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CASE REPORT

Acute intermittent porphyria in a 23-year-old man: case report

Porfiria intermitente aguda em um homem de 23 anos: relato de caso

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ABSTRACT

Introduction: Porphyrias are metabolic disorders caused by enzymatic alterations in the biosynthesis of the heme group of heme proteins. The clinical spectrum of porphyrias is associated with the location of the damage in the heme formation chain, which can range from neurovisceral manifestations to cutaneous alterations related to photosensitivity. The diagnosis of this pathology can be difficult since it is a rare disease and the symptoms are nonspecific. **Objectives:** The present study reports the diagnosis steps and clinical suspicion of a case of acute intermittent porphyria. **Case Report:** A 23-years-old male patient initially presented with nonspecific abdominal pain to the Emergency Room of Hospital João XXIII (Belo Horizonte/MG). The diagnostic investigation became more directed because of the positive family history for porphyria; until this information was provided, approaching the case was challenging. Diagnostic accuracy is essential considering the risk of using medications commonly used in the Emergency Room and which are aggravating for porphyria. The case was managed with symptom support and caloric intake until the medication (hematina) was acquired through judicialization. **Conclusion:** Acute hepatic porphyrias are a group of rare diseases with severe and nonspecific manifestations. However, patients with unexplained abdominal pain, mainly associated with neuropsychiatric symptoms and positive family history, should be screened for urinary porphyrins because recognizing the disease is essential, and hematin therapy should be promptly introduced.

Keywords: Acute intermittent porphyria; Acute abdominal pain; Hematin; δ-aminolevulinic acid; porphobilinogen.

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RESUMO

Introdução: Porfirias são desordens metabólicas causadas por alterações enzimáticas na biossíntese do grupo heme de heme-proteínas. O espectro clínico das porfirias associa-se à localização do dano na cadeia de formação do heme, podendo variar de manifestações neuroviscerais a alterações cutâneas relacionadas à fotosensibilidade. O diagnóstico desta patologia pode ser laborioso considerando-se a sua raridade e a inespecificidade dos sintomas. **Objetivos:** O presente estudo relata as etapas diagnósticas e a suspeição clínica diante de um caso de porfiria intermitente aguda. **Relato de Caso:** Um paciente do sexo masculino de 23 anos se apresentou inicialmente com uma dor abdominal inespecífica no Pronto Atendimento do Hospital João XXIII. A investigação diagnóstica tornou-se mais direcionada diante da história familiar positiva para porfiria e até a percepção dessa informação houve dificuldade na abordagem do caso. A precisão diagnóstica torna-se fundamental considerando-se o risco de uso de medicações comumente usadas no pronto-socorro e que são agravantes para a porfiria. O caso foi manejado com suporte de sintomas e aporte calórico, até a aquisição da medicação definitiva (hematina) por meio de judicialização. **Conclusão:** As porfirias hepáticas agudas são um grupo de doenças extremamente raras e com manifestações graves e inespecíficas. Entretanto, pacientes com dores abdominais sem causa aparente, principalmente associada a sintomas neuropsiquiátricos e história familiar positiva, devem ser submetidos à pesquisa de porfirinas urinárias, porque o reconhecimento da doença é essencial e a terapia com hematina deve ser prontamente instituída.

Palavras-chave: Porfiria intermitente aguda; Dor abdominal aguda; Hematina; Ácido δ-aminolevulínico; Porfobilinogênio.

Introduction

Acute intermittent porphyria (AIP) is a member of a rare family of blood disorders resulting from a partial deficiency of the enzyme porphobilinogen deaminase (PBGD), which is involved in the biosynthesis of the heme group[1-3]. The impaired function of PBGD leads to the accumulation of heme synthesis intermediates such as δ-aminolevulinic acid (ALA) and porphobilinogen (PBG)[4]. These two metabolites induce biochemical changes and degeneration of central and peripheral nervous systems[5]. Therefore, AIP manifests as a neurovisceral disease with a multisystem clinical spectrum and, therefore, the symptomatologic pattern is nonspecific and widely variable[2,5].

Genetically, AIP is characterized by an autosomal dominant inheritance with low penetrance in which symptoms are affected by various exacerbating factors[3]. Despite its well-characterized molecular genetics, the diagnosis of AIP is challenging because it is a rare disease with nonspecific symptoms, thus presenting multiple possibilities for differential diagnoses[6]. In addition, family history clues may not be evident due to the absence of symptoms in most mutation carriers[3,5,6].

Even if AIP is considered, many physicians are not familiar with the proper workup, which can delay the diagnosis and correct therapeutic management of the disease[7,8]. Thus, this report aims to exemplify and clarify some important points for the diagnosis of AIP to institute an earlier treatment for the patients. In addition, the multidisciplinary health team must be aware of the data available in the literature regarding the possibility of AIP among patients with neurological symptoms.

Case Report

A 23-years-old white male patient was admitted to the Hospital João XXIII emergency department (Belo Horizonte, MG) on January 7, 2022, complaining of abdominal pain,

mainly in the mesogastrium and hypogastrium, which had been evolving for about 20 days from admission. He referred to an episode of vomiting at the beginning of the condition, without recurrence. It was also reported dark/reddish urine and constipation. The patient denied fever or pain complaints in other sites of the body. He had a depressed mood with suicidal thoughts and paresthesia in the lower limbs. Previous history of smoking, alcoholism, cocaine abuse, and hypertension, without being able to specify the time of diagnosis or use of antihypertensive drugs. Furthermore, he reported hospitalization for 1 week in the previous year due to similar abdominal pain.

Initially, an acute inflammatory abdomen was questioned, using empirical ceftriaxone and metronidazole for three days (January 8 to 11, 2022). Imaging workup at admission ruled out the acute abdomen and mesenteric ischemia, with abdominal ultrasound and upper digestive endoscopy findings within the normal range and computed tomography angiography of the abdomen and pelvis only with nonspecific pulmonary findings (e.g., mucoid secretion in bronchi and centrilobular nodules). Regarding laboratory alterations, the hypothesis of the nephritic syndrome was initially questioned due to findings of hematuria, arterial hypertension and increased renal slag. However, these findings normalized in later examinations and the serum complement dosage was within the normal range. A workup was also requested for hepatitis B and hepatitis C, with negative HbsAg and anti-HCV. HIV serology was also negative. Autoantibodies, such as anti-nucleus factor and anti-streptolysin O antibody, were also negative.

Later analysis revealed a positive family history of porphyria (probable diagnosis of his sister, who died at the age of 17 due to complications from this disease). In this scenario, the diagnostic hypothesis of porphyria was considered by adding the family history to the clinical findings of abdominal pain, vomiting, constipation, hypertension, renal failure, brownish urine, paresthesia, and psychiatric alterations. In partnership with external laboratories, qualitative measurement of PBG and ALA was performed in 24-hour urine. The result was positive, establishing the definitive diagnosis of acute porphyria (Table 1).

Faced with the probable diagnostic of porphyria (while there was still no official result for ALA and PBG), symptoms were managed with medication adjustment according to lists of non-harmful drugs found on the website of ABRAPO (*Associação Brasileira de Porfiria*), UpToDate and the Potentially safe Medication List from the UK Porphyria Medicines Information Service (UKPMIS) and Cardiff Porphyria Service. The list of allowed drugs was attached to the patient's medical record, and the team was instructed, as well as the patient himself, about the risk of improper medication.

The patient showed improvement in symptoms with the initial palliative treatment, given the difficulty in acquiring Hematin. The disease management focused on oral and intravenous morphine-based analgesia, a controlled diet under follow-up with a nutritionist (intake of 300 g/day of carbohydrates), physical therapy and psychiatric support (using nortriptyline associated with psychotherapy). He was discharged for outpatient follow-up with the internal medicine and pain outpatient clinic. The results of the ALA and PBG tests were released in February 2022. Given the diagnostic confirmation, a report was made so that the patient could acquire the Hematin through judicialization.

Discussion

Porphyrias are hereditary diseases characterized by the deficiency of enzymes involved in the synthesis of heme, which constitutes the nucleus of molecules called heme-proteins (e.g., hemoglobin and myoglobin)[1]. The deficiency of any of the eight enzymes involved in this anabolic chain causes the accumulation of its precursors. The intermediates that accumulate begin to reach toxic levels, and depending on the deficient enzyme – and consequently on which metabolite is concentrated – different clinical conditions are triggered[1,9]. In most cases, the porphyria-causing mutation affects the gene that encodes some enzyme relevant to heme synthesis. However, the mutation can also affect a regulatory gene, not the enzyme itself[10,11]. In this study, we did not verify the origin of the patient's genetic mutation.

Four of the eight existing porphyrias produce clinical manifestations restricted to the skin[11], and the other four can cause acute attacks with systemic manifestations, therefore classified as acute porphyrias[12]. Within this last group, AIP stands out, which etiology is linked to the loss-of-function mutation of the PBGD enzyme[1-8]. This is the third enzyme in the heme biosynthetic pathway, encoded by two distinct mRNA species expressed in a tissue-specific manner from a single gene[4]. Different classes of mutations have been described to influence the level of this protein, suggesting that it is a heterogeneous disease[3,12].

Table 1. Results of δ-aminolevulinic acid (ALA) and porphobilinogen (PBG) measurements in the patient's 24-hour urine.

Biomarker	Concentration		Dosage method
	Result	Reference value#	
δ-aminolevulinic acid	>12mg/g creatinine	4.5mg/g creatinine	Colorimetric
Porphobilinogen	30.4mg/24h	<2mg/24h	Spectrophotometric

Legend: *The 24-h urine volume was 1,400mL; # The reference values recommended in NR 7 (Occupational Health Medical Control Program) of the Ministry of Labor published on December 29, 1994, were considered.

AIP has a prevalence of 1-2 cases per 100,000 inhabitants, but we must consider limiting factors for this estimation, such as geographic differences, undiagnosed cases, and incomplete penetrance[13]. Approximately 80% of people with this disorder remain asymptomatic. Among the symptomatic individuals, the disease rarely manifests before puberty, being common in women over thirty years of age exposed to situations or factors that predispose to a decrease in enzymatic activity[3,13]. This epidemiological profile can help justify the diagnosis of the patient in this case report only during adulthood (23 years old).

Porphyritic crises constitute a critical medical emergency, occurring when the triggering factors are not removed or controlled[1,9,11]. They usually present with continuous severe abdominal pain, accompanied by neurological manifestations such as paresthesia, paralysis, and coma. Furthermore, if not treated early, they can cause death or leave irreversible neurological sequelae[5,6,12]. In the case of AIP, there are four groups of precipitating factors that can trigger an acute symptomatic crisis. These include certain drugs and medications, steroids, fasting, and infections[1,6,13]. The report of the use of amphetamines (heroin) by the patient in this study may be associated with a porphyritic crisis presented by him during admission to our health care center.

Despite the symptomatological picture being quite broad and nonspecific, AIP presents some relevant signs. Abdominal pain is the most frequent symptom. This pain is diffuse and not localized and is often accompanied by other symptoms such as nausea, vomiting, distention, constipation, and sometimes diarrhea[14]. In this case, we see many of these signs during patient admission. Other symptoms include insomnia (often an early symptom), palpitations, seizures (sometimes due to hyponatremia), restlessness, hallucinations, and other acute psychiatric symptoms as reported in this case report (i.e., depression and suicidal thoughts)[13]. Hyponatremia may result from the involvement of the hypothalamic centers and inadequate secretion of antidiuretic hormone[13] or even from excessive loss of sodium through the gastrointestinal and/or renal pathways[14]. Neuropathy in AIP is predominantly motor and is recognized by distal paresis, with characteristic wrist drop and foot drop. Paresis is often symmetrical but may be asymmetrical or even markedly focal. Mild sensory manifestations often accompany motor neuropathy, with areas of paresthesia, dysesthesia, and loss of sensitivity[5,15].

Among the main acute complications of AIP, the sudden death of presumably arrhythmogenic origin stands out[13]. A severe attack can also progress to peripheral neuropathy, which sometimes resembles Guillain-Barré syndrome[5,15]. Long-term complications include chronic arterial hypertension and renal and liver failure[2]. Some patients experience chronic neuropathic pain, which may be responsible for an increased risk of depression and suicide[6], as observed in our patient.

The most effective standard treatment for several decades has been the administration of human hemin (hematin)[7-9]. Hemin, the final product of the heme metabolic chain, inhibits the reactions of synthesis of this molecule by a negative feedback mechanism, preventing the accumulation of toxic intermediate metabolites (ALA and PBG). When administered early in acute crises, hemin prevents the progression of neurological lesions, enabling the reversal of the condition and often saving the patient's life[16]. Treatment with hemin should not be delayed in the search for diagnostic confirmation. However, samples for laboratory tests should be collected before the start of therapy, considering that the urinary levels of PBG and porphyrins in the urine will decrease[1]. Due to the therapeutic benefits provided by hemin, the patient in the present report was guided to treatment with this drug, requiring access through judicialization.

However, other therapeutic options are currently available to treat AIP and can be considered in cases of unavailability of hemin. Givosiran is a small interfering RNA (siRNA) that inhibits hepatic aminolevulinate synthetase 1 (ALAS1), which acts on heme synthesis, reducing the accumulation of toxic metabolites (ALA and PBG)[17]. Another therapeutic option is the intravenous infusion of carbohydrates. This strategy can be used as a provisional measure, but not definitive, as its therapeutic effects are more discreet than those of hematin and givosiran[7-9]. Glucose and other carbohydrates inhibit ALA synthetase, with a consequent decrease in the formation of ALA and PBG[18]. The amount of carbohydrates should be 300 grams daily, and administration is usually well tolerated. However, the infusion of glucose solution can increase the risk of hyponatremia and hyperglycemia, with the need for monitoring such disorders by clinical examinations and regular monitoring with laboratory measurements[8].

After a properly treated crisis, patients should be informed which medications they cannot use and some recommendations for specific lifestyle changes. If these measures are carried out, it is possible that, in most cases, new crises will be prevented[1,13]. For this reason, we guided the multi-professional team and the patient on the therapeutic and nutritional substances that should be avoided.

Conclusion

Acute hepatic porphyrias are a group of extremely rare diseases with severe and nonspecific manifestations, thus lacking a high degree of suspicion for the diagnosis. Patients with unexplained abdominal pain, mainly associated with neuropsychiatric symptoms and a positive family history, should be tested for urinary porphyrins. Recognition of the disease is essential, and hematin therapy should be promptly instituted in crises. Patient education about triggering factors of acute crises is essential to prevent their recurrence.

Copyright

Authors' Contribution

We describe contributions to the papers using the taxanomy (CRediT) provide above. All authors contributed in all phases of protocol execution and writing of the work. Conceptualization, Investigation, Methodology, Visualization & Writing – analysis and editing, Project Management, Supervision & Writing – original draft, Validation, Software, Data Curation & Formal Analysis.

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