A Case of Early-onset Stroke

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Current Admission

34 year old presented with 3 days of diffuse headache

Associated Symptoms:
  • Nausea
  • Memory loss
  • Difficulty with word finding

Past Medical History: Stroke at 31, preceded by similar headache

Family History:
  • Mom with seizures and stroke at 25 and deceased at age 50 from another CVA.
  • Maternal aunt with stroke at early age and seizures
Current Admission

Physical Exam
- Vitals normal. Height 5’2’’
- Mild dysarthria
- Slow response to questions
- Difficulty recalling details of past several days
- Strength and sensation intact

Pertinent Diagnostic Studies
- Serum Lactic acid level of 7.4
- Echocardiogram revealed mildly reduced EF
- MRI negative for acute findings
Age 31 - First admission

Symptoms:
- Headache
- Memory loss
- Difficulty with word finding

Exam
- Stable vitals without any neurologic deficits

Work ups
- CBC, CMP, lipid profile, A1C, echocardiogram all unremarkable
- MRI showed increased FLAIR at left posterior parietal, occipital, temporal lobes and right cerebellum
- **Multi-lobar involvement NOT following vascular pattern**
MRI FLAIR
MRI FLAIR
Our Thoughts

Further Diagnostic Studies

- **Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS) suspected**
- CSF Lactic acid to pyruvic acid ratio of 29.2, (>20 suggests mitochondrial dysfunction)
- Muscle biopsy and genetic testing ordered
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)

- Maternally inherited mitochondrial disease with multi-system involvement

- Diagnosis criteria
  - Stroke-like episode before age 40
  - Encephalopathy secondary to seizure or dementia
  - Mitochondrial myopathy evident by lactic acidosis or ragged-red fibers

- Additional confirmatory criteria (2 out of 3)
  - Normal early development
  - Recurrent headaches
  - Recurrent vomiting
## Prevalence/ Onset

Northern Finland: 16.3: 100,000  
Australian 236: 100,000

<table>
<thead>
<tr>
<th>Age of Onset (87 individuals)</th>
<th>Number of Individuals</th>
<th>Percent (%)</th>
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<tbody>
<tr>
<td>&lt;2 years</td>
<td>7</td>
<td>8</td>
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<tr>
<td>2-5 years</td>
<td>17</td>
<td>20</td>
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<tr>
<td>6-10 years</td>
<td>27</td>
<td>31</td>
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<td>11-20 years</td>
<td>15</td>
<td>17</td>
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<td>21-40 years</td>
<td>20</td>
<td>23</td>
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<tr>
<td>&gt;40 years</td>
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</tbody>
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Symptoms

• CNS
  • Stroke-like episodes (99%)
  • Seizures (96%)
  • Hemiparesis (83%)
  • Headache (77%)
  • Memory impairment (50-74%)

• Musculoskeletal
  • Exercise intolerance (100%)
  • Limb weakness (89%)
  • Short stature (82%)
  • Myoclonus (38%)

• Endocrine
  • Diabetes Mellitus (5%)

• GI
  • Nausea/vomiting (77%)

• Cardiac
  • Congestive heart failure (18%)
  • Wolf-Parkinson-White (14%)
Age 34- Third admission

Symptoms:
- Altered mental status, headache

Exam
- Alert, but oriented x0, complaining of hearing loss, photophobia, nausea

Work ups
- EEG showed non-convulsive status epilepticus
- Loaded with lacosamide and levetiracetam
- Received L- arginine infusion
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Genetics

• Most common defect - m3243A>G (80% of cases) in the MT-TL1 gene
  • Mitochondrially encoded tRNA Leucine 1
  • Possibly affecting complex I and IV, however, no clear mechanism identified so far
  • Organs with high energy demand
• Maternally inherited with heteroplasmy and variable symptoms
  • Study in Japan has shown some correlation between increased mutation load in muscle tissue to symptoms

• Our patient had 83% m3243A>G on muscle biopsy
Muscle Biopsy & Ragged Red Fibers

-Mitochondria proliferation that stains with modified Gomori trichome stain

-Biopsy did not show the characteristic RRF pattern on trichome

-Sent for electron microscopy and other mitochondrial stains
  - Enlarged mitochondria with concentric cristae
  - Pericrystalline inclusions within the mitochondria
  - Mitochondrial aggregates on NADH and SDH stain

-Supportive of mitochondrial dysfunction and diagnosis of MELAS
Treatment

There is no specific curative therapy for MELAS, treatment largely involves symptomatic management.

• Seizure control is treated with AEDS
• Migraine treated with standard analgesic therapy
• Physical therapy to decrease symptoms of exercise intolerance
• L-Arginine infusion therapy during acute phase has been shown to decrease symptoms
• Oral L-arginine also has been shown to decrease frequency and severity of stroke-like episodes
• Other supplements such as Co-enzyme Q10, creatine, L-carnitine have all been used to support the ETC, however evidence is limited
Prognosis

• Residual deficits from stroke like episodes eventually lead to impaired motor, vision and mentation.
• Symptomatic individuals have 17 fold mortality rate compared with asymptomatic carriers
• Average age of death in affected individuals 34.5±19 yrs
• Median survival time 16.9 years from age of symptom onset
Therapy under investigation

Because the defect is located on the mitochondrial DNA, transplant of fertilized zygote nucleus to a donor egg should bypass the inheritance.

- Proof of this concept has been shown in vitro.
Take Home point

- Keep metabolic syndromes in mind when a patient presents with early onset stroke without other risk factors.

- Lactic acidosis can also be from mitochondrial dysfunction.
Questions?