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CASE REPORT

Erythropoeitic protoporphyria: clinical presentation in a child misdiagnosed as cutaneous lupus erythematosus

Charles Marques Lourenco[1], Rafael Bogas[1], Ricardo Calvo[1], Ygor Brasil[1], Zumira A. Carneiro[1]

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Abstract

Erythropoietic protoporphyria (EPP) is a metabolic error in the biosynthesis of the heme group, the enzyme ferrochelatase (FEHC) deficiency culminates in the excessive accumulation of free protoporphyrin in erythroid cells, plasma, skin, and liver. The excess of this metabolite generates symptoms like skin pain, burning, pruritus during the sun exposure, that arise from this the childhood. This article reports the case of a 4-year and 6-month patient who, after prolonged sun exposure, opened a typical photosensitivity picture of erythropoietic protoporphyria. Erythema malar led to a misdiagnosis of cutaneous erythematosus lupus. EPP diagnosis was confirmed by the measurement of serum protoporphyria and corroborated by the genetic test that shows defect in the gene that transcribes the FEHC enzyme. The treatment is based on measures of photoprotection, recently medications such as afamelanotide and hematin have been shown to be effective for the control of the disease. In order to elucidate the difference between the diagnosis of cutaneous lupus and PPE, this article brings the clinical difference between these pathologies, in addition to the EPP laboratory diagnosis.

[1] Faculty of Medicine Centro Universitario Estacio de Ribeirao Preto, Clinical Genetics - RIBEIRAO PRETO - SAO PAULO - Brazil.

Correspondence to:
Charles Marques Lourenco.
Estácio University Center of Ribeirão Preto. Rua Abrahão Issa Halach, nº 980, Ribeirânia.
Ribeirão Preto - SP. Brazil. CEP: 14096-160. E-mail: charlesgenetica@gmail.com

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INTRODUCTION

Porphyrias are a group of rare metabolic disorders - hereditary or acquired - caused by failure of the heme biosynthetic pathway[1]. Each type of porphyria results from a specific deficiency in one of the enzymes involved in the heme production pathway. Traditionally, they are classified into two major groups: acute porphyrias and exclusively cutaneous porphyrias.

Cutaneous porphyrias have the increase in plasma porphyrins as the most sensitive biochemical marker, although not specific[2].

Among the most common cutaneous porphyrias, we highlight erythropoietic protoporphyria (EPP). It is a chronic erythropoietic porphyria , associated with excessive accumulation of free protoporphyrin in erythroid cells , plasma, skin and liver . Patients affected by this disease characteristically report skin pain , burning and itching during sun exposure, often accompanied by erythema and edema[3]. A small percentage (approximately 2%) of patients with PPE, in addition to cutaneous symptoms, may develop hepatobiliary complications, which, in some cases, culminate in liver failure[1-3].

The laboratory diagnosis of erythropoietic protoporphyria is made through serum protoporphyrin measurement[3] and later confirmed by molecular-genetic analysis.

Often, PPE can be misdiagnosed like other pathologies, which contributes to the relative delay in the diagnosis of this disease and, therefore, the correct therapeutic management of the patient[3]. The main strategy in the management of PPE is to avoid exposure to light[4-5], although new therapeutic perspectives are under study.

CASE REPORT

Patient, female, 14 years old, daughter of young and non-consanguineous parents, was referred for investigation of photosensitivity.

During the gestational period, during the performance of a transabdominal ultrasound, an abnormality was observed in the measurement of the nuchal translucency, with no abnormality of other ultrasound parameters. The mother reports an uneventful pregnancy. There were no complications during delivery and the patient was born at term, weighing 3.295kg, measuring 49cm and with a head circumference of 33.5cm. He evolved with satisfactory conditions, with good suction, did not develop early jaundice and was discharged on the first day.

Neurodevelopmental history shows that the patient presented neuropsychomotor milestones within the normal range. Attends regular education with good performance.

At about 4 years and 6 months of age, a previously healthy patient, after going to the beach for the first time, was exposed to more sunlight than usual, presenting, hours later, significant swelling on the face with erythema, in the bilateral malar region, nasal region and hands and feet (Figure 1 and Figure 2).



Figure 1. Facial swelling with erythema, bilateral malar region and nasal region. Source: The Authors (2018).



Figure 2. Note erythema and edema in the right lower limb. Source: The Authors (2018).

A few days after the onset of the condition, it evolved with desquamation at the site of the lesions, and these evolved with the formation of a secondary crust, taking up to a month to disappear. On other occasions, after exposure to sunlight, even briefly, the patient had only erythema with mild local edema and disappeared within a few days. The initial investigation carried out after the episode was not able to elucidate the etiology of the condition.

A possible solar dermatitis was suspected, which was ruled out after investigation in the immunology department. Due to the pattern of alteration in the malar region, a possible condition of childhood systemic lupus erythematosus was suspected, which was also later ruled out in an evaluation with a rheumatologist and complementary exams.

In view of the lack of a diagnostic definition, the patient underwent a skin biopsy, whose results showed, in the epidermis, the presence of parakeratosis and irregular acanthosis, papillary dermis with deposition of eosinophilic amorphous material, predominantly vascular and in eccrine glands; Positive PAS resistant to diathesis, extravasation of red blood cells was also visualized.

Skin biopsy results pointed to the suspicion of cutaneous porphyria, but without identification of the subtype. The patient was referred to a geneticist who suspected the possibility of erythropoietic protoporphyria, due to the clinical presentation of photosensitivity without blistering, and biochemical tests were requested based on this suspicion (Table 1 and Table 2).

Biochemical tests confirmed the diagnosis of erythropoietic protoporphyria (EPP), which was then confirmed by the genetic study of the ferrochelatase gene, which showed that the patient had a pathogenic mutation (c.215dupT) and a polymorphism (IVS3-48T> C) that decreases the activity of the activity of this enzyme, each one being inherited from different parents.

In view of the correctly established diagnosis, the patient was instructed to adopt photoprotection measures, such as the use of sunscreen with a high protection factor and the use of oral beta-carotene.

DISCUSSION

Erythropoietic protoporphyria (EPP) is one of the most common forms of genetically determined porphyria and the second most common form of cutaneous porphyria, surpassed only in frequency by porphyria cutanea tarda[3].

It is worth mentioning that there are two forms of PPE, one linked to the X chromosome and the other of pseudodominant inheritance, as represented by the patient in this report. It is known that, biochemically, there is a difference between the two types of the disease. In the X-linked form, as in cases of hemolytic anemia, there is a preferential increase in zinc-linked protoporphyrin. In the pseudodominant form, there is an increase in free protoporphyrins. The latter is named because of the need for the disease to have a mutation in one allele and a polymorphism in the other allele for it to manifest itself, so the disease is dominant but behaves , from a molecular point of view, like a recessive disease[3].

In addition to cutaneous manifestations, hepatobiliary disease occurs in up to 20% of patients with PPE; however, only 5% develop advanced liver disease with cholestasis and even liver failure. Such a presentation can be explained by the presence of gallstones with a high content of protoporphyrin that are generated due to the accumulation of insoluble protoporphyrin and increased concentration of biliary protoporphyrin. Clinical manifestations of liver disease in PPE include: cholelithiasis with possible obstructive episodes and chronic liver disease progressing to acute liver failure. The patient in the report evolved with signs of mild liver dysfunction, defined by altered levels of liver enzymes and abdominal ultrasound. Liver transplantation is the treatment

Table 1. Exames bioquímicos.

BIOCHEMICAL EXAMS	VALUES	VALOR DE REFERÊNCIA
HEMOGLOBIN	12.3	10.5 - 12.7
VCM	70 fL	81 - 91 fL
ALPHA FETTO PROTEIN	1.2 (VR <5.5)	<5.5
CPK	75	<198
TGO	31	<32
TGP	32	<31
IRON FIXING LATENT CAPACITY	227	140 - 280
SERUM IRON	147	40 - 160 ug/dl
FERRITIN	16.9	40 - 160 ug/dl
PORPHOBILINOGENE	0.4 mg	0 - 2 mg
ACID. DELTA AMINOLEVULINUM (ALA)	2.2 mg/L	1.3 - 7 mg/24h
PORPHYRIINS PROFILE	113.1mc.dl vr <1mg.dl	< 1mg/dl
DOSAGE OF PROTOPORPHYRIN IN ERYTHROCYTES	1842mc/dl	< 80 mc/dl

Source: The Authors (2018).

Table 2. Biochemical tests.

ERYTHROCYTES		Unit	Reference value
Protoporphyrin	1842	mcg/dl	20 - 80
Zinc Protoporphyrin	3	% of total	
Free protoporphyrin	97	% of total	
Hematocrit	39	%	

Source: The Authors (2018).

for end-stage liver disease in patients with PPE. It is evident that liver transplantation does not change the consequences of ferrochelatase deficiency, therefore, patients with PPE continue to have typical cutaneous symptoms and the same risks of protoporphyrin accumulation in the transplanted liver. In cases of patients who have already undergone liver transplantation, the possibility of bone marrow transplantation (BMT) should also be considered and, in fact, the ideal treatment should be sequential liver and bone marrow transplantation, which has already been performed with success[3,6].

Patients with PES with only cutaneous manifestations, a priori, do not have an indication for performing BMT as a specific therapy. It is not yet possible to predict the clinical evolution of the liver of the patient in the report, so monitoring of liver function and follow-up with a pediatric hepatology service are essential.

When photoexposed, patients with PPE may present erythema in the malar region, which can be confused in many cases with systemic lupus erythematosus (SLE). The similarity between SLE and Erythropoietic Protoporphyria (EPP) cases represents a major diagnostic challenge for physicians, due to their similar clinical presentations. SLE is a chronic inflammatory disease of tissues and organs, whose evolution results in outbreaks of varied activities, often causing erythematous macular lesions in the dermis, with firm and adherent scales to the surface[7]. Thus, the lesions found in SLE are similar to those in PPE, but it is noted that, in lesions of Protoporphyria, edema is found in the sites affected by sun exposure, unlike what is seen in SLE. In addition, another factor that distinguishes them is the lesions of SLE, which are generalized, affecting any tissue and part of the body, and in PPE they affect only photoexposed areas. To carry out the differential diagnosis, follow-up with specialists should be carried out, these being a Rheumatologist and Geneticist, who requested biochemical and rheumatological tests to establish the differential diagnosis of the patient reported here[3,7].

As PPE lesions are caused by sun exposure, the basis of treatment for these patients is photoprotection, which can lead to comorbidities related to lack of sun exposure. Vitamin D deficiency is described in many patients with PPE, since, without sun exposure, there is no conversion of 25 hydroxycholecalciferol into 1,25 dihydrocholecalciferol in the liver and thus vitamin D is not present in its active form, causing damage to the liver. calcium cycle in the body, which may evolve, for example, with osteopenia and osteoporosis. However, our patient did not have abnormal levels of vitamin D[8].

In order to minimize the effects of phototoxicity in patients with PPE, new therapeutic perspectives have been developed. More recently, a drug known as Afamelanotide, a human α -melanocyte stimulating hormone analogue, has been used to treat cutaneous manifestations in patients with PPE. It binds to the melanocyte receptor and increases the production of eumelanin in the dermis without the damage caused by ultraviolet light from the sun's rays. This melanin in the form of eumelanin is photoprotective, as it absorbs, disperses and extinguishes ultraviolet rays, and also eliminates free radicals acting as a neutral density filter aimed at reducing light wavelengths. It was shown from phase III clinical studies that the action of afamelanotide allowed patients with PPE to tolerate more direct exposure to sunlight without pain[9].

In the absence of specific therapy to avoid the effect of exposure to sunlight, patients with PPE should still follow care with photoexposure as therapy; The use of beta-carotene may bring slight benefits to the patient's symptoms, but it does not prevent the development of clinical symptoms in most patients, as was observed in our patient.

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