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When the diagnosis is written in the DNA: a case of erythropoietic protoporphyria in a patient with a chromosome 18 deletion

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Abstract

We present a case of erythropoietic protoporphyria (EPP) in a 21-year-old man who sought medical attention in April 2022 due to diffuse edema and erythema of the hands, which he had been experiencing since childhood and occurring shortly after sun exposure. The patient's medical history revealed a partial deletion of the long arm of chromosome 18. Based on the patient's medical background and clinical symptoms, we conducted various tests, including measuring total erythrocyte protoporphyrin levels and evaluating the fluorometric emission peak of plasma porphyrins using a spectrofluorometer. Additionally, a genetic analysis revealed a complete deletion of the FECH gene on one allele and the presence of an intronic variant on the other allele, identified as c.315–48T>C (IVS3–48T>C) and classified as a susceptibility polymorphism. In June 2022, the patient underwent an Afamelanotide implant, which resulted in an improvement in his clinical condition.

Introduction

Erythropoietic protoporphyria (EPP) is a rare metabolic disorder caused by a deficiency of the ferrochelatase (FECH) gene, which, in most cases, results from inherited mutations in the FECH gene[1]. EPP has a prevalence ranging between 1:75,000 and 1:180,000 in Europe. Due Low levels of ferrochelatase, excessive amounts of protoporphyrin IX (PPIX) accumulate in the skin, the bone marrow, blood plasma and red blood cells[2]. The major symptom associated to this disorder is acute phototoxicity upon sun exposure, as a result of an excited energy states of the accumulated porphyrins causing tissue and endothelial damage. Some patients may also develop some grades of hepatotoxicity and, eventually, liver failure due to deposition in bile and/or hepatocytes[3]. Over 190 mutations have been reported in the FECH gene, and genetically driven cases typically present in early childhood. Onset in adulthood has rarely been reported, usually in association with myelodysplastic syndrome (MDS) [4].

Case report

We present the case of a 21-years-old man who came to our attention in April 2022 due to a diffuse edema and erythema of the hands (Figure 1). The patient complained a burning, stinging sensation and intense pain, occuring in few minutes upon sun exposure, and which would be followed by redness and swelling that persisted for several days. He also described a worsening of the symptoms upon heat exposure. This condition significantly impacted his quality of life, avoiding any light-associated behavior. The patient clinical history was significant as he presented a psychomotor retardation and facial dysmorphisms, attributed to a partial deletion of the long arm of chromosome 18[5]. In previous dermatological evaluations solar urticaria was primarly suspected, but the atypical

appearance of the skin lesions and their painful nature led us to consider EPP as the primary diagnosis. We conducted several tests, including erythrocyte protoporphyrin levels and fluorometric emission peak of plasma porphyrins, which confirmed our supect (Figure 2).

To confirm the diagnosis, we conducted a genetic analysis on the patient's peripheral blood that showed the deletion of the entire FECH-gene on one allele, while on the other allele was found an intronic variant, which is classified in the literature as a susceptibility polymorphism: c.315–48T>C (IVS3–48T>C).

Our patient underwent an Afamelanotide - an α-melanocyte-stimulating hormone analog - implant in June 2022. About 3 weeks after implantation, at the first follow-up visit, the patient reported an improvement in his clinical condition.

Discussion and conclusions

Genetic analysis revealed a complete deletion of the FECH gene on one patient's allele, resulting from the partial deletion of the long arm of chromosome 18. The other allele exhibited an intronic variant (IVS3-48T>C), classified as a susceptibility polymorphism[1]. These findings definitively confirmed the diagnosis of EPP due to FECH variants, with an autosomal recessive pattern of inheritance. Traditionally, EPP management has focused on light avoidance, photoprotection, and symptomatic treatment[5]. However, a recent breakthrough in treatment options is the use of Afamelanotide, an α-melanocyte-stimulating hormone analog, administered as a subcutaneous implant[6]. Afamelanotide improves light tolerance and overall quality of life in EPP patients by activating eumelanogenesis and providing photoprotection[7]. In summary, the authors presented this case as a case of EPP caused by a rare form of a severe FECH variant (complete deletion of the gene caused by the partial deletion of the long arm of chromosome 18) paired with the common low-expression variant allele (IVS3-48T/C) which had a good response to the treatment with Afamelanotide.

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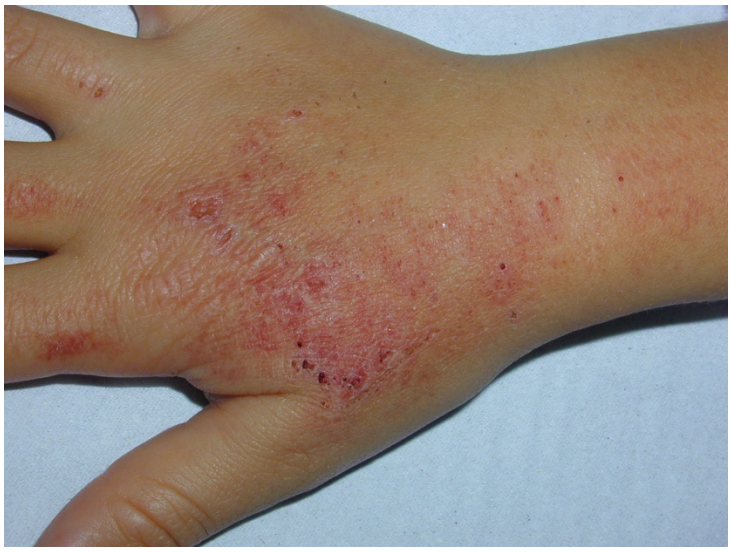

Figure 1. Intense painful lesions on the right hand of the patient.

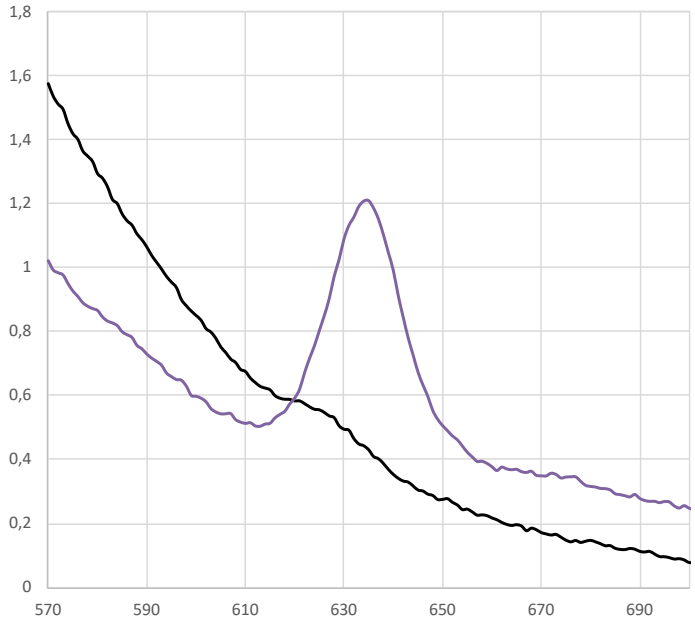

Figure 2. Fluorimetric emission curve of a healthy subject (black) and a subject affected by erythropoietic protoporphyria (purple).