Case 1

RAIN 2011 Difficult Diagnosis
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Case 1 Summary:

58 year-old previously healthy woman with:
- Subacute onset of fluctuating confusion and psychiatric symptoms.
- Seizures occurring 3/hr despite divalproex and levetiracetam.

Outside Labs:
- Hyponatremia
- NI CSF; neg HSV PCR; neg anti- yo, ri, hu, Gad-65

Outside Studies:
- MRI s/f right mesial temporal swelling and FLAIR abnormality.
- EEG confirmed bilateral temporal lobe seizures.

Case 1 MRI

Case 1 Summary:

PE:
- Normal except disorientation to year, decreased digit span (4 forward, 3 reverse), 0/4 recall, flat affect and “slow response time”

CSF:
- WBC 13 (89%L), RBC 1, P 25, G 65
- IgG 0.9, no OCB

VPA 61

Normal TFTs, Thyroglobulin Ab negative
Which clinical syndrome best fits this presentation:
A. Morvan’s Syndrome
B. Limbic Encephalitis
C. TLE with Hippocampal Sclerosis
D. Hashimoto’s Encephalopathy

Limbic Encephalitis
- Inflammatory CNS disorder with subacute onset (days or weeks)
- Fluctuating confusional state with memory impairment, personality changes, hallucinations
- Limbic involvement often manifest as temporal lobe seizures (bilateral) and mesial temporal imaging abnormalities (hippocampal)
- Paraneoplastic or idiopathic

The work-up for limbic encephalitis should include:
A. Exclusion of other, particularly treatable, causes of cognitive decline
B. Evaluation for cancer
C. Autoantibody testing (paraneoplastic and idiopathic)
D. All of the above
Treatable Causes of Cognitive Impairment

- **Autoimmune encephalopathies** (paraneoplastic, idiopathic)
- **Other inflammatory CNS disorders** (MS, neurosarcoïdosis, ADEM)
- **Vasculopathies** (Vasculitis, posterior reversible leukoencephalopathy)
- **Neoplasm** (Primary CNS lymphoma)
- **Seizure disorders** (NCSE)
- **Toxic, Nutritional, or Iatrogenic** (Alcohol, B12, Thiamine, Folate, Neuropsych meds)
- **Infectious** (HIV, HSV, Whipples, neurosyphilis, HHV6, cryptococcus, mycobacterial)
- **Metabolic** (Organ dysfunction, OSA, mitochondrial diseases)
- **Endocrine** (Pituitary, thyroid, or adrenal dysfunction)

Neural-Specific Autoantibodies

- **VGKC**
- **NMDA receptor**
- **GAD65**
- **AMPA receptor**
- **GABA-B receptor**
- **ANNA-1 (Anti-Hu)**
- **ANNA-2 (Anti-Ri)**
- **LGI 1**
- **CASPR2**
- **ANNA-3**
- **AGNA (SOX-1)**
- **PCA-2**
- **CRMP-5 (Anti-CV2)**
- **Amphiphysin**
- **Ma/Ta Proteins**
- **NMO-IgG**
- **nNSA’s**

Syndromes associated with VGKC antibodies

- **Neuromyotonia or Isaac’s Syndrome:**
  - Muscle cramps and stiffness associated with nerve hyperexcitability
- **Morvan’s Syndrome:**
  - Neuromyotonia with autonomic and CNS dysfunction with insomnia
- **Limbic Encephalitis:**
  - Amnesia, confusion, seizures, personality changes or psychosis, and hippocampal abnormalities on MRI

Which antibody target is MOST likely associated with this patient’s LE:

- **A.** LGI 1
- **B.** VGKC
- **C.** ADAM22
- **D.** CASPR2
Clinical Spectrum of “VGKC” LE

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<tbody>
<tr>
<td>Seizures</td>
<td>86%</td>
<td>90%</td>
<td>75%</td>
<td>58%</td>
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<tr>
<td>Mesial temporal MRI abnormality</td>
<td>100%</td>
<td>80%</td>
<td>100% (92% bilateral)</td>
<td>42% (25% bilateral)</td>
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<tr>
<td>Hyponatremia</td>
<td>100%</td>
<td>57%</td>
<td>80%</td>
<td>83%</td>
<td>36%</td>
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<tr>
<td>Hypersalivation</td>
<td>0%</td>
<td>14%</td>
<td>0%</td>
<td>10%</td>
<td>33%</td>
<td>17%</td>
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<tr>
<td>Malignancy</td>
<td>50%</td>
<td>14%</td>
<td>Thymoma</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>Associated</td>
<td>15% SCLC, BrCA (SOX1 or amphyphysin)</td>
<td>47% SCLC, thymic carcinoma, PCA, hematologic, BrCA, colon, squamous ca (25% had Hu, PCA-2, amphyphysin, CMIP-5...)</td>
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<tr>
<td>Spontaneous</td>
<td>50%</td>
<td>14%</td>
<td>0%</td>
<td>0%</td>
<td>50%</td>
<td>39%</td>
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<td>Recovery:</td>
<td>Full or marked</td>
<td>78%</td>
<td>16%</td>
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<tr>
<td>Disables:</td>
<td>30%</td>
<td>30%</td>
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LGI 1 is the auto-antigen in previously named “VGKC-mediated LE”

LGI 1:
- **1998**: Isolated from glioblastoma cell line
- **2002**: Linked to ADLTE
- **2009**: Regulates excitatory transmission, dendritic spine density and seizure threshold

| Seizures | Lai N=57 (2010) | 82% |
| Mesial temporal MRI abnormality | 75% | 56% |
| Associated: | Hyponatremia | 60% | 62% |
| Associated: | ANS dysfunction | - | 15% |
| Associated: | Neuromyotonia | - | 4% |
| Malignancy | 11% | 0% |
| Recovery: | Full or marked | 78% | 16% |
| Disables: | 30% | 30% |

Which factor predicts a favorable treatment response for this patient:

1. Seizures
2. Elevated IgG index
3. “VGKC” Antibody
4. Psychiatric symptoms

LGI1 Function: WT and ADLTE

Predictors of Response to Therapy in Suspected Autoimmune Dementia

**PREDICTIVE**
- Subacute onset (1-6w)
- Fluctuating course
- Tremor
- CSF protein >100
- CSF WBC >5
- Cation channel complex autoantibody (VGKC)
- Shorter delay to treatment (~1y v 2y)

**NOT PREDICTIVE**
- Headache (p=0.06)
- ↑IgG index and OCB
- Co-existent or FH of autoimmune disease
- TPO antibodies
- Seizures
- Anxiety, depression, or psychosis
- FH of dementia

Hospital Course

- **January Hospitalization:**
  - Solumedrol 1g IV x 5d
  - Malignancy work-up negative

- **February Hospitalization:**
  - VGKC Abs 906 pMol
  - IVIG x 4d, Solumedrol repeated, PLEX x 5cycles
  - NCSE

- **Long-term cognitive outcome:**
  - MMSE 18/30 in June on oral steroids
  - MMSE 24/30 by November on weaning steroids
  - Independent on IADLs except driving

Epilepsy Directions...

- Features of LE overlap with features of mesial temporal lobe epilepsy
- 24% of adult onset TLE with HS could be classified retrospectively as having LE
- 11% of a select cohort of patients with epilepsy, many with autoimmune disease, were positive for VGKC antibodies

CASE 2
Case 2 Summary:

- 63 year-old otherwise healthy woman presents for characterization of spells:
  - Onset age 32; currently 2x/month
  - 30 seconds of staring, fumbling
  - Sudden fall with injuries

- Medications:
  - LTG 150mg BID
  - Carbamazepine 400mg/200mg/400mg

- PE and MRI were normal.
The clinical correlate to this seizure would be most likely to include:

1. Left sided clonic activity
2. Sudden fall
3. Pseudosecondary generalization
4. B and D

Ictal Asystole

**Frequency:**
- 0.27% - 0.4% of patients at recorded epilepsy centers
- No known risk factors

**Semiology:**
- 20 sec after clinical onset
- Duration 4-60 sec (mean=13 sec)
- Sudden atonia if > 8 sec
- Myoclonic jerks or other movements
- "Pseudo-secondary generalization"

**Delayed loss of tone during a focal dyscognitive seizure is a red flag for IA:**
- Half of TLE pts with IA had a history of unexplained "drop attacks"

Patients with Ictal Asystole are MOST likely to have:

1. Benefit from pacemaker placement
2. Seizures with ictal tachycardia
3. Seizures lateralized to the left
4. Increased risk of SUDEP

Cardiac Rhythm Changes in Epilepsy

- Ambulatory EEG-EKG recordings have demonstrated ictal tachycardia:
  - >100 in 92%
  - >120 in 67%
  - >140 in 30%
  - >160 in 12%

- Original work characterized IA from left insular stimulation, but lateralization has not held up.

Preventing SUDEP?

- Prospective data from patients with IA receiving DDD pacemakers:
  - No event triggers in 5 years after DDD placement
  - Other case reports of reduced falls
  - RCT of DDD for neurocardiogenic syncope reveals no benefit
  - Probably reasonable to consider, but not proven

- Retrospective data from patients with SUDEP:
  - More extreme ictal tachycardia (149bpm v 126bpm)
  - Lengthening of QTc with epileptiform discharges
  - Post-mortem data show cardiac injury

What is the risk of SUDEP?

- Incidence:
  - 0.7 - 1.3/1000 patient-years for those with epilepsy
  - 3.5 – 4.1/1000 patient-years at surgical centers
  - Risk SUDEP 24x baseline risk sudden death
  - Pediatric cohort had 3x mortality rate overall with a 7% cumulative risk of SUDEP over 40 years

- Risk factors:
  - Tonic-Clonic Seizures
  - Treatment with >2 AEDs
  - Full-scale IQ <70

References:

Hospital Course

- Transferred to cardiology for DDD pacemaker placement.
- Subsequently lost to follow-up...

Thank you!