ERYTHROPOIETIN PROTOPORPHYRIA

Case Presentation and Discussion
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CASE: BACKGROUND

53 yo woman with lifelong history of EPP, presented to UWMC August 10, 2013 with new acute liver failure.

- Diagnosed EPP at age 3 after sunburns
- 1970s Liver Biopsy showing focal cholestasis
- 1996: 1st pregnancy, severe cholestasis, hand/foot syndrome
  - 2nd pregnancy managed with Ursodiol, no complications
- 2003: Abnl LFTs: Liver biopsy dark brown pigments (non polarizable)
  - Also with cholestasis, cholecystectomy
- 2005/06: HMC, normal LFTs, normal liver US, Plasma PP 1460 (0-30)
  - 2010: Liver biopsy showing cirrhosis, 2 EGDs with varices
- PMH: knee surg 2002, bladder suspension surgery
- Social: Worked at Port of Seattle, no ETOH, no tobacco
- Family history: siblings, children without EPP or liver disease
Aug 10\textsuperscript{th} 2013-19\textsuperscript{th} 2013: First hospitalization

- Presented with acute abdominal pain, jaundice, anorexia
- Initial labs: AST 680, ALT 790, alk phos 190, T Bili 6.3
  - Plasma Protoporphyrins 322, RBC Protoporphyrins 4737 (<80)
  - Liver biopsy: birefringent dark brown spots, polarizable
    - Maltese Cross, bridging fibrosis, cirrhosis
- QD plasmapheresis (TPE) with hematin infusions
- Single red cell exchange 12 U (RCE), transfuse to goal hgb >11
  - Improvement: Plasma PP 237, RBC PP 1995
  - Improvement in LFTs, bilirubin (T Bili 7.4->4.2)

- Discharged with QOD TPE, 2x/wk hematin
  - Ursodiol, cholestyramine, Vit E continued
PROTOPORPHYRIN DEPOSITS IN THE LIVER

Readmitted Sept 4\textsuperscript{th}-19\textsuperscript{th} 2013: 2\textsuperscript{nd} hospitalization

- Recurrent N/V, pain, anorexia, jaundice, fatigue
  - Plasma protoporphyrin level 489, T bil 6.0
- Restarted QD TPE, hematin infusion, RCE x1, hgb >11
  - Plasma protoporphyrins decreased slightly to 390 then ↑1051
- Hydrea started (suppress erythropoiesis), daily NAC
- Transitioned to QOD TPE; LFTs, bili ↑ on off days

- Evaluated by liver transplant team, MELD 22
  - Cleared for OLT but not actively listed

- Discharged with QOD TPE, NAC, lactulose, cholestyramine
  - F/U Sept 23\textsuperscript{rd}: Plasma protoporphyrins >1600, RBC 3600
Re-admitted Sept 26\textsuperscript{th}, 2013: 3\textsuperscript{rd} hospitalization

- Worsening n/v, pain and new AMS, MELD 24
- \textit{Klebsiella} UTI, started on vanc/meropenem
- Re-started QD TPE, single RCE x 1
- Day 3 developed worsening AMS, transferred to ICU
  - Alkalemic (pH 7.59), Cr 2.07
  - Declining respiratory status, required intubation
  - NIFF showed – 15, very weak diaphragm

Family moved to comfort care, patient died
LAB TRENDS

**Lab Trend: 'Bilirubin (Total)'**

- mg/dL
- 14-Aug 21-Aug 28-Aug 4-Sep 11-Sep 18-Sep 25-Sep 2-Oct

**Lab Trend: 'Porphyrins, Total'**

- mcg/dL
- 14-Aug 21-Aug 28-Aug 4-Sep 11-Sep
EPP: INTRO

• First described in 1961
• Affects men and women equally
• Prevalence: 1:75,000-1:200,000
• Usually manifests in early infancy with sun exposure
  • Rarely late onset, assoc. heme malignancies
• Varied genetics/inheritance
• Most common deficiencies in Ferrochelatase (FECH)
• Life threatening complication: Rapidly progressive ESLD
HEME BIOSYNTHETIC PATHWAY

Aminolevulinic acid (ALA) synthase
Aminolevulinic acid dehydrogenase
Porphobilinogen deaminase
Uroporphyrinogen III cosynthase
Uroporphyrinogen decarboxylase
Coproporphyrinogen oxidase
Protoporphyrinogen oxidase

Ferrochelatase (FECH)

Glycine + succinyl coenzyme A
5-aminolevulinic acid
Porphobilinogen
Hydroxymethylbilane
Uroporphyrinogen III
Coproporphyrinogen III
Protoporphyriongen IX
Protoporphyrin IX

Fe ++
Heme
ROLE OF FECH

- FECH catalyzes the insertion of iron into PP ring
  - Negative feedback loop
    - ↑ intracellular heme ↓ ALA synthase ↓ FECH
  
- 80% heme produced in bone marrow, 15% hepatocytes
  - In EPP: free PP accumulates in RBCs
  
- PP in erythroid fluoresce red 634 nm, excitation 405 nm
  - PP diffuses from RBCs into plasma, binds to albumin
  - PP hydrophobic, transported to liver
  - Enters enterohepatic circulation
  - Accumulates in hepatocytes
  - Excreted in feces
PROTOPORPHYRIN PATHWAY

15%–20% of PPIX is produced by the liver.

Free PPIX in plasma is extracted by the liver.

80% of PPIX is produced by bone marrow.

Enteroh-penic circulation of PPIX.

Reticulocytes and new erythrocytes have high concentrations of PPIX.

Free PPIX diffuses across red cell membranes and binds to plasma proteins.

Anstey, Hift. Postgrad Med J 2007 Dec; 83 (986) 739-48
PROTOPORPHYPREIN IN THE LIVER

• PP in hepatocytes excreted into bile
  • Forms crystalline depositions in bile canaliculi
    • Leads to cholestasis, gallstone formation
    • Deposits birefringent, Maltese cross

• PP in bile toxic to biliary epithelium $\rightarrow$ fibrosis

• PP in hepatocyte induces oxidative stress
  • Excess PP $\rightarrow$ dysfunction of Na+K+ ATP-ase pump
  • Further reduces excretion

• Heme Synthesis in the liver
  • Regulated at 1st step (ALA synthase) pathway
  • Heme used for synthesis of proteins, cytochrome P450
  • PP from Liver PP may contribute to liver disease

LIVER IN EPP

Anstey, Hift. Postgrad Med J. 2007 Dec; 83 (986) 739-48
INHERITANCE

- 95% Autosomal Dominant
  - Mutated Allele
    - Defect in gene encoding ferrochelatase (FECH)
    - Chromosome 18 (18q21.3), incomplete penetrance
      - Enzyme activity < 35% in symptomatic individuals
  - Low expression Allele
    - 2002: discovery of polymorphism intron 3 of FECH gene
      - Exchange of single nucleotide IVs3 48T>C
      - Aberrant mRNA → decreased protein
      - Japan 43%, Europe 12%, Africa 1%
  - Both alleles have to be transmitted for EPP
    - Liver disease risk 5%

• Autosomal Recessive 4%
  • Two copies of mutated allele
  • 20 cases reported
  • Similar features to Autosomal Dominant except
    • Risk of developing severe liver disease 40%

• ~ 1-2% Dominant X linked form
  • Gain of function of ALAS2, increased heme synthesis
  • Higher total PP levels, 40% PP bound to zinc
  • 17% liver disease

• Acquired form: 15 cases, assoc. MDS, 1 case liver dz

• Discovery of 56 new FECH mutations, UK study of 191 pts
Mutations in FECH

CLINICAL MANIFESTATIONS: SKIN

- Protoporphyrin in skin $\Rightarrow$ acute photosensitivity
  - Absorption of light: PP excites at 405 nm
  - Free radicals formed, toxic to skin
- Short term: erythema, edema, on face/dorsa of hands
  - Reactions last hours to days, can get 2\textsuperscript{nd} degree burns
  - \textit{Usually NOT} vesicles or bullae
- Over time: waxy or leathery appearance
  - Hyperkeratosis, linear furrows round mouth
SKIN CHANGES

Clinical manifestations: Liver

- **Cholelithiasis** ~ 20%
  - Due to excess free and biliary PP in bile canaliculi
  - Stones: high concentration of protoporphyrin
    - Birefringent under polarized light, Maltese cross shape

- **Mild Liver Disease** ~ 20%
  - Mild transaminitis, ↑ alk phos, usually no symptoms

- **ESLD** 1-5%
  - Inciting event unclear
  - Rapid onset, progressive, usually irreversible
  - Thought secondary to accumulation PP in liver
ESLD

- Elevations in AST/ALT, bilirubin, Alk Phos
  - Abdominal pain, malaise, jaundice

- Splenomegaly, splenic sequestration of erythrocytes
  - Hemolysis ↑ erythropoiesis and PP generation

- Elevations in protoporphyrins in RBCs and plasma
  - Fecal levels of PP decrease
NEUROPATHY

• **Neuropathy**: Usually assoc. with hepatic porphyrias

• Review of 10 cases between 1987-1998\(^1\)
  - Peripheral Neuropathy (PN) 5 patients
    - All in setting of elevated PP, hepatic failure
    - 4 patients developed severe proximal weakness
    - Respiratory muscle weakness

• Review of 17 EPP patients undergoing liver transplant\(^2\)
  - 6 patients with neuropathy, 2 before tx, 4 after
  - 4 patients required prolonged ventilation

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Microcytic Anemia

- Microcytic, Hypochromic Anemia
- Review of 178 dEPP patients
  - Mean Hgb 12 g/L; 48% women, 33% men anemic
  - Mild, asymptomatic
- Iron Stores
  - Iron stores decreased by 2/3, Ferritin decreased by 2/3
  - Normal serum soluble transferrin and Iron concentration
- Suggest erythropoiesis not limited by iron supply
- Unclear etiology

Diagnosis

Pain photosensitivity on sun exposed skin *without blisters*

- Plasma fluoresce peak at 634 nm
- Plasma and erythrocytic protoporphyrin concentration + fecal protoporphyrin concentration

Diagnosis EPP

- Determination of FECH level
- Evaluate for liver disease
- Genetic testing

Medical Management

- **Sun Protection**

- **Cholestyramine, Activated Charcoal**
  - Binds to protoporphyrin in intestine, interrupting EHC

- **Ursodiol**
  - Induce bile flow

- **Beta-Carotene**
  - Causes mild skin discoloration, ↓ free radicals
  - May improve tolerance to sunlight

- **NAC**: May reduce free radicals, ? protect hepatocytes
MEDICAL MANAGEMENT

• **Iron**
  - Controversial, mechanism unknown
  - In theory, should stimulate heme synthesis
  - May worsen hepatic function

• **Hematin infusions**
  - Iron containing porphyrin
  - Given 3-4 mg/kg IV
  - PP production via feedback inhibition of ALA synthase
  - Does not seem to prevent ultimate liver failure
TRANSFUSION THERAPY

- **RBC Hypertransfusion** \(^1,^2\)
  - ? Negative feedback mechanism on heme synthesis
  - Reports of diminished photosensitivity, ↓PP

- **RBC Exchange Transfusion**
  - Some cases report improvement LFTs, PP
  - More recently, *Eichbaum* et al (2005) reviewed 2 cases\(^3\)
    - ↓PP in RBCs and plasma, ↓Bilirubin, LFTs
    - RBC PP did not immediately decrease
    - In vitro assessment, exchanged RBCs act as PP “sink”?*
  - Post-OLT recurrent EPP, RCE ↓PP\(^4\)

- Labor intensive and costly, unclear if prevent ESLD

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**Plasmapheresis (TPE) controversial**

- **Review of 17 patients pre-OLT in US Study¹**
  - Pre OLT: ↓ bilirubin, ↓PP ↓ MELD
  - Post OLT: 4 received hematin; 3 received hematin plus TPE
    - ↓Bilirubin, ↓PP-- although 3 died
- **Review of 2 cases of TPE pre and post OLT²,³**
  - Pre-OLT improvement in plasma and RBC PP levels
  - Post OLT ↓LFTs, ↓bilirubin, ↓PP, ↓polarizable crystals
- **Review of 17 European pre-OLT patients⁴**
  - 17 patients rec’d pre-op TPE, RCE, hematin infusions
  - “unable to draw conclusions”
- **Case study from UWMC: TPE, RCE did not prevent death**

• **OLT**: First transplant 1979, at least 40 worldwide

• Review of 17 patients in US
  - Avg age 31, MELD 21
  - 11/17 (65%) patients had recurrent disease >2 months
    - Early deaths: 3 died within 2 mos of sepsis
    - 3 re-transplanted for EPP (2 died); 3 severe EPP died
  - Survival similar to non-EPP liver tx
    - EPP: 85% 1 yr, 69% 5 yr, 47% 10 yr;
    - Non EPP: 86% 1 yr, 75% 5 yr, 50% 10 yr

1. McGuire
• **OLT**: European Review\(^1\)
  - 31 patients 1983-2008, avg age 39, MELD 21
  - Overall recurrence rate reported at 69%, adjusted to 37%,
    - 4 re-transplanted due to recurrent disease
  - Survival similar to previous study (77% 1 yr, 66% 5, 10 yr)

• **UK Review\(^2\)**
  - 5 patients 1987-2009: median age 40, MELD 22
  - 2 patients died: 1 cause not known, 2\(^{nd}\) after BMT
  - 80% recurrence of graft with EPP within 2 years

1. Wahlin, *Liver Transplantation*
2. Dowman
OLT SPECIAL CONSIDERATIONS

• **Phototoxic Injuries** European Study, 31 patients
  • 5 - no filter: Intrabdominal burns, bowel perf, 1 death
  • 2 - reduced light: 1 burn, 1 death
  • 17 – filter: used– no injury

• **UWMC patient**
  • Fulminant hepatic failure developed after exposure to OR lights for knee replacement

• Prevention: Filter that blocks light under 460 nm

• **BMT**: first for EPP 2002 in MDS → AML patient
  - Alive and well after 3 years

• 5 BMTs reported by *Wahlin et al*
  - 2 boys with EPP: OLT then BMT
    - One young patient s/p OLT → auto tx, still alive
    - 2nd young patient s/p OLT → HSCT, d. viral infection
  - 57 yo man s/p OLT d. infectious complications at 3 mos.
  - 20 year old man (Fr) s/p OLT did not achieve engraftment
  - 62 year old man w/o prior OLT underwent 2 BMTs
    - Pre-OLT rec’d transfusion, TPE and RCE; 1st BMT no engraft
    - 2nd BMT successful

1. Wahlin, *BMT*
• Review of UK study
  • 1/5 patients underwent BMT after OLT
    • Fully functioning liver, normal PP levels
    • Died of cerebral TB 2.7 years later

• McGuire
  • Study of 17 US patients, one patient s/p OLT
    • Received BMT, died within 3 months of sepsis

Conclusions and Questions

• Conclusions:
  • RCE, TPE, hematin may lower MELD, PP
    • May not prevent ESLD
  • OLT appears necessary for ESLD in EPP
    • Does not cure underlying defect
    • BMT appears to fix the underlying enzyme deficiency
  
  • When is the optimal time for BMT?
  
  • Should consideration for lower MELD be given to EPP patients as plasmapheresis/RCE appears to lower MELD?
References

REFERENCES