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# Genetic and clinical approach in acute intermittent porphyria and porphyria cutanea tarda.

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## Abstract

This article examines the genetic and clinical features of two main types of porphyrias: acute intermittent porphyria (AIP) and porphyria cutanea tarda (PCT). AIP, a common hereditary disorder in young women, is characterized by severe neurovisceral crises, with abdominal pain, neuromuscular dysfunction and psychiatric disturbances, which are caused by mutations in the HMBS gene, affecting heme synthesis, causing intense symptoms in the nervous and gastrointestinal systems. PCT manifests mainly in adults, associated with photosensitivity, skin lesions and risk of hepatocellular carcinoma, resulting from deficiency of the enzyme uroporphyrinogen decarboxylase (UROD), which causes an accumulation of photosensitive compounds in the skin and liver.

The importance of genetic sequencing tests to identify possible alterations in the specific HMBS and UROD genes, essential to confirm the diagnosis and facilitate appropriate treatment, is emphasized. The need for early diagnosis and management of triggering factors to reduce morbidity and improve patients' quality of life is highlighted. The findings emphasize the importance of increasing the investigation of these pathologies, given that the initial symptoms may confuse the diagnosis, delaying detection and increasing the risk of complications.

**Keywords:** Porphyria; Pseudo scleroderma; Porphyrin; Genes

## 1. Introduction

The word “porphyria” derives from the Greek “porphyra”, meaning purple, named after the red color of urine when exposed to sunlight as a result of the polymerization of porphobilinogen. This disease arises from a heterogeneous group of metabolic disorders, which are caused by enzymatic deficiency in the biosynthesis of the heme group, which is incorporated into hemoglobin and myoglobin and interferes with aerobic metabolism and the production of adenosine triphosphate (ATP), caused by deficiency of the enzyme porphobilinogen deaminase, also called hydroxymethylbilane synthase [1, 2].

The accumulation of porphyrin precursors (delta-aminolevulinic acid and porphobilinogen) causes the neuro-visceral crises of acute porphyria, which leads to severe abdominal pain when expressed clinically. During the crisis, porphobilinogen and delta-aminolevulinic acid are released via the urinary tract. The high concentration of porphobilinogen in urine is measured with the Hoesch test [2].

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The main clinical manifestations occur at birth or early childhood [3, 4] and with similar frequency in females and males [3].

Among the most common manifestations are blistering lesions, which begin in adulthood and are expressed as subepidermal vesicles, blisters and erosions that form crusts and heal slowly; this is related to sun exposure, especially on the face and hands. Other findings manifested in the skin are milia, scarring, skin thickening (pseudo scleroderma) and areas of decreased and increased skin pigmentation [5, 6].

Abdominal pain is characteristic of this pathology, may be accompanied by constipation, back pain, chest and limb pain. In addition, signs and symptoms such as anxiety, seizures, motor neuropathy, muscle weakness with evolution to quadriparesis and respiratory paralysis develop. Acute attacks can be severe with a high probability of mortality [5].

Seizures are caused by exposure to endogenous and exogenous factors, however, it is difficult to determine the origin of these or a specific causative agent is not identified [7]. The main manifestation is pink to dark red coloration of the urine. Hemolytic anemia is common and can be mild to severe [4].

Porphyrin deposition can lead to corneal ulcers and scarring, reddish brown coloration of the teeth (erythrodontia), and bone loss or bone marrow expansion. However, the clinical manifestations are diverse, ranging from non-immune hydrops fetalis in utero to late disease with cutaneous manifestations in adulthood [4]. The onset of acute attacks most commonly occurs between the second and third decade of life [7].

There are several types of porphyrias, which differ in both their genetic origin and clinical manifestations (Table 1).

**Table 1** Genes, enzymes and clinical manifestations involved in some types of porphyria [8-15]

| **Name** | **Clinical features** | **Gene involved** | **Enzyme involved** |
|---|---|---|---|
| Porphyria Cutanea Tarda (PCT) | Light-sensitive dermatitis in adulthood<br>Large amounts of uroporphyrin excretion<br>Ulcerative lesions (blisters)<br>Hyperpigmentation<br>Hypertrichosis | UROD (1p34.1) | UROD (Uroporphyrinogen decarboxylase) |
| Porphyria Variegata (VP) | Photosensitivity<br>Blistering<br>Fragility of the skin with chronic scarring of exposed areas<br>Hyperpigmentation (post-inflammatory)<br>Hypertrichosis<br>Abdominal pain<br>Constipation<br>Tachycardia and hypertension<br>Muscle paralysis<br>Sensory disturbances | PPOX (1q22) | PPOX (Protoporphyrinogen oxidase) |
| Acute Intermittent Porphyria (AIP) | Abdominal pain<br>Constipation<br>Urinary retention<br>Paresthesias<br>Paralysis (respiratory) | HMBS (11q23.3) | PBG deaminase (Porphobilinogen deaminase) |
| Hereditary Coproporphyria | Excessive coproporphyrin III excretion<br>Constipation<br>Abdominal colic | CPOX (3q12) | CPOX (Coproporphyrinogen oxidase) |

| | | | |
|---|---|---|---|
| Erythropoietic Protoporphyria | Light-sensitive dermatitis (childhood, before 10 years)<br>Itching<br>Burning<br>Erythema due to exposure to bright light | FECH (18q21.3) | FECH (Ferrochelatase) |
| Hepato erythropoietic porphyria | Severe photosensitivity<br>Blistering rash followed by scarring<br>Prominent hypertrichosis<br>Dark brown urine | UROD (1p34.1) | UROD (Uroporphyrinogen decarboxylase) |

Two of these porphyrias, AIP and PCT, have been identified as having the highest incidence in the population and are therefore of special interest. Thus, understanding the distinctive characteristics of these diseases is essential for an accurate diagnosis and proper management of patients, as well as allowing us to differentiate them from other diseases with similar symptoms and to establish an accurate diagnosis.

## 2. Acute intermittent porphyria (AIP)

Most cases of acute intermittent porphyria are the result of mutations in the HMBS gene, this gene encodes the enzyme hydroxymethylbilane synthase (also called porphobilinogen deaminase). Located on chromosome 11q23.3 of the long arm [16].

Acute intermittent porphyria (AIP) has an autosomal dominant inheritance, which means that it is sufficient for only one mutated copy of the gene to be present for a person to develop the disorder.

This enzymatic defect causes an excess accumulation of porphyrin precursors, which will have negative effects mainly in the central nervous system (CNS), peripheral nervous system (PNS), as well as in the digestive system.

Acute attacks are more frequent in post-pubertal women and are usually triggered by certain factors, including drugs, infections, fasting, alcohol and steroid hormones [17].

**Table 2** Classification of AIP according to frequency of attacks and urine porphobilinogen (PBG) levels [7]

| **Active AIP** | **Occurrence of an attack in the last two years.** |
|---|---|
| Symptomatic high excretor | No attacks in the last two years, with prolonged chronic expressions. |
| Asymptomatic high excretor | No attacks and no expressions |
| Asymptomatic AIP | No expressions in the last two years, one attack has occurred in the past. |
| Latent AIP | No demonstrations |

It is a rare disease, but it is the most common of the porphyrias, with a prevalence of 1:2,000 and incidence of 1:1,000. It mainly affects women between 18 and 40 years of age (1.5-2 :1) [18].

Heme production is highest in the erythroblastic system and liver. The imbalance of production leads to the accumulation of toxic substances that manifest themselves in neurological and psychiatric symptoms [19]. They manifest in three progressive stages: prodromal, visceral and neurological symptoms, beginning with nonspecific symptoms such as nausea and fatigue, progressing to severe abdominal pain, and culminating in neuropsychiatric complications [20].

Diagnosis is difficult due to the lack of specific symptoms; its treatment consists of administering hematin intravenously, although in severe cases this may not be sufficient to prevent complications [21]. Prevention focuses on triggering factors, and the administrationof hemo, therapies such as Givosiran regulate the production of substances involved in the disease, and prolonged follow-up includes monitoring liver function to detect complications such as liver cancer [22] (Table 3).

**Table 3** Clinical Manifestations AIP [23-30]

| **Organ/Region** | **Clinical Manifestations** |
|---|---|
| Abdomen and Digestive System | Abdominal pain<br>Constipation<br>Vomiting<br>Nausea<br>Cloudy urine without hematuria<br>Red urine<br>Choluric urine<br>Emesis<br>Metrorrhagia<br>Hematuria |
| Respiratory System | Hypoxemic respiratory failure<br>Apnea<br>Difficulty in swallowing and speaking<br>Respiratory difficulty<br>Tachypnea<br>Pulmonary hemorrhage |
| Cardiovascular System | Tachycardia<br>Hypertension<br>Sinus tachycardia |
| Neurological System | Asthenia<br>Areflexic flaccid, quadriparesis flaccida<br>Generalized tonic-clonic seizure<br>Hypoosmolar hypovolemic hyponatremia<br>Proximal tetraparesis<br>Adynamia<br>Tetraparesis of proximal and greaterinvolvement in upper extremities.<br>Comic tonic-clonic seizures<br>Motor axonal polyneuropathy<br>Tetraparesis with total dependence<br>Progressive tetraparesis with hyponatremia<br>Comic seizure<br>Horizontal nystagmus<br>Diplopia in lateral visual fields<br>Proximalmotor neuropathic disorder<br>Paresthesia and tremors in lower extremities<br>Bilateral facial palsy<br>Porphyria crisis<br>Bulbarinvolvement<br>Cranial nerve disorders with dysphoniaand dysphagia<br>Nervousness<br>Emotional lability<br>Psychomotor agitation Mental confusion Psychiatric alterationsNeuropathic pain in extremities |

| | |
|---|---|
| Endocrine/Metabolic System | Severe hyponatremia<br>Hyponatremia Hypoosmolar<br>Hypokalemia<br>Hypochloremia<br>Hypomagnesemia<br>Hypophosphatemia<br>Hypocalcemia<br>Severe electroyte disturbances |
| General/Muscular | Myalgia<br>Asthenia<br>Progressive tetraparesis |

## 3. Porphyria cutanea tarda (PCT)

It is a rare liver disorder that mainly affects the skin, causing recurrent blistering and scarring in sun-exposed areas that do not hurt [31]. Especially on the hands, the skin becomes fragile in minor trauma, hypertrichosis and facial hyperpigmentation, thickening of the skin and increases the risk of hepatocellular carcinoma [32].

This type is the most common in adults; acquired PCT (PCT type 1) and inherited PCT are recognized in those individuals with a genetic predisposition to develop the disorder (PCT type 2 or familial PCT). However, the fact that individuals present the genetic mutation does not mean that they will develop symptomatic PCT, since, although the mutation is a predisposing factor, it is not sufficient, since triggering factors are necessary for the development of the disorder in these individuals [33] , this disorder is caused by an enzymatic deficiency of uroporphyrin decarboxylase (UROD), accumulating photosensitive substances that spill into the blood circulation and are excreted in the urine. There are different factors that can trigger it, such as hormonal therapies, hemodialysis, alcohol, viral hepatitis, which lead to an excess of iron. It is associated with hematological diseases such as multiple myeloma, chronic lymphocytic leukemia, hairy cell leukemia, thalassemia, chronic myeloid leukemia and acute myeloblastic leukemia [34] (Tables 4 and 5).

It affects 1:10 000 people, mainly adults of both sexes [35].

**Table 4** Classification of PCT [36]

| **Type of porphyria cutanea tarda** | **Features** |
|---|---|
| PCT type 1 "sporadic". | Sporadic type<br>More common<br>Normal UROD levels<br>Reduced UROD activity in liver |
| PCT type 2 "family" | Hereditary origin<br>Reduced enzyme activity in all cells |
| PCT type 3 | Similar to PCT type I<br>UROD deficiency is limited to the liver.<br>Possible environmental causes |

**Table 5** Clinical manifestations PCT [37-41]

| Organ/Region | Clinical manifestations |
|---|---|
| Integumentary system | Skin lesions Skinfragility Generalized pruritus<br>Light-sensitive dermatitis<br>Ulcerative lesions<br>Blisters<br>Hyperpigmented areas<br>Hypopigmented areas<br>Hematic crusts<br>Erosions |
| Abdomen | Erosive, vesicular and painful lesions. |
| Upper extremities | Limitation of mobility in interphalangealjoints in both hands<br>Erosive, vesicular and painful lesions worsenwith sun exposure.<br>Ulcerative lesions<br>Broken blisters on back of both hands |
| Liver | Marked steatosis<br>Micronodular incipient cirrhosis<br>Hepatic volume reduction Venous short-circuit in the falciform ligament |
| Lower extremities | Erosive, vesicular and painful lesions worsenwith sun exposure. |
| General/Articular/Muscular | Arthralgias |
| Urinary system | Porphyrins in urine<br>Venous short-circuit in spleno-renal ligament |

## 4. Conclusion

The porphyrias are a group of metabolic disorders that can have a profound impact on patients' quality of life, from painful crises to chronic complications, even life-threatening. This article has focused on two main types: acute intermittent porphyria, which most often affects women, and porphyria cutanea tarda, which occurs mainly in adults. Both present with varied symptoms that in some cases are debilitating. It is essential to increase awareness of porphyrias among health professionals and the general population to achieve a more timely diagnosis and proper management, as initial symptoms such as abdominal pain can be confused with other pathologies. The lack of specific tests and the low incidence make detection even more difficult, highlighting the need for more research and awareness to enable timely care.

To achieve an accurate diagnosis, DNA sequencing tests can identify mutations in specific genes associated with different types of porphyria, the ALAD, HMBS, UROS and UROD genes, confirming the presence of the disease, which is essential for adequate treatment of the disease. The analysis of mutations in individuals with a family history or populations with a high prevalence accelerates the process and reduces costs. The importance of promoting access to genetic testing and research in this area is emphasized, in order to improve the clinical management and quality of life of patients with these pathologies.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

There is not conflict of interest to declare.

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