CLINICAL EVOLUTION OF PORPHYRIA CUTANEA TARDA (PCT) IN HCV MONO-INFECTED AND HIV/HCV CO-INFECTED PATIENTS AFTER VIRAL ERADICATION WITH DIRECT ACTING AGENTS (DAA)

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Enfermedades Infecciosas – Aparato Digestivo
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Porphyrias result from deficiencies of different enzyme of in the heme pathway which gets to accumulation of porphyrins within the liver or bone marrow.

Porphyria cutanea tarda (PCT)
The most common porphyria among general population.

PCT Epidemiology

- **Global prevalence**: 1/10,000 people with a nearly equal sex ratio.³

- Prevalence of PCT is variable throughout the world.
  - USA: 1/25,000 is affected
  - Czech Republic and Slovakia: 1/5000 ⁴
  - Norway: 1/100,000 ⁵
PCT Classification

- **TYPE I** (spontaneous or acquired) 70–80% of p.
  - Enzymatic disfunction.
  - Most of the time patients maintain normal levels of UROD and are asymptomatic.

- **TYPE II** (familial or inherited) 20% of p.
  - Inherited in autosomal dominant way, incomplete penetrance (typically heterozygous*).
  - Deficient UROD in all tissues (not only the liver).
  - UROD functioning at ~ 50% of normal.

*Homozygosis for UROD mutation: hepatoerythropoietic porphyria (HEP).
3 possible mechanisms.

1. Disruption of the UROD activity in the heme-biosynthetic pathway.

2. Increase the rate of uroporphyrinogen to be oxidized to uroporphyrin → can inhibit UROD.
   - **Key link** among PCT, chronic liver disease, and iron overload states!!

3. Increase in activity of other enzymes (hepatic 5-aminolevulinic acid synthase [5-ALAS]) → increased levels of uroporphyrinogen in hepatocytes.

   - UROD activity decreases <20-25% → uroporphyrin in organs (skin and liver).

   - Photochemical reaction upon exposure to sunlight → skin manifestations of PCT.
     - Photo-activation of complement system leads to activation of mast cells and proteases, and this causes dermal-epidermal splitting.
PCT – Clinical manifestations

- **Cutaneous photosensitivity**
  - Increased skin fragility (milia cysts, vesicles, bullae, erosions, and crusts) - 33.3% of p.
    - Most commonly on dorsum of hands but also on forearms, face, legs, and feet.
    - Rupture of blisters leave areas of atrophy and scarring
  - Non-virilizing hypertrichosis (temples/cheeks, most noticeable in females)
    - **Most prevalent:** 84.8% of p.
  - Pruritus (sun-exposed) - 27.3% of w. (< in m.)
Characteristic bullae most commonly occur on the dorsum of the hands. Hypertrichosis in temples and scarring in neck.

Gift from Dermatology Unit in Hospital Universitario de La Princesa.
Clinical examination is insufficient.

**Porphyrians of the blood, urine, and feces.**
- Urine sample
- Isocoproporphyrin in stool (elevated)

UROD activity (erythrocytes): reduction of activity in hereditary PCT but not acquired.

Histologic evaluation of a fresh blister:
- Subepidermal blister with an upward projection of the dermal papillae (festooning)
- Little inflammation and eosinophilia.
- Linear basement membrane material that resembles dyskeratotic cells on the blister roof (“Caterpillar bodies”).
Thickened stratum corneum and blister fluid separating dermal layers, expanded dermal papillae, and fibrosis and sclerodermoid skin changes.

Gift from Anatomical Pathology Unit in Hospital Universitario de La Princesa.
Associations/ Risks factors

- Alcohol
- Iron
- Hemochromatosis (1/200–300 of European descent)
- Estrogens
- Hepatitis C Virus
- Human Immunodeficiency Virus
- Hepatic Siderosis and Cirrhosis
- Diabetes Mellitus
- Smoking
- Sjögren’s Syndrome or Systemic Lupus Erythematosus
- Cancer Treatment
- Olmesartan
- Agent Orange (Vietnam War)
Classical treatment

- **Repeated phlebotomy**  
  → reduce hepatic iron overload.

- **Chloroquine/hydroxychloroquine**  
  Twice per week (+/- phlebotomy)
PCT & HCV

- **Strong correlation** (higher in type I)\(^9\)
  - 50% prevalence of HCV in those with PCT\(^{11}\)
  - 5% reported prevalence of PCT in those with HCV\(^{12}\).
- Strong regional factors:
  - Southern Europe: between 70 and 90\%\(^{11}\) - Italy: above 50\%\(^8\)
  - Northern Europe, Australia, England: 20\%\(^{10}\)
  - Germany: 8\% (Stölzel; 1995).
  - United States: 56\%\(^{10}\).

- **Treatment PCT + HCV**
  - Phlebotomy:
    - Restricts progression and reduces severity of chronic HCV + reduce risk of HCC.
    - May improve response to IFN-based treatment\(^{13}\).
  - PCT to be induced by IFN/ribavirin therapies (hemolytic anemia by RBV).\(^{14}\)
  - These individuals might strongly benefit from therapy with DAAs.
OBJECTIVES

We want to analyse the effect on PCT symptoms of achieving HCV eradication with DAA.
MATERIAL AND METHODS

- Descriptive retrospective study - medical histories review
- HCV Patients + DAA in our hospital (Infectious + Digestive Units).
- Baseline characteristics:
  - Age, sex, group of risk -GR-.
  - HIV infection (when positive, CD4 count cell + HIV VL).
  - HCV: genotype, HCV VL, fibroscan® and fibrosis stage, DAA regimen and virological outcome.
- PCT:
  - Associated risk factors (HT, DM, DL, smoking, alcohol, gen. polymorphisms HFE and UROD).
  - Clinical diagnosis
  - Previous treatment (phlebotomies/chloroquine).
  - Evolution of the cutaneous symptoms before/after achieving virological response.
Statistics by SPSS22.0
BASELINE CHARACTERISTICS (n = 13)

<table>
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<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age (mean)</td>
<td>57 y</td>
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<tr>
<td>Female sex (n)</td>
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<tr>
<td>Group of risk</td>
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<tr>
<td>Former IVDU</td>
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<tr>
<td>MSM</td>
<td>1</td>
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<tr>
<td>HIV coinf.</td>
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<tr>
<td>N</td>
<td>8</td>
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<tr>
<td>HIV VL &lt; 20 cop</td>
<td>7</td>
</tr>
<tr>
<td>CD4 cell (med)</td>
<td>663</td>
</tr>
<tr>
<td>Fibroscan® (med)</td>
<td>10.2 kPa</td>
</tr>
</tbody>
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HCV GENOTYPE

- G1a
- G1b
- G3
- G4

FIBROSIS

- F0-2
- F3
- F4

DAA

- 3D
- 3D+DAC
- 3D+SIM
- RBV

SVR12

- 100%

RVS

RESULTS
**RISK FACTORS**
- Smokers: 12
- Alcohol: 9
- HT: 6
- DL: 3
- DM: 2

**URINE PORPHYRINS**
- HIGH: 6

**GENETIC POLIMORPH**
- UROD: 3
- H63D: 2
- G282Y: 1

**SKIN MANIFESTATIONS**
- Blisters: 10
- Scarring: 8
- Hypertri.: 6

**CLASS. TREATMENT**
- Phlebo.: 10
- Chloro.: 8

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**Pre - DAA**
- 13
- 3
- 2
- 8
  - 5 – Partial improv.
  - 3 – Total improv.
  - Asymptomatic
  - No change

**Post - DAA**
- 13
- 7
- 6
- 13
  - Previously asymptomatic
  - Improvement
CONCLUSIONS

- Strong correlation between PCT & HCV
- PCT could be induced by IFN/ribavirin therapies\textsuperscript{14}
- Classical treatment often failed to control symptoms.
- These patients benefit from DAAs therapies
  - Control of the cutaneous activity is achieved in all our patients after viral eradication with DAA.
Thank you for your attention