Autoimmune Encephalitis

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Medicine Review Course, 24\textsuperscript{th} July 2016
Disclosures

• Received travel grants from UCB and Merck
Encephalitis

- Inflammation of the brain parenchyma

- Clinical manifestations
  - Confusion, drowsiness
  - Seizures
  - Focal neurological deficits
  - Behavioral and neuropsychiatric symptoms
Infective Encephalitis

**Viral**
- Herpes simplex virus 1/2
- Varicella zoster virus
- Enterovirus
- Parechovirus
- Adenovirus
- Human herpesvirus-6/7 (<30 years)

**Bacterial**
- Bacillus anthracis, Bartonella henselae, Chlamydia psittaci,
- Chlamydia trachomatis, Legionella pneumophila, Leptospira spp,
- Listeria monocytogenes, Borrelia burgdorferi,
- Mycoplasma pneumoniae, Mycobacterium tuberculosis,
- Salmonella spp, Streptococcus pneumoniae,
- Streptococcus pyogenes

**Rickettsial**
- Coxiella burnetii, Rickettsia rickettsii

**Parasitic**
- Toxoplasma gondii

**Fungal**
- Histoplasma capsulatum

Autoimmune Encephalitis

- Encephalitis caused by aberrant immune response to self antigen

- Abnormal immune response triggered by tumors, infections, or yet unknown mechanisms

- Diagnosis based on clinical features and often, the identification of specific neuronal autoantibodies in serum/CSF
Why is it important?

- Important differential of infective encephalitis
- Potentially treatable with immunotherapy
- May be paraneoplastic
Autoimmune Encephalitis: Epidemiology

• Multicenter population-based prospective study on encephalitis in England
  – 42 of 203 patients (21%) → etiology was immune mediated
  – 38% of them had neuronal autoantibodies

• California encephalitis project
  – Frequency of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis surpassed that of any individual viral etiology in individuals ≤ 30 yrs old (HSV, VZV, enterovirus)


Gable MS, et al. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis 2012;54:899–904
Autoimmune Encephalitis: Overview

**Onconeuronal (intracellular) antibodies**

- Phenotype
  - Classical paraneoplastic limbic encephalitis
  - Brainstem encephalitis
  - Encephalomyelitis
- Paraneoplastic
- Severe course, poor response to immunotherapy

**Neuronal surface/synaptic antibodies**

- Phenotype
  - Limbic encephalitis
- May be paraneoplastic, para/postinfectious, yet unknown mechanisms
- Good response to immunotherapy
Neuronal Surface/Synaptic vs Onconeural Antibodies

Autoimmune Encephalitis: Presentations

• Limbic encephalitis
  – Sub-acute onset
    • Psychiatric symptoms, confusion
    • Short term memory loss
    • Seizures
  – Can have forme fruste presentations

• Less common
  – Epilepsy
  – Rapidly progressive dementia
  – Psychiatric (psychosis, anxiety, depression)
  – Movement disorders (chorea)
Autoimmune Encephalitis: Investigations

- MRI brain
  - Uni/bilateral increased T2/FLAIR signal in the medial temporal lobes without contrast enhancement
  - Multiple cortical-subcortical T2/FLAIR lesions
  - Normal

Autoimmune Encephalitis: Investigations

- **CSF**
  - Lymphocytic pleocytosis milder than viral etiologies
  - Normal glucose levels
  - Normal or mildly increased protein concentration
  - Can be totally normal

- **EEG**
  - Slowing
  - Epileptiform activity
  - Electrographic seizures

The beginnings of a new field....
‘Classical’ Onconeural Antibodies

- Paraneoplastic neurological syndromes
  - Paraneoplastic cerebellar degeneration
  - Paraneoplastic sensory neuronopathy
  - Paraneoplastic encephalitis
    - Limbic
    - Brainstem
    - Encephalomyelitis
  - Paraneoplastic movement disorders
    - Chorea
    - Stiff person syndrome
    - Opsoclonus-myoclonus

# Onconeuronal Antibodies: Limbic Encephalitis

## Table 1. Antibodies associated with paraneoplastic syndromes

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Neurologic syndrome</th>
<th>Common cancer association</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Onconeuronal antibodies&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-Hu (ANNA-1)</strong></td>
<td>Encephalomyelitis often with PSN</td>
<td>SCLC</td>
<td>Poor response to treatment</td>
</tr>
<tr>
<td>Anti-CV2/CRMP5</td>
<td>Encephalomyelitis and PSN (may have motor involvement, uveitis, chorea)</td>
<td>SCLC, thymoma</td>
<td>Poor response to treatment</td>
</tr>
<tr>
<td>Anti-Yo (PCA-1)</td>
<td>PCD</td>
<td>Ovary, breast</td>
<td>Poor response to treatment</td>
</tr>
<tr>
<td>Anti-Ri (ANNA-2)</td>
<td>PCD, opsoclonus</td>
<td>Gynecologic, breast</td>
<td>Poor response to treatment</td>
</tr>
<tr>
<td>Anti-Tr/DNER</td>
<td>PCD</td>
<td>Hodgkin’s lymphoma</td>
<td>80% of patients are men &lt;45 years</td>
</tr>
<tr>
<td><strong>Anti-Ma proteins</strong></td>
<td>Limbic, brainstem and hypothalamic encephalitis</td>
<td>Ma2: Men &lt;45 years: germ cell tumors of the testis</td>
<td>About one-third of young men improve with treatment; older patients rarely improve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other Ma: men or women with a variety of solid tumors</td>
<td></td>
</tr>
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<td>Antiamphiphysin</td>
<td>Stiff-person syndrome, encephalomyelitis, PCD</td>
<td>Breast, SCLC</td>
<td>Often improves with treatment</td>
</tr>
<tr>
<td><strong>Anti-GAD</strong></td>
<td>Limbic encephalitis, cerebellar ataxia, stiff-person syndrome</td>
<td>Neuroendocrine</td>
<td>Risk of cancer increases with age, male sex, presence of concurrent neuronal cell-surface antibodies, and limbic encephalitis</td>
</tr>
</tbody>
</table>
Onconeural Antigens

- Antibodies when detected indicate that the disorder is paraneoplastic.
- Antibodies in this group target intracellular neuronal antigens that are also expressed by the cancer.
- Role of antibodies in pathogenesis unclear.
  - Multiple failed attempts to produce an animal model by passive transfer experiments or active vaccination with the antigen strongly suggest these antibodies are not pathogenic.
- Neuronal dysfunction is mediated by cytotoxic T cells irreversible neuronal damage and death → poor response to treatment.

- Onconeural proteins expressed in nucleus, cytoplasm or nucleolus of tumors
- Antigens are also expressed in neural cells
- Antigens displayed on upregulated MHC class-I molecules in a pro-inflammatory cytokine milieu after proteasomal degradation and are then accessible to cytotoxic T cells
Neuronal Surface/Synaptic Antibodies

- Limbic encephalitis or forme fruste
- May be paraneoplastic, para/postinfectious. Most cases → yet unknown mechanisms
- Antibodies target proteins or receptors that reside on the neuronal cell surface/synapses (pathogenic)
- These antibodies mediate neuronal dysfunction by direct interaction with the target antigens → good response to treatment
### Neuronal Surface/Synaptic Antibodies

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<td>Characteristic pattern of symptom progression. Partial syndromes or less severe phenotypes can occur; almost all patients develop several elements of the syndrome.</td>
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<td>Anti-AMPAR</td>
<td>Limbic encephalitis with prominent psychiatric features</td>
<td>~70% of cases: SCLC, thymoma, breast</td>
<td>Responds well to treatment.</td>
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<td>Anti-GABA(B)R</td>
<td>Limbic encephalitis with severe seizures</td>
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<td>LGI1</td>
<td>Limbic encephalitis</td>
<td>&lt;10% of cases: Thymoma</td>
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<td>Caspr2</td>
<td>Neuromyotonia +/- CNS involvement</td>
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<tr>
<td>Anti-GluR5</td>
<td>Limbic encephalitis</td>
<td>Hodgkin lymphoma</td>
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**References:**

Neural proteins expressed on plasma membrane of tumors
Antigens are also expressed in neural cells
Antibodies targeting plasma membrane antigens are effectors of injury

Neuronal Surface/Synaptic Antibodies Pathogenicity: In Vitro

Neuronal Surface/Synaptic Antibodies Pathogenicity: In Vivo

- NMDA encephalitis patients’ CSF → mice
  - Memory deficits
  - Anhedonic
  - Depressive-like behaviours
  - Spares behavioural and locomotor tasks

- Mice brain tissue
  - Progressive increase of brain bound human NMDAR antibodies predominantly in the hippocampus
  - Immunoblot analysis of the hippocampus showed progressive decrease of the density of total and synaptic NMDAR clusters and total NMDAR protein concentration

Anti-NMDA Receptor Encephalitis

Most common and first well characterized cell surface antibody encephalitis
Anti-NMDA Receptor Encephalitis

• Typical clinical course
  – Viral prodrome → neuropsychiatric manifestation → seizures → dysautonomia → dyskinesias and obtundation

• Associated with ovarian teratomas ~ 40 to 50% in young women

• Can affect males, children, elderly

Dyskinesias in Anti-NMDA Receptor Encephalitis

EEG: Extreme Delta Brush
Treatment and Outcome

• Treatment
  – 1\textsuperscript{st} line: Steroids, IVIG, Plasmapheresis
  – 2\textsuperscript{nd} line: Rituximab, Cyclophosphamide
  – Teratoma removal, if present

• Severe clinical course but usually good outcome

Good Outcome = mRS ≤ 2

81% All pts

97% Pts who responded to 1st line immunotherapy

Clinical Outcome

Pts who failed 1\textsuperscript{st} line immunotherapy and did not receive 2\textsuperscript{nd} line immunotherapy

Pts who failed 1\textsuperscript{st} line immunotherapy and received 2\textsuperscript{nd} line immunotherapy

Anti-NMDA Receptor Encephalitis after Herpes Simplex Virus 1 Encephalitis

- Occurs few weeks after HSVE
- Adults
  - Neuropsychiatric/behavioural manifestations
- Children
  - Movement disorders (choreathetosis)
  - Encephalopathy
- MRI shows increased enhancement
- HSV triggers autoimmunity within CNS

Likely to account for previous cases of ‘HSV relapses’
- Acyclovir resistance rare
- Treatment with immunotherapy

Movement Disorders in Anti-NMDA Receptor Encephalitis after Herpes Simplex Virus 1 Encephalitis
Anti-Voltage Gated Potassium Channel (VGKC) Encephalitis

- **VGKC complex antibodies**
  - LGI1 (central)
  - CASPR2 (central, peripheral)

- **Phenotype**
  - Limbic encephalitis, faciobrachial dystonic seizures (LGI1)
  - Issac’s syndrome (CASPR2)
    - Peripheral nerve hyperexcitability/neuromyotonia
  - Morvan’s syndrome (CASPR2>LGI1)
    - Neuromyotonia, pain, hyperhydrosis, weight loss, severe insomnia and hallucinations


Anti-VGKC (LGI1) Encephalitis

• Equal gender distribution

• Hyponatremia is a characteristic feature
  – 30% to 60%
  – SIADH

• Weakly associated with tumors
  – Thymomas, SCLC

Faciobrachial Dystonic Seizures Precedes LGI1 Limbic Encephalitis


Anti-VGKC (LGI1) Encephalitis

- Usually shows good response to early 1st line immunotherapy
  - Steroids, IVIG, plasmapheresis
  - Combination therapy vs monotherapy


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<td>Females/males $&gt;45$ years: rare association with solid tumors</td>
<td>Responds well to treatment; recovery may be prolonged.</td>
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<tr>
<td>Anti-α-GlyR</td>
<td>PERM</td>
<td>Infrequent: thymoma, lymphoma</td>
<td>Responds well to treatment</td>
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Autoantibodies Detection

Autoantibodies Detection

Autoantibodies Detection

Images courtesy of Euroimmun

GABA$_B$

NMDAR
Challenges: Refining Phenotypes and Antibody Assays

- Sera from over 4,000 healthy and disease controls (schizophrenia, affective disorders, stroke, Parkinson disease, amyotrophic lateral sclerosis, personality disorder) tested for neuronal surface and intracellular-targeted antibodies

- NMDA
  - Seroprevalence similar in disease and healthy controls
  - 11% positive [IgM (6 %), IgA (5 %) and IgG (1%)]
  - Titres from 1:10 to 1:1,000

- Amphiphysin (2.0%), CASPR2 (0.9%), MOG (0.8%), GAD65 (0.5%), Ma2 (0.5%), Yo (0.4%) and Ma1 (0.4%), also with similar frequencies in disease and healthy controls

- Implications
  - Antibody testing needs to be interpreted in the appropriate clinical context
  - Standardization of assays/detection threshold

Challenges: Defining Specific Antigenic Targets and Pathogenesis

• VGKC antibodies lacking LGI1 and CASPR2
  – Creuzfeld Jacob disease
  – VGKC-complex antibodies (amongst others) are generated in abattoir workers after exposure to aerosolized porcine neural tissue
  – Likely reflects secondary antibody production against other parts of the VGKC complex

• More studies to prove antibody-mediated pathogenicity


Conclusion

• Exciting developments
  – Paradigm shift in the diagnostic approach of encephalitis
  – Important implications for epilepsy, psychiatry and cognitive sciences

• Challenges ahead
  – Pathogenesis, immunological mechanisms
  – Assay standardization
  – Treatment standardization