FANCONI SYNDROME IN CYSTINOSIS

Ewa Elenberg, MD
Texas Children’s Hospital
Baylor College of Medicine
Houston, Texas
We cannot change the direction of the wind, but we can adjust the sails to reach our destination.
In 1936 Dr. Guido Fanconi described several children with combination of:

- Acidosis
- Hypophosphatemic rickets
- Glucosuria
- Proteinuria

Dr. Guido Fanconi
1892-1979
Professor of Pediatrics
University of Zurich
Switzerland
CHARACTERISTICS OF FANCONI SYNDROME

- Generalized dysfunction of Proximal tubules
- Impaired net reabsorption of:
  - Bicarbonate
  - Phosphate
  - Glucose
  - Amino acids
  - Urate
- Hypophosphatemic rickets
## Cause of Fanconi Syndrome

<table>
<thead>
<tr>
<th>Inherited</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystinosis</td>
<td>Drugs:</td>
</tr>
<tr>
<td>Primary idiopathic</td>
<td>Ifosfamide, cisplatinum,</td>
</tr>
<tr>
<td>Tyrosinemia type I</td>
<td>valproic acid, cephalothin</td>
</tr>
<tr>
<td>Lowe's syndrome</td>
<td>aminoglycosides, cidofovir</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>Toxins</td>
</tr>
<tr>
<td>Fructosemia</td>
<td>Heavy metals</td>
</tr>
<tr>
<td>Fanconi-Bickel syndrome</td>
<td>cadmium, mercury, lead</td>
</tr>
<tr>
<td>Dent's disease</td>
<td>Glue (toluene) sniffing</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>Disease states:</td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
<td>Nephrotic syndrome, RVT,</td>
</tr>
<tr>
<td></td>
<td>AIN, renal transplant,</td>
</tr>
<tr>
<td></td>
<td>malignancy</td>
</tr>
</tbody>
</table>

Cystinosis is the most common inherited cause of Fanconi syndrome.
UNDERSTANDING OF FANCONI SYNDROME

Kidney contains over one million of functional units called nephrons.
UNDERSTANDING FANCONI SYNDROME

- Nephrons filter the blood and produce urine
- Nephron consists of glomerulus and tubule
UNDERSTANDING OF FANCONI SYNDROME
**PROXIMAL TUBULE BIOPSY**

**FANCONI SYNDROME**

- **Proximal tubules:**
  - Poorly developed
  - Disorganized

- **Characteristic feature:**
  - **Swan-neck deformity** (narrowing of prox tubule)
  - Corresponds to the development of Fanconi's syndrome
  - Not unique to cystinosis

**Proximal tubule in Cystinosis**

<table>
<thead>
<tr>
<th>Age</th>
<th>5 mo</th>
<th>14mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Swan neck</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pedi Neph: 15, 2000, 50-57*
WHY FANCONI SYNDROME
IN CYSTINOSIS?

- The kidney appears particularly susceptible to the adverse effects of cystine accumulation in cystinosis.

- The morphologic changes in the kidney vary with the stage of the disease.

- Kidneys from patients with benign adult cystinosis do not demonstrate any abnormalities.
MECHANISMS LEADING TO FANCONI SYNDROME
ACIDOSIS IN FANCONI SYNDROME

- Fanconi syndrome patients have significant bicarbonate wasting leading to RTA (renal tubular acidosis)
  - The nature of bicarbonate wasting is unknown
- Characteristic features of RTA
  - Hyperchloremic metabolic acidosis
  - Normal serum anion gap
    - \([\text{Na} - (\text{Cl} + \text{HCO}_3)] = 8-12 \text{ mEq/L}\)
  - Urine pH <5.5 during severe acidosis
  - Urine anion gap negative
    - \([(\text{Na} + \text{K}) - \text{Cl}]\)
MECHANISMS
LEADING TO FANCONI SYNDROME
IN CYSTINOSIS

- Exact mechanisms are unknown
- Postulated mechanisms:
  - Defective lysosomal transport
  - Proximal tubule membrane defects affecting:
    - Reabsorption of solutes
    - Cotransporters
    - Dysfunction of Na-K-ATPase pump
    - Solute back flux (maleic acid toxicity)
- Such generalized dysfunction causes
  - Severe sodium, water and other electrolyte losses
PROXIMAL RENAL TUBULAR CELL TRANSPORT

Urinary space

- HCO$_3^-$
- $H_2CO_3 \leftrightarrow H^+$
- CA
- $H_2O + CO_2$

Proximal tubule cell

- Na$^+$
- H$^+$
- HCO$_3^-$
- CO$_2 + H_2O$
- Na$^+$
- 2K$^+$
- 2Na$^+$
- Aminoacids
- Glucose
- Solutes
- HPO$_4^{2-}$

Blood space

- Na$^+$
- 3HCO$_3^-$
- 3Na$^+$
- Aminoacids
- Glucose
- Solutes
- HPO$_4^{2-}$

CYSTINOSIS

- NaH exchanger
- Cotransporters
- NaK ATPase

postulated mechanisms

diffusion

(+) diffusion

(-) diffusion
A generalized aminoaciduria results in the excretion of amino acids at concentrations that are 10 times the normal values.

The urinary cystine concentration is elevated to the same extent as the concentration of other amino acids.

Cystine stones do not form.

Not like in the disease called cystinuria.
PROTEIN REABSORPTION
MEGALIN-ENDOCYTIC PATHWAY

- Protein - Megalin complex incorporated into endosome
- Proton pump (H-ATPase) incorporated into endosome
- CIC-5 (Chloride channel)
- Dissociation
- Megalin recycling
- Lysosome
- LMW Protein - endocytic receptor

- Protein binds to Megalin - endocytic receptor

Vascular space

Free Aminoacids

CYSTINOSIS
ANIMAL MODELS
FANCONI SYNDROME

- Spontaneous Fanconi syndrome:
  - Basenji dogs
    - Idiopathic Fanconi syndrome model
- Reversible Fanconi syndrome:
  - Dogs or rats
    - Toxin-induced (maleate or cadmium)
FANCONI SYNDROME
TOXIN MODELS
Maleic acid and cadmium

- Reversible Fanconi syndrome in dogs or rats
- Toxins are concentrated within mitochondria:
  - Enlarged and dysfunctional
  - Decreased activity of mitochondrial enzymes:
    - ATP concentration
    - Na-K-ATPase activity
    - Intracellular phosphate
    - Renal coenzyme-A levels
- Partial inhibition of proximal tubule endocytosis
Cell model:
- Cystine loading of isolated proximal tubules reduces:
  - Volume of absorption
  - ATP flux
  - Glucose and bicarbonate transport
  - Oxygen consumption

Exfoliated human proximal tubular cells
- Cultured cells from 9 cystinosis children + 8 controls
- In vitro model of cystinosis and Fanconi syndrome
- Demonstrated the absence of cystinosin in affected but not in control cells
- Non-invasive model; requires 1 urine sample

Van’t Hoff et al; Ped Nephrol; 20:136-140; 2005
EXPERIMENTAL CYSTINOSIS ANIMAL MODELS

- **Rat model:**
  - Rats treated with cystine dimethyl ester
  - Develop intralysosomal cystine accumulation
  - Exhibit features of Fanconi syndrome

- **Knock-out mice model of cystinosis:**
  - Ctns+ mice accumulates cystine in all tissues
  - Ocular abnormalities similar to humans
  - High level of cystine accumulates in the kidney
  - ? Mice does not demonstrate proximal tubulopathy or renal dysfunction

*Kalatzis, Antignac; Ped Nephrol; 18:207-215; 2003*
CLINICAL FEATURES
OF FANCONI SYNDROME
CLINICAL FEATURES OF FANCONI SYNDROME

- Polyuria
  - Increased thirst
  - Dehydration
- Delayed Growth
- Rickets
LABORATORY FEATURES OF FANCONI SYNDROME

**URINE**
- Polyuria
- Increased excretion:
  - Aminoacids
  - Glucose
  - Phosphate
  - Bicarbonate
  - Potassium

**BLOOD**
- Hyperchloremic metabolic acidosis
- Low serum level:
  - Sodium
  - Phosphorus
  - Calcium
  - Potassium
  - Carnitine
  - Uric acid
SUSPECTED FANCONI SYNDROME
INITIAL WORK-UP

SERUM ELECTROLYTES:
• Hypokalemia
• Hyponatremia
• Hyperchloremia
• Hypophosphatemia
• Low bicarbonate
• Hyperchloremia

URINALYSIS:
• Low pH & osmolality
• Proteinuria
• Glucosuria

URINE ELECTROLYTES:
• Bicarbonate
• Sodium
• Potassium
• Phosphate
• Calcium
• Creatinine

VENOUS BLOOD GAS:
• Metabolic acidosis

OPHTALMOLOGIC EXAM:
• Corneal crystals

RADIOLOGY:
• X-ray of wrists & knees
• Renal ultrasound
DIAGNOSIS OF CYSTINOSIS

MEASUREMENT of:
Cystine levels in PMN leukocytes
\( \frac{1}{2} \text{cystine/mg cell protein} \)

NORMAL
Less than 0.2 nmol

HOMOZYGOTES
5-10 nmol

HETEROZYGOTES
Less than 1.0 nmol

Test used also to monitor the effect of therapy
FANCONI SYNDROME
POLYURIA

- Daily excretion 2 to 6 L of dilute urine
- Rapid development of electrolyte abnormalities
- Episodes of dehydration
  - Rapid progression
  - May be associated with mild, chronic fever
  - Infants may die of dehydration
PHOSPHATURIA
FANCONI SYNDROME

- Phosphaturia leads to:
  - Hypophosphatemic rickets

- Clinical characteristics:
  - Rickets
    - Metaphyseal widening
    - Rachitic rosary
    - Frontal bossing
  - Genu varus/valgum
  - Failure to walk
UNUSUAL FOOD PREFERENCE

- Patients crave for:
  - Salty, hot and spicy food

- Cause:
  - Urine loss of salts
  - Cystine crystals deposits in the taste buds
FANCONI SYNDROME IN RENAL FAILURE

- With progressive renal failure
  - Fanconi syndrome gets better
    - Urine output is decreasing and patients drink less water
    - Potassium and phosphorus are improving and patients need less supplementation
  - Acidosis and calcium levels are becoming worse and patients need more supplementation of bicarbonate and calcium
  - Poor growth continues
- With renal transplantation
  - Fanconi syndrome does not occur
FANCONI SYNDROME

THERAPY
FANCONI SYNDROME
THERAPY

- Tubular dysfunction
  - Managed with electrolyte supplementation

- Excessive urinary water loss
  - Managed with large water intake

- Rickets
  - Treated with a combination of
    - Phosphate
    - Vitamin D
      - to increase intestinal absorption and decrease urinary losses of phosphate
SODIUM

- Sodium chloride
  - Tablets
- Sodium bicarbonate
  - Tablets
  - Liquid
- Sodium phosphate
  - Liquid
SODIUM BICARBONATE

SUPPLIED:

- Tablet
- Liquid
  - Bicitra
    - 1 ml = 1 mEq Na, 1 mEq bicarbonate
  - Polycitra
    - 1 ml = 1 mEq Na, 2 mEq bicarb, 1 mEq K
  - Polycitra K
    - 1 ml = 1 mEq Na, 2 mEq bicarb, 2 mEq K

CITRATE
converted in liver to bicarbonate
SODIUM BICARBONATE
SIDE EFFECTS

■ GI:
  ■ Belching
  ■ Flatulence
  ■ Gastric distension

■ To improve salty taste:
  ■ dilute with water
  ■ chilling improves flavor

■ To prevent diarrhea:
  ■ give after meals
PHOSPHATE

- OPTIONS of supplements:
  - Sodium phosphate = Fleet Phospho-Soda®
    - Liquid
  - Potassium phosphate = Neutra-Phos®
    - Powder for oral solution (packets)
    - Liquid (prepared by pharmacy)

- SIDE-EFFECTS:
  - GI:
    - Diarrhea, nausea, vomiting
    - Stomach pain, flatulence
CALCIUM

- OPTIONS of supplements:
  - Calcium Carbonate - tablets, capsules, liquid
  - Calcium Glubionate - liquid
  - Calcium Gluconate - tablets
  - Calcium Lactate - tablets

- REQUIREMENTS:
  - Take on *empty* stomach (*better absorption*)

- OTHER USE:
  - Antacid effect (*neutralizes gastric acid*)
  - In renal failure as phosphate binder

- SIDE EFFECTS: None (well tolerated)
POTASSIUM

- OPTIONS of supplements:
  - Potassium chloride
    - Capsules
    - Liquid
    - Powder (packets)
  - Potassium phosphate
    - Powder for oral solution (packets)
    - Liquid (prepared by pharmacy)
  - Potassium citrate
    - Liquid (Polycitra® with sodium)

- SIDE-EFFECTS:
  - GI - diarrhea, nausea, vomiting, stomach pain, flatulence
VITAMIN D
ROCALTROL®

- It is used for management of bone disease

- SUPPLIED:
  - Capsule
  - Solution
INDOMETHACIN

- Leads to improved growth in cystinosis

Decreased urine volume

Decreased water intake

Improved appetite

Improved growth

**WARNING:**

- Can decrease kidney function in pts with:
  - Chronic renal failure or dehydration
- Can cause GI side effects
HOW TO IMPROVE ADHERANCE

- Set up regular times for medication intake
- Be consistent with daily routine
- Learn what the medications do
- Ask about alternatives
- Consider the best route of administration
  - Mouth
  - Gastric tube/button
  - Intravenous – if other modes fail
HOW TO IMPROVE ADHERANCE

- Improve **flavor & taste** of liquid medication
  - FLAVORx™ *(42 flavors)*
  - Syrpalta® *(grape, cherry flavor)*
- Change from **solid to liquid**:  
  - Ora-Plus™
  - Ora-Sweet™ or Ora-Sweet SF™
- Change from **tablet or powder to capsule**
  - Capsuline™
HOW TO IMPROVE ADHERANCE

- Set up regular times for medication intake
- Be consistent with daily routine
- Learn what the medications do
- Ask about alternatives
- Consider the best route of administration
  - Mouth
  - Gastric tube/button
  - Intravenous – if other modes fail
The medical field advances so quickly, it is hard to keep up on the latest and greatest. We never stop learning, so hang on to hope!