Autoimmune Neurology: Encephalopathy, Dementia & Epilepsy

Andrew McKeon, MD
Mayo Clinic, Rochester, MN

Disclosures

• I receive research support from and have consulted for Medimmune
Learning Objectives

• Recognize key clinical features of autoimmune encephalopathies, dementias and epilepsies
• Select evaluations
• Select treatments

Outline

• What are Autoimmune Encephalopathies?
• How do patients present?
• Why do they occur?
• How do I evaluate further?
  - Basic serum/CSF testing
  - Neural antibody (Ab) testing
  - Treatment trial in suspected cases
What are Autoimmune Encephalopathies?

Autoimmune Neurological Disorders

- Nervous system disorders caused by aberrant immune response
- Antigen-specific
- May be paraneoplastic or idiopathic
- Often unified by Ab marker detected in serum or cerebrospinal fluid (CSF)
How do patients present?

- Subacute onset of one or more of:
  - Cognitive change
  - Seizures
  - Mood/personality change
- Fluctuating course
- Can have symptoms/signs affecting any other neurological domain
- Often multifocal
- Think rostrocaudal
What are the risk factors?

- **Not age**: Occur in all age groups
- Occur in women and men
- Coexisting autoimmune disease, e.g. thyroid disease, type 1 diabetes mellitus
- Smoking history
- Family history of autoimmune disease or cancer

How do I evaluate further?

- Determine extent of neurological involvement:
  - Neurological examination
  - Mental status testing
  - Neuropsychometric testing
  - MRI imaging
  - Electrophysiology (EEG)
  - Functional imaging
How do I evaluate further?

• **Ab testing, serum:**
  - Non-neural Abs: e.g. thyroid peroxidase Abs, connective tissue cascade
  - Neural Abs: main subject of this course

• **CSF testing:** protein, white cell count, IgG index and synthesis rate, oligoclonal bands, neural Abs

In general…

• Some Abs have limited associated phenotypes e.g. NMDA
• Others Abs have more diverse associated phenotypes e.g. VGKC complex Abs
• Cancer positive predictive values vary
• Ab profiles may be informative for cancer diagnosis

*Pittock et al, Ann Neurol 2004*
*Horta et al, Clin Cancer Research 2014*
Why do autoimmune encephalitides occur?

McKeon & Pittock, Acta Neuropath 2011
**Neural Abs Overview**

IgG Antibodies targeting

- **Neural cell surface antigens**
  - (ion channels, receptors, synapses)
  - e.g. VGKC complex Ab, NMDA-R Ab, GlyR

- **Immunotherapy**

- **Neuronal nuclear, cytoplasmic antigens**
  - e.g. ANNA-1, PCA-1, CRMP-5 IgG

- **Oncological therapy**

**How Are Patients Evaluated in the Laboratory?**
Tissue-based Immunofluorescence

PCA-1  PCA-1  ANNA-1

NMO-IgG  NMDA-R IgG

Western blot

Yu, Kryzer Ann Neurol 2001
**Immunoprecipitation**

Auto Ab to AChR

Precipitation

Positive result

Testing for:
- Muscle AChR Abs
- Neuronal AChR Abs (α3)
- Calcium channel Abs (N or P/Q types)
- VGKC complex Abs
- GAD65 Ab

**ELISA**

Ag coated well + Patient Ab in test sample + Ag-Biotin

Testing for:
- Striational Abs
- AQP4-IgG

Detect Ag-Biotin bound by addition of streptavidin peroxidase and colorogenic substrate.
Cell-based Immunofluorescence

HEK-293 cells transfected with GFP-tagged aquaporin-4


Testing for:
- NMDA-R Ab
- AMPA-R Ab
- GABA-B R Ab
- Glycine receptor Ab

Classic Paraneoplastic Autoantibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Oncological association</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANNA-1</td>
<td>Small-cell carcinoma</td>
</tr>
<tr>
<td>ANNA-2</td>
<td>Small-cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Breast adenocarcinoma</td>
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<tr>
<td>ANNA-3</td>
<td>Aerodigestive carcinomas</td>
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<tr>
<td>AGNA</td>
<td>Small-cell carcinoma</td>
</tr>
<tr>
<td>PCA-1</td>
<td>Gynecological adenocarcinomas</td>
</tr>
<tr>
<td></td>
<td>Breast adenocarcinoma</td>
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<tr>
<td>PCA-2</td>
<td>Small-cell carcinoma</td>
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<tr>
<td>PCA-Tr</td>
<td>Hodgkin lymphoma</td>
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<tr>
<td>CRMP-5 IgG</td>
<td>Small-cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Thymoma</td>
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<tr>
<td>Amphiphysin IgG</td>
<td>Small-cell carcinoma</td>
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<tr>
<td></td>
<td>Breast adenocarcinoma</td>
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</tbody>
</table>
Synaptic Autoantibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Oncological association</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGKC- complex</td>
<td>Small-cell lung carcinoma, thymoma, adenocarcinoma of breast, prostate</td>
</tr>
<tr>
<td>NMDA receptor</td>
<td>Ovarian teratoma</td>
</tr>
<tr>
<td>AMPA receptor</td>
<td>Thymoma, lung carcinoma, breast carcinoma</td>
</tr>
<tr>
<td>GABA-B receptor</td>
<td>Small-cell lung carcinoma</td>
</tr>
<tr>
<td>P/Q and N type calcium channel</td>
<td>Small-cell carcinoma, breast or gynecological adenocarcinoma</td>
</tr>
<tr>
<td>Neuronal ganglionic AChR</td>
<td>Adenocarcinoma, thymoma, small-cell carcinoma</td>
</tr>
<tr>
<td>NMO-IgG</td>
<td>Uncommon (breast adenocarcinoma, carcinoid, teratoma, thymoma, lymphoma)</td>
</tr>
<tr>
<td>DPPX-IgG</td>
<td>B cell neoplasms</td>
</tr>
</tbody>
</table>

Some Examples of Autoimmune Encephalopathies, Dementias & Epilepsies
Encephalitis

- Memory, mood, personality changes, seizures: limbic encephalitis
- Diverse autoantibody associations:
  - ANNA-1, 2 (anti Hu, Ri)
  - CRMP-5 IgG
  - VGKC complex IgGs
  - GAD65 Ab (High titer)
  - AMPA, GABA-B receptor Abs
  - mGluR5 Ab

NMDA-R Encephalitis

- Stereotyped course:
  Psych → seizures, encephalopathy
  → movement disorder, dysautonomia
  → hypoventilation+coma
- F>M
- 50% have ovarian teratoma
- CSF testing: more sensitive and specific
- Treatment: steroids/IVIg or PLEX/rituximab/cyclophosphamide
- 80% get to mild or no disability

Titulaer, Lancet Neurology 2013
The assays

Encephalitis and Antibodies to Dipeptidyl-Peptidase–Like Protein-6, a Subunit of Kv4.2 Potassium Channels

Anna Boronat, BS,1 Jeffrey M. Golfer, MD,2 Nita Giesa-Ambaras, PhD,1 Hyo-Young Jeong, PhD,1 Michael Walsh, MD,3 Kirk Roberts, MD,4 Eugenia Martinez-Hernandez, MD,5 Myrna R. Rosenfield, MD, PhD,1,6 Rita Balice-Gordon, PhD,6 Francesco Graus, MD,1
Bernardo Rudy, PhD,1,7 and Josep Dalmau, MD, PhD1,7

Objective: To report a novel cell surface antigen of encephalitis that is a crucial regulatory subunit of the Kv4.2 potassium channel.

Methods: Antibodies with specificity for various epitopes and peptides with a similar pattern of neuronal brain immunoreactivity were selected for autologous characterization. Techniques included immunoprecipitation, mass spectrometry, cell-based experiments with Kv4.2 and 

Results: Immuno precipitation and Western blot analysis identified DPP6 as the target antigen. A cell-based assay confirmed that all 4 patients, but not 31 controls, had DPP6 antibodies. Symptoms included agitation, confusion, dysarthria, seizures, and other neurologic findings; 1 patient with enhanced and 17 had depressed C.

A

B

C

SM

LM

G
DPPX-IgG binds to CNS & ENS synapses

Tobin et al, Neurology, 2014

Manifestations of DPPX autoimmunity: 20 patients

<table>
<thead>
<tr>
<th>Neurological</th>
<th>Central hyperexcitability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive disorders</td>
<td>PERM (Rigidity + myoclonus)</td>
</tr>
<tr>
<td>Brainstem/spinal cord disorders</td>
<td>Myoclonus</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Startle</td>
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<tr>
<td>Myoclonus or tremor</td>
<td>Rigidity</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>Brisk reflexes</td>
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<tr>
<td>Gastrointestinal dysautonomia</td>
<td>Stiff-man syndrome</td>
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<tr>
<td>Delirium</td>
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<td>Cerebellar dysfunction</td>
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<td>Urinary symptoms</td>
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<tr>
<td>Psychosis</td>
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<tr>
<td>Depression</td>
<td></td>
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<td>Seizures</td>
<td></td>
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<tr>
<td>Cardiac dysrhythmia</td>
<td></td>
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<tr>
<td>Diaphoresis</td>
<td></td>
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<tr>
<td>Temperature dysregulation</td>
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Cancer

| B cell neoplasia | 2 |
Cognitive disorders

- Patients may present with cognitive-predominant presentations, not typical for limbic encephalitis
- May have coexisting neurological problems (e.g. tremor, neuropathy)
- Thyroid autoimmunity common
- VGKC complex Abs > GAD65 Ab > N or P/Q type calcium channel Abs > ANNA-1 (anti-Hu)
- Pre- and post objective testing helpful in defining treatment response

Flanagan et al, Mayo Clinic Proceedings 2010

Immunotherapy-Responsive Cognitive Impairment: Clinical Course & Predictors of Improvement

- **Criteria:**
  1. Predominant cognitive impairment
  2. Suspected autoimmune basis
  3. Trial of immunotherapy
  4. Before and after evaluation
     - 72 patients
     - 46 (64%) responded

Flanagan et al, Mayo Clinic Proceedings 2010
Immunotherapy Responders

- 35% initially diagnosed neurodegenerative
- Objective improvements
  - Physician reported
  - Kokmen short test of mental status (a bit like the MMSE)
  - Neuropsychometric testing
- Relapse during immunotherapy taper (57%)
- Shortcomings (not blinded, bias)

Neuropsychological Evaluations in 6 Patients Before and After Treatment

![Graph showing neuropsychological evaluations for 6 patients before and after treatment.](image-url)
Neuroimaging

MRI (A – D) and SPECT (F) before and after treatment

Responders Non-responders P value
Subacute onset 93% 35% <0.001
Fluctuating course 91% 19% <0.001
Tremor 43% 8% 0.0013
CSF protein (>100 mg/dL) or pleocytosis 35% 9% 0.036
Neuronal ion channel autoantibody 41% 10% 0.009
Mean time to treatment (months) 11 25 <0.001

Predictors of Immunotherapy Response
Autoimmune epilepsy

Retrospective Analysis of 32 Patients

**Inclusion criteria:**

1. Predominant presentation: recurrent seizures of unknown etiology

2. Autoimmune basis suspected due to:
   - neural autoantibody detection,
   - inflammatory CSF, or
   - MRI findings suggesting inflammation

*Quek et al, Arch Neurol. 2012*
Clues to Autoimmunity

Neural Autoantibodies, 91%

- VGKC-complex, 56%
  Lgi1 (44%), Caspr2 (3%), neither (9%)
- GAD-65, 22%
- Other, 16%
  CRMP-5, Ma-1/Ma-2, NMDAR, Neuronal ganglionic AChR

Quek et al, Arch Neurol. 2012

Seizure Characteristics

- **Type**
  - Complex partial, 81%
  - Simple partial, 69%
  - Generalized tonic clonic, 44%
- **Medically intractable**
  - Failed 2+ antiepileptic drugs, 81%
  - Daily, 81%
- **Other findings**
  - Cognitive deficits, 63%
  - Personality changes, 25%
  - Depression / anxiety, 19%
  - None, 34%
Non-medial temporal lesions

Immunotherapy (n=27)
IVMP, 12; IVIG, 3; IVMP + IVIg, or other, 12

- Improved, 82%
  - Seizure free, 64%
  - Median 9 months (2-48)
  - Seizure frequency ↓, 18%

- No response, 18%
Movement disorder or epilepsy?

- 61 yo Male
- Hx of AIDP, IVIg responsive age 43
- Jan 2010: spells right facial contraction, left facial contraction, then arm posturing
- Diagnosis ‘Psychogenic’ at home
- Video EEG: ictal activity left frontoparietal region
- VGKC complex Ab positive, 2.58 nmol/L
- Neoplastic evaluation negative
- Seizures stopped, EEG normalized with combined immunotherapy/AED
- Mild residual amnesia


Steroids, IVIg or both?

Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy

Abstract

Objective To evaluate a trial of immunotherapy as an aid to diagnosis in suspected autoimmune epilepsy.

Methods We reviewed the charts of 110 patients seen at our autoimmune neurology clinic with seizures as a chief complaint. Twenty-nine patients met the following inclusion criteria: (1) autoimmune epilepsy suspected based on the presence of ≥1 neural autoantibody (n = 28), personal or family history or physical stigma of autoimmunity, and frequent or medically intractable seizures, and (2) initiated a 6- to 12-week trial of IV methylprednisolone (IVMP), IV immune globulin (IVIg), or both. Patients were defined as responders if there was a 50% or greater reduction in seizure frequency.

Results Eighteen patients (62%) responded, of whom 10 (34%) became seizure-free; 52% improved with the first agent. Of those receiving a second agent, after not responding to the first, 43% improved. A favorable response correlated with shorter interval between symptoms onset and treatment initiation (av 9.5 vs 22 months, p = 0.046). Responders included 14/16.
Patients

• 29 with seizures seen in our autoimmune neurology clinic
  - Neural antibody positive (23)
  - Or other features supporting autoimmune cause
  - Medically intractable epilepsy
  - Underwent trial of immunotherapy

Results

• 18/29 (62% responded)
• 10 became seizure free
• 52% responded to the first drug
• 40% of those treated responded to the 2nd drug
Evaluation for cancer

- Based on: specific Ab finding(s)
  OR
- Age, sex, family history
  - CT chest, abdomen, pelvis
  - Pelvic ultrasound (incl. transvaginal views)
  - Testicular ultrasound
  - Mammogram
  - Exploratory surgery

*Increased cancer detection rate ~ 20%

McKeon et al, Arch Neurol, 2010
Treatment: principles

- Trials of immunotherapy
- Measure improvement objectively
- Determining if short-term or long term treatment required
- Consider steroid-sparing agent

Cytotoxic T cell mediated disorders

- Paraneoplastic disorders
  - Do not generally have good responses to steroids, IV Ig or plasma exchange
- General approach:
  - Oncological therapy (surgery, chemotherapy, radiation therapy)
  - Cyclophosphamide

Vernino et al, Neuro Oncol. 2004;6:55-62
Antibody-mediated disorders (definite or possible)

- Acute (early important)
  - Corticosteroids
  - Intravenous immune globulin (IVIg)
  - Plasma exchange
- Chronic
  - Mycophenolate mofetil
  - Azathioprine
  - Rituximab, cyclophosphamide

**Objective baseline measurements**

**Acute treatment, "Diagnostic Test"**
- IV methylprednisolone or IVIg or Plasma exchange

If no improvement, consider alternative acute therapy or no further therapy.

**Chronic treatment**
- Continue acute IV therapy, and taper or Oral prednisone taper and Oral azathioprine or Oral mycophenolate mofetil or Other options

*McKeon, Lennon, Pittock, Continuum, 2010.*
Summary

- Autoimmune CNS disorders are important to consider
  - Potentially treatable
  - May be indicative of occult cancer
- Clues may emanate from
  - history
  - examination
  - serum & CSF Ab evaluations
  - response to treatment

Thank you

Andrew McKeon
mckeon.andrew@mayo.edu
507-266-3196