Antibodies and Psychosis – What do Psychiatrists need to know

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Overview

• The new disorders of antibody mediated encephalitis – psychiatric relevance
• Prevalence of pathogenic antibodies in first episode psychosis
• Clinical and demographic characteristics of patients with psychosis and antibodies
• Clinical recommendations
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 2010
- Glycine receptor 2012
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)

Ion channel disturbance in schizophrenia

Genome Wide Association Studies – associations with CACNA1C, ANK3 (Ankyrin-G), KCNQ5,

Hyponatraemia associated with schizophrenia pre antipsychotics

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

Irani et al. Brain 2010

Infection/headache/fever (20%)
Psychiatric (77%)
Seizures (82%)
Hypersomnia (27%)
Cognitive dysfunction (91%)
Insomnia (34%)
No Infect/headache/fever (45%)
Movement disorder (89%)
Fall in consciousness (45%)
Gaze deviation (14%)
Autonomic (72%)

Cortical
Subcortical

Days since onset
Responsive to immunotherapy
Irani et al Brain 2010
NMDA dysfunction as a model for schizophrenia

Pathology

Glantz and Lewis
Arch Gen Psych 2000

Genes

Harrison and Weinberger Mol
Psych 2005

ketamine

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. (CAMEO)

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).
- 1 had VGKC-complex antibodies (1435 pM; normal<100).
Further cases identified

• 13 psychiatric cases Nov 09 – May 2012 (11 NMDA, 2 VGKC). 51 requests

• Referrer – AMH (9), CAMH(3), LD(1)

• Reason for testing: first episode psychosis screening (n=9), treatment resistance (n=2), catatonia (n=1), cognitive impairment (n=1)

• Negative findings in chronic schizophrenia (n=300 AV personal communication)
Clinical and demographic characteristics of patients with psychosis and NMDA receptor antibodies
Family History of Schizophrenia

No FH
No FH
No FH
No FH
No FH
One 1st (D)
One 1st (D)
One 1st (D)
One 2nd (S)
One 2nd (S)
One 2nd (S)
One 1st and one 2nd (S)
One 1st and two 2nd (S)
Two 1st (S)

3 1st degree relative with schizophrenia
0/13 cannabis use in the last month

Substance use in the past month (age-adjusted)

% population

Cannabis
Class A
Any drug

National
Cameo
More unwell on PANSS than other early psychosis patients
4 had a catatonic presentation with mutism, ambitendence and stereotypies mixed with periods of excitement.

Orofacial dyskinesia in 2
No progressive encephalopathy

• None have developed ‘classical’ autoimmune encephalopathy or other neurological diagnosis.

• No seizures

• Normal brain MRI, negative investigations for tumours, other autoimmune diseases.

• EEG changes 3/7 (fronto temporal slowing)
Antipsychotic Treatment

3 had ‘collapses’ on atypical antipsychotics

4 ‘treatment resistant’ to antipsychotics
23 F NMDAR

- Inpatient ‘1\textsuperscript{st} episode psychosis’
- 1 month confusion, paranoid delusions, auditory hallucinations, insomnia, agitated, catatonic, posturing
- Collapse after 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
Outcome Measures
- Antibody levels
- Modified Rankin Score
- Returned to occupation part time
- Returned to occupation full time

Interventions
- Methylprednisolone 0.5-1g bd for 3-5 days
- Plasma exchange
- Mycophenolate mofetil
- Citalopram
- Risperidone
35 M NMDAR

- Psychiatry Ward ‘schizophrenia’
- 3 year history deterioration self care, social withdrawal.
- Initial paranoia about food, dysmorphophobia
- Prominent negative symptoms: poor motivation, passive social withdrawal, lack spontaneity, blunted affect, stereotyped thinking
- No response to 6 months of antipsychotics
Treatment

- Antipsychotics stopped
- Plasma Exchange, Steroids
- Improved after 3 weeks, discharged home
- Further deterioration behaviour at 6/12, antibody positive.
- Further course plasma exchange
- Further improvement
- Antibody negative
- Mycophenylate mofetil
- Continued functional improvement
Addenbrooke’s Cognitive Examination-R

Effect of Treatment

- Attention and Orientation
- Memory
- Verbal fluency
- Language
- Visuospatial

Comparison between:
- Pre 1st plasmaphoresis
- Post 1st plasmaphoresis
- Pre 2nd plasmaphoresis
- Post 2nd plasmaphoresis
Clinical recommendations
Who to test

- Acute onset paranoid psychosis (within last 3 months)
- 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)
Neurological treatment

- **Induction of remission**: 3 days of methylprednisolone (500-1000mg) orally or intravenously followed by oral prednisolone 40mg daily, in association with 5 days of plasma exchange.

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

- Regular benzodiazepines eg diazepam 2-5mg mg tds
- Avoid dopamine blocking antipsychotics in NMDAr ab positive cases.
- Need liaison psychiatry closely involved
- Mental health nursing expertise in general hospital
Antibodies against neuronal cell surface targets are a cause of some cases of schizophrenia.

6.3% cases first episode psychosis may be caused by these antibodies

Patients may be more unwell, with prominent movement disorder and cognitive impairment

Patients respond to treatment with immunotherapy rather than antipsychotics.

It is important to test and treat early in the course of the illness