[97] Undiagnosed patients may also inadvertently continue to take drugs that exacerbate symptoms or trigger acute attacks.[98]

Treatment and management of symptoms also pose significant challenges to patients and the medical community. Treatments generally focus on rapid management of symptoms and complications, rather than long-term prevention. Management of acute and chronic pain caused by AHP involves use of analgesics and opioids, which carries risks of addiction or somnolence.[98] Avoiding precipitating factors and adherence to lifestyle modifications requires patient education and compliance, which must be monitored by health care professionals.[102] The current standard of care for managing acute attacks is intravenous hemin, which needs to be administered immediately upon admission.[103] Side effects of hemin include thrombophlebitis, headache, and hepatic iron accumulation.[98] Off-label prophylactic use of hemin has been effective in some patients, but requires indwelling central venous catheters and can lead to thrombosis, iron overload, and even sepsis.[103] Givosiran, an siRNA-based therapeutic that targets ALAS1, rapidly reduces the levels of ALA and PBG levels and also lowers the rate of acute attacks.[55] Side effects were

rare but included increased transaminase levels, increased blood homocysteine, pancreatitis, and worsening of chronic renal failure.[104] Additionally, both hemin and Givosiran are expensive, with the average annual cost of hemin estimated to be approximately $106,000, while Givosiran is $575,000 ($442,000 after discounts).[105] Given the limitations of current therapeutics, emerging therapies are urgently needed.

Treatments on the horizon

As discussed above, management of AHPs is centered around palliative care during acute attacks and prophylaxis in daily routine. Hemin and Givosiran, the current treatments, are not curative and not without side effects.[37,46,106–108] However, recent innovation and technological development have enabled major advancements in the treatment of AHP, particularly AIP (Table 1, Figure 4).[44,109]

Gene Therapy

Gene therapy represents a promising therapeutic option for patients with porphyria. Studies in mice have shown that retroviral adeno-associated liver-directed gene therapy provides complete protection against motor neuropathy caused by AIP and could equally offer patients immense benefits.[110] Gene therapy mediated improvement of neuropathy is in contrast to hemin therapy which fails to cross the blood-brain barrier and is only effective in the early stages of neurological manifestations. AIP in particular presents an attractive opportunity for liver-targeted gene therapy because only a few functional hepatocytes expressing HMBS are needed to metabolize ALA/PBG in order to avert acute attacks.[111,112] Additionally, restored hepatic heme content should initiate negative feedback mechanism that maintains both heme and ALAS1 activity.[110] Feasibility, safety, and success pose no concern as proposed gene therapies like first-generation adenoviral vectors and hydrodynamic delivery of therapeutic plasmids to hepatocytes have been tested in patients with AIP.

Adeno-associated viruses (AAV)—AAV vectors allow for long-term expression of the intended protein after a single administration unlike siRNA therapies that require repeated administrations. AAV-mediated gene therapy for AIP utilizing recombinant AAV8-based serotype vector encoding murine HMBS (rAAV2/8-*HMBS*) under the liver-specific transcriptional control of a hepatocyte enhancer and promoter has been tested in mice with AIP. rAAV2/8-HMBS provides rapid and prolonged HMBS activity that effectively prevented phenobarbital induction of ALA and PBG for more than 36 weeks. Additionally, neuromotor function was improved in presymptomatic mice. Although delivered to nonhepatic tissues, expression was only detected in the liver. Use of tissue-specific promoters guarantee elevated levels of transgene expression for extended periods of time.[110] Based on these findings, the rAAV2/5-*HMBS* prototype vector (Patents: P6021400EP and P6021400US) received Orphan Drug Designation for phase I/II studies. A first-in-human Phase I clinical trial (NTC02082860) tested and confirmed the safety and tolerability of AAV2/5-EalpAAT-PBGD gene therapy in patients.[113] Although serious adverse events were absent, the necessary reduction in toxic porphyrin precursors ALA and PBG was not observed, perhaps because higher doses and more efficient vectors are required to obtain

therapeutic expression of the transgene.[113] Another possibility is that the human immune system effectively targeted the viral capsid antigens.[44,114]

There are ongoing efforts to improve the efficacy of rAAV-gene therapy. A new bioengineered *HMBS* comprising two amino acid substitutions was designed to lower the effective therapeutic dose. The inclusion of amino acid substitutions HMBS-1291M/N340S into the AAV vector improves protection against biochemical attacks induced in mice with AIP at doses three times lower than the dose required to achieve full protection with the control vector.[115] Vectors may also be improved by enhancing the expression of the therapeutic transgene during increased demand for hepatic heme synthesis and subsequent acute attacks. Data from a study testing AAV containing an inducible promoter sequence responsive to porphyrinogenic factors found a strong induction of transgene expression that mitigated the impact of porphyrin precursors.[116]

Vector immunogenicity, persistent high-titer neutralizing antibodies, and induction of capsid-specific $CD8^+$ T cells responses that facilitate clearance of AAV transduced cells are major impediments in re-administration of AAV vectors. Mitigating the immunogenicity to AAV is challenging due to its size, repetitive display of antigenic epitopes on the capsid, and high degree of antibody suppression required to prevent vector neutralization. A recent study found that co-administration of Rapamycin-loaded poly(lactic acid) (PLA) nanoparticles (SVP(Rapa)) with AAV vectors prevents the formation of neutralizing antibodies and enables successful vector re-administration in mice and nonhuman primates in an antigen selective manner, in addition to allowing for repeat dosing of AAV vectors to increase expression of a transgene in the liver.[114] Human trials have indicated that induction of $CD8^+$ T cell responses directed to AAV capsid correlates with liver inflammation and can limit the duration of transgene expression. (SVP(Rapa)) modulates both humoral and cell-mediated responses to the AAV capsid and inhibits anti-capsid immune responses. The safety and efficacy of (SVP(Rapa)) was demonstrated in a phase 1 clinical trial (NCT02648269).

Chaperone Therapies—Pharmacological chaperones are unique as they can specifically target, bind, and stabilize a protein. This property is especially beneficial for treatment of protein misfolding diseases such as lysosomal storage disorder. These small molecular weight compounds protect their target protein from early degradation while increasing the half-life and enhancing cellular activity. Pharmacological therapy like this presents a conundrum as many drugs have a porphyrinogenic property and can exacerbate or elicit acute attacks. Very recently, the discovery and identification of prospective pharmacological chaperones to treat AIP was facilitated by *in vitro* high-throughput screening and validation of candidate molecules that stabilized recombinant WT-*HMBS*. *HMBS*-deficient mice challenged with phenobarbital responded with increase in steady-state levels of HMBS protein, activity, and a substantial decrease of porphyrin precursors in the liver after treatment with small-molecule chaperones. This therapy may be more advantageous than other gene therapies because it eliminates risk of adverse immunological reactions and because it can be used as both a prophylactic and interventional therapy before and during acute attacks, respectively.[117]

Apolipoprotein AI (ApoAI) is a component of high-density lipoprotein (HDL), a lipoprotein that mediates transport of cholesterol from the periphery to the liver. ApoAI receptors are abundantly expressed by liver parenchymal cells. A fusion protein formed by linking ApoAI to the N-terminus of *HMBS (*rhApoAI-HMBS) was shown to have an extended half-life, penetrate hepatocytes, cross the blood-brain barrier via a saturable transport mechanism, and enhance enzymatic liver functions, thus raising and sustaining HMBS activity in mice while providing long-lasting protection against porphyric attacks. Interestingly, the therapeutic effect was observed regardless of administration route and in both the liver and brain, two organs most susceptible to overproduction and accumulation of toxic porphyrins. Additionally, rhApoAI-HMBS was preferentially taken up by zone 3 hepatocytes; it has been reported that genes involved in heme biosynthesis are preferentially expressed in zone 3. As with other enzyme replacement therapies, repeated administration of a fusion protein may induce neutralizing antibodies. However, none of the mice in the study developed antibodies even after receiving four weekly doses of murine fusion proteins. In a prior clinical trial where patients with AIP received intravenous rh*HMBS*, no substantial neutralizing antibodies nor adverse reactions against the recombinant proteins was observed.[118]

Lipid nanoparticles (LNPs) have emerged as potential vehicles for safe and effective delivery of therapeutics in a variety of diseases. Packaging HMBS into LNPs is perhaps a cheaper and less immunogenic strategy than rAAV-gene therapy, as this option allows for fast and efficient delivery to the liver as well as biodegradability. The nanoparticles are composed of ionizable cationic lipids and polyethylene glycol-conjugated lipids that allow timely escape from phagocytic cells. In hepatocytes, internalization is mediated by the low-density lipoprotein receptor. Escape from the endosomal compartment is induced by ionizable cationic lipids, allowing release of mRNA cargo into the cytoplasm.[44] Hepatic human HMBS mRNA formulated into LNPs (LNP-hHMBS) administered to AIP mice rapidly normalized urinary ALA and PBG accumulation, and the duration of effect was superior to hemin therapy. In addition to mitigation of biochemical abnormalities LNP-hHMBS also prevented acute attacks. The translatability of this approach was also demonstrated with repeated-dose administration in nonhuman primates, which demonstrated maintenance of HMBS activity with no increase in serum liver function tests nor production of destructive antibodies. In a rabbit model of porphyria where porphyrin precursors were induced using AIA and rifampicin, use of LNP-hHMBS provided protection against induction of porphyrin precursors and demonstrated tolerability. Indeed, this new treatment modality shows sustained efficacy and safety after both single and repeated administration across three different species including mouse, rabbit, and nonhuman primates, and represents a promising interventional strategy for AIP.[119]

Pharmacological inhibition using β-catenin DsiRNA formulated into a lipid nanoparticle was recently tested as a possible therapeutic strategy for porphyria in a murine model. The Wnt signaling pathway is important for hepatic homeostasis and contributes to unique hepatic attributes such as metabolic zonation and regeneration.[120] Inhibiting β-catenin reduced porphyrin accumulation after induction of porphyria due to inhibition of ALAS and ALAD which in turn decreases production of pathway intermediates such as PPIX. Loss of these toxic porphyrins also results in decreased protein aggregation, which reduces

subsequent downstream effects such as endoplasmic reticulum stress and autophagy. β-catenin DsiRNA LNPs thus represent a novel therapeutic opportunity to suppress the heme biosynthesis pathway.[121]

Concluding Remarks

In this review we have summarized the hepatic porphyrias, providing clinical symptoms, susceptibility factors, and current treatments for each. A common theme in all of the hepatic porphyrias is the significant unmet clinical need, which presents opportunities for more effective means of treatment. While current treatments focus on symptomatic, palliative, and preventive patient care, future therapeutics should focus on replacement, repair, or compensation of the nonfunctional and/or deficient enzyme through hepatic delivery of the gene or protein. In addition, comprehensive management of porphyria should also address systemic effects of porphyrin accumulation, such as mitochondrial dysfunction, neurological dysfunction, alterations in glucose, lipid metabolism, insulin resistance, hormonal fluctuations, and proteasomal and autophagic protein aggregation. Although much work has been done to characterize these processes, additional mechanistic studies are needed in order to develop targeted therapies and aid in drug discovery. The final article in this series will highlight the animal models used to study porphyria and how they can contribute to our understanding of disease pathogenesis[122].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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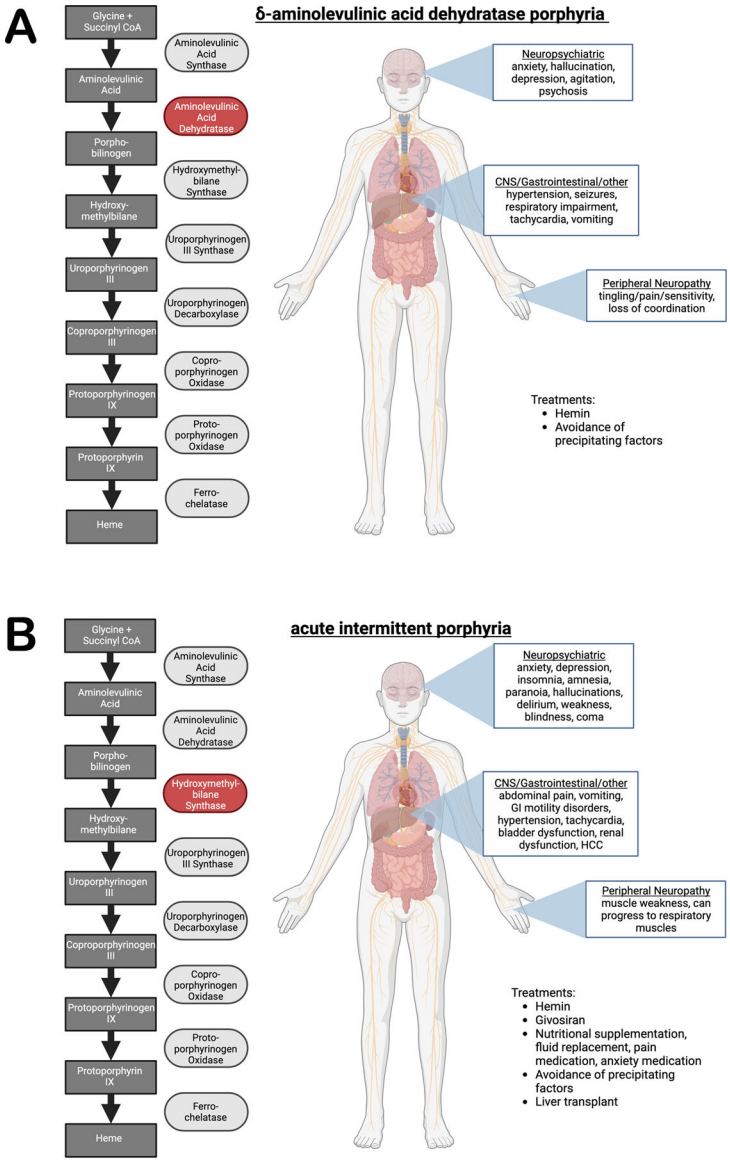

Figure 1.

A. δ-aminolevulinic acid dehydratase porphyria (ADP). Patients with ADP have a deficiency in the enzyme ALAD. Symptoms attributed to the accumulation of ALA include acute attacks and neurological and gastrointestinal manifestations of disease. Hemin is an effective treatment in some cases, and avoidance of precipitating factors such as alcohol are strongly recommended. **B. Acute intermittent porphyria.** The most prevalent form of acute porphyria, AIP is caused by mutations in *HMBS* that result in overproduction of ALA and PBG. Life-threatening crises are commonly caused by precipitating factors and include both gastrointestinal and neurological symptoms. Patients prone to recurrent attacks are at increased risk for HCC and renal dysfunction. Both hemin and Givosiran are effective in treating AIP patients with acute attacks, as are prophylactic measures such as nutrient supplementation.

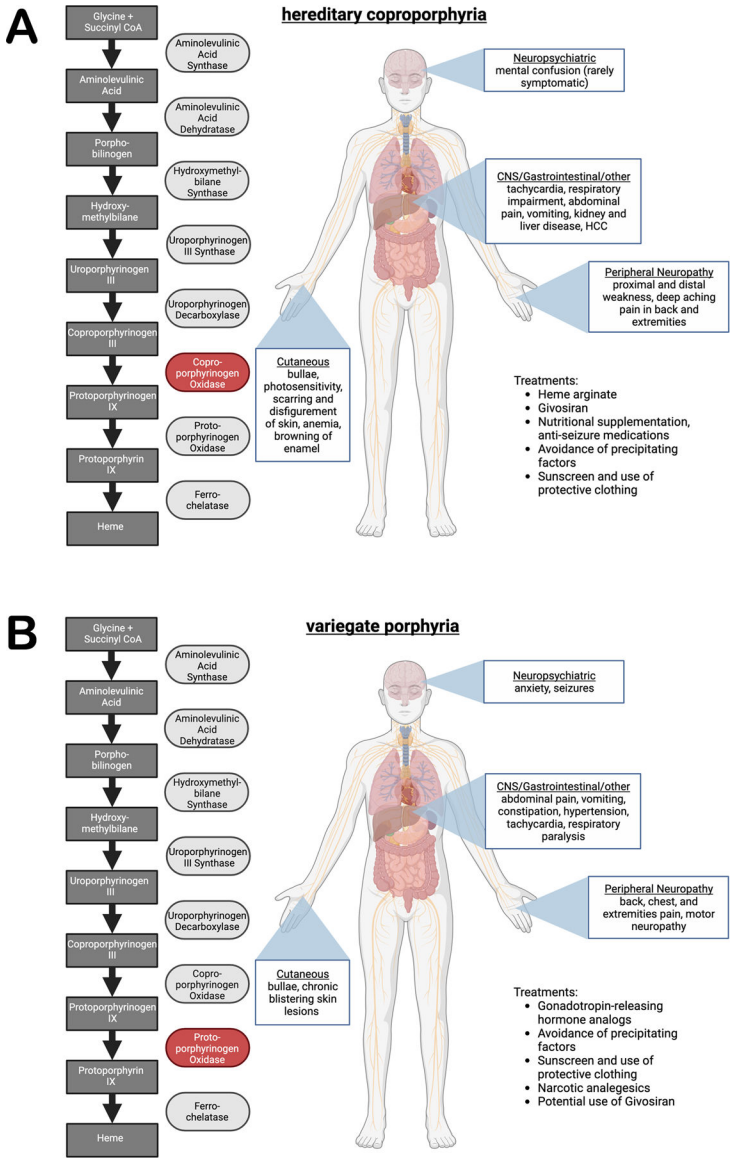

Figure 2.

A. Hereditary coprophorphyria. In HCP, coporporphyrinogen and uroporphyrinogen accumulate in patients, causing acute attacks, abdominal pain, and motor neuropathy. Cutaenous manifestations including photosensitivity also occur. Heme arginate is an effective treatment for HCP, and Givosiran may also prevent the development of symptoms. **B. Variegate porphyria.** VP is caused by decreased activity of PPOX, which causes accumulation of protoporphyrinogen and coproporphyrinogen. VP is both an acute/neurovisceral and cutaneous porphyrin, with acute episodes resembling AIP and cutaneous manifestations resembling PCT. There is no recognized treatment effective for VP, and avoidance of sunlight and precipitating factors are the current forms of management.

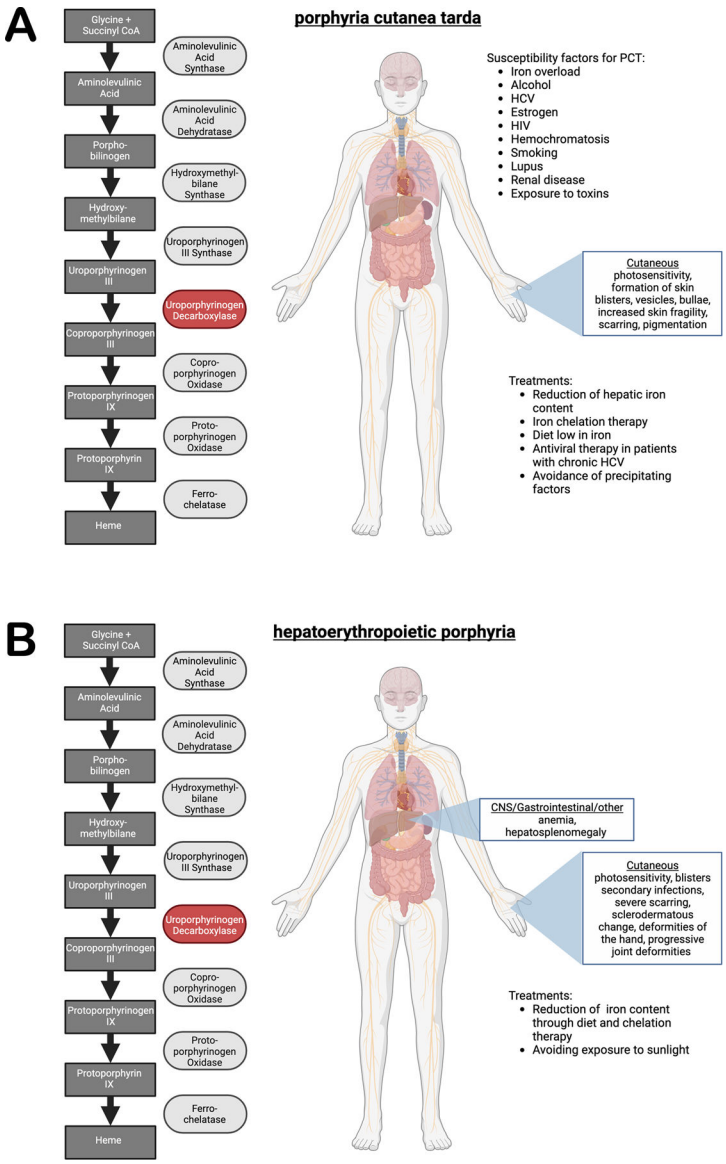

Figure 3.

A. Porphyria cutanea tarda. PCT is caused by deficiency in UROD, and is subdivided into two categories: Type 1, or sporadic, and Type 2, or familial. PCT presents mainly with skin manifestations which are triggered by susceptibility factors such as alcohol, HCV, estrogen, hemochromatosis, smoking, and others. It is the most common type of porphyria, and is managed by reduction of hepatic iron content and avoidance of susceptibility factors. **B. Hepatoerythropoietic porphyria.** HEP is the autosomal recessive form of PCT, caused by a severe form of UROD deficiency. Symptoms include extensive scarring and deformities, along with occasional anemia and hepatosplenomegaly. Treatment is symptomatic, with a focus on reducing exposure to the sun.

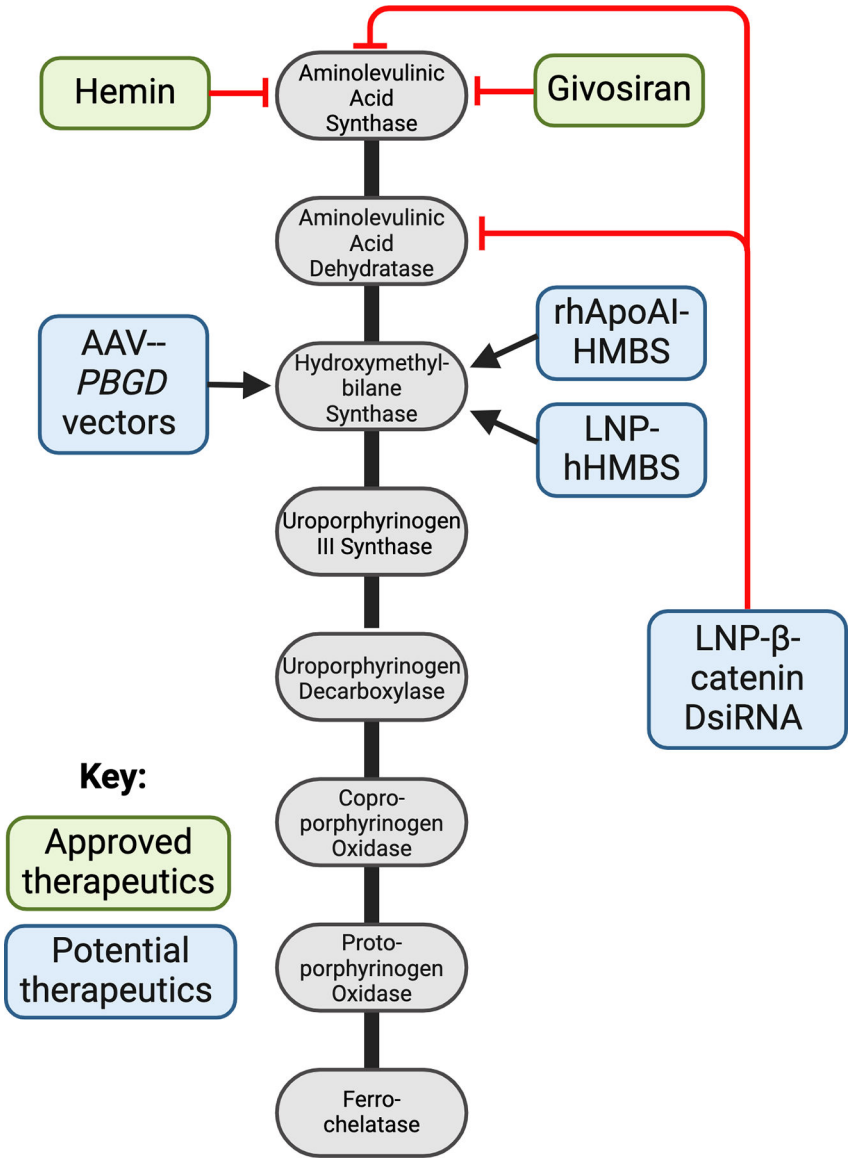

Figure 4: Overview of current and potential treatments for hepatic porphyrias and their targets.

Current standard of care treatments are shown in green boxes and include hemin and Givosiran, both of which inhibit *ALAS1*. Potential and future therapeutics are shown in blue boxes and include AAV-based therapies, ApoA1-conjugated therapies, and lipid nanoparticle-conjugated therapies, all of which enhance HMBS/PBGD expression. LNP-conjugated β-catenin DsiRNA decreases both ALAS and ALAD expression.

Table 1:

Therapeutics in Development for Treatment of Hepatic Porphyrias

Therapy	Mechanism of action	Tested in	Trial outcomes	Limitations of study/ drug
AAV2/5- EalpAAT-*PBGD* [113]	Expresses HMBS/PBGD	Phase I clinical trial	Confirmed safety and tolerability; no reduction in ALA and PBG; no efficacy in preventing frequent attacks	Possible targeting of virus capsid by immune system
AAV2/8-PBGD-*I291M/N340S*[115]	Expresses hyperfunctional HMBS/PBGD; lowers effective therapeutic dose	Preclinical (mouse AIP model)	Full protection against phenobarbital-induced attack	Not yet tested in humans
AAV2/8–2 × ADRES-EalpAAT-*PBGD*[116]	Induces HMBS/PBGD expression in the presence of porphyrinogenic factors	Preclinical (mouse AIP model)	Protects against phenobarbital-induced attack; reduces effective dose 10-fold	Not yet tested in humans
SVP(Rapa) + AAV[114]	Prevents induction of anti-capsid responses; allows for vector re-administration	Phase I clinical trial	Confirmed safety and tolerability	Not yet tested in porphyria patients
rhApoAI-HMBS[118]	Increase HMBS/PBGD expression in hepatocytes	Preclinical (mouse AIP model)	Extended half-life, penetrate hepatocytes, cross the blood-brain barrier, enhance enzymatic liver functions. Works intravenously or subcutaneously	Not yet tested in porphyria patients
rhHMBS [123]	HMBS/PBGD expression	Phase I clinical trial	No substantial neutralizing antibodies nor adverse reactions against recombinant proteins	Only tested in healthy and asymptomatic AIP patients; short-lived effects
LNP-hHMBS[119]	Delivery of HMBS/PBGD to hepatocytes	Preclinical (mouse, rabbit) AIP models); healthy non-human primates	Confirmed tolerability; protects against induction of porphyrin precursors and recurrent attacks; repeated administration does not cause adverse effects	Not yet tested in porphyria patients
β-catenin DsiRNA conjugated to LNP[121]	Inhibits expression of multiple heme enzymes (ALAS, ALAD)	Preclinical (DDC mouse model of hepatic porphyria)	Reduces porphyrin-induced injury; increases autophagy of unfolded proteins	Not yet tested in porphyria patients