Auto-immune Encephalitis: An ever expanding field

SJH Immunology Laboratory Educational Meeting 04/11/15

Dr Caríosa Lee-Brennan
• Autoimmune Encephalitis

• Autoimmune Cerebellar Ataxia

• Paraneoplastic Antibodies
Auto-immune encephalitis

- Limbic Encephalitis
  - personality change/psychiatric symptoms
  - memory impairment
- Seizures
Auto-immune encephalitis

- "My tongue twisted when I spoke; I drooled and, when I was tired, let my tongue hang out of the side of my mouth like an overheated dog."

- "What I remember most vividly is the fear. Fear and anger."
Autoantibodies associated with Encephalitis

- NMDA Receptor
- LGI1
- Caspr2
- AMPA Receptor
- GABA-B & A Receptor
- Metabotropic Glutamate Receptor : mGluR5
- Glycine Receptor (GlyR)
- DPXX
- GAD65
- Dopamine 2 Receptor
- IgLON5
Beaumont Immunology Laboratory:

NMDAR antibody testing

VGKC antibody testing
NMDA, VGKC, Neuronal test numbers

- Neuronal Abs.
- NMDA Receptor Abs.
- Vol. Gated KC Abs
Euroimmun

- Mosaic BIOCHIP
- HEK293 transfected cells
- Serum & CSF
- NMDAR
- LGI1
- CASPR2
- AMPAR1
- AMPAR2
- GABABR
NMDAR encephalitis
NMDAR Encephalitis

- **Vitaliani et al 2005:**
  - Syndrome of encephalitis, psychiatric symptoms and hypoventilation in ovarian teratoma

- **Dalmau et al 2007:**
  - Detection of anti-NMDAR antibodies
Demographics

- Women: 80-90%
- Reported in all ages
  - 8 months-85 years *Titulaer et al 2013*
- Most commonly in age 18-35 years
- Males are usually < 12 or >45 years
- 20-60% have a tumour
Tumour distribution by age and sex
Tumour types

- Ovarian teratoma
  - 94% of tumours  \textit{Titulaer et al 2013}
  - Tumours show intense expression of NR2 subunit of the NMDAR
- Extraovarian teratomas
  - mediastinum, testis
- Other tumours
  - neuroblastoma, Hodgkin’s, sex cord-stromal tumour, SCC of lung, pancreas, thymic carcinoma, breast, ovarian
Clinical Features

Prodrome
- Agitation
- Psychosis
- Catatonia
- Memory deficit
- Speech reduction
- Abnormal movements
- +/- Seizures

Clinical Worsening
- Coma
- Hypoventilation
- +/- Dysautonomia

Clinical Improvement
Clinical Features

- **Prodrome:**
  - 70%
  - headaches, fever, vomiting, URT symptoms
  - Inflammatory event causing temporary or localised disruption of the blood-brain barrier
  - Allows antibodies to gain entry to the CNS
- Reported after vaccination
- Reported after Herpes Simplex Encephalitis (HSE)
Clinical Features

- Psychiatric Symptoms
  - Within 2-3 weeks
  - Anxiety, paranoia, delusions, agitation, bizarre behaviour, grandiosity, mania, hyper-religiosity
- Short term memory loss
- Loss of language
- Children
  - Temper tantrums, irritability, hyperactivity
Clinical Features

- Seizures
- Movement disorders
  - Tremor, writhing, rigidity, abnormal eye movements, abnormal posture, elaborate motions of arms and legs
  - More common in children
  - Atypical features: hemiparesis, cerebellar ataxia also commoner in children
Clinical Features

- Autonomic Dysfunction
  - Hyperthermia, tachycardia, hypertension, hypersalivation, bradycardia, hypotension, urinary incontinence, erectile dysfunction

- Hypoventilation requiring ventilation
Treatment & Outcomes

- Tumour removal
- Steroids, IVIg, Plasma exchange, Rituximab, cyclophosphamide, MMF

- Recovery or mild disease: 75-80%
- Relapse: 12-25%
- Mortality: 4-6%

- Prolonged recovery
VGKC-associated encephalitis
VGKC antibodies: Associated conditions

- Limbic encephalitis
- Acquired neuromyotonia
  - Peripheral nerve hyperexcitability
  - Muscle cramps & stiffness, slow relaxation, twitching
- Morvan’s Syndrome
  - Neuromyotonia, autonomic dysfunction, insomnia
LGI1 antibody-associated Disease

- Limbic encephalitis: amnesia, confusion, neuropsychiatric disturbance, seizures
- Hyponatraemia (SIADH)

- Males: 65%
- Age 30-80 (median 60)
- <20% tumour: thymoma, lung

*Irani et al Brain 2010*
Caspr2-associated disease

- Morvan’s Syndrome
  - Neuromyotonia
  - Autonomic dysfunction: sweating, cardiovascular instability, constipation, urinary complaints
  - Encephalopathy: confusion, hallucinations, agitation, infrequent seizures, insomnia
  - Neuropathic pain
  - Weight loss
  - Thymoma: 40%
  - Male: 85-93%
  - Age 19-80 years (median 57)

Caspr2-associated disease

- Neuromyotonia only
- Encephalitis only
- Cerebellar ataxia
  - 9/88 cases positive
  - Tremor, abnormal gait
  - Subacute or insidious onset
  - 1 patient also had encephalitis and was positive for VGKC antibodies

*Becker et al JNNP 2012*
Both LGI1 and Caspr2 antibodies
  - Encephalitis
  - Neuromyotonia
  - Neuropathic pain

*Klein et al 2013*
  - 26% VGKC positives were positive for LGI1 or Caspr2
  - Low positive VGKC antibodies were clinically significant

Contactin 2 antibodies
  - Found in 3 patients with Caspr2 antibodies and cardiovascular instability
  - Expressed in cardiac conduction tissue
GABAR encephalitis
GABA-B R encephalitis

- 16-77 years
- Male:Female 3:2
- Limbic encephalitis: Seizures, memory loss, confusion, Hallucinations, personality change
- Hofstberger et al 2013
  - Status epilepticus
  - Ataxia
  - Opsoclonus-myoclonus: rapid eye movements, twitching
GABA-B R encephalitis

- 50% Tumours
  - SCLC
  - Male
- Neurological symptoms respond to immunotherapy or cancer treatment
- Poorer prognosis
  - Presence of other antibodies: Amphiphysin, SOX1, Ri
  - Those with SCLC

Hoftberger et al 2013
GABA-A R encephalitis

- 6 patients
- 3-63 years, 5 males
- Encephalitis with refractory seizures and status epilepticus
- Hodgkin’s: 1 patient
- CSF & serum

- Low titre, Serum only:
  - other autoantibodies: GAD65, NMDAR, ANA
  - Encephalitis, stiff-person syndrome, opsoclonus-myoclonus
AMPAR encephalitis
AMPAR encephalitis

- 2/3 Female
- 7-92 years
- Encephalitis: memory loss, behaviour change, agitation
- Seizures less common
- Tumours: 50-70% (lung, breast, thymic carcinoma, thymoma, ovarian)
- Cerebral atrophy: 20%

Joubert B. et al JAMA Neurology 2015
mGluR5 encephalitis
mGluR5 antibody-associated disease

- Ophelia Syndrome
- Limbic encephalitis
  - Depression
  - Personality change
  - Memory deficits
  - Delusions, hallucinations
  - Seizures
- Myoclonus
- Hodgkin’s Lymphoma
GlyR encephalitis
Glycine receptor antibody-associated disease

- Age 1-75 years (median 50)
- 2/3 females
- Progressive encephalomyelitis
- Rigidity
- Myoclonus: Brief involuntary twitching
- Hyperekplexia: Pronounced startle responses
- Malignancy: uncommon
  - Thymoma, lymphoma, breast
DPXX encephalitis
DPXX encephalitis

- 4 cases
  - 2 males
  - 45-76 years
  - 3: prodromal diarrhoea and weight loss
  - Encephalitis

- 3 cases
  - PERM: progressive encephalomyelitis, rigidity and myoclonus
  - 2 had GIT symptoms
GAD65 encephalitis
GAD65 encephalitis

- Stiff-person syndrome
- Limbic encephalitis
- Cerebellar ataxia

- Tumours: lung, thymic

- Epilepsy
  - Young women
  - Non-malignant
Dopamine 2 (D2) receptor encephalitis
D2 receptor encephalitis

- 12 children
- Movement disorders
  - Dystonias, tremor, parkinsonism, chorea
- Agitation, anxiety, psychosis, sleep disorders
- Responds to immunotherapy but residual deficits seen

- Subset of patients with Sydenhams’ chorea
  - Rheumatic fever
IgLON5 encephalitis
IgLON5 encephalitis

- **Sabateur et al Lancet Neurol 2014**
  - 8 patients
  - 52-76 years
  - 5 females
  - Subacute/prolonged presentation: 6 months-12 years
  - Sleep disorders
    - Abnormal movements, OSA, stridor
    - Dysarthria, dysphagia, ataxia, chorea
  - No response to immunotherapy
  - 6 dead at time of publication
  - Neuronal loss, extensive deposition of hyperphosphorylated tau
Autoimmune Cerebellar Ataxia
Cerebellar ataxia

- Unsteady gait, falls, swaying
- Tremor
- Difficulty with rapid movements
- Inaccurate movement: pass-pointing
- Speech abnormalities
- Nystagmus: abnormal eye movements

- Paraneoplastic & non-paraneoplastic

- 12 antibodies: staining resembles a Gorgon’s head
### Autoimmune cerebellar ataxia

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Features</th>
<th>Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yo</td>
<td>Ataxia</td>
<td>Ovary, breast, uterus, fallopian tubes, cervix</td>
</tr>
<tr>
<td></td>
<td>Poor prognosis</td>
<td></td>
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<tr>
<td></td>
<td>Rare in men</td>
<td></td>
</tr>
<tr>
<td>Tr/DNER</td>
<td>Ataxia</td>
<td>Hodgkin’s Lymphoma</td>
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<tr>
<td></td>
<td>Cerebellar atrophy</td>
<td></td>
</tr>
<tr>
<td>mGlyR1</td>
<td>Ataxia</td>
<td>3/5: Hodgkin’s, prostate</td>
</tr>
<tr>
<td></td>
<td>Encephalitis</td>
<td></td>
</tr>
<tr>
<td>VGCC</td>
<td>Ataxia</td>
<td>SCLC, prostate, NHL, non-paraneoplastic</td>
</tr>
<tr>
<td></td>
<td>LEMS</td>
<td></td>
</tr>
<tr>
<td>PCA-2</td>
<td>Ataxia, encephalitis, neuropathy: non-specific</td>
<td>SCLC</td>
</tr>
<tr>
<td>Antibody</td>
<td>Features</td>
<td>Tumour</td>
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</tr>
<tr>
<td>Homer-3</td>
<td>Ataxia, encephalitis (1)</td>
<td>1/4 : lung</td>
</tr>
<tr>
<td>Sj/ITPR1</td>
<td>No response to steroids</td>
<td>None yet</td>
</tr>
<tr>
<td>CARP VIII</td>
<td>2 patients. Poor prognosis</td>
<td>Melanoma, ovary</td>
</tr>
<tr>
<td>PKC-gamma</td>
<td>Symptoms precede tumour x 2-3 months</td>
<td>2/2: Non-small cell lung, liver</td>
</tr>
<tr>
<td>Ca/ARHGAP26</td>
<td>MRI: progressive atrophy 50%: post-infection</td>
<td>1/6: Ovary</td>
</tr>
<tr>
<td>Nb/AP3B2</td>
<td>1 patient: ataxia,</td>
<td>None</td>
</tr>
<tr>
<td>GluRσ2</td>
<td>Ataxia, encephalitis (GluRe2) Associated with infection or vaccination</td>
<td>None</td>
</tr>
</tbody>
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Paraneoplastic neuronal antibodies
# Encephalitis associated with Paraneoplastic antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tumour</th>
<th>Associated conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma1</td>
<td>Breast, other tumours</td>
<td>Brainstem encephalitis</td>
</tr>
<tr>
<td>Ta/Ma2</td>
<td>Testicular</td>
<td></td>
</tr>
<tr>
<td>CV2/CRMP5</td>
<td>Small Cell lung Cancer (SCLC), thymoma</td>
<td>Polyneuropathy, optic neuritis, cerebellar degeneration</td>
</tr>
<tr>
<td>Hu</td>
<td>SCLC, neuroblastoma</td>
<td>Cerebellar degeneration, neuropathy</td>
</tr>
<tr>
<td>PCA2</td>
<td>SCLC</td>
<td>Polyneuropathy, LEMS, ataxia</td>
</tr>
<tr>
<td>ANNA3</td>
<td>SCLC</td>
<td>Neuropathy, cerebellar degeneration</td>
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Other paraneoplastic antibodies

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<thead>
<tr>
<th>Antibody</th>
<th>Disease</th>
<th>Tumour</th>
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</thead>
<tbody>
<tr>
<td>Yo</td>
<td>Cerebellar degeneration</td>
<td>Breast, ovarian</td>
</tr>
<tr>
<td>Ri</td>
<td>Opsoclonus-myoclonus, cerebellar degeneration</td>
<td>Breast</td>
</tr>
<tr>
<td>Amphiphysin</td>
<td>Stiff person syndrome</td>
<td>Breast, SCLC</td>
</tr>
<tr>
<td>GAD</td>
<td>Stiff person syndrome</td>
<td>Breast, SCLC, colon</td>
</tr>
<tr>
<td>MAG</td>
<td>Peripheral neuropathy</td>
<td>MM, Waldenstrom’s</td>
</tr>
<tr>
<td>VGCC</td>
<td>LEMS</td>
<td>SCLC</td>
</tr>
<tr>
<td>Tr1</td>
<td>Cerebellar degeneration</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Recoverin</td>
<td>Retinopathy</td>
<td>SCLC</td>
</tr>
<tr>
<td>SOX1</td>
<td>LEMS</td>
<td>SCLC</td>
</tr>
<tr>
<td>ZIC4</td>
<td>Cerebellar degeneration</td>
<td>SCLC</td>
</tr>
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Any Questions?