Autoimmune encephalopathy: New Frontiers

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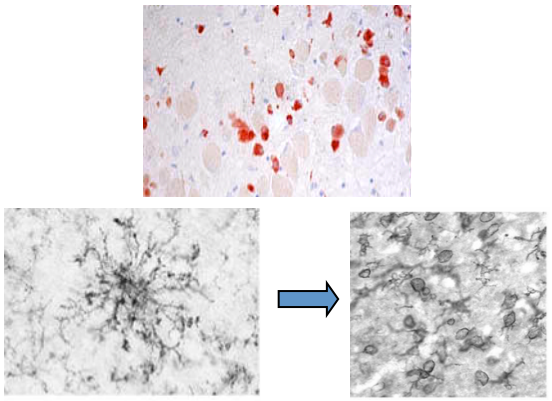
Summary

- Childhood central nervous system autoimmune disease
- What are we learning about neurobiology
- How do we measure disease
- How can we optimise treatment further

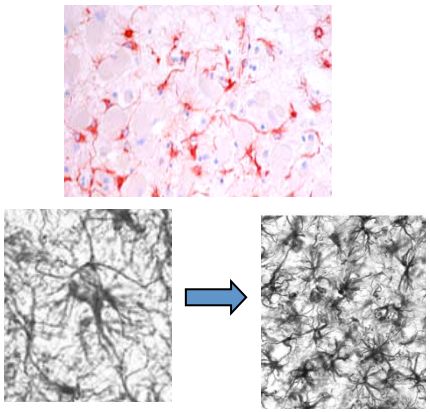
Inflammation in the brain

Primary localized glial activation

Microglia



Astrocytes

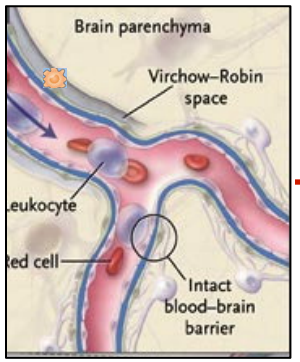


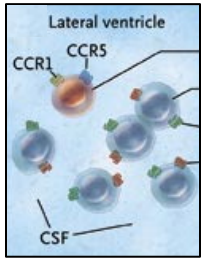
The molecular effectors
Compromise of the blood brain barrier

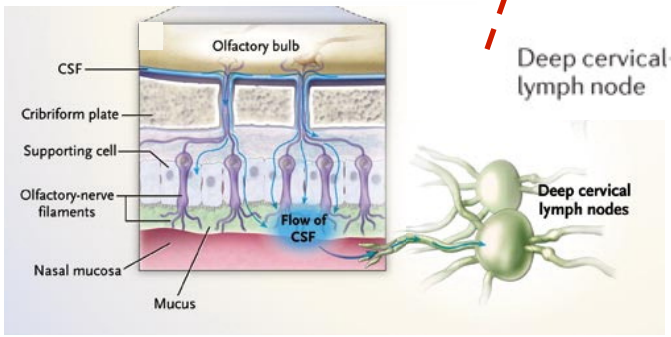
Upregulation of the adaptive immune system

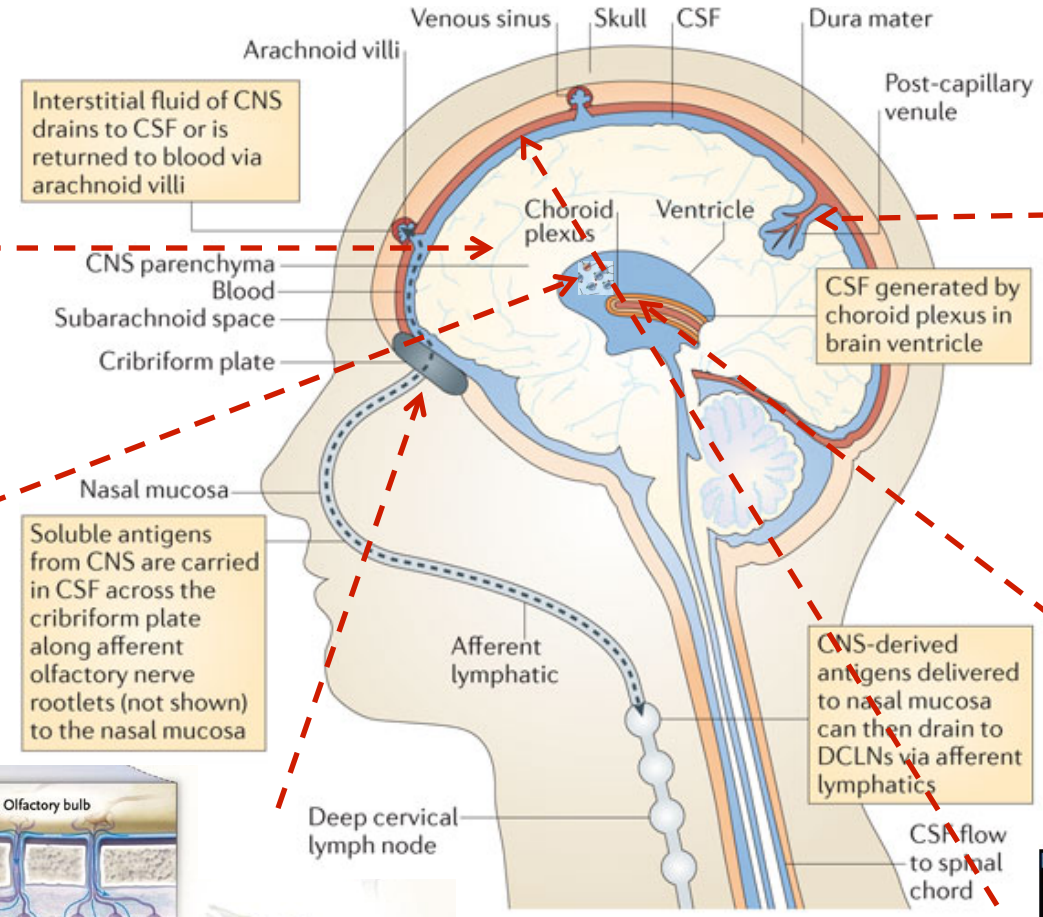
Lim 2011 ***DMCN*** 53: 298-304
Bhat & Steinman ***Neuron*** 65: 123-132

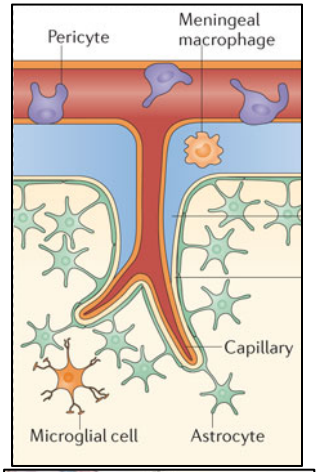
Immune surveillance in the brain

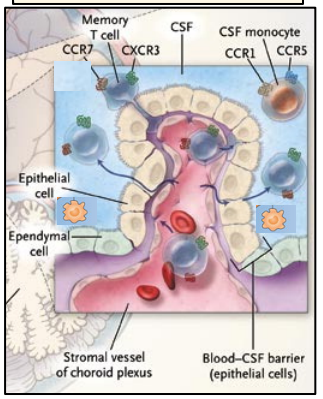


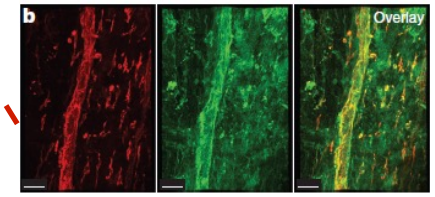












Louveau et al 2015
Nature; 523: 337-341

Ransohoff and Engelhardt 2012 ***Nat Rev Immunol*** 12(9): 623-35

Inflammation in the brain

Cell type	Condition
Th1	MS, ADEM, Rassmussen encephalitis
Th2	SLE
B cell	MS, NMO, demyelination, **autoimmune encephalitis**
Innate	HLH, SLE, Behcet, Sarcoid

Encephalopathy

Behavioural change, e.g., confusion, excessive irritability
Alteration in consciousness, e.g., lethargy, coma

Encephalitis

Encephalopathy was present with 2 or more of:

Fever or history of fever (≥38°C)

Seizures and/or focal neurological findings (with evidence of brain parenchyma involvement)

Cerebrospinal fluid (CSF) pleocytosis (> 4 white blood cells/µl)

Electroencephalogram (EEG) findings in keeping with encephalitis

Neuroimaging in keeping with encephalitis

Granerod et al., 2010 ***Lancet Infect Dis***. 10(12):835-44.

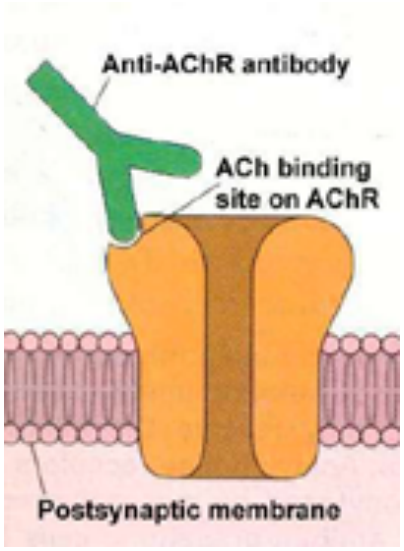
Clinical syndromes in CNS autoimmunity in children

- **Limbic encephalitis**
- **Seizures**
  - FBDS
  - **PERM**
  - **Catastrophic/severe seizures**
- **Movement disorder**
  - Encephalitis lethargica
- Neuropsychiatric
- Others
  - Cross over with peripheral syndromes
  - Demyelination

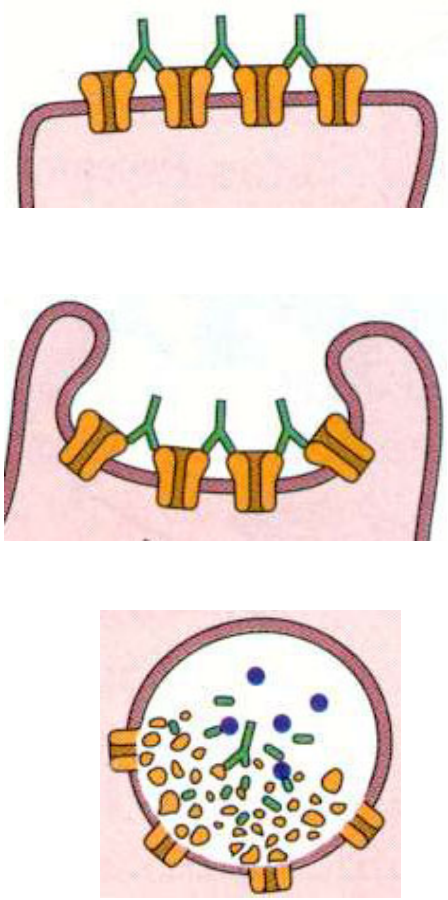
Lim & Gorman 2016

Autoantibodies and CNS inflammation

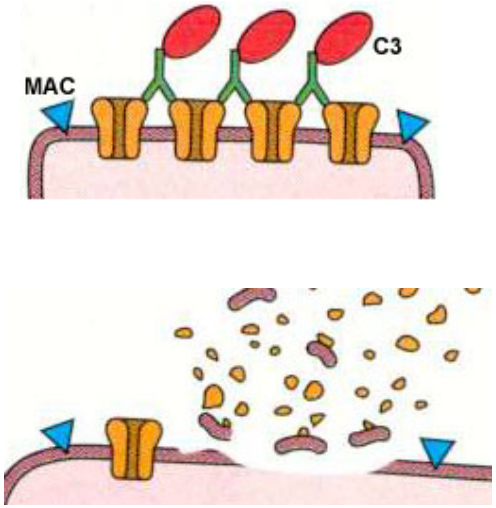
Mechanisms of antibody-induced pathology



Direct block



Internalisation



Complement-dependent lysis

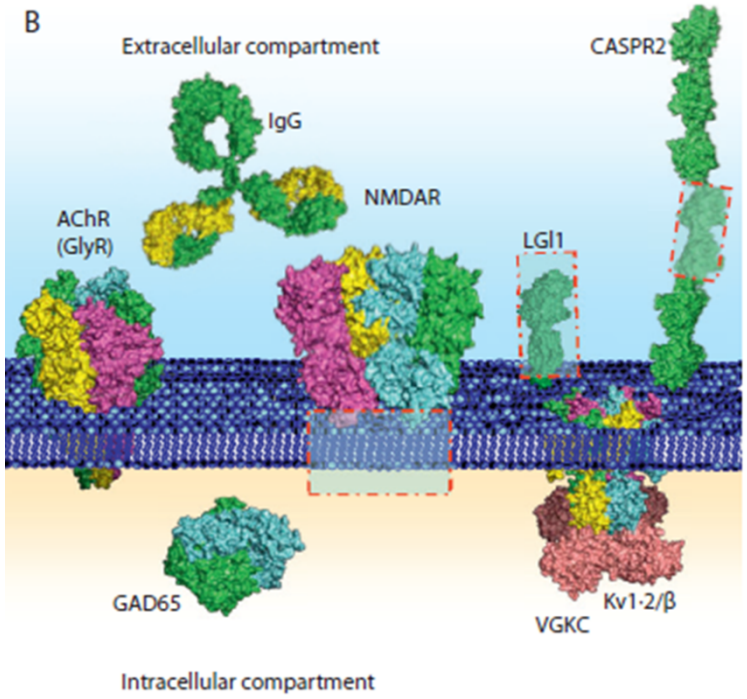
Anti neural-antibodies and CNS autoimmunity

Antibodies against neuronal surface antigens

- **VGKC** (LGI, CASPR2 and Contactin), AMPAR, GABA(A+B)R, **NMDAR**, Glycine R, D2R, DPPX

Antibodies against intracellular antigens

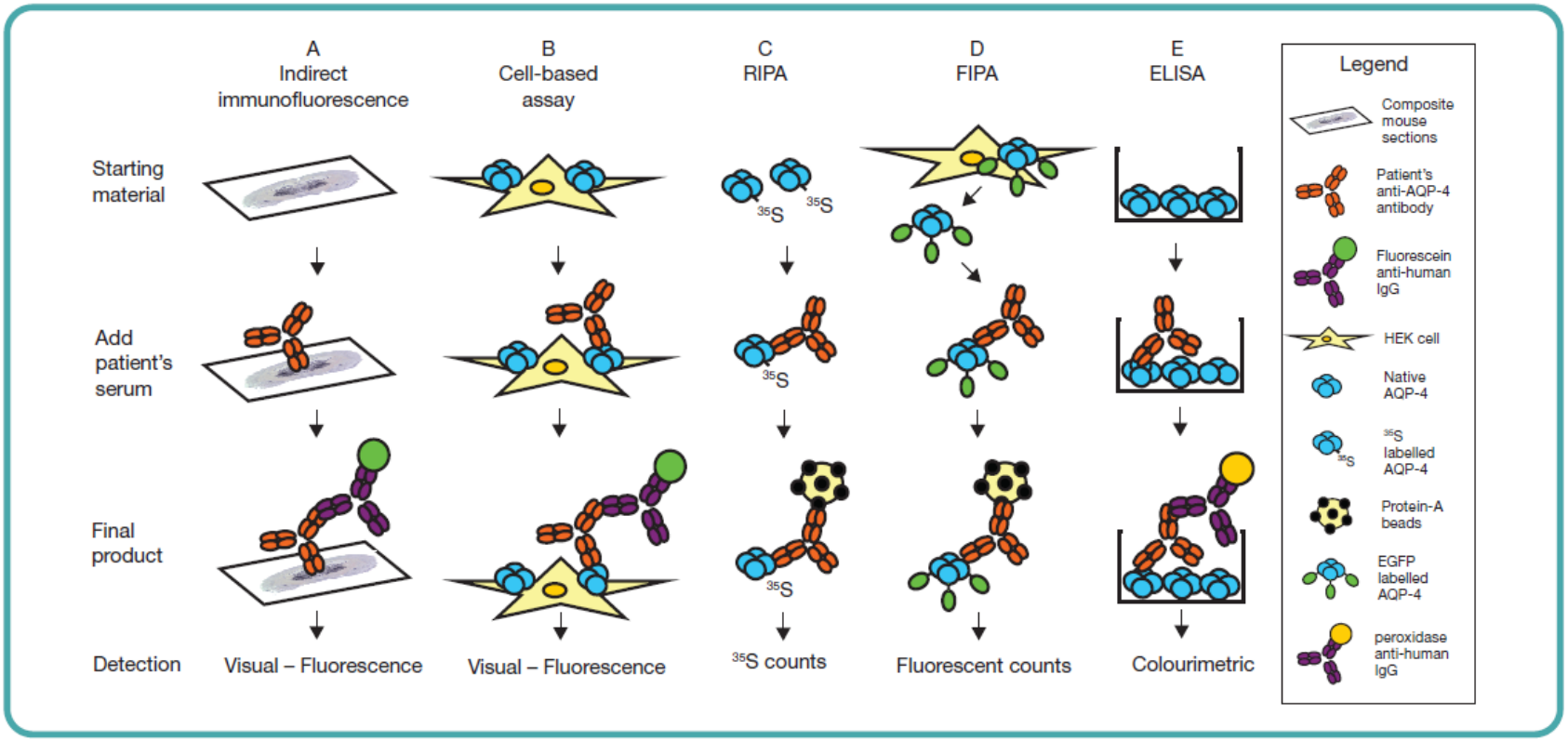
- Onconeural antibodies; Hu, Yo, Ri, CV2, amphipysin, Ma2.
- **GAD**



Vincent et al., 2011 ***Lancet Neurol*** 10(8):759-72

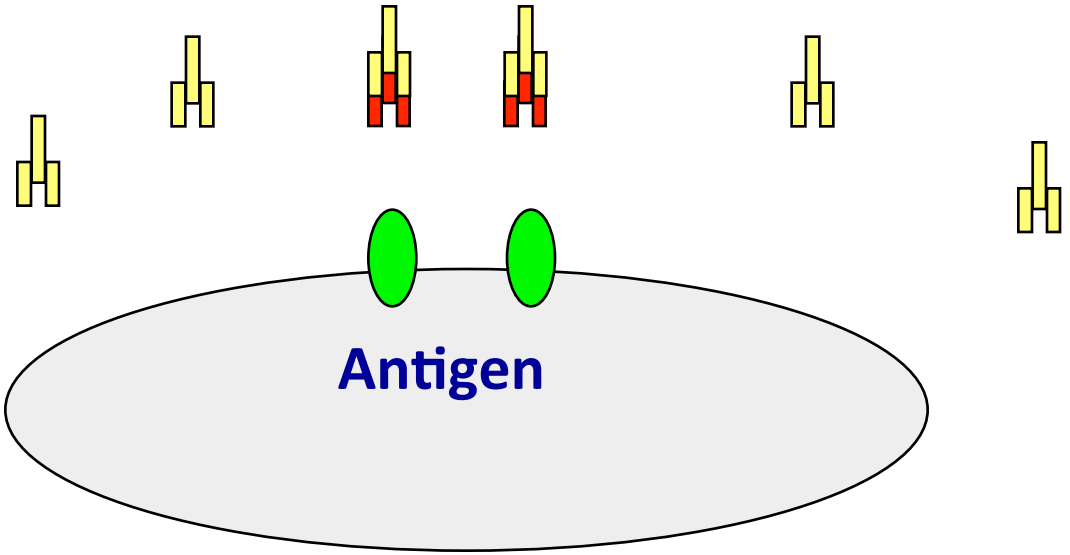
Lim et al., 2015 ***Pediatr Clin North Am*** 62(3):667-85

Measuring antibodies



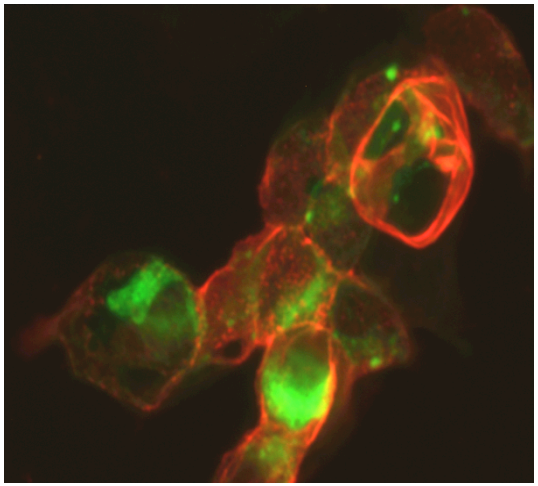
Courtesy of **Dr Patrick Waters**
NDCN, Oxford

Cell-based assays



Patient has antibodies

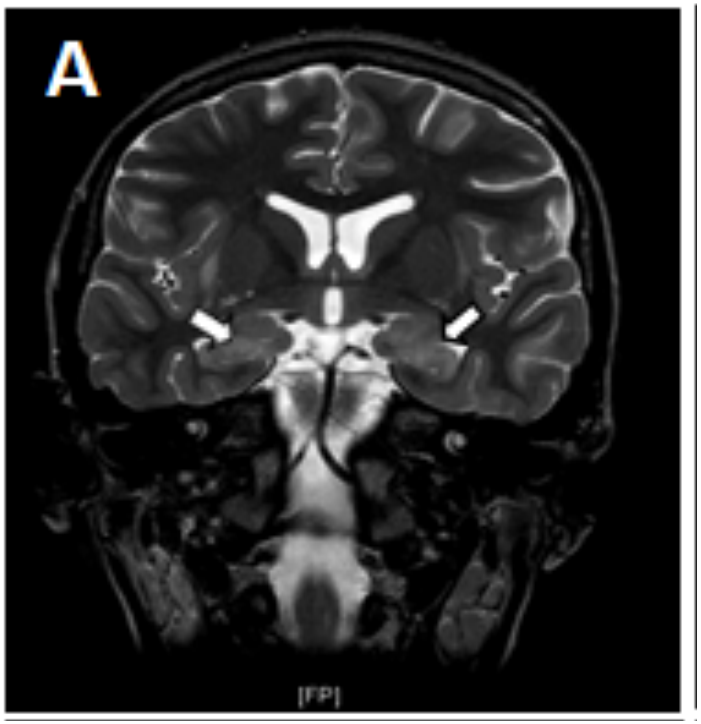
Binding can be scored visually or titrations performed



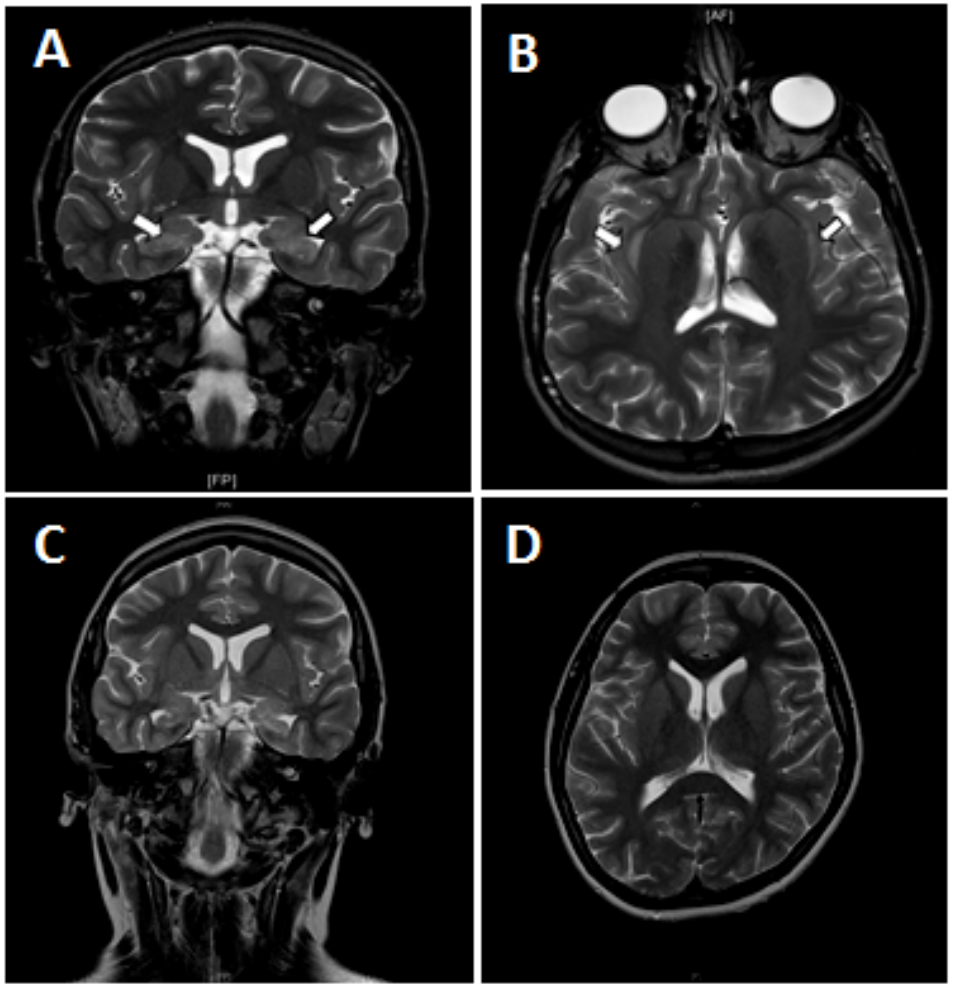
Courtesy of **Professor Vincent**
NDCN, Oxford

Case 1 15yr F

- GTCS
- 1/52 feeling unwell/rundown.
- Known to social services for violent episodes and regular cannabis use.
- Generalised +Rt Focal seizures. I +V for seizure control.
- Hallucination (auditory and visual), complaining of extreme pruritis, violent outbursts, delirious state.
- EEG slow wave Rt>Lt. Sharp wave Rt fronto-temporal parietal.



Case 1: progress



A treatable form of limbic encephalitis

Sub-acute onset of memory loss, seizures and personality change

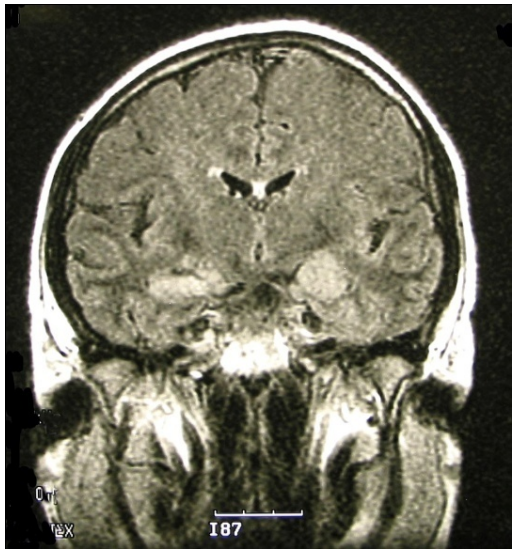
Sometimes seizures or psychosis only

Often low plasma sodium

VGKC-complex antibodies often very high titre

<10% tumours

Most respond well to immunotherapies



Vincent et al., 2004 ***Brain*** 127; 701-12
Buckley et al., 2011 ***Ann Neurol***. Jul;50(1):73-8.

Syndromes associated with antibodies to the VGKC-complex

- At least three accessory proteins; CASPR2, LGI1 and Contactin-2
  - CASPR2 found in patients with Morvan's syndrome or neuromyotonia, many of whom have paraneoplastic, often thymomas .
  - LGI1 found in patients with medial temporal lobe seizures associated with limbic encephalitis. Without an associated tumour

Irani et al., 2010 ***Brain*** 133(9):2734-48

- A distinct clinical syndrome – Faciobracial dystonic seizures (brief facial grimacing and ipsilateral arm dystonia) – associated with antibodies to LGI1

Irani et al., 2011 ***Ann Neurol*** 69(5): 892-900

Limbic encephalitis in children

- Haberlandt et al., 2011 ***Arch Dis Child.*** 96(2): 186-91

  10 patients from 12 centres

  8 patients have antibodies

  3 patients had VGKC

  Hu, Ma, 3 GAD

Range of paediatric VGKC positive patients

- **VGKC antibodies in paediatric encephalitis presenting with status epilepticus**

  Suleiman et al., 2011 ***Neurology*** 76 ; 1252-5

- **Immune-mediated steroid-responsive epileptic spasms and epileptic encephalopathy associated with VGKC-complex antibodies.**

  Suleiman et al., 2011 ***Dev Med Child Neurol*** 53(11); 1058-60.

- **Elevated VGKC-complex antibodies in a boy with fever-induced refractory epileptic encephalopathy in school-age children (FIRES).**

  Illingworth et al., 2011 ***Dev Med Child Neurol*** 53(11); 1053-7.

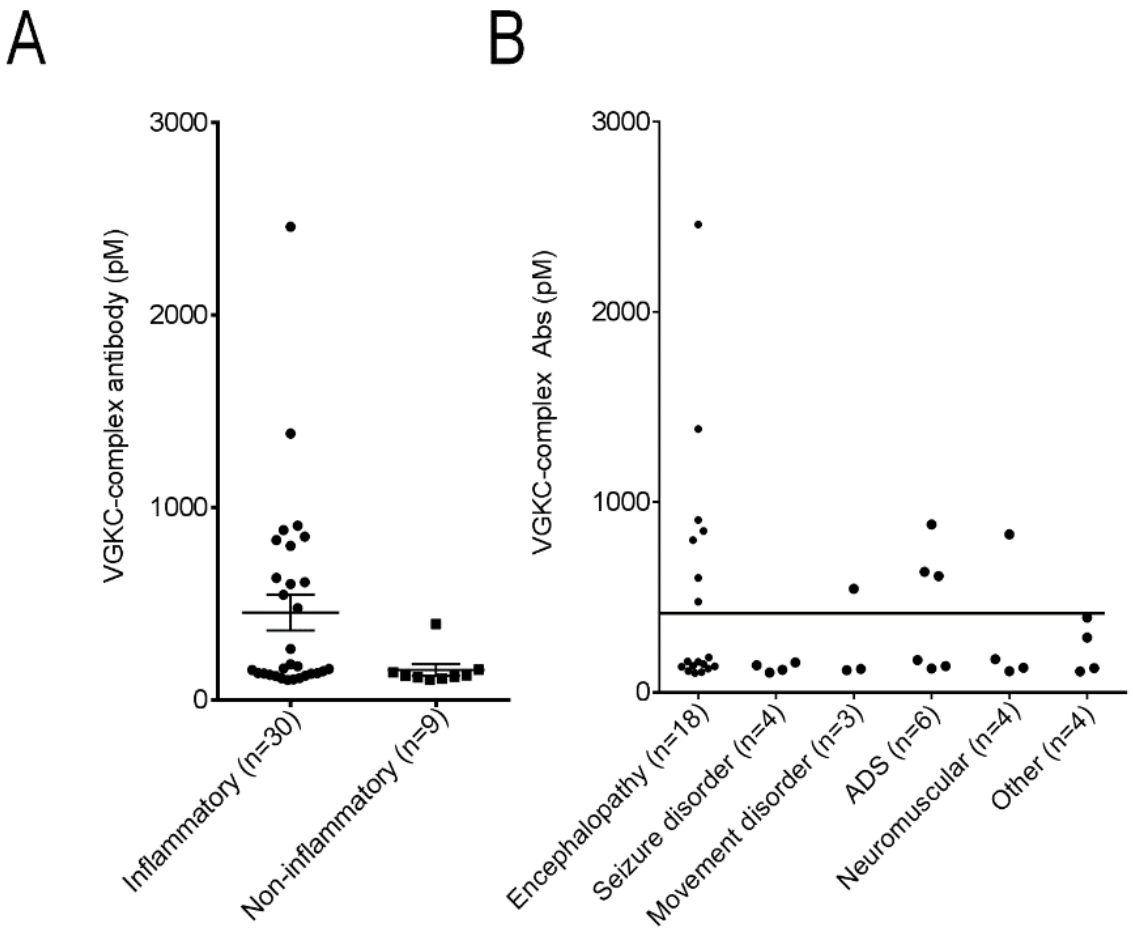
- **VGKC-complex antibody mediated encephalitis presenting with psychiatric features and neuroleptic malignant syndrome - further expanding the phenotype.**

  Iyer et al., 2012 ***Dev Med Child Neurol*** 54(6); 575-6

- **A clinico-radiological phenotype of voltage gated potassium channel (VGKC) complex antibody mediated disorder presenting with seizures and basal ganglia changes.**

  Hacohen et al., 2012 ***Dev Med Child Neurol*** 54(12); 1157-1159

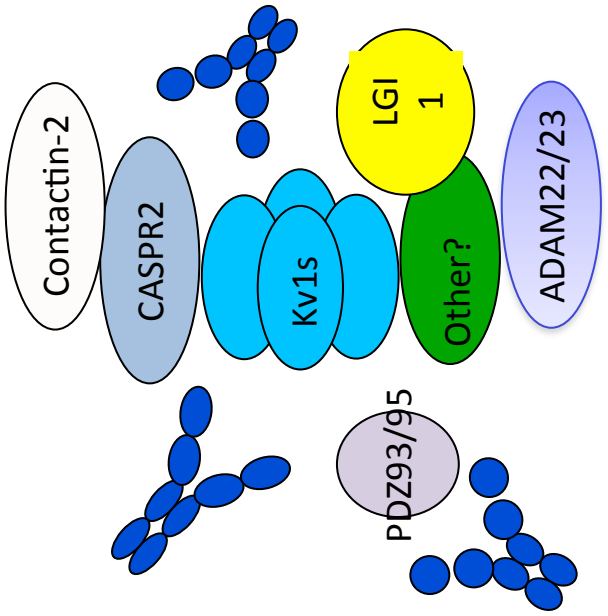
VGKC antibodies in children: what do they mean?



Hacohen et al., 2015 ***Neurology.*** Aug 21 [Epub ahead of print]

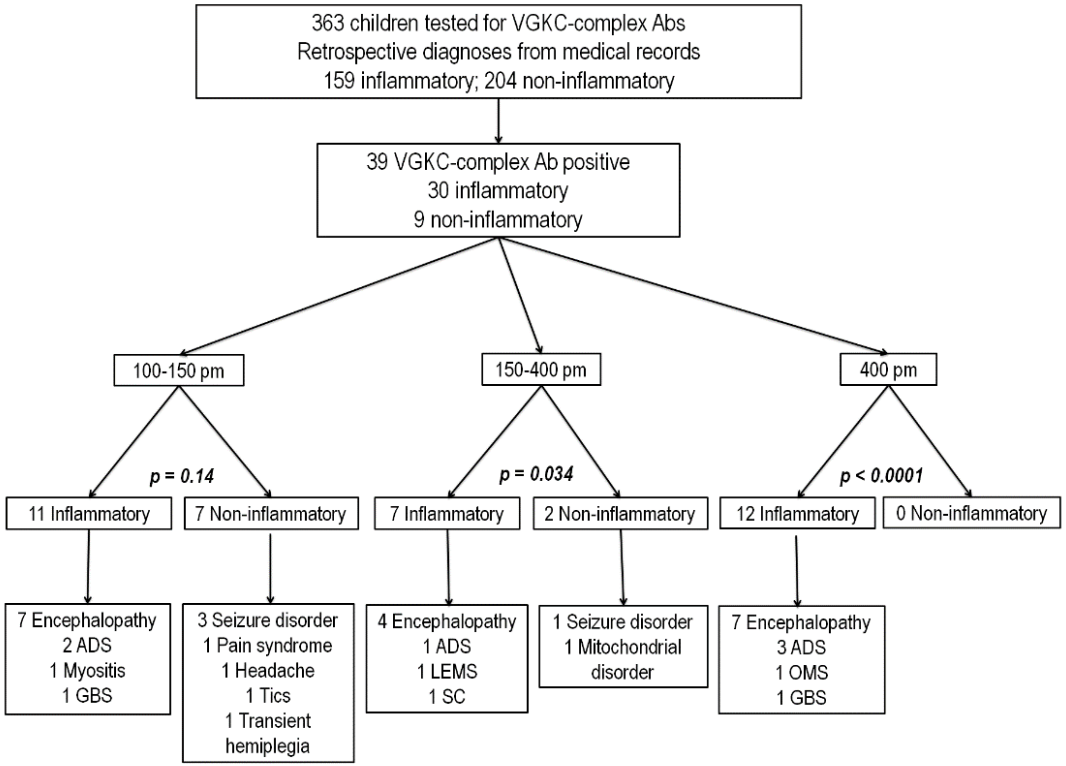
VGKC complex antigen identification in children

Antibody test	
Hippocampal neurons	4/39
LGI1	1/39*
CASPR 2	1/39*
Contactin-2	0/39
ADAM 22	0/39
ADAM 23	0/39
KV 1.1, 1.2, 1.6 (B2)	0/39
NMDAR	2/39



Hacohen et al., 2015 ***Neurology.*** Aug 21 [Epub ahead of print]

VGKC antibodies in children: what do they mean?



Hacohen et al., 2015 ***Neurology.*** Aug 21 [Epub ahead of print]

VGKC antibodies in children: what do they mean?

- Positivity of VGKC-complex Abs in children does not indicate specific syndrome
- Most sera do not bind to neurons
- Cell surface VGKC-associated proteins (LGI1, CASPR2) are not the target in the majority
- But …. VGKC-complex Abs appear to be non-disease specific biomarker of inflammatory conditions which may be immunotherapy response?

Other CNS antibodies associated with limbic encephalitis in children

- Glutamic acid decarboxylase (GAD)
  - Younger and often only had seizures without the other limbic feature
  - None had tumours
  - CSF active (OLB Positive)
  - More chronic disease

  Malter et al., 2010 ***Ann Neurol*** 67: 470-478
- GABA (B) receptor

  Lancaster et al., 2010 ***Lancet Neurol*** 9: 67-76
- GABA (A) receptor
  - Multifocal encephalitis

  Petit-Pedrol et al., 2014 ***Lancet Neurol*** 13(3):276-86

  Pettingill et al., 2015 ***Neurology*** 84(12):1233-41.

Other CNS antibodies associated with limbic encephalitis in children

- AMPA receptor

  Lai et al., 2009 ***Ann Neurol*** 67: 470-78

- Glycine receptor

  Refractory epilpesy syndrome in children

  PERM rare

  Hutchinson et al., 2008 ***Neurology*** 71(16) : 1291-2

  Carvajal-González et al., 2014 Brain. 137(Pt 8):2178-92

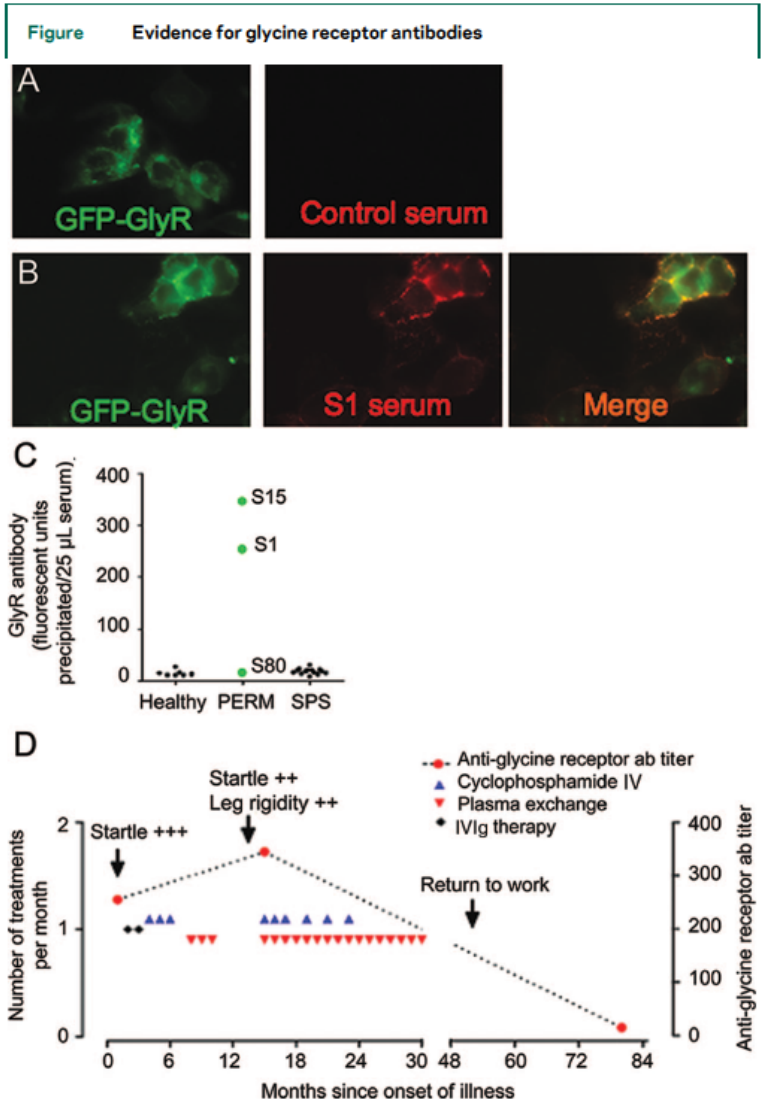
- Thyroid Abs

  Haberlandt et al., 2011 ***Arch Dis Child*** 96(2): 186-91

Case 2

Courtesy of **Dr Darshan Das**
Kings College Hospital, London.

Damásio et al 2013
JAMA Neurol. 70(4):498-501.



Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody

Hutchinson et al 2008 ***Neurology*** 71(16):1291-2

Progressive encephalomyelitis with rigidity and myoclonus (PERM)

- CNS spectrum of stiff person syndrome
  - GAD65
  - Amphiphysin
  - $GABA_A$ receptor associated protein
- Immunotherapy with IVIG benefits non paraneoplastic disorders

Panzer and Dalmau 2011 ***Curr Opin Neurol*** 24(4):346-53

PERM syndromes and GlyR Abs

Brainstem - startle, oculomotor abnormalities
Spinal cord - muscle rigidity and stiffness
spasms , very painful
Autonomic – sweating, urinary retention,
tachycardia, other
Encephalopathy in some patients

- Inhibitory synaptic transmission mediated by GABA and glycine is critical for regulating motor neuron excitability in the brainstem and spinal cord
- Loss of this input result in CNS hyper excitability causing exaggerated startle, stiffness, and spasms of the axis and limbs.

Carvajal-González et al 2014 ***Brain*** 137(Pt 8):2178-92

Paediatric GlyR-Ab

- 6 female patients; median age 7.5 yrs (range 1-15yrs)
- Initial Presentation
  - Refractory focal seizures (2)
  - Cognitive/behavioural changes (4)
    - Tremor and gait abnormalities (2)
    - PERM (1)
- Clinical progress
  - Seizures (total 5)
  - Cognitive/behavioural changes (6)
- **Diagnosis of encephalitis (3), auto-immune epilepsy (2) and PERM (1).**

Gadian et al., (manuscript in preparation)

Case 3

Presentation

6 weeks

NMDAR antibody encephalitis

- Antibodies to the N-methyl-D-aspartate subtype of glutamate receptors
- Both paraneoplastic and non-paraneoplastic forms
- Young women with ovarian teratomas
- Presentation with seizures, cognitive problems or psychiatric features

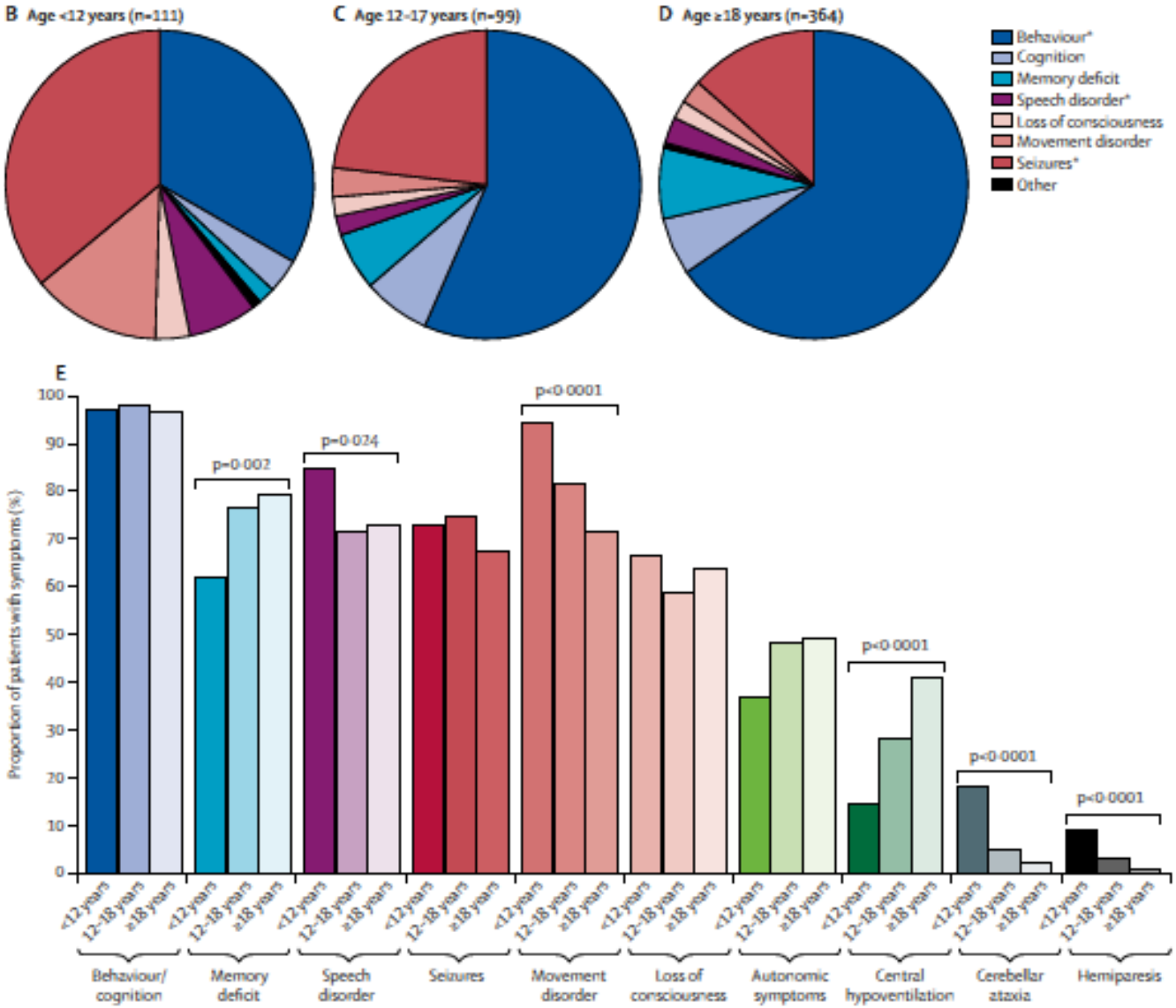
Dalmau et al., 2007 ***Ann Neurol*** 61(1); 25-36

NMDAR encephalitis in children and adolescents

- up to 40% <18
- Phenotype resembles that of the adults.
- Present in males
- Younger female patients are less likely to have tumors.
- Behavioral and speech problems, seizures and abnormal movement are common early symptoms.
- Dysautonomia and hypoventilation less frequent
- Good recovery

Florance et al., 2009 ***Ann Neurol*** 66: 11-18

Wright et al., 2015 ***Arch Dis Child.*** 100(6):521-6

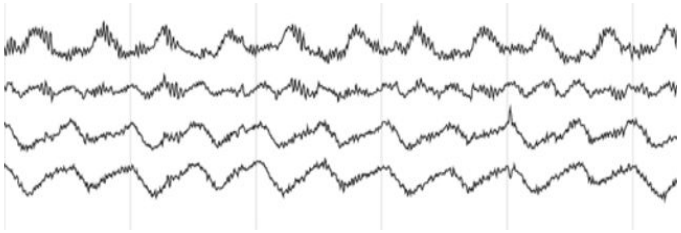


Titulaer et al., 2013 ***Lancet Neurol***. 12(2):157-65

Neurophysiology

- Extreme delta brush

Schmitt et al., 2012 ***Neurology*** 79:1094-1100



- Diffuse vs unilateral/focal correlates with poorer outcome

  Gitiaux et al., 2013 ***Clin Neurophysiol*** 124(12):2354-61

- 4 longitudinal electroencephalographic phases

  Nosadini et al., 2015 ***J Child Neurol.*** 30(2):238-45

Neuroimaging

- The clinical-radiological paradox
  - MRI abnormal in 33%
  - Reversible, subtle, non-enhancing lesions in both the grey and white matter.

  Titulaer et al., 2013 ***Lancet Neurol*** 61(1); 25-36

- Distinct white matter syndromes

  Hacohen et al., 2014 ***Neurol Neuroimmunol Neuroinflamm.*** 1(1):e2

- Overlapping syndrome

  Titulaer et al., 2014 ***Ann Neurol.*** 2014 Mar;75(3):411-28