Autoantibodies associated with diseases of the CNS: new developments and future challenges

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AV and the Oxford Department hold patents and receive royalties and payments for antibody assays
From myasthenia to encephalitis
Autoantibodies causing neurological diseases
Receptor aggregating protein at the synapse (RAPsyn)

Acetylcholinesterase (AChE)

Acetylcholine receptor (AChR)

Muscle specific kinase (MuSK)

Voltage-gated calcium channel (VGCC)

Voltage-gated potassium channel (VGKC)
Antibodies bind to the extracellular domain of the acetylcholine receptor. They reduce the number of acetylcholine receptors. Patients improve with plasma exchange, steroids, IvIg and other immunotherapies.
Myasthenia gravis

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

Can be measured easily in serum

Antibodies cause loss of function

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

Antibodies alone can transfer disease to mice

MORE COMMON IN ELDERLY MEN THAN YOUNGER WOMEN!
1990s
Autoantibodies in paraneoplastic neurological syndromes (PNS)

Antibodies to “onconeural” antigens found in patients with tumour-related neurological diseases

Onconeural antigens shared between the tumour and the nervous system

Hu, Yo, Ri, Ma2, CRMP5, Amphiphysin
All intracellular proteins

Antibodies not pathogenic and patients don’t usually respond to treatments
Antibodies to CNS disorders that are thought to be causative

Bind to extracellular domain of important neuronal or glial proteins

Patients respond to immunotherapies

Antibodies to AQP4, VGKC, NMDA and glycine receptors
Neuromyelitis optica (NMO) – antibodies to a water channel on astrocytes

Females 88%

Inflammation of optic nerve and spinal cord

Relapsing remitting disease with increasing disability

Wheelchair common within five years

Needs to be distinguished from MS

AQP4-antibodies found

Lennon et al 2004/2005
“NMO-IgG” binding to microvessels, the pia and outlining the Virchow Robin spaces
Found in sera from around 75% of NMO patients and 50% at high risk

Lennon et al Lancet 2004
Jarius et al Neurology 2007
Autoantibodies to AQP4 – a glial water channel

Present in patients with neuromyelitis optica, previously thought to be a form of multiple sclerosis

Now being used diagnostically

Neuromyelitis optica is now considered an antibody-mediated disease
Which are the best assays for AQP4 antibodies?

Waters et al Neurology 2012
Results

All highly specific

Concordance very good

Sensitivity:

Cell-based assays > ELISA > NMO-IgG IF

Waters et al Neurology 2012
The way to measure disease-relevant antibodies
The cell-based assays are the way forward

Cell surface protein

Negative for antibody  Positive for antibody
Two isoforms of AQP4 – M1 and M23

M23 forms orthogonal arrays of proteins (OAPs)

Many patient sera bind more strongly to M23

From Papadopoulos and Verkmann
Lancet Neurology 2012

Waters et al 2008 unpublished
Also see Mader et al Plos One 2010
Autoimmune channelopathies
paraneoplastic or non-paraneoplastic associated with
specific anti-neuronal autoantibodies

VGKC-complex Ab associated limbic encephalitis or
Morvan’s syndrome usually without tumours
(thymomas, SCLC)
(Vincent et al 2004, Irani et al 2010)

NMDAR-Ab associated encephalitis with or without
ovarian teratoma
(Dalmau et al 2008; Irani et al 2010)

GlyR-Abs in encephalomyelitis
Acquired neuromyotonia with antibodies to potassium channels – peripheral motor nerve hyperexcitability causing continuous muscle activity

Patient of Dr George Ebers; Turner et al 2006
Traditional limbic encephalitis

Personality change or psychiatric features, memory loss, seizures

High signal on MRI

Traditionally associated with tumours and poor prognosis
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Personality change or psychiatric features, memory loss, seizures

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Patients with VGKC-complex antibodies:

Much more common

Low plasma sodium (SIADH) common at onset

Usually non-paraneoplastic and respond to immunotherapies

Vincent et al 2004
Irani et al 2010
Steroids, PI Ex, IvIg

Schott et al 2003
Vincent et al 2004
All high VGKC-Ab positives >400 pM detected by Oxford 2001-2009
Males>females   Adults>children

The majority have limbic encephalitis but some only have seizures
UK patients identified with high VGKC antibodies 2002-2006

Males > females; the majority are over 40 years – why?

![Diagram showing age at presentation for females and males]
Improvement in modified Rankin Scores following variable immunotherapies in 45 adult patients with VGKC-Ab limbic encephalitis

Irani et al Brain 2010
Serum VGKC antibodies always higher than CSF antibodies
Which are the culprits?

Leslie Jacobson unpublished
Very frequent brief facio-brachial dystonic seizures (FBDS) associated with high VGKC antibodies

Poor response to AEDs

Good response to immunotherapies

Often precede limbic encephalitis

Irani et al 2008; Irani et al Ann Neurol 2011
Potassium channel antibodies - challenges

Why do the antibodies sometimes cause peripheral nerve hyperexcitability and sometimes epilepsy and amnesia?

How do the antibodies get into the brain?

Why is the hippocampus so often the target when VGKC-complexes are expressed throughout the brain?
Antibodies to voltage-gated potassium channels in acquired neuromyotonia

Hart et al 1997; Hart, Maddison et al Brain 2002

$^{125}$I-dendrotoxin bound to tetramers of Kv1 subunits
VGKCs are COMPLEXES of different proteins such as LGI1, CASPR2 and Contactin-2

Antibodies to these proteins can immunoprecipitate VGKCs
Many “VGKC” antibodies bind to LGI1
Mostly found in limbic encephalitis and FBDS epilepsy

LGI1 is mainly expressed in the CNS particularly the hippocampus

Irani et al Brain 2010a
Lai et al Lancet Neurology 2010
Some “VGKC” antibodies bind to CASPR2
Mostly found in patients with peripheral nerve neuromyotonia

CASPR2 has important role in clustering VGKCs at juxtaparanodes of PNS and CNS

Also widely expressed in the brain

Irani et al Brain 2010
Lancaster et al Ann Neurol 2011
How does one measure disease-relevant antibodies? The cell-based assays are the way forward?

Negative for antibody  Positive for antibody
NMDA receptor antibody encephalitis

NMDA receptors are part of the glutamate receptor family

NMDAR Abs in young females with ovarian teratoma-associated encephalopathies

Dalmau et al Ann Neurol 2007

100 cases described

Dalmau et al Lancet Neurology 2008

Review

Dalmau et al Lancet Neurology 2011
Anti-NMDAR encephalitis

NMDAR is expressed in the ovarian tumours

Hippocampal expression is reduced in brain but not much evidence of inflammation or permanent damage

Measuring NMDAR-Abs

Binding to “neuropil” of rat hippocampus

Binding to cultured hippocampal neurons

NMDAR-Abs

NMDAR-Abs

NMDAR-Abs

Merge
Tumours in young females BUT many patients DON’T have tumours detected
High proportion of children
Serum or CSF?

Serum levels higher than CSF
(but serum has to be diluted at least 1:20 fold for testing)
Questions

What causes NMDAR-Ab encephalitis in children and adults without ovarian tumours

Is intrathecal synthesis of antibody essential for disease?

Why isn’t it more inflammatory when the antibodies are IgG1?
Glycine receptors are involved in spinal inhibition

Antibodies to GlyRs present and fell after treatment with very good recovery

Hutchinson et al. Neurology 2008
Very good treatment response but required extensive immunotherapies.
Some of the big questions

Demographics

How common are these diseases?

Are the antibodies found in more common diseases such as

  Epilepsy?
  Psychosis?
  Dementia?

Why do some occur in young women and others more often in older men?

How can they be diagnosed promptly in all centres?
Multiple cell-based assays for testing patients with different forms of encephalitis

Euroimmun AG

However, fixed rather than live cells used and sensitivity may be different.
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Patrick Waters
Isabel Leite
Bethan Lang
Kasia Bera
Philippa Pettingill
Camilla Buckley
Luigi Zuliani
Sukhvir Wright
Linda Clover
Leslie Jacobson

Susan Maxwell
David Beeson

The late John Newsom-Davis
and Ian Hart
and many neurologists
in UK and elsewhere