2015 AANP: Diagnostic Slide Session

Case 6

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No relevant financial relationships or conflicts of interest
Clinical History

- A 35-year-old African-American man
- 5 years of slowly progressive gait disturbance and dysarthria
- HIV, poor adherence to antiretroviral medications (CD4+ nadir of 16)
- In his 20s - a boxer, had sustained a total of 3 knockouts
- No family history of neurologic disease

Neurologic examination at presentation
- Normal mental status
- Gait - wide-based, unsteady
- Dysarthria, decreased facial expression, slow saccades, mild impairment of upward gaze
- Mild symmetric lower extremity weakness (distal and proximal), spasticity
- Mildly reduced vibratory sense in the toes

Progressive neurologic course: nystagmus, dysmetric saccades, ataxia, spasticity involving UE, worsening dysarthria and hypophonia, peripheral neuropathy
- MRI of the brain: a mild, diffuse cerebral and cerebellar atrophy, more marked brainstem atrophy.

A diagnostic molecular test was performed

At the time of death (50yo) - bed bound, tracheostomy, communicates via blinking his eyes.
Cerebellum and pons
Spinal cord
1. What was the diagnostic molecular test?

2. What is the diagnosis?

3. Is the neuropathology typical of this disorder?
Testing for the CAG repeat expansion (Ataxia profile) was performed at **Athena Diagnostics, Inc.**

- **SCA1 allele 1**: 30 CAG repeats (N: ≤34)
- **SCA1 allele 2**: 30 CAG repeats
- **SCA2 allele 1**: 23 CAG repeats (N: ≤31)
- **SCA2 allele 2**: 23 CAG repeats
- **MJD (SCA3) allele 1**: 72 CAG repeats (N: ≤40, B: 41-60)
- **MJD (SCA3) allele 2**: 38 CAG repeats
- **SCA6 allele 1**: 13 CAG repeats (N: ≤18)
- **SCA6 allele 2**: 11 CAG repeats
- **SCA7 allele 1**: 10 CAG repeats (N: ≤18)
- **SCA7 allele 2**: 10 CAG repeats
Neuropathology Findings
Midbrain with s. nigra
Corticospinal fibers preserved

Pontocerebellar fiber loss

Pontine nuclei degeneration

Middle CP

Corticospinal fibers preserved
Spinal cord, upper thoracic
Spinal cord, upper thoracic, Bielschowsky

Clarke’s column
Diagnosis

Spinocerebellar ataxia type 3 (SCA3)/Machado-Joseph disease (MJD) with numerous polyglucosan bodies in HIV+ African-American male with history of head trauma
# Hereditary ataxias

<table>
<thead>
<tr>
<th>Hereditary ataxias</th>
<th><a href="http://neuromuscular.wustl.edu/ataxia/recatax.html">updated list</a></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD</strong></td>
<td><strong>AR</strong></td>
</tr>
<tr>
<td>1. <strong>SCA 1-41</strong></td>
<td>1. <strong>Friedreich ataxia</strong></td>
</tr>
<tr>
<td>Repeat expansion, &gt; CAG, mutations</td>
<td>9q <em>FRDA</em> – frataxin:</td>
</tr>
<tr>
<td>• Cerebellar cortical atrophy,</td>
<td>95% - GAA 500-1000 (n- 6-34)</td>
</tr>
<tr>
<td>• OPCA</td>
<td>Degeneration:</td>
</tr>
<tr>
<td>• Spinocerebellar degeneration</td>
<td>• Spinal cord - post columns, distal spinocerebellar and pyramidal tracts, Clarke’s</td>
</tr>
<tr>
<td>2. <strong>DRPLA</strong></td>
<td>2. <strong>Ataxia w vit E def</strong></td>
</tr>
<tr>
<td>CAG expansion in atrophin-1 (12p) - 49-75 (n – 7-23)</td>
<td><em>α</em>-tocopherol transfer protein, similar to FA</td>
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<tr>
<td>• Chorea, myoclonic epi, dementia (simul of HD)</td>
<td></td>
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<tr>
<td>• Neuronal loss: DN, GP, subthalamic, caudate, putamen, SN, inf olives</td>
<td></td>
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<tr>
<td>• Atrophy of sup CP</td>
<td>a. SCAE – cerebellar and sensory</td>
</tr>
<tr>
<td>• Degeneration of post spinal columns and spinocerebellar tracts</td>
<td>b. SANDO – sensory ataxia w. periph neuropathy, dysarthria and ophthalmoplegia</td>
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<tr>
<td>3. <strong>Episodic ataxias EA1-8</strong></td>
<td>4. <strong>DNA repair s-mes (AT, XP, Cockayne ERCC, MRE11A)</strong></td>
</tr>
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<td>4. <strong>Dominant ataxia s-mes</strong></td>
<td>5. <strong>SCAR 1-20</strong></td>
</tr>
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</table>
Spinocerebellar ataxia type 3 (SCA3)/Machado-Joseph disease (MJD)

- The most frequent subtype of AD SCA. Originated from founders in the Iberia Peninsula, who migrated to the Azores
- CAG repeat expansion > 55 units in the ATXN3 gene, 14q32.1 region
- Intranuclear aggregates of ataxin-3, proteasome subunits and transcription factors (TBP and CBP)
- The clinical variability: length of repeats and the age at onset
- Anticipation of the phenotype: most frequently a/w paternal transmission
- Neuronal loss in midbrain, pons, medulla oblongata, cerebellum, Clarke’s columns, +/- BG, thalamus, cerebral cortex

Why are so many corpora amylacea? Has this been described before?

- Adult polyglucosan body disease: AR or sporadic a/w the diffuse accumulation of abnormally branched glycogen in polyglucosan bodies.
- 5th – 7th decades: neurogenic bladder and motor neuron dysfunction, +/- dementia, peripheral neuropathy and cerebellar dysfunction
- Familial APBD due to mutations in the Glycogen branching enzyme gene (GBE1, 3p12.2)
- Mutations in GBE1 are also causative of Glycogen Storage Disease type IV (GSDIV) - usually infantile liver disease or skeletal/cardiac myopathy

Nucleotide variations in case #6: T507A, Y114Y, two additional nucleotide variations in introns
Case reports:


Thank You!

Susan Morgello, MD
Mary Fowkes, MD, PhD
Nadia Tsankova, MD, PhD
John Crary MD, PhD
Dushyant Purohit, MD

Sergey Zhadanov, MD, PhD


Q1. Why does an African-American have a disease typically associated with the Portuguese ancestry?

Two main ancestral haplotypes in MJD:

1. The Machado lineage, predominant in families of Portuguese extraction
2. The Joseph lineage, which is much older and worldwide spread, postulated to have an Asian origin.

Patient’s (ID – 47) ancestry markers:
~76% African American,
~24% European American