IRON RESTRICTION AS A THERAPEUTIC STRATEGY FOR CONGENITAL ERYTHROPOIETIC PORPHYRIA

Daniel Egan, MD
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Faculty Discussant: Janis Abkowitz, MD
OUTLINE

1. Brief overview of the pathophysiology, clinical manifestations and treatment of Congenital Erythropoietic Porphyria (CEP)

2. Case presentation: Iron restriction in CEP patient

3. In vitro studies using CEP marrow-derived cells

4. Future directions
I.

A BRIEF OVERVIEW OF CONGENITAL ERYTHROPOIETIC PORPHYRIA (CEP)
HEME SYNTHESIS & THE PORPHYRIAS

Mitochondrial cytochromes for oxidative phosphorylation

Myoglobin

Hemoglobin

Hepatic cytochrome P₄₅₀ enzymes

Image from Oxford Dictionary of Chemistry
HEME SYNTHESIS & THE PORPHYRIAS

8 enzymatic steps

Enzymes are present in all cells, but highest in liver and erythroid cells

The first and rate-limiting step in heme synthesis in all tissues is the conversion of TCA cycle intermediates SUCCINYL CoA and GLYCINE by ALA SYNTHASE to form ALA.

Under negative feedback by heme, glucose; inducible by drugs, estrogen

Regulated by available iron

HEME SYNTHESIS & THE PORPHYRIAS

Final four enzyme are identical in all cells

Last step is insertion of iron into protoporphyrin IX

HEME SYNTHESIS & THE PORPHYRIAS

Porphyrias = Back-up of porphyrin metabolites and their aberrant breakdown

- ALA Dehydratase-deficient porphyria (ADP)
- Acute intermittent porphyria (AIP)
- Congenital erythropoietic porphyria (CEP)
- Porphyria cutanea tarda (PCT)
- Hereditary coproporphyria (HCP)
- Variegate porphyria (VP)
- Erythropoietic protoporphyria (EPP)
- X-linked sideroblastic anemia
- X-linked protoporphyria (XLP)

Mitochondria

Cytoplasm
# HISTORY OF CEP

<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1874</td>
<td>J.H. Schulz</td>
<td>Described a 33 year-old male with lifelong skin photosensitivity, splenomegaly and wine-colored urine</td>
</tr>
<tr>
<td>1911</td>
<td>H. Günther</td>
<td>Defined the disease entity “haematoporphyrina congenita” as an inborn error of metabolism</td>
</tr>
<tr>
<td>1969</td>
<td>G. Romeo &amp; E.Y. Levin</td>
<td>Identified the specific enzyme defect in uroporphyrinogen III synthase</td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td>Approximately 150 cases reported</td>
</tr>
</tbody>
</table>
PATHOPHYSIOLOGY: DEFECT IN UROPORPHYRINOGEN III SYNTHASE

(Aadapted from Desnick and Astrin, Br J Haematol. 2002)
PATHOPHYSIOLOGY: MUTATIONS IN *UROS*

PATHOPHYSIOLOGY: MUTATIONS IN UROS

Loss of function mutations → CEP is transmitted in an autosomal recessive manner.

## CLINICAL MANIFESTATIONS OF CEP

Uroporphyrin I & Coproporphyrin I are toxic (generate oxygen radicals) and are photoreactive. Accumulation in tissues leads to disease manifestations.

<table>
<thead>
<tr>
<th>Erythroid cells</th>
<th>Ineffective hematopoiesis, chronic hemolysis, anemia, splenomegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Cutaneous photosensitivity, skin blistering and scarring, contractures and “photomutilation”, bullous rupture and secondary infections, hypertrichosis</td>
</tr>
<tr>
<td>Eyes</td>
<td>Keratitis and corneal scarring</td>
</tr>
<tr>
<td>Teeth</td>
<td>Erythrodontia</td>
</tr>
<tr>
<td>Bones</td>
<td>Osteoporosis (secondary to deposition in bone, as well as hyperplastic marrow)</td>
</tr>
</tbody>
</table>
CLINICAL MANIFESTATIONS OF CEP

There is considerable heterogeneity in the severity of disease.

Degree of porphyrin excess correlates with disease severity.

Freesemann et al (Arch Dermatol Res, 1997;289:272)
# Genotype-Phenotype Correlations


<table>
<thead>
<tr>
<th>Proband</th>
<th>Sex/age (years)</th>
<th>Ethnic background</th>
<th>Genotype</th>
<th>Luciferase activity* (%) of wild type</th>
<th>E. coli expression†</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid-specific promoter mutations:*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>fetus/FD</td>
<td>French</td>
<td>-70C/C73R</td>
<td>2.9*/&lt; 1.0†</td>
<td>Hydrops fetalis</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M/49</td>
<td>American</td>
<td>-76A/C73R</td>
<td>53.9*/&lt; 1.0†</td>
<td>Mild cutaneous disease</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F/19</td>
<td>Scandinavian</td>
<td>-86A/C73R</td>
<td>43.3*/&lt; 1.0†</td>
<td>Mild cutaneous disease</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M/33</td>
<td>English</td>
<td>-90A/G225S</td>
<td>8.3*/1.2†</td>
<td>Moderately severe disease</td>
<td></td>
</tr>
<tr>
<td>Coding region mutations:†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M/1</td>
<td>Hispanic</td>
<td>C73R/C73R</td>
<td>&lt; 1.0/&lt; 1.0</td>
<td>Hydrops fetalis</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M/15</td>
<td>English/Irish</td>
<td>Y19C/G225S</td>
<td>1.1/1.2</td>
<td>Severe disease</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F/20</td>
<td>Unknown</td>
<td>C73R/P53L</td>
<td>&lt; 1.0/&lt; 1.0</td>
<td>Severe disease</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F/9</td>
<td>Tunisian</td>
<td>P53L/P53L</td>
<td>&lt; 1.0/&lt; 1.0</td>
<td>Severe disease</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M/17</td>
<td>Romanian</td>
<td>C73R/T228M</td>
<td>&lt; 1.0/&lt; 1.0</td>
<td>Severe disease</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F/13</td>
<td>Alaskan Indian</td>
<td>C73R/A104V</td>
<td>&lt; 1.0/7.7</td>
<td>Moderately severe disease</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M/58</td>
<td>African Black</td>
<td>V99A/633insA</td>
<td>5.6/1.2</td>
<td>Moderately severe disease</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>M/18</td>
<td>Northern European</td>
<td>L4F/IVS2+1</td>
<td>1.8/‡</td>
<td>Moderately severe disease</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>M/17</td>
<td>Scottish, Irish/German</td>
<td>C73R/A66V</td>
<td>&lt; 1.0/14.5</td>
<td>Mild cutaneous disease</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>F/9</td>
<td>Italian</td>
<td>L4F/V82F</td>
<td>1.8/35.8</td>
<td>Mild cutaneous disease</td>
<td></td>
</tr>
</tbody>
</table>
## DIAGNOSIS

Send-out testing required. Note: Urinary ALA and PBG are not elevated in CEP.

<table>
<thead>
<tr>
<th>Type of porphyria</th>
<th>Urine</th>
<th>Stool</th>
<th>Erythrocytes</th>
<th>Plasma*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALADP</td>
<td>ALA, coproporphyrin III</td>
<td>Little or no increases</td>
<td>Zinc protoporphyrin</td>
<td>ALA</td>
</tr>
<tr>
<td>AIP</td>
<td>ALA, PBG, uroporphyrin I</td>
<td>Little or no increases</td>
<td>Little or no increase in porphyrins</td>
<td>ALA, PBG (mild increase in uroporphyrin I (~620 nm)</td>
</tr>
<tr>
<td>CEP</td>
<td>Uroporphyrin I, coproporphyrin I</td>
<td>Coproporphyrin I</td>
<td>Uroporphyrin I, coproporphyrin I</td>
<td>Uroporphyrin I, coproporphyrin I (~620 nm)</td>
</tr>
<tr>
<td>PCT and HEP</td>
<td>Uroporphyrin, heptacarboxyl porphyrin</td>
<td>Heptacarboxyl porphyrin, isocopro</td>
<td>Zinc protoporphyrin (in HEP)</td>
<td>Uroporphyrin, heptacarboxyl porphyrin (~620 nm)</td>
</tr>
<tr>
<td>HCP</td>
<td>ALA, PBG, coproporphyrin III</td>
<td>Coproporphyrin III</td>
<td>Little or no increase</td>
<td>Coproporphyrin (~620 nm)</td>
</tr>
<tr>
<td>VP</td>
<td>ALA, PBG, coproporphyrin III</td>
<td>Coproporphyrin III, protoporphyrin</td>
<td>Little or no increase</td>
<td>Porphyrin-peptide conjugate (~626-628 nm)</td>
</tr>
<tr>
<td>EPP</td>
<td>Coproporphyrin III, only with hepatopathy</td>
<td>Protoporphyrin normal or increased</td>
<td>Free protoporphyrin**</td>
<td>Protoporphyrin (~634 nm)</td>
</tr>
</tbody>
</table>

In utero testing of amniotic fluid, and genetic testing also available.
MANAGEMENT OF CEP

• Supportive measures
  – Sun avoidance
  – Beta carotene: to decrease oxygen radicals
    • Anecdototal evidence in a minority of patients
  – Transfusional support
  – Calcium, vitamin D, or bisphosphonates
  – Ophthalmologic care

• Splenectomy: to decrease hemolysis and reduce erythropoietic drive; may help with leukopenia and thrombocytopenia or symptomatic splenomegaly

• Bone marrow transplant
HYPERTHERANNFUSION FOR CEP

Rationale:
to reduce erythropoiesis

NEJM Case Report -
10 year-old boy with CEP treated with a hypertransfusion strategy
(Piomelli, NEJM 1996;314:1029)
ORAL CHARCOAL FOR CEP

- Rationale is to absorb porphyrins from enterohepatic circulation in the gut and reduce circulating levels
- Case reports with laboratory parameters
- Overall consensus is that charcoal is ineffective

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Journal</th>
<th>Patient</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hift et al</td>
<td>1993</td>
<td>Br J Dermatol</td>
<td>14 yo Male</td>
<td>Partial improvement then exacerbation</td>
</tr>
<tr>
<td>Tischler &amp; Winston</td>
<td>1990</td>
<td>Meth Find Exp Clin Pharm</td>
<td>16 yo Male</td>
<td>Urine: Ø changes plasma &amp; RBC: decr. porphyrins Ø clinical benefit reported</td>
</tr>
<tr>
<td>Gorchein et al</td>
<td>1988</td>
<td>Biomedical Chromatography</td>
<td>23 yo Male</td>
<td>Ø benefit</td>
</tr>
<tr>
<td>Minder et al</td>
<td>1994</td>
<td>NEJM</td>
<td>44 yo (gender not specified)</td>
<td>Ø benefit</td>
</tr>
</tbody>
</table>
II.
CASE PRESENTATION
CASE PRESENTATION

• A female patient of Alaskan Native descent was diagnosed with CEP at approximately 1 year of age, after presenting with red urine, green-brown teeth, and blisters on her cheeks.
  – Urine and teeth fluoresced under UV light
  – Urine coproporphyrin I was markedly elevated

• There was no prior family history of porphyria, though a younger female sibling would ultimately be diagnosed with CEP, as well.

• Genetic testing revealed heterozygosity for the C73R and A104V mutations in UROS.
CASE PRESENTATION

• From childhood onward, she suffered from photosensitivity and resultant skin blistering, scarring and contractures, requiring judicious sun avoidance. She also experienced chronic hemolysis, with anemia and red-brown urine.

• In 1996, a trial of oral charcoal was initiated but did not result in any discernable improvement in photosensitivity.

• In 2002, she underwent a splenectomy for worsening hemolytic anemia and symptomatic splenomegaly.

• The option of a bone marrow transplantation was raised, but the patient decided firmly against it.
CASE PRESENTATION

• In 2008, she began to require occasional transfusional support with packed red blood cells, though mostly maintained and tolerated a Hct in the range of 22-28%.

• No accessory spleen was identified on nuclear imaging.

• With cumulative volume of transfusions, and presumably with increased iron absorption related to ineffective erythropoiesis, iron stores increased. In January 2009, deferasirox was initiated at a serum ferritin of 910 ng/mL. Chelation continued until ferritin was 93 ng/mL in September 2009.
CASE PRESENTATION

• In the spring of 2010, despite discontinuation of deferasirox, serum ferritin continued to decrease. A nadir of 13 ng/mL was attained in May 2010.

• An extensive work-up for gastrointestinal losses was unrevealing, but this remained the most likely explanation for occult iron losses.

• Curiously, the patient reported a spontaneous improvement in her cutaneous photosensitivity, normalization in urine color, reduced scleral icterus, and improvement in energy level without need for transfusional support.

• Upon normalization of ferritin levels, symptoms returned.
ALAS2 MODIFIES CEP PHENOTYPE

2008: Group led by H. Puy

Identified a gain-of-function mutations in ALAS2 which explained an EPP phenotype in several families without a mutation in FECH (ferrochelatase): X-linked dominant erythropoietic protoporphyria (XLDPP)

2011: Group hypothesized that variations in ALAS2 might modulate CEP phenotype (and explain deviations from expected)

Tested by sequencing 4 individuals with identical compound heterozygous UROS genotype (C73R/P248Q) but with different disease phenotypes (3 “mild” disease severity and 1 “moderate” disease)

Y586F mutation in ALAS2 in the pt with severe disease

ALAS2 MODIFIES CEP PHENOTYPE

Rates of ALA formation in bacterial lysates with expression of 1) WT, 2) negative control, 3) positive gain-of-function control and 4) patient ALA2 mutant.

30% Increase with Y586F

ALAS2 MODIFIES CEP PHENOTYPE

Proposed mechanism for role of ALAS2 as a modifier gene in CEP:

IRON IN ALAS2 REGULATION

• Iron-responsive element (IRE): highly conserved stem-loop structure in certain mRNA transcripts

• Two iron-regulatory proteins: IRP1 & IRP2
• IRP1/2 binding to IRE either augments or decreases translation of mRNA
ROLE OF IRON IN ALAS2 REGULATION

CASE PRESENTATION CONT.

Hypothesis:

Iatrogenic iron deficiency (via downregulation of ALAS2 translation – and consequent decrease in the rate-limiting enzymatic step) may attenuate the CEP disease phenotype

Intervention:

Deferasirox to maintain a state of iron deficiency (ferritin 10-15 ng/mL targeted)
CASE PRESENTATION

• With iron deficiency resulting from a combination of GI losses and chelation therapy, the patient had a sustained improvement in symptoms (and a considerably improvement quality of life) for approximately 3 years.

• In late 2012 and early 2013, the patient developed worsening hepatic function of uncertain etiology (biopsy negative for cirrhosis).

• Serum ferritin increased: initially logistical delay in restarting deferasirox, but then withheld because of concerns of liver function.

• Unfortunately, in March 2013 the patient died from complications of hepatic and renal failure, in the setting of ineffective hematopoiesis and worsening hemolysis.
III.

PHYSIOLOGIC STUDIES WITH MARROW-DERIVED CELLS
PHYSIOLOGIC STUDIES WITH MARROW-DERIVED ERYTHROID CELLS

• Marrow acquisition
  • With parental consent, bone marrow was obtained from the patient post-mortem (*CEP patient #1*).
  • Bone marrow had previously been obtained with IRB approval from her sister (*CEP patient #2*).

• Marrow-derived mononuclear cells from both CEP patients and from normal individuals were grown using special culture conditions to allow for erythroid differentiation
  (protocol modified from Giarratana et al, Blood. 2011;118:5071.)

• Assessments of ERYTHROID MATURATION and PROLIFERATION were performed after 10-17 days in culture

Acknowledgment: Zhantao Yang, MD (Abkowitz Lab)
ERYTHROID MATURATION IS DELAYED IN CEP COMPARED TO NORMAL

- Cells from CEP patient #2 marrow versus normal marrow
- Grown in iron-replete culture conditions
- After 10, 13 and 17 days, cell populations were analyzed by flow cytometry to assess differentiation.

Sequence of erythroid maturation

<table>
<thead>
<tr>
<th>Step 1: Day 10</th>
<th>Step 2: Day 13</th>
<th>Step 3: Day 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFU-E</td>
<td>CFU-E / Pro</td>
<td>Retic</td>
</tr>
<tr>
<td>Pro / Norm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

64.4 % 55.4 % 83.6 %
57.8 % 73.0 %
33.1 %
ERYTHROID PROLIFERATION IS DECREASED IN CEP COMPARED TO NORMAL

- Cells from CEP patient #2 marrow and normal marrow
- Grown in iron-replete culture conditions
- After 10 days, cells were counted on a HEMAVET analyzer

*Not shown:* Cell death likely resulted from apoptosis, as suggested by an increased apoptotic rate in CEP on day 7
FURTHER PHYSIOLOGIC STUDIES WITH VARYING IRON CONCENTRATION

To determine the effect of iron concentration on erythroid growth and differentiation:

• As before, marrow-derived mononuclear cells from the CEP samples were grown using a modified cell culture protocol special culture conditions to allow for erythroid differentiation.

• However, different ratios of holo-Transferrin (holo-Tf) and apo-Transferrin (apo-Tf) were used to manipulate available iron conditions:

<table>
<thead>
<tr>
<th>Decreasing iron concentration in media</th>
<th>Holo-Tf 100%</th>
<th>Holo-Tf 75% : Apo-Tf 25%</th>
<th>Holo-Tf 50% : Apo-Tf 50%</th>
<th>Holo-Tf 25% : Apo-Tf 75%</th>
<th>Apo-Tf 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>μM iron</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
CEP ERYTHROID MATURATION IN VITRO IS OPTIMAL UNDER CONDITIONS OF PARTIAL IRON RESTRICTION

- Cells from CEP patient #1 marrow at varying holo-Tf : apo-Tf ratios
- After 10 days, highest proportion of cells in 3rd compartment at 50%:50% ratio

Data not shown: For normal marrow, maturation was delayed for all conditions less than 100% holo-Tf

<table>
<thead>
<tr>
<th>Holo-Tf 100%</th>
<th>Holo-Tf 75% : Apo-Tf 25%</th>
<th>Holo-Tf 50% : Apo-Tf 50%</th>
<th>Holo-Tf 25% : Apo-Tf 75%</th>
<th>Apo-Tf 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>57.0%</td>
<td>65.0%</td>
<td>82.7%</td>
<td>65.6%</td>
<td>43.6%</td>
</tr>
<tr>
<td>60.1%</td>
<td>67.0%</td>
<td>84.3%</td>
<td>67.0%</td>
<td>46.9%</td>
</tr>
</tbody>
</table>
PROLIFERATION OF CEP ERYTHROID CELLS IS ALSO INCREASED WITH PARTIAL IRON RESTRICTION

Total cell count on day 10 was highest in 50% holo-Tf:50% apo-Tf

*Data not shown:* Growth of normal cells did not differ among the various iron concentrations
SUMMARY OF LABORATORY FINDINGS

• Comparative studies of normal versus CEP marrow-derived mononuclear cells show that under iron-replete, in vitro cell culture conditions, erythroid maturation is delayed and proliferation is reduced in CEP cells.

• Reducing the available iron concentration (by altering holo-Tf and apo-Tf content in culture) resulted in relative improvement in erythroid maturation and increased proliferation in CEP cells grown under conditions of partial iron restriction.

• In contrast to CEP cells, reducing available iron caused maturation delay in normal cells.
IV.

FUTURE DIRECTIONS
Iron restriction may be effective in CEP

What about other porphyrias?

– Porphyrins of hepatic origin are synthesized via ALAS1, which is not translationally regulated by the IRE/IRP system

– Other erythropoietic porphyrias:
  • X-linked protoporphyria (XLP)
  • Erythropoietic protoporphyria (EPP)

Possible evidence of harm. Ferrochelatase enzyme is stabilized by presence of iron and degrades faster in iron deficiency.  

In fact, multiple case reports of iron supplementation as effective therapy in EPP:
IRON RESTRICTION IN PORPHYRIA CUTANEA TARDA

Phlebotomy (targeting ferritin < 20 ng/mL) is effective at reducing symptoms

- Hepatic in origin, cutaneous symptoms
- Deficiency in uroporphyrin decarboxylase (URO-D)
  - Clinical expression of disease when URO-D activity is 20% or less
  - May be inherited or sporadic
  - An inhibitor of URO-D (uroporphomethene)
- Iron is necessary for formation of uroporphomethene

But... this is a different physiology

Iron restriction in MDS?

• Prospective studies have demonstrated a reduction in serum ferritin from chelation in patients with transfusion-dependent MDS and iron overload.

• Curiously, an improvement in hematologic parameters is seen in a significant proportion of patients.
  – For example, in the EPIC trial [Gatterman et al, Haematologica 2012; 97: 1364]
    involving 347 MDS patients receiving deferasirox for baseline ferritin ~3000:
    • 21% had improvement in Hb > 1.5 or reduction of 4 units / 8 weeks

• Retrospective studies suggest a survival benefit to chelation in low-risk MDS patients with iron overload [Rose et al, Leuk Res. 2010; 34:864.]

• A proposed mechanism is that iron toxicity causes destruction of early erythroid cells

• Unpublished data from the Abkowitz lab suggests an alternative relevant physiology in MDS
Iron restriction in MDS?

Del(5q) MDS is characterized by haploinsufficiency of ribosomal protein RPS14, and an erythroid marrow failure similar to Diamond Blackfan Anemia

Led the group to hypothesize that in these disorders, poor ribosome assembly impacts globin synthesis, resulting in excess free heme relative to globin → toxicity to early erythroid progenitors

• In vitro studies del(5q) and DBA cells:
  – Impaired erythroid proliferation
  – Reduced globin production
  – Cells which do survive express higher FLVCR (exports free heme out of cell) and lower ALAS2

• Perhaps iron restriction, via downregulation of heme synthesis, may be of benefit in these disorders
PROTEASOME INHIBITORS: ANOTHER FUTURE THERAPY FOR CEP?


- French group previously showed that most missense mutations in UROS resulted in reduced protein recovery in prokaryote expression model
- With structural modeling, common C73R mutation did not affect the catalytic site. In vitro studies showed protein unfolding and markedly reduced stability of the protein
- Proteasome degradation pathway identified
- In cell lines, proteasome inhibition restored protein levels

Blouin et al. *PNAS.* 2013;110:18238

- Mouse CEP model (C73R & P248Q)
- Bortezomib 0.5 – 1 mg/kg q48h x 9 wks
PROTEASOME INHIBITORS: ANOTHER FUTURE THERAPY FOR CEP?

Post-treatment decrease in urinary porphyrins, and a decrease in “fluorocytes” (RBCs with porphyrin) detected in CEP mice.

No change in hemolytic parameters, but improved photosensitivity.

Mice shaved and exposed to 8 J/m² of UVA radiation.

THANK YOU.

Acknowledgements:

Janis Abkowitz, MD
Zhantao Yang, MD
John Phillips, PhD

The patient and her family.