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PORPHYRIA VARIEGATA AND PROTOPORPHYRINOGEN OXIDASE (PPOX) GENE: A CASE REPORT AND LITERATURE REVIEW

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Abstract: Variegated porphyria (VP) is a rare hereditary disease caused by mutations in the protoporphyrinogen oxidase (PPOX) gene. This deficiency is associated with the accumulation of porphyrins and porphyrin precursors in the body, which in turn can potentially result in a variety of cutaneous and neurological symptoms.
Keywords: Porphyria Variegata, PPOX gene.

INTRODUCTION

Porphyrias are a group of rare genetic metabolic disorders that are characterized by a wide range of clinical symptoms based on specific subtypes. This disease is associated with the overproduction of porphyrins due to genetic mutations of enzymes involved in the heme biosynthetic pathway. Variegated porphyria (VP) is part of a group of porphyrias caused by mutations in the protoporphyrinogen oxidase (PPOX) gene, the enzyme that catalyzes the penultimate step of heme synthesis, is defective, leading to the accumulation of porphyrin precursors that manifest as symptoms. neurological, dermatological and abdominal.

The typical prevalence of PV is 0.5 per 100,000; however, its prevalence in South Africa is as high as 3 per 1,000. In the world with order, affecting about 1 in 200,000 of the general population. Medically, it is administered with pain management as well as hemin infusions that inhibit ALA Synthase1, the rate-limiting step of heme synthesis that converts succinyl-CoA and glycine to aminolevulinic acid so that toxic heme precursors do not accumulate and cause pain or neurovisceral symptoms.

This defect is associated with the accumulation of porphyrin or its precursors and results in a variety of symptoms that vary from one person to another. Patients may present with cutaneous and neurological symptoms. Common skin symptoms include

fragility and blisters on sun-exposed skin, but vomiting, nausea, constipation, abdominal pain, anxiety, restlessness, and seizures, as well as pain and weakness are the most common neurological symptoms. Studies show that various mutations of the PPOX gene are responsible for VP in different families. Although the PPOX gene mutation is inherited as an autosomal dominant trait, many individuals do not experience any symptoms. Although the incidence of PV is very rare, early diagnosis of different variants and treatment of the disease are important. Here, we report a 7-year-old Iranian boy presenting with multiple clinical features and a homozygous pathogenic variant in the PPOX gene, c.1072G > A (p.G358R).

Porphyrias are hereditary pathologies associated with metabolic defects in the heme biosynthesis pathway. The pathway of heme formation is catalyzed in eight enzymatic stages. When the enzymatic defect is potentially significant, it results in the overproduction, accumulation and excessive excretion of porphyrins and their precursors, mainly delta amino-levulinic acid (ALA) and porphobilinogen (PBG).), which represent an acute form with a neurotoxic effect.

Porphyrias are essentially genetic diseases, with acute porphyrias being inherited in an autosomal dominant pattern that include (PIA, CPH and PV), while acute porphyria due to ALA dehydratase deficiency (PAD) is an autosomal recessive hereditary condition.

Acute intermittent porphyria is the most frequently found acute type in clinical practice, but we highlight Variegated Porphyria. PV is estimated to occur in one out of 150,000 people in Europe, but the prevalence in South Africa is much higher, estimated at 3/1,000 in the white population as a result of a founder mutation that was introduced from the Netherlands in 1688. Da similarly, AIP is estimated to occur in one in 75,000 people in Europe, except Sweden, where the condition is seen in one in 1,000 due to a founder effect.

The prevalence of mutations in Western populations is approximately 1 carrier per 2,000 people. 5,6 However, acute attacks occur in less than 10% of the population at risk; this reflects a key role of environmental factors and possibly genetic modifiers.

CLINICAL MANIFESTATIONS

PV may present with neurological and cutaneous symptoms, and is sometimes referred to as the mixed type. Its clinical manifestations include abdominal pain, neurological symptoms and sensorimotor polyneuropathy. The development of symptoms is associated with several exacerbating factors, from medications to oral ingestion insufficient or stress, in patients with genetic factors.

Porphyric neuropathy is typically described as a motor axonal neuropathy with preceding (a few days to weeks) abdominal pain. Your symptoms, signs, and cerebrospinal fluid (CSF) analysis results are similar to those of Guillain-Barré

An acute porphyric attack can be precipitated by a number of factors, including hunger, certain medications, and hormonal fluctuations. The typical attack begins with severe abdominal pain and autonomic hyperactivity, followed by psychiatric disturbances and possibly neuropathy. While most patients recover well from acute porphyric attacks, neurological complications can occur; these include electrolyte disturbances and seizures, confusional states, autonomic dysfunction, and severe quadriparesis.

We describe the clinical presentation and course of four patients with acute porphyria who presented to a neurology unit in Pretoria, South Africa (SA), for one year, emphasizing that the presentation of acute porphyric neuropathy may be similar to that of Guillain

syndrome. Barré and occur in the absence of acute abdominal pain.

Abdominal pain is the most common symptom of the crisis, being diffuse and nonspecific8 and usually accompanied by nausea, vomiting, constipation or diarrhea; triggered by gastroparesis and pseudo-obstruction by splanchnic neuropathy. Tachycardia is another common manifestation and may precede peripheral neuropathy by several weeks. There may be sphincter dysfunction, diaphoresis, hypertension, and less commonly postural hypotension. Cardiac arrhythmias can occur and are an important cause of death.

Contrary to urban legend, it is not difficult to establish or rule out a diagnosis of AHP as long as doctors or other professionals think about the diagnosis and perform the appropriate diagnostic tests. As in the clinical vignette described, HPA must be considered in any patient, but especially in women of childbearing age who have recurrent and severe episodes of abdominal pain. The pain can also occur in other places, including the back, extremities, or chest, but it's mostly in the abdomen. The first test of choice for diagnosis is a single random urine screening for ALA, PBG and creatinine – not porphyrins. In our experience, the most frequent mistakes are not considering the diagnosis in a timely manner, and ordering a random urine screening for porphyrins instead of ALA and PBG. As described later (in the "Secondary Porphyrinuria" section), many patients without any form of porphyria will have mild to moderate increases in urinary porphyrins, especially coproporphyrins I and III. When these are found in patients with diverse symptoms, including abdominal pain, joint pain, muscle pain, fibromyalgia, anxiety, and chronic fatigue syndrome, these patients are unfortunately labeled as having porphyria when they do not. This often leads patients and their doctors to attribute a multitude of symptoms to an inaccurate diagnosis. Unfortunately, some of these patients had central venous lines inserted and were treated with recurrent infusions of intravenous heme, sometimes with disastrous results.

Another misconception is that the pains and other features of AHP are transient and fleeting; they are not. Instead, they occur with a patient's typical prodrome, with a gradual crescendo. The pain usually lasts for several days and only gradually subsides. Many patients try to treat their recurring, often monthly, attacks during the luteal phase of their menstrual cycles (when progesterone levels are at their highest) with narcotics or other pain relievers and with increases in glucose intake. They try to avoid having to go to the emergency room or urgent care, because often, prompt and appropriate specific treatment with intravenous dextrose and heme and adequate narcotic analgesics is delayed or not provided. These unhappy patients are often labeled as "drug seekers" or pretenders.

The specific type of acute porphyria that is now present is usually established by genetic testing, with sequencing of the four genes that are defective in acute porphyrias (ie ALAD, HMBS, CPOX, and PPOX) (Fig.(Figure 1.1). These tests are commercially available from several laboratories, including Invitae (San Francisco, CA), Mayo Medical Labs (Rochester, MN) and Department of Genetics, Icahn School of Medicine (New York, NY). Another test of considerable use for the diagnosis of PV is the fluorescence of serums diluted at physiological pH. Sera from individuals with PV, especially those with biochemical activity, have a single plasma porphyrin peptide that peaks in fluorescence at approximately 626 nm after excitation by light at 410 nm (the Soret band). In contrast, sera from individuals with biochemically active AIP, CEP, HCP, HEP, or

PCT have emission peaks at approximately 619 nm to 620 nm, while those with EPP or XLP have protoporphyrin emission peaks at approximately 634 nm.

Data are scarce regarding the prognosis of individuals with AHP due to the rarity of the conditions. Previous studies have shown increased mortality in patients with severe clinical manifestations. 22 However, since the introduction of heme therapy, mortality has improved in these patients. Overall, patients may have a good prognosis, especially if the disease remains latent. When diagnosis is made in a timely manner, acute attacks are managed quickly and future attacks are prevented.

Patients with severe, intractable and disabling heme-refractory attacks may be considered for orthotopic liver transplantation (OLT), which has been shown to be curative for these patients. 33 However, due to the high morbidity and mortality associated with TOF, it is considered a treatment of last resort. Furthermore, it was not successful in patients with advanced neuropathy. The effects are also less clear for patients with ADP or severe homozygous HMBS. 34 Some patients with intractable recurrent attacks and end-stage kidney disease have benefited from combined liver and kidney transplantation.

CASE REPORT

A 35-year-old black woman, single, born and residing in Valença-RJ, with a previous history of laparotomy for 5 years, where since then she remained with diffuse, intermittent abdominal pain, associated with changes in bowel habits, without clinical investigation.

She went to the emergency room of Hospital Escola de Valença (HEV) in August / 2021 for the third time in 5 days due to severe abdominal pain, which progressed to cessation of elimination of flatus and feces, uncontrollable vomiting and distension. abdominal. The pregnancy test was negative. A CT scan of the abdomen and pelvis was performed, which showed no pathological changes, as well as ultrasound of the kidneys and urinary tract. In view of the situation, hospital admission was chosen, where initially a N°20 nasogastric tube was placed in siphoning and zero diet. She evolved with improvement in abdominal distension, but worsened after all attempts at oral feeding. It was then opted for exploratory laparotomy on 08/31/2021, considering an obstructive abdomen. In the operative report, the presence of a distended transverse colon with a small adhesion near the splenic angle was described, where lysis of adhesions was performed, without intercurrences.

Patient was referred to ICU in the immediate postoperative period due to protocol measures. She was discharged from the ICU to the ward in 48 hours, with SNG with low output, a liquid diet was introduced, evolving to pasty without intercurrences, and without success with the use of glycerin enema. The patient evolved with progressive hyponatremia without response to venous replacement, and on the fifth postoperative day, the patient evolved with prostration, fever with leukocytosis, desaturation, a significant drop in hematocrit from 11.9 to 6.3, without externalization of bleeding, hyponatremia 116mmol/l, hypertension, tachycardia and red-brown urine, without the presence of red blood cells in the urine analysis 1. Therefore, a protocol for sepsis was opened, transferred again to the ICU and transfusion of 1 packed red blood cell was performed.

The following day, the patient evolved with a sudden deterioration in the level of consciousness, with acute flaccid paralysis, with plegia, hypotonia and hyporeflexia in the limbs, evolving to respiratory failure culminating in the need for invasive mechanical ventilation.

Initially, the diagnostic hypothesis of Guillain Barre Syndrome (GBS) was raised, so a computed tomography of the skull

was performed, within the normal range, followed by CSF puncture which was similar to the GBS picture, protein/cell dissociation (1276g/3cells) and treatment with immunoglobulin 2g/kg for 5 days (450g kg/d) was promptly instituted with no definitive effect. In addition, a serological panel was requested (HIV, syphilis, CMV, Epstein Baar, hepatitis, arbovirus, COVID-19), all negative, and the etiological hypothesis of a reaction to the Astrazene vaccine (RNA) for COVID-19 carried out in July 2021.

However, in the face of abdominal pain, neurological symptoms, severe polyneuropathy without immunoglobulin response, associated with brownish urine without the presence of hematuria, screening for porphyria was requested. Requested urinary porphobilinogen, urinary delta-aminolevulinic acid, salivary genetic test, the last being positive.

What was the closing? At discharge and then are you using any medication? Did you keep up with the follow-up? Are you asymptomatic?

DISCUSSION

Porphyrias are rare hereditary diseases, with subjective complaints that can be used in the simulation scenario. The prevalence of the disease is estimated at 1 in 200,000, but in groups with a South African or Dutch heritage the prevalence is estimated at 1 in 200,000. 300, likely due to a founder mutation in the PPOX1 gene. Recent studies have shown that in 20% of cases, both cutaneous lesions and neurovisceral symptoms are present, similar to the presentation in our case, while up to 60% of cases present only cutaneous symptoms2. The subjective nature of porphyria symptoms2 makes it difficult to distinguish between a patient seeking drugs and a patient who actually needs medical intervention. The main complaints presented in our case: gastrointestinal disorders, neurological complaints, including numbness3 and photosensitive dermatitis, are difficult to confirm in a patient who reports such pain that he does not want to be examined3 or to have lights on.

Variegated porphyria is a very rare, autosomal dominant disease caused by mutations in protoporphyrinogen oxidase. PPOX is one of the key enzymes responsible for the synthesis of heme, as a major part of hemoglobin and other hemoproteins. Porphyrins are essential for the function of hemoglobin. When PPOX is deficient, porphyrins are oxidized to protoporphyrin and coproporphyrin, transported in blood plasma and cause increased skin sensitivity to sunlight. PV symptoms usually begin in adulthood and vary from person to person. It may be associated with cutaneous or neurological symptoms or both. Sun sensitivity, blisters, sores, and discoloration after sun exposure are the most common types of skin symptoms in patients with PV. Acute attacks are neurological symptoms that can occur as a result of exposure to hormonal changes, certain medications and diet. Abdominal pain, nausea, vomiting, diarrhea and constipation are the other symptoms that a person with VP experiences. Muscle weakness, seizures, hypertension, and increased heart rate may also occur. Anxiety and hallucinations have been reported as mental changes.

To the best of our knowledge, few cases with homozygous PV have been reported worldwide. Here, we report the case of homozygous VP with a new mutation in the PPOX gene. Our case had a history of GCT episodes with a history of developmental delay. Similarly, Hif et al., reported a case of PV who developed epilepsy at 5 months and developmental delay. Our case had a rough, hairy facial feature. The most common skin

symptoms in our patient were scars from erosive lesions, hyperpigmentation, fragility and blisters on the skin exposed to the sun, in addition to thickening of the skin of the hands and feet. Limb weakness, leg tremor when walking and brachydactyly were the other findings in this case. Hif et al., reported blisters and fragility of the face and hands, hyperpigmentation, hypertrichosis, erosions, crusting, pigmentation and milia, scarring of sun-exposed areas, as well as shortened, stubby fingers and toes, brachydactyly, developmental delay motor as the most common skin and neurological symptoms in two cases with PV. A previous study reported mental retardation in a 14-year-old girl. A more recent study reported mental retardation and aggressive behavior in an Italian case during long-term follow-up. Shimizu et al., reported a 30-year-old woman with PV who had multiple cutaneous and neurological symptoms. Repeated vesicles and brownish pigmentation in the upper extremities were the most common skin symptoms in this case. Moderate weakness, dysesthesia, and hyperreflexia in all limbs were the most common neurologic findings in this patient. Some studies have reported reddish and dark urine in patients with PV. The existence of amyloid and amyloidosis in a 35-year-old woman with PV who was complicated by end-stage renal failure and gastrointestinal symptoms. A previous study reported a case of young VP with epilepsy, mental retardation and premature adrenarche symptoms, but death occurred later. Hepatocellular carcinoma in PV has been described in at least eight cases with PV, indicating the risk of cancer in these patients. All these data emphasize that there are various cutaneous and neurological symptoms in these patients. There are patients who may have minor symptoms without marked clinical manifestations. The severity of PV symptoms depends on the type of PPOX mutations. Therefore, early diagnosis and treatment of the clinical features of the disease are important to improve the quality of life of these cases. Some studies reported different missense mutations in the PPOX gene that were correlated with the occurrence of PV. A previous study identified two underlying missense mutations in the PPOXgene, consisting of a G-to-A transition in exon 6 (G169E), and a G-to-A transition in exon 10 (G358R), which were correlated with homozygous VP. In another study, they reported two missense mutations (D349A and A433P) in the PPOX gene that may be correlated with PV without clinical penetrance in heterozygotes. Poblete-Gutierrez et al., found two different mutations in exon 7 and exon 13 of the PPOX gene in a 7-year-old boy. More recently, Bonuglia et al. reported a new mutation in the PPOX gene (1061C > T/397G > A) in an Italian case. Another study showed two new mutations in PPOXgene (c. 657–658 insertion and IVS 11–1 G → A transition) in a 36-year-old woman with PV. Therefore, these findings emphasize the importance of molecular genetic testing to find any mutations in the PPOX gene and their correlation with PV occurrence and disease severity.

More importantly, the genetic basis of the disease must be considered. Although no evidence of similar conditions was reported in our patient's family. Therefore, elucidation of the genetic basis in this family is important for genetic counseling. Also, each child of an individual with VP has a 50% chance of inheriting the mutation. Offspring who inherit the PPOX mutation may be more or less severely affected than their parents. Therefore, we believe that the case presented here reinforces the general importance of genetic studies in porphyrias.

FINAL CONSIDERATIONS

Here, we report a case of VP with a mutation in the PPOX gene. Various cutaneous and neurological symptoms can be found in these patients, probably due to different mutations in the PPOX gene. Therefore, further studies are needed to assess the relationship between disease genotype and phenotype. The diagnosis of PV depends primarily on clinical findings, especially cutaneous and neurological symptoms. Once a case is suspected of having PV, extra laboratory tests of urine, blood, and stool may be performed. As most studies have reported elevated protoporphyrin levels in cases of homozygous PV, measurement of protoporphyrin or coproporphyrin in blood, urine, and stool is helpful. However, the most sensitive screening test is the assessment of plasma porphyrin. Genetic testing of the PPOX gene is valuable in confirming the diagnosis of the disease. There may be a relationship between the incidence of PV and consanguineous marriage. Therefore, other considerations are necessary to assess the correlation. Therefore, premarital genetic counseling and education can be helpful. To avoid excessive sun exposure can reduce blisters and skin lesions in these cases.

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