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Cutanea Tarda Porphyria

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Introduction

Porphyrias are a spectrum of metabolic disorders arising from a defect or alteration of enzymes in the heme biosynthesis pathway which present with either neurovisceral symptoms, cutaneous symptoms, or a combination of the two. Porphyria cutanea tarda (PCT), the most common porphyria, is the result of a deficiency of the enzyme uroporphyrinogen decarboxylase (UROD). The hallmark of this disorder is photosensitivity.[1][2] Hepatic UROD is tasked with the conversion of uroporphyrinogen III to coproporphyrinogen III, and failure to do so results in the accumulation of the preceding compounds in the liver that eventually appears in the plasma and urine.[3]

Hepatoerythropoietic porphyria (HEP) is another rare form of porphyria which is clinically very similar to PCT but occurs due to homozygous mutation of UROD genes, whereas in PCT, the mutation in UROD gene, when present, is usually heterozygous.

In this article, we discuss the different causes of UROD deficiency, along with clinically pertinent information for diagnosing and managing patients with PCT.

Etiology

Porphyria cutanea tarda is seen in patients with the reduced or absent enzymatic activity of uroporphyrinogen decarboxylase, which leads to a build-up of highly carboxylated porphyrinogens like uroporphyrinogen. These compounds get oxidized to their respective porphyrins, uroporphyrin, and heptacarboxyl porphyrins. The accumulation of these toxic compounds in different organs, especially the liver and skin, leads to the clinical manifestations seen in patients. An important point to note is that the enzymatic activity should drop below 20% before clinical manifestations can be seen.[4]

Classification of PCT

- Type I PCT: This is the sporadic type of PCT and is the most common form accounting for 80% of cases. The UROD enzyme levels will be normal, with decreased *activity* confined to the liver likely caused by a UROD inhibitor and the susceptibility factors listed below.[3][2]
- Type II PCT: This is the familial type of PCT, which is inherited in an autosomal dominant fashion. It constitutes about 20% of all PCT cases. The important difference in this type is the reduction of enzymatic activity in all cells by 50%.[5] Since only 20% of UROD enzyme activity is adequate to maintain physiologic function, the presence of environmental factors or a UROD inhibitor is needed to express symptoms. This explains why most gene carriers are asymptomatic.
- Type III PCT: This rare type of PCT is very similar to type I because of normal UROD genes. Yet, this type is observed in more than one family member suggesting the presence of a genetic mechanism other than UROD mutation.

UROD Inhibitor

The importance of iron in the pathogenesis of PCT has been realized due to alteration in iron metabolism with iron overload and elevated ferritin levels. [6] Iron overload facilitates the formation of oxygen-free radicals, which in turn

helps the formation of a UROD inhibitor and also increases the photosensitizer potential of uroporphyrin.

Other susceptibility factors are also thought to be contributing to the development of UROD inhibitors.

Susceptibility Factors

The following is a list of factors that can trigger the clinical manifestations of PCT, and in most cases, a combination of two or more is required to do so:

- Alcohol: Alcohol downregulates hepcidin and also increases the absorption of iron. It increases the ALA synthase (delta-aminolevulinic acid synthase) activity while inhibiting uroporphyrinogen decarboxylase. About 80% to 90% of patients with PCT manifestations have a history of heavy alcohol consumption.[7]
- Hepatitis C Virus (HCV): There are several proposed mechanisms for HCV contributing to PCT, including increased hepatocyte iron, increased oxidative stress on hepatocytes, decreased intracellular glutathione concentration, and the formation of a UROD inhibitor. But it is important to note that the pathogenesis here is not related to a reduced enzyme activity but direct damage to the liver cells.[8]
- Estrogen: Although the mechanism by which estrogen exposure causes PCT manifestations is unknown, 66% of PCT patients report exogenous estrogen use.[9] However, there is evidence that diethylstilbesterol can induce ALA synthase and increase the build-up of porphyrins.[10]
- HIV: 13% of PCT patients report HIV infection.[9] The effect of HIV on PCT is thought to be due to a higher incidence of concurrent HCV infection in these patients. Interestingly, the HIV virus can be detected in the blister fluid of patients with HIV and PCT.[11]
- Hemochromatosis: 53% of PCT patients have a hemochromatosis gene mutation.[4][9] C282Y and H63D are two important mutations to be considered in the association between hemochromatosis and PCT.[12]
- Smoking: The percentage of patients with PCT who have admitted to smoking at some point is very high (81%). The mechanism here is the induction of CYP1A2 synthesis, which in turn induces synthesis of the UROD inhibitor.

Chemical Porphyria: Clinical presentation is similar to PCT. This variant was most famously seen in Turkey during the 1950s famine, where thousands of children and adults consumed wheat treated with the fungicide hexachlorobenzene.[13]

Epidemiology

PCT is the most common type of porphyria worldwide.[4] It has a prevalence of about 1 in 10,000 people according to a Norwegian study and occurs most commonly in middle-aged adults.[14] A 1 in 25000 prevalence has been reported in the United States.

PCT usually affects both males and females equally. Some of the susceptibility factors favor one sex over the other at times like estrogen use in women and alcohol, HCV in men.

Pathophysiology

To understand the pathophysiology of PCT, we should discuss the interplay between the various cell processes that take place to give rise to the cutaneous manifestations of this condition. The deficiency or absence of the enzyme uroporphyrinogen decarboxylase causes an accumulation of porphyrins. This spills into the bloodstream, where it interacts with external sources of light, especially blue light, with a wavelength of 410 nm. This initially excites the porphyrin molecules. They subsequently go back to their original ground state after releasing energy. This energy is transferred to molecular oxygen and creates 'singlet-excited oxygen,' which is implicated in oxidizing several essential biological compounds like lipids, proteins, and causes peroxidation of cell membrane lipids, disintegrates cell membrane, and eventually leads to cell death.[15]

This situation presents clinically as skin fragility and blister formation.[16] The complement system can get activated, leading to degranulation of mast cells and accumulation of transforming growth factor–β (TGF-β), which has been shown to contribute to the tissue sclerosis seen in PCT.[17]

Histopathology

Cutaneous pathologic findings: Sub-epidermal bullae and thick hyalinized blood vessels in the upper dermis are seen. Caterpillar bodies, which are linear globules that stain PAS-positive, are present at the roof of the blisters and represent disintegrating keratinocytes and basement membrane material. Dermal sclerosis may also be present, which can be histologically identical to scleroderma.

Hepatic pathologic findings: Focal steatosis and lobular necrosis with pigment laden macrophages can be seen along with portal inflammation and periportal siderosis. The accumulation of porphyrins can be demonstrated by red autofluorescence upon exposure to UV light. Acicular inclusions, which are birefringent needle-like cytoplasmic inclusions, are specific to PCT and represent uroporphyrin accumulation.[11]

History and Physical

Clinically, type I and type II PCT are similar, and the need for differentiating the two arises only during the management and patient counseling. The patients should be asked in detail about any of the susceptibility factors discussed above, like alcohol, smoking, chemical, or estrogen exposures. Any evidence of neurovisceral symptoms can help point to other porphyrias. Family history is usually not helpful, and a detailed medication history might be beneficial to rule out any drug-related eruptions. Since the porphyrin accumulation in the PCT can change the urine color to reddish-brown, a complete history will also include questions about the patient's urine color.

Cutaneous Manifestations

Photosensitivity, along with the formation of skin blisters, vesicles, bullae, and increased fragility of the skin, is seen on sun-exposed parts of the body. This most commonly involves the back of the hands, forearms, neck, face, and feet. These repeated insults to the skin later resolve, leaving behind hyper- and hypopigmented scars and milia, which are small yellowish-white keratin filled papules.[10] Since PCT is delayed blistering photosensitivity, most patients do not associate sun exposure with their skin lesions.[4] These skin lesions arise from minor trauma and sometimes may get infected, causing intense pain and inflammation.[18] The scarring may lead to contractures mimicking the skin findings of a patient with scleroderma, thus labeling this phenomenon as "pseudoscleroderma."[19] Scarring alopecia on the scalp can lead to a diffuse hair loss.

Pigment changes can be seen in the facial, orbital, or malar regions ranging from blue to purplish-brown colors.[11] Occasionally an appearance akin to the plethora of polycythemia vera can be seen as an erythematous suffusion on sun-exposed areas.[10]

A non-virilizing type of hypertrichosis around the cheeks, temple, and forearms can be seen in women. Sometimes, this could be the only physical manifestation seen in PCT patients.

Evaluation

Evaluation of a patient with porphyria includes:

Urine or plasma levels of total porphyrins: Elevated in both PCT and Hepatoerythropoietic porphyria. Uroporphyrin and heptacarboxyl porphyrin are usually elevated along with normal levels of urinary ALA and Porphobilinogen. Checking for porphyrin levels in feces is not needed for diagnosis but may be useful in patients undergoing hemodialysis.

Once the level of porphyrins has been found to be elevated, porphyrin fractionation and other tests are required to pinpoint PCT as the underlying cause of the skin lesions. Water-soluble carboxylated porphyrins are found in the urine point towards PCT and HEP, whereas increased levels of coproporphyrin do not. HEP shows a very high level of erythrocyte protoporphyrin and hence can be distinguished from PCT.[20] Using the plasma fluorescence peak wavelength at neutral pH, PCT can be differentiated from variegate porphyria, which is easily mistaken for the other on initial diagnosis.

A patient’s urine, blood, and stool can be tested for increased porphyrin levels. Below is the pattern of porphyrin accumulation specific to PCT.[10]

- **Urine**: ↑ Uroporphyrin, ↑ Coproporphyrin, normal Porphobilinogen, normal ALA

- **Stool**: ↑ Uroporphyrin, ↑ Isocoproporphyrin, ↑ Protoporphyrin
- **Red blood cells**: normal Uroporphyrin, Coproporphyrin, and Porphobilinogen
- **Plasma**: ↑ Uroporphyrin

Skin Biopsy: This is not needed for diagnosis and may only help in excluding some other skin conditions from the cutaneous porphyrias. Subepidermal blisters and depositions in vessel walls are some of the biopsy findings seen in porphyrias.[21]

Treatment / Management

The first step in the management of PCT is the avoidance of precipitating and susceptibility factors. Since this is a photosensitive skin condition, sunlight avoidance is the key until the porphyrin levels have normalized. The wavelengths inducing porphyrins are in the range of 400-410nm, and only titanium dioxide or zinc oxide containing sunscreen is effective.[10] Protective clothing is also helpful in protecting the skin from harmful sunlight rays. Any affected skin areas should be kept clean to prevent the development of skin infections, and associated pain can be managed with oral analgesics. Other things to strictly avoid include alcohol, smoking, and estrogen therapy, along with limiting any excess intake of iron.

The mainstay therapies of PCT are phlebotomy and hydroxychloroquine. Depending on the specific comorbidities and susceptibility factors, we can choose one over the other.

Phlebotomy: Any condition leading to iron overload in the patient is a clear indication for phlebotomy, and in such cases, phlebotomy is preferred over hydroxychloroquine. Different protocols have been tried, such as removing one unit or 450 ml of blood every two weeks. Strict serial monitoring of ferritin levels is done, and a downward trend in serum ferritin level is the goal of phlebotomy (till a ferritin level of less than 20 ng/ml is seen).[22][23] Alternatively, 300ml of blood removed weekly is another treatment strategy that can be used. Care should be taken not to induce anemia or hemoglobin less than 10 gm/dL. The skin manifestations resolve within four months, but the porphyrin levels can take up to 12 months to normalize. Serum ferritin levels may be used as an indicator to monitor for relapse of this condition since the levels change before porphyrin levels.[11] Contraindications to phlebotomy include patients with pulmonary or coronary artery disease.

Hydroxychloroquine or chloroquine: These are preferred therapies in cases where ferritin levels are not elevated (below 600 ng/mL) or a patient without an HFE mutation. They act by inhibiting the formation and secretion of porphyrins.[11] Chloroquine 125mg twice weekly or in cases of intolerance, hydroxychloroquine can be used twice weekly at a dose of 200mg. The latter may be safer in terms of retinal toxicity.[24] These regimens can take between 6-9 months for complete remission. Contraindications to these drugs include pregnancy, liver disease, retinal disease, and the concomitant use of other hepatotoxic drugs. Regular ophthalmologic examination and liver function tests monitoring are required.

Chelation therapy: Iron chelation was considered to be an alternative in people with iron overload-induced PCT, but after comparative studies with phlebotomy and hydroxychloroquine, it was not found to be as efficient. However, deferoxamine and deferasirox can be used in patients with contraindications to both phlebotomy and hydroxychloroquine. The disadvantages of chelation therapy other than being expensive due to the use of a subcutaneous pump were the failure to normalize the porphyrin level even after 12 months of treatment.

Differential Diagnosis

The most important differentials in a patient with suspected PCT include hereditary coproporphyria, variegate porphyria, and congenital erythropoietic porphyria due to the cutaneous manifestations seen in all four along with elevated porphyrin levels. As mentioned above for PCT, all other conditions will have specific patterns of porphyrin elevation, which would be diagnostic of that disease. Variegate porphyria, for example, would have an increased urinary level of coproporphyrins, ALA, and porphobilinogen, whereas congenital erythropoietic porphyria would have normal urinary ALA and porphobilinogen levels. However, both variegate porphyria and hereditary coproporphyria can be clinically differentiated from PCT based on their presenting neurovisceral symptoms, which is lacking in patients with PCT.[10]

Blistering skin diseases: Epidermolysis bullosa, polymorphous light eruptions, and pseudoporphyria cutanea trade. All three conditions, although clinically similar to PCT, will not cause a rise in porphyrin levels and hence can be distinguished from PCT using laboratory investigations.

- Pseudoporphyria cutanea tarda is clinically and histologically indistinguishable from PCT but without the porphyrin elevation. It is associated with Nonsteroidal anti-inflammatory drugs (NSAIDs), furosemide, antibiotics (nalidixic acid, tetracyclines), or retinoid use.[10]
- Epidermolysis bullosa acquisita is an autoimmune blistering disorder that presents with widespread blisters not limited to sun-exposed skin surfaces.[25]
- Polymorphous light eruption is a photo distributed pruritic rash that develops minutes to hours after sunlight exposure and is characterized by erythematous papules, vesicles, and plaques that are nonscarring.[26]

Porphyrin elevation is also seen in liver disease, advanced renal disease, and other porphyrias. However, they will not show the typical cutaneous manifestations seen in patients with PCT.

Prognosis

Life expectancy in patients of PCT is expected to be normal unless there are comorbid conditions like HCV that could lead to liver disease or carcinoma. Full remission is achievable, but recurrence, however, is possible. Relapses of up to 35% have been recorded over a follow-up period of up to 11 years.[27] Patients with elevated iron levels may need periodic phlebotomy. Patients who continue to be exposed to susceptibility factors, such as excessive alcohol consumption and smoking, are also more likely to relapse. Annual monitoring of urine and plasma uroporphyrin levels is recommended to detect biochemical relapses before the clinical manifestations of the disease appear.[28]

Complications

Although the clinical manifestations of PCT are limited to the skin, patients are also at a high risk of hepatic complications. Liver biopsies usually reveal fatty changes along with porphyrin deposits and sometimes lobular necrosis. PCT independently increases the risk of liver cirrhosis and hepatocellular carcinoma, which may be accentuated by co-existing HCV infection, alcoholic hepatitis, or iron overload.[29]

Deterrence and Patient Education

Patients should be educated about the entire disease process and reassured about the non-fatality of this condition. Phlebotomy should be explained along with the need for regular appointments to check porphyrin levels in the blood. Avoidance of susceptibility factors like cessation of smoking, alcohol, estrogen, and iron therapies along with the importance of sun-protective measures like sunscreens, hats, and protective clothing should be emphasized. Any prior history of HCV or HIV should be disclosed, and the patient should strictly adhere to the treatment regimens advised by the treating physician.

Testing for ferritin levels, infections, and genetic testing are all part of the treatment strategy for PCT, and the patient should be made aware of this.

Pearls and Other Issues

- Porphyria cutanea tarda is the most common porphyria caused by decreased activity in the uroporphyrinogen decarboxylase enzyme, leading to the accumulation of porphyrins.
- Alcohol, estrogen use, viral infections, smoking, and iron overload are susceptibility factors that are commonly associated with the development of porphyria cutanea tarda.
- Excessive circulating porphyrins react with light causing a delayed skin reaction manifesting as blisters, hypertrichosis, hyperpigmentation, and scleroderma-like changes on sun-exposed surfaces.
- Porphyria cutanea tarda may be treated by simply avoiding the precipitating factors. However, phlebotomy and hydroxychloroquine are both effective in achieving biochemical and clinical remission.

Enhancing Healthcare Team Outcomes

Porphyria cutanea tarda is one of the many porphyrias that result due to an abnormal enzyme in the heme biosynthesis pathway. Patients present with a blistering skin manifestation and notably lack any neurovisceral symptoms. It is essential to consider a urinalysis, stool analysis, and blood tests to establish the diagnosis. Along with this, a detailed account to uncover all susceptibility factors should be a priority as the avoidance of these factors is a vital aspect of the patient's management.

Although an internist or a hematologist would generally handle this case, it is important to note the involvement of all other specialties in the diagnosis and management of this patient. The primary care physician or internist who might see the patient first should take a detailed personal and family history before they refer the patient to a dermatologist or a hematologist. The dermatologist plays a vital role in identifying this as a blistering skin condition, which would help narrow down the differentials. A skin biopsy is not necessary for diagnosis but may be done. If it is done, the role of the pathologist comes into play to view the specimen and give more clues that point to the diagnosis. The evaluation and management will be centered on the hematologist.

Laboratory investigations are required such as urine, fecal, and blood samples are usually sent for the measurement of porphyrin levels. This would typically establish the diagnosis, although porphyrin fractionation is needed to differentiate between porphyrias that present similarly biochemically. The management is centered on weekly or bi-weekly phlebotomies and hydroxychloroquine. Phlebotomists are, therefore, also an essential part of the treatment team. The nurse monitors the blood pressure of the patient at every visit and is part of the core team to educate the patient and families. Complications involving the liver can arise, which would require consultations with a hepatologist or gastroenterologist. Counselors are integral to help patients avoid or cease any habits that might be a trigger for the manifestation of this disease like smoking, alcohol, etc. Since PCT might have a familial component, the opinion and consultation with a genetic counselor may also be required.

To improve patient care and provide the best line of management for these patients, an interprofessional collaboration between different specialties is highly recommended.[30]

Continuing Education / Review Questions

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