Brains on Fire – Autoimmune causes of psychosis

Dr Belinda Lennox
Department of Psychiatry,
University of Oxford
Belinda.lennox@psych.ox.ac.uk

RCPsych Brighton 16th
October 2014
Overview

• The new disorders of antibody mediated encephalitis – psychiatric relevance
• Prevalence of pathogenic antibodies in psychosis
• Early experience and challenges of treating patients with psychosis with immunotherapy
New disorders antibody mediated encephalitis

- Voltage Gated Potassium Channel complex (LGI1, CASPR2, contactin-2) 2001
- N-Methyl-D-aspartate receptor (NMDA) 2008
- AMPA receptor 2009
- GABA-B 2008
- Glycine receptor 2012
- D2 receptor 2013
- GABA-A receptor 2014
Neuronal cell surface antibodies = pathogenic
Subacute amnesia
Seizures,
Hallucinations,
behavioural change,
sleep impairment, depression
Hyponatraemia
Responsive to immunotherapy


$r^2=0.58; \ p=0.053$

Improvement in mean memory scores (percentile change)

Fall in VGKC antibody

(% fall between first and second neuropsychology testing)

NMDA-receptor encephalitis:

- Progressive life threatening limbic encephalitis,
- Fits, cognitive impairment, autonomic instability, coma and dystonic movement disorder
- 20-50% paraneoplastic (ovarian teratomas)
- 66-80% women, age 5-80 (mean 23)
- 1% all admissions to ITU

Psychosis common as an early feature

Irani et al Brain 2010
Better outcome with first and second line immunotherapy

Titulaer et al Lancet 2013
NMDA dysfunction as a model for schizophrenia

Pathology

Genes

ketamine

Glantz and Lewis  
Arch Gen Psych 2000

Harrison and Weinberger Mol Psych 2005
Prevalence of pathogenic antibodies in first episode psychosis
First episode psychosis cohort

Serum collected prospectively from 46 patients on entry to Early Intervention Psychosis service.

Follow up for 3 years where possible.

Screened for NMDAR and VGKC antibodies.

Patients with antibodies seen retrospectively by neurologist.
3 of 46 patients with first episode psychosis had pathogenic antibodies, prevalence 6.3% (1.9-16.5) (Zandi et al J Neurol 2011)

- All three of the patients have DSMIV schizophrenia.

- None of the patients had developed further neurological symptoms or signs. Normal MRI, negative paraneoplastic screen, no other autoimmune disorder

- None of the group as a whole developed typical autoimmune encephalitis or other neurological diagnosis.

- 2 had NMDAR antibodies (score 2, score 1.5).
- 1 had VGKC-complex antibodies (1435 pM; normal<100).
Do patients with psychosis and antibodies respond to treatment with immunotherapy rather than antipsychotics?
No difference in Ab scores between encephalitis and psychosis. Significant drop in level after treatment.
Atypical patients lower mRs to start, still respond to treatment

p = 0.014

p = <=0.001

p = 0.009

Morris et al Neurology 2014
Neurolological assessment and treatment needed
Barriers to change: Psychiatric

• “We don’t do blood tests”
• “We don’t see patients”
• “We don’t believe it”
• “If there’s a cause then it’s not schizophrenia”
Barriers to change: Neurological

• “Psychosis doesn’t warrant treatment”
• “Patients are too difficult to manage in neurology ward”
• “It’s psychiatric (ie not a proper brain disorder)”
The nature of ‘psychiatric’ disease has evolved

Categories of illness (from annual report of St Lawrence's Hospital, 1877)

<table>
<thead>
<tr>
<th>Cause</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moral</strong></td>
<td></td>
</tr>
<tr>
<td>Domestic trouble</td>
<td>3</td>
</tr>
<tr>
<td>Religious excitement</td>
<td>8</td>
</tr>
<tr>
<td>Business and pecuniary</td>
<td>4</td>
</tr>
<tr>
<td>Mental anxiety and worry</td>
<td>8</td>
</tr>
<tr>
<td>Fright and various shocks</td>
<td>3</td>
</tr>
<tr>
<td><strong>Physical</strong></td>
<td></td>
</tr>
<tr>
<td>Intemperance</td>
<td>8</td>
</tr>
<tr>
<td>Accident and injury</td>
<td>1</td>
</tr>
<tr>
<td>Puerperal</td>
<td>5</td>
</tr>
<tr>
<td>Brain disease and general paralysis</td>
<td>6</td>
</tr>
<tr>
<td>Brain disease with epilepsy</td>
<td>10</td>
</tr>
<tr>
<td>Other forms of brain disease</td>
<td>4</td>
</tr>
<tr>
<td>Sunstroke</td>
<td>2</td>
</tr>
<tr>
<td>Hereditary</td>
<td>7</td>
</tr>
<tr>
<td>Congenital</td>
<td>1</td>
</tr>
<tr>
<td>Unascertained</td>
<td>27</td>
</tr>
</tbody>
</table>
Next steps

• Blinded RCT of immunotherapy in those with psychosis and antibodies
• Further discovery science – what’s causing the other 90%?
• System change in mental health/neurological services to enable detection and treatment
Who to test

- Acute onset paranoid psychosis
- Psychosis with prodromal illness (fever, headaches, malaise)
- Psychosis with cognitive impairment (disorientation, poor recall)
- Psychosis with movement disorder (orofacial dykinesia, catatonia)
- Adverse reaction to antipsychotics, ?NMS (collapse, blood pressure drop)
What to test

• Send serum for: NMDAR and VGKC abs (clinical immunology request form)

• Also test: ANA, CRP, ESR, FBC, U+E (low sodium in VGKC abs)

• If strong suspicion: EEG (if suggestive of encephalopathy would support early treatment)

• MRI head (medial temporal hyperintensity would support early treatment)
Acknowledgements

• All 37 EI teams and PIs on MRC PPIP study
• Professor Angela Vincent, Dr Sarosh Irani, Dr Camilla Buckley, Dr Ester Coutinho, Dr Katrina Morris
  Neuroimmunology Group, University of Oxford
• Prof. Peter Jones, Dr Julia Deakin,
  Department of Psychiatry, University of Cambridge
  CAMEO, Cambridgeshire and Peterborough NHS Foundation Trust
• Dr. Alasdair Coles, Dr Mike Zandi, Dr Amanda Cox
  Therapeutic Immunology Group, University of Cambridge
  Cambridge University Hospitals NHS Foundation Trust
• Funding support National Institute for Health Research, Medical Research Council NIHR CRN Mental Health