Acute immunology, temporal lobe epilepsy and other disorders

Ming Lim
Children’s Neurosciences, Evelina London Children’s Hospital, Kings Health Partner’s AHSC Clinical Neurosciences Laboratory, Oxford University.
Summary

• Adaptive and innate immune system in the brain
• Effects of neuro-inflammation on the brain
• Clinical syndromes in childhood autoimmune disease
• Auto-immune epilepsy?
Overview of immune system

**INNATE IMMUNITY**
- First line of defence
- Rapid action
- Not specific
- Limited diversity / flexibility
- No memory

- Phagocytes, DCs, NKs, mast cells, eosinophils, basophils
- Complement, cytokines, defensins

**ADAPTIVE IMMUNITY**
- Role in eliminating infection
- Time lag (days)
- Antigen specific
- Diverse and flexible
- Memory response

- Lymphocytes
- Antibodies, cytokines
Inflammation in the brain

Primary localized glial activation

Microglia

Astrocytes

The molecular effectors
Compromise of the blood brain barrier

Upregulation of the adaptive immune system

Lim 2011 *DMCN* 53: 298-304
Bhat & Steinman *Neuron* 65: 123-132
Immune surveillance in the brain

Interstitial fluid of CNS drains to CSF or is returned to blood via arachnoid villi

CNS parenchyma Blood Subarachnoid space Cribriform plate

Venous sinus Skull CSF

Dura mater Post-capillary venule

Choroid plexus Ventricle

CSF generated by choroid plexus in brain ventricle

Afferent lymphatic

Nasal mucosa

Soluble antigens from CNS are carried in CSF across the cribriform plate along afferent olfactory nerve rootlets (not shown) to the nasal mucosa

Deep cervical lymph node

CNS-derived antigens delivered to nasal mucosa can then drain to DCLNs via afferent lymphatics

CSF flow to spinal cord

Louveau et al 2015 Nature; 523: 337-341

Effects of inflammation in the brain

- Is inflammation beneficial?
- Immunobiology versus neurobiology
“Friend and foe”

- Initial response required to remove insult
  Streit 2002 *Glia* 40: 133-139

- Overactivation harmful
  Block et al 2007 *Nat Rev Neurosci* 8: 57-69

- Chronicity harmful
  Aktas et al 2007 *Arch Neurol* 64: 185-189

- Senescence of glia
  Streit 2004 *J Neurosci Res* 77: 1-8
Inflammation has a protective role

Schwartz & Kipnis 2002 *Trends Immunol* 23(11): 530-534
Cytokines can have dual roles

Cells can have dual roles

<table>
<thead>
<tr>
<th></th>
<th>M1 (Classic activation)</th>
<th>M2 (Alternative activation: wound healing)</th>
<th>M2 (Alternative activation: regulatory)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alternative terms</strong></td>
<td>Interferon-γ, TNF-α</td>
<td>Tissue repair</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td><strong>Stimulus</strong></td>
<td>Natural killer, T helper 1 lymphocytes.</td>
<td>IL-4, IL-13, TREM2?</td>
<td>IL-10, glucocorticoids</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td></td>
<td>Granulocytes responding to tissue injury, fungi and parasites (chitin), T helper 2 lymphocytes</td>
<td>Macrophage</td>
</tr>
<tr>
<td><strong>Macrophage products</strong></td>
<td>Pro-inflammatory cytokines: IL-1β, TNF-α, IL-6, IL-23, Oxygen free radicals</td>
<td>Extracellular matrix components</td>
<td>TGFβ1, IL-10</td>
</tr>
<tr>
<td><strong>Cell surface proteins</strong></td>
<td>MHC II?</td>
<td>Arginase 1</td>
<td>Mannose receptor (CD206)</td>
</tr>
<tr>
<td><strong>Functions</strong></td>
<td>Kill micro-organisms and other cellular targets. Phagocytosis</td>
<td>Phagocytosis</td>
<td>Inhibits inflammation</td>
</tr>
<tr>
<td></td>
<td>Present antigen to lymphocytes. May cause collateral damage to host cells.</td>
<td>Tissue repair/wound healing</td>
<td>Phagocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phagocytosis</td>
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<tr>
<td></td>
<td></td>
<td>Increases production/remodelling of extracellular matrix</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Mosser and Edwards (2008) [22]. TNF, tumour necrosis factor; IL, interleukin; TREM2, Triggering Receptor Expressed on Myeloid cells; MHC, major histocompatibility complex.

Boche et al., 2013 *Neuropathol Appl Neurobiol* 39(1):3-188
Microglial phenotypes....

- Multiple ‘activated’ roles (Phenotypes)
  - Cytotoxic (M1)
  - Repair and Regeneration (M2a)
  - Immunomodulation (M2b)

- Characteristic markers of phenotype
  - Related to function

Courtesy of Bobbi Fleiss
Centre for Brain Development, Kings College Hospital
Microglial phenotypes....

M1-Cytotoxic:
- COX2
- iNOS
- IL-6
- TNF-a

M2b
Immunomodulatory:
- SOCS3
- IL-1Ra
- IL-4R
- SphK1

M2a- Repair and Regeneration:
- IGF-1
- Gal3
- CD206
- Arg1

Courtesy of Bobbi Fleiss
Centre for Brain Development, Kings College Hospital
Effects of inflammation in the brain

- Is inflammation beneficial?
- Immunobiology versus neurobiology
Chemokines and Chemokine Receptors: Standing at the Crossroads of Immunobiology and Neurobiology

Richard M. Ransohoff1,*
1Neuroinflammation Research Center (Lerner Research Institute) and Mellen Center for MS Treatment and Research (Neurological Institute), Cleveland Clinic, Mail Code NC30, 9500 Euclid Avenue, Cleveland, OH 44195, USA
*Correspondence: ransohr@ccf.org
DOI 10.1016/j.immuni.2009.09.010
<table>
<thead>
<tr>
<th>Function</th>
<th>Examples</th>
</tr>
</thead>
</table>
| CNS development | - Phagocytic activity during neuronal/synaptic development likely represents ‘pruning’ of redundant neurons and connections  
- Development influenced by secretion of cytokines, neurotrophins and growth factors |
| Recognition of pathogens (innate immune function) | - Receptors (e.g. Toll-like receptors, TLRs) recognize evolutionarily conserved antigens on surface of pathogens known as pathogen-associated molecular patterns (PAMPs) such as the endotoxin lipopolysaccharide (LPS)  
- Similar mechanisms possibly also involved in response to extracellular protein accumulations (e.g. amyloid plaques) |
| Phagocytosis | Ingestion and destruction by digestive enzymes in lysosomes of:  
- Multiple types of damaged cells (e.g. infarct)  
- Neurons (e.g. neuronophagia, Wallerian degeneration, tract degeneration)  
- Micro-organisms (e.g. abscess)  
- Virally infected cells (e.g. herpes encephalitis)  
- Erythrocytes and haemoglobin breakdown products (e.g. haemosiderin) following haemorrhage |
| Antigen presentation | - Presentation of pathogens (e.g. in bacterial, fungal, viral infections) bound to MHC for activation of T lymphocytes  
- Possibly relevant also in autoimmune disease |
| Recognition of bound antibody (adaptive immune function) | - Respond to antibodies bound to pathogens (opsonization)  
- Possibly also relevant to autoimmune disease (e.g. demyelination, paraneoplastic syndromes) |
| Cytotoxicity | - Reactive oxygen species/respiratory burst (H₂O₂, NO)  
- Cytokines (e.g. IL, TNF, interferons, TGF, CSF)  
- Secretion of glutamate, aspartate |
| Extracellular matrix remodelling | - Proteases (MMPs degrade extracellular matrix) |
| Modulation of inflammation/immune responses | - Chemokines (attract other inflammatory cells)  
- CD200 receptor (CD200 secreted by neurons has anti-inflammatory role)  
- Interferon-γ (promotes further microglial activation) |
| Repair | - Removal of cell debris facilitates plasticity and synaptogenesis |
| Stem cells | - Regulation of stem cell proliferation (e.g. granule cell neurons of hippocampus) |
| Tumours | - Response to neoplastic cells, possible regulation of tumour cell proliferation |
| Lipid transport | - Secretion of lipoprotein particles which deliver lipids to neurons for maintenance of cell membranes and synapses, facilitating synaptic plasticity |
| Viral entry into CNS | - CCR5 and CD4 are receptors for entry of HIV into macrophages and hence into CNS |
| Support mycobacteria | - Permits intracytoplasmic survival of mycobacteria (e.g. tuberculosis) |
| Demyelination | - Myelin destruction/phagocytosis (e.g. multiple sclerosis) |

CNS, central nervous system; MHC, major histocompatibility complex; IL, interleukin; TGF, transforming growth factor; CSF, colony-stimulating factor; MMP, matrix metalloproteinase; HIV, human immunodeficiency virus; CCR5, C–C chemokine receptor 5.
Inflammation in the brain

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th1</td>
<td>MS, ADEM, Rassmussen encephalitis</td>
</tr>
<tr>
<td>Th2</td>
<td>SLE</td>
</tr>
<tr>
<td>B cell</td>
<td>MS, NMO, demyelination, autoimmune encephalitis</td>
</tr>
<tr>
<td>Innate</td>
<td>HLH, SLE, Behcet, Sarcoid</td>
</tr>
</tbody>
</table>
Anti neural-antibodies and CNS autoimmunity

Antibodies against neuronal surface antigens
- **VGKC** (LGI, CASPR2 and Contactin), AMPAR, GABA(A+B)R, **NMDAR**, Glycine R, D2R, DPPX

Antibodies against intracellular antigens
- Onconeural antibodies; **Hu**, Yo, Ri, CV2, amphipysin, **Ma2**.
- **GAD**

Vincent et al., 2011 *Lancet Neurol* 10(8):759-72
Clinical syndromes in CNS autoimmunity in children

- Limbic encephalitis
- Seizures
  - FBDS
  - PERM
  - Catastrophic/severe seizures
- Movement disorder
  - Encephalitis lethargica
- Neuropsychiatric
- Others
  - Cross over with peripheral syndromes
  - Demyelination

Lim & Gorman (In Press)
Case 1 15yr F

- GTCS
- 1/52 feeling unwell/rundown.
- Known to social services for violent episodes and regular cannabis use.
- Generalised +Rt Focal seizures. I+V for seizure control.
- Hallucination (auditory and visual), complaining of extreme pruritis, violent outbursts, delirious state.
- EEG slow wave Rt>Lt. Sharp wave Rt fronto-temporal parietal.
Case 1: progress
A treatable form of limbic encephalitis

Sub-acute onset of memory loss, seizures and personality change

Sometimes seizures or psychosis only

Often low plasma sodium

**VGKC-complex** antibodies often very high titre

<10% tumours

Most respond well to immunotherapies

Vincent et al., 2004 *Brain* 127; 701-12
Syndromes associated with antibodies to the VGKC-complex

- At least three accessory proteins; CASPR2, LGI1 and Contactin-2
  - CASPR2 found in patients with Morvan’s syndrome or neuromyotonia, many of whom have paraneoplastic, often thymomas.
  - LGI1 found in patients with medial temporal lobe seizures associated with limbic encephalitis. Without an associated tumour
    Irani et al., 2010 *Brain* 133(9):2734-48

- A distinct clinical syndrome – Faciobrachial dystonic seizures (brief facial grimacing and ipsilateral arm dystonia) – associated with antibodies to LGI1
  Irani et al., 2011 *Ann Neurol* 69(5): 892-900
**VGKC complex antigen identification in children**

<table>
<thead>
<tr>
<th>Antibody test</th>
<th>4/39</th>
<th>1/39*</th>
<th>0/39</th>
<th>0/39</th>
<th>0/39</th>
<th>0/39</th>
<th>2/39</th>
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<tbody>
<tr>
<td><strong>Hippocampal neurons</strong></td>
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<tr>
<td>LGI1</td>
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<td>CASPR 2</td>
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<tr>
<td>Contactin-2</td>
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<tr>
<td>ADAM 22</td>
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<tr>
<td>ADAM 23</td>
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<tr>
<td>KV 1.1, 1.2, 1.6 (B2)</td>
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<tr>
<td>NMDAR</td>
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</tbody>
</table>

Hacohen et al., 2015 *Neurology*. Aug 21 [Epub ahead of print]
Limbic encephalitis in children

- Haberlandt et al., 2011 *Arch Dis Child.* 96(2):186-91

  10 patients from 12 centres

  8 patients have antibodies

    3 patients had VGKC
    Hu, Ma, 3 GAD
Other CNS antibodies associated with limbic encephalitis in children

- **Glutamic acid decarboxylase (GAD)**
  - Younger and often only had seizures without the other limbic feature
  - None had tumours
  - CSF active (OLB Positive)
  - More chronic disease
  - Malter et al., 2010 *Ann Neurol* 67: 470-478

- **GABA (B) receptor**
  - Lancaster et al., 2010 *Lancet Neurol* 9: 67-76

- **GABA (A) receptor**
  - Multifocal encephalitis
  - Petit-Pedrol et al., 2014 *Lancet Neurol* 13(3):276-86
  - Pettingill et al., 2015 *Neurology* 84(12):1233-41.
Other CNS antibodies associated with limbic encephalitis in children

• **AMPA receptor**
  Lai et al., 2009 *Ann Neurol* 67: 470-78

• **Glycine receptor**
  Refractory epilepsy syndrome in children
  PERM rare
  Hutchinson et al., 2008 *Neurology* 71(16): 1291-2
  Carvajal-González et al., 2014 Brain. 137(Pt 8):2178-92

• **Thyroid Abs**
  Haberlandt et al., 2011 *Arch Dis Child* 96(2): 186-91
Range of paediatric VGKC positive patients

• VGKC antibodies in paediatric encephalitis presenting with status epilepticus
  Suleiman et al., 2011 *Neurology* 76; 1252-5

• Immune-mediated steroid-responsive epileptic spasms and epileptic encephalopathy associated with VGKC-complex antibodies.
  Suleiman et al., 2011 *Dev Med Child Neurol* 53(11); 1058-60.

• Elevated VGKC-complex antibodies in a boy with fever-induced refractory epileptic encephalopathy in school-age children (FIRES).
  Illingworth et al., 2011 *Dev Med Child Neurol* 53(11); 1053-7.

• VGKC-complex antibody mediated encephalitis presenting with psychiatric features and neuroleptic malignant syndrome - further expanding the phenotype.
  Iyer et al., 2012 *Dev Med Child Neurol* 54(6); 575-6

• A clinico-radiological phenotype of voltage gated potassium channel (VGKC) complex antibody mediated disorder presenting with seizures and basal ganglia changes.
  Hacohen et al., 2012 *Dev Med Child Neurol* 54(12); 1157-1159
Case 2

Presentation

6 weeks
NMDAR encephalitis in children and adolescents

- up to 40% <18
- Phenotype resembles that of the adults.
- Present in males
- Younger female patients are less likely to have tumors.
- Behavioral and speech problems, seizures and abnormal movement are common early symptoms.
- Dysautonomia and hypoventilation less frequent
- Good recovery

Florance et al., 2009 *Ann Neurol* 66: 11-18
Wright et al., 2015 *Arch Dis Child.* 100(6):521-6.
NMDAR encephalitis in children and adolescents- MRI features

Case 3

Courtesy of Dr Darshan Das
Kings College Hospital, London.

Damásio et al 2013
PERM syndromes and GlyR Abs

Brainstem - startle, oculomotor abnormalities
Spinal cord - muscle rigidity and stiffness
spasms, very painful
Autonomic – sweating, urinary retention,
tachycardia, other
Encephalopathy in some patients

• Inhibitory synaptic transmission mediated by GABA and glycine is critical for regulating motor neuron excitability in the brainstem and spinal cord
• Loss of this input result in CNS hyper excitability causing exaggerated startle, stiffness, and spasms of the axis and limbs.

Carvajal-González et al 2014 *Brain* 137(Pt 8):2178-92
Paediatric GlyR-Ab

- 6 female patients; median age 7.5 yrs (range 1-15yrs)
- Initial Presentation
  - Refractory focal seizures (2)
  - Cognitive/behavioural changes (4)
  - Tremor and gait abnormalities (2)
  - PERM (1)
- Clinical progress
  - Seizures (total 5)
  - Cognitive/behavioural changes (6)
- Diagnosis of encephalitis (3), auto-immune epilepsy (2) and PERM (1).

Gadian et al., (manuscript in preparation)
Mechanisms of antibody-induced pathology

- **Direct block**
- **Internalisation**
- **Complement-dependent lysis**
VGKC/LGI1 Ab IgG elicits epileptiform activity in the CA3 area of hippocampus in brain slices

Extracellular potentials recorded in the stratum lucidum of CA3 pyramidal cell layer with extracellular stimulation of mossy fibres

VGKC/Lgi1 IgG increases burst activity in CA3

Reduces no of failures to stimulation

Effects similar to dendrotoxin

Lalic et al., 2011 *Epilepsia* 52(1):121-31
Antibodies internalise NMDARs in hippocampal neurons and reduce NMDARs after injection into mice

Hughes et al., 2010 *J Neurosci*. 28;30(17):5866-75
NMDAR antibodies associated with minimal T cells
VGKC-complex antibodies associated with CD8 T cell infiltrates and perforin release

Bien et al., 2012 *Brain* 135(Pt 5):1622-38.
VGKC-complex antibodies associated with neuronal loss and APP deposits. NMDAR antibodies associated with no neuronal loss or deposits

Bien et al., 2012 *Brain* 135(Pt 5):1622-38.
Medium term outcome following immune encephalitis

28/48 patients presenting with autoimmune encephalitis had residual problems

Hacohen et al., 2013 *J Neurol Neurosurg Psychiatry*. 84(7):748-55
Treatment improves outcome in anti-NMDAR encephalitis

Early treatment improves long-term outcome in children with NMDAR-Ab encephalitis

80 children included from 34 studies

Complete recovery the mean time from onset to treatment was 14.9 days. Incomplete recovery who were treated at a mean of 21 days; p=0.002

No difference in follow-up time

Mean mRS was lower in the group treated less than 15 days (0.6) compared to those treated later (1.6, p=0.015)
Treatment improves outcome in paediatric autoimmune encephalitis

Table 4 Comparison of immunotherapy response and outcome in paediatric patients with antibody positive and antibody negative encephalopathy

<table>
<thead>
<tr>
<th></th>
<th>Antibody positive (n=21)</th>
<th>Antibody negative (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy received</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids only</td>
<td>17 (80%)</td>
<td>17 (63%)</td>
</tr>
<tr>
<td>IVIG only</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Corticosteroids + IVIG</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Additional PLEX</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Disease modifying drugs</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Immunotherapy response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable response</td>
<td>16 (94%)</td>
<td>16 (94%)</td>
</tr>
<tr>
<td>Definite response</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>DEF</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Modified Rankin scale score (for children) at nadir</td>
<td>4.5±0.60</td>
<td>4.5±0.58</td>
</tr>
<tr>
<td>Modified Rankin scale score (for children) at follow-up</td>
<td>1.8±0.75</td>
<td>1.6±0.84</td>
</tr>
<tr>
<td>Ongoing problems (further details in figure 3)</td>
<td>15 (71%)</td>
<td>13 (48%)</td>
</tr>
<tr>
<td>10/14 (71%) untreated</td>
<td>3/4 (75%)</td>
<td>13 (48%)</td>
</tr>
<tr>
<td>18/34 (52%) treated</td>
<td>12/17 (70%)</td>
<td>6/17 (35%)</td>
</tr>
</tbody>
</table>

No significant difference was seen in immunotherapy response and outcome. Antibody positive patients were more likely to receive PLEX and second line immunotherapy. IVIG, intravenous immunoglobulins; PLEX, plasma exchange.

Hacohen et al., 2013 J Neurol Neurosurg Psychiatry. 84(7):748-55
Long term sequelae following autoimmune encephalitis

Esseveld et al., 2012
*Am J Psychiatry* 170 21-2

Finke et al., 2013
*Ann Neurol.* 74(2):284-96
Patient CSF reduces dendritic density of GluN2B and GluN2A
Prevents LTP of glutamate synapses

Mikasova 2012 Brain 135; 1606–1621
Febrile infection-related epilepsy syndrome (FIRES)
Baalen et al., 2010 *Epilepsia* 51(7); 1323-1328

- Idiopathic catastrophic
  Baxter et al., 2003 *Seizure* 12; 379-87
- Devastating epileptic encephalopathy in school age children (DESC)
  Mikaeloff et al., 2006 *Epilepsy Res* 69; 67-69
- Acute encephalitis with refractory, repetitive partial seizures (AERRPS)
  Sakuma et al., 2010 *Acta Neurol Scand* 121(4):251-6

Previously well
Febrile prodrome followed by encephalopathy and fulminant seizures
Refractory seizures (not invariable)

Acute encephalopathy with inflammation-mediated status epilepticus

Nabbout et al., 2011 *Lancet Neurol*. 10(1); 99-108
Nabbout 2012 *Epilepsia* 2012 53 Suppl 4; 58-62
Rasmussen Encephalitis

- Localised form of inflammation and focal refractory seizures
- Glial activation and cytotoxic T cells infiltration
- Immunomodulation and epilepsy surgery
  - Tacrolimus improves motor and cognition but no effect in seizures

Bien et al., 2005 *Brain* 128(3): 454-71
Epileptic inflammation

Primary localized glial activation

The molecular effectors
Compromise of the blood brain barrier

Upregulation of the adaptive immune system

Vezzani et al., 2011 *Nat Rev Neurol* 7(1): 31-40
Beghi and Shorvon 2011 *Epilepsia* 52(Suppl 3): 40-44
Impaired inhibitory neurotransmission
→ Hyperexcitability and -function of principal neurons

Impaired excitatory neurotransmission
→ Hypoexcitability and -function of principal neurons

Meltzer et al., 2015 *Front Neurol* 6:171
Autoimmune Epilepsy

Clinical Characteristics and Response to Immunotherapy

Amy M. L. Quek, MBBS; Jeffrey W. Britton, MD; Andrew McKeon, MD; Elson So, MD; Vanda A. Lennon, MD, PhD; Cheolsu Shin, MD; Christopher J. Klein, MD; Robert E. Watson Jr, MD, PhD; Amy L. Kotsenas, MD; Terrence D. Lagerlund, MD; Gregory D. Cascino, MD; Gregory A. Worrell, MD, PhD; Elaine C. Wirrell, MD; Katherine C. Nickels, MD; Allen J. Aksamit, MD; Katherine H. Noe, MD; Sean J. Pittock, MD

- Patients seen in immunology clinic
- Antibody positive in 90%
  - VGKC primarily
- Initially refractory seizures
- Generally good outcome after immunotherapy

<table>
<thead>
<tr>
<th>Table 3. Epilepsy Outcome</th>
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<tbody>
<tr>
<td>Outcome</td>
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<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Immunotherapy for epilepsy (n = 27)</td>
</tr>
<tr>
<td>Duration of follow-up, mo, median (range)</td>
</tr>
<tr>
<td>Seizure freedom</td>
</tr>
<tr>
<td>Duration of seizure freedom, mo, median (range) [IQR]</td>
</tr>
<tr>
<td>Seizure freedom ≤3 mo after immunotherapy</td>
</tr>
<tr>
<td>Seizure freedom &gt;3 mo after immunotherapy</td>
</tr>
<tr>
<td>Seizure improvement</td>
</tr>
<tr>
<td>No change</td>
</tr>
<tr>
<td>Resolved after cancer detected and treated</td>
</tr>
<tr>
<td>Recommended but declined</td>
</tr>
</tbody>
</table>
Antibodies in epilepsy

235 follow-up and 181 new onset epilepsy patients screened plus 148 controls

11%* of patients had antibodies to one or more antigen

Paediatric epilepsy cohorts

Dutch and Australian cohort of children with first onset seizures

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy (no. of patients)</td>
<td>35</td>
<td>255</td>
<td>290*</td>
</tr>
<tr>
<td>Controls (no. of patients)</td>
<td>11</td>
<td>169</td>
<td>180</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>424</td>
<td>470</td>
</tr>
</tbody>
</table>

*N=114 published in Suleiman & Wright et al., 2013 *Epilepsia* 54(12):2091-100
Autoimmune epilepsy?

<table>
<thead>
<tr>
<th>Table I: Clinical and other features suggestive of autoimmune encephalitis in patients with seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
</tr>
<tr>
<td>Focal seizures, particularly focal motor and focal dysexecutive, secondary generalized seizures*</td>
</tr>
<tr>
<td>Seizure clusters: status epilepticus</td>
</tr>
<tr>
<td>Seizures and epilepsy of ‘unknown’ cause</td>
</tr>
<tr>
<td>Refractory seizures</td>
</tr>
<tr>
<td>Associated features: encephalopathy, movement disorders, neuropsychiatric symptoms, cognitive or memory impairment</td>
</tr>
<tr>
<td>History of other autoimmune diseases (personal or family)</td>
</tr>
<tr>
<td><strong>Imaging and other investigations</strong></td>
</tr>
<tr>
<td>Positive CSF findings suggestive of inflammation (pleocytosis, elevated neopterin, oligoclonal bands)</td>
</tr>
<tr>
<td>Inflammatory MRI changes of high T2 or FLAIR signal in medial temporal structures, cortical or subcortical areas, as well as cerebellum and basal ganglia</td>
</tr>
<tr>
<td>Focal (or multifocal) electrographic changes including slowing and/or epileptiform activity, particularly involving temporal lobe(s)</td>
</tr>
<tr>
<td>Histopathological findings compatible with inflammation (such as lymphocytic infiltrates) on biopsy</td>
</tr>
<tr>
<td>Positive cell-surface neuronal autoantibodies (serum or CSF)</td>
</tr>
<tr>
<td><strong>Treatment response</strong></td>
</tr>
<tr>
<td>Resistance to conventional antiepileptic drugs</td>
</tr>
<tr>
<td>Response to immunotherapy (including steroids, immunoglobulin, and immunosuppressive agents)</td>
</tr>
<tr>
<td>No other explanation</td>
</tr>
</tbody>
</table>

*Generalized seizures alone are less likely to be associated with autoimmune encephalitis. CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery.

Suleiman and Dale 2015 *Dev Med Child Neurol* 57(5):431-40
What do we know?

- Morbidity is significant
- Immune mediated/triggered but not sustained
  - Particularly in children and part of infectious aetiology
- Need for rapid diagnosis and treatment
- Other factors that can improve outcome
  - MDT
  - Understanding biology further to harness better function
The role of immunotherapy maybe beyond immune suppression

Zito and Scheuss 2009
The effects of antibodies on immune system

• Activation of microglial N-Methyl-D aspartate receptors Triggers inflammation and neuronal cell death
  – Kaindl et al., 2012 *Ann Neurol* 72:536–549

• N-methyl-D-aspartate receptor (and other) antibodies interacts with microglia?

UK & Ireland Childhood CNS Inflammatory Demyelination Working Group

Daniel Carranza Roja
Hock Sin Heng
Yaiza Hernandez
Georgios Niotakis
Rahul Singh

Angela Vincent
Bethan Lang
Patrick Waters
C. Buckley
M. Leite

Yael Hacohen
Sukhvir Wright
M. Woodhall
L. Jacobs
Linda Gardiner
N-methyl-D-aspartate receptor antibodies interacts with microglia in-vitro

Gadian, Lim, Fleiss and Gressen (Unpublished observations)
N-methyl-D-aspartate receptor antibodies upregulates the regenerative M2a phenotype?

M1-Cytotoxic: ↔ COX2 ↔ iNOS

M2b
Immunomodulatory: ↓ SOCS3

M2a- Repair and Regeneration:
↑ CD206
↑ Arg1

Gadian, Lim, Fleiss and Gressen (Unpublished observations)
Pathogenic role of autoantibodies

IgGs/autoantibodies can target CNS

Presence of autoantibody

IgGs are at target sites in CNS

Autoantigen/antibody as part of the disease
Working out the biology of receptors

Paoletti et al., 2013 *Nat Rev Neurosci* 14(6):383-400
Paoletti et al., 2013 *Nat Rev Neurosci* 14(6):383-400
CLINICALLY SUSPECTED AUTOIMMUNE CNS DISORDER

1. Acute or sub acute (<12 weeks) onset of a recognisable syndrome:
   Antibody specific presentation (NMDAR, GlycineR, D2R, DPPX)
   Limbic encephalitis
   Facial Brachial Dystonic Seizures

2. If i) partial syndrome or ii) encephalopathy with either seizures, movement disorder, neuropsychiatric or cognitive dysfunction one additional supportive clinical feature required:
   Previously normal
   Viral or fever prodrome
   History of autoimmunity
   Or evidence of CNS inflammation

INVESTIGATIONS

START TREATMENT
Once excluded infective and life-threatening metabolic causes

Maintenance immunotherapy
- 3-6 months
  Oral steroids 3-6 months
  +/- 4 weekly IVIG for 6 months
  Tailor according to antibody

Maintenance immunotherapy
- 6-12 months
  Oral Steroids
  +/- Mycophenolate or Azathioprine
  Tailor according to antibody

Maintenance immunotherapy
- 1-2 years
  Oral Steroids (often with steroid sparing agent)
  Using 2nd line acute agents for longer period

EEG

Imaging studies
- MRI and MRA
- MRS, PET
- Exclude tumours

CSF studies
- Microscopy and infective investigations
- Oligoclonal bands and IgG Index
- Antibody studies (store and perform following discussion)
- Neopterins

ACUTE TREATMENT 1st line immunotherapy
High dose intravenous steroids 3-5 days then oral steroids IVIG

ACUTE TREATMENT 1st Line immunotherapy
Plasma Exchange

ACUTE TREATMENT 2nd line immunotherapy
Cyclophosphamide or Rituximab

IF NO RESPONSE EVALUATE DIAGNOSIS AGAIN
Infection and auto-immunity in schizophrenia

Increased risk after infection

Increased risk of autoimmunity in patients

Benros et al., 2012 *Ann N Y Acad Sci.* 1262:56-66
HLA associations in schizophrenia

- Common disease, common variant model.
- A region of association of common SNPs with schizophrenia was identified at the MHC region.
- Pathway analysis of GWAS: pathways consistently found relate to metabolism of glutamate, the process of apoptosis, inflammation, and immune system.

Stefansson et al., 2009 *Nature* 460(7256): 744–747
Jia et al., 2010 *Schizophr Res.* 122(1-3):38-42
Innate system upregulation in schizophrenia

- Activated microglia in post-mortem studies.
- Increased blood brain-barrier permeability.
- Elevated levels of IL6 and altered IL2/IFN-g system regulation.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Observations in schizophrenia</th>
<th>Clinical associations in schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>Increased levels</td>
<td>Age of onset [101]</td>
</tr>
<tr>
<td></td>
<td>(also lower levels noted in some studies)</td>
<td>Bizarre behavior [99]</td>
</tr>
<tr>
<td></td>
<td>[20,22,25,26,28,29,98]</td>
<td>Formal thought disorder [99]</td>
</tr>
<tr>
<td>Soluble IL-2 receptor</td>
<td>Increased levels [22]</td>
<td>Positive symptoms [28]</td>
</tr>
<tr>
<td>IL-4</td>
<td>Increased CSF levels [30]</td>
<td>Relapse prone [100]</td>
</tr>
<tr>
<td>IL-6</td>
<td>Increased levels [18]</td>
<td>Decrease after treatment [28]</td>
</tr>
<tr>
<td>Soluble IL-6 receptor</td>
<td>Increased levels</td>
<td>Especially in younger patients [24]</td>
</tr>
<tr>
<td>IL-10</td>
<td>Increased levels [29]</td>
<td>Acute psychosis [23,24]</td>
</tr>
<tr>
<td>TNFα</td>
<td>Increased levels [6,98]</td>
<td>Poor prognosis [102]</td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>Decreased mitogen stimulated levels [27]</td>
<td>Lower in positive symptoms [102]</td>
</tr>
</tbody>
</table>

|                      |                                                     |
| IL, interleukin; TNF, tumor necrosis factor; CSF, cerebrospinal fluid. |

Autoimmunity and neuropsychiatric disorders

- Patients present prominent psychiatric alterations, among other neurological manifestations, usually responsive to immunotherapy

- Autoantibodies against synaptic receptors and trans-synaptic proteins are found

<table>
<thead>
<tr>
<th>Target Antigen</th>
<th>Primary Symptoms</th>
<th>Other Manifestations</th>
<th>Associated Tumor(s)</th>
<th>Demographic Data</th>
<th>Outcomes With Proper Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDA receptor</td>
<td>Psychosis, seizures, autonomic instability, dyskinesias</td>
<td>Viral prodrome, changes in speech, cataleptic features, hypoventilation</td>
<td>Ovarian teratoma*</td>
<td>75% women; 35% children and adolescents</td>
<td>75%-80% substantial improvement or full recovery</td>
</tr>
<tr>
<td>AMPA receptor</td>
<td>Memory loss, confusion, agitation, seizures</td>
<td>Psychotic symptoms, affective changes</td>
<td>Breast or lung cancer, thymoma</td>
<td>Predominates in women, ages 50–70</td>
<td>Most improve; frequent relapse</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; receptor</td>
<td>Seizures, memory loss, confusion</td>
<td>Hallucinations, paranoia, odd behaviors</td>
<td>Small-cell lung cancer</td>
<td>Either gender, middle-aged</td>
<td>~50% improve</td>
</tr>
<tr>
<td>LGI1</td>
<td>Amnesia, seizures, confusion, disorientation</td>
<td>Autonomic dysfunction, apathy/irritability, hypotension</td>
<td>Rare, thymoma</td>
<td>~2:1 male:female, middle-aged</td>
<td>~80% full recovery or mild deficits</td>
</tr>
<tr>
<td>Caspr2</td>
<td>Neuropathy, dysautonomia, confusion, insomnia</td>
<td>Amnesia, seizures, neuropathic pain, weight loss</td>
<td>Rare, thymoma</td>
<td>~4:1 male:female, middle-aged</td>
<td>~80% substantial improvement</td>
</tr>
</tbody>
</table>

Autoimmunity and neuropsychiatric disorders

Presence of autoantibodies against brain, brain structures and receptors

Table 1  Autoantibodies detected in people with schizophrenia compared with controls

<table>
<thead>
<tr>
<th>Autoantibody to</th>
<th>Finding</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Significantly higher</td>
<td>51,63,64,112,113</td>
</tr>
<tr>
<td>Brain septal region</td>
<td>No difference</td>
<td>65</td>
</tr>
<tr>
<td>Brain lipids</td>
<td>No difference</td>
<td>67</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Significantly higher</td>
<td>61</td>
</tr>
<tr>
<td>Gangliosides</td>
<td>No difference</td>
<td>68</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>No difference</td>
<td>66</td>
</tr>
<tr>
<td>Cell nuclei</td>
<td>Significantly higher</td>
<td>76, 78</td>
</tr>
<tr>
<td>Lymphocyte nuclei</td>
<td>Significantly higher</td>
<td>120</td>
</tr>
<tr>
<td>DNA</td>
<td>Significantly higher</td>
<td>77</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>None detected</td>
<td>78</td>
</tr>
<tr>
<td>Heat shock proteins</td>
<td>Significantly higher</td>
<td>121</td>
</tr>
<tr>
<td>Gastric parietal cells</td>
<td>Higher frequency</td>
<td>79</td>
</tr>
<tr>
<td>Platelets</td>
<td>Significantly higher</td>
<td>124</td>
</tr>
<tr>
<td>Neurotransmitter receptors</td>
<td>Significantly higher</td>
<td>70, 72-75</td>
</tr>
</tbody>
</table>

Jones et al., 2005  *Immunol Cell Biol*  83(1):9-17

Tanaka et al., 2003  *Neuroimmunol*  141(1-2):155-64.
Autoimmunity and neuropsychiatric disorders

  One small study screened NMDA receptor and VGKC antibodies in first psychotic episode
  Almost 9% (4/46) had autoantibodies, exhibiting no differentiating clinical features from other psychotic patients

- Irani et al., 2010 *Brain* 133(Pt 6):1655-67
  8% had initial psychiatric symptoms

- Hacohen et al., 2013 *J Neurol Neurosurg Psychiatry*. 84(7):748-55
  Antibody positive 62%; Antibody negative 52%
  1 had isolated psychiatric presentation

- Case reports describing these autoimmune encephalitis with isolated neuropsychiatric manifestations
  Iyer et al., 2012 *Dev Med Child Neurol* 54(6):575-6
Immune neuropsychiatric disorders

• Rarely occur in isolation
  • Part of a wider encephalopathy
  • Symptoms can predate for a while

• Primary or secondary

• Paraneoplastic on adults and less so in kids

• Start treatment before results
  • Need to treat early and long for best outcome

• Aetiological or still causing a problem?