The Spectrum of Autoimmune CNS Disorders

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Disclosures

- I receive research support from Medimmune & Euroimmun
- I have consulted for Medimmune, Euroimmun & Grifols (no personal compensation)
- I have patents applications for GFAP and MAP1B Abs as markers of neurological disease and cancer
Learning Objectives

• Recognize key characteristics of autoimmune CNS disorders
• Request appropriate antibody testing for those disorders
• Choose appropriate immune therapies

Outline

• What are Autoimmune CNS Disorders?
• 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
    ‘The diagnostic test’
What are Autoimmune CNS Disorders?

Autoimmune CNS Disorders

• CNS 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 symptoms
- Fluctuating course
- Can affect any neurological domain
- Often multifocal
- Think rostrocaudal
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?

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

Classic Paraneoplastic Autoantibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Oncological association</th>
</tr>
</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>
</tr>
<tr>
<td>ANNA-3</td>
<td>Aerodigestive carcinomas</td>
</tr>
<tr>
<td>AGNA (SOX-1)</td>
<td>Small-cell carcinoma</td>
</tr>
<tr>
<td>PCA-1 (anti-Yo)</td>
<td>Gynecological adenocarcinomas</td>
</tr>
<tr>
<td>PCA-2</td>
<td>Breast adenocarcinoma</td>
</tr>
<tr>
<td>PCA-Tr (DNER)</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>CRMP-5 IgG (anti-CV2)</td>
<td>Small-cell carcinoma</td>
</tr>
<tr>
<td>Amphiphysin IgG</td>
<td>Small-cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Breast adenocarcinoma</td>
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</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>50% Ovarian teratoma</td>
</tr>
<tr>
<td>AMPA receptor</td>
<td>70% Thymoma, lung carcinoma, breast carcinoma</td>
</tr>
<tr>
<td>GABA-B receptor</td>
<td>50% 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>Muscle AChR</td>
<td>Thymoma, thymic carcinoma, lung carcinoma, endometrial carcinoma, prostate carcinoma</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&gt; carcinoid, teratoma, thymoma, 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 Autoimmune CNS Disorders

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

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
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

Quek et al, Arch Neurol 2012

Localizations
- Mesial temporal
- Neocortical temporal
- Precentral

GABA-B Receptor IgG

- Limbic encephalitis
- Seizures often prominent
- Some present with status epilepticus
- Rare reports of OMS & ataxia
- Cancer detected in 50% (usually small cell carcinoma)

Hutbberger et al, Neurology, 2013
Opsoclonus-Myoclonus

- Children
  - Neuroblastoma
  - ANNA-1 in a minority
- Adults
  - 15% paraneoplastic
  - ANNA-2 > ANNA-1 = NMDA-R Ab
  - 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 opsoconlus
  - 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
Movement Disorder or Epilepsy?

- 61-year-old 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

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

Non-classic disorders also occur
**mGluR1 Ab**

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

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

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**Brainstem**

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

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

Improved with immunotherapy
5 of 6 GlyR-IgG+ patients
7 of 25 GlyR IgG- patients (p=0.02)
Sleep Disorders

- VGKC complex-IgG
- DPPX-IgG
- IgLON-5-IgG
  - 8 patients
  - Chorea, ataxia
  - Dysarthria, dysphagia
  - Sleep apnea
  - Central hypoventilation
  - IgG4 Ab
  - Tauopathy

DPPX Autoimmunity, Manifestations in 20 Patients

<table>
<thead>
<tr>
<th>Neurological</th>
<th>Central hyperexcitability</th>
</tr>
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<tbody>
<tr>
<td>Cognitive disorders</td>
<td>PERM (Rigidity + myoclonus)</td>
</tr>
<tr>
<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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<tr>
<td>Myoclonus or tremor</td>
<td>Rigidity</td>
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<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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<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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<tr>
<td>Depression</td>
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<td>Seizures</td>
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<td>Cardiac dysrhythmia</td>
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<tr>
<td>Diaphoresis</td>
<td></td>
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<tr>
<td>Temperature dysregulation</td>
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Sabater et al, Lancet Neurology, 2014
Tobin et al, Neurology, 2014
IgLON5

- Sleep disorders
- Brainstem disorders
- Stiff-person spectrum
- Dysautonomia
- ? Treatment responsive

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

Neuromyelitis Optica

- Autoimmune CNS disorder distinct from MS
- Severe (including bilateral) optic neuritis
- Myelitis: Long spinal cord lesions
- Intractable hiccoughs, nausea, vomiting
- Encephalopathy (mimicking ADEM) in children
- Can improve dramatically with steroids, PLEX, IVIg
- Need immunosuppression to maintain remission

NMO-IgG/AQP4-IgG

- Distinguishes NMO from classical MS
- Specificity >90%
- Tissue IF: 58% sensitivity
- New antigen-specific assays 70-80% sensitivity

Lennon, et al Lancet 2004
Fryer, et al, N2, 2014
MOG Ab

- Assay: Cell-based format
  - IgG1 anti-human secondary Ab
- Syndromes
  - Optic neuritis
  - Myelitis
  - ADEM or ADEM-like
  - Brainstem disorders
  - NMO
- Clinical course
  - Monophasic, relapsing often ++ steroid responsive

Inflammatory CNS disorder
- Meningitis
- Encephalitis
- Myelitis
- Inflammatory CSF
- Sometimes paraneoplastic
- Steroid responsive
GFAP-IgG

Flanagan et al, Ann Neurol, 2017
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

PET-CT

*Increased cancer detection rate ~ 20%
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
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
- IVIg
- Plasma exchange

- **Consider alternative acute therapy or no further therapy**

- **No improvement**

- **Improvement**

**Confirms diagnosis**

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

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!

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Questions & Discussion