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Teaching Course 2

Autoimmune causes of epilepsy - Level 3

Pathophysiology of autoimmune epilepsies - from antibodies to hyperexcitable neuronal networks

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Pathophysiology of Autoimmune Epilepsies – From antibodies to hyperexcitable neuronal networks

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Disclosures

AV and University of Oxford receive payments and royalties for MuSK, LGI1 and CASPR2 antibody assays
Plan of presentation

Myasthenia gravis as a model of antibody-mediated diseases

Background to autoimmune epilepsy

Epileptic encephalopathies

What do we mean by autoimmune epilepsy?

How common is it?

How do antibodies alter cellular functions and generate seizures?

Myasthenia gravis as a model of antibody-mediated diseases

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

Antibodies measured in serum

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

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

Injection of patient IgG affects target functions in vitro and transfers disease to mice
Mechanisms of antibodies illustrated by AChR-Abs in myasthenia gravis
IgG1 and IgG3 antibodies are divalent and cause complement-mediated
damage (a), increased internalisation (b) and occasionally direct inhibition of
AChR function (c)

Note that activation of the receptor by antibody is very uncommon

From Crisp, Kullmann and Vincent Nature Reviews Neurology 2016

But MuSK antibodies are IgG4 > IgG1-3.

IgG4 antibodies are hybrid and monovalent because they exchange
arms with other IgG4 molecules. They do not activate complement or cause
internalisation. They act mainly by inhibiting the binding of LRP4 to MuSK
which is required for clustering AChRs at the neuromuscular junction
Loss of postsynaptic membrane reduces sodium channels and leads to increase in threshold for CMAP
Ruff and Lennon 1998

Rate of AChR synthesis increases to compensate

Release of ACh increases to compensate
Plomp et al 1995

Modifying mechanisms can occur at ALL synapses

What factors might determine whether antibodies cause neuronal hyperexcitability in CNS neurons?

Access of antibodies via blood flow/interstitial fluid require changes in BBB and/or intrathecal synthesis

IgG subclass determines potential mechanisms

Reduction in receptor or ion channel numbers or function usually result therefore target should be “inhibitory” not “excitatory”

Morphological damage by complement can contribute

But complement regulators may limit damage

Compensatory pre- and post-synaptic changes likely

Final result is unpredictable!
Background to autoimmune epilepsy

Kasper et al.
Brain 2010

Corsellis JAN, Goldberg GJ, Norton AR 1968

Not all patients had a tumour
GluR3 antibodies in Rasmussen’s encephalitis and response to plasma exchange. Rogers, Andrews….McNamarra Science 1994

UPDATE 2017: AMPAR2/3 (GluR2/3) antibodies in 2/54 Rasmussen’s encephalitis patients but GluR2/3 Abs may be secondary, not primary.

Anjan Nibber, Beth Lang, Christian Bien et al EJPN 2016
Four patients

Young onset, subacute, intractable TLE, verbal and visual memory defects, affective disorders.

Increased T2 signal in limbic structures, inflammation on biopsy.

No virus or tumour identified

Non-paraneoplastic limbic encephalitis should be included in the differential diagnosis of adult patients with temporal lobe epilepsy.

Neurology 2000

Acquired neuromyotonia – an autoimmune voltage-gated potassium channel (VGKC) disease causing neuronal hyperexcitability

Peripheral nerve hyperexcitability

Twitching, cramps, weakness, sweating

Improves after plasma exchange or IvIg

VGKC-Abs detected in some patients

Some had CNS involvement

Hart et al Ann Neurol 1997; Brain 2002; Turner et al JNNP 2006
Limbic encephalitis: A treatable or spontaneously improving form of limbic encephalitis – mostly >40 years, M>F

Unexplained onset of severe memory loss, confusion, personality changes, seizures

Inflammation in the hippocampus on magnetic resonance imaging or neuropathology

Tumours <10%
Hyponatraemia common

VGKC-Ab positive – 100+ per year in UK

Buckley et al Neurology 2001; Vincent et al Brain 2004

But the antibodies are directed at VGKC-complexes

Antibodies to any of these proteins can be positive in the $^{125}$I-α-dendrotoxin-VGKC-complex Ab assay

Irani et al Brain 2010
VGKC-complex/LGI1 Abs most common
LGI1 expressed on cultured hippocampal neurons
Strongly associated with limbic encephalitis

LGI1 is mutated in autosomal dominant lateral temporal lobe epilepsy with auditory hallucinations
Heterozygous transgenic mice cause seizure susceptibility. Fukata group, Japan

Antibodies to cell-surface, extracellular antigens
Live cell-based assays

Patient has specific antibodies, intensity can be scored visually
Patient does not have specific antibodies

Most labs use fixed tissue/fixed cells
Improvement in modified Rankin Scores following variable immunotherapies in 45 adult patients with VGKC-Ab limbic encephalitis

- **P<0.0001**

- **Death**

- **Modified Rankin Scores in LGI1-Ab positive patients**

  - Pre-treatment
  - Post-treatment

- **Normal**

**Irani et al Brain 2010**

- **20 Oxford patients, years after successful treatment. Majority LGI1-Abs. Epilepsy remits readily in most.**

- **Neuropsychology testing shows normalisation in most modalities but verbal memory is still impaired**

  - **Butler et al JNNP 2014**

- **LGI1 antibodies associated with poor memory recovery and hippocampal atrophy**

  - **Malter……..Bien J Neurol 2014**

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**VGKC/LGI1 Ab IgG elicits epileptiform activity in the CA3 area of hippocampus in brain slices**

- **Extracellular potentials recorded in the stratum lucidum of CA3 pyramidal cell layer with extracellular stimulation of mossy fibres**

  - **LGI1-antibody positive IgG increased burst activity in CA3**

**Lalic et al**

- **Epilepsia 2010**

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**Graph and Diagram Visualizations**

- **Acetylcholinesterase (AChE) activity**

  - **ACSF**
  - **CONTROL IgG**
  - **LGI1 IgG**

- **Bar chart**

  - **ACSF (n=12)**
  - **CONTROL IgG (n=10)**
  - **LGI1 IgG (n=10)**
LGI1-antibody positive IgG increased the release probability of mossy fibre-CA3 pyramidal cell synapses
Effects similar to blocking Kv1s with dendrotoxin

Lalic et al Epilepsia 2010

![Graph showing effects of LGI1 on evoked excitatory postsynaptic currents (EPSCs)].

Reduced no of “failures” in evoked excitatory postsynaptic currents (EPSCs) – more hyperexcitability

LGI1 forms bridge between pre and postsynaptic membranes
LGI1-Abs mainly IgG4; direct block of LGI1 function

LGI1-Ab disrupt binding of LGI1 to ADAM22
and reduce postsynaptic AMPARs
Ohkawa et al J Neurosci 2013
Majority of VGKC/LGI1 antibodies are IgG4 but nevertheless the pathology includes neuronal loss, T cell infiltrates and immunoglobulin and complement deposits. How is this?

See Bien et al Brain 2012

VGKC/LGI1 antibodies in cats cause a similar syndrome with similar pathology

Pakozdy et al 2014; Klang et al 2014
Neuropsychiatric and movement disorders with NMDAR-Abs

Presented with neuropsychiatric features, amnesia, seizures

Became mute

Developed facial grimacing and chewing, choreoathetoid limb movements

Loss of consciousness

No tumour found

Very good recovery

Seizures are found in 70% of children and adults

Titulaer et al Lancet Neurology 2012
Seizures are common at first presentation, but do not dominate.

Irani et al Brain 2010
Vincent, Bien, Irani, Waters
Lancet Neurology review 2011

NMDAR-Abs bind to hippocampal neurons and reduce the number of NMDARs on both excitatory and inhibitory neurons
Hughes et al 2010; Moscato et al Ann Neurol 2014

In mice, intraventricular infusion of NMDAR-Ab CSFs caused cognitive defects and anhedonia
Planaguma et al Brain 2014;
D1 Insert electrodes  
D7 Inject IgG icv  
D9 Inject proconvulsant pentylenetetrazol (PTZ)

Wright et al. Brain 2015

Seizure score related to IgG bound

No overall loss of NMDARs

How do the NMDAR-Abs cause increased seizure susceptibility in this model?
GABA$_{A}$R antibody

Patients selected from archived samples

Alpha and beta subunit antibodies

Six patients higher titres, refractory seizures or SE

Other patients low titre and some had other antibodies eg GAD, GABAR

Antibodies to GABA$_{A}$ receptor $\alpha1$ and $\gamma2$ subunits

Clinical and serologic characterization

Routine referrals

Alpha1 and gamma2 subunit IgG antibodies and IgM antibodies

Clinical features at presentation were diverse

Seizures (47%), memory impairment (47%), hallucinations (33%) or anxiety (20%) but few given immunotherapy

Pettingill et al Neurology 2015
Can antibodies cause seizures without other evident neurological features?
Very frequent brief dystonic events with high VGKC-complex/LGI1Abs often PRECEDE limbic encephalitis

Irani et al Neurology 2008;
Irani et al Ann Neurol 2011;
Irani et al Brain 2013

Thompson……………………..Irani 2017 submitted
Autoimmune epilepsy in general

1. Epilepsy associated with autoimmune disorders

Survey from USA health insurance: incidence of epilepsy (0.4% in population) and risk of epilepsy in patients with autoimmune disorders 1.9 – 9.0 (mean 3.8), with highest risk in antiphospholipid syndrome and SLE. 1.3% of epilepsy cases associated with autoimmune disorder (ie approx 5/100,000 prevalence).

Ong et al JAMA Neurol 2014

The Mayo Clinic definition of autoimmune epilepsy?

- Acute to subacute onset (maximal seizure frequency ≤ 3 months)
- Multiple seizure types or faciobrachial dystonic seizures
- AED resistance
- Personal or family history (1st degree relative) of autoimmunity
- History of recent or past neoplasia
- Viral prodrome
- Evidence of CNS inflammation
  - CSF (elevated protein, pleocytosis, oligoclonal bands, + CSF index)
  - MRI (mesial temporal or parenchymal T2 hyperintensity)
  - Hypermetabolism on functional imaging (PET)
- Detection of neural autoantibody

M. Toledano et al. Neurology 2014;82:1578-158616
How common are autoimmune epilepsies?
78 new patients in 21 months; 13 “autoimmune” (ie. approx 17%)

What other forms of autoimmune epilepsy are there?

2. Status epilepticus occurring with specific neuronal antibodies

Survey from 7 centres, 8 years, only identified 13 patients with status epilepticus

12F, 1M
Epilepsy first feature in most
5/13 had tumours
8/13 NMDAR-Abs,
no Abs to LGI1 (or GABA_A R not available at the time)

Holtzer et al European Neurology 2012
3. Typical epilepsy occurring with specific neuronal antibodies

111 patients with long-standing MTLE 2011-2014

25 had antibodies
11 CASPR2
1 GABAAR
4 NMDAR
5 GlyR
4 VGKC-complex only

Vanli-Yavuz et al JNNP 2016

BUT we need to know when antibody testing performed in relation to onset of seizures – are antibodies primary or secondary to neuroinflammation?

Antibodies to VGKC-complexes found in proportion of patients with unselected epilepsy, particularly focal epilepsies, in adults and children, but usually low levels and significance unclear

Brenner et al Epilepsia 2013,

21
Historic cohort of paediatric cases, no immunotherapies. Antibodies were not associated with AED resistance, and some fell spontaneously, or appeared de novo over time. It may be secondary, not primary.

Pyramidal neuron receives input from dendrites which are controlled by Cav (L,T), HCN and Kv4.2.

Pyramidal dendrites and cell body are also modulated by inhibitory neurons via nAChR and GABA_A R.

Action initial segment initiates activity via Nav1.2; Kv1 and 7 control axonal activity.

From Lerche, Shah et al J Physiol 2013
Targets for autoimmune epilepsy

Antibodies cause loss of function
Therefore candidate antigens are those for which “loss of function” gene mutations or perhaps modifiers? cause increased excitability

<table>
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<th>Gene targets</th>
<th>Loss of function mutation</th>
<th>Gain of function mutation</th>
<th>Modifiers of disease</th>
<th>Increased excitability predicted</th>
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Taken from Lerche, Shah J Physiol et al 2013

(a) Activation of pyramidal cells by glutamate release onto AMPAR and NMDARs.
Output also stimulates GABAergic neurons via glutamate/NMDARs
GABA release onto pyramidal neuron provides a feedback loop and regulates activity

(b) Antibody-mediated reduction of NMDARs on GABAergic neurons leads to unregulated pyramidal cell activity and seizures

But how do NMDAR-Abs cause seizures?

Wright and Vincent Current Op Neurol 2016
Autoimmune epilepsy – some questions

How many immunotherapy-responsive epilepsy patients are there?

Are they being missed or over-diagnosed?

Is positive NMDAR-Ab CSF relevant to autoimmune epilepsy or only to encephalitis?

Can brain damage induce autoantibodies to these antigens (eg. post-HSV encephalitis, NMDAR-Abs)?

Should we be looking at candidate epilepsy antigens (eg. HCN)?
References


