18 year old with Kearns Sayre Syndrome

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Endorama
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History of Present Illness

Consulted for “possible endocrinopathies associated with Kearns Sayre Syndrome” in an 18 year old woman admitted for cardiogenic shock.
Kearns Sayre Syndrome

- Rare mitochondrial myopathy due to large-scale heteroplasmic deletions of mitochondrial DNA.
  - Usually spontaneous
  - No predilection for race or sex
  - No known risk factors
- Characterized by a triad of:
  - Chronic progressive external ophthalmoplegia
  - Cardiac conduction abnormalities
  - Bilateral pigmentary retinopathy
- Additional features include myopathy, skeletal muscle weakness, exercise intolerance, bulbar symptoms (dysarthria, dystonia, dysphagia, facial weakness, deafness), cerebellar ataxia, dementia, proximal tubular acidosis, cataracts, and various endocrinopathies.
- Presents before age 20.

Kearns Sayre Syndrome

- Laboratory features: normal or moderately elevated CK, elevated lactate and pyruvate
- Histology features: red ragged fibers and large irregularly shaped mitochondria on muscle biopsy.
- Radiographic features: basal ganglia calcification on CT, spongiform encephalopathy on CT/MRI.
- No disease-modifying therapy.
  - Coenzyme Q10 and vitamin supplements.
- Death is common in 3rd and 4th decades of life.

Kearns Sayre Syndrome

Immunofluorescence for complex IV-I (A) and complex IV-IV (B) of the electron transport chain. Muscle fibers with total (arrows) or partial (arrow heads) deficiency.

18 year old AA woman with known history of Kearns-Sayre Syndrome diagnosed 5 years ago who was transferred from OSH with cardiogenic shock on multiple pressor support and balloon pump here for advanced care.

- Initially presented to the OSH ER with 3 weeks of worsening generalized weakness, fatigue, and gait imbalance.
- ROS also positive for generalized fever/chills, cough, dyspnea, diminished appetite, nausea, 5-7 lb recent weight loss.
- Has often had generalized muscle weakness with KSS but never generalized fatigue. No history of cardiac complications from KSS.
  - Prior TTE (4/15/09) normal LV/RV, trivial MR and TR
History of Present Illness

- Recently seen as outpatient 3 weeks ago for sore throat, was strep negative and was felt to have GERD and started on Pepcid.
  - Labs were notable for elevated CK 3626 (baseline 1000s), elevated AST/ALT and Cr 0.5.
- On presentation to OSH pt was afebrile, HR 122, BP 98/62, and RR 20s. During the hospitalization her BP continued to trend downward and was started on dobutamine, milrinone, amiodarone, furosemide, and heparin gtts.
  - Initial labs at the OSH were notable CK 7725
  - TTE: LVEF: 10-15%
- Placed on ECMO.
- Underwent heart transplant.
Past Medical History:
- Kearns Sayre Syndrome
  - Diagnosed 5 years ago
  - Initially presented with fatigue and muscle weakness
  - Had ptosis eyelid surgery in 2010.
- Osgood-Schlatter Disease
- Asthma
- Recurrent otitis media

Medications:
- Leucovorin 5 mg BID
- Levocarnitine 330 mg TID
- Loratidine 10 mg QD
- Pepcid 20 mg BID
- Vit D3
- Systane Ultra eyedrops

Allergies: Augmentin

Social History:
- Went to her senior prom
- College student at Bradley University, majoring in graphic design
- Lives with her parents
- No tobacco, etoh, recreational drug use

Family History:
- Mother: thyroid problem; history of congestive heart failure
- Father: DM, HTN
Admission Physical Exam

- **VITALS:** Temp 97F, BP 93/53, HR 119, RR 20, 96%, 51 kg
- **GEN:** NAD, lethargic/somnolent, minimal verbal response reactive to verbal commands and answers questions appropriately
- **NEURO:** CN II-XII intact. Pupils 3 mm and sluggishly reactive to light, intact gag
- **HEENT:** Normocephalic, atraumatic, no gross craniofacial abnormalities, pupils sluggish to light, trachea midline, no cervical/submandibular/supraclavicular lymphadenopathy, no thyromegaly, mucous membranes dry and erythematous, no notable petechiae
- **CV:** irregularly irregular, tachycardic, pounding chest wall, no murmurs/rubs/gallops appreciated, JVP to ear lobe.
- **PULM:** minimal crackles at bases bilaterally. Respirations nonlabored. No wheezing/rubs
- **GI:** Soft, non-tender, non-distended, no rebounding, + guarding, no hepatomegaly, no splenomegaly, normal bowel sounds present.
- **GU:** No suprapubic or costovertebral angle tenderness.
- **SKIN:** No signs of peripheral edema. Extremities cold to touch. Petechial, non blanching rash to anterior chest
- **EXT:** <1 sec capillary refill in upper extremities and lower extremities bilaterally.
- **DEVICES:** balloon pump to right femoral groin. Right subclavian 4LC.

Consulted for “possible associated endocrinopathies.”
KSS and associated endocrine abnormalities

- Short stature: 85/226 (38%)
- Male hypogonadism: 26/123 (21%)
- Female hypogonadism: 18/102 (18%)
- Diabetes mellitus: 29/226 (13%)
  - Insulin-dependent: 14 cases
- Hypoparathyroidism: 14/226 (7%)
- Bone or tooth abnormalities: 13/226 (6%)
- Thyroid disease: 7/226 (3%)
- Hyperaldosteronism: 7/226 (3%)
- Hypomagnesemia: 8/226 (4%)

- Adrenal insufficiency: 4 case reports

Variability in KSS

Table 1. Proportion of the different recombinant forms of mtDNA in ten tissues from the KSS patient (on molecular basis)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>%Normal</th>
<th>%Duplication</th>
<th>%Deletion</th>
<th>%Deletion dimer</th>
</tr>
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<tbody>
<tr>
<td>Cerebral cortex</td>
<td>58</td>
<td>3</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>67</td>
<td>10</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Heart</td>
<td>87</td>
<td>6</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Muscle 1</td>
<td>80</td>
<td>10</td>
<td>&lt;1</td>
<td>9</td>
</tr>
<tr>
<td>Muscle 2</td>
<td>52</td>
<td>1</td>
<td>3</td>
<td>44</td>
</tr>
<tr>
<td>Liver</td>
<td>34</td>
<td>1</td>
<td>62</td>
<td>2</td>
</tr>
<tr>
<td>Kidney</td>
<td>30</td>
<td>16</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>Pituitary</td>
<td>55</td>
<td>11</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>Pancreas</td>
<td>59</td>
<td>10</td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td>Ovary</td>
<td>84</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Spleen</td>
<td>65</td>
<td>7</td>
<td>18</td>
<td>9</td>
</tr>
</tbody>
</table>

All these samples were taken at post-mortem except muscle 1 which was a biopsy taken 10 years prior to death.

Possible mechanisms of associated endocrinopathies

- Defective hormone production or secretion of hormone from deficiency of cellular metabolism.
- Hypothalamic damage
  - Spongiform degeneration of the brain
- Autoimmunity
  - Coincidental v. causally linked
  - Deficiency of cellular metabolism may lead to destruction of endocrine cells, abnormal presentation of autoantigens, production of autoantibodies, and secondary autoimmune endocrinopathy

Status at time of consult

- Medications:
  - Dobutamine gtt
  - Dopamine gtt
  - Heparin gtt
  - Methylprednisolone 100 mg q8 hr
  - Mycophenolate 750 mg q12 hr
  - Cefepime 1 gm q12 hr
  - Vancomycin 1 gm q 24 hr
  - Ganciclovir 5mg/kg q24 hr
  - Famotidine 20 mg qhs
  - Duoneb nebulizer q4 hr
  - Ascorbic acid 500 mg TID
  - Ferrous sulfate 300 mg TID

- D5NS at 40 cc/hr
- PRNs:
  - Magnesium
  - Potassium
  - Morphine
  - Zofran
  - Benadryl

- Physical Exam:
  - Intubated
  - Anasarca, chemosis
  - Unable to elicit DTRs
  - No Chvestok’s sign.
Admission labs

137  103  30  113
3.8   17   2.2  10.3
Ca 8.1, Phos 2.8, Mg 1.9  12.1  85
2.8, Mg 1.9  31.0

Total protein 6.1, alb 3.4  78N, 12L, 10 M
Prealbumin 11 (21-41)  PT 17.9, PTT 51.2, INR 1.6
Tbili 1.6, alk phos 49
AST 282, ALT 205
LDH 1159
Lactic acid 5.6

CK 1459, CK MB 27.1,
Trop T 0.14
Endocrine labs

- **Outpatient clinic visit, 2 weeks prior to presentation:**
  - TSH 1.234
  - Ca 9.1
  - Alb 4.1
  - Alk phos 47

- **Admission:**
  - Ca 8.1 (corr 8.6)
  - Phos 2.8

- **Glucose:** 67-194
  - On high dose steroids, continuous tube feeds

- **HgbA1c 5.7%**

- **TFTs:**
  - TSH 3.05
  - T4 6.6 (5.0-11.6)
  - T3 52 (80-195)
  - fT3 129 (230-420)
  - rT3 1547 (160-353)
Calcium Trend

- CaCl 3 gm
- PTH 28
- iCa 5.0

- Calcium (8.4-10.2)
- Ionized calcium (4.6-5.4)
- Phos (2.5-4.4)
Assessment and Plan:

- Hypoparathyroidism: Likely previously had mild hypoparathyroidism that was compensated and this was unmasked by blood transfusions and ECMO. Low alk phos is also c/w hypoparathyroidism.
  - Recommended monitoring total and ionized calcium q8 hours and IV calcium gtt for repletion.
- Steroid-induced hyperglycemia:
  - Low dose NISS q 4 hours → insulin gtt
- Thyroid function: sick euthyroid and amiodarone use
- Gonads: seemed to have been intact given regular menses
- Adrenal: on high dose steroids
- Growth hormone: 5’2”
KSS and Hypoparathyroidism

- May be presenting feature:
  - 10/14 cases presented with tetany.
- Associated with more severe disease.
- Unclear etiology—no reports have shown evidence of dietary, malabsorption, vitamin D disorders, or autoimmune mechanism
  - May be partially related to hypomagnesemia
- Autopsy of 2 cases:
  - Absent parathyroid glands
  - One parathyroid gland identified

KSS and Diabetes

- Diabetes associated with mtDNA rearrangements commonly present with insulin-dependent diabetes at a young age with eventual complete loss of β cell function.
- Impaired insulin secretion is likely related to lack of ATP to close potassium channels in the β cell membrane.
- No evidence of autoimmune etiology.

Back to the patient

- Started on CVVH.
- Noted to have anisocoric sluggish pupils and persistent unresponsiveness.
- CT head showed ICH/IVH/SAH with associated cerebral edema, midline shift, brainstem compression and herniation through Foramen Magnum.
References