Porphyria Cutanea Tarda

Background

1. Definition
   - Porphyria cutanea tarda (PCT) involves malfunctioning of uroporphyrinogen decarboxylase (UROD) and the resulting buildup of upstream porphyrin metabolites of the heme synthesis pathway, particularly uroporphyrinogen III
2. Types:
   - Type 1 - acquired or sporadic
     - Occur in individuals with a genetic predisposition after exposure to hepatotoxins or in the context of hepatic tumors
   - Type II - familial
     - UROD gene mutations, most commonly autosomal dominant transmission
3. The fungicide hexachlorobenzene (potent UROD inhibitor) caused an outbreak of PCT in 1955[2]

Pathophysiology

1. When UROD activity falls below a critical threshold, porphyrin by-products of the heme biosynthetic pathway are overproduced
   - This may result from
     - Substance toxic to UROD (Type I)
     - Defective UROD gene (Type II)
     - Both a clear environmental trigger and a family history (Type III) but when tested the UROD gene appears to be normal
2. All porphyrins and byproducts can cause formation of singlet oxygen which is tissue toxic
   - In PCT, water soluble uroporphyrinogen permeates up through the dermoepidermal junction, where upon exposure to light forms toxic singlet oxygen
3. With no available heme to attach itself to iron has a tendency to accumulate in PCT
   - Counterintuitively, iron can inhibit UROD
   - Iron overload may be the precipitating event in PCT
   - 15% of patients with PCT may be secondary iron overload from hemochromatosis
4. Gradual onset
   - Unlike other porphyrias PCT results as a chronic buildup of porphyrins, iron or both
   - Onset later in life, hence the name "tarda"
5. Prevalence
   - Estimated 1/25,000-50,000
   - Prevalence may be underestimated:
     - In neurology clinic in Helsinki 21% of patients with undiagnosed neuropathy had elevated urine porphyrobilinogens
   - PCT is the most common of porphyrias
   - Slightly more prevalent in men

6. Risk factors
    - Type I Exposure to known porphyrinogenic compounds:
        - Hexachlorobenzene
        - Dioxin
    - Type II (People that have deficiency in UROD gene)
        - Sun exposure
        - Alcohol
        - Estrogen therapy (either hormone replacement or contraception)
        - Liver injury:
            - Acquired Immunodeficiency Syndrome (AIDS)
            - Hepatitis C virus infection
            - Hemodialysis
            - Hemochromatosis
7. Morbidity, mortality
    - PCT probably least dangerous of porphyrias
    - Normal life expectancy with
        - Avoidance of triggers, including some medications (estrogens)

Diagnostics

1. History
    - Middle-aged and male
    - Painful blisters on sun-exposed skin
    - "Fragile skin"
    - Exposure to alcohol or estrogen
    - Family history in a minority of patients
    - Note:
        - Severe abdominal pain and neurologic symptoms associated with other acute porphyrias is NOT a feature of PCT
        - Anemia associated with the erythropoietic porphyrias is NOT a feature of PCT
            - In fact, phlebotomy is an excellent treatment for PCT to reduce iron stores
2. Physical exam
    - Blisters
    - Hypertrichosis - etiology uncertain
3. Diagnostic testing
    - Nonspecific testing
        - Complete blood count (CBC) - rule out anemia and/or assess baseline parameters if phlebotomy is being considered
        - Liver enzymes to assess liver damage
        - Consider hepatitis profile
        - Iron studies
        - Culture lesions (particularly if bullous impetigo or herpes is being considered)
    - Specific testing
        - Note:
            - Protect samples from light and have them analyzed promptly
        - Screening
            - Total plasma porphyrin

- Further testing may be indicated if condition cannot be distinguished from other porphyrias that feature blistering lesions
- Although urine porphyrobilinogen (PBG) is used as a rapid screen in the acute porphyrias (in which case the patient is shrieking and writhing in pain) urine PBG can be elevated in a number of other illnesses that affect the liver and/or bone marrow
- Excess porphyrins in plasma and urine in PCT are mostly uroporphyrin (octacarboxylporphyrin) and heptacarboxylporphyrin
- Predominance of fecal isocoproporphyrins is highly specific for PCT but is only performed in specialty laboratories
- Genetic testing can be considered, especially if there is a family history of similar illnesses

Differential Diagnosis

1. Contact dermatitis
2. Herpes simplex
3. Epidermolysis bullosa (Similar to porphyria cutanea tarda, but not associated with hypertrichosis)
4. Epidermolysis bullosa acquisita
5. Hydroa vacciniforme
6. Pemphigus vulgaris (Flaccid bullae, large painful erosions)
7. Lupus erythematosus, bullous
8. Pseudoporphyria (many diseases can cause elevated porphyrin level)
9. Variegate porphyria
10. Erythropoietic porphyria

Therapeutics

1. Acute treatment
    - Supportive
        - Fresh blisters should be kept free from infection
2. Long-term care
    - Monitor for iron overload
    - Hydroxychloroquine 200 mg by PO twice a week
    - Phlebotomy 400 ml removed every 2 weeks until iron overload is relieved
    - Erythropoietin may be used to treat anemia resulting from phlebotomy and is thought to mobilize iron stores

Follow-Up

1. Return to office
    - Monitor closely while patient is undergoing phlebotomy (every 2-4 weeks)
    - Urine porphyrins every 3 months[6]
    - Recommendations for earlier follow-up if experiencing increase in lesions
2. Refer to specialist
    - Dermatologists may have the most experience in treating this condition

Prognosis

1. In a Swedish prevalence study, life expectancy was normal[7]
2. 20% of patients can develop sclerodermatous lesions
3. Rarely patients may develop hepatoma

Prevention

1. Type I - ban or limit the use of causative agents (which was done in the case of chlorohexabenzene
2. Consider genetic screening of family members for type II to personalize recommendations regarding precipitating factors
3. Avoid precipitating factors listed in risk factors above

Patient Education

1. American Porphyria Foundation:
    - http://www.porphyriafoundation.com

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