15-year-old girl with new-onset refractory epilepsy, myoclonus, and progressive cognitive decline

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Resident Presenters: Areeba Basit, Jennifer Griffith, Bobby Rudock, Inder Singh
Disclosures

- Drs. Guerriero, Basit, Griffith, Rudock and Singh have no relevant financial interests to disclose
Dr. “Gary – Arrow”
Meet Dr. Guerriero

- Born in Morristown, New Jersey
- Grew up in Spofford, New Hampshire
- B.S. Neuroscience with Minor in Philosophy – Bates College, Lewiston, ME
- 4 years – Manager of Molecular and Developmental Neuroscience lab at MGH
On a personal note

Dr. Guerriero.. The Kicker!

- Football - tied Bates College career record for field goals
- "I have never been associated with a tougher competitor than Rej. He is one of the most dedicated players in the program, and it paid off on the field."
Professional Career

- D.O. – New England College of Osteopathic Medicine, Biddeford, ME
  - President/Treasurer of Neurology and Psychiatry club
  - Co-president of New England research club
- Pediatric residency – Tufts
- Pediatric Neurology residency – Mass General and Boston Children’s Hospital
  - Co-chief resident
- Fellowships in Brain Injury, Epilepsy and Neurophysiology – Boston Children’s Hospital
- Joined Washington University School of Medicine/St. Louis Children’s Hospital faculty 2016
  - Assistant Professor of Neurology
  - Director of Critical Care-EEG program
  - Associate Residency Program Director
History of Present Illness

9 - 10 months prior:
- Family vacation in Mexico, diarrheal illness
- First GTC seizure 1 day after returning home

7 months prior:
- Second GTC; started on levetiracetam

5 months prior:
- New headache
- Staring spells and myoclonic jerks

1 month prior:
- Third GTC; started on valproate

Referred to SLCH for second opinion
Differential diagnosis?
Differential diagnosis?

- Metabolic
- Autoimmune
- Degenerative
- Vascular
- Neoplastic
- Infectious
- Toxic
Past History

Past medical history
- Late preterm birth
- No major medical problems

Past surgical history
- None

Medications
- Levetiracetam
- Valproate
- Ethosuximide
- Citalopram

Allergies
- NKDA

Immunizations
- Up to date

Family History
- 17 y/o brother – epilepsy, on VPA
- Parents from same small village in Mexico

Social History
- Freshman, declining grades
- No longer plays piano or violin
- No EtOH, smoking or drug use
- Not sexually active

ROS
- Otherwise negative
General Exam

**Vital signs:**
- Weight 46.5 kg (23%ile)
- Height 147 cm (1%ile)
- OFC 54 cm (50%ile)
- BMI 21 (68%ile)
- Temp 36.7
- HR 83
- RR 16
- BP 125/74

**Respiratory:**
- Clear to auscultation bilaterally

**Cardiovascular:**
- Regular rate and rhythm, no murmur

**Abdomen/GU:**
- Soft, nontender, without organomegaly
- Tanner stage 5

**Musculoskeletal:**
- Extremities symmetric, normal joints
- Spine is straight

**Skin:**
- No neurocutaneous stigmata

**Constitutional:**
- Teenage girl, well-nourished

**HEENT:**
- Normocephalic
- No dysmorphic features
Neurologic Exam

**Mental status:**
- Intermittently somnolent, easily arousable to voice
- Follows simple commands with frequent repetition
- Spells WORLD forward only
- Disinhibited behavior
- Slow to respond to questions

**Cranial nerves:**
- No papilledema
- PERRL, EOMI
- Visual acuity 20/20 OD, “blurry” OS
- Visual fields appear grossly intact
- Face symmetric
- No dysarthria
- Rest of the cranial nerves intact

**Motor:**
- 5/5 strength throughout
- Normal tone

**Sensory:**
- Intact to light touch, temperature, joint position sense
- Negative Romberg

**Reflexes:**
- 2+ throughout
- Flexor plantar response

**Gait:**
- Narrow-based, hesitant gait
- Able to tandem walk

**Coordination:**
- Finger-nose-finger with mild dysmetria on L
Workup

Labs – serum & urine
Labs – CSF
Ophthalmology

EEG
MRI
Genetic tests
Cont’d course
Labs – serum & urine

- Ammonia <10
- VPA level 75
- Lipid panel normal
- Lactate 1.8 (0.5-1.5), pyruvate 0.16 (0.03-0.08), ratio 11 (normal)
- TSH 2.65, fT4 1.37
- Serum thyroid peroxidase Ab <60

- Serum Amino Acids:
  - Alanine 565 (150-500)
  - Glycine 441 (125-300)
  - Otherwise normal
- Carnitine 25 (35-80), free carnitine 20 (20-65)
- Acylcarnitine 5

- Serum autoimmune encephalitis panel negative
- Urine organic acids normal
- Urine drug screen normal
Laboratory Studies - CSF

- Total cells 0
- Nucleated cells 0
- Glucose 53 (serum 91)
- Protein 15.5
- CSF culture negative
- CSF lactate 1.6, pyruvate 0.12, ratio 13 (normal)

- CSF autoimmune encephalitis panel: negative
- CSF neurotransmitter profile
  - 5-HIAA 51 (67-140)
  - HVA, 3-O-MD, BH4 and neopterin normal
Ophthalmologic exam

- Eyelid myoclonus
- Visual acuity 20/20 OU
- No papilledema
- Small flat yellow lesion on R retina, incidental
- Otherwise normal
EEG - routine
MRI - brain
Genetic testing

- Tests pending…
Continued Course

Rapid med changes
- VPA decreased
- Ethosuximide continued
- LVT increased
- Onfi added

1 month from presentation
- More tonic seizures
- Tantrums, “more aggressive and agitated”
- Intermittent “blurry vision”

2 months from presentation
- More encephalopathic in clinic
- Readmitted
Continuous VEEG – 2 months
Continued course

Rapid med changes
- Onfi increased
- Other AEDs → zonisamide, methsuximide

3 months from presentation
- Cognitive regression, failing classes
- Urinary incontinence
- Gait difficulty
- Psychomotor slowing
- Readmitted
Continuous VEEG- 3 months
Comparison to initial EEG
Course Summary

- Previously healthy 15 year old girl
- Refractory epilepsy – GTC, myoclonic, tonic, absence
- Progressive cognitive decline
- Progressive gait difficulty
- Intermittent visual changes
- Progressive background slowing and epileptiform discharges on serial EEG
- Brother with epilepsy
- Possible parental consanguinity
Genetic testing returns

- PPT-1 and TPP-1 enzyme activity normal
- POLG testing negative
- Progressive myoclonic epilepsy panel:
  Homozygous pathogenic variant (R241X) in EPM2A
Lafora Disease

- Multiple Names
  - Progressive Myoclonic Epilepsy-Type 2
  - Lafora Disease
  - Lafora Body Disease
  - Lafora Progressive Myoclonic Epilepsy
  - Myoclonic Epilepsy of Lafora
History – Lafora Disease

- Dr. Gonzalo Rodriguez-Lafora (1886-1971)
  - born and died in Madrid, Spain
  - Ramón y Cajal
- 1911 – described inclusion bodies
History – Lafora Disease

• 1965 – Schwarz and Yanoff describe clinical presentation
  • Sibling pair with seizures in mid-teens → dementia, blindness
  → death by early-twenties
History – Lafora disease

- 1979 – Norio and Koskiniemi describe “Progressive Myoclonic Epilepsies”

  Heterogeneous group of neurodegenerative diseases characterized by:
  1. Seizures: predominantly GTC; can be focal, tonic, or absence
  2. Myoclonus: focal or segmental; arrhythmic, asynchronous, and asymmetric
  3. Neurologic decline: progressive cognitive decline, ataxia, neuropathy and/or myopathy
# Progressive Myoclonus Epilepsies (PME)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Diagnostic investigations in different progressive myoclonus epilepsies (PMEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unverricht-Lundborg disease (EPM1)</td>
<td>Gene test: EPM1 (CSTB) mutation analysis</td>
</tr>
<tr>
<td>2. Lafora body disease (EPM2)</td>
<td>Skin biopsy: Lafora bodies</td>
</tr>
<tr>
<td>3. Neuronal ceroid lipofuscinoses (NCL)</td>
<td>Gene tests: EPM2A or EPMP2B (NHLRC1) mutation analysis</td>
</tr>
<tr>
<td></td>
<td>Skin biopsy: Granular osmophilic deposit</td>
</tr>
<tr>
<td></td>
<td>Leukocyte enzyme analyses: PPT1, TPP1, CTSD</td>
</tr>
<tr>
<td>4. Sialidosis</td>
<td>Urine: Sialo-oligosaccharides</td>
</tr>
<tr>
<td></td>
<td>Leukocyte enzyme analysis: Neuraminidase</td>
</tr>
<tr>
<td>5. Myoclonus epilepsy and ragged-red fibers (MERFF)</td>
<td>Gene test: NEU1 mutation analysis</td>
</tr>
<tr>
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<td>Plasma lactate and pyruvate</td>
</tr>
<tr>
<td></td>
<td>Muscle biopsy: Ragged-red fibers</td>
</tr>
<tr>
<td>6. Type 3 neuronopathic Gaucher disease</td>
<td>Gene test: MT-TK mutation analysis</td>
</tr>
<tr>
<td></td>
<td>Leukocyte enzyme analysis (β-glucocerebrosidase)</td>
</tr>
<tr>
<td>7. Dentatorubral-pallidolysian atrophy</td>
<td>Gene test: DRPLA mutation analysis</td>
</tr>
<tr>
<td>8. Action myoclonus-renal failure syndrome (AMRF; EPM4)</td>
<td>Gene test: SCARB2/LIMP2 mutation analysis</td>
</tr>
<tr>
<td>9. PME-ataxia syndrome (EPM5)</td>
<td>Gene test: PRICKLE1 mutation analysis</td>
</tr>
<tr>
<td>10. North Sea PME (EPM6)</td>
<td>Gene test: GOSR2 mutation analysis</td>
</tr>
</tbody>
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Unverricht-Lundborg Disease (EPM1)

- a.k.a. Progressive myoclonus Epilepsy – Type 1
- most common PME (worldwide prevalence unknown, but in Finland ~4 in 100,000
- Presentation
  - onset: 6 to 16 years (10 on average)
  - Seizures
  - action activated and stimulus-sensitive myoclonus (light triggered, stress triggered, noise triggered), tends to be more proximal
  - cognitive decline < motor decline (1/3 become wheelchair bound)
- \textit{CSTB} gene: cysteine proteinase inhibitor; thought to be protective against intracellular proteinases that leak from lysosomes
- Prognosis: with improved supportive care (seizure control, rehab, social support), life expectancy into adulthood
Lafora disease

• Prevalence
  • largely unknown, ~1 in 1-9 per million

• Presentation
  • Presents in late childhood or adolescence
  • Most common initial symptom is a GTC with myoclonus
  • Neurologic decline beginning within months

• Course
  • Medically refractory seizures
  • Visual seizures → visual loss
  • Myoclonus: fragmentary, symmetric, or massive
  • Emotional disturbances, depression → dementia
  • Pyramidal and cerebellar signs → vegetative state

• Early death
  • status epilepticus and/or pneumonia
  • within 10 years of symptom onset
History – Lafora disease

- 1986 – Accurate diagnosis by axillary skin biopsy
  - Lafora bodies in CNS, retina, spinal nerves, heart, liver, muscle
  - Only cerebral accumulations are thought to be clinically relevant
Lafora bodies

Lafora Bodies

History – Lafora disease

- 1990s – Pathophysiology and genetics elucidated
  - Lafora bodies are comprised of abnormal glycogen accumulations (polyglucosan)
  - Autosomal recessive inheritance
  - Loss of function mutation
    - *EPM2A* – encodes laforin
    - *NHLRC1* – encodes malin
    - *EPM2A* and *NHLRC1* are phenotypically indistinguishable

A zebra among horses...

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<thead>
<tr>
<th></th>
<th>Lafora Disease</th>
<th>Juvenile Myoclonic Epilepsy</th>
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</thead>
<tbody>
<tr>
<td>Age of Onset</td>
<td>9 to 18 years</td>
<td>12 to 18 years</td>
</tr>
<tr>
<td>Initial Presentation</td>
<td>GTC, myoclonus</td>
<td>GTC, myoclonus, absence</td>
</tr>
<tr>
<td>Early EEG</td>
<td>Generalized and Multifocal</td>
<td>Polyspike and Slow-wave</td>
</tr>
<tr>
<td></td>
<td>Posterior Predominance</td>
<td>Frontal Predominance</td>
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<td>Normal to Slow Background</td>
<td>Normal Background</td>
</tr>
<tr>
<td>Clinical Course</td>
<td>Severe Motor &amp; Cognitive</td>
<td>Mild Learning Disabilities</td>
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<td>impairment, vision loss</td>
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<tr>
<td>Late EEG</td>
<td>Near continuous discharges</td>
<td>Continued or resolved discharges</td>
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<td></td>
<td>Significant Generalized Slowing</td>
<td>Normal Background</td>
</tr>
<tr>
<td>Genetics</td>
<td><em>EPM2A</em> and <em>NHLRC1</em></td>
<td>Polygenic and Multifocal</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Death within 10 years</td>
<td>Normal life expectancy</td>
</tr>
</tbody>
</table>
References


- http://www.orpha.net/consor4.01/www/cgi-bin/OC_Exp.php?lng=EN&Expert=501

- https://www.omim.org/entry/254780

Thank You

Dr. Réjean Guerriero

Dr. Mary Bertrand  Dr. Robert Bucelli  Dr. Beau Ances