Renal Fanconi Syndrome

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RFS is specific

RFS is generalised

RFS is generalised
Clinical diagnosis

Clinical:
- Rickets
- Failure-to-thrive
- Lowish BP

Blood:
- Metabolic acidosis
- Hypokalaemia
- Hypophosphataemia
- ?vitamin D deficiency

Urine:
- Calcium
- LMWP protein
- Phosphate
- Glucose
- Aminoacids
- Organic acids
- Potassium
- Bicarbonate

Remarks on the Relations between Renal Rickets (Renal Dwarfism) and Renal Diabetes.

By Prof. O. DE TONI M.D., Bologna, Italy.

I shall describe shortly the case of a little girl at present almost five years old, whose clinical history is of some interest.

1. Alesandina, born September 19, 1898. The parents are first cousins; otherwise the family history offers nothing of importance. The child was born after four healthy and living sires the first born suffered from rachitic manifestations in early infancy, which healed perfectly. The pregnancy and parturition in the case of the patient were normal. The baby was not weighed at birth; the mother noted, however, that she was somewhat small, but well proportioned. She was fed for eight months exclusively by the breast; then on a mixed diet until seventeen months old.

The mother noticed that even though the baby was normal mentally, as far as she could judge, yet there was a very late bodily growth. Dentition was delayed; at two years the baby had only six teeth. She began to walk at the age of three. At this time she was afflicted by whooping cough, after which she again went off her feet. The child was treated for a long time by other doctors, with irradiated ergosterol, phosphates and haemotherapy; these treatments, according to the mother, did not give very satisfactory results.

Acta Paediatrica, 1933, 16, 479-484
### Syndromic RFS: metabolic toxicity

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>Associated features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystinosis</td>
<td>CTNS</td>
<td>Neuromuscular dysfunction, endocrinopathies</td>
</tr>
<tr>
<td>Galactosaemia</td>
<td>GALT</td>
<td>Liver dysfunction, jaundice, encephalopathy, sepsis</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>FAH</td>
<td>Poor growth, hepatic dysfunction</td>
</tr>
<tr>
<td>Congenital Fructose</td>
<td>ALDOB</td>
<td>Rapid onset after fructose ingestion, vomiting, hypoglycemia, hepatomegaly</td>
</tr>
<tr>
<td>Intolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fanzoni Bickel syndrome</td>
<td>GLUT2</td>
<td>Hepatomegaly, hypoglycemia, severe glycosuria, galactosuria</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>ATP7B</td>
<td>Hepatic &amp; neurological disease, Kayser-Fleischer rings</td>
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</tbody>
</table>
### Syndromic RFS: impaired energy supply or endocytosis

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<tr>
<th>Disorder</th>
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<th>Associated features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrial cytopathies</td>
<td>multiple</td>
<td>Usually multisystem dysfunction (brain, muscle, liver, heart)</td>
</tr>
<tr>
<td>Lowe's syndrome</td>
<td>OCRL</td>
<td>Males (X-linked), cataracts, muscular hypotonia, developmental delay</td>
</tr>
<tr>
<td>Dent Disease</td>
<td>CLCN5</td>
<td>Males (X-linked), nephrocalcinosis</td>
</tr>
<tr>
<td>ARC syndrome</td>
<td>FPS35B</td>
<td>Anthropyrosis, cholestasis</td>
</tr>
<tr>
<td>MODY1</td>
<td>HNF4A</td>
<td>Neonatal hyperinsulin, MODY, Yeast</td>
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</tbody>
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### Acquired RFS: Drugs and Toxins

**Anticancer drugs**
- Ifosfamide
- Streptozocin

**Antibiotics**
- Aminoglycoside
- Expired tetracyclines
- Amphotericin

**Antiretrovirals**
- Adefovir/Cidofovir/Tenofovir
- ddl

**Heavy metals**
- Lead poisoning
- Cadmium

**Antiepileptic**
- Sodium Valproate

**Toxins**
- Aristolecic acid (Chinese herb nephropathy)
- Toluene/GluSniffing
- Fumaric Acid
- Suramin
- Paraquat
- L-Lysine

### Isolated inherited RFS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
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<tbody>
<tr>
<td>FRTS1</td>
<td>?</td>
</tr>
<tr>
<td>FRTS2</td>
<td>SLC34A1</td>
</tr>
<tr>
<td>FRTS3</td>
<td>EHHADH</td>
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</tbody>
</table>
A geneticist’s dream…
Another patient

- 8 y old girl with short stature, genu varus, rickety rosary, widening of wrists
- History of severe dehydration, age 2y, at that time metabolic acidosis
- Labs, plasma: Na: 140, Cl: 114, HCO2: 7, PO4: 0.51 mmol/l
- Urine: LMWP, glycosuria, aminoaciduria, hypercalciuria, TRP: 53%

Fanconi Syndrome without kidney failure


Fanconi Syndrome without kidney failure
Fanconi Syndrome without kidney failure

Urine profiling

Fanconi Syndrome without kidney failure

Fanconi Syndrome without kidney failure
A mutation in EHHADH segregates with the disease Fanconi Syndrome without kidney failure.

WT

EHHADH^/- mouse

Fanconi Syndrome without kidney failure

EHHADH

EHHADH mut
Fanconin - cellular pathophysiology

Mitochondrial oxygen consumption

normal

FA

Mitochondrium

Peroxisome

EHHADH
Conclusions

- RFS refers to generalised dysfunction of the proximal tubule
- Clinical consequences typically include failure-to-thrive and rickets
- FRTS3 reveals a new disease mechanism: dominant negative effect of mistargeting
- Highlights importance of fatty acid oxidation for energy supply of PT