Autoimmune encephalitis – what do psychiatrists need to know

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Overview

• Autoimmune encephalitis - psychiatric aspects
• Clinical relevance of antibodies in psychiatric presentations
• Who to test
• What to do
Potential psychiatric relevance for all identified neuronal cell surface antibodies:

• Voltage Gated Potassium Channel complex (LGI1, CASPR2, contactin-2) 2001
• N-Methyl-D-aspartate (NMDA) 2007
• Glycine 2008
• AMPA 2009
• GABA-B 2013
• GABA-A 2014
• D2 2014
Neuronal cell surface antibodies = pathogenic
VGKC complex antibody encephalitis – a neuropsychiatric syndrome

Subacute amnesia
Seizures
Hallucinations
Behavioural change
Sleep impairment
Depression
Autonomic dysfunction
Hyponatraemia
Faciobrachiodystonic seizures
Neuromyotonia
Responsive to immunotherapy


$\text{r}^2 = 0.58; \ p = 0.053$

Improvement in mean memory scores (percentile change) vs. Fall in VGKC antibody (% fall between first and second neuropsychology testing)
Evidence for VGKC disturbance in schizophrenia

CASPR2 mutations associated with psychosis, autism, refractory seizures, mental retardation, neuromyotonia

Hyponatraemia associated with schizophrenia pre antipsychotics (Rowntree Archives of Internal Medicine 1923).

Up to 10% those with chronic schizophrenia

Effect of lithium and anticonvulsants
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 of NMDAR ab encephalitis.

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

Titulaer et al. Lancet 2013
‘Dementia Praecox and Paraphrenia ‘ Emil Kraepelin 1916

‘a seizure is not very infrequently the first sign of the approaching disease’ in 16% of observed series

‘distortion of the corners of the mouth, irregular movements of the tongue and lips’

‘Blood pressure is as a rule lowered; it fluctuates however, considerably. Respiration shows many irregularities’

‘consciousness is for the most part somewhat clouded in catatonic morbid states sometimes even very considerably’
Are NMDAR and VGKC complex abs relevant in people with psychosis without other symptoms of encephalitis?
Growing awareness

- National psychosis screening study - MRC PPiP study 230 FEP - 6.1% v controls 1%
- Joint encephalitis clinic national referrals (typical cases) 16 NMDAR, 30 VGKC
- Referrals from psychiatric services through ad hoc screening (atypical cases) – NMDAR 30, VGKC 7
Antibody positive patients not clinically distinct from other patients with psychosis
• What about treatment response to immunotherapy?
20 F VGKC

- 4 months abrupt onset insomnia, persecutory delusions, delusions reference, depressed mood.
- Thought disordered, poor recall
- Treated with Risperidone then Olanzapine plus citalopram. No improvement. Memory worsening
- U+E, MRI, EEG, CT chest all NAD
- Rising titre VGKC abs 529 → 805
Treatment

- Stopped olanzapine
- IVIG 2g/kg infusion 3/7 + methylpred 1g
- Steroids 40mg 3/12 then reduce and stop
- Rapid sustained improvement psychosis after 4/52. voluntary work
- Memory and mood improved after 4/12. back to college
- Discharged
26 F NMDAR

- Inpatient ‘1\textsuperscript{st} episode psychosis’
- 1 month confusion, paranoid delusions, auditory hallucinations, insomnia, agitated, catatonic, posturing
- 2 days antipsychotics, stopped.
- Disorientated, poor recall, perseverative, poor frontal function (verbal fluency, proverb interpretation)
- MRI normal
- EEG non specific frontal slow waves at times
Treatment

- Steroids, plasma exchange
- Very disruptive on neurology ward. Required ‘specialling’
- Memory and psychosis improved after 2 weeks
- Back at work after 2 months
- Relapse at 8 months. Further steroid and plasma exchange, further response
- Maintained on mycophenylate mofetil
- No antipsychotics
Patients with psychosis respond in the same way as those with encephalitis (Morris et al 2014)
Treatment response to immunotherapy and not to antipsychotics in patients with NMDAR ab psychosis (n=18) (Zandi et al 2014)
Screening of people with acute psychosis for antibodies (n=c. 2461). First Consent: clinical assessment & venepuncture. Stop when 160 antibody positive cases identified, 80 patients randomised or 1st endpoint reached.

Screening of c. 160 antibody-positive people with acute psychosis for eligibility to trial. Second Consent: to participate in a blinded trial of immunotherapy. (Any antipsychotic treatment continues). Stop when 80 patients randomised or 1st endpoint reached.

Randomise 80 eligible patients

Immunotherapy (n=40)
IVIG on days 1-4 and 1g rituximab on days 7-10 and 14 days later (& antipsychotic treatment as usual)

Placebo immunotherapy (n=40)
Placebo infusions (& antipsychotic treatment as usual)

Patient withdrawals (up to 12 per arm will not disrupt power)

Month 12: END. primary outcome measure: time to sustained remission over 6 months, as per the Andreasen 2005 criteria.
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, or ?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)
Neurological treatment

- **Induction of remission:** 3 days of methylprednisolone (500-1000mg) and either plasma exchange, or IVIG

- **Maintenance of remission:** either (1) steroids alone; (2) steroids with a steroid-sparing agent, such as azathioprine or mycophenolate mofetil; (3) rituximab.
Psychiatric treatment

• Symptomatic treatment only
• Care with antipsychotics and plasma exchange – rebound arousal (amisulpiride least plasma bound).
• Need liaison psychiatry closely involved
• Mental health nursing expertise in general hospital
• Taper and stop antipsychotics when better
Autoimmune encephalitides are true neuropsychiatric disorders. They do not respect DSM

6% cases first episode psychosis may be caused by antibodies

Some patients respond to treatment with immunotherapy and not antipsychotics. We need blinded RCT of immunotherapy in those with psychosis and antibodies

Neurology and psychiatry need to re-unite to advance understanding and treatment.
Acknowledgements

• Prof. Alasdair Coles, Dr Mike Zandi  
  Therapeutic Immunology Group, University of Cambridge
• Prof Angela Vincent, Dr Camilla Buckley, Dr M. Isabel Leite, Dr Ester Coutinho, Dr Sarosh Irani, Dr Leslie Jacobsen  
  Neuroimmunology Group, NDCN, University of Oxford
• Dr Emma Palmer-Cooper, Prof Paul Harrison  
  Department of Psychiatry, University of Oxford
• Prof. Peter Jones, Dr Julia Deakin  
  Department of Psychiatry, University of Cambridge

• 37 PIs and CRN: Mental Health staff across England

• Funding support: National Institute for Health Research, Medical Research Council, Stanley Medical Research Institute.