Autoimmune Neurology: Paraneoplastic Disorders & Beyond

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Mayo Clinic
Disclosures

• I receive research support from Euroimmun

• I have consulted for Medimmune, Euroimmun & Grifols (no personal compensation)

• I have patent applications for MAP1B and Septin 5 Abs as markers of neurological disease and cancer.
Outline

• Risk factors for autoimmune neurological disorders?
• How do I evaluate further?
  - Basic serum/CSF testing
  - Neural antibody (Ab) testing
  - Treatment trial in suspected cases
  ‘The diagnostic test’
Why Suspect an Autoimmune Neurological Disorders?
Phenotype

- Rapid onset
- Rapid progression
- Classic phenotypes
- Atypical phenotypes
- Multifocal disorders
Classic Disorders

• Limbic encephalitis
• Chorea
• Cerebellar degeneration
• Brainstem encephalitis
• Opsoclonus-myoclonus syndrome
• Myelopathy
• Stiff-person syndrome
• Sensory ganglionopathy/neuronopathy
• Lambert-Eaton myasthenic syndrome (LEMS)
Beyond Classical Phenotypes

Disorders at presentation may be:

**Limited**
- Epilepsy
- Dementia
- Stiff-limb

**More widespread/multifocal**
- Encephalomyelitis
- Chorea + neuropathy
- Ataxia and LEMS
What are the risk factors?

- Sometimes none
- Coexisting autoimmune disease, e.g. thyroid disease, type 1 diabetes mellitus
- Cancer history
- 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, EMG, SSEPs)
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
Why do autoimmune neurological diseases occur?
The diagram illustrates the immune response to antigen presentation and cell activation.

**IgG effectors**
- Plasma membrane antigen
- Antibodies (tumoricidal potential)
- Antigen (△, ■) presentation + immune cell activation

**T-cell effectors**
- Cytotoxic T-cells
- Intracellular antigen

**Cell death**
- Proteasomal degradation → peptide → MHC1

**Antigen internalization**
- Endo-lysosomal degradation

**Adaptive immune response**
- Plasma cell: stimulates B-cell activation through ADCC (Antibody-Dependent Cellular Cytotoxicity)
- B-cell: produces antibodies
- Complement activation
- Fc receptor activation

**Cellular targets**
- Neuron or Astrocyte
- Nucleus
Neural Abs Overview

IgG Antibodies targeting

Neural cell surface antigens

(iion 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
### Neuronal nuclear or cytoplasmic Abs

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Oncological association</th>
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</thead>
<tbody>
<tr>
<td>ANNA-1 (anti-Hu)</td>
<td>Small-cell carcinoma</td>
</tr>
<tr>
<td>ANNA-2 (anti-Ri)</td>
<td>Small-cell carcinoma</td>
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<tr>
<td></td>
<td>Breast adenocarcinoma</td>
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<tr>
<td>ANNA-3</td>
<td>Aerodigestive carcinomas</td>
</tr>
<tr>
<td>AGNA (SOX-1)</td>
<td>Small-cell carcinoma</td>
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<tr>
<td>PCA-1 (anti-Yo)</td>
<td>Gynecological adenocarcinomas</td>
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<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>CRMP-5 IgG (anti-CV2)</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>
</tr>
<tr>
<td></td>
<td>Breast adenocarcinoma</td>
</tr>
<tr>
<td>GFAP-IgG</td>
<td>Teratoma, other</td>
</tr>
<tr>
<td>NIF-IgGs</td>
<td>Neuroendocrine (small cell, Merkel cell, other)</td>
</tr>
</tbody>
</table>
## Synaptic Autoantibodies

<table>
<thead>
<tr>
<th>Antibody</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Lgi1/CASPR2</td>
<td>Thymoma, other</td>
</tr>
<tr>
<td>NMDA receptor</td>
<td><strong>50%</strong> Ovarian teratoma</td>
</tr>
<tr>
<td>AMPA receptor</td>
<td><strong>70%</strong> Thymoma, lung carcinoma, breast carcinoma</td>
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<tr>
<td>GABA-B receptor</td>
<td><strong>50%</strong> Small-cell lung carcinoma</td>
</tr>
<tr>
<td>P/Q &amp; N type calcium channel</td>
<td>Small-cell carcinoma, breast or gynecological adenocarcinoma</td>
</tr>
<tr>
<td>GlyR</td>
<td>Thymoma</td>
</tr>
<tr>
<td>DPPX</td>
<td>Occasional B cell neoplasm</td>
</tr>
<tr>
<td>IgLON5</td>
<td>None</td>
</tr>
<tr>
<td>PCA-Tr (DNER)</td>
<td>Hodgkin lymphoma</td>
</tr>
</tbody>
</table>
How Are Patients Evaluated in the Laboratory?
How are Abs detected?

**Indirect immunofluorescence screening**

**Confirmation by:**
- Western blot
- Cell based assay
- Immunoprecipitation

**Immunoprecipitation assay screening**

**Cell based assay screening**
Examples of Abs Accompanying Autoimmune CNS Disorders
Encephalitis

- Memory, mood, personality changes, seizures: limbic encephalitis
- *Diverse autoantibody associations:*
  - ANNA-1, 2 (anti-Hu, Ri)
  - CRMP-5 IgG
  - Lgi1, CASPR2 IgGs
  - GAD65 Ab (High titer)
  - AMPA, GABA-B receptor Abs
  - mGluR5 Ab
Cognitive disorders

- 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
Autoimmune Epilepsy

- May have seizure predominant presentation
- Scan may be normal at onset in half
- **Dx:** EEG, CSF, Ab testing
- VGKC complex Abs > GAD65 Ab > CRMP-5 IgG > Ma2 = NMDA receptor Ab = GABA-B-R-IgG
- GABA-A-R-IgG


Localizations

- Mesial temporal
- Neocortical temporal
- Precentral
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*
ADEM: AQP4 and MOG Abs

- **Assay**: Cell-based format
  
  IgG1 anti-human secondary Ab for MOG

- **Syndromes**: Optic neuritis, Myelitis, ADEM or ADEM-like, Brainstem disorders, NMO

- **Clinical course**: monophasic, relapsing
  often ++ steroid responsive

*Lopez et al, in press, JAMA Neurol, 2018.*
• Inflammatory CNS disorder
• Meningitis
• Encephalitis
• Myelitis
• Inflammatory CSF
• Sometimes paraneoplastic
• Steroid responsive
GFAP-IgG

Symptom onset treated with IVIG, IVMP & prednisone 80 mg/day

1 month after onset improved; prednisone 80 mg/day maintained with planned taper & mycophenolate 2g/day added

16 months after onset relapsed on prednisone 7.5 mg/day; added IVMP; increased prednisone to 60 mg/day & mycophenolate to 2.5 g/day

20 months after onset improved

Flanagan et al, Ann Neurol, 2017
Opsoclonus-myoclonus

- **Children**
  - Neuroblastoma
  - ANNA-1 in a minority
- **Adults**
  - 15% paraneoplastic
  - ANNA-2 > ANNA-1 = NMDA-R
  - Frequently idiopathic autoimmune (immunotherapy responsive)

*Klaas et al, Arch Neurol 2012*
Opsoclonus OR myoclonus

‘Opsoclonus only’
- ANNA-2 (anti-Ri)
- Breast adenocarcinoma

‘Whole body tremor’
- Small amplitude generalized polymyoclonus
- No opsoclonus
- 25% have autoimmune cause
- Occult cancer possible
- VGKC, Alpha 3 ganglionic, CRMP-5 IgG

McKeon et al, Arch Neurol, 2007
Chorea

- Paraneoplastic or idiopathic autoimmune

  - **Paraneoplastic:**
    - CRMP-5 IgG
    - ANNA-1
    - GAD65

  - **Idiopathic autoimmune:**
    - Lupus, APL Ab syndrome
    - CASPR2

*O’Toole et al, Neurology 2013*
Chorea

- *Paraneoplastic patients more likely:*
  - Older
  - Male
  - More frequent weight loss
  - More frequent coexisting peripheral neuropathy
  - Some improved with immunotherapy/cancer therapy
- *Idiopathic*
  - Often milder course
  - Improved/resolved with steroids

*O’Toole et al, Neurology, 2013*
Cerebellar ataxia

- Symptoms frequently overlap with brainstem disorders
- Rapid-onset dysarthria, incoordination, gait disturbance, vertigo
- **Prototypic disorder:** PCA-1 (anti-Yo) associated cerebellar degeneration in women with mullerian or breast adenocarcinoma
- **Other Abs:** P/Q-type calcium channel Ab, GAD65 Ab, PCA-Tr, mGluR1 Ab

*Peterson et al, Neurology 1992*
*McKeon et al, Arch Neurol 2010*
mGluR1 Ab

**Neurological**
- Ataxia
- Limbic symptoms (rare, at onset)
- Dysgeusia (40%, at onset)

**Cancer**
- Lymphoma (HD, non-HD), prostate adenocarcinoma

*Sillevis-Smitt, NEJM, 2000*
*Lopez et al, Neurology, 2016.*
Septin-5-IgG

- Cerebellar ataxia
- Oscillopsia, vertigo
- Improvements with immunotherapy

- GTP-binding neural protein
- Neurotransmitter exocytosis

_Honorat et al, N2, in press_
Brainstem

- Eye movement disorders
- Dysphagia, dysarthria
- Parkinsonism
- Sleep disorders
- e.g. ANNA-2, MaTa

*Pittock et al, Ann Neurol 2003*
*Dalmau et al, Ann Neurol 2004*

- **Video:**
  - Initial Dx: PSP
  - Parkinsonism, narcolepsy-cataplexy
  - Ma1, Ma2 Ab positive
  - Tonsillar carcinoma

*Adams et al, Arch Neurol 2011*
IgLON5

- Sleep disorders
- Chorea
- Parkinsonism
- Dysphagia
- Dysautonomia
- Stiff-person syndrome
- ? Treatment responsive

Honorat et al, 2017, N2
First case seen in 1924.

Reported in 1956 with 13 other cases.

GlyR-IgG in Stiff-man Syndrome

• 10/81 patients tested positive (12%, GlyR cell binding assay)

GAD65-IgG + N=60

Classic SMS  Variant SMS  PERM

GAD65-IgG - N=21

Classic SMS  Variant SMS  PERM  Hyperekplexia

N=43  N=16  N=1

N=4  N=14  N=2  N=1

GlyR-IgG +

2  4  0

2  1  1  0

Improved with immunotherapy

5 of 6 GlyR-IgG + patients

7 of 25 GlyR IgG - patients (p=0.02)

Mayo, Barcelona JAMA Neurol, 2013
GlyR-IgG

- GlyRα1-IgG +:
  - 21/247 patients
  - 8/190 healthy subjects (4%)
- Only SPS spectrum patients serums internalize GlyRα1
- SPS spectrum phenotypes:
  - PERM (8)
  - Classic SPS (5),
  - Stiff-limb (5)
  - Stiff-trunk (1)
  - Isolated exaggerated startle (hyperekplexia, 1).

Hinson et al, N2, 2018
GlyR-IgG Modulating Assay

Hinson et al, N2, 2018
DPPX Autoimmunity, Manifestations in 20 patients

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<tr>
<th>Neurological</th>
<th>Central hyperexcitability</th>
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<tr>
<td>Cognitive disorders</td>
<td>PERM (R rigidity + myoclonus</td>
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<td>Brainstem/spinal cord disorders</td>
<td>Myoclonus</td>
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<tr>
<td>Weight loss</td>
<td>Startle</td>
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<td>Myoclonus or tremor</td>
<td>Rigidity</td>
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<td>Sleep disorder</td>
<td>Brisk reflexes</td>
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<td>Stiff-man syndrome</td>
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<td>Delirium</td>
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<td>Cerebellar dysfunction</td>
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<td>Urinary symptoms</td>
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<td>Psychosis</td>
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Tobin et al, Neurology, 2014
Paraneoplastic Myelopathy

- Subacute or insidious onset
- Lung, breast, kidney, thyroid, ovary/endometrium, melanoma, or other.
- Amphiphysin IgG, CRMP-5 IgG, ANNA-1, PCA-1, ANNA-3
- Minority improve with treatment
- 50% Wheelchair bound

Neuronal Intermediate Filaments

- Encephalopathy
- Ataxia
- Myelopathy
- Small cell carcinoma
- Merkel cell carcinoma
- 5 NIF targets
  - α internexin
  - Light chain
  - Medium chain
  - Heavy chain
  - Peripherin

*Basal et al, AAN, Los Angeles, Friday 4-27-18*
Cancer screening

- **Small cell/neuroendocrine**: PET-CT, CT
- **Other lung cancer types**: PET-CT, CT
- **Thymoma**: high res CT or MRI
- **Lymphoma**: PET-CT
- **Breast**: mammogram/breast exam
- **Lymph node disease**: PET-CT
- **Prostate**: digital rectal exam, PSA
- **Gynecological**: clinical exam, US with transvaginal
- **Renal**: CT
- **GI**: endoscopies
- **Thyroid**: ultrasound, PET-CT
- **Skin**: dermatologist exam
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, IVIg or plasma exchange

- General approach:
  - Oncological therapy (surgery, chemotherapy, radiation therapy)
  - Cyclophosphamide

McKeon, Curr Treat Options Neurol, 2013
Antibody-mediated disorders (definite or possible)

- Acute (early important)
  - Corticosteroids
  - Intravenous immune globulin (IVIg)
  - Plasma exchange
- Chronic
  - Mycophenolate mofetil
  - Azathioprine
  - Rituximab, cyclophosphamide
Autoimmune Ataxia: Treatments & Outcomes

50% wheelchair dependent by 25.5 months

*Jones et al, JAMA Neurol 2015*
‘Checkpoint’ inhibitors

- **Peripheral**: block PD-1 (pembrolizumab, nivolumab)
- **Central**: CTLA-4
- **Outcome**: Autoimmunity
  - Retinopathy
  - Encephalitis
  - Myasthenia gravis
  - Necrotizing myopathy

*Kao et al, JAMA Neurol, 2017*
Summary

- Autoimmune neurological 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

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