Autoimmune encephalitis

Angela Vincent
and the Neurosciences Group

Nuffield Department of Clinical Neurosciences, Oxford University, UK
Disclosures

Angela Vincent and the University of Oxford hold patents, and receive royalties and payments for antibody tests including VGKC-complex antigens LGI1 and CASPR2.

Angela Vincent has recently received honoraria for lectures from GSK, UCB Pharma and Serono.

This is the version that should have been presented – slightly different from that you saw.
Autoantibodies causing neurological diseases
From myasthenia to encephalitis and a growing number of wider conditions
The neuromuscular junction in myasthenia

Antibodies cause loss of the AChRs

Patients improve with treatments that reduce the AChR antibody levels
Plasma exchange for myasthenia

John Newsom-Davis 1932-2007

Newsom-Davis et al 1978
Crisp, Kullmann and Vincent
Nature Reviews Neuroscience 2016
Antibody-mediated diseases

Antibodies that bind to extracellular domain of membrane protein on target tissue

Antibodies measured easily in serum (and cerebrospinal fluid (CSF) if relevant)

Antibodies cause loss of the target protein and/or damage to the cell

Patients can improve with immunotherapies: steroids, plasma exchange, intravenous immunoglobulins

Pathogenicity can be demonstrated by animal studies
MG with MuSK antibodies, AChR antibodies negative
Plasma exchange provided a diagnostic test!
But long-term marked and persistent facial weakness and atrophy, difficult to treat

Patient of John Newsom-Davis; courtesy of patient
MuSK-MG is IgG4>IgG1,2,3

MuSK-MG is a very interesting even if rare disease

IgG4 antibodies block LRP4-MuSK interaction and interfere with downstream phosphorylation
Koneczny, Verschuuren and Burden groups

But IgG1-3 can also play a role
Koneczny et al 2014

((MuSK-MG could be a model for diseases caused by antibodies to growth-factor receptors and other tyrosine kinase receptors))
Antibodies cause loss of MuSK function with dispersal of AChRs
2000 -> Autoimmune CNS channelopathies

Pathogenic antibodies in CNS disorders

Bind to extracellular domain of important neuronal or glial proteins

Patients respond to immunotherapies

Antibodies to AQP4, VGKC-complex, NMDAR and glycine receptors and many others

Widening implications for diagnosis of immunotherapy-responsive diseases
Neurological (and psychiatric) presentations associated with

Antibodies to
- CASPR2
- LGI1
- GlyRs
- NMDAR

Some experimental studies
Acquired neuromyotonia – an autoimmune voltage-gated potassium channel (VGKC) disease?

Spontaneous muscle activity due to peripheral nerve hyperexcitability

Improves after plasma exchange or steroids etc.

Antibodies to a “voltage-gated potassium channel (VGKC)” in 40% patients

Hart et al al Brain 2002; Turner et al JNNP 2006
Voltage-gated potassium channels are part of a complex of proteins (VGKC-complex).

Antibodies to any of these proteins can immunoprecipitate Kv1 VGKCs.

Irani, Alexander, Waters, Kleopa et al. Brain 2010
Measuring antibodies to *cell-surface antigens*

**Live cell-based assays**

Patient has specific antibodies. Intensity of binding can be scored visually.

Patient does not have specific antibodies.

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Patrick Waters
Clinical features in 64 NMT patients  
37M:27F; 12-85 years

<table>
<thead>
<tr>
<th>Symptom Type</th>
<th>Number (N)</th>
<th>Percentage</th>
<th>Symptoms/Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor symptoms/signs N=64</td>
<td></td>
<td></td>
<td>Twitching, Weakness, stiffness, pseudomyotonia</td>
</tr>
<tr>
<td>Sensory symptoms N=26</td>
<td></td>
<td>40%</td>
<td>Paraesthesia, pain</td>
</tr>
<tr>
<td>Autonomic symptoms N=21</td>
<td></td>
<td>33%</td>
<td>Sweating, constipation/diarrhoea, hypersecretion, tachycardia</td>
</tr>
<tr>
<td>Central symptoms N=13</td>
<td></td>
<td>20%</td>
<td>Anxiety, insomnia, other sleep disturbance, depression</td>
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</tbody>
</table>

Patient data and sera from Prof Matthew Kiernan, Sydney and Dr Osamu Watanabe, Kagoshima
Pain is a common feature in patients with VGKC-complex antibodies, particularly CASPR2.

CASPR2 antibodies alter CASPR2 expression and reduce surface VGKCs in cultured neurons.

Injection of CASPR2 antibodies into mice lowers threshold for mechanical sensitivity.

Antibodies to CASPR2 may be a direct cause of some pain related to the reduction in VGKCs with consequent hyperexcitability of sensory nerves.
Limbic encephalitis with VGKC-complex antibodies

Quite common, usually non-paraneoplastic

MRI signs restricted to medial temporal lobes (and amygdala)

LOW plasma sodium common

VGKC-complex antibodies fall with immunotherapies and substantial clinical improvement

Mainly older adults

Buckley et al 2001
Vincent et al 2004
LGI1-Abs cause a form of epilepsy
Very frequent brief dystonic events
often PRECEDE limbic encephalitis

Video available in Irani et al Ann Neurol 2011

Irani et al Neurology 2008;
Irani et al Ann Neurol 2011;
Irani et al Brain 2013; Thompson et al submitted 2017
FBDS disappears when IT used

Treat FBDS with steroids or other immunotherapies and prevent cognitive impairment
54-year old prison officer presenting with whole-body jerks triggered by auditory and tactile stimuli

No GAD or paraneoplastic antibodies

Video available in Hutchinson et al 2008

Progressive encephalomyelitis with rigidity and myoclonus

PERM
Glycine receptors are essential for controlling motor function. GlyR loss of function mutations are found in genetic forms of hyperekplexia in babies and adults. Are there antibodies to GlyR in this patient?

Ballint and Bhatia
Curr Op Neurology 2016

Hutchinson, Waters et al 2008
PERM in a 14 month old girl
Relapsing remitting course with
good recovery to date

Video available in Damasio et al 2013

J Damasio et al JAMA Neurol 2013
Relapsing/remitting PERM in Damasio et al 2013

Treatment

IVIG

IV Steroids

Oral Steroids

GlyR alpha-1-EGFP Patient Serum Merge

Serum

CSF

Glrα1 Ab Titremg/kg

Relapses

0 5 10

Mild

Time from onset (days)

0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750

0

-0.1

0

0.5

1.0

1.5

2.0

400

300

200

100

0
Patients with GlyR antibodies (n=45)

2– 74 years, both sexes

4 children

Rigidity
Painful muscle spasms
Excessive startle to sound or touch
Ocular and other brainstem disturbance
Autonomic - urinary retention, tachycardia
Ataxia or seizures in <20%

Thymomas, lymphoma 10%

All responded to PLEX, IvIg, steroids etc

Carvajal-Gonzalez et al Brain 2014
“Anti-NMDAR encephalitis”

NMDAR Abs in young females with ovarian teratoma-associated encephalopathies

Dalmau et al Ann Neurol 2007
Dalmau et al Lancet Neurology 2008

600+ cases described

Reviewed in
Dalmau et al 2011, Titulaer et al 2012
Teenage girl, presented with neuropsychiatric features, amnesia, seizures

Facial grimacing and chewing and choreoathetoid limb movements

Mutism, reduced consciousness

No ovarian teratoma in this patient. Very good response to immunotherapies
22 month child with behavioural changes, sleep disturbance, general seizures, and then movement disorder. Eventually responded to immunotherapies but recovery not complete.

Video not available

Courtesy Dr Sukhvir Wright and the Consultants at Birmingham Children's Hospital
NMDAR antibodies detected by CSF IgG binding to brain tissue (as in Gresa-Arribas et al 2015). CSF is more specific but not more sensitive than serum IgG binding to live HEK-NMDAR cells.
M Titulaer, J Dalmau et al Lancet Neurology 2010

NMDAR-Ab encephalitis and other autoimmune encephalitides

Scan for tumours

First line: Steroids, PIEx, IvIg

Second line: Rituximab, cyclophosphamide

Maintenance if relapses: variably applied; azathioprine, mycophenolate etc
NMDAR-Abs can be responsible for HSV relapses

2 year old male with HSV encephalitis treated, followed by clinical deterioration, leukoencephalopathy and appearance of NMDAR antibodies, then recovery

Hacohen et al Neurology Neuroinmunology, Neuroinflammation 2014
Antibodies bind to the surface of cultured neurons. Internalise NMDARs and reduce NMDAR expression.

Hughes et al 2010; Dalmau et al Lancet Neurology 2011
Can we show that the antibodies are pathogenic?

This is where plasmapheresis material comes into play!
Infusion of pooled CSFs bilaterally into mouse ventricles for 18 days – Planaguma et al Brain 2014

IgG deposition and “progressive memory deficits, anhedonic and depressive-like behaviours”. Reversed when infusion stopped. No seizures or movement disorder.
A single intraventricular injection of purified plasma NMDAR antibody IgG increases sensitivity to seizures.

**No spontaneous seizures but subthreshold dose (40 mg/kg) of the chemo-convulsant pentylenetetrazol (PTZ) showed increased seizures in NMDAR-IgG injected mice.**
Recording EEG events from mice after ICV IgG and PTZ

NMDAR antibodies can cause seizure susceptibility – but still no movement disorder

Wright et al Brain 2015
Antibodies and neurodevelopment. A new aspect?

Maternal AChR antibodies can cause neonatal MG

Very rare cases have permanent arthrogryposis or muscle hypotonia

This condition can be modelled in mice by injecting antibodies into pregnant mice

Could anti-CNS antibodies cause neurodevelopmental disorders?
Maternal antibody-mediated arthrogryposis passively transferred to fetuses by injecting the pregnant mouse dams with maternal IgG

Pregnant dams injected daily with plasma from mothers of:

AMC-baby

Healthy baby

Leslie Jacobson


Maternal antibodies can affect fetal development
An unknown maternal antibody affects brain development

Maternal Neuronal Antibodies Associated with Autism and a Language Disorder

Paola Dalton, DPhil,1 Robert Deacon, DPhil,2 Andy Blamire, PhD,3 Michael Pike, FRCPCH,4 Ian McKinlay, FRCPCH,5 John Stein, FRCP,6 Peter Styles, DPhil,3 and Angela Vincent, FRCPath1

Maternal-to-fetal transfer resulted in motor incoordination but no specific antibody was identified 2003

USA groups took up the story
NMDAR and CASPR2 are possible candidates for maternal antibodies.

Mutations in NMDAR or CASPR2 found in some patients with rare forms of autism and a variety of other neurodevelopmental disorders.
CASPR2 autoantibodies are raised mid-gestation in mothers of children with disorders of mild intellectual and psychological development.

<table>
<thead>
<tr>
<th></th>
<th>Total number</th>
<th>CASPR2 antibodies</th>
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</thead>
<tbody>
<tr>
<td><strong>Intellectual and psychological disorders (could include autism)</strong></td>
<td>181</td>
<td>4.4%</td>
</tr>
<tr>
<td><strong>Age- and parity-matched controls</strong></td>
<td>348</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

*Fisher’s exact test*  
*p=0.01*
6 days of maternal-to-foetal transfer of CASPR2 antibodies caused IgG binding to brain in embryos and persistent autistic-like abnormalities in adult mice.

Ester Coutinho, David Menassa, Leslie Jacobson, Bethan Lang, Paul J Harrison, David Bannerman, Angela Vincent (submitted for pub)
12 months after in utero exposure, mice showed persistent increased microglial cells (CD68) and decreased glutaminergic synapses (PSD) in their brains.

Coutinho, Menassa et al under revision
Conclusions

Autoimmune encephalitides are rare but now “mainstream” diagnoses in neurology.

Patients improve with immunotherapies particularly plasmapheresis.

Difficult to show that antibodies cause the full phenotype of NMDAR- (or GlyR, LGI1) antibody diseases.

Maternal antibodies may be a rare but potentially “treatable in future pregnancies” cause of some neurodevelopmental disorders.
Ester Coutinho
David Menassa
Leslie Jacobson
Sukhvir Wright
Yael Hacohen
Sarosh Irani
Alexander Carvajal
Ming Lim
Patrick Waters
Bethan Lang
Mark Woodhall
Linda Clover

Camilla Buckley
Isabel Leite
Susan Maxwell
Judith Cossins
David Beeson

Neurologists all over the world