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REVIEW

Neurological and neuropsychiatric manifestations of porphyria

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ABSTRACT

Porphyrias are inherited disorders of the heme biosynthetic pathway, usually characterized by dermatological changes due to the accumulation of byproducts in the pathway. Select porphyrias also affect the nervous system, namely hereditary coproporphyria, acute intermittent porphyria and variegate porphyria. Complications include paralysis, hyponatremia which can risk central pontine myelinolysis, seizures and coma. Neurological complications usually result from severe episodes of acute attacks. Acute attacks may also elicit neuropsychiatric symptoms such as confusion, hallucinations, anxiety and psychosis. However, these manifestations are generally self-limiting. Due to the generally low incidence of porphyria and full knowledge the associated neurological and psychiatric manifestations, we review the relevant porphyrias along with their clinical manifestations, evaluation, and management to raise its awareness in the clinical picture and to prevent misdiagnosis. Porphyria should be considered within the differential diagnosis for unexplained neurological symptoms.

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Introduction

Porphyria refers to a group of disorders that results from a defect in the heme biosynthetic pathway. Most heme in mammals is produced in erythroid cells. The central and peripheral nervous systems may be affected as well as various other organ systems. The subtypes of porphyria can be categorized as hereditary coproporphyria (HC), acute intermittent porphyria (AIP), variegate porphyria (VP) and porphyria cutanea tarda. Not all types cause neurologic problems. HC, AIP and VP are hepatic pathologies with neurologic manifestations that are inherited in an autosomal dominant pattern [1]. Porphyria cutanea tarda, which is the most common among patients, and erythropoietic protoporphyria are not neurologic, but have cutaneous manifestations [2]. A physician should suspect porphyria if the patient has motor-predominant peripheral neuropathy, gastrointestinal distress, dermatologic, and neuropsychiatricrelated complications. According to Anderson et al., porphyria occurs in about 0.5 to 10 per 100,000 people [2].

Methods

A comprehensive MEDLINE® search of the literature, with an emphasis on the past ten years, was conducted combining the search term "porphyria" with the following search criteria: "neurology," "psychiatry," "neuropathy," and "encephalopathy." No specific exclusion criteria were set. Publication quality was assessed using the relative citation ratio derived from iCite bibliometrics.

Historical perspectives

Congenital erythropoietic porphyria (CEP) is the most rare type of porphyria which was first described by Schultz in 1874 in a 33-year-old man who excreted red urine containing hematoporphyrin [3–5]. In 1913, the photosensitizing properties of porphyrin were tested by Meyer-Betz by self-injecting hematoporphyrin into his vein. He observed photosensitizing lesions uncovered areas of his skin [6]. A study in 1895 by Stokvis revealed that rabbits died when they were injected with dark red urine that contained hematoporphyrin [6, 7].

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Heme biosynthesis pathway

8 Glycine and 8 succinyl-Coa is used by δ-aminolevulinic acid synthase (ALAS) to make ALA within the mitochondria. ALAS-1 expression is activated by PGC-1α within hepatocytes. PGC-1α normally plays a role in liver energy homeostasis. However, PGC-1α is also an important factor that controls that expression of ALAS-1 [8]. PGC-1α may also be activated by the liver in vivo. ALAS enzymatic action is limiting step in heme production due to its feedback inhibition [1]. The ALA is shuttled into the cytoplasm, and becomes porphobilinogen (PBG) with the use of δ- aminolevulinate dehydratase (ALAD). PBG becomes hydroxymethylbilane (HMB) catalyzed by porphobilinogen deaminase (PBG-D). Then, HMB becomes (uroporphyrinogen III) Uro-P with Uroporphrinogen III cosynthase, and coproporphyrinogen (Copro-P) is made with Uroporphyrinogen decarboxylase. Copro-P is then shuttled into the mitcohondria to become proptoporphyrinogen IX by combining with coproporphyrinogen oxidase (CPO). Proto-P is oxidized by protoporphyrinogen oxidase to become protoporphyrin. Protoporphyrin becomes heme by addition of Fe^{2+} and ferrochelatase [1, 8]. Heme may be produced within the liver or bone marrow. The difference lies in the regulation, as heme regulates the production of heme by inhibiting ALAS which causes the synthesis of heme to slow. The bone marrow, however, contains erythropoietin which controls the formation of heme. Any disorder within these steps except for ALA synthase can cause toxic precursors to accumulate within the body (Figure 1).

Etiology and classification

Hereditary coproporphyria

HC results when coproporphyrinogen III oxidase does not function properly. Coproporphyrinogen III oxidase is a mitochondrial enzyme that is responsible for catalyzing the sixth step of heme biosynthesis. This defect in enzyme is inherited as an autosomal dominant disorder [9]. When patients with HC are tested, it is revealed threat their δ-aminolaevulinic acid synthase is increased and coproporhyringogen oxidase is depressed. This supports the inference that an enzyme is malfunctional within the heme biosynthetic pathway, causing this disease to manifest [10]. This defect can cause gastrointestinal and neuropsychiatric symptoms as well as skin lesions. Skin photosensitivity are also sometimes present. A study by Brodie et al. determined that around 23% of people had neurologic manifestations, 23% had psychiatric disorders, 29% were sensitive to light, and 80% had pain within the abdominal regions [11].

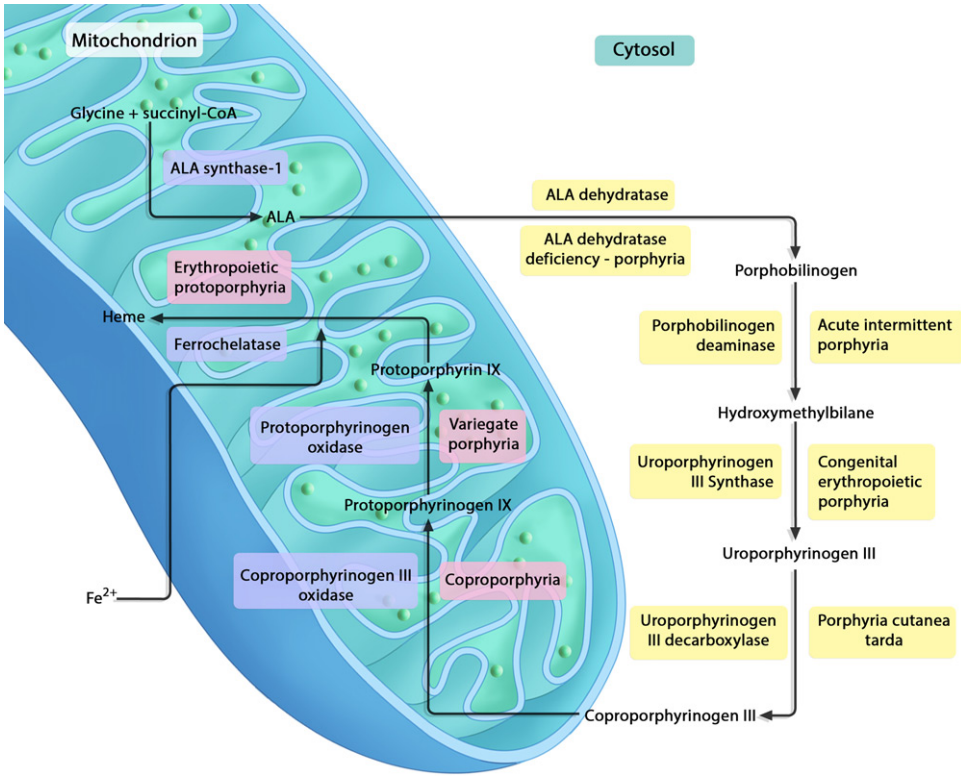

Figure 1. Heme biosynthesis pathway. The enzymes involved at each step are listed above the arrows, and the type of porphyria that is associated with a deficiency of each enzyme is shown within the arrowed boxes above each enzyme.

Acute intermittent porphyria

AIP is inherited at birth, and is difficult to diagnose in prepubescent children. A mutation in the hydroxymethylbilane synthase gene will result in loss-of-function of prophobilinogen deaminase to function. It is not guaranteed one will develop porphyria if he or she possesses this mutation, as only 10% of people who possess the mutation show symptoms of porphyria [1]. Sweden has higher occurrences with 1 in 10,000 people possessing this disease [12]. It has been observed that 89% of people with AIP have mutations in the W198X, R173W, and R167W genes, with more clinical manifestations occurring in women [1, 13]. Heterozygous missense variants within the *HMBS* gene may also be attributed to causing encephalopathy in AIP [14]. A single base-pair insertion (887insA) in exon 14 or a missense mutation (Arg26His) in exon 2 within the porphobilinogen deaminase (PBG-D) gene can also cause acute intermittent porphyria [15, 16].

It is also interesting to note that most patients with AIP were taking medication to treat hypertension [1]. Certain medications can induce acute porphyria. Sulfamethoxazole is in the high-risk category, while oxybutynin and metronidazole are within the high potential risk category. In a certain case study by Shen et al., a woman with Arnold Chiari malformation type II disease contracted acute porphyria after taking a combination of oxybutynin, sulfamethoxazole/trimethoprim, and metronidazole [17].

Porphyria may also manifest concomitantly with anorexia nervosa. In a case study by Martins et al., a correlation between anorexia nervosa and AIP was found. Patients who had a carbohydrate restriction and significant weight loss had recurrent porphyric attacks with acute symmetrical flaccid lower limb weakness that eventually spread to paresthesia in all four limbs [18].

Variegate porphyria

A defect in protoporphrinogen oxidase will cause VP. It occurs more commonly among the white South African population [1]. VP occurs more frequently in older patients, with the incidence between men and women being almost equal. Drug use also demonstrated to correlate with VP. A study showed that patients harboring mutation on the *I12T* gene in the highly conserved FAD-binding domain of the *PPOX* gene had increased incidence of VP [19]. It is also possible that a c.40G > C mutation (p.G14R) in the *PPOX* gene can be responsible for VP with cholelithiasis [20].

Table 1. Neurological manifestations of porphyria.

- Motor paresis [22]
- Impairment of bulbar function [22, 23]
- Impairment of respiratory function [22]
- Motor neuropathy [2, 24]
- Consciousness disturbance [22]
- Seizure [22, 25–27]
- Behavior change [22]
- Paralysis [28]
- Sensitive neuropathy [29]
- Autonomic visceral neuropathy [24, 29]
- Schizoaffective disorder [29]
- Depression [29]
- Psychosis [29]
- Peripheral neuropathy [25, 26, 30, 31]
- Impairment of muscular function [30]
- Tetraplegia [26, 31]
- Quadriplegia [27]
- Coma [27]
- Visual impairment [24]
- Vasospasm [32–34]
- Paresthesia [35]
- Cortical laminar necrosis [33]
- Central pontine and extrapontine myelinolysis [33]
- Stroke [34]
- Cortical blindness [36]
- Brain lesions [36]
- Motor neuropathy [22, 37–39]
- Optic atrophy [14]
- Paralysis [28]
- Peripheral neuropathy [14, 33]
- Posterior reversible encephalopathy [40, 41]
- Autonomic neuropathy [33, 39, 42]
- Sexual dysfunction [35]
- Constipation [28, 35, 42]
- Disturbance in consciousness [22, 42]
- Hallucinations [39]

Clinical manifestations

As fatality can result, it is critical to identify the symptoms of porphyria early on. When porphyrins accumulate within erythrocytes and the skin is exposed to the sun, photosensitivity, and skin eruptions may result. Cutaneous manifestations may be composed of skin fragility and blistering in the hand and facial region which can cause scarring, hyperpigmentation and hypertrichosis with reoccurring skin eruptions [21]. These problems are a consequence of free radical oxygens and damage from the sun's UV rays. Dermatological changes are possible in patients with HC.

Patients with porphyria commonly have symptoms of gastrointestinal distress and severe pain. It is also possible for neuropsychiatric symptoms such as psychosis and hallucinations. Seizures have been known to occur, but may be hard to treat due to the limitations of allowed medications for porphyria. The patient may have hypertension, constipation, tachycardia, and peripheral neuropathy. The patient may also have syndrome of inappropriate antidiuretic hormone secretion. Urine may be observed as being a red color as the porphyrin precursors oxidize the urine. Some

atypical manifestations can include bilateral radial neuropathies as well as subarachnoid hemorrhage.

General neurological manifestations of porphyria are listed in Table 1.

Acute intermittent porphyria

In patients with AIP, enzymatic deficiency within the heme biosynthetic pathway can cause porphyrin precursors to accumulate. One of the precursors that may accumulate is delta-aminolaevulinic acid (ALA), which can cause detrimental effects upon the peripheral, central, and autonomic nervous systems.

Posterior reversible encephalopathy syndrome (PRES) can be associated with patients who have AIP, as AIP can affect the autonomic, peripheral, and central nervous systems. PRES can cause patients to have headaches, seizures, varied states of consciousness, and visual abnormalities. Physicians may also develop symptoms including tachycardia, hypertension, vomiting, abdominal pain, seizures, and tea-colored urine as indications of AIP with PRES. Upon a brain MRI, hyperintense, hypointense, or isointense gyriform lesions may be present on the parieto-occipital lobes [42].

Neurovisceral attacks can be triggered by diet, medication, and hormones. These attacks may simulate symptoms of Guillain-Barré syndrome. Quadriparesis can rapidly progress, as reflexes are suppressed and weakness follows. Patients may be unable to breathe, and may need mechanical ventilation [43]. Electrophysiological investigations should be performed to determine motor axonal neuropathy.

Encephalopathy with AIP may cause early childhood fatality. Patients may observe cerebellar atrophy, spastic paraparesis, peripheral neuropathy and cerebellar ataxia. In one case study, the patient experienced optic atrophy, vertical gaze, and nystagmus in addition to convergence palsies [14].

Different enzymatic defects may cause different types of acute porphyria, but generally the symptoms may include a combination as seen within Table 2.

Comorbidities are common among patients with porphyria. In a case study by Shen et al., a woman suffered from Rasmussen encephalitis and AIP. These diseases caused her to have refractory partial seizures and progressive hemispheric atrophy which was associated with abdominal pain, dark urine, and hyponatremia. Comorbidities like these may be difficult to treat due to the effect of drugs on porphyria. The patient required antiepileptic drugs such as phenobarbital and valproate to treat her seizures. However, problems arise because these drugs are also porphyrinogenic. Attempts to discontinue the drugs caused the seizures to worsen. In addition, brain edema and coma developed, causing the patient to not be able to take phenobarbital [44].

Table 2. Clinical manifestations of acute porphyria.

- Abdominal pain [42, 44, 45]
- Behavior change [22]
- Brain atrophy [44]
- Brain edema [44]
- Cerebellar ataxia [14]
- Chronic renal failure [46]
- Chronic renal failure [46]
- Coma [44]
- Confusion [42]
- Decreased limb function
- Delirium
- Diarrhea [28]
- Hyponatremia [33, 44]
- Metabolic disturbance [28]
- Nausea [42]
- Psychosis
- Seizures [22, 33, 39]
- Tachychardia [42]
- Vomiting [42]

Acute porphyria may have an insidious onset with symptoms that are nonspecific. For this reason, diagnosis of acute porphyria may be difficult, especially among patients who have comorbidities. A woman who had Arnold Chiari malformation was treated with trimethoprim/sulfamethoxazole for neurogenic bladder and recurrent urinary tract infections. However, after receiving metronidazole to treat *C. difficile* colitis, the patient presented with additional symptoms, including ascending paralysis, metabolic difficulties, and psychosis [28]. Due to the similarities of symptoms, porphyria is frequently misdiagnosed as Guillain-Barré syndrome [18]. Thus, it is essential to consider acute porphyria as a possible diagnosis to prevent disability and improve the prognoses of patients.

Variegate porphyria

Skin changes are quite common among patients who have VP. This type of porphyria is unique due to its ability to induce simultaneous or separate acute neurovisceral attacks and cutaneous lesions. Patients who have VP can have alternate complications such as cholelithiasis which may worsen photosensitivity and affect porphyrin-heme biosynthesis [20].

In a case study by Barraza et al., a patient had VP with porphyric crises, where the brainstem stopped functioning. It was hypothesized that the dysfunction was caused by neurotoxic effects of porphyrin precursors as well as the osmolarity changes from hyponatremia [47].

Table 3. Laboratory outcomes of hereditary coproporphyria.

Urine concentration	Porphobilinogen concentration is higher than aminolaevulinic acid Coprophyrinogen III
Presence of fecal porphyrin	Isocoprophyrinogen, heptacarboxylate
Porphyrins in erythrocytes	Not increased

Table 4. Laboratory outcomes of acute intermittent porphyria.

Urine concentration	Porphobilinogen concentration is greater than aminolaevulinic acid Porphyrin is mainly from porphobilinogen
Presence of fecal porphyrin	Usually normal but slight increase in coproporphyrinogen and protoporphyrin
Porphyrins in erythrocytes	Test for reduced red cell hydroxymethylbilane synthase activity [21]

Table 5. Laboratory results of variegate porphyria.

Urine concentration	High urinary porphyrin levels during attacks Coproporphyrin > uroporphyrin
Presence of fecal porphyrin	High total fecal porphyrin excretion of elevated protoporphyrin and coproporphyrin [49] Protoporphyrin ≥ coproporphyrin
Porphyrins in erythrocytes	Normal

Evaluation

Physicians should remain cognizant of the physical manifestations of porphyria, especially when they are associated with mental and motor dysfunction. In such cases, a full neurological examination with electrophysiology may be necessary.

Laboratory studies

Laboratory studies may often be unreliable, however, as concentrations of urinary aminolaevulinic acid and porphobilinogen are usually normal despite an existing pathology. One should test for reduced red cell hydroxymethylbilane synthase activity, as it can be indicative of AIP [21]. Tables 3–5 demonstrate the expected results of urine, fecal, and erythrocyte tests for HC, AIP, and VP, respectively. It is important to note that the Watson-Schwartz screening method shows poor sensitivity to urinary porphobilinogen [48], so it may not be the most reliable method to use.

Imaging

MRI can monitor the resolution of parieto-occipital lesions, which can confirm comorbidities such as PRES [42]. An ultrasound should be administered for patients greater than 50 years old [50].

Management

The severity of acute symptoms can be lessened by intravenous glucose and saline. The glucose lowers ALAS1 gene expression while hypoglycemia induces ALAS1 synthesis. For patients that have severe AIP, intravenous hemin should be administered as it can directly inhibit ALAS1 gene expression. Barbiturates should not be prescribed due to its ability to stimulate cytochrome P450 synthesis causing toxic ALA levels and death [51]. Pharmacological and hormonal agents that allow for the production of heme should be utilized, as use of porphyrinogenic agents should cease. The most effective method of managing porphyria is to avoid the overstimulation of the cytochrome P450 pathway. This includes discontinuing use of phenytoin, phenobarbital, and carbamazepine. A list of drugs to avoid should be given to the patient, as certain drugs can precipitate acute attacks of porphyria (Table 6).

Table 6. Drugs to avoid if diagnosed with porphyria.

Inhalational agents	• Enflurane [52] • Isoflurane [53] • Sevoflurane [54]
Intravenous induction agents	• Desflurane [55] • Barbiturates [56, 57] • Etomidate [58, 59] • Ketamine [60] • Thiopental [58, 59]
Analgesics	• Diclophenac sodium [56] • Pentazocine [58, 59] • Phenacetin [55] • Pyrazolones [56] • Tilidine [55]
Neuromuscular-blocking agents	• Alcuronium [61] • Atracurium [55] • Mivacurium [55] • Rocuronium [55] • Vecuronium [55]
Local anesthetics	• Cocaine [58] • Mepivacaine [58, 61, 62] • Ropivacaine [58, 62] • Lidocane and its derivatives [61]
Sedatives	• Benzodiazepine [58] • Chlordiazepoxide [58] • Cimetidine [62] • Diazepam [62] • Lorazepam [55] • Metoclopramide [62] • Midazolam [55] • Nitrazepam [58] • Ondansetron [62] • Oxazepam [55] • Ranitidine [62]
Cardiovascular agents	• Diltiazem [62] • Disopyramide [62] • Hydralazine [55] • Nifedipine [55] • Phenoxybenzamine [55] • Sodium nitroprusside [55] • Verapamil [62]
Anticonvulsants	• Carbamazepine [58] • Valproate [58] • Phenytoin [58]
Antibiotics	• Griseofulvin [56] • Noviobiocin [56]

Patients should eat a caloric, high carbohydrate diet and avoid fasting, as the heme synthetic pathway can become upregulated causing an increase in the chance of acquiring porphyria. The patient should follow nutritional guidelines and ensure adequate fluid intake. Intravenous high-dose glucose treatment can improve symptoms [42]. Vitamin E and C supplements have been shown to decrease oxidative damage and enhance erythrocyte activities of catalase and glutathione reductase activities [63]. Vitamin B6 and glucose therapy have also shown to be useful in porphyria treatment [35].

For women who experience premenstrual attacks of acute porphyria, taking luteinizing hormones may attenuate these attacks further.

Opiates or paracetamol, with the exception of tramadol, can be used to manage pain associated with the disease. Remifentanil is an opioid that can be used for porphyric patients as it does not interfere with heme metabolism [64]. Hypertension and tachycardia may be treated by use of beta-blockers. Seizures may arise which should be treated by gabapentin, and status epilepticus should be treated with levetirecetam. Refractory status epilepticus can be treated by use of propofol [65].

Acute treatment can be administered by hematin or heme arginate intake. By taking hematin or heme arginate, heme will be replenished in the body, causing an increase of ALAS function which reduces the creation of porphyrin precursors. A standard dosage of 3 mg/kg of intravenous infusion should be given daily for a duration of 4 days [65]. This method may reduce the length of acute attacks, but cannot guarantee a permanent treatment. After a 10 day hemin treatment, porphobilinogen levels within the urine may decrease to zero [17].

For patients with severe recurrent attacks of porphyria, liver transplantation can be considered. Follow up is essential to monitor potential long-term complications such as chronic hypertension, chronic pain syndrome, hepatocellular carcinoma, and chronic kidney failure. It is also important to screen family members for gene mutations responsible for porphyria.

Pain management is important to increase the quality of life for the patient. If a patient has neurovisceral pain, gabapentin may be administered to reduce pain. Gabapentin can also be used with morphine to alleviate residual neurovisceral pain [66].

Conclusion

Neurological manifestations of porphyria include cranial neuropathy, peripheral neuropathy, autonomic neuropathy, sensory loss over the trunk, as well as rare cerebellar, basal ganglia, and pyramidal tract involvement. Neuropsychiatric manifestations include seizures, coma, anxiety, depression and hallucinations. Such manifestations can occur during a severe acute attack which may be precipitated by select drugs, steroids, infections, and low carbohydrate diets. Proper laboratory studies and imaging must be conducted to evaluate the condition. Management include immediate addressing of the acute attacks in terms of intravenous glucose and heme. Improper management may lead to relapse of porphyria, worsening peripheral nervous system involvement.

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Disclosure statement

The authors have no conflicts of interest to declare.

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