The Acute Porphyrias
Düsseldorf, Sept 13th 2015

- Clinical features
- Triggers of the acute attack
- Diagnosis
- Late complications
- Treatment
- Various
- What’s on
- Where to get more info

Christer Andersson 2015, prof. Family Medicine University of Umeå, Sweden
Porphyrias are compounds that make grass green and blood red/ Hans Fisher 1930
Porphyria, The red disease, The family disease

- Always the same uncomfortable feeling for me – What did those patients suffer from – I had no idea…
- Peculiar cases …..Sudden severe abdominal pain or increasing paresis….
- After a few days the attack was over…New attacks…
  Suspected almost all abdominal causes….
- Her strength declined. The pults rate increased….
  Having enough of life she welcomed her death when it one evening came as respiratory paralysis.
HEME BIOSYNTHESIS AND HEREDITARY PORPHYRIAS

**Cytoplasm**
- **ALA synthase**
- **ALA dehydratase**
- **PBG deaminase**
- **Uro’gen III syntase**
- **Uro’gen decarboxylase**

**Mitochondria**
- **Glycine + SuccinylCoA** → **HEME**
- **Ferrochelatase**
- **Copro’gen oxidase**
- **Copro’gen oxidase**

**Protoporphyrin**
- **Proto’gen**
- **Protoporphyrin**
- **HMB**

**Heme degradation**

**ALa-dehydratase (ALAD) deficiency porphyria, ADP. Autosomal recessive. Six cases**


**Congenital erythropoietic porphyria, CEP.**

**Porphyria cutanea tarda, PCT. Photosensitivity with blisters and fragile skin. No neurological symptoms. 1500 registered cases in Sweden.**

**Variegate porphyria, VP. Autosomal dominant. Chrom. 1. Limited penetrance. Debut from puberty. Symptoms like AIP + photosensitivity with blisters and fragile skin. Precipitating factors as in AIP. 70 gene carriers registered in Sweden.**

**Hereditary coproporphyria, HCP. Autosomal dominant. Limited penetrance. Debut from puberty. Symptom like AIP + photosensitivity with blisters and fragile skin. Precipitating factors as in AIP. 30 gene carriers registered in Sweden.**

**X-linked dominant Protoporphyria**

**Erythropoietisk protoporphyri, EPP. Debut from infancy. Photosensitivity with skin pain. Risk for severe liver damage.**
Acute intermittent porphyria, AIP

- Inherited metabolic disorder– defect in the heme biosynthetic pathway (mutations)
- Combination of heredity and environment – Drugs
- Manifest AIP (10 - 40%).
  - Acute attack:
    - Severe abdominal pain • Muscle pain / paresthesia
    - Muscle weakness – Paresis • Psychiatric symptoms
- Autonomic, Periferal and Central nervous system
- Red urine (gr. porphyros, purpur)
- Women in fertile age are most severely affected
AIP, Important rare disease

- Frequent in certain areas
- Dramatic and severe symptoms – potentially life-threatening attacks
- Hereditary – can be traced
- Prevention and information of utmost importance
Symptoms during AIP attacks

- Autonomic nervous system
  - Abdominal pain
  - heart frequency,
  - Hypertension
  - Bladder paresis
- CNS
  - Restless, Anxiety
  - Depression
  - Confusion, Hallucination
  - Hypothalamus
    - ＊Sodium levels
- Peripheral nervous system
  - Pain in Muscles and Back
  - Muscle weakness, Paresis
  - Sensory disturbances
- Red urine
- Serious signs:
  - Paresis, bulbar paralysis
  - Confusion
  - Severe hyponatremia
  - Respiratory paresis
Clinical features in various acute porphyrias

AIP: Acute intermittent porphyria
HC: Hereditary coprophoria
VP: Variegate porphyria

468 patients with AIP diagnosis

82 Children

386 ≥ 18 yrs

30 non-participants

356 participants (92%)

MAIP 149 (42%)
Mean age 52
Men 53 (35%)
Women 96 (65%)

LAIP 207 (58%)
Mean age 40
Men 123 (60%)
Women 84 (40%)
Prevalence of symptoms in 149 patients with Manifest AIP (96 w, 53 m)

Abdominal pain + 1-2 other symptoms (90%)

- Sensory impairment
- Paresis
- Muscle pain
- Palpitations
- Fatigue
- Psychiotics
- Headache
- Constipation
- Vomiting
- Abdominal pain

Percentage of patients experiencing each symptom combination.
Precipitating factors in 149 patients with Manifest AIP (96 women, 53 men)
AIP Attacks

Women severely affected!

- Manifest AIP: 2/3 women, 1/3 men
- Number of AIP attacks
  - > 20 attacker: 40% of women, 25% of men
- Duration
  - Usually 3-7 days
  - > 10 days: 15% of women, 2% of men

- Most troublesome age
  - Women: 15 – 39 yrs, max 25-30 yrs (most fertile age)
  - Men: max > 40 yrs

- Hospital care
  - > 20 times: women 12%, men 6%
Diagnosis of AIP

- Acute attack: U-PBG increased
- Investigation of gene carriers:
  - Known AIP family: DNA diagnostics
  - Unknown AIP family: Urine test for ALA, PBG
    Blood test for enzyme analysis
Late complications of AIP

- Chronic impairment (20%)
- Slight sensory or motor neuropathy (15-20%)
  - Few cases with severe paresis
- Chronic Hypertension MAIP 40% (Odds ratio x 4)
- Renal impairment MAIP 30%

Liver cancer (HCC)
- AIP is a high risk group for developing HCC (RR 60 folds)
- Screening Ultrasonography from 50 yrs age
Follow up

- Blood pressure
- Renal check
- Liver (yearly from 50 yrs age)
- Attacks, ALA and PBG levels
- Other gene carriers in the family?
- Patient-focused information
Mechanisms underlying acute attacks in porphyria

- **Mitochondria**
  - Heme degradation
  - Erythropoietisk protoporphyri, EPP. Debut from infancy. Photosensitivity with skin pain. Risk for severe liver damage
  - Ferrochelatase, EPP
  - ALA synthase
  - ALA dehydratase (ALAD) deficiency porphyria, ADP. Autosomal recessive. Six cases
  - ALA dehydratase ADP
  - PBG
  - PBG deaminase AIP
  - HEME
  - Cytoplasm
  - HMB
  - Uro´gen III syntase CEP
  - Uro´gen
  - Uro´gen decarboxylase PCT
  - Copro´gen

- **Cytoplasm**
  - Heme proteins
  - Protoporphyrin
  - Copro´gen oxidase HCP

- **Nerve injury**
  - X-linked dominant Protoporphyria

- **Red Urine**

- **Congenital erythropoietic porphyria, CEP.

- **Porphyria cutanea tarda, PCT.** Photosensitivity with blisters and fragile skin. No neurological symptoms. 1500 registered cases in Sweden.

- **Familiar PCT:** Onset from child.

- **Sporadic PCT:** Middle age, alcohol

- **Secondary and toxic PCT.**
Treatment of the acute attack

- **Triggering factors**
  - Eliminate: drugs, infection

- **Specific treatment**
  - 10% Glucose infusion, 2-3 l/d
  - Severe cases – Heme arginat Normosang 3 mg/kg/d, 3-4d

- **Symptomatic treatment**
  - **Nutrition**: Adequate calorie intake
  - **Pain**: Opioid – Morphine
  - **Nausea/vomiting**: Clorpromazine, Ondansetron
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<th>Treatment, cont.</th>
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<td><strong>Constipation</strong></td>
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<td><strong>Hyponatremia</strong></td>
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<td><strong>Psychiatric symptoms</strong></td>
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<td><strong>Hypertoni</strong></td>
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<td><strong>Seizures</strong></td>
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Treatment of menstrual related attacks and treatments in the future

- Cyclic attacks
  - GnRH agonister (chemical castration) with add back

- Future??
  - Recombinant PBGD
  - Gene therapy
  - Livertransplantation
AIP in Northern Sweden
Population-based studies

- Penetrance for various AIP mutations
- Porphyria, women and sex hormones
- Surveillance of Liver cancer
AIP-NORRLAND STUDY 1995-99

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Clinical penetrance for three AIP mutations

- First mutation in the AIP gene 1989
- 350-400 various mutations, 40 in Sweden
- Different severity of the mutations?
Three mutations: Manifest-Latent AIP

<table>
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<tr>
<th>Mutations</th>
<th>Total (%)</th>
<th>Manifest (%)</th>
<th>OR</th>
<th>CI (95%)</th>
<th>p</th>
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<tbody>
<tr>
<td>R167W</td>
<td>24 (6)</td>
<td>3 (13)</td>
<td>1.00</td>
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<tr>
<td>W198X</td>
<td>338 (91)</td>
<td>147 (44)</td>
<td>7.92</td>
<td>2.13-29.40</td>
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<td>R173W</td>
<td>10 (3)</td>
<td>5 (50)</td>
<td>6.38</td>
<td>0.98-41.59</td>
<td>0.053</td>
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Conclusion: Various penetrance for different mutations – Attention for late complications
Female sex hormones and AIP

**Aims**

Disadvantages in AIP?
- Use of contraceptive pills
- Use of postmenopausal hormone replacement therapy
- Pregnancy
Female sex hormones play a key role in the clinical expression of AIP

- Symptoms rarely before puberty
- Manifest AIP is more common among women than men (3/2)
- Premenstrual cyclic attacks (30%)
- Fewer attacks after menopause
- GnRH agonist may ameliorate premenstrual attacks
- Contraceptive pills may provoke attacks
Clinical course of AIP in 50 women with manifest AIP and used P-pills (57%)

- Provoked any attack: 12 (24%)
  - First attack: 9 (18%)

- Relief of AIP symptoms: 1
Conclusions, female sex hormones

- 1 of 4 women with manifest AIP reported attacks associated with their use of oral contraceptives
  - Caution still recommended

- Post menopausal sex hormone replacement seldom affects AIP
  - Can be used

- Pregnancy seldom affects AIP
  - 10% experienced more attacks but 23% felt more healthy
Primary liver cancer and acute intermittent porphyria

Screening for hepatocellular carcinoma in acute intermittent porphyria – a 15-year prospective follow-up in northern Sweden

Innala E, Andersson C. JIM 2010
Results Liver cancer

- 22 patients with AIP Porfyri had liver cancer (men:women 12:10), 73% MAIP

- The yearly incidens of Liver cancer in AIP: 0.8%

- The increased risk (incidence rate ratio) for Liver cancer in AIP:
  - in total: x 64
  - men: x 52
  - women: x 93
Results Liver cancer – survival

3-year Survival
Group A (5 vs 0)
Group B (3 vs 11)
p = 0.005

5-year Survival
Group A (4 vs 1)
Group B (3 vs 11)
p = 0.04

Eligible for surgery
Group A (7 vs 1)
Group B (4 vs 10)
p = 0.02

Kaplan-Meier Group A (repeated screening, < 2 yrs) compared with Group B, p = 0.004
CONCLUSIONS 1
Acute porphyrias and liver cancer (HCC)

- Increased risk of HCC in acute porphyria gene carriers > 50 yrs of age

- The porphyria specific risk factors are unclear
  - ALA, Oxidative stress. Attack – defence
  - Oncogene / Tumor suppressor gene linked to the mutation in porphyria?
CONCLUSIONS 2
Acute porphyrias and liver cancer

- Surveillance for HCC in acute porphyria gene carriers enables early diagnosis and potentially curative treatments.

- Liver function tests and α-fetoprotein are not useful in surveillance of HCC.

- Biochemical and/or clinical relapse of the porphyric condition may be associated with the development of HCC.

- Annual surveillance using liver imaging (Ultrasonography) is recommended for gene carriers aged > 50 years.

- Swedish National Guidelines for Liver Cancer 2011
Treatment of AIP – What’s on?

- Liver transplantation
- Liver cell transplantation
- Enzyme replacement therapy – Recombinant PBGD
- Gene therapy
Treatment of very severe AIP by liver transplantation. Case

- Woman 19 yrs
- Frequent, not menstrual related attacks, during 2,5 yrs.
  37 hospital admissions, 200 days
- Severe abdominal pain, pain in the legs with peripher paresis,
  Na, Renal impairment
- Aunt died due to AIP at 35 yrs of age
Liver transplantation as treatment of AIP

The Lancet Febr 28 2004
After liver transplantation

- Follow up 5,5 år: No AIP attacks. Nerve function normal
- U-ALA and U-PBG normal levels
- High Quality of life, children

Around 20 liver transplantations performed due to AIP, (1 due to VP) 3 cases of double transplantation ie liver and kidney
Gene therapy in AIP

- Recombinant inert **Virus** targeted to the liver *carrying a normal AIP gene*
- I.v. injection – transfecting 20-30% of the liver cells
- Porfyri knock out mice
  - PBGD enzyme levels in the liver normalized
  - Symptom reduction
  - Power for >2 yrs
- Clinical and experimental studies ongoing

- **RNA interference (RNAi)**
- Professor Desnick knows all about this interesting approach:
  1. Treatment of acute attacks
  2. Profylax in patients with recurrent attacks

Clinical and experimental studies ongoing
Where to get more info

International Drug data base for acute porphyria

www.drugs-porphyria.org
Goals in the care of Porphyria

- Understand that the patient has porphyria!
- The patient must be understood!
- High quality of -
  - Prevention – no attacks by mistake!!!
    - Drugs???
  - Control and treatment of Porphyria / Late complications (Blood pressure, Kidney function, Liver cancer surveillance)
- Increased Q of life for patients with Porphyria
  Patient organisations