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SHORT REPORT

Erythropoietic protoporphyria without skin symptoms-you do not always see what they feel

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Abstract Erythropoietic protoporphyria (EPP) is an inherited disorder of the porphyrin metabolism that often remains undiagnosed in children. We report on a 4-year-old girl who had been suffering for 1 year from recurrent painful crises affecting her hands, feet, and nose following sun exposure. Objective skin lesions were absent until the age of 6. Porphyrin analysis revealed elevated free erythrocyte protoporphyrin (FEP) levels confirming the diagnosis of EPP. This illustrates that skin lesions might be completely absent in children affected with EPP, a fact that has only been reported once previously. Because EPP can manifest with few and unspecific cutaneous symptoms or no skin lesions at all, like in this patient, the diagnosis of EPP might be delayed or missed. EPP should be excluded in all photosensitive children, especially when discomfort is disproportionate to the extent of the cutaneous lesions. The clinic, pathophysiology, diagnosis, complications, and therapy of EPP are discussed.

Keywords Porphyrias · Erythropoietic protoporphyria · Ferrochelatase · Photosensitivity

Abbreviations

EPP	erythropoietic protoporphyria
FECH	ferrochelatase
ROS	reactive oxygen species
FEP	free erythrocyte protoporphyrin
UV	ultraviolet
UVB	ultraviolet-B
ALA	δ-aminolevulinic acid

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Introduction

Erythropoietic protoporphyria (EPP) (OMIM 177000) results from a partial deficiency of ferrochelatase (FECH), the last enzyme in heme biosynthesis that is located in the mitochondrium [10, 13]. FECH catalyzes the insertion of iron into protoporphyrin IX to form heme (Fig. 1) [10]. Although overall EPP is a rare disease, it is the most common type of porphyria manifesting in childhood with an estimated prevalence of 1 in 130,000 [10, 13, 23].

The disease has no racial or sex predilection and no precipitating factors have been described to date [10, 20]. The major clinical feature of EPP is cutaneous photosensitivity that usually commences early in infancy or childhood, affects the sun-exposed body sites, and worsens

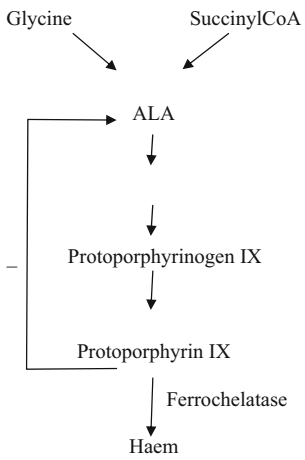

Fig. 1 In the mitochondrium, ferrochelatase catalyzes the formation of heme from protoporphyrin IX. *ALA: δ-aminolevulinic acid*

in spring and summer [10]. The symptoms include pain, burning, itching, erythema, and swelling, which can develop within minutes of sun exposure [4, 10, 13, 14]. Petechiae, purpura, and vesicles may be seen, but are uncommon [4]. Typically, children experience relief when cooling the skin with cold water or wet towels [11]. Chronic UV (ultraviolet) exposure can lead to lichenification, postinflammatory hyperpigmentation, and scarring, particularly over the knuckles and on the nose [13, 23]. Of note, the cutaneous symptoms can be discrete and barely notable in early childhood despite significant subjective discomfort including burning and stinging sensations in the skin.

Here, we describe a girl with EPP with an unusual clinical course, demonstrating that parents and physicians cannot always recognize how much the patients suffer.

Case report

An otherwise healthy, 4-year-old Dutch Caucasian girl presented with a 1-year history of suddenly occurring severe itching and pain in the hands, feet, and nose after sunlight exposure. These sensations lasted up to 3 days, and she reported on three such incidents during the last 12 months. The symptoms developed either immediately or up to 8 h after UV exposure. Erythema or other skin manifestations were not seen. The condition worsened in the summer months and during vacations in sunny climates. Itching commenced immediately after sunlight exposure and reached a maximum at night. After a few hours, the itching changed into pain. Application of wet towels or cold baths led to partial relief, and the symptoms usually vanished spontaneously after a couple of cloudy days without intense UV exposure. Looking back, her parents also remembered that at the age of 1 year, during a summer vacation, she had suffered from an unexplained acute swelling of the hands and feet. At that time no specific diagnosis was made, besides the suspicion of an allergy. During that vacation at the sea side, the overall family life was disturbed because she was continuously agitated, cried a lot without an apparent reason, and did not sleep well.

Upon physical examination in our outpatient clinic at the age of 4, she showed no skin symptoms except for few minimal excoriations on the dorsal aspects of the feet. The family history revealed eczema in the mother and atopy in the paternal grandmother, but was unremarkable regarding increased photosensitivity. Eventually, a pediatrician suggested the differential diagnoses polymorphic light eruption, warmth intolerance, or hypochondria, and the girl was treated unsuccessfully with antihistamines.

Due to continuation of her complaints, a pediatric dermatologist was consulted who suspected EPP despite the absence of cutaneous manifestations. Blood porphyrin analysis revealed elevated free erythrocyte protoporphyrin (FEP) levels of 9,821 μg/l (normal 0–300 μg/l), confirming the diagnosis of EPP. Affirmative phototesting showed maximal cutaneous sensitivity at a wavelength of 400 nm (violet light). Full blood count and liver enzymes were normal.

Therapeutically, strict UV light avoidance, protective sunscreens, and annual follow-up visits were advised. Still, her photosensitivity did not improve, and mild hyperpigmentation and sores at her nose and upper lip as well as pronounced knuckles and progressive lichenification developed at the age of 6. To date, she has not shown liver enzyme alterations.

Discussion

Here we present a girl with EPP who suffered from a significant decrease of quality of life due to severe itching and pain of the skin. Clinically, EPP is characterized by cutaneous photosensitivity manifesting early in life. Acute photosensitivity episodes include burning, stinging, and pruritus in sun-exposed skin, particularly on the nose, cheeks, and dorsal aspects of the hands, followed by erythema, edema, and wax-like scarring. Skin symptoms can occur within minutes of sun exposure, often starting early in spring time, continuing through the summer, and diminishing in fall and winter.

Interestingly though, our patient did not show any visible skin lesions until the age of 6. Over the last 30 years there have been ten reports on children with EPP who developed mild to severe cutaneous photosensitivity and specific skin manifestations [1, 2, 11, 15, 19–21, 23, 30, 31]. With mild or absent visible skin symptoms, however, diagnosis may be delayed for several years or is not made at all because the discomfort experienced by the young patients is disproportionate to the objective cutaneous

manifestations [22, 23]. Thus, children with EPP are often labeled as hysterical, hypochondriac, or even malingering, a distressing situation for both the patients and their parents [2, 22]. To the best of our knowledge the complete absence of visible skin lesions in early childhood EPP has only been described once to date [12].

The symptoms in EPP are associated with an overproduction and accumulation of lipophilic protoporphyrin as a result of FECH deficiency [28]. Excess deposition of protoporphyrin in the skin leads to cutaneous photosensitivity upon UV light exposure with maximum susceptibility at a wavelength around 400 nm (Soret band) [22]. Upon excitation, protoporphyrin exerts its phototoxic effects through the generation of reactive oxygen species (ROS). ROS can induce lipid peroxidation, oxidation of amino acids, and mediator release from mast cells, contributing to the acute photosensitivity, and protein cross-linking leading to cell membrane damage and cell death [3, 7, 13, 17, 25].

The diagnosis of EPP is based on the clinical symptoms and verified by a significant increase of FEP (more than five times the normal level of 0 to 300 μg/l) in peripheral erythrocytes [15, 18, 28]. Since protoporphyrin is a hydrophobic metabolite, it is not renally excreted. Hence, urinary porphyrin values are usually normal [15, 23]. *Another diagnostic modality includes fluorescence microscopy of erythrocytes* [2, 17].

Histological changes are predominantly seen in the upper dermis and include deposition of amorphous material containing immunoglobulins, complement components, glycoproteins, acid glycosaminoglycans, and lipids around blood vessels [5, 21, 24, 26, 27, 29]. However, these alterations are not specific. Regardless of the aforementioned finding, we emphasize that it is unnecessary to take a skin biopsy if one of the cutaneous porphyrias is suspected because of two reasons. Firstly, simple non-invasive biochemical laboratory techniques can easily prove or exclude the presumptive diagnosis of porphyria. Secondly, any kind of external trauma, such as a biopsy or excision, inevitably constitutes an unnecessary risk for delayed or disturbed wound healing in porphyria patients.

The differential diagnoses of EPP include solar dermatitis, solar urticaria, polymorphous light eruption, lipoid proteinosis, hydroa vacciniforme, and lupus erythematosus [2, 22]. Elevated FEP levels can also be found in lead poisoning, anemia, renal failure, cholestasis, and liver failure. However, these conditions are not associated with photosensitivity [13, 18, 23].

Beside the cutaneous manifestations, the most important concern in EPP patients is the development of cholestasis with rapid accumulation of protoporphyrin in hepatobiliary structures resulting in severe liver damage and hepatic failure. Although rarely occurring, progressive liver failure is a well-recognized complication in EPP, and about one third of EPP patients show biochemical liver abnormalities [6, 13]. Therefore, liver function tests should be performed annually [13, 28]. In our patient, no liver dysfunction has been detected so far.

Although in rare instances an autosomal recessive inheritance pattern has been described, EPP is a predominantly autosomal dominantly transmitted disorder with incomplete penetrance resulting from mutations in the *FECH* gene on chromosome 18q21.3 [31, 32]. To date, more than 65 different *FECH* mutations have been reported, reflecting the genetic heterogeneity encountered in EPP [13, 28]. Recently, the genetic mechanisms underlying the cutaneous symptoms in EPP have been uncovered. It is clear now that only those individuals will develop skin symptoms who not only inherit a heterozygous *FECH* gene mutation on one parental allele, but also a specific intronic *FECH* polymorphism on the other parental allele [8]. Thus, clinically overt EPP results from a marked deficiency of FECH activity below a certain threshold due to co-inheritance of a specific FECH gene mutation with a low-penetrance IVS3-48C allele. Recent studies indicate that the frequency of the IVS3-48C allele shows a high degree of variability in different ethnic groups [9]. The identification of the molecular mechanisms underlying the manifestation of photosensitivity in EPP certainly has to be considered a milestone in porphyria research. Still, the development of protoporphyrin-induced hepatic disease and the molecular mechanisms governing the phenotype with severe liver injury are not well understood. It seems that other as yet unidentified factors may contribute to the pathogenesis of severe liver failure in EPP.

The current treatment modalities for EPP are limited and not effective in all patients [13]. In an ideal scenario, the harmful effects of exposure to visible light should be prevented. This can partially be achieved with sunscreens containing titanium oxide or zinc oxide. Common sunscreens, even those with high UV absorption capacity, do not block visible light and, thus, have no protective effect [2, 28].Consequent avoidance of UV light exposure and sun protection by protective clothing remains the most important measure in preventing acute photosensitivity and was also advised to our patient [13, 14, 18, 28]. The effectiveness of other modalities such as antioxidants (e.g., beta-carotene), cysteine, narrow-band UVB-phototherapy, and oral antihistamines remains doubtful and is certainly not of benefit in all patients. In the future, gene therapy approaches might play a role in the treatment of EPP because, e.g., normal ferrochelatase activity could be restored in vitro by transferring a wild-type copy of the *FECH* gene into cultured fibroblasts of EPP patients [16].

In conclusion, the diagnosis of EPP is often delayed or missed. Therefore, EPP should always be considered in photosensitive children, especially when the subjective

discomfort is disproportionate to the extent of visible skin manifestations because we obviously do not always see what these patients feel. If cutaneous symptoms are completely absent, an accurate diagnosis is difficult and requires all diagnostic abilities of the attending physicians.

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