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Portuguese Consensus on Acute Porphyrias: Diagnosis, Treatment, Monitoring and Patient Referral

Consenso Português de Porfirias Agudas: Diagnóstico, Tratamento, Monitorização e Referenciação

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ABSTRACT

Acute porphyrias are a group of rare genetic metabolic disorders, caused by a defect in one of the enzymes involved in the heme biosynthesis, which results in an abnormally high accumulation of toxic intermediates. Acute porphyrias are characterized by potentially life-threatening attacks and, for some patients, by chronic manifestations that negatively impact daily functioning and quality of life. Clinical manifestations include a nonspecific set of gastrointestinal, neuropsychiatric, and/or cutaneous symptoms. Effective diagnostic methods are widely available, but due to their clinical heterogeneity and non-specificity, many years often elapse from symptom onset to diagnosis of acute porphyrias, delaying the treatment and increasing morbidity. Therefore, increased awareness of acute porphyrias among healthcare professionals is paramount to reducing disease burden. Treatment of acute porphyrias is centered on eliminating the potential precipitants, symptomatic treatment, and suppressing the hepatic heme pathway, through the administration of hemin or givosiran. Moreover, properly monitoring patients with acute porphyrias and their relatives is fundamental to preventing acute attacks, hospitalization, and long-term complications. Considering this, a multidisciplinary panel elaborated a consensus paper, aiming to provide guidance for an efficient and timely diagnosis of acute porphyrias, and evidence-based recommendations for treating and monitoring patients and their families in Portugal. To this end, all authors exhaustively reviewed and discussed the current scientific evidence on acute porphyrias available in the literature, between November 2022 and May 2023.
Keywords: Consensus; Porphyria, Acute Intermittent/diagnosis; Porphyria, Acute Intermittent/therapy; Porphyrias/diagnosis; Porphyrias/therapy; Portugal; Referral and Consultation

RESUMO

As porfirias agudas são um grupo de doenças metabólicas raras, causadas pela deficiência numa das enzimas envolvidas na biossíntese do heme, originando uma elevada e anormal acumulação de intermediários tóxicos. As porfirias agudas são caracterizadas por crises potencialmente fatais e, em alguns doentes, por manifestações crónicas que têm um impacto negativo no funcionamento diário e na qualidade de vida. As manifestações clínicas incluem um amplo espetro de sintomas gastrointestinais, neuropsiquiátricos e/ou dermatológicos. Existem métodos de diagnóstico eficazes amplamente disponíveis, mas devido à heterogeneidade e inespecificidade das manifestações clínicas, muitas vezes decorrem vários anos desde o início dos sintomas até ao diagnóstico das porfirias agudas, atrasando o tratamento e aumentando a morbilidade. Assim, o aumento da consciencialização para as porfirias agudas entre os profissionais de saúde é considerado fundamental para reduzir o impacto da doença. O tratamento centra-se na eliminação dos potenciais precipitantes, tratamento sintomático e supressão da via hepática de síntese do heme, através da administração de hemina ou givosiran. Além disso, a monitorização adequada dos doentes com porfirias agudas e dos seus familiares é crucial para prevenir crises agudas, hospitalização e complicações a longo prazo. Considerando isto, um painel multidisciplinar elaborou um consenso nacional, com o objetivo de fornecer orientações para o diagnóstico rápido e eficiente das porfirias agudas, assim como recomendações, baseadas em evidência científica, para o tratamento e monitorização de doentes com estas patologias e as suas famílias, em Portugal. Para tal, a evidência científica atual sobre porfirias agudas disponível na literatura foi exaustivamente revista e discutida por todos os autores entre novembro de 2022 e maio de 2023.
Palavras-chave: Consenso; Encaminhamento e Consulta; Porfirias/diagnóstico; Porfirias/tratamento; Porfiria Aguda Intermitente/diagnóstico; Porfiria Aguda Intermitente/tratamento; Portugal

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INTRODUCTION

Porphyrias are a group of rare, genetic metabolic disorders caused by a defect in an enzyme of the heme biosynthesis pathway, leading to the accumulation of specific heme precursors.[1,2] Porphyrias can be categorized as acute or non-acute photocutaneous porphyrias, characterized by intermittent neurovisceral attacks or moderate to severe cutaneous photosensitivity, respectively.[3-5]

Acute porphyrias comprise three autosomal dominant disorders, acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), and the rare autosomal recessive disorder aminolevulinic acid dehydratase deficiency porphyria (ADP).[3,5,6]

Acute porphyrias are characterized by potentially life-threatening acute attacks, which most frequently consist of pain accompanied or preceded by neuropsychiatric symptoms and peripheral neuropathy. In VP and HCP, cutaneous blistering can also occur in sunlight-exposed skin. Recurrent acute attacks increasingly predispose patients to chronic symptoms and long-term complications may occur during the natural course of acute porphyrias.[7-9]

PATHOPHYSIOLOGY

Acute porphyrias are caused by a genetic mutation leading to a partial deficiency in one of four specific enzymes in the heme biosynthetic pathway. In detail, ADP is caused by an abnormal function of ALA dehydratase; AIP is caused by a deficiency in the hydroxymethylbilane synthase; HCP is caused by a defect in the coproporphyrinogen oxidase, and VP is caused by a deficiency in the protoporphyrinogen oxidase.[3,5,6]

The defective function of these enzymes is an essential but not a sufficient condition to develop acute porphyria. In fact, the activity of aminolevulinic acid synthase 1 (ALAS1), the first and rate-limiting enzyme in the heme biosynthetic pathway in the liver, is determinant for the development of acute porphyria. The ALAS1 activity can be induced directly or indirectly by several environmental and physiological factors, such as certain drugs, stress, infection, caloric restriction, alcohol use, smoking, and fluctuating levels of female sex hormones.[3,5]

ALAS1 upregulation associated with the deficiency in one of the downstream enzymes leads to an abnormal and toxic accumulation of porphyrins and their precursors, namely aminolevulinic acid (ALA) and porphobilinogen (PBG). The increased release of these intermediates into the circulation can cause injuries to the nervous system and other organs.[3,5,10]

EPIDEMIOLOGY

Acute porphyrias have a combined prevalence rate of approximately five cases per 100 000 subjects worldwide.[5,10-12] AIP is the most common type, with an estimated prevalence rate of the disease-related mutations varying from 1:1299 to 1:1700 in the general population.[13,14] In European countries, the incidence rate was calculated as 0.13, 0.08, and 0.02 new cases/year per million inhabitants for AIP, VP, and HCP, respectively, and the prevalence rate was determined as 5.4 and 3.2 per million inhabitants for AIP and VP, respectively.[12] ADP is an extremely rare porphyria, with fewer than 10 cases described in the literature.[3] In Portugal, the incidence and prevalence rates of acute porphyrias are currently unknown.

The clinical penetrance of acute porphyrias is low, estimated at 1% for the patients with an AIP mutation, suggesting a critical role of modifying genes and/or environmental factors for triggering the acute attacks.[13,14]

DIAGNOSIS

Acute porphyrias are rare and characterized by a non-specific range of manifestations, and therefore many patients remain undiagnosed or are often misdiagnosed with other medical conditions. A population-based study reported an up to 15-year delay from symptom onset to diagnosis of acute porphyrias.[15] An earlier diagnosis is fundamental for rapid and effective treatment, reduced healthcare costs and improved outcomes.[16]

Clinical and laboratory findings

Acute attacks

Acute attacks may occur in all acute porphyrias and are clinically indistinguishable. Patients usually present a non-specific constellation of signs and symptoms caused by dysfunction across the autonomic, central, and peripheral nervous systems (Fig. 1). Classically, abdominal pain, peripheral neuropathy, and changes in mental status constitute the symptomatic triad of an acute attack.[6,7,17]

Severe abdominal pain is often the initial symptom of an attack, and it is the most common symptom reported by patients (74% - 100%). Pain typically lasts hours to several days, and gradually abates. The pain pattern is diffuse, colicky in nature, and it is commonly accompanied by nausea and vomiting (42% - 88%) and constipation (50%). The abdominal examination is often unremarkable. Pain in the back, legs, arms or chest is common (72% - 77%).[6,7,18]

Behavioral changes can precede an acute crisis and a myriad of psychiatric symptoms can occur during an attack. Among patients with acute porphyrias, 20% to 58% have neuropsychiatric symptoms before and during acute exacerbations. The broad spectrum of psychiatric manifestations includes irritability and subtle mood disturbances, anxiety, behavioral and sleep disorders, severe depression, psychosis, personality changes, catatonia, and dementia.[19-21] The

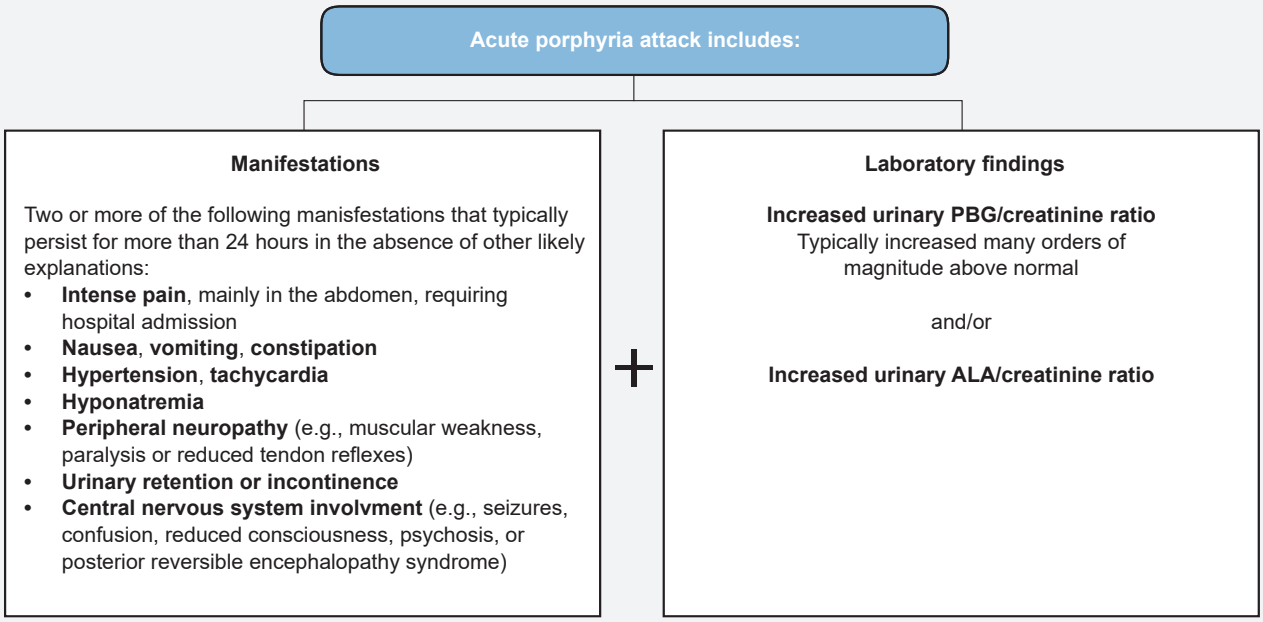

Figure 1 – Key manifestations and specific laboratory findings indicating an attack of acute porphyria

same patient may have variable psychiatric manifestations in each attack.[22]

Patients may also experience motor weakness and sensitivity changes typically mild in severity, which improve as the pain resolves. Rarely, progressive motor weakness may evolve to complete paralysis, incontinence or urinary retention, swallowing difficulties and respiratory failure.[5,20,23]

Hyponatremia is a common feature (25% - 60% of acute attacks), and a marker of the severity of the crisis. Hyponatremia is mainly due to hypothalamic involvement, resulting in the syndrome of inappropriate diuretic hormone secretion (SIADH).[24] Other non-specific laboratory abnormalities such as hypomagnesemia, mild aminotransferases elevations, anemia, leukocytosis, and increased C-reactive protein, can also be detected.[4,25,26]

Seizures occur in up to 20% of AIP patients, and they are often associated with severe hyponatremia.[2,20,27] Cases of porphyria-induced posterior reversible encephalopathy syndrome have been reported.[28]

Increased sympathetic activity leads to tachycardia, excess sweating, and hypertension, which occur in about 60% of acute attacks. Cardiac dysrhythmias occur in rare situations.[7]

Most patients experience either none or only a few acute attacks during their lifetime; yet a few patients experience recurrent attacks (≥ four attacks/year) and/or have severe and chronic symptoms.[12,29] By definition, symptomatic patients are those who have experienced at least one acute porphyria attack within the last two years; whereas asymptomatic patients are those who have experienced at least one acute porphyria attack in the past but have had no acute porphyria related manifestations during the last two years. Asymptomatic patients can be further distinguished as patients in remission or high excreters, according to the urine PBG/creatinine ratio – lower or higher than four times the upper limit of normal, respectively.[6]

Cutaneous manifestations

Variegate porphyria and HCP can be associated with photocutaneous skin lesions, which result from the overproduction and skin accumulation of photoreactive porphyrins.[30] Skin manifestations can occur either alone or during acute symptoms, and in 60% of VP patients these may be the only sign of the condition.[31,32]

Clinically, bullae, blisters or vesicular lesions are limited to sun-exposed skin, such as the back of hands and feet, face, neck, and legs. Other cutaneous manifestations include skin fragility, hypertrichosis, and increased pigmentation of sun-exposed areas. Cutaneous manifestations change seasonally, being more intense in the summer and in the autumn.[31]

Chronic symptoms

Most symptomatic patients with acute porphyria have complete resolution of their symptoms between attacks, although those with multiple recurrent attacks may develop chronic symptoms. In a four-year natural history study, almost 75% of patients reported chronic symptoms between

attacks.[33] In a different observational study, chronic symptoms were reported in 85% of AIP patients with sporadic attacks (< four attacks/year) and 46% of patients with latent AIP (no attacks).[34]

Chronic pain is usually the most commonly reported symptom, followed by tiredness, anxiety, nausea and sleeping disorders.[29,34-36] Chronic manifestations negatively impact many aspects of daily living, and health-related quality of life is considerably reduced in patients with acute porphyria.[29,34,36]

Long-term complications

Subclinical liver disease is common in acute porphyria and manifests as progressive transaminitis, fibrosis, cirrhosis, or hepatocellular carcinoma leading to premature death. In a recent systematic review enrolling 7381 patients with porphyria, primary liver cancer was diagnosed in 4.8% of patients, of whom 3.3% (of the total) had hepatocellular carcinoma.[37] Advanced liver fibrosis and cirrhosis are not a prerequisite for the development of hepatocellular carcinoma in patients with acute porphyria.[37,38]

Chronic kidney disease is also common, particularly in symptomatic AIP patients. In a 10-year cohort study, chronic kidney disease occurred in up to 59% of the symptomatic AIP patients, with a decline in glomerular filtration rate of ~1 mL/min/1.73 m^2 annually.[39] Among these patients, 2.7% developed end-stage renal disease.[39] Additionally, a recent study reported a five-fold higher risk of advanced chronic kidney disease in patients with acute porphyria than in the general population.[40] Porphyria-associated kidney disease is typically presented as chronic tubulointerstitial damage and chronic fibrous intimal hyperplasia associated with focal cortical atrophy.[41,42]

The decline of renal function may also be related with chronic hypertension. In fact, in the abovementioned 10-year study, hypertension was present in 62% of symptomatic patients.[39] Moreover, hypertension can also occur with normal renal function. Chronic hypertension was more frequent in the symptomatic cases (71% - 73%), than in the asymptomatic control group (26%).[43]

Ultimately, death can occur in acute attacks and as an outcome of long-term complications.[44,45]

Laboratory diagnosis

First-line testing

In symptomatic patients, first-line biochemical diagnosis consists of a single random urine screening for PBG, ALA, and porphyrins. The use of Hoesch Test, with Erhlich reagent is a rapid test for screening PBG in urine.[46] The optimal time to collect a urine sample is during or shortly after an attack, when PBG or ALA levels will have peaked. Reddish, purple, or brown urine color is common during acute attacks, and urine may darken further upon exposure to light. The urine sample should be protected from light and frozen (preferentially) or refrigerated for transport and storage. Results should be normalized to the creatinine concentration for a more reliable interpretation (please consult the article by Stein *et al*[6] for detailed considerations in the interpretation of the urine PBG/creatinine ratio).[6,17,46,47]

Diagnosis of AIP, VP and HCP requires the presence of increased urinary PBG levels, often many orders of magnitude above normal, which do not occur in any other medical condition (Table 1).[6,48] This high degree of specificity enables prompt identification and treatment. Exceptionally in the ultra-rare ADP, PBG levels are normal, but ALA levels are typically elevated.[17,46,47]

Measurement of urine porphyrins is important to ensure that VP or HCP are

Table 1 – Diagnostic test outcomes for each subtype of acute porphyria. Adapted from[47]

Acute porphyria subtype	Clinical presentation	First-line testing			Second-line testing		Third-line testing
		Urinary PBG	Urinary ALA	Urinary porphyrins	Plasma porphyrins with fluorescence scan	Fecal porphyrins	Genetic testing
ADP	Acute attacks	Normal or slight ↑	↑↑	↑ COPRO III	No peak or ~619 nm	Normal or slight ↑	*ALAD*
AIP	Acute attacks	↑↑	↑	↑ URO, COPRO III	No peak or ~619 nm	Normal or slight ↑	*PBGD*
HCP	Acute attacks and/or cutaneous symptoms	↑	↑	↑ or normal URO, COPRO III	No peak or ~619 nm	↑↑ COPRO III COPRO III/COPRO I > 2	*CPOX*
VP	Acute attacks and/or cutaneous symptoms	↑	↑	↑ or normal URO, COPRO III	~626 nm	↑ PROTO >> COPRO III	*PPOX*

ADP: ALA dehydratase deficiency porphyria; AIP: acute intermittent porphyria; ALA: aminolevulinic acid; COPRO III: coproporphyrin III; HCP: hereditary coproporphyria; PBG: porphobilinogen; PROTO: protoporphyrin; URO: uroporphyrin; VP: variegate porphyria; ↑ increased.

not misdiagnosed, because urinary PBG levels are often less elevated and return to normal more rapidly in VP and HCP than in AIP.[6] General increases in porphyrins are not specific to porphyrias and can be found in hepatic disease of all causes; nevertheless, a specific pattern of porphyrins exists for each subtype of acute porphyria (Table 1).[17,46,47]

Second-line testing

Measurement of plasma and fecal porphyrins and plasma fluorescence scanning are useful second-line diagnostic tests to confirm or exclude porphyrias or to determine the subtype of acute porphyria (Table 1). In HCP, coproporphyrin (COPRO) III isomer is more elevated in feces than in urine, and the ratio of COPROIII/COPRO I is usually greater than two; in VP there is a distinct plasma porphyrin fluorescence emission peak at 624 - 628 nm and, in feces, the level of protoporphyrin (PROTO) is higher compared to COPRO III isomer.[17,46,47]

Third-line testing

Genetic testing of the acute porphyria genes can identify the pathogenic familial mutation and is useful to fully characterize the index case and to prevent acute attacks in at-risk patients with a pathogenic mutation (Table 1).[49,50] Demonstration of an acute porphyria mutation identifies a genetic trait for porphyria, but, by itself, is insufficient to establish a diagnosis or determine a biochemically active acute porphyria, due to the low clinical penetrance of acute porphyrias.[13,14,46,47]

Differential diagnosis

The symptoms of acute porphyria often resemble those of other gastrointestinal, neurological or neuropsychiatric diseases (Table 2).[21,51-55]

Table 2 – Common clinical conditions mimicked by an acute attack of acute porphyria[21,51-55]

Gastrointestinal conditions	Acute gastroenteritis
	Appendicitis
	Biliary colic/ acute cholecystitis
	Intestinal occlusion
	Pancreatitis
	Peptic ulcer disease
	Peritonitis
Genitourinary conditions	Nephrolithiasis
	Urinary tract infection
	Pelvic inflammatory disease
	Pregnancy complications
Metabolic/endocrine conditions	Acute hypoadrenalism (Addisonian crisis)
	Acute hypoparathyroidism and hypocalcemic crisis
	Pheocromocytoma
Neuropsychiatric conditions	Acute myopathies
	Acute psychotic episode
	Delirium
	Epilepsy
	Hemicrania
	Guillain–Barré syndrome
	Panic attack/ anxiety
Cardiovascular conditions	Hypertensive crisis
	Tachyarrhythmia
Hematological conditions	Acute drepanocytic crisis
	Acute hemolytic crisis
Other conditions	Lead poisoning
	Pseudoporphyria
	Tyrosinemia

Acute porphyria should be suspected when severe abdominal pain of unknown cause is accompanied by other symptoms that suggest central, peripheral, or autonomic nervous system involvement (Fig. 1). In addition, acute porphyria should be considered when factors often associated with attacks are present, such as female sex, luteal phase of the menstrual cycle, weight loss, alcohol abuse, stress, infection, or porphyrinogenic drugs which can induce porphyria attacks (the database for porphyrinogenic drugs can be accessed on www.drugs-porphyria.org).[11,17,51]

In acute porphyria, the most important differential feature is the presence of markedly elevated levels of urine PBG and/or ALA (Fig. 1). Lead intoxication and hereditary tyrosinemia can also present with elevated ALA levels (but normal PBG), and symptoms that are indistinguishable from acute ADP attacks.[56,57] In case of lead intoxication, measuring the blood lead level is definitive for diagnosis. In the case of hereditary tyrosinemia, it usually manifests during infancy or early childhood, whereas acute porphyria is rarely active before puberty.[58]

TREATMENT

Porphyrinogenic drugs can potentially trigger an attack of acute porphyria.[11] Therefore, before initiating any pharmacological treatment in patients with acute porphyria, the Norwegian-IPNET drugs database (www.drugs-porphyria.org) should be consulted to assess the porphyrinogenic potential of the different medications.[59]

Treatment of acute attacks

Acute attacks may progress into severe and potential life-threatening outcomes, if not properly treated. The treatment should be initiated immediately after the manifestation of typical symptoms and detection of increased urinary PBG.[7,60,61]

Hospitalization is usually required, particularly when intravenous therapies and close observation are necessary. When the vital capacity is compromised, admission to an intensive care unit is mandatory. In case of well-characterized patients with a similar pattern of recurrent attacks, and which respond promptly to treatment, management can be performed in outpatient settings.[17]

Treatment should be primarily focused on the suppression of ALAS1 activity, and symptomatic management (Fig. 2). All the potential precipitating factors should be identified and eliminated. For early symptoms of an attack (e.g., mild pain, no paresis), a high carbohydrate diet should be started, if oral intake is tolerated. If not tolerated, carbohydrates can be provided as intravenous 5% dextrose in normal saline up to 2 L per day. Patients should be under regular clinical monitoring, including the evaluation of pain score, neurological function, and plasma sodium levels. If symptoms do not improve or escalate into severe pain, with significant hyponatremia, peripheral neuropathy, urinary retention or incontinence, central nervous system involvement, or arrhythmias, hemin 3 mg/kg daily (up to 250 mg/day) should be intravenously administered for four consecutive days. When hemin is not available, intravenous 10% - 20% glucose in normal saline in up to 2 L daily is indicated.[7,60-66]

Symptomatic treatment should be started as needed (Fig. 2). For mild pain, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are first-line analgesic agents, whereas for severe and unbearable pain, parenteral opioid medications should be administrated. Benzodiazepines, such as lorazepam, can be used to potentiate the analgesic effect and to decrease the concomitant anxiety. Gabapentin and pregabalin should be used when clear neuropathic features are present.[18]

Nausea and vomiting can be effectively managed with ondansetron, chlorpromazine or promethazine, and constipation can be treated with lactulose or repeated enemas. Control of tachycardia and systemic arterial hypertension can be achieved with beta blockers, angiotensin-converting enzyme inhibitors, or calcium channel blockers.[7,61]

Seizures should be treated with benzodiazepines, gabapentin, or levetiracetam; status epilepticus requires sedation with propofol. Careful correction of hyponatremia is necessary, particularly when associated with seizures. In acute porphyria, hyponatremia is commonly linked to SIADH, and its correction should be performed according to the specific guidelines.[67,68] Even though fluid restriction is the best option to treat SIADH, it is poorly tolerated. Infusion with saline solution and loop diuretics are second- and third-line options for SIADH, respectively.[7,61]

Anxiety and insomnia can be managed with low-dose benzodiazepines and hypnotics. Agitation and psychosis should be treated with olanzapine, clozapine, or haloperidol. For depression, fluoxetine, venlafaxine, or duloxetine can be safely prescribed for patients with acute porphyria.[19,61,69]

Long-term treatment

Patient education is a critical aspect of long-term management. Patients should be counseled to avoid or minimize triggering factors and to maintain a balanced diet with an appropriate carbohydrate and caloric intake.[61,64,66] Alongside, management of persistent symptoms and/or the administration of disease-modifying therapies should be individually considered for each patient.

Symptomatic treatment

First-line options for chronic neuropathic pain include the antidepressants duloxetine, fluoxetine, and amitriptyline, and the antiepileptics pregabalin and gabapentin.

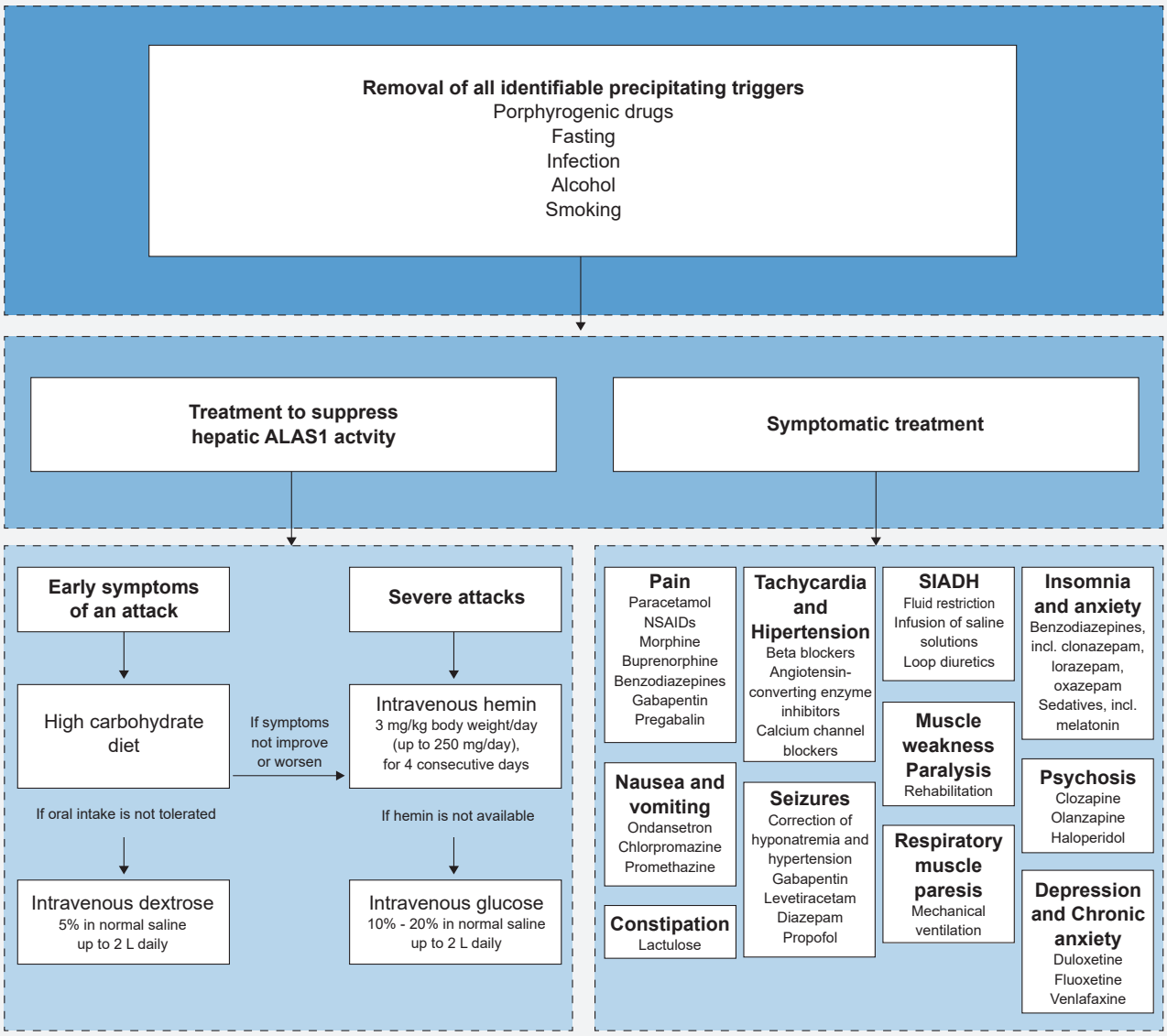

Figure 2 – Treatment algorithm for acute porphyria

Second- and third-line options include tramadol and stronger opioids, like oxycodone and hydrocodone, respectively; but these should be prescribed after evaluating the addiction risk. NSAIDs and paracetamol are only recommended for mild musculoskeletal pain.[18]

Patients with muscular weakness and/or paralysis will need regular intensive physiotherapy for recovery of function, which typically takes six to 12 months. In case of respiratory muscle paresis or failure, artificial ventilation may be needed for a period of several months.[7,61] Other chronic symptoms can be treated with the pharmacological options presented in Fig. 2.

Disease-modifying treatment

Givosiran is a small interfering RNA therapy which decreases the expression of ALAS1 in hepatocytes, resulting in reduced circulating levels of the neurotoxic intermediates ALA and PBG. Givosiran is approved for the treatment of acute porphyrias in patients aged ≥ 12 years, with a recommended dose of 2.5 mg/kg once monthly, subcutaneously.[70-72]

The six-month phase 3 study (givosiran 2.5 mg/kg *versus* placebo),[73] and the 24-month data from the open label extension (givosiran 2.5 mg/kg or 1.25 mg/kg)[74] demonstrated that AIP patients with recurrent attacks treated with givosiran had a significant reduction in acute attacks

number and sustained reduction in urinary ALA and PBG levels, as well as decreased daily pain and improved quality of life.[70,75,76] Real-world experience demonstrated that givosiran prevented recurrent attacks in patients with severe AIP and it is most effective when given early in the disease course.[77] Of note, efficacy and safety data of givosiran in VP, HCP and ADP are limited.

Givosiran has potential adverse effects, especially risk of hepatic, renal and cutaneous adverse effects and of hyperhomocysteinemia.[70,78,79] In the clinical trials, alanine aminotransferase (ALT) elevations were observed between three and six months after starting givosiran; most of these elevations were transient and/or resolved with decreased monthly doses.[70] Givosiran is also associated with an early and reversible decline of renal function; however, it is difficult to distinguish the long-term effects of givosiran from the natural progression of acute porphyria-associated renal disease.[78] The clinical significance of givosiran-associated hyperhomocysteinemia is not completely understood, but can potentially lead to cardiovascular diseases, and pancreatitis. An optimal strategy to minimize hyperhomocysteinemia is being debated, and currently 80 mg/day vitamin B6 seems to be the best available regimen.[79]

Prevention of attacks

Appropriate education of patients to avoid precipitating factors and potential porphyrinogenic drugs is fundamental to preventing acute attacks.[10,58]

Additionally, off-label prophylactic hemin preparations are used in many countries to prevent recurrent attacks. Weekly prophylaxis with hemin (3 - 4 mg/kg) decreased acute attacks and increased quality of life in patients with recurrent attacks.[80,81] Nevertheless, long-term use of hemin may be associated with hepatic iron overload, thrombocytopenia, phlebitis, and tachyphylaxis.[66,80]

In women suffering from catamenial-associated attacks, the use of gonadotropin-releasing hormone agonists to suppress ovulation may provide relief, but most patients experience severe estrogen deficiency side effects.[82] Progestins are identified as triggering agents; therefore, hormonal contraceptives should generally be avoided.[7,10]

For cutaneous manifestations, the treatment should be centered on avoiding sunlight exposure and wearing protective clothing. Dietary supplementation with vitamins C and E may mitigate oxidative damage in VP, although evidence for its benefit is scarce.[83-85]

In extreme cases of recurrent attacks not responding to other therapies, liver transplant could be an option. Liver transplant effectively restores the heme biosynthesis pathway in the liver and is curative. In a study reviewing the European experience with liver transplantation, the one-year and five-year survival rates were similar between AIP patients and patients who received transplants for other metabolic diseases for an equal period. Improved porphyria-related neuropathy was observed, but severe neuropathy and advanced pretransplant renal impairment increased the risk of poor outcomes.[86] Overall, given the shortage of donors and the high risks associated with the procedure, this option should be reserved as the final option.[7,65]

MONITORING

Monitoring of patients with acute porphyria must be individualized, and it is paramount to prevent acute attacks, hospitalization, and long-term complications.

Patients should receive proper information about their disease, potential porphyrinogenic drugs, and precipitating factors. Signs and symptoms during and between attacks, medications, and potential precipitants should be thoroughly documented in the electronic health records of the patient. In addition, symptomatic patients should be routinely monitored for acute porphyria activity, long-term complications, and treatment safety through laboratory and other diagnostic tests (Table 3). Asymptomatic patients should be monitored annually.

Pregnancy increases the susceptibility of women to acute attacks, although most patients have completely normal pregnancies.[87] A pre-conception evaluation is recommended, and patients should be followed by an obstetrician during pregnancy and during the postpartum period.[7,87]

RECOMMENDATIONS FOR FAMILY STUDY

Patients with acute porphyrias are likely to have genetically affected relatives, who are often asymptomatic. Family screening to identify those with latent disease is essential to minimize their risk of acute attacks.[7,8,32]

DNA analysis is the method of choice; once the familial mutation is identified, first-degree family members should undergo reliable targeted mutation analysis.[17,50] Relatives who have inherited a pathogenic mutation are at risk for developing symptoms, and therefore they should be properly educated on how to recognize disease symptoms early on and avoid precipitants. At-risk patients with an acute porphyria mutation should be evaluated clinically and undergo biochemical testing to assess disease activity annually.[47]

PATIENT REFERRAL

In Portugal, patients with a diagnosis or suspicion of acute porphyria should be referred to the reference centers for inherited metabolic disorders (RC-IMD; Centros de Referência de Doenças Hereditárias do Metabolismo). There are 5 RC-IMDs, namely Centro Hospitalar e Universitário de Coimbra, Centro Hospitalar e Universitário de Lisboa Central, Centro Hospitalar e Universitário de Lisboa Norte, Centro Hospitalar e Universitário de São João, and

Table 3 – Monitoring of patients with acute porphyrias[5-7,10,17,20,38,41,58,61,70]

Parameter	Frequency	
	Symptomatic patients (≥ 1 attack within the last 2 years)	
	Sporadic attacks (1 - 3 attacks/year)	Recurrent attacks (≥ 4 attacks/year)
Clinical monitoring		
Clinical history of acute porphyria manifestations	Every 6 months	Every 3 months
Physical examination	Every 6 months	Every 3 months
Medication review	Every 6 months	Every 3 months
Quality of life	Every 6 months	Every 3 months
Laboratory monitoring		
Biomarkers for acute porphyria Urine ALA and PBG	Every 6 months and as clinically indicated	
Exosomal ALAS1 mRNA	As clinically indicated – investigational biomarker (still not available in clinical routine)	
Standard blood and urine tests Complete blood count Comprehensive metabolic panel Renal function panel Hepatic function panel	Every 6 months and in acute attacks	
Plasma homocysteine*	Annually	
Alpha-fetoprotein	Annually	
If receiving treatment with givosiran Total plasma homocysteine Vitamin B6, B9, B12 Liver function tests Renal function tests	Monthly for the first 3 months Then, every 3 - 6 months	
If receiving prophylactic hemin therapy Ferritin with iron studies	Every 3 months	
Monitoring by complementary methods of diagnosis and therapy		
Brain magnetic resonance imaging	If clinically indicated or annually in symptomatic patients or with recurrent attacks	
Electromyography	Annually or if clinically indicated	
Holter monitoring	Annually	
TILT test	Annually	
Abdominal ultrasound	Annually	
Renal ultrasound	Annually	
Ambulatory Blood Pressure Monitoring	Annually	
Echocardiogram	Annually	
If receiving GnRH analogue Dual-energy X-ray absorptiometry Gynecological screening	 Annually Annually	
Asymptomatic patients (no attacks within the last 2 years) should be monitored annually		

* If homocysteine persistently elevated perform genetic test for homocystinuria

Centro Hospitalar e Universitário do Porto.[88] The RC-IMDs provide an initial porphyria screening, which includes assessment of PBG, ALA, and urinary porphyrins. For complete and accurate biochemical and genetic testing, the samples should be sent to Unidade de Rastreio Neonatal, Metabolismo e Genética (URN) - Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA, Porto).

Patients with acute porphyria should be followed by a core multidisciplinary team with an internist or pediatrician, neurologist, psychiatrist, and dermatologist. Additional

support may be required from a nephrologist, cardiologist, gastroenterologist, geneticist, gynecologist and/or hematologist. Social care support, a psychologist, and a nutritionist should also be involved in patient care. All healthcare team members should have a solid background in porphyria.

An online database is currently being developed for the epidemiological registry of patients with acute porphyrias in Portugal. For additional information on this database and how to register acute porphyria patients, use the following email address: registonacionaldasporfirias@outlook.pt.

CONCLUSION

Given the rarity of acute porphyrias and their heterogeneous and often non-specific presentation, patients remain undiagnosed or misdiagnosed with other medical conditions. A delay of several years usually occurs between symptom onset and the diagnosis. Therefore, increasing awareness of acute porphyrias among healthcare professionals is essential for making an earlier diagnosis and initiating rapid and accurate treatment. In addition, new evidence on breakthrough therapies is emerging. In this consensus paper, guidance is provided for a timely diagnosis of acute porphyrias, as well as evidence-based recommendations for the treatment and monitoring of patients and their families.

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AUTHOR CONTRIBUTIONS

LBA: Coordination of the project, study design, and writing of the manuscript.

LP, AO, FiF, PF, ICR, EC, FaF, AAP, PM, SM: Study design and writing of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

COMPETING INTERESTS

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