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Porphyrias: A clinically based approach

Joana Rigor[a,*], Sara Almeida Pinto[a], Daniela Martins-Mendes[a,b,c]

[a] Internal Medicine Department, Vila Nova de Gaia/Espinho Hospital Center, E.P.E., Rua Conceição Fernandes, s/n, 4434-502 Vila Nova de Gaia, Portugal
[b] Biomedicine Department, Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
[c] i3S - Instituto de Investigação e Inovação em Saúde da Universidade do Porto, Porto, Portugal, R. Alfredo Allen, 4200-135 Porto, Portugal

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ABSTRACT

Background: Porphyrias are a group of metabolic diseases, individually rare but with an important combined prevalence. Because of their pathological complexity and clinical heterogeneity, they present a challenging diagnosis. The present review aims to provide a clinically based approach to the recognition and treatment of these disorders.
Methods: We carried out a search in PubMed, with the keyword "porphyria", for reviews published in English from 2010 until 2017.
Results: The research yielded 196 papers, of which 64 were included in the final narrative review.
Conclusions: Porphyrias can be divided based on clinical presentation in acute neurovisceral, chronic cutaneous bullous, chronic cutaneous non-bullous and acute neurovisceral/chronic cutaneous bullous. Each individual porphyria presents a characteristic pattern of porphyrins in plasma, urine, stool and red blood cells. As such, diagnosis is easily obtained by following a simple diagnostic algorithm. Early recognition is key in managing these diseases. Neurovisceral porphyrias require acute support therapy and chronic eviction of precipitating factors. Cutaneous prophyrias, as photosensitivity disorders, rely on sunlight avoidance and, in some cases, specific therapeutic interventions. Given the rarity of these conditions, physician awareness is crucial.

1. Introduction

Clinical porphyria was first described in the late 19th century and, by the 1960's, the pathogenesis of this group of diseases was well established. Porphyrias are an heterogenous group of metabolic diseases of the heme synthesis. Also known as porphyrin synthesis, heme synthesis is a multistep process that occurs chiefly in the liver and bone marrow. Each step of this pathway is mediated by a different enzyme. Porphyrias manifest when an enzyme deficiency occurs, leading to the accumulation of a heme precursor. There are 8 different porphyrias, each one associated with a specific enzyme deficiency. Most of the porphyrias are genetic diseases, and their inheritance pattern is known [1–25]. Porphyrias are rare disorders, with a combined prevalence of 12–20:100,000, and their signs and symptoms are most often non-specific. As such, the major barrier for timely diagnosis and treatment is physician awareness. Clinically, it is possible to classify these diseases by their manifestations, as patients usually present with either neurovisceral (most often abdominal pain) or cutaneous (photosensitivity) findings. This allows for a systematic and step-wise approach to the diagnosis and treatment [3–5,9,16–18,20–22,26].

The authors wish to present a structured approach to these diseases, based on the patient and clinical features, to serve as a tool for management and clinical decision.

2. Material and methods

A search of review articles was performed using the following query in MEDLINE: ("porphyrias" [MeSH Terms] OR "porphyrias" [All Fields] OR "porphyria" [All Fields]) AND (Review[ptyp] AND ("2010/01/01" [PDAT]: "2017/12/31" [PDAT])) and pertinent articles, in English, were selected.

3. Results

The query yielded 196 articles, of which 38 were excluded as they were written in a language other than English. After text analysis, 64 articles were included. Below, we will review their main findings.

Abbreviations: ALA, delta-aminolevulinic acid; ALAD, delta-aminolevulinic acid dehydratase; ALAS2, delta′-aminolevulinate synthase 2; CPOX, coproporphyrinogen oxidase; FECH, ferrochelatase; GATA1, erythroid transcription factor; HFE, human hemochromatosis; PBG, porphobilinogen; PBGD, porphobilinogen deaminase; PCT, porphyria cutanea tarda; PPOX, protoporphyrinogen oxidase; RBC, red blood cells; UROD, uroporphyrinogen decarboxylase; UROS, uroporphyrinogen III synthase

* Corresponding author.
E-mail address: rigorj.md@gmail.com (J. Rigor).

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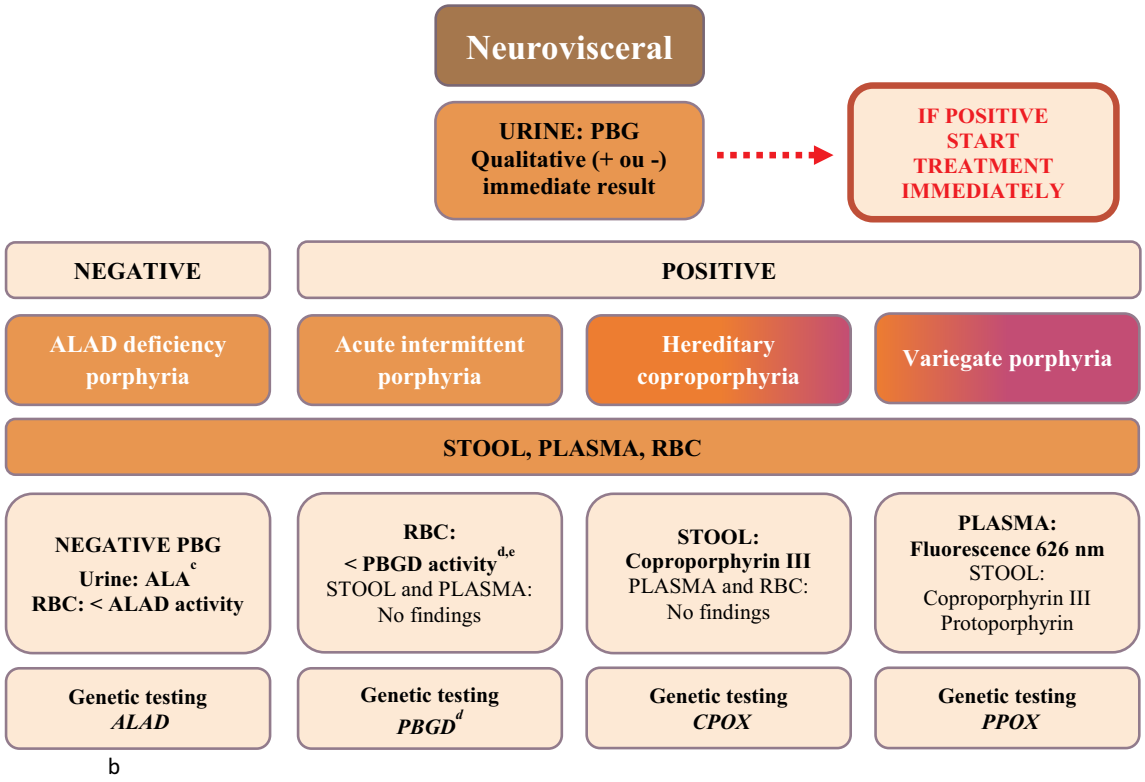

Fig. 1. Diagnostic algorithm for neurovisceral porphyrias. After recognizing a neurovisceral porphyria, diagnosis is confirmed, except in the case of ALAD deficiency porphyria, by the detection of PBG in urine. On positive result, treatment should be initiated immediately. To determine the specific porphyria, stool, plasma and RBC should be analyzed. If a neurovisceral porphyria is strongly suspected but PBG is negative, urine should be tested for the presence of ALA. Genetic testing may be ordered, although it is not necessary for diagnosis given adequate clinical context. (ALA – delta-aminolevulinic acid; ALAD – delta-aminolevulinic acid dehydratase; CPOX – coproporphyrinogen oxidase; PBG – porphobilinogen; PBGD – porphobilinogen deaminase; PPOX – protoporphyrinogen oxidase; RBC – red blood cells; [a] Plasma/stool if end-stage renal disease; [b] and elevated total porphyrins; [c] also present in lead poisoning; [d] some mutations are only expressed in the liver, variable according to erythropoiesis; [e] also present in asymptomatic patients). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.1. Clinical features

The porphyrias can be grouped, according to symptoms, into neurovisceral and cutaneous (or, in some cases, an overlap of both) [1,3–6,8,12–14,16–27]. Neurovisceral porphyrias are also called acute, while cutaneous are named chronic [2–5,8,9,13,14,16–18,22,24,26,27]. However, this nomenclature is not completely accurate: in acute porphyrias, the metabolic impairment is chronic, even if asymptomatic, while in chronic porphyrias, precipitating factors can lead to an acute presentation [2–4,8,17]. Another classification frequently employed separates these diseases into hepatic and erythropoietic, according to where the affected enzyme predominantly acts [2–4,8–10,12,13,16,18,21,22,25,27]. This division is of little use in the clinical setting and, as such, will be mostly omitted in this review.

3.1.1. Neurovisceral porphyrias

The neurovisceral porphyrias are characterized by neurological (motor, sensitive and autonomic) symptoms [3–5,8–13,15–18,20,22,23,26,28–32]. The most common is abdominal pain, which is found in 90%–95% of patients [1,3–5,8–13,15–18,20–24,28–33]. The pain is intense, diffuse and persistent, but no findings are present on physical examination [4,15–17,22–24,26,28,30]. This symptom usually appears in isolation, but may be accompanied by nausea, vomiting, constipation or diarrhea; rarely, paralytic ileus is found [3–5,8–12,15–17,20–22,24,26,28,29,32]. Spastic contraction of the Oddi sphincter, secondary to autonomic neuropathy, may lead to pancreatitis [34].

Typically, non-visceral features present days to weeks after the onset of abdominal pain [1,4,8,9,28]. The most common is progressive muscle weakness that develops proximally to distally [1,3,8–10,16,17,21,28,35], within hour to days (generally 24 h–48 h) [9,29], and which may rarely culminate in progressive bulbar palsy, a potentially deadly complication warranting ventilatory support [1,4,5,8,10,11,15–17,20,23–26,28,29]. Neurosensitive symptoms are rarer and display a “glove and stocking” or “bathing trunk” distribution, respectively hands and feet or central truncal, roughly from mid-abdomen to the knees [5,8,9,26,28,35]. Up to 75% of patients have some evidence of cranial nerve involvement [5,8,9,16,28,35]. Arterial hypertension and tachycardia are common and may be the result of dysautonomia or simply a response to intense abdominal pain [3,5,8–11,15–17,20–26,28,30,32].

There have been reports of seizures [1,3–5,8,9,16–18,20,21,23,28–30], in some cases secondary to hyponatremia [1,3,4,8,9,16,17,20,21,24,26,28–30]. Psychiatric manifestations, mostly insomnia and anxiety (rarely psychosis), may be evident in up to 30% of patients [3–5,8–10,12,13,15–18,21–24,26,28–33,35,36]. In the presence of end-stage renal disease (ESRD), chronic cutaneous lesions, like the ones in bullous cutaneous porphyrias, may be observed [4,17,23].

Although the clinical features of neurovisceral porphyrias are highly variable, most patients present with the same constellation of symptoms in each episode [4]. The most important differential diagnoses include lead poisoning, Guillain-Barré Syndrome, vasculitis and polymyositis [9,23,33].

Usually, no significant findings are apparent on diagnostic testing. The hallmark of porphyrias is reddish-brown urine that resembles hematuria but is negative on a test strip, due to the presence of urinary porphyrins. However, this characteristic is neither sensitive nor specific enough to be of diagnostic value [2,3,9,17,20–23,25,28,30,37]. On blood work-up, 30%–90%

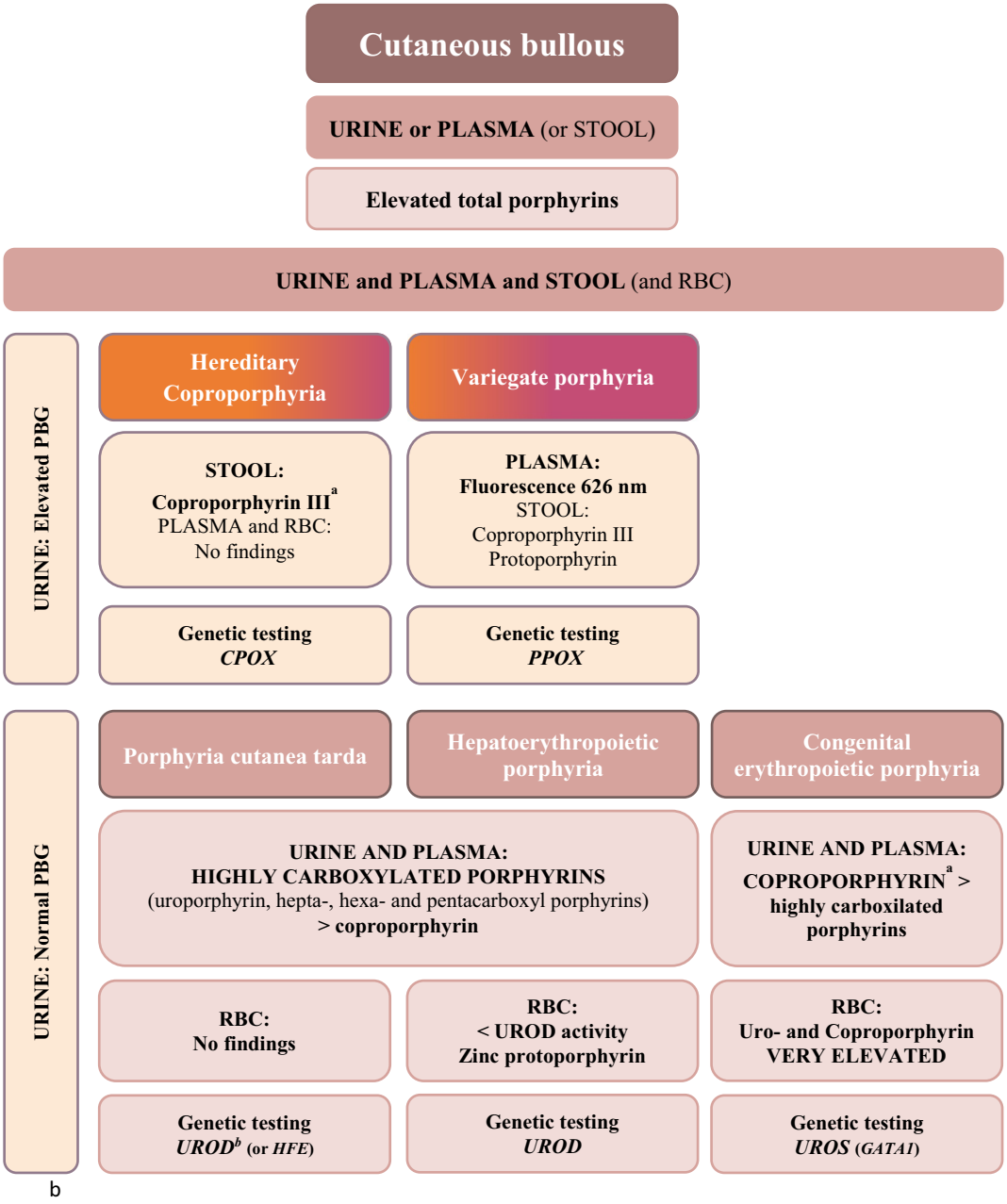

Fig. 2. Diagnostic algorithm for cutaneous bullous porphyrias. Given adequate clinical context, the first step for diagnosis is the finding of elevated total porphyrins in urine, plasma or stool. Subsequently, analyzing the specific pattern of porphryins in urine, plasma, stool and RBC permits the diagnosis of the specific porphyria. Genetic testing may be ordered, although it usually is not necessary for diagnosis. (CPOX – coproporphyrinogen oxidase; GATA1 - erythroid transcription factor; HFE – human hemochromatosis; PBGD – porphobilinogen deaminase; PPOX – protoporphyrinogen oxidase; RBC – red blood cells; UROD – uroporphyrinogen decarboxylase; UROS – uroporphyrinogen III synthase; [a]Also present in hepatobiliary disorders; [b]present in < 20%). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of patients present with hyponatremia, which is rarely significant. This finding can be attributed to syndrome of inappropriate antidiuretic hormone secretion and vomiting [3,8,9,16–18,20,21,23,29,30]. In a minority of patients, slight leukocytosis and elevation of transaminases may be found [4]. If cerebrospinal fluid analysis is performed, normal protein concentration differentiates this disease from Guillain-Barré Syndrome [4,9,21,29,30]. Features of posterior reversible encephalopathy are sometimes apparent on cerebral magnetic resonance imaging [3,5,8,9,15,21,28,30].

Usually, acute porphyria attacks are the result of a precipitating insult; the classic example are cytochrome P450 (CYP450) inducing drugs, namely sulphonamides, barbiturics, estrogens and progestins [1,3,4,8,9,11,13–17,20,21,23,25,26,28–30,33,38]. The American Porphyria Foundation and the European Porphyria Network, among others, provide updated lists of causative drugs [1,3–5,8,11,13,16,17,20,21,23,26,28,29]. Caloric or carbohydrate intake restriction, premenstrual and menstrual hormone fluctuations, metabolic stress, alcohol consumption and smoking have also been implicated [3–5,8,9,11,14–17,20,21,23–25,28–30,33,38,39]. As such, these diseases are most often seen in women, despite a similar incidence of genetic mutations in both genders, and are exceedingly rare in children [3–5,13,15–18,20–25,28,29].

In the long run and in the setting of multiple acute episodes, chronic complications, such as arterial hypertension, chronic kidney disease, cirrhosis and hepatocellular carcinoma, may arise [3,5,15–18,20,23,24,26,28–30,38,40,41].

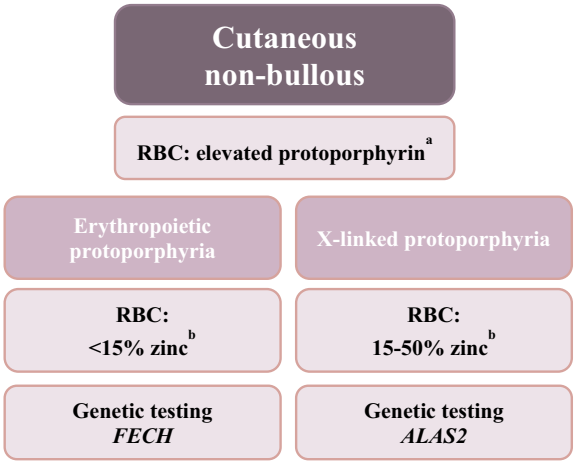

Fig. 3. Diagnostic algorithm for cutaneous non-bullous porphyrias. Diagnosis is based on the finding of elevated protoporphyrin in RBC, with the percentage of zinc differentiating between the two porphyrias of this group. Diagnosis can be confirmed with genetic testing. (ALAS2 – delta′-aminolevulinate synthase 2; FECH – ferrochelatase; RBC – red blood cells; [a]Non-hydrosoluble – no urinary excretion; [b] > 50% Zinc in other RBC diseases). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.1.2. Cutaneous porphyrias

The cutaneous porphyrias are a group of photosensitivity disorders than can further be divided into bullous and non-bullous [6,7,19–25,27,37,38,42–46]. Pruritus is frequent, and pain can be severe [4,16,20,21,25,27,38,42,46,47].

Non-bullous porphyrias are characterized by erythema and macular, sometimes petechial, exanthema that appears within minutes of sun exposure, regresses with sunlight avoidance in hours to days, and does not leave sequelae [6,16,20–25,27,38,46–48]. In the setting of frequent and prolonged exposure, some patients may develop chronic skin injuries such as lichenification and pseudovesicles [6,16,21–25,27,47].

In bullous porphyrias, lesions are more exuberant. Cutaneous fragility is marked and bullae filled with serohematic fluid eventually lead to permanent scarring, pseudoscleroderma, hyperpigmentation and hypertrichosis [4,7,9,15,16,19–25,27,37,38,42,43,45,46,48–53]. As with non-bullous porphyrias, lesions are strictly found in areas of sun exposure [4,7,15,16,24,42,43,51].

Cutaneous porphyrias also present with signs and symptoms involving the two most important sites of heme synthesis, the liver and the erythrocyte. Liver manifestations are the most common, with up to 30% of patients with non-bullous porphyrias having some form of liver impairment [5,6,16,23,24,27,47] and 60%–70% of patients with porphyria cutanea tarda (PCT), the most common of bullous porphyrias, being found to have hepatic siderosis [7,16,20,21,23,25]. All cutaneous porphyrias can lead to cirrhosis and hepatocellular carcinoma, but a specific liver disease called protoporphyrin hepatopathy may develop secondarily to non-bullous porphyrias and is associated with negative outcomes [2,4–7,16,18,20–25,27,38,40,42,46,47,49,51,54,55]. Injuries to the liver (hepatotoxic drugs, alcohol, hepatotropic viruses and hemochromatosis) may be a causative or aggravating factor in bullous porphyrias [2,5,7,16,20–27,37,39,44–46,48,50,51,54]. Notably, about 50% (5%–92%, depending on country or region) of patients with PCT are infected with Hepatitis C (HCV) [2,7,16,23,25,37,41,43–45,51,53,54,56]. Regarding the hematopoietic system, anemia is often present: in bullous autossomic recessive pophyrias it is hemolytic and can lead to splenomegaly and cholelitiasis; in non-bullous porphyrias it is usually microcytic and hypochromic and frequently requires transfusions [5,10,20–22,24,25,27,42,49,50].

Pseudo-porphyria is a condition found in patients with ESRD and is characterized by lesions similar to those found in bullous porphyrias [5,7,16,21,24,25,51,52].

3.2. Classification

As mentioned previously, the porphyrias can be divided in cutaneous non-bullous (erythropoietic protoporphyria and X-linked protoporphyria), cutaneous bullous (porphyria cutanea tarda, hepatoerythropoietic porphyria and congenital erythropoietic porphyria) and neurovisceral [acute intermittent porphyria and aminolevulinic acid dehydratase (ALAD) deficiency porphyria]. The remaining porphyrias may present with both cutaneous bullous and visceral symptoms. Of these, hereditary coproporphyria is mostly neurovisceral while variegate porphyria is mostly cutaneous [2,4,5,7,9,12,16,21,24,25,27–29,46,47].

At the base of the majority of these diseases are genetic mutations [1,4–13,15,16,20–28,30,33,35,42,47,49–52,57,58]. In PCT, 75%–80% of patients have the acquired sporadic type (or type 1); type 2 is inherited via enzyme mutation, while type 3 is secondary to hereditary hemochromatosis [2,4,5,7,16,19–25,27,37,43,44,46,51,52,54,57].

Penetrance is highly variable, ranging from 10% to 100%, depending on the specific porphyria; in general, autosomal recessive porphyrias have complete penetrance [1,3–5,8,10,12,13,15,20–24,28,29,35,47,49–51,57].

3.3. Diagnosis

Each metabolite of heme synthesis has a specific excretion pattern and solubility in stool, urine, plasma and erythrocyte [1,3–5,8–10,12,16–18,20–30,37,47,49–52,57]. General increases in porphyrins are not specific to porphyrias and can be found in hepatic disease of all causes and with any drugs that affect CYP450; however, a specific pattern of porphyrins exists for each porphyria and allows for a simple diagnosis [1,3–9,12,16–18,20,21,23,24,26,29,30,37,47,49–51]. Porphyrins are easily degradable, requiring care in the storage and transportation of samples, namely the immediate protection from light of urine samples [1,24,25,28].

As porphyrias are mostly genetic and enzyme-related illnesses, diagnosis can be achieved by either measurement of erythrocyte enzyme activity or genetic testing [1,3–10,12,16–18,20–30,35,37,47,49–52,57,58]. Generally, genetic testing is not necessary for diagnosis, but allows family studies and the identification of previously unknown mutations [1,3–8,10,12,16–18,20–22,24,27–30,47,49–51]. There is no genotype-phenotype correlation for most of the porphyrias [4,5,22,24,25,28,29,47,49–51]. Skin biopsies seldom assist in diagnosis and are reserved for exclusion of other causes [7,16,21,24,25,27,37,54,56,59–62].

Given the multitude of both porphyrias and their markers, porphyrins, a systematic diagnostic approach is needed. In Fig. 1, [1,4,5,8,15–18,20–26,28–30,35,57,58] Fig. 2, [4,5,7,15,16,20–25,27,29,37,42,49–52,54,57,58] and Fig. 3, [5,6,16,21–25,27,47,57,58] the authors suggest an diagnostic algorithm for each group of porphyrias (visceral, cutaneous bullous and cutaneous non-bullous, respectively).

3.4. Treatment

Treatment of neurovisceral porphyrias includes acute support therapy and chronic eviction of precipitating factors [1,3,5,8–10,16,17,20,21,23,24,26–29,31,35,38].

Time to treatment is the most important predictor of survival; without treatment, the mortality rate is 5% to 20% [16,25,26,30]. Worse outcomes are associated with extensive neuropathy (especially in the presence of bulbar palsy), altered mental status and hyponatremia [9]. Some patients require admission to an Intensive Care Unit [4,17,21,23,30]. As such, treatment should be started as soon as a neurovisceral porphyria is identified, usually by detection of porphobilinogen (PBG) in urine; at this stage, it is unnecessary to determine the specific porphyria, [4,21,23,24,28–30] as hemin (1 to 4 mg/kg/day for 3 to 14 days) is the specific treatment for all neurovisceral porphyrias [1,3–5,8–10,12,16–18,20–24,26–30,35,38]. This drug stops progression, betters prognosis and accelerates recovery; however, it does not reverse an established neuropathy [5,8,21]. Response to hemin can be monitored by clinical course or serial measurement of urinary

PBG [1,5,21,29]. In less severe episodes, or in cases where hemin is not promptly available, administration of glucose or dextrose, orally or intravenously, is an adequate alternative [1,4,9,10,12,16,17,20–23,26,28–30,38,39]. However, if improvement is not apparent in 24 to 48 h, treatment with hemin is imperative [22,28–30]. Most uncomplicated attacks end with full recovery in 5 to 14 days, but neurological sequelae may appear in the context of serious or frequent episodes [5,8,16,17,20,21]. In rare cases, patients progress to organ failure requiring urgent liver transplant [1,3].

Supportive measures include correction of hyponatremia with fluids [1,5,8,17,20,21,23,28–30], proper analgesia, that frequently requires opioids and sedation [1,4,5,9,16,20–24,27–30], and control of hypertension and tachycardia with beta-blockers [5,9,16,17,21,23,28,30]. Seizures should be treated with benzodiazepines, gabapentin, levetiracetam or magnesium sulfate; status epilepticus requires sedation with propofol [1,3,9,16,17,21,23,28–30]. Pulmonary monitoring, with the aid of bedside spirometry, is crucial in the early detection of progressive bulbar palsy [4,5,30].

The central aspect of chronic management is patient education; counselling regarding appropriate carbohydrate and caloric intake and a list of drugs to avoid must be provided [4,5,9,10,16,17,20,21,28–31,35,38]. In some cases, ovulatory suppression with a gonadotropin analogue may be necessary [1,3,4,9,16–18,24,28–30,38]. Oral contraceptives should generally be avoided [1,4,9,29,30]. Less than 10% of patients have frequent episodes requiring prophylactic treatment with regular (every one to two weeks) infusions of hemin [1,4,5,16,18,20,21,24,28,30,35,38]. Liver transplant may be needed in extreme situations [5,9,10,16–18,20–24,26,28–30].

In the group of cutaneous porphyrias, PCT is the only one with the possibility for a functional “cure”. Firstly, treatment or management of underlying factors is paramount. In the case of HCV, the use of new direct antiviral agents has extended the rate of treatment and cure, with expected changes in the epidemiology of PCT [19,43]. Of note, drug combinations including ribavirin might precipitate PCT by inducing hemolytic anemia and subsequent iron overload [38,43]. As for the management of PCT, the treatment mainstays are phlebotomies or hydroxychloroquine (or chloroquine), which have similar success rates; choice should be made on a case-by-case basis [5,7,10,16,18–24,27,37,38,43,44,46,48,51,52,54]. Phlebotomies are particularly useful when PCT is associated with iron overload, as is frequent in hemochromatosis and HCV infection [19,23,24,37,38,43,48,51]. About 450 ml of blood are removed every two weeks until hemoglobin is < 11 g/dl or ferritin < 20 ng/ml [5,7,16,20–24,37,38,51,54,63]. Hydroxychloroquine is preferred in children and the dosage is 100 mg (125 mg to 250 mg for chloroquine) twice a week. These drugs do, however, have many contraindications, namely pregnancy, breastfeeding, ESRD, glucose-6-phosphate dehydrogenase deficiency, psoriasis, retinopathy and current alcohol or hepatotoxic drug use [5,7,16,21–24,27,37,38,52].

Regardless of the treatment chosen, management should include dosing of plasma and/or urinary porphyrins every 1 to 3 months; if remission is achieved, and the precipitating factor removed, therapy can be stopped [5,20–22,24,27,38,51,54].

For the remaining cutaneous porphyrias, treatment is centered on avoidance of solar exposure [4,5,16,18,20,21,23,24,27,29,38,47–50]. Pain and pruritus may be difficult to manage, particularly in nonbullous porphyrias, as opioids are frequently ineffective [22,27,47], and most patients report no relief with anti-histamines [38]. Due to sun avoidance, all patients must be prescribed a vitamin D supplement [16,24,38,39,47,49,50].

Afamelanotide, an analogue of α-melanocyte stimulating hormone, and, to a lesser extent, beta-carotene, can be used as adjuvant therapy in patients with non-bullous cutaneous porphyrias, as these compounds reduce skin penetration of ultra-violet light [5,10,16,20,21,24,27,38,39,46,48,64]. In bullous porphyrias, these drugs do not have proven efficacy, and as such, their use is not recommended [4,23,47,49]. Congenital erythropoietic porphyria can be cured by hematopoietic transplant [5,20,22–24,27,38,42,49].

Many treatments for non-PCT cutaneous porphyrias have been described, but evidence is inconsistent or anecdotic; these include activated charcoal [5,6,16,20–22,38], cysteine and alpha-cysteine [6,16,38,39,48], alpha-tocopherol [16,38,39], ascorbic acid [38,39], pyridoxin [38,48], cholestyramine [5,6,16,20–23,27,38,46,47], ursodeoxycholic acid [6,16,23,38], transfusion of red blood cells [6,16,21–23,27,38,46], hydroxyurea [16,38], plasmapheresis [6,16,22,23,47], splenectomy [5,16,20,21,23,27,38], and hematopoietic transplant [5,6,16,22,24,27,38,46,49].

3.5. Long term management and prognosis

Patients with neurovisceral porphyrias presenting with multiple episodes should have creatinine and hepatic enzymes monitored yearly [3,16,18,28–30,40].

In the case of cutaneous non-bullous porphyria, given the risk of hepatic disease, especially protoporphyrin hepatopathy, yearly hepatic enzymes monitoring is recommended [5,6,16,18,20,21,24,25,47]. The only treatment for established protoporphyrin hepatopathy is hepatic transplant [6,16,18,21,22,24,25,38,46,47]. If cholelithiasis is suspected, abdominal imaging is warranted [23,47].

Patients with PCT who achieve clinical remission should maintain yearly monitoring, including dosing of urinary porphyrins; treatment should be reinitiated if a new elevation is detected [16,21,24,51].

All of those afflicted with cutaneous bullous porphyria that maintain persistent elevation of porphyrins, as well as those with neurovisceral porphyria and frequent attacks, should begin screening for hepatic carcinoma at age 45 to 50 years old, every 6 to 12 months, via liver imaging [4,16,17,20,27–30,40,51].

4. Conclusion

As rare diseases, porphyrias can pose a challenging diagnosis. Physicians need to be aware of this group of diseases, and recognize its main clinical findings, be them acute neurovisceral or chronic cutaneous. Diagnosis is possible following simple algorithms, as each porphyria has a specific pattern of porphyrin excretion in plasma, urine, stool and RBC. Genetic testing is generally not necessary for confirmation. Following diagnosis, and particularly in the case of acute neurovisceral porphyrias, timing to treatment is the most important factor in ensuring quality of life. Patients need to be educated about their condition as avoiding precipitating factors is key to a successful treatment. Follow-up of patients depends on the specific porphyria and on the severity and frequency of attacks; it generally includes monitoring of creatinine and hepatic enzymes and screening for hepatic carcinoma.

Conflict of interest statement

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