AANP DSS 2014
Case 8

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No conflicts of interest to disclose
• previously well 18 yo male, 2 month h/a, clumsiness, difficulty walking
• neurological exam: nystagmus, dysarthria, ataxia
• CSF:
  – 69 WBC/hpf, ↑pro (0.468 g/L)
  – negative micro, cytology, flow cytometry
• DDx:
  – viral cerebellitis
  – lymphoproliferative disorder
  – (when worsened with cog dysfunction, visual hallucinations)
    added paraneoplastic, autoimmune
    • CT chest abdo pelvis, testicular U/S, PET scan were normal
    • serum samples were sent for measurement of autoantibodies*
      – NMDA (NR1), VGKC (LGI1, CASPR2), Amphiphysin, GAD-65, CV2/CRMP5, Recoverin, SOX1, Titin, Hu, Yo, Ri and PNMA2 (Ma2, Ta)

*Mitogen Diagnostics, Calgary, Alberta, Canada
Audience comments?
Additional path findings and DDx

• No evidence of malignancy
• Infectious
  – no microglial nodules, viral inclusions, organisms
  – JCV? No PML, SV40 negative
• Neurodegenerative
  – clinical (young, acute), inflammation, no spongiosis, p62 negative
• Autoimmune encephalitis
• Paraneoplastic cerebellar degeneration
  – usually selective Purkinje cell loss
Clinical course

• During the days following bx the patient declined
  – ↓ LOC
  – generalized myoclonus
  – prominent involuntary movements of orofacial musculature
Diagnosis

• 4 weeks following presentation (5 days post biopsy) results from the serum autoantibodies:
  – LGI1 autoantibodies present in serum

LGI1 Ab associated encephalitis with presenting symptoms and signs localized to the cerebellum
Clinical course

• Treated with IVIg
• 24 hours after IVIG completed LOC improved and myoclonus resolved
• Repeat MRI brain showed improvement in cerebellar lesions
• Discharged home 3 weeks later (cognitively intact with mild ataxia)
• Normal 9 months later
Antibody associated CNS disorders

**Paraneoplastic disorders**
- Ab target intra-cellular neuronal Ag, T cell mediated, poor Rx response

**Autoimmune encephalitis**
- +/- tumour, Ab target neuronal cell surface or synaptic receptors, Ab cause primary pathogenic effect, good Rx response
# Autoimmune encephalitis update

**Josep Dalmau and Myrna R. Rosenfeld**

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**Table 2.** Autoimmune encephalitis associated with antibodies against neuronal cell-surface or synaptic proteins

<table>
<thead>
<tr>
<th>Antigen Target</th>
<th>Syndrome</th>
<th>Cancer Association if Present</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDA receptor</td>
<td>Characteristic neuropsychiatric syndrome with movement disorders, seizures, autonomic dysfunction</td>
<td>Age-related association with ovarian teratoma</td>
<td>Predominantly affects young adults, adolescents, and children</td>
</tr>
<tr>
<td>AMPA receptor</td>
<td>Limbic encephalitis, psychosis</td>
<td>Lung, breast, thymus in ~70% of cases</td>
<td>Frequent coexisting autoimmunities</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;b&lt;/sub&gt; receptor</td>
<td>Limbic encephalitis with early, prominent, and severe seizures</td>
<td>SCLC or other neuroendocrine tumor of lung in ~50% of cases</td>
<td>Frequent coexisting autoimmunities</td>
</tr>
<tr>
<td>LG11</td>
<td>Limbic encephalitis, seizures, hyponatremia, myoclonus</td>
<td>Thymoma in &lt;10% of cases</td>
<td>Frequent tonic seizures that may be misdiagnosed as myoclonus or startle</td>
</tr>
<tr>
<td>Caspr2</td>
<td>Encephalitis and/or peripheral nerve hyperexcitability</td>
<td>Rarely thymoma</td>
<td>Symptoms of overlapping immune disorders such as myasthenia have led to misdiagnosis of motor neuron disease</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;a&lt;/sub&gt; receptor</td>
<td>Status epilepticus or refractory seizures and encephalitis</td>
<td>None</td>
<td>Frequent coexisting autoimmunities; extensive and often multifocal MRI abnormalities</td>
</tr>
<tr>
<td>DPPX</td>
<td>Encephalopathy, agitation, tremor, startle with muscle rigidity, seizures, and gastrointestinal dysfunction</td>
<td>None</td>
<td>Severe gastrointestinal symptoms can mislead diagnoses</td>
</tr>
<tr>
<td>Glycine receptor</td>
<td>Stiff-person, hyperekplexia, PERM, and encephalitis</td>
<td>Rare associations with cancer but usually not paraneoplastic</td>
<td></td>
</tr>
<tr>
<td>mGluR1</td>
<td>Cerebellar ataxia</td>
<td>Hodgkin lymphoma</td>
<td></td>
</tr>
<tr>
<td>mGluR5</td>
<td>Limbic encephalitis</td>
<td>Hodgkin lymphoma</td>
<td></td>
</tr>
<tr>
<td>Dopamine-2 receptor</td>
<td>Basal ganglia encephalitis, Sydenham chorea</td>
<td>None</td>
<td>Known as Opheila syndrome</td>
</tr>
<tr>
<td>Amphiphysin</td>
<td>Stiff-man syndrome</td>
<td>Breast, SCLC</td>
<td></td>
</tr>
<tr>
<td>GAD</td>
<td>Stiff-man syndrome at times with cerebellar ataxia, refractory seizures</td>
<td>Rarely thymoma or other tumors</td>
<td></td>
</tr>
</tbody>
</table>

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*Note: NMDA, AMPA, and GABA receptors are ionotropic glutamate receptors that play a crucial role in neuronal signaling. LG11 and Caspr2 are calcium-dependent protease-activated receptors (Ca<sub>2+</sub>-P Arlington kinase receptors) that are involved in the regulation of neuronal excitability. DPPX, a member of the DPP family, is a cytosolic protein that has been implicated in various neurological disorders. Glycine receptors are ion channels that are activated by glycine, a fast-acting inhibitory neurotransmitter. mGluR1 and mGluR5 are metabotropic glutamate receptors that mediate various physiological functions. Dopamine-2 receptors are metabotropic dopamine receptors that are involved in the regulation of motor functions. Amphiphysin is a synaptic vesicle-related protein that is implicated in synaptic plasticity. GAD (Glutamic Acid Decarboxylase) is an enzyme involved in the synthesis of GABA, the primary inhibitory neurotransmitter in the central nervous system.*
Leucine-rich Glioma Inactivating Protein 1

LGI proteins in the nervous system

Linde Kegel*, Eerik Aunin*, Dies Meijer*¹ and John R. Bermingham, Jr†¹,²

Autoantibodies to Epilepsy-Related LGI1 in Limbic Encephalitis Neutralize LGI1-ADAM22 Interaction and Reduce Synaptic AMPA Receptors

Toshika Ohkawa,¹,² Yuko Fukata,¹,² Miwako Yamasaki,³ Taisuke Miyazaki,³ Norihiko Yokoi,¹,² Hiroshi Takashima,⁴ Masahiko Watanabe,³,⁵ Osamu Watanabe,⁴* and Masaki Fukata¹,²*
Typical LGI1 encephalitis presentation:

- Faciobrachial dystonic seizures, then insidious cognitive impairment
- 10% associated teratoma
Criteria for ‘possible neuronal surface antibody syndrome’ warranting Ab testing:

1. Acute or subacute onset of sx
2. Exclusion of other causes (infectious, toxic, metabolic, tumour, trauma, demyelinating)
3. Evidence of CNS inflammation:
   - either on CSF, imaging or inflammatory neuropathology
Compared pathology of 17 Ab mediated encephalitis cases
pts w Ab to cell surface R had:
  – variable T lymph inflammation (LGI1 had more than NMDA)
  – LGI1 had cortical neuronal loss
2 autopsy case reports describing
  – mild limbic encephalitis, T lymphocytic
  – one emphasizes extensive neuronal loss in mesial temporal structures – *can look degenerative*
Dx: LGI1 Ab associated encephalitis
with presenting symptoms and signs localized to the cerebellum

• Take-home points:
  – Remarkable response to immunotherapy
  – What is the neuropathologist’s role in the identification of biopsied atypical cases?


Kegel L et al. LGI proteins in the nervous system. *ASN Neuro* 5(3).


References
Compared neuronal loss and immunopathology of 17 Ab mediated encephalitis cases

- patients with LGI1 encephalitis had variable T lymphocytic inflammation, cortical neuronal loss, plus IgG and complement deposition
Figure 1: Immunocytochemistry and immunoprecipitation of LGI1 with sera from patients with limbic encephalitis previously attributed to voltage-gated potassium channels.

(A) Immunostaining of a rat hippocampal neuron with serum of a patient (patient 1) with antibodies previously attributed to voltage-gated potassium channels. The nucleus of the neuron is visualised with DAPI.

(B) Immunoprecipitates obtained using serum from a patient and a control individual were separated by gel electrophoresis and the gel stained with coomassie blue. A band of about 60 kDa was detected in the sample from the patient and, by mass spectrometry, was identified as LGI1. This band was not present in the sample from the control individual. The protein bands at 55 kDa and 52 kDa correspond to fragments of human LGI1. (C) Immunoblot of the precipitates obtained with the sera from patient 1, another patient (patient 2), and a control individual (control). LGI1 was present in the neuronal immunoprecipitates obtained using sera from both patients but not the control individual. The antibody used in this analysis was a polyclonal LGI1 antibody that is commercially available.