Porphyria: clinical presentations, diagnosis and treatment

Riga, 11 February 2016

Wouter Meersseman, MD, PhD
Porphyria

• Introduction

• Classification
  – Acute porphyria
  – Cutaneous porphyria
  – Rare recessive porphyrias

• Conclusion
History

- **Porphyra**: purple pigment
- Described by Hippocrates
- 1871, Felix Hoppe-Seyer: causal link with porphyrine
- 1889, Dr. Stokvis: porphyria as a clinical syndrome
- King George III
- Vampires and werewolves
Porphyria

• Metabolic disease

• Defect in 1 of the 8 enzymes involved in synthesis of haem

• Build up of haem precursors
  -> symptoms (neurovisceral and/or cutaneous)

• Inborn - acquired
Haem

• Synthetized in every cell

• 80% in bone marrow (hemoglobin)

• 15% in liver: production of cytochrome P450 enzymes (CYP’s)

• Other haem-containing proteins: myoglobin, respiratory cytochrome, catalase, NO-synthase
Haem synthesis

SuccinylCoA + Glycine

→ ALA

ALAD

→ PBG

PBG dioxygenase

→ Protoporphyrin IX

Protoporphyrin IX

→ Haem

neurotoxic

→ Acute porphyria attack

Porphyrines

→ fototoxic

→ skin
Figure 1: Haem biosynthetic pathway and porphyrias

• Regulation

  – **ALAS1**: *in liver and other cells*
    
    • Rate limiting enzyme
    • Negative feedback by haem (R/haemtreatment in acute porphyria)
    • Haem required for CYP’s
      -> induction of CYP’s (bv medication,...) -> induction of ALAS1

  – **ALAS2**: *only in erythroblasts in bone marrow*
    
    • No inhibition by haem
    • Dependent on iron and EPO availability

    – (**ALAD**: inhibited by lead, tyrosinaemia type I)
Porphyria

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  – Acute porphyria
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• Conclusion
2. Classification

Hepatic  Erythropoïëtic

Acute  Cutaneous
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* Very rare recessive form
A. Acute porphyrias

- Protoporphyrinogen oxidase
  - 1/150,000
  - 80% skin lesions

- Coproporphyrinogen oxidase
  - 2/1,000,000
  - 5% skin lesions

- Acute intermittent porphyria
  - Autosomal dominant with low penetrance
  - Porphobilinogen deaminase (PBGD)
    - 1/75,000 (Sweden 1/1000)
    - Never skin problems

- X-linked dominant protoporphyria
- ALAS2
- ALAS1
- ALA dehydratase porphyria
- PBG

- Variegata porphyria
- Hereditary coproporphyria

- Erythropoietic protoporphyria
- Protoporphyrid IX
- CPO
- PPOX
- FECH
- Succinyl CoA + Glycine
- Haem
- ALA
- ALAD
- PBGD

- Spontaneous cyclisation
- Congenital erythropoietic porphyria
- Uroerythrocruorin III
- Uroerythrocruorin I
- Uroporphyrinogen III
- Uroporphyrinogen I
- Porphyria cutanea tarda
Pathogenesis

- Overproduction of precursors in liver (PBG, ALA) -> neurotoxic

- Attacks provoked by events that
  - Induce ALAS1
  - Give rise increased breakdown of haem
• **Events:**
  – Hormonal fluctuations (menstrual cycle)
  – Not enough nutritional intake
  – Smoking
  – Alcohol
  – Porphyrinogen medication
    • CYP induction
  – Inflammation/infection
    • Induction of haem oxygenase 1 (acute phase reactant) -> breakdown of haem
Clinical presentation

- Women (80%) > men (20%)
- Between 20 and 40 yrs of age

- Acute attacks with neurovisceral pain
  - Visceral
    - Abdominal pain!
    - Pain in the back, in the area of the quadriceps (less frequently)
    - Nausea, vomiting, constipation
    - Normal clinical examination
    - Abdominal X-ray: sometimes ileus, distended colon
• Neurological
  – Mental disturbances
    » Anxious, depressive, disoriented, hallucinations, paranoia, confusion, decreased level of consciousness

  – Neuropathy
    » Motor neuropathy
    » Pain and weakness in the muscles (proximal, arms > legs)
    » If not recognized: tetraplegia with respiratory and bulbar paralysis
    » Cave: porphyrinogenic drugs during attack

  – Pyramidal signs, ataxia, transient blindness (PRES)
- Increased sympathicus activity
  - Hypertension
  - Tachycardia
  - Sweating

- Electrolyte abnormalities (hyponatremia due to SIADH, hypomagnesemia)
  -> epilepsy

- Red or darkcolored urine

- Duration attack: 1 to 2 weeks
- Great majority of patients: only 1 to 3 attacks during life
- 10% frequent attacks
Diagnosis

• Samples (urine, plasma, faeces) should always be protected from light

• During attack
  – Sample of urine
    • Porphobilinogen (PBG)
      » Semi-quantitative/qualitative
      » Quantitative test
    • ALA
      – Lead intoxication and ALAD

  -> increased in AIP, HCP and VP (concentrations highest in AIP)
• **For further identification**
  – Porphyrine measurement in
    • **Plasma**: fluorescence emission spectroscopy
      – VP: peak at 624-628 nm
      – HCP (en AIP): peak at 620 nm
  
  • **Faeces**
    – AIP: normal
    – VP: raised proto > copro
    – HCP: raised copro (III > I)

  • **Urine**
    – No substantial added value, sometimes subtle abnormalities in liver disease and bone marrow diseases
    – If normal and PBG/ALA also normal: acute porphyria excluded
    – Levels raised in AIP but to a much lesser extent than in PCT

  • **Voor confirmatie**: enzyme activity, mutation analysis
• **During remission:**
  
  – Normale porphyrin levels in urine, faeces and plasma

  – AIP: PBG and ALA raised during several months after the attack (sens 88%, spec 61%)

  – VP: Plasma fluorescence, peak at 624-628 nm (sens 60%, spec 100%)

  – HCP: ratio faecal copro isomer III/I > 2

  – Enzyme activity/DNA analysis
Treatment

- Avoid precipitating agents
- Treat infection
- Symptomatic
  - Pain killers (opioids)
  - Anti-emetics
  - IV fluids (cave hyponatremia)
  - Anti-psychotics
  - In case of epilepsy: correction electrolytes, benzo’s, gabapentin, clonazepam
  - Intensive care

Chart 2. Safe and contraindicated drugs for bearers of acute porphyria 4.5.12

<table>
<thead>
<tr>
<th>Contraindicated</th>
<th>Safe</th>
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<tbody>
<tr>
<td>Valproic acid</td>
<td>Acetaminofen</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Narcotic analgesics</td>
</tr>
<tr>
<td>Barbiturics</td>
<td>Aspirin</td>
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<tr>
<td>Calcium channel blockers</td>
<td>Atropine</td>
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<tr>
<td>Carbamazepin</td>
<td>Betablockers</td>
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<tr>
<td>Carisoprodol</td>
<td>Bromides</td>
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<tr>
<td>Clonazepam (high doses)</td>
<td>Cimetidine</td>
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<tr>
<td>Danazol</td>
<td>Chlorpromazine</td>
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<tr>
<td>Diclofenaco</td>
<td>Diazepam</td>
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<tr>
<td>Ergots</td>
<td>Erythropoetine</td>
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<tr>
<td>Estrogen</td>
<td>Streptomycin</td>
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<td>Phenytoin</td>
<td>Phenothiazines</td>
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<tr>
<td>Grisofulvin</td>
<td>Gabapentine</td>
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<tr>
<td>Pyrazinamide</td>
<td>Glucocorticoids</td>
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<td>Progesterone</td>
<td>Chloral hydrate</td>
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<td>Rifampicin</td>
<td>Serotonin reuptake inhibitors (anti-depressants)</td>
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<td>Sulphonamides</td>
<td>Insulin</td>
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<td>Penicillin and derivatives Ranitidine</td>
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• Intravenous haem!
  – Inhibition of ALAS1
  – Human hemine (normosang)
  – 4 mg/kg for 3-4 days

• Repeated attacks
  – Consider maintenance treatment with haem
  – In severe cases: consider liver transplantation
Acute attack
- unexplained abdominal pain
- vomiting, constipation
- neuropsychiatric S/
- Hyponatremia

PBG (en ALA) in urine +

Treatment (IV haem)

Porphyrin in plasma, urine and faeces
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B. Cutaneous porphyrias with blisters

Porphyrins that build up in the skin
UV light
Excitation and oxidative stress
Blisters
Porphyria cutanea tarda

- By far most frequent porphyria (prevalence 1/5000 – 1/25000)

- 20% familial
  - Autosomal dominant with low penetrance
  - heterozygote -> 50% enzyme activity
  - Precipitating agents required for <20% enzyme activity and disease
  - Men = women
  - Early onset

- 80% sporadic, acquired
  - No mutation, acquired inhibition of UROD
  - Men > women
• Pathogenesis PCT
  – Always a component of acquired inhibition of UROD in PCT

  – Risk factors
    • Iron deposition!
      – Hepatic siderosis in liver biopsy specimens
      – Increased iron parameters (transferrin saturation, iron, ferritin)
      – HFE mutation frequently found
      – Decreased expression of hepcidine
      – Ijzeropstapeling alleen = onvoldoende voor PCT

  – alcohol, smoking, Hep C, HIV, oestrogens, CNI

  – Uroporphyrinogen -> CYP1A2 induction in the presence of iron -> uroporphomethen -> inhibition of UROD
Clinical presentation

- Blisters in sun exposed areas
- Fragile skin
- Hyperpigmentation
- Milia (small white lesions)
- Hypertrichosis
- Rarely ocular signs (pain, photophobia)
- Liver function abnormalities
  - In association with alcohol
  - Cirrhosis and HCC
Diagnosis

• Screening
  – Porphyrines in plasma
    • VP: peak at 624-628 nm - PCT: peak 620 nm
    • Chronically elevated

• Further differentiation
  – Urinary and faecal porphyrins
    • PCT
      – Urine: uroporphyrin, heptacarboxyl porphyrin
      – Faeces: isocoproporphyrins

• DNA-analysis, UROD activity in RBC
  – In hereditary cases
Porphyryins: light absorption
Porphyrides: fluorescence
Colourless

Porphyrinogen

Oxidation

Pink-red

Porphyrin
Treatment

- Protection from sunlight
- Avoid precipitating factors (alcohol, roken, E, ...)
- In PCT:
  - *Chloroquine* 100-200 mg 2x/week
    - Complex with porphyrins -> increased excretion in urine
  - *Phlebotomy*
    - 300-500 cc weekly until transferrin sat < 16%, normal ferritin
    - Treatment of choice in hemochromatosis
- Combination
- Monitoring:
  - plasma and urinary porphyrin concentration: should normalize after 9 months
Erosive photodermatitis
- Blisters
- Fragile skin
- hypertrichosis

Porphyrynes in plasma
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C. Acute painful photosensitive porphyria

- **Erythropoietic protoporphyria**
  - 1/75,000 – 1/200,000
  - Ferrochelatase deficiency (< 35%)
  - Inherited
    - Pseudodominant:
      - 1 mutant allele (no activity) – 1 polymorph allele with reduced activity
    - Homo- or compound heterozygote: severe disease with liver involvement
  - Acquired
    - Myelodysplasia and myeloproliferative disorders

- **X-linked protoporphyria (XLDPP)**
  - Men > women
  - Increase ALAS2 activity
  - Gain of function mutation
  - Liver involvement
Pathogenesis

Protoporphyrin accumulation in RBC, skin, liver, bile and faeces

-> painful photosensitivity and to a lesser extent cholestatic liver disease
Clinical presentation

• **Acute photosensitivity**
  – Begins in childhood
  – Burning painful sensation after a few minutes of sun exposure
  – Relief with cold water
  – Edema and erythema

• **Chronic**
  • Skin tighter
  • Scars in the face
• Liver abnormalities
  – In 10-20% of cases
  – Protoporphyrin gall stones
  – Cholestatic liver failure in 2%
    • Accumulation of protoporphyrin in hepatocytes/bile canaliculi
Diagnosis

• Protoporphyrin is lipidsoluble
  -> no urinary excretion

• Increased concentration free protoporphyrin in RBC and in plasma (peak at 634 nm)

• EPP
  – Enzyme activity of FECH < 35%
  – DNA-analysis

• XLDPP
  – Increased free and zinc protoporphyrin
  – Normal FECH activity
  – DNA-analysis
Treatment

- Protection from the sun
- UVB fototherapy
- Afamelanotide (alfa-MSH) → melanin formation
- Beta-carotene (75-200 mg/day)

- In case of liver abnormalities
  - Cholestyramin (?)
  - Active coal (?)
  - Liver failure → liverTx (combination with stem cellTx?)
  - Cave light exposition during surgery
Acute painful photosensitivity

Burning pain and itching in sunexposed areas

Protoporphyrin IX in RBC
### Acute porphyria

- **Acute intermittent porphyria (AIP)**
  - ALA dehydratase porphyria (ADP)*

### Cutaneous porphyria

**With blisters:**
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* Very rare recessive form
Congenital erythropoietic porphyria (Gunther’s disease)
Congenital erythropoietic porphyria (Gunther’s disease)

- 1/2.000.000

**Presentation**
- Very severe photosensitivity
  - bullae, scars
  - ulcerative keratitis
- Erythodontia
- Osteodystrophy
- Red urine
- Haemolysis and big spleen

**R/**
- Sun protection
- Transfusions, splenectomy
- Bone marrow transplantation
Porphyria

• Introduction

• Classification
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  – Rare recessive porphyrias

• Conclusion
Conclusions

- Deficiency in one of the eight enzymes required for haem synthesis

- Classification
  - Acute porphyrias
    - Neurovisceral symptoms
    - Acute intermittent porphyria
  - Cutaneous porphyrias
    - With blisters: porfyría cutanea tarda
    - Without blisters: erythropoietic porphyria
  - Rare recessive other entities
**Acute attacks**
- Unexplained abdominal pain
- Nausea, vomiting, constipation
- Neuropsychiatric symptoms
- +Hyponatraemia

**Erosive photodermatosis**
- Blisters
- Skin fragility
- Hypertrichosis

**Acute painful photosensitivity**
- Burning sensation after sun exposure

**Neonatal porphyrias**
- Neonatal icterus
- Haemolytic anaemia
- Bullae
- Severe neurological defects

**Assessments**
- **PBG (and ALA) in urine**
- **Plasma fluorescence emission peak**
- **Protoporphyrin IX in erythrocytes**
- **PBG, ALA, and porphyrins in urine**
• If you want to know more on inborn errors of metabolism
  Saudubray et al Inborn metabolic disorders
• Previous summer school in Brighton Aunt Minnie’s popquiz