A RARE CASE OF HEMOLYTIC ANEMIA

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History

1 yr old male child, 1\textsuperscript{st} born of 3\textsuperscript{rd} degree consanguineous marriage with

- c/o \textit{abdominal distension} 9 months,
  admitted in Salem GH, suspected as a case of hemolytic anemia & referred to ICH for further evaluation

- No jaundice
- No previous transfusion
- No bleeds
- No chronic drug intake
- No oliguria /facial puffiness.
Contd. . .

- Antenatal /birth history: uneventful
- Development: normal
- Family history: 1st born of 3rd degree CM
  no h/o hematological/hepatic disorders
- Adequately immunised till date
- No h/o contact with TB.
General examination

- Alert
- Afebrile
- *Diffuse hyperpigmentation +*
- Anemic
- *Hair: sparse, hypopigmented*
- No icterus
- No clubbing
- No cyanosis
- No significant lymphadenopathy
- No pedal edema
- Anthropometry: normal
- Vitals: wnl
Abdomen was soft

- Firm splenomegaly (8cm)
- Firm hepatomegaly (LS 7cm)

- No free fluid / bruit or venous hum
- Flanks & hernial orifices were free/ genitalia normal.

- Other systems were normal.
Provisional diagnosis

Anemia with spleno hepatomegaly
- Hemolytic anemia
- Chronic malaria
- Storage disorder
- Osteopetrosis
- Myelofibrosis
- Leukemia
Initial workup

- TC/DC: normal
- *Hb- low*
- *Peripheral smear: hemolytic picture with thrombocytopenia*
- MP smear: neg
- LFT & RFT normal
- Coombs test: neg
- HIV NR
- Vitamin B12 assay: wnl
- Hb Electrophoresis: normal
- BMA: hypocellular marrow. M:E 3:1. blasts <2%. No abnormal cells s/o storage disorder
- USG abdomen: splenohepatomegaly
- UMS: neg
- Stool for occult blood: nil
- Mantoux neg
- CXR/ Xray long bones: normal
Initial investigations were not contributory
Mother gives h/o passing *high coloured urine* 6months
Urine analysis

- Urine *albumin trace* /Sugar nil
- RBC nil
- 24hr urine protein: wnl
- Urine Hb nil
Macroscopic examination

- reddish brown which changed to purplish red on standing
Literature review

Hyperpigmentation
Blond hair
Portwine urine

Hemolytic anemia
Splenomegaly

PORPHYRIA
Discussion

- Porphyrias (*greek: purple*) are a group of inborn errors of metabolism associated with the biosynthesis of heme.
- Most cases are inherited, some may be acquired.
- Depending on the types of genetic mutations enzyme deficiencies can be either partial or nearly complete.
- Types:
  - I. Acute hepatic => **Neurovisceral symptoms**
  - II. Chronic hepatic => **Cutaneous Photosensitivity**
  - III. Erythropoietic
Figure 1: Haem biosynthetic pathway and porphyrias
CPO=coproporphyrinogen oxidase. PPOX=protoporphyrinogen oxidase. FECH=ferrochelatase. Fe\(^{2+}\)=ferrous iron.
Fig 1. Classification of porphyrias. Enzymatic defects, associated diseases, major symptoms and principal accumulation products are shown. ALAS2 defect is responsible for X-linked sideroblastic anaemia (XLSA) but is not associated with any porphyria, since the enzymatic defect blocks production of ALA, the obligatory precursor for porphyrin formation. ALA dehydratase porphyria (ADP) and acute intermittent porphyria (AIP) are accompanied by acute hepatic porphyria but not by photocutaneous porphyrin, because their enzymatic defects do not result in an increase in porphyrin synthesis. Enzymatic defects beyond uroporphyrinogen synthase (UROS) are all associated with photocutaneous porphyrinas, because they produce excessive amounts of various porphyrins. Hereditary coproporphyria (HCP) and variegate porphyria (VP) are additionally associated with acute hepatic porphyria. Suc. CoA, succinyl coenzyme A; P’gen, protoporphyrinogen; Proto, protoporphyrin; U’gen, uroporphyrinogen; C’gen, coproporphyrinogen. Adapted from Sassa S & Shibahara S. Disorders of Heme Production and Catabolism. In Handin RI, Lux SE, and Stossel TP, eds, Blood: Principles and Practice of Hematology, 2nd ed, Philadelphia, Lippincott Williams & Wilkins, 2003, with permission.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Disease</th>
<th>Type</th>
<th>Symptoms</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALAS2</td>
<td>XLSA</td>
<td>Erythroid</td>
<td>Microcytic anaemia</td>
<td>Sideroblasts</td>
</tr>
<tr>
<td>ALAD</td>
<td>ADP</td>
<td>Hepatic</td>
<td>Neurovisceral</td>
<td>Urinary ALA</td>
</tr>
<tr>
<td>HMBS</td>
<td>AIP</td>
<td>Hepatic</td>
<td>Neurovisceral</td>
<td>Urinary ALA, PBG</td>
</tr>
<tr>
<td>UROS</td>
<td>CEP</td>
<td>Erythropoietic</td>
<td>Photosensitivity, Haemolytic</td>
<td>Urinary &amp; RBC, U’gen I, C’gen I</td>
</tr>
<tr>
<td>UROD</td>
<td>PCT</td>
<td>Hepatic/Hepatic</td>
<td>Photosensitivity, Haemolytic</td>
<td>7-C porphyrin, faecal isocoprotoporphyrin</td>
</tr>
<tr>
<td>CPOX</td>
<td>HCP</td>
<td>Hepatic</td>
<td>Neurovisceral &amp; Photosensitivity</td>
<td>Urinary ALA, PBG, coproporphyrin</td>
</tr>
<tr>
<td>PPOX</td>
<td>VP</td>
<td>Hepatic</td>
<td>Neurovisceral Photosensitivity</td>
<td>Urinary ALA, PBG; faecal protoporphyrin</td>
</tr>
<tr>
<td>FECH</td>
<td>EPP</td>
<td>Erythropoietic</td>
<td>Photosensitivity</td>
<td>RBC protoporphyrin faecal protoporphyrin</td>
</tr>
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</table>
Pathogenesis:

- Porphyrins produce free radicals when exposed to uv light leading to skin damage in cutaneous porphyria.
- Porphyrins vary in their solubility which accounts for their presence in various body fluids.
- Neurotoxicity: excess PBG/ALA inhibiting GABA release, heme deficiency l/t degenerative changes in brain, reduced tryptophan pyrrolase l/t increased brain tryptophan and turnover of serotonin.
<table>
<thead>
<tr>
<th><strong>CONGENITAL ERYTHROPOEITIC PORPHYRIA:</strong></th>
<th><strong>HEPATO ERYTHROPOEITIC PORPHYRIA:</strong></th>
<th><strong>ERYTHROPOEITIC PROTO PORPHYRIA:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complete absence of UROS activity</td>
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<td>• Partial deficiency of ferrochelatase.</td>
</tr>
<tr>
<td>• Only porphyria that produce type 1 isomers in excess.</td>
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<td>• MC erythropoetic porphyria.</td>
</tr>
<tr>
<td>• Mild to severe haemolysis</td>
<td>• Mild to severe haemolysis</td>
<td>• Skin lichenification, leathery pseudovesicles.</td>
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<td>• Secondary splenomegaly</td>
<td>• Secondary splenomegaly</td>
<td>• Elevated free protoporphyrin.</td>
</tr>
<tr>
<td>• Severe cutaneous photosensitivity -early infancy.</td>
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<tr>
<td>• Erythrodontia</td>
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</tbody>
</table>

- *CEP*: Congenital erythropoietic porphyria
- *UROS*: Uroporphyrinogen III synthase
- *UROD*: Uroporphyrinogen decarboxylase
- *MC*: Maculopathy
<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>CEP</th>
<th>PCT and HEP</th>
<th>EPP</th>
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<tbody>
<tr>
<td>Photosensitivity</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Skin fragility</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Scarring</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Hyper- and hypo pigmentation</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>X severe</td>
<td>X mild</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Erythrodotia</td>
<td>X</td>
<td></td>
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</table>
Cutaneous scars
Facial hypertrichosis
Teeth discoloration
Clinical diagnosis

Hyperpigmentation+facial
hypertrichosis + cutaneous scars
+teeth discolouration(erythropoietic)+
reddish urine(burgundy color) +
hemolytic anemia +splenomegaly

Congenital erythropoietic porphyria
Initial evaluation of porphyria

- Urinary porphyrins
- Woods lamp examination
- Erythrocyte fluorescence
Urine porphyrins elevated >700mg/day
Woods lamp examination - teeth
Urine under woods lamp
Erythrocyte fluorescence testing was strongly positive
Final diagnosis

Hyperpigmentation + facial hypertrichosis + cutaneous scars + teeth discolouration (erythrodontia) + burgundy urine

Urinary porphyrins + fluorescence of teeth/urine/RBC under UV light

CONGENITAL ERYTHROPOEITIC PORPHYRIA
CEP

- CEP (Gunther disease) is a rare autosomal recessive disease identified in early 1923
- Deficiency of uroporphyrinogen III synthase
- Characteristic presentation is reddish urine
- Reddish fluorescence of teeth (*erythrodontia*) under UV light is pathognomonic for CEP
- Prenatal diagnosis by red-brown discoloration & increased porphyrins in amniotic fluid, fetal erythrocytes.
Treatment:

- Recognition and avoidance of precipitating events is the first key part of treatment.
- Protection from sunlight and UV exposure
- Meticulous skin care
- Red cell transfusions
- Beta-carotene
- Hydroxyurea to reduce bone marrow porphyrin synthesis.
- Splenectomy to reduce transfusion requirements
- Oral charcoal to facilitate fecal porphyrin excretion
- Definitive treatment is BMT
Drugs unsafe in porphyria

- Barbiturates
- Sulfonamides
- ketoconazole
- Rifampicin
- Pyrazinamide
- Phenytoin
- Carbamazepine
- Valproate
- ACE inhibitors
- Calcium channel blockers
Confirmatory test

- Measurement of UROS activity
- Gene mutation
Literature review

- Around 200 cases have been reported worldwide
- In ICH this is the 2nd case report of CEP
Mythology

- Porphyria has been suggested as an explanation for the origin of vampires and werewolf legends, based upon certain perceived similarities.
Dept. of dermatology
THANK YOU!