Mitochondrial Disorder?

Yes  Maybe!

Joyce Lee, MD
March 23, 2012

Presentation
- 5 YO WCC, 4 months of polyuria, polydipsia, and weight loss
- Weight 15.5 kg (50th → 10th %)
- Height 104 cm (50th → 25th %)
- PE unremarkable except for stable bilateral photophobia
- Screening UA: large glucose
- Fingerstick glucose: 144 mg/dL

Birth History
- 34 weeks GA secondary to pre-term labor
- Mild respiratory distress and delayed oral feeding
- Complete resolution without sequelae
- Age appropriate growth and development until presentation at 5 YO

Past Medical History
- Photophobia since infancy with increasing severity throughout childhood
- Ophthalmologic exam revealed bilateral corneal clouding and edema with normal intraocular pressure
- Bilateral corneal transplants at 4 YO and 5 YO
- Abnormal corneal epithelium with membrane vacuoles suggestive of mitochondrial or lysosomal storage disease without mucopolysaccharide deposition

Laboratory

<table>
<thead>
<tr>
<th>Phosphate</th>
<th>Uric Acid</th>
<th>Phosphate</th>
<th>Uric Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7</td>
<td>0.9</td>
<td>13.7</td>
<td>14.7</td>
</tr>
<tr>
<td>100 mg/dL</td>
<td>1000 mg/dL</td>
<td>10 mg/dL</td>
<td>10 mg/dL</td>
</tr>
</tbody>
</table>

De Toni – Debre – Fanconi Syndrome
- Proximal tubular dysfunction:
  - Bicarbonaturia → hyperchloremic acidosis
  - Phosphaturia, glucosuria, proteinuria, organic aciduria
- Initiated oral phosphate and bicarbonate supplementation

Guido Fanconi, 1892 – 1979
### Congenital Causes

<table>
<thead>
<tr>
<th>Onset</th>
<th>Disorder</th>
<th>Associated Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td>Galactosemia</td>
<td>Hepatic dysfunction, jaundice, encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial Disease</td>
<td>Multisystemic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Tyrosoninemia</td>
<td>Poor growth, hepatic dysfunction</td>
</tr>
<tr>
<td>Infancy</td>
<td>Fructosemia</td>
<td>Onset after fructose ingestion – vomiting, hypoglycemia, hepatomegaly</td>
</tr>
<tr>
<td></td>
<td>Cystinosis</td>
<td>Poor growth, rickets, corneal cystine crystals</td>
</tr>
<tr>
<td>Lowe’s Syndrome</td>
<td></td>
<td>X-linked, cataracts, hypotonia, developmental delay</td>
</tr>
<tr>
<td>Childhood</td>
<td>Cystinosis</td>
<td>Poor growth, rickets, corneal cystine crystals</td>
</tr>
<tr>
<td></td>
<td>Dent’s Disease</td>
<td>X-linked, hypercalcuria, nephrocalcinosis</td>
</tr>
<tr>
<td></td>
<td>Wilson’s Disease</td>
<td>Hepatic and neurologic dysfunction</td>
</tr>
</tbody>
</table>

### Etiologic Work-Up

<table>
<thead>
<tr>
<th>Onset</th>
<th>Disorder</th>
<th>Work Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td>Galactosemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mitochondrial Disease</td>
<td>Multisystemic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Tyrosoninemia</td>
<td></td>
</tr>
<tr>
<td>Infancy</td>
<td>Fructosemia</td>
<td>Normal leukocyte cystine assay</td>
</tr>
<tr>
<td></td>
<td>Cystinosis</td>
<td>Female, no associated features</td>
</tr>
<tr>
<td>Lowe’s Syndrome</td>
<td></td>
<td>Female, no hematuria, nephrocalcinosis on RUS, no nephrolithiasis</td>
</tr>
<tr>
<td>Childhood</td>
<td>Cystinosis</td>
<td>Normal leukocyte cystine assay</td>
</tr>
<tr>
<td></td>
<td>Dent’s Disease</td>
<td>Female, no hematuria, nephrocalcinosis on RUS, no nephrolithiasis</td>
</tr>
<tr>
<td></td>
<td>Wilson’s Disease</td>
<td></td>
</tr>
</tbody>
</table>

### Renal Manifestations

- 5 - 50% of pediatric mitochondrial disease case series
- Most common renal manifestation = de Toni Debre Fanconi syndrome
- FSGS, Bartter Syndrome, and tubulointerstitial disease

Roberto Debre, 1882 - 1978

### Mitochondrial Disease

#### Screening
- Lactate: 1.3 mmol/L (0.5 – 2)
- Pyruvate: 0.6 mg/dL (0.3-0.7)
- Urine organic acids: Markedly elevations lactate, pyruvate, and ketoacids

#### Confirmatory
- Genetic testing: blood leukocyte DNA – mtDNA deletion nt 8,648 – 16,072
- Large, novel, heteroplasmic, de novo, 7,424 base pair deletion
- Maternal leukocyte mtDNA analysis normal
Mitochondrial Disorder? Yes! Maybe!

Joyce J. Lee, MD
Fellow in Pediatric Nephrology

Richard W. Erbe, MD
Chief, Division of Genetics, WCHOB; Professor of Pediatrics, UB

Mitochondrial Disorders

- A complex group of conditions caused by inherited or sporadic mutations in genes underlying the electron transport chain (ETC)/oxidative phosphorylation (OXPHOS)
- Mitochondria are uniquely controlled by two genomes
  - 13 of the 80+ proteins that comprise the ETC are encoded by 3 dozen genes in mitochondrial DNA (mtDNA) which is polyploid (present in ~3-10 copies/ organelle)
  - Remaining proteins and other functions are encoded in 110-1500 nuclear genes

Extreme clinical and genetic variability is attributable to...

- mtDNA heteroplasmy (= the presence of a mixture of different mtDNA populations indiffent tissues)
- Random replicative segregation of mtDNA (which can significantly change heteroplasmy over time)
- Allelic and locus heterogeneity (in which one mutation can cause a variety of different phenotypes, or one condition may be caused by mutations at several different loci)
- External factors, including diet, medications, metabolic stress (fever, prolonged fasting) and intercurrent illness, exert variable effects
The Mitochondrial Genome

- Circular; 16,659 bp
- Polymorphic, 0.3% variation between individuals; 7-10x mutation rate of nuclear genome
- 2-10 copies/mt
- Encodes 13 peptides (OX PHOS), 22 tRNAs, 2 rRNAs
- Unique genetic code

Mitochondrial Disease

- Nuclear and mt DNA mutations
- Maternal, cytoplasmic inheritance (for mt DNA)
- Heteroplasmy – mitochondria form a population within cells; threshold effect
- Phenotypes may vary with age
- Affect tissues with high energy demands

Symptoms Suggesting a Mt Disorder

- CNS - hypotonia, ataxia, MR, seizures, migraines, dementia, neurosensory hearing loss
- Eyes - RP, optic atrophy, nystagamus
- Muscle - weakness, exercise intolerance, red ragged fibers
- Cardiac - hypertrophic cardiomyopathy, arrhythmias, heart block
- Hematologic - macrocytic anemia, pancytopenia

Symptoms Suggesting a Mt Disorder

- Endocrine - diabetes mellitus, diabetes insipidus, exocrine pancreatic dysfunction, short stature
- GI - dysfunction, intestinal pseudo-obstruction
- Liver -dysfunction, failure
- Renal - RTA, Fanconi syndrome

Many pts, particularly infants, do not present with classic phenotypes; consider Mt disorder in differential if pt has 2 or more suggestive findings

Inherited Defects in Mt Function

- A few are named as syndromes (but usually with multiple possible genetic bases) but most have nonspecific findings in several systems
- Genetic bases
  - Defects in nuclear genes
    - Single function deficiencies
    - Mt biogenesis and replication defects
  - mtDNA point mutations
  - mtDNA deletions / insertions

Some Mt Disorders Caused by Mutations in the Nuclear Genome

- Defects in OxPhos
  - ~ 80-90% of the patients have nuclear defects
  - All complexes of the electron transport chain (ETC) have subunits encoded in nuclear genome
  - AR inheritance
- Leigh syndrome
  - Onset late infancy with regression; MRI abnl
  - Heterogeneous with nuclear & Mt mutations; ~50% are in SURF1 (involved in assembly cytochrome oxidase, Complex IV)

See: DiMauro & Schon NEJM 348: 2656, 2003
Smetting et al, Nat Rev Genet 2: 342, 2001
Some Disorders Caused by Point Mutations in the mtDNA

• LHON (Leber hereditary optic neuropathy - adult onset optic neuropathy; most homoplasmic missense muts

• NARP (neuropathy, ataxia & and retinitis pigmentosa) - most patients have missense mutations in ATP synthase (Complex V)

• Maternally inherited deafness - point mutations in mt rRNA; also associated with susceptibility to aminoglycoside ototoxicity

Some Disorders Caused by Point Mutations in the mtDNA

• mtDNA mutations in tRNA gene
  - MERRF (myoclonic epilepsy with ragged red fibers) - heteroplasmic point mutations in mt tRNA^Leu (~80%)
  - MELAS - heteroplasmic point mutations in RNA^Leu (most)

• Mechanism not known; symptoms may relate to inability to synthesize several Mt proteins and lack of normal processing of transcripts

mtDNA Deletions: Kearns-Sayre Syndrome (KSS)

• Ptosis
• Ophthalmoplegia
• Heteroplasmic mitochondrial deletion
• Invariant triad
  – Onset <20 years
  – Ophthalmoplegia
  – Pigmentary retinopathy

MELAS: Myoclonic Epilepsy, Lactic Acidosis and Stroke

• Episodes of metabolic decompensation ass’d with high risk for stroke

  = 3243 A>G tRNA^Leu (~90%)
  3271 T>C tRNA^Leu (~7%) Heteroplasmic
Some Disorders Caused by Mt DNA Deletions and/or Duplications

- Diabetes and deafness
- Pearson syndrome - anemia
  2’ marrow failure; lactic acidosis; exocrine pancreatic failure: RTA
- CPEO – chronic progressive external ophthalmoplegia
- Kearns-Sayre – PEO, cardiac conduction block, RP, ataxia, lactic acidosis, ataxia; sporadic

Laboratory Diagnosis of Mt Disorders

- Lactate, pyruvate (peripheral, CNS), increased ratio; increased alanine
- MRI of brain
- Consider muscle (quad, deltoi) and/or liver bx (most involved tissue)
- OXPHOS analysis, including enzyme assays
- DNA analysis for specific mtDNA/nuclear mutations

Diagnostic Problems

- Symptoms of excessive fatigue, fibromyalgia as basis for Dx
- Labs: elevated plasma lactate concentration, elevated plasma alanine on amino acid profile – procedural problems
- Non-standard procedure used in ‘forearm test’
- Tissue: nonspecific, nondiagnostic findings in muscle biopsy are often presumed to represent mitochondrial disorder
- Mother without confirmed diagnosis brings children because presumed affected (maternal inheritance)
- Repeated symptom Hx of “mitochondrial dysfunction” gets incorporated into record as a diagnosis
- No rigorously confirmed diagnostic algorithm

Rx of Mitochondrial Disorders

- No proposed treatments have been evidence-based
- Can give levo-carnitine (Carnitor) 30-200 mg/kg/d; coenzyme Q10 5-15 mg/kg/d; riboflavin (B2 – for complexes I,) 100-400 mg/d; nicotinamide (B3) 100-200 mg/d; thiamine (B1) 100-200 mg/d; folic acid 1 mg/d; vitamins C & E; L-arginine for MELAS to reduce stroke risk
- Avoid Na valproate & barbiturates (inhibit ETC & may precipitate hepatic failure in ETC-deficient children); tetracyclines & chloramphenicol (inhibit mitochondrial protein synthesis)

Genetic Counseling

- Mt disorders can be inherited patterns that are autosomal recessive or autosomal dominant (nuclear gene defects) or maternal/matrilineal
- Although all sons and daughters of an affected female inherit at least some mutant mtDNA, offspring will express most, some or none of the phenotypic abnormalities (penetrance)
- Extremely complex because of shortcomings in diagnostic methods, heterogeneity, variable expression, frequency of new mutations, etc.