NMO and Other Antibody-Mediated Neurological Diseases

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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
From myasthenia to myelitis and encephalitis
Autoantibodies causing neurological diseases
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
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 and immunosuppressants

Paradigm for antibody-mediated neurological diseases
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, NMDA and glycine receptors and others emerging

Widening implications for diagnosis of immunotherapy-responsive diseases
Neuromyelitis optica – Devic’s disease

Combinations of optic neuritis with visual disturbance and transverse myelitis with paralysis, sensory disturbance, autonomic disturbance and pain

Courtesy of Dr. Lucy Matthews
Neuromyelitis optica

Severe attacks of optic neuritis, with pain and visual loss
or
Transverse myelitis with longitudinally-extensive lesions causing sensory and motor loss, pain, sphincter problems
or less often

Brainstem and hypothalamic hicouphs and intractable vomiting

Most have relapsing disease

Now recognised to be a severe relapsing-remitting disorder of the CNS distinct from MS
MS
Can be relapsing remitting for many years before progression

NMO
Has step-wise progression to severe disability within a few years

Relapsing-remitting followed by progressive course

Stepwise progression can be prevented by prompt immunotherapies

- Multiple sclerosis
- Neuromyelitis optica
IgG/M and complement deposits in lesions

IgM or C9neo (complement) on perivascular rim or in rosettes around vessels in NMO

Lucchinetti et al Brain 2002
A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis

Lancet 2004; 364: 2106–12  Vanda A Lennon,

Mouse cerebellum stained with patient’s serum IgG shows the typical Pattern of binding of NMO-IgG

NMO-IgG +ve
73% of NMO patients
42% LETM
25% Rec ON
9% MS
Aquaporin-4 antibodies in neuromyelitis optica

Lennon et al Mayo Clinic
NMO-IgG defined, Lancet 2004,
AQP4 identified as the antigen, J Exp Med 2005

Antibodies proving useful in early diagnosis
and disease monitoring

In UK identifying about 1/million new patients each year
AQP4 – an astrocyte antigen
Each tetramer forms a water channel
Expressed strongly on astrocyte end-feet abutting the endothelial or pial cells

Papdopoulous & Verkmann
Lancet Neurology 2012

Jarius et al
Nat Clin Pract 2008
What's a cell-based assay?
How do we measure antibodies to AQP4?
How do we measure antibodies to AQP4?

Patient has AQP4 antibodies. Intensity of binding can be scored visually.

Patient does not have AQP4 antibodies.
Two isoforms of AQP4 – M1 and M23
M23 forms orthogonal arrays of proteins (OAPs)
Many patient sera bind more strongly to M23

Wolberg et al 2011

Waters et al 2008 unpublished
Is NMO an antibody-mediated disease?

The antibody levels correlate with relapses if carefully followed over time.

The patients respond to immunotherapies that reduce antibody levels.

The disease can be transferred to experimental animals with antibodies.
Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan

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Non-Caucasians about 15% in the UK overall
Permanent motor disability more likely in adults
Permanent visual disability more likely in children
With prompt and adequate treatment of relapses, neuromyelitis optica can be stabilized.

Relapsing-remitting followed by progressive course

Stepwise progression can be prevented by prompt immunotherapies.
Acute relapses must be treated aggressively

IVMP 1g/day for 5/7. Commence oral prednisolone 60mg od and reduce by 5mg/month to maintenance 20mg alternate days

Plasma exchange if no improvement after 5/7 or if previous poor recovery

IVIG is an alternative to plasma exchange
Serial AQP4-antibody measurement can be very helpful in individual cases – small male child with unusually severe NMO.

Leite, Woodhall, Wasserman, Palace et al unpublished results.
Serial AQP4-antibody measurement can be very helpful in individual cases – small male child with unusually severe NMO

Leite, Woodhall, Wasserman, Palace et al unpublished results
Autoimmune channelopathies
paraneoplastic or non-paraneoplastic
associated with specific autoantibodies

VGKC-complex Ab associated limbic encephalitis
and facio-brachial dystonic seizures
(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
Traditional limbic encephalitis

Personality change or psychiatric features, memory loss, seizures

High signal on MRI

Traditionally associated with tumours and poor prognosis

Patients with VGKC-complex antibodies:

More common

Low plasma sodium (SIADH) common at onset

Usually non-paraneoplastic and respond to immunotherapies

Vincent et al 2004
Irani et al 2010
VGKC antibody (pM)

Steroids, Pl Ex, IvIg

Schott et al 2003
Vincent et al 2004
Improvement in modified Rankin Scores following immunotherapies in 45 adult patients with VGKC-Ab limbic encephalitis

Irani et al Brain 2010
Very frequent brief dystonic seizures (FBDS) associated with high VGKC-complex/LGI1 antibodies

Poor response to AEDs

Good response to immunotherapies

Often precede limbic encephalitis and treatment may prevent encephalitis

Very frequent brief dystonic seizures associated with high VGKC-complex/LGI1 antibodies

Irani et al 2008; Irani et al Ann Neurol; Irani et al Brain 2013
NMDA receptor antibody encephalitis

NMDA receptors are part of the glutamate receptor family essential for brain activity

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 of treatments
Titulaer et al Lancet Neurology 2013
Movement disorder in NMDAR-Ab encephalitis

Limbic presentation
Psychiatric, seizures, cognitive problems

Usually progresses to
Facial grimacing and chewing, choreoathetoid limb movements, mutism
Loss of consciousness
Autonomic instability

Ovarian teratomas common in younger females

Video courtesy of the patient and Dr G Vasello, Manchester
22 month child presented with behavioural changes and sleep disturbance, then general seizures, then movement disorder. No tumour. Eventually responded to immunotherapies

After treatment

Courtesy Dr Sukhvir Wright and the Consultants at Birmingham Children's Hospital
54-year old prison officer presenting with whole-body jerks triggered by auditory and tactile stimuli

Progressive encephalomyelitis with rigidity and myoclonus
PERM
Hutchinson et al Neurology 2008
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.
Resolved after thymoma removal and plasma exchange
Clerinx..............Vandenberghe, Neurology 2011
General summary

There are a growing number of antibodies to channels and receptors in CNS diseases and to ion channel associated/modifying proteins.

Presentations include amnesia, epilepsy, startle, psychosis, sleep, autonomic and movement disorders.

Patients include children.

Preceding or coexisting tumours and infections may play a role but in most its unclear.

Plasma exchange is an important therapeutic option.
Some of the big questions

How common are these diseases?

Are antibodies found in more common diseases:
   Epilepsy?
   Psychosis?
   Dementia?

How can they be diagnosed promptly in all centres?

What are the best and fastest treatments?
Can antibodies cause “psychosis”?

Catatonic schizophrenia-like illness in teenage boy
Antibody to a GABA_A receptor detected and good response
to plasma exchange over two distinct episodes
Dr J Coebergh, London; Pettingill et al in prep
Sarosh Irani
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