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Case report

Rare mutation of the PPOX gene in a patient with Porphyria Variegate: a case report in Peru

Mutación rara del gen PPOX en un paciente con Porfiria Variegata: reporte de un caso en Perú

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ABSTRACT

Introduction: Variegate porphyria (VP) is a rare disease, resulting from mutation of the protoporphyrinogen oxidase (PPOX) enzyme gene, and it is characterized by cutaneous manifestations and acute neuro-visceral symptoms. **Case report:** We describe the case of a 21-year-old woman from Peruvian highlands. The patient came to the emergency department for abdominal pain, quadriparesis and reddish urine. The patient also presented the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), motor neuropathy and respiratory failure. These clinical features were diagnosed as consequence of a porphyria crisis. The specific diagnosis was made with an elevated urinary porphobilinogen level (185.7 mg/24hours) and genetic analysis, which showed a rare pathogenic variant of the PPOX gene (nucleotide change: c.78C>A and protein change: p.Cys26*). The patient required intensive care until the administration of specific treatment with hemin. **Conclusion:** We report a case of VP with a pathogenic variant in the PPOX gene.

Keywords: Hepatic Porphyrias, Variegate Porphyria, Protoporphyrinogen Oxidase, Inappropriate ADH syndrome, Peru (Source: MeSH-NLM).

RESUMEN

Introducción: La porfiria variegada (PV) es una enfermedad rara, resultante de la mutación del gen de la enzima protoporfirinógeno oxidasa (PPOX), se caracteriza por manifestaciones cutáneas y síntomas neuroviscerales agudos. **Reporte de caso:** Describimos el caso de una mujer de 21 años de la sierra peruana. La paciente acudió al servicio de urgencias por dolor abdominal, cuadriparesia y orina rojiza. La paciente también presentó el síndrome de secreción inapropiada de hormona antidiurética (SIADH), neuropatía motora e insuficiencia respiratoria. Estas características clínicas fueron diagnosticadas como consecuencia de una crisis de porfiria. El diagnóstico específico se realizó con un nivel elevado de porfobilinógeno en orina (185,7 mg/24horas) y el análisis genético, evidenció un rara variante patogénica del gen PPOX (cambio de nucleótido: c.78C>A y consecuentemente cambio de proteína: p.Cys26*). La paciente requirió cuidados intensivos hasta la administración de un tratamiento específico con hemina. **Conclusion:** Reportamos un caso de VP con una rara variante mutagénica en el gen PPOX.

Palabras clave: Porfirias Hepáticas, Porfiria Variegada, Protoporfirinógeno Oxidasa, Síndrome de ADH Inapropiada, Perú (Fuente: DeCS-BIREME).

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AUTHORS CONTRIBUTION

AKR: conceptualized, participated in data collection, wrote the initial draft, revised and approved the final version.
BCC: conceptualized, participated in data collection, wrote the initial draft, revised and approved the final version.
DFG: conceptualized, participated in data collection, wrote the initial draft, revised and approved the final version.

CONFLICT OF INTEREST

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INTRODUCTION

Variegate porphyria (VP) is a rare metabolic disorder caused by an alteration in the porphyrin biosynthesis pathway, including the heme group of hemoglobin protein[1].

This enzymatic alteration produces the deposition of heme precursors (porphyrin, 5-aminolevulinic acid [ALA] and porphobilinogen) in different tissues, mainly in the liver and erythrocytes[2]. Consequently, it can cause various non-specific symptoms such as abdominal pain, nausea, and vomiting. This clinical presentation and the low prevalence of the disease, makes diagnosis and proper management difficult[3]. VP generates acute neuro-visceral manifestations (abdominal, psychiatric, neurological or severe cardiovascular symptoms) with the risk of hepatic and renal complications[4], and often triggers skin lesions in sun-exposed areas such as skin fragility, erosions, blisters, milia and pigmentary changes[5].

In many cases the diagnosis is delayed for several years which may result in inadequate treatments and thus probably increase morbidity and the use of unnecessary medical resources. The following is a case of VP in a young Peruvian woman with a nonspecific clinical presentation and severe complications, which were associated with a mutation of the porphyrinogen oxidase enzyme gene (PPOX) not previously reported with VP.

CASE REPORT

A 21-year-old woman from the southern region of Peru, with ancestry from the Peruvian highlands, presented to a lower complexity hospital (Regional Hospital of Moquegua) complaining of 7 days of diffuse cramping abdominal pain of moderate intensity. The patient also presented emesis, constipation and asthenia. She reported a history of dysmenorrhea and consumption of nonsteroidal anti-inflammatory drugs (NSAIDs). She did not report any other personal or family history of interest. After ruling out a surgical cause for abdominal pain, the patient was admitted in hospitalization for further studies. During hospitalization, on the third day she presented moderate hyponatremia (129 mEq/L) and on the seventh day a generalized tonic-clonic seizure that evolved to status epilepticus, requiring management by an intensive care unit (ICU) (Figure 1).

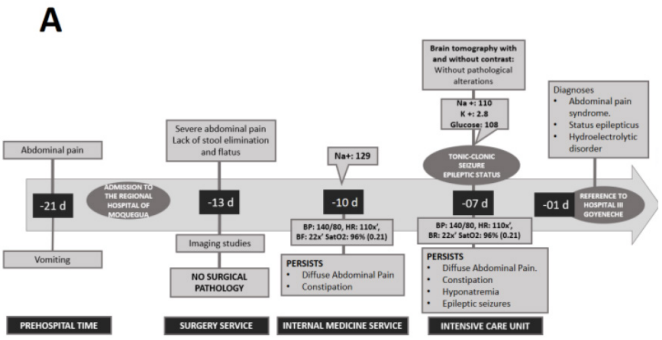

Figure 1. Timeline of the patient's clinical evolution before referral to Hospital III Goyeneche

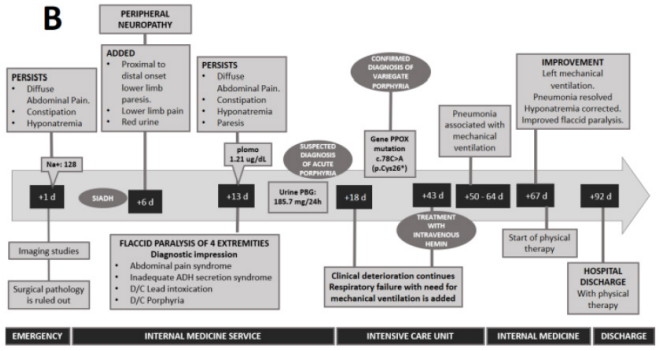

Figure 2. Timeline of clinical evolution, diagnosis and management at Hospital III Goyeneche

After stabilization, she was referred to the ICU of a higher complexity hospital (Hospital III Goyeneche) due to persistent abdominal pain, constipation for 8 days, red urine for 7 days and hydroelectrolyte disorder (hypokalemia and severe hyponatremia). Physical examination revealed poor hydration status and normal vital signs. The abdomen was painful on palpation with decreased sounds and no signs of peritoneal irritation. Neurological examination showed somnolence and ascending paresis of the lower extremities. The rest of the physical examination was normal, with no skin lesions or signs. Laboratory tests showed the following values: hemoglobin 14.2mg/dL, leukocytes 5 170 103/mm3, amylase 153 (U/L), lipase 204 (U/L), sodium 128 mEq/L, osmolarity 261 mOsm and lead 1.21ug/dL. Urinalysis showed red color, with 2-4 erythrocytes per field. Abdominal radiography showed mild dilatation of loops with hydroaerial levels, abdominal ultrasound showed signs of mild fatty liver and moderate intestinal ileus. The simple chest X-ray, abdominal and cerebral tomography did not show any alterations.

With all these findings, the possibility of surgical, neoplastic, infectious pathology, acute pancreatitis or lead intoxication were ruled out (Figure 2).

The alteration of sodium and osmolarity, together with the tonic-clonic coma, led to the diagnosis of inappropriate antidiuretic hormone secretion (SIADH). Likewise, the presence of red urine, paresis of lower limbs progressing to flaccid paralysis with respiratory failure led to the suspicion of acute porphyria. Therefore, urinary porphobilinogen (185.7 mg/24h) was requested, confirming the diagnosis of porphyria. To specify the type of porphyria, a genetic panel analysis for acute hepatic porphyrias was performed. Regarding this genetic panel, it includes deletion/duplication analysis and sequence analysis of the entire coding region for the following genes: ALAD, CPOX, HMBS and PPOX. In this case, it was reported a mutation in the enzyme porphyrinogen oxidase (PPOX variant; nucleotide change: c.78C > A and protein change: p.Cys26*) which confirmed the diagnosis of variegate porphyria (VP). Family screening by genetic testing or urine PBG analysis was not performed.

After administration of hemin arginate (25 days after diagnosis), the patient was weaned from mechanical ventilation and hyponatremia was corrected (Figure 2). However, recovery from paresis was slow and progressive, and after six months of rehabilitation the patient had limitations in lifting in her daily activities. After two years, the patient has no functional limitation in her daily activities and has not presented any disease flare-ups.

DISCUSSION

We present the case of a young patient with a confirmed diagnosis of VP after presenting an acute neuro-visceral crisis of porphyria, without cutaneous manifestations, with neurological and respiratory complications. The rare pathogenic variant of PPOX gen (PPOX variant; nucleotide change: c.78C > A and protein change: p.Cys26*) was identified.

In Europe, the prevalence of VP varies between 2.4 to 4 cases per million(3) and since its initial description in 1937(18), more than 140 mutations have been identified. In South Africa, a higher prevalence has been reported, with 1 case per 300 births[6,7]. In contrast, in Latin America it is rare[8,9]. In Chile, 105 cases of acute porphyria have been reported over a 17-year period, with VP being the most frequently reported (21%)[9]. According to the available literature, we present the first case of VP reported in Peru.

VP presents an autosomal dominant inheritance, with mutation in the enzyme protoporphyrinogen oxidase (PPOX) which is the penultimate enzyme of the heme pathway[10]. VP affects more females and typically presents in adolescence or young adulthood[4,9], as in our patient.

Regarding the clinical picture, although the cutaneous presentation (60-82%) is the most predominant[3,4,10], its absence has been reported in 13% of cases of VP[3] and has been associated with mutation of the I12T allele of the PPOX gene[11]. These photosensitivity symptoms are produced by the precipitation of heme precursors after exposure to UVA light[12]. Our patient came from Moquegua, a region in the southern coast of Peru with high exposure to UV rays[13], therefore, the absence of cutaneous symptoms in VP was of great interest.

Regarding the acute neuro-visceral manifestations, it is known that they are typically nonspecific, the most common being the presence of acute, intermittent, diffuse abdominal pain, without peritoneal signs, which may or may not be accompanied by vomiting and constipation(5). This coincides with the presentation of our patient. The presence of these acute attacks has been related to triggering factors (drugs such as barbiturates, contraceptives, alcohol and tobacco consumption, metabolic stress, among others)[14]. However, in our case there was no evidence of any of these factors.

The patient presented red urine, which was due to increased metabolic wastes related to PPOX enzyme deficiency[1]. The disorientation and tonic-clonic seizures could have been caused by the direct effect of the accumulation of porphyrins in the neurons or by the hyponatremia resulting from the SIADH consequent to VP[15]. Similarly, peripheral motor neuropathy in acute porphyrias generates neuromuscular weakness, from proximal to distal direction, with an increased risk of quadriparesis and respiratory failure[15].
The diagnosis of VP is determined by increased urinary porphobilinogen (PBG) excretion and genetic confirmation[12]. In our patient, an elevated

urinary PBG (185.7mg/24h) was found and the diagnosis of VP was confirmed by genetic analysis, which revealed a rare pathogenic variant (PPOX variant; nucleotide change: c.78C > A and protein change: p.Cys26*). This pathogenic variant has been previously identified in the literature in some cases of VP in Europe, but has not been reported in Latin American countries[16,17,18].

The goal of treatment is to reduce hepatic ALA synthetase-1 (ALAS-1) activity, which can be regulated by carbohydrate administration (300 g glucose per day)[2]. However, the most effective therapy is the administration of intravenous heme, which results in the decrease of ALA and PBG in urine and plasma[2,19], and in a clinical improvement in 4 days generally[14]. In the case presented, recovery of respiratory failure and hyponatremia was observed after hemin administration. In addition to a progressive recovery of muscle strength.

This case shows a particular presentation of VP and emphasizes the importance of considering the diagnosis even among patients with no family history, who do not present cutaneous manifestations and in countries where the incidence is practically unrecorded. Early diagnosis and treatment are of great importance to avoid life-threatening complications.

CONCLUSION

In conclusion, we report the case of a 21-year-old female patient with VP with acute symptoms of a severe neuro-visceral crisis without cutaneous manifestations and biochemical abnormalities, which was associated with a rare pathogenic variant (PPOX variant; nucleotide change: c.78C>A and protein change: p.Cys26*) in the PPOX gene. The importance of clinical investigations in patients with genetic mutations is essential to establish a genotype-phenotype correlation that facilitates the clinical approach and management in these patients. In addition to recognizing that timely diagnosis and treatment is essential to avoid seizures and severe complications.

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