CNS Syndromes Associated with Antineuronal Antibodies

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- Incoming Editor of the Neurology Podcast
Objectives

• Define Autoimmune Neurology

• Approach to recognition and diagnosis of neurologic autoimmunity

• Discuss typical and atypical cases to highlight approaches in the management of complex patients
What is Autoimmune Neurology?

Immune-mediated disease affecting the nervous system
- Often with systemic manifestations, and associated neural antibodies.

Two main categories:
Paraneoplastic
Autoimmune

Intersection of Neurology Subspecialties
Autoimmune Neurologic Disorders

Paraneoplastic:
Expression of neuronal proteins by a cancer breaks immune tolerance to proteins normally expressed in the nervous system

Paraneoplastic Disorders develop before diagnosis of cancer in $\frac{2}{3}$ cases

Parainflammatory/Autoimmune:
Infectious or other trigger
Autoimmune Neurological Disorders

Antibodies: **Markers** of paraneoplastic or autoimmune origin of neurologic symptoms

- Rarely does clinical presentation predict specific antibody, with few exceptions

- Pathogenic role proven for few thus far
Autoantibodies in Paraneoplastic Neurological Syndromes

- Are present in many but not all patients
  - Unclassified antibodies

- Often present in both serum and CSF

- CSF antibody derived from two sources
  - Diffusion across blood-brain barrier (*early in disease*)
  - Local synthesis within brain
    - May result in oligoclonal bands
Identified Neural Autoantibodies

ANNA-1/Hu
ANNA-2/Ri
ANNA-3
TRIM46
Aquaporin-4
mGluR5
PCA-2
PCA-1/Yo
Ma1/Ma2
MOG
GlyR
Striational neurexin-3α
CRMP-5
GAD65
VGCC (N-type and P/Q-type)
DPPX
IgLON5
AGNA
AMPAR
GFAP astrocytopathy
Zic4
mGluR1
NMDAR
GABA-A
Amphiphysin
GABA-B
GABA-A
PCA-Tr
GANGLON5
LGI1
CASPR2
neuropilin-1
MOG
GlyR
GABA receptor
neurexin
GFAP astrocytopathy
Zic4
Antineuronal Antibody-Associated Neurological Syndromes

**Antibodies to cell surface antigens**
- Examples: Anti-VGKC (LGI1, Caspr2), NMDAR, AMPA receptors
- Syndromes may occur with *or without* cancer

*Bataller et al. Neurology 2010;74:265*

**Antibodies to intracellular antigens**
- Examples: Anti-Yo, anti-Hu, Anti-Ri
- Syndromes almost always associated with cancer
<table>
<thead>
<tr>
<th>Antigen</th>
<th>Neurologic phenotype</th>
<th>Common cancer associations</th>
<th>Cancer frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>AChR (muscle)</td>
<td>Myasthenia gravis</td>
<td>Thymoma</td>
<td>Up to 25%</td>
</tr>
<tr>
<td>AChR (ganglionic)</td>
<td>Autonomic dysfunction</td>
<td>Breast, Prostate, Lung, Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>AQP4</td>
<td>Optic neuritis, transverse myelitis*, intractable hiccups, emesis, encephalopathy</td>
<td>Breast, Lung, Thymic, Carcinoid, B-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>CASPR2</td>
<td>Neuromyotonia, LE</td>
<td>Up to 25%</td>
<td></td>
</tr>
<tr>
<td>DPPX</td>
<td>LE, tremor, myoclonus, nystagmus, ataxia, diarrhea and profound weight loss</td>
<td>prostate, Lung, Neuroendocrine</td>
<td></td>
</tr>
<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;R</td>
<td>Refractory seizures, SE or EPC, stiff person syndrome, opsoconlus</td>
<td>Lung, Neuroendocrine</td>
<td>25 – 50%</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;B&lt;/sub&gt;R</td>
<td>LE, prominent seizures including SE</td>
<td></td>
<td>25 – 50%</td>
</tr>
<tr>
<td>Glycine R</td>
<td>SPS, PERM, LE, cerebellar degeneration, optic neuritis</td>
<td>Ovarian, Hodgkin’s lymphoma, Non-Hodgkin’s lymphoma, Thymoma</td>
<td>Up to 25%</td>
</tr>
<tr>
<td>IgLON5</td>
<td>Bizarre sleep movements, OSA, stridor, bulbar symptoms, chorea; poor response to immunotherapy</td>
<td>Non-Hodgkin’s lymphoma, prostate, Breast</td>
<td>Rare</td>
</tr>
<tr>
<td>LG1-1</td>
<td>LE, dystonic faciobrachial seizures, hyponatremia, REM sleep disorders, myoclonus</td>
<td>SCLC, Thymoma</td>
<td>Rare</td>
</tr>
<tr>
<td>mGluR1</td>
<td>Cerebellar degeneration</td>
<td>Hodgkin’s lymphoma</td>
<td>Few cases to date</td>
</tr>
<tr>
<td>mGluR5</td>
<td>LE, myoclonus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOG</td>
<td>Optic neuritis (can be bilateral, recurrent) transverse myelitis*, ADEM</td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td>NMDAR</td>
<td>Dense psychiatric manifestation, catatonia, insomnia, seizures, reduced verbal output, autonomic instability</td>
<td>Ovarian teratoma, Carcinoma, Medulloblastoma in children</td>
<td>Near 50%, less in children</td>
</tr>
<tr>
<td>PCA-Tr /DNER</td>
<td>Cerebellar degeneration</td>
<td></td>
<td>Over 75%</td>
</tr>
<tr>
<td>Neurexin 3a</td>
<td>Seizures, LE, orofacial dyskinesia</td>
<td></td>
<td>None reported</td>
</tr>
<tr>
<td>VGCC (P/Q,N type)</td>
<td>LEMS, cerebellar degeneration, seizures, encephalopathy</td>
<td></td>
<td>SCLC</td>
</tr>
</tbody>
</table>
Clues to Autoimmune Neurologic Disease

- Often multifocal, bizarre presentation
- Subacute onset and/or Stuttering course
- CSF abnormalities
  - Mild elevation of WBCs or protein, + Oligoclonal bands (unique or matched)
- Tobacco use or other cancer risk factors
- Personal/Family history of autoimmunity
  (Thyroid, DM-1, Lupus, Vitiligo, etc.)
- Personal/Family History of malignancy
- Suggestive MRI abnormalities (mesial temporal T2 hyperintensity)
- Hypermetabolism or -- more often -- hypometabolism on functional imaging (e.g., positron emission tomography)
- Recent onset cryptogenic epilepsy with frequent events or new onset refractory status epilepticus, with antiepileptic drug resistance
The Differential

- Infectious
- Inflammatory
- Toxic/Metabolic
- (Psychiatric)
<table>
<thead>
<tr>
<th>Pachymeningeal Disease</th>
<th>Leptomeningeal Disease</th>
<th>Cranial Neuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG4-related disease</td>
<td>Behçet disease</td>
<td>Sjögren syndrome</td>
</tr>
<tr>
<td>ANCA-associated vasculitis</td>
<td>Vogt-Koyanagi-Harada syndrome</td>
<td>SLE</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Sarcoidosis</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>IgG4-related disease</td>
<td>IgG-4 related disease (usually in the setting of associated pachymeningeal or leptomeningeal disease)</td>
</tr>
<tr>
<td></td>
<td>(rarely causes isolated leptomeningeal disease)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphoma/malignancy</td>
<td>Lymphoma/malignancy</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Parenchymal Brain Disease</th>
<th>Myelopathy</th>
<th>Peripheral Neuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>NMO</td>
<td>Sjögren syndrome</td>
</tr>
<tr>
<td>Behçet disease</td>
<td>Sarcoidosis</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>ADEM</td>
<td>ADEM</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>APLS</td>
<td>Multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Sjögren syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vasculitis (rarely)</td>
<td></td>
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</tbody>
</table>

Table adapted from Piquet and Clardy, “Infection, Immunodeficiency, and Inflammatory Diseases in Autoimmune Neurology” in Seminars in Neurology
A Few Typical Presentations
Case 1

68 yo male with presented with involuntary movements, increasing over several weeks.

- History of cardiac arrest secondary to ventricular fibrillation
Case 2
Case 2

- Initial MRI (4 weeks prior) was normal
- Repeat MRI: increased right hippocampal and amygdala hyperintensity
Case 2

- CSF cell count, protein, glucose: normal
Diagnosis:

Lessons Learned:
- Antibody testing is in its infancy – treat the patient, not the test.
- EEG can be helpful but unreliable in limbic encephalitis.
- SIADH
- Everyone still deserves a trial of steroids
Case 2

21 year old black male with 3 spells

1st episode:
Not feeling well, generalized body aches, mouth ulcers, sore throat. Found outside, walking around without a shirt or shoes, had broken into someone’s car.
- WBCs 15K and Transaminases into hundreds

Discharge Dx: Acute delirium or encephalopathy
Viral syndrome vs. Atypical seizure
2nd episode, 9 months later: ED for achiness, sore throat, again “bumps” on top of mouth causing difficulty swallowing. Seizure in ED requiring intubation. Discharged within 24 hours.

3rd episode, 2 months later: 2 day admission for seizure. EEG normal.

Thoughtful workup (CSF, Chest X-ray and CT Head) unremarkable.
Outpatient Evaluation

- **FH:**
  - Brother - bipolar disorder
  - Mother - thyroid goiter
  - Maternal cousin - lupus
  - Maternal uncle - stroke at a young age

- **PMH:**
  - Long QT syndrome, diagnosed age 9
  - Drug and alcohol abuse - marijuana and ecstasy - clean 2 years
  - Mild developmental delay
Patient History:

- Vertigo, lacrimation, and lower extremity weakness with strong odors

- 1-2 episodes weekly of dysarthria, drooling, hearing loss with right upper extremity automatisms

- Early satiety – 10 pound weight loss

- New intermittent diplopia

- Stiffening right lower extremity with emotion
Exam:

- Reduced sensation right V1-V3 distribution

- Reflexes brisk throughout

- No Hoffman, mildly positive jaw jerk

- Increased tone right lower extremity

- Mildly wide-based gait, possibly mild right spastic component
Initial Outpatient Evaluation

**Ambulatory EEG**

*Frequent, generalized bursts of spike wave discharges*, moderate amplitude <0.5 seconds duration.

**CSF**

- <1 WBC
- 0 RBC
- Protein 33
- Glucose 63
- IgG Index mildly elevated (0.66)
- Synthesis rate: 1.2
- **5 oligoclonal bands**
Additional Evaluation

CT Chest/Abd/Pelvis
  Unremarkable
NMDA receptor Ab
  Negative
Muscle Biopsy
  Unremarkable
Body PET
  Negative
Testicular Ultrasound
  Negative
Diagnosis

Underwent treatment with IVIG and cyclophosphamide.
Case 3

68 yo professional male – Seen in clinic late 2014

- Wife passed away Spring 2010
- Fall 2010, obvious behavioral and psychiatric decline:
  - Contacted distant friend to help with his money
- Late 2010: Checked himself into hospital -- recognition that he had psychiatric problem.
  - Socially: loud laugh; stand up at odd times
  - Police found him wandering with no ID
  - Poor diet, late on bills -- barely managing to get by
- Sharp decline early 2013 -- Found at home, malnourished and dehydrated, confused, incontinent.
- Admitted December 2013 for increased agitation.
- PCR+ HSV encephalitis; treated with full course Acyclovir
Case 3

- Continued decline over following year:
  - Paranoid behaviors, not wanting people in his room to clean or bring food
  - Hoarding cat food and own food; perseverated on well-being of cats
- Pertinent Exam:
  - 4-extremity intermittent myoclonus.
  - Perseverative, frequent "yeah yeah, right."
  - Increased tone UpExt > LowExt. Cogwheel rigidity bilateral upper extremities.
  - Gait intact, mild reduction in bilateral arm swing.
  - Reflexes reduced throughout.
Case 3

- CSF: 0 WBC, Protein 68, +16 oligoclonal bands, Elevated CSF IgG and IgG index
- MRI:
Case 3

- Chronic active encephalitis of right mesial temporal lobe and brainstem.
- Neuronal degeneration, gliosis, microglial activation, and mononuclear infiltrates involving right mesial temporal lobe, pontine tegmentum, substantia nigra.
- Chronic multifocal meningeal inflammation.
Diagnosis:

Lessons Learned:
- Antibody testing is in its infancy – treat the patient, not the test.
- HSV history relevant
- At the end of the day, discuss risk/benefit and offer treatment
Treatment of Syndromes Associated with Antibodies to Cell Surface Proteins

• First line agents
  ▫ Corticosteroids (IV methylprednisolone)
  ▫ Plasma exchange
  ▫ Intravenous IgG
  • SAVE Serum/CSF Prior to treatment!

• Second line agents
  ▫ Mycophenolate mofetil, azathioprine
  ▫ Rituximab
  ▫ Cyclophosphamide
  ▫ Other targeted monoclonals
Autoimmune Neurology

**Summary:**

- If you are going to stick a needle in someone’s back -
  1. Get extra CSF and save it
  2. Always order oligoclonal bands

- Patients frequently have comorbid systemic and psychiatric symptoms.

- Documentation of **objective abnormalities** essential for diagnosis AND to compare the effectiveness of immunotherapy treatment trials.
Summary:
- If it is a hard-to-diagnose “mystery” patient, it is usually either infectious or immune-mediated
- Autoimmune Neurologic conditions are not as rare as you were taught
- In new onset, unexplained status epilepticus, MUST rule out autoimmune epilepsy
Autoimmune Neurology

**Summary:**
- Systemic Autoimmunity (Rheumatology) often manifests in the CNS
- Autoimmune encephalitis can follow Infectious Encephalitis (patients can get both)
- If immune-mediated, be patient (recovery time)
- It is all in the History
  - COMPLETE Personal and Family
  - Course of the illness is always informative (acute/subacute/chronic/stuttering).
Autoimmune Neurology

Summary:
- Freeze Serum and CSF before you treat!!!!
  1. Send both CSF and serum for neuronal antibody testing
  2. Be aware that some tests are only available in research labs

- Empiric treatment often warranted, but treatment may interfere with ability to achieve a diagnosis, so ALWAYS save pretreatment serum and CSF.
Summary:

- EEG may only show delta slowing or other nonspecific abnormality

- Contact a colleague EARLY
Thank you!

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