Recent Advances in Neurology
Difficult Diagnosis

Liliana Ramirez Gomez M.D.
Assistant Clinical Professor of Neurology
February 10, 2017

CC: “Difficulties with gait and slurred speech”
59 y.o. RH Caucasian female

**August 2015**: Back pain and left leg pain
- Progressive loss of balance and frequent falls
- Changes in speech and handwriting

**October 2015**: She had a fall while carrying her (less than one year-old) grandson

**December 2015**: She started enacting her dreams at night
- Sleep study: demonstrated evidence of OSA and REM sleep behavior disorder.

**March 2016**: Started using a cane and reported changes in mood

Past Medical and Surgical History:
- Degenerative spine disease (lumbar), OA and depression
- Past surgical history significant for Gastric Bypass (2005)

Family History:
- Mother endometrial cancer, rheumatoid arthritis and late onset Alzheimer’s disease in her late 70s
- Father deceased at age 83 suffered from possible ALS and Myelodysplasia

**Neurological Exam**

- Mental status exam was normal. MoCA was 29/30
- CN: Saccadic intrusions to smooth pursuits
- Motor, sensory and DTR exam was normal
- Coordination: moderate dysmetria with FTN (L > R), ataxic finger taps, and mild-to-moderate dysdiadochokinesia (L > R).
- Gait: Wide-based, unsteady, and ataxic. She was unable to tandem walk.
Previous work up (outside studies)

**August 2015:** Normal CBC, CMP, TSH, B12 and vitamin D level

**October 2015:** EMG/NCS lower limbs were normal

**December 2015:** Sleep study
Moderate degree of sleep apnea and REM sleep behavior disorder

**January 2016:** EEG normal awake

---

**Brain MRI August 2015**

---

**C spine MRI August 2015**

---

**Differential diagnosis**

- Acquired causes
- Genetic causes
- Idiopathic causes

- Nutritional
- Endocrine
- Metabolic
- Infectious
- Inflammatory
- Neoplastic
- Paraneoplastic
- Autoimmune
- Toxic

- Dominant
- Recessive
- Mitochondrial
- Metabolic
- X linked
- Other

- Neurodegeneration

Modified from Fogel et al 2011.
Based on the history what do you think is the most likely etiology in this case?

A. Metabolic/nutritional/toxic
B. Neurodegenerative
C. Genetic
D. Immune mediated: autoimmune or paraneoplastic
E. Demyelinating disease

Tempo of Illness as a Clue to Diagnosis

Brain MRI March 2016
Cerebellar peduncles hyperintensities

- **Vascular:** vascular malformations or stroke
- **Infectious:** PML, Lyme disease, Listeria rhombencephalitis, Whipple
- **Toxic/Traumatic:** Heroin induced leukoencephalopathy
- **Autoimmune:** neurosarcoid, vasculitis (e.g., Bechet’s), CLIPPERS
- **Metabolic:** osmotic demyelination syndrome
- **Inherited/Genetic:** Fragile X associated tremor-ataxia syndrome
- **Neurodegenerative:** MSA-C
- **Neoplastic:** lymphoma or glioblastomas
- **Demyelinating:** MS or ADEM

---

**Multiple system atrophy of cerebellar type (MSA-C)**

---

**Fragile X-associated tremor/ataxia syndrome**
Based on the radiological findings what do you think is the most likely diagnosis in this case?

A. MSA C
B. Primary progressive MS
C. Fragile X-associated tremor/ataxia syndrome
D. An autoimmune or paraneoplastic disorder

33% 31% 27% 10%

REM Sleep Behavior Disorder and RBD associated disorders

- α-synucleinopathies
- Narcolepsy
- Secondary to medications (SSRIs, SNRIs)
- Others:
  - Wilson’s disease, PSP, FTD, ALS,
  - MS, brainstem infarction, subarachnoid hemorrhage
  - VGKC antibody-associated limbic encephalitis.

Laboratory work up

- Hematologic and metabolic work up was normal
  - Vitamin E, Thiamine, Serum copper
  - Heavy metals in urine (lead, mercury, arsenic): negative
  - VLCFA, plasma amino acids, urine organic acids were nl
  - Pyruvate: 0.98 nl  AFP: 3.9 nl

- Genetic Fragile X testing showed 30/22 CGG repeats

- Infectious: RPR, HIV, Lyme, Hep B and C negative

- Autoimmune: ESR, RF, ANA, SSA, SSB, cANCA, pANCA
  - TTG, anti gliadin Ab were all negative

Courtesy of Dr. Lisa Ashbrook
**CSF** 3/24/16 and 6/13/16

RBC 3 WBC 2 Glucose 52/63 Protein 38/37 IgG index: normal

2 unique oligoclonal bands in CSF were detected compared to serum

---Repeat LP in June showed no OGB

ACE level in CSF 0.9 nl (0-2.5) Lyme IgG, IgM: no bands detected

VDRL negative

Serum paraneoplastic panel: (Ataxia panel at Mayo x2)

Patient tested positive for P/Q-type calcium channel (VGCC) antibodies 0.15

---

**P/Q-type voltage-gated calcium channel (VGCC)**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Associated malignancy</th>
<th>Manifestations additional to cerebellar ataxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Hu</td>
<td>Small cell lung cancer</td>
<td>Encephalomyelitis</td>
</tr>
<tr>
<td>Anti-Yo (PCA1)</td>
<td>Breast and ovarian cancer</td>
<td>Brain stem encephalitis</td>
</tr>
<tr>
<td>Anti-Ri (ANNA-2)</td>
<td>Breast and ovarian cancer</td>
<td>Opocchias myelitis syndrome</td>
</tr>
<tr>
<td>Anti-Tr</td>
<td>Hodgkin's lymphoma</td>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>Anti-Ma2</td>
<td>Small cell lung cancer</td>
<td>Limbic and brain stem encephalitis</td>
</tr>
<tr>
<td>Anti-CV2 (CRMP5)</td>
<td>Small cell lung cancer</td>
<td>Nystagmus, parkinsonism</td>
</tr>
<tr>
<td>Anti-CV2 (CRMP5)</td>
<td>Non-Hodgkin's lymphoma</td>
<td>Chorea, dystonia</td>
</tr>
<tr>
<td>Anti-GABA1</td>
<td>Hodgkin's lymphoma</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Anti-VGCC</td>
<td>Small cell lung cancer</td>
<td>Lambert Eaton myelitis syndrome</td>
</tr>
<tr>
<td>Anti-GABA</td>
<td>Small cell lung cancer</td>
<td>Encephalomyelitis</td>
</tr>
<tr>
<td>Anti-GAD</td>
<td>Thymoma</td>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>Anti-GAD</td>
<td>Thymoma</td>
<td>Diabetes mellitus</td>
</tr>
</tbody>
</table>

Treatment

Outcome measure:
Scale for the assessment and rating of ataxia (SARA)

- Course of IV pulse steroids x 5 days
- High dose prednisone for 2 months with a slow taper
- Course of IVIG

What would you do next?

A. Try a different immunosuppressive treatment
B. Genetic testing
C. Advise a “watch and wait” approach
D. Counsel that nothing else can be done

Responses to and Outcomes of Treatment of Autoimmune Cerebellar Ataxia in Adults

- 118 patients from the Mayo clinic with autoimmune ataxia
- Median age at onset was 58 years, 73.7% were women
- 63 patients had paraneoplastic and 55 patients had nonparaneoplastic ataxic disorders.
- Improvements were significantly more common among patients with nonparaneoplastic disorders and those with exclusively PMP antibodies

Jones AL, McKeon et al. JAMA Neurol. 2015;72(11):1304-1312

Additional immunosuppressive treatment

- IV pulse cyclophosphamide
- 15 mg/kg per CYCLOPS protocol (used in vasculitis)

Genetic testing

- Complete evaluation for autosomal dominant and recessive panel associated with ataxia
  - **Dominant:** none
  - **Recessive:**
    - A pathogenic heterozygous frameshift mutation for SYNE1
    - A heterozygous missense mutation as a variant of unknown significance on SYNE1 (unclear if on same allele)

SYNE1 mutations in autosomal recessive cerebellar ataxia

- Mutations in the synaptic nuclear envelope protein 1 (SYNE1) gene, located on chromosome 6p25, were first reported in patients from a province of Quebec, Canada.
- Autosomal recessive cerebellar ataxia type I, is a slowly progressive ataxia that leads to moderate disability and diffuse cerebellar atrophy on brain imaging.
- With a relative frequency of ~5%, SYNE1 is one of the more common recessive ataxias worldwide

Refined differential diagnosis and treatment

- **Differential:**
  - Autoimmune cerebellar Ataxia: positive VGCC +P/Q
  - Neurodegenerative MSA C
  - SYNE1 mutation may play a role

- **Treatment:**
  - Immunosuppressive therapy
  - Periodic surveillance for malignancy
  - Supportive care

Acknowledgments

- Thank you to Dr. Jeff Gelfand at UCSF
- We welcome your referrals at the:

  **General Neurology Clinic**
  **400 Parnassus Ave., Eighth Floor**
  **San Francisco, CA 94143**
  **Phone: (415) 353-2273 Fax: (415) 353-2898**