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Pseudoporphyria

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Introduction

Background

Porphyrias are metabolic disorders of heme synthesis. Partial enzymic deficiencies result in excessive accumulation and excretion of 5-aminolevulinic acid, porphobilinogen, and/or porphyrins. Porphyria cutanea tarda (PCT) is the most common of the porphyrias in North America and Europe. First described by Waldenström in 1937, this blistering disorder is caused by a deficiency of uroporphyrinogen decarboxylase, an enzyme in heme biosynthesis.[1] Porphyrins accumulate in the liver, are transported in plasma, and are excessively excreted in the urine. Exposure of patients with porphyria cutanea tarda to sunlight results in increased skin fragility, vesicles, bullae, hypertrichosis, hyperpigmentation, sclerodermoid changes, dystrophic calcification, milia, and scarring in a photodistribution. Porphyria cutanea tarda can be inherited or acquired. Treatment options include phlebotomy and antimalarial medications.

Pseudoporphyria describes a bullous photosensitivity that clinically and histologically mimics porphyria cutanea tarda. However, no demonstrable porphyrin abnormalities are present. In 1964, Zelickson was first to describe this type of phototoxic reaction in patients after the use of nalidixic acid.[2] The skin lesions were indistinguishable from those observed in patients with porphyria cutanea tarda. Since this initial report, many other drugs have been incriminated in mediating this type of bullous photosensitivity.[3] Pseudoporphyria has been reported in patients with chronic renal failure treated with hemodialysis and in those with excessive exposure to ultraviolet A (UV-A) by tanning beds.[4,5]

Pathophysiology

The precise pathophysiologic mechanism of pseudoporphyria is not fully understood. In 1983, Keane et al developed an animal model for nalidixic acid photosensitivity in CF-1 female mice.[6] Animals injected with nalidixic acid and then exposed to ultraviolet radiation for 10 weeks exhibited more severe cutaneous manifestations than mice treated with sodium chloride solution. Light and electron microscopy demonstrated a subepidermal split beneath the basal lamina at the same level as seen in histologic examination of porphyria cutanea tarda and pseudoporphyria. The authors suggested that a photosensitizing drug might behave in a similar fashion to photoactivated endogenous porphyrins and target similar structures in the skin. Several other authors have corroborated these findings.

Other mechanisms have been proposed to explain the role of ultraviolet or visible light radiation in drug-induced pseudoporphyria. An alternative theory is based on the finding that exogenous photosensitizers are deposited along

the endothelium of blood vessels of lesional and nonlesional skin. An immune response targeted against antigens is proposed to develop after phototoxic injury to the dermal microvascular endothelium. Dabski and Beutner proposed a multistep mechanism in which exogenous photosensitizers (drugs) damage the vascular endothelium by the release of proteases after sunlight exposure.[7] Then, immunoglobulin G (IgG) and immunoreactants bind to the damaged endothelium, causing formation of bullae at the level of the lamina lucida as a secondary or tertiary event.

The pathophysiology of pseudoporphyria associated with hemodialysis has not been fully explained. Aluminum hydroxide has been implicated in hemodialysis-associated pseudoporphyria. Aluminum hydroxide is found in dialysis solution and has been shown to produce a porphyrialike disorder after long-term administration in rats.

Frequency

United States

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Pseudoporphyria is not uncommon. Although fewer than 100 cases are documented, pseudoporphyria is most likely underreported in the literature.

Race

Although pseudoporphyria has no predilection toward any one race, it has been shown that fair-skinned children who are highly prone to sunburn are more likely to develop naproxen-induced pseudoporphyria than those children with skin types III or higher. Wallace et al demonstrated that even in the absence of a history of blistering, children with light skin and blue or green eyes are at an increased risk of developing shallow scars on the face while taking naproxen.[8]

Sex

Pseudoporphyria affects males and females equally.

Age

The ages of patients reported with pseudoporphyria range from 2-81 years.

Clinical

History

- A careful history is of utmost importance when the diagnosis of pseudoporphyria is being considered. A personal and family history of hepatitis, porphyria, or photosensitivity disorder must be sought.
- Although a genetic factor has not been considered in pseudoporphyria, one case of monozygotic twins developing pseudoporphyria after excessive UV-A exposure from long-term tanning bed use has been documented.[5]
- The patient should be thoroughly questioned regarding any symptoms of connective tissue disorder, which may be the underlying pathology of the photosensitivity. Some reports suggest that a connective-tissue disorder may be a predisposing factor in patients using nonsteroidal anti-inflammatory drugs (NSAIDs) who develop pseudoporphyria.

Physical

- Pseudoporphyria is clinically characterized by increased skin fragility; erythema; and the appearance of tense bullae and erosions on sun-exposed skin, which are identical to those seen in patients with porphyria cutanea tarda. However, a clinical pearl that may prove helpful in differentiating between pseudoporphyria and porphyria cutanea tarda is that the classic features of hypertrichosis, hyperpigmentation, and sclerodermoid changes found with porphyria cutanea tarda are unusual with pseudoporphyria.
- A second clinical pattern of pseudoporphyria has a similar presentation to erythropoietic protoporphyria (EPP), an autosomal dominant porphyria resulting from a reduced activity of ferrochelatase.
    - In contrast to porphyria cutanea tarda, erythropoietic protoporphyria usually begins in childhood with a history of photosensitivity, often described as a burning sensation immediately after sunlight exposure.
    - Clinically, erythropoietic protoporphyria is characterized by erythema, edema, shallow scars, and waxy induration of the skin, particularly on the face.
    - Pseudoporphyria that clinically mimics erythropoietic protoporphyria has been described almost exclusively in children taking naproxen for juvenile rheumatoid arthritis.[9] Naproxen-induced pseudoporphyria seems to have a dimorphic presentation with the porphyria cutanea tarda–like pattern more often seen in the adult population and the erythropoietic protoporphyria–like pattern more commonly seen in children, although some overlap has been documented.

Causes

- Pseudoporphyria can be induced by a wide range of medications, excessive UV-A exposure, and hemodialysis.
- As recognition of pseudoporphyria increases and the number of new medications expands, the list of etiologic agents associated with pseudoporphyria will most likely continue to grow. Agents associated with pseudoporphyria are as follows[10]:
    - Propionic acid derivatives (NSAIDs)[11,12] - Naproxen,[10,13,14,15,16,17,18] diflunisal, ketoprofen, nabumetone,[19,20] oxaprozin,[21] mefenamic acid,[22] rofecoxib[23]
    - Antibiotics - Nalidixic acid,[24,25] tetracycline,[26] oxytetracycline,[27] ampicillin-sulbactam, cefepime,[28] ciprofloxacin[29]
    - Antifungals - Voriconazole[30,31]
    - Diuretics - Furosemide,[32] chlorthalidone,[33] butamide, triamterene/hydrochlorothiazide, torsemide,[34] bumetanide[35]
    - Antiarrhythmics - Amiodarone[36]
    - Chemotherapy - 5-Fluorouracil,[37] imatinib[38]
    - Immunosuppressants - Cyclosporine
    - Sulfones - Dapsone
    - Vitamins - Brewers' yeast,[17] pyridoxine[39]
    - Vitamin A derivatives - Etretinate,[40] isotretinoin[41]
    - Muscle relaxants - Carisoprodol, aspirin[42]
    - Nonsteroidal antiandrogens - Flutamide[43]
    - Other - Hemodialysis,[44] excessive UV-A, cola,[45] oral contraceptive pills (levonorgestrel and ethinyl estradiol), narrowband UV-B[46] phototherapy (rarely)

- Vitiligo may be associated with pseudoporphyria.[47,48] Several reports describe patients with vesicles, bullae, and scarring confined to areas of vitiligo on the dorsa of the hands with sparing of normally pigmented skin while taking medications known to cause pseudoporphyria. It is well established that the clinical findings of pseudoporphyria may be precipitated or exacerbated by sunlight. One author suggests that the presence of melanin in healthy skin may be adequate protection to prevent the development of pseudoporphyria in patients with vitiligo.

Differential Diagnoses

Bullous Pemphigoid
Epidermolysis Bullosa
Epidermolysis Bullosa Acquisita
Erythropoietic Protoporphyria
Lupus Erythematosus, Bullous
Porphyria Cutanea Tarda

Workup

Laboratory Studies

- Of critical importance in the diagnosis of pseudoporphyria is the exclusion of true porphyria.
    - The most important test is a serum/plasma porphyrin assay. If this result is negative, the patient does not have a true porphyria.
    - If the serum/plasma porphyrin assay is unavailable, erythrocytes, urine, and stool may be evaluated for abnormal porphyrin levels.
- Other causes of photosensitivity, such as connective tissue disease, must be excluded by obtaining a serum antinuclear antibody titer and more specific studies, such as antibodies to Ro, La, ribonucleoprotein, Smith, and double-stranded DNA.

Procedures

- If the diagnosis of pseudoporphyria is suspected, biopsies for histologic evaluation with hematoxylin and eosin stains and direct immunofluorescence should be performed. Serum samples may also be obtained for indirect immunofluorescence evaluation to aid in the exclusion of bullous pemphigoid.

Histologic Findings

The histologic features of pseudoporphyria are similar to those of porphyria cutanea tarda (PCT) with subepidermal bullae and festooning of the dermal papillae. The thickness of the blood vessel wall may prove helpful in differentiating pseudoporphyria from porphyria cutanea tarda.

In a comparative histologic study from biopsy samples of patients with porphyria cutanea tarda and pseudoporphyria, Maynard and Peters found thickened blood vessel walls in 11 of 13 patients with porphyria cutanea tarda. In contrast, similar findings in only 1 of 9 patients with pseudoporphyria were present.[49]

Porphyria cutanea tarda and pseudoporphyria have similar, nonspecific direct immunofluorescence findings of granular deposits of immunoglobulins, mostly IgG, and C3 at the basement membrane zone and in the perivascular region. Although direct immunofluorescence is not a useful tool in distinguishing pseudoporphyria from porphyria cutanea tarda, it is helpful in the evaluation of other entities in the differential diagnosis of pseudoporphyria, specifically epidermolysis bullosa acquisita. Epidermolysis bullosa acquisita can be ruled out by the lack of intense, linear immunoreactants at the dermal-epidermal junction. Neither porphyria cutanea tarda nor pseudoporphyria has circulating autoantibodies detected by indirect immunofluorescence study.

Treatment

Medical Care

- The primary treatment of pseudoporphyria is to discontinue the offending agent whenever possible.
- Resolution of the clinical findings may take many months, particularly in drug-induced pseudoporphyria.

Follow-up

Prognosis

- The prognosis is good for pseudoporphyria once the offending agent has been discontinued. However, it may take several months for all the skin lesions to resolve, and some patients are left with permanent scarring.

Patient Education

- Educating patients about the causes of pseudoporphyria is important.
    - Patients should avoid solar and tanning salon radiation.
    - If the condition was drug related, patients should avoid medications in a similar class of drugs (eg, other propionic acid NSAIDs) whenever possible.

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