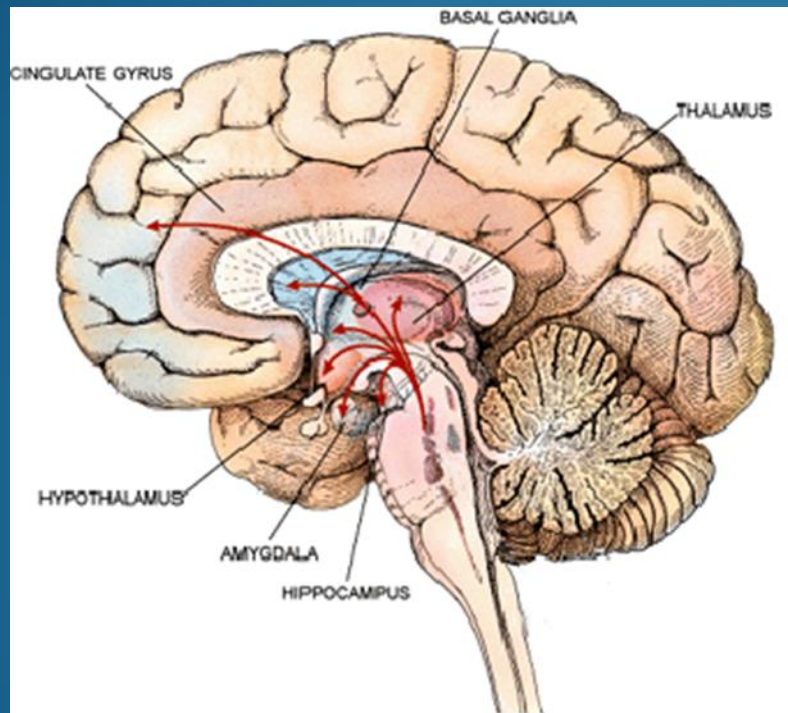
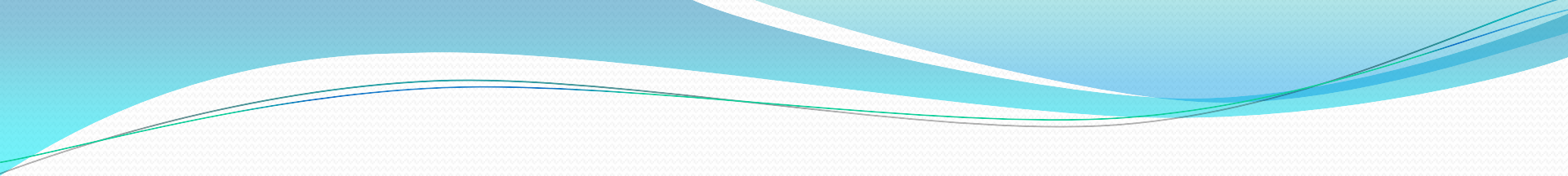


Auto-immune Encephalitis: An ever expanding field



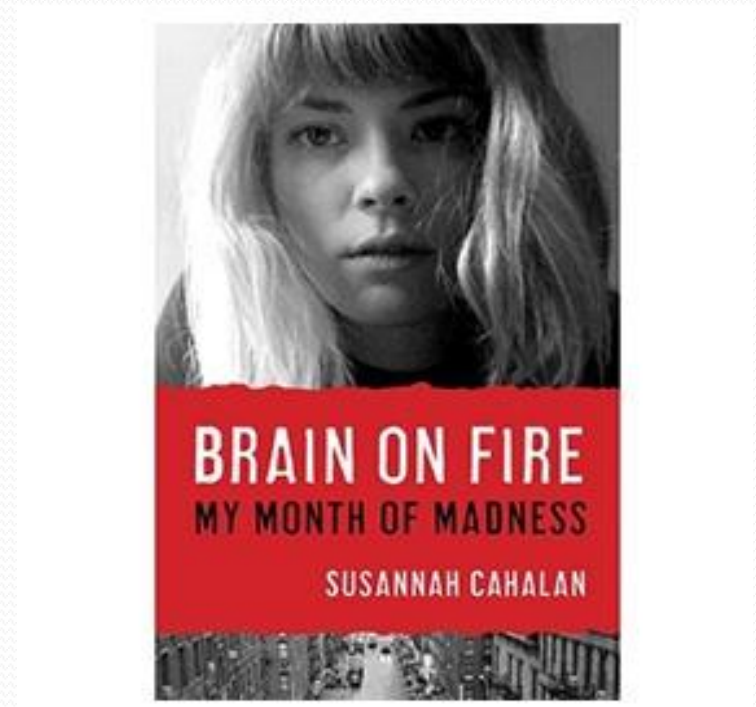
SJH Immunology Laboratory
Educational Meeting 04/11/15

Dr Caríosa Lee-Brennan

- 
- Autoimmune Encephalitis
 - Autoimmune Cerebellar Ataxia
 - Paraneoplastic Antibodies

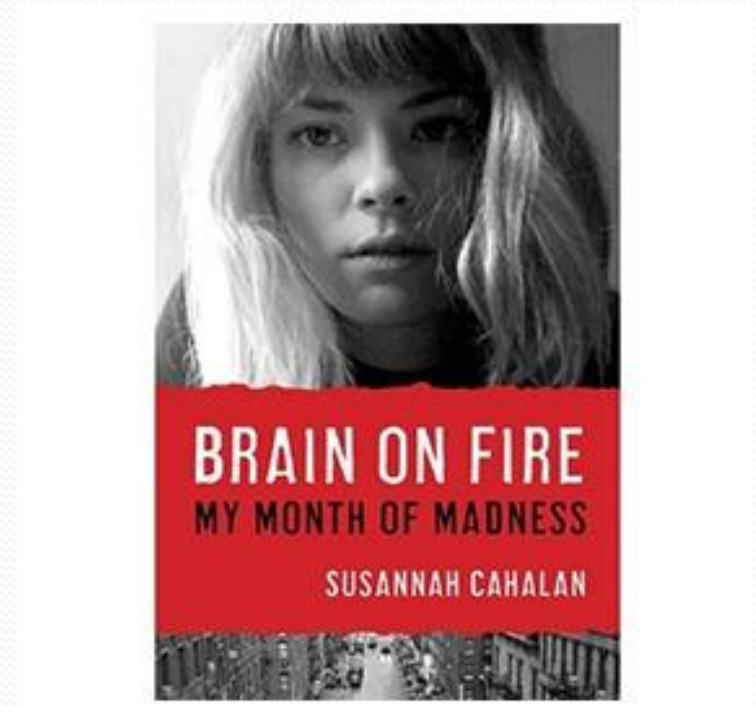
Auto-immune encephalitis

- Limbic Encephalitis
 - personality change/psychiatric symptoms
 - memory impairment
 - Seizures



Auto-immune encephalitis

- "My tongue twisted when I spoke; I drooled and, when I was tired, let my tongue hang out of the side of my mouth like an overheated dog."
- "What I remember most vividly is the fear. Fear and anger."

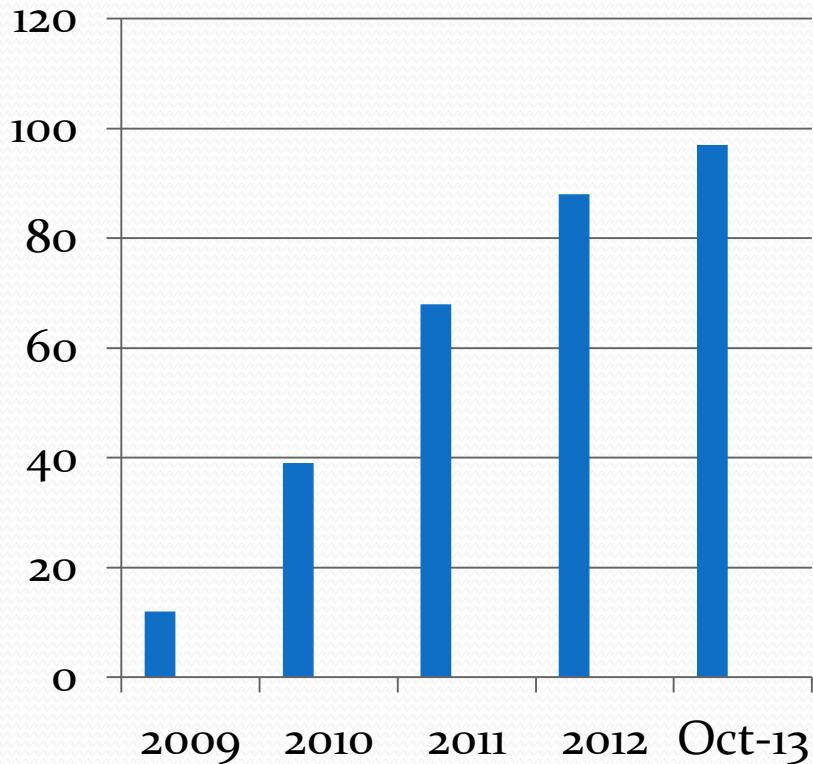


Autoantibodies associated with Encephalitis

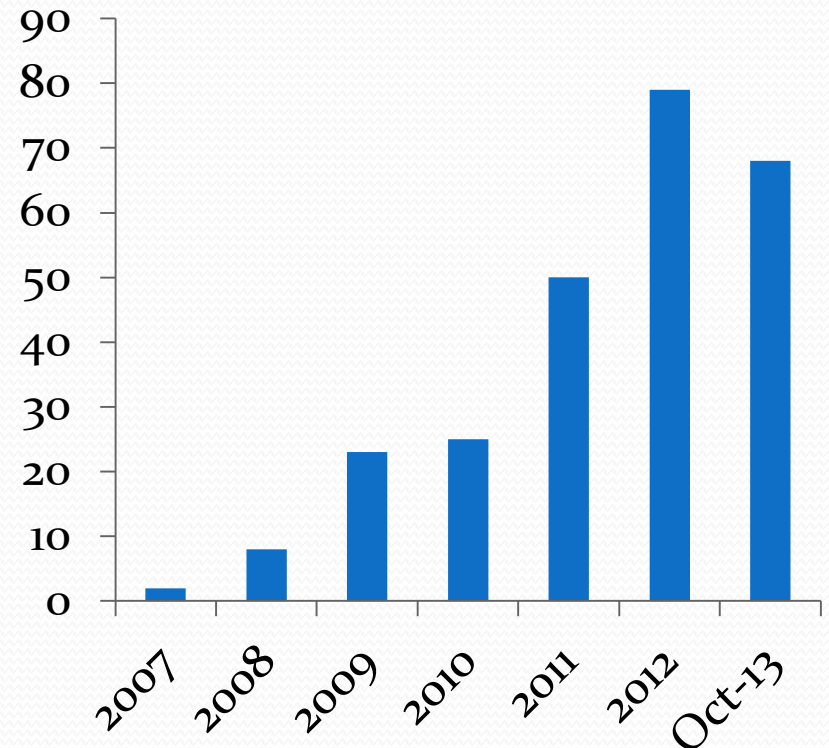
- NMDA Receptor
- LGI1
- Caspr2
- AMPA Receptor
- GABA-B & A Receptor
- Metabotropic Glutamate Receptor : mGluR5
- Glycine Receptor (GlyR)
- DPXX
- GAD65
- Dopamine 2 Receptor
- IgLON5

Beaumont Immunology Laboratory:

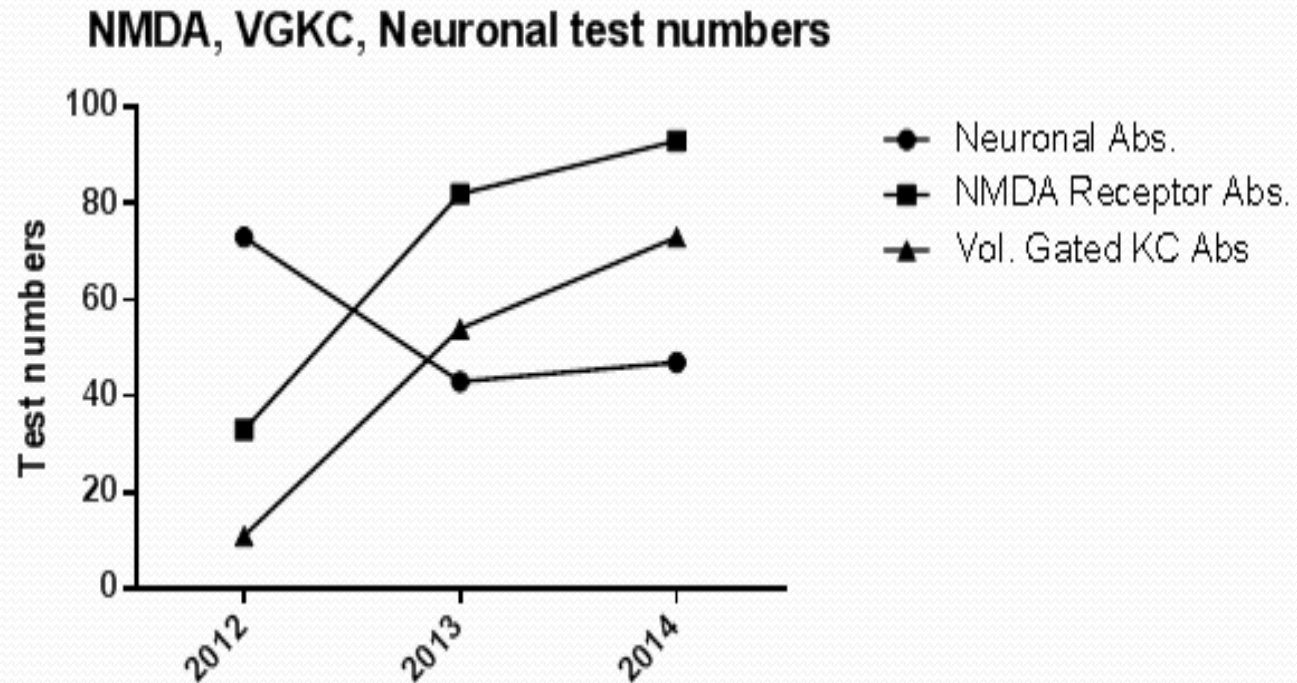
NMDAR antibody testing



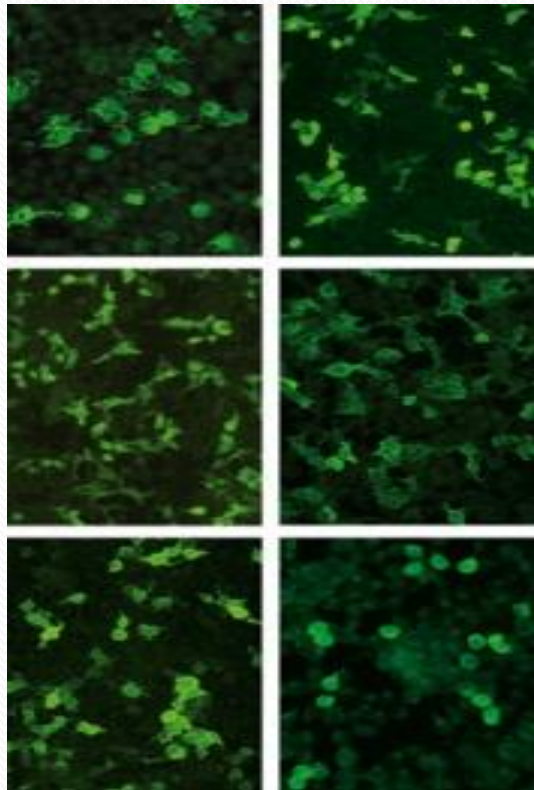
VGKC antibody testing



SJH Immunology Laboratory

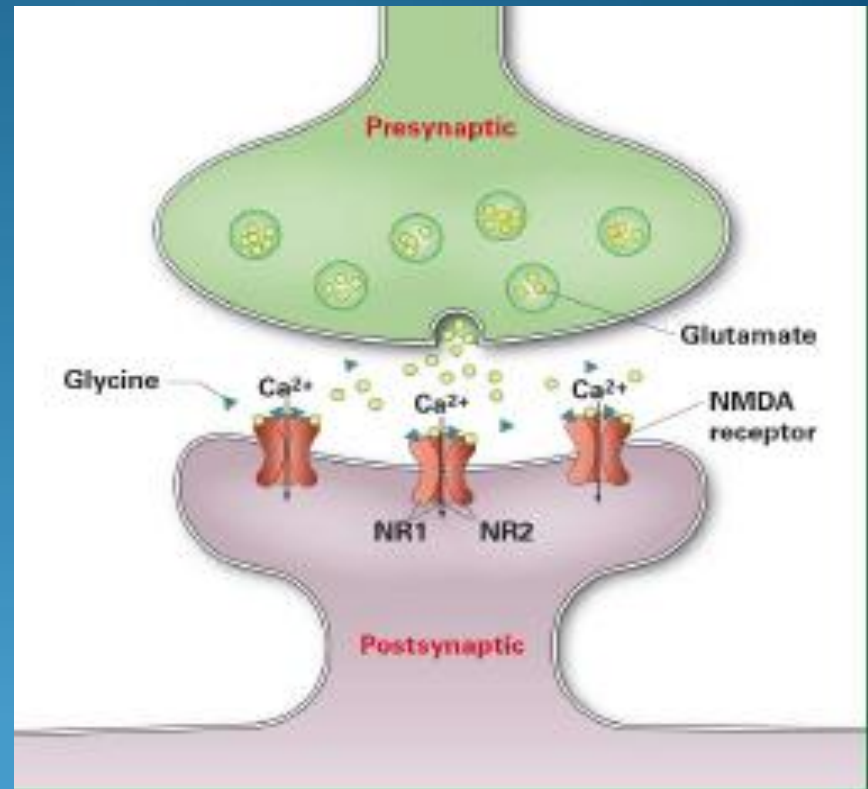


Euroimmun



- Mosaic BIOCHIP
- HEK293 transfected cells
- Serum & CSF
- NMDAR
- LGI₁
- CASPR₂
- AMPAR₁
- AMPAR₂
- GABABR

NMDAR encephalitis



NMDAR Encephalitis

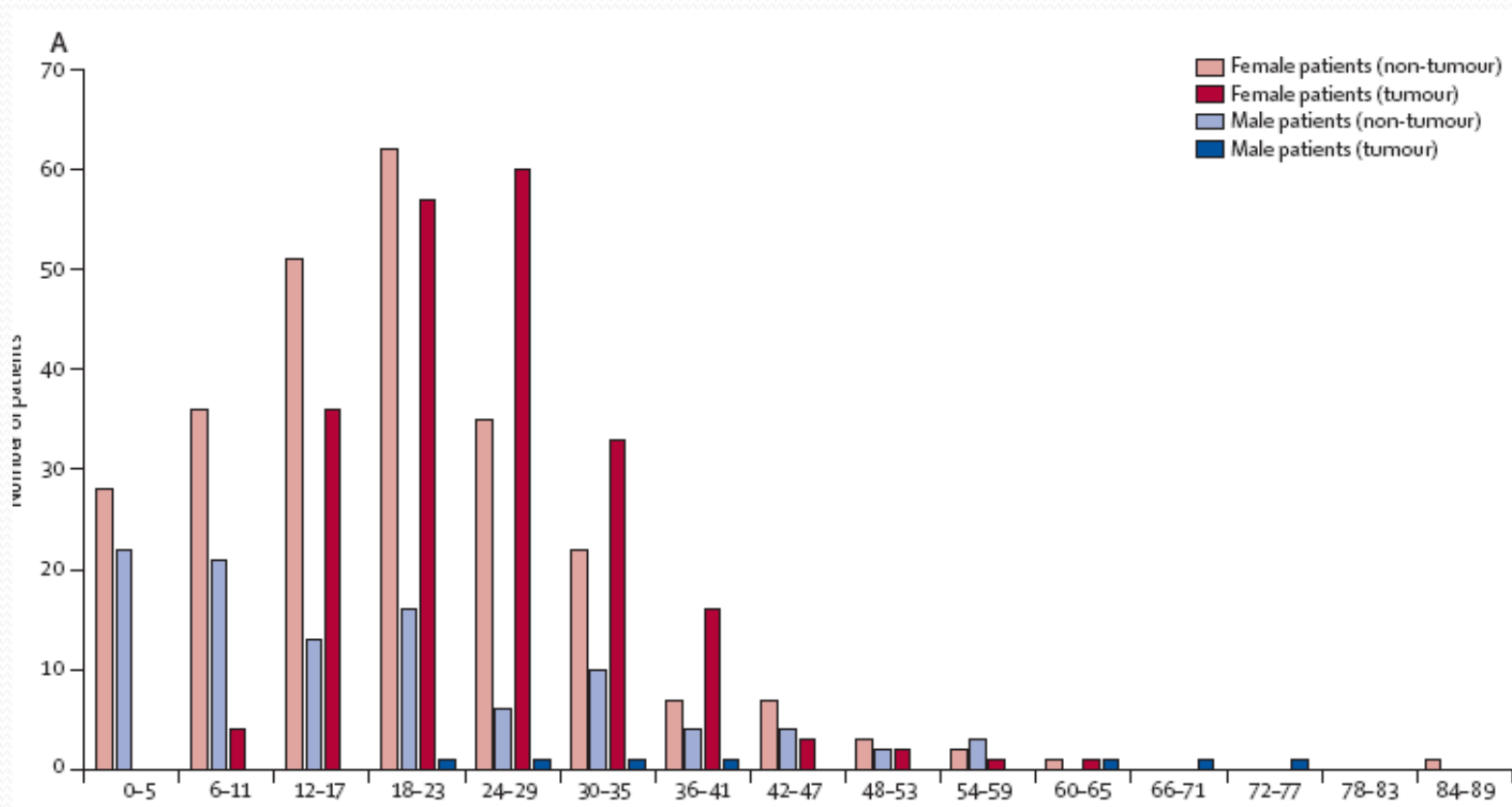
- *Vitaliani et al 2005:*
 - Syndrome of encephalitis, psychiatric symptoms and hypoventilation in ovarian teratoma
- *Dalmau et al 2007:*
 - Detection of anti-NMDAR antibodies



Demographics

- Women: 80-90%
- Reported in all ages
 - 8 months-85 years *Titulaer et al 2013*
- Most commonly in age 18-35 years
- Males are usually < 12 or >45 years
- 20-60% have a tumour

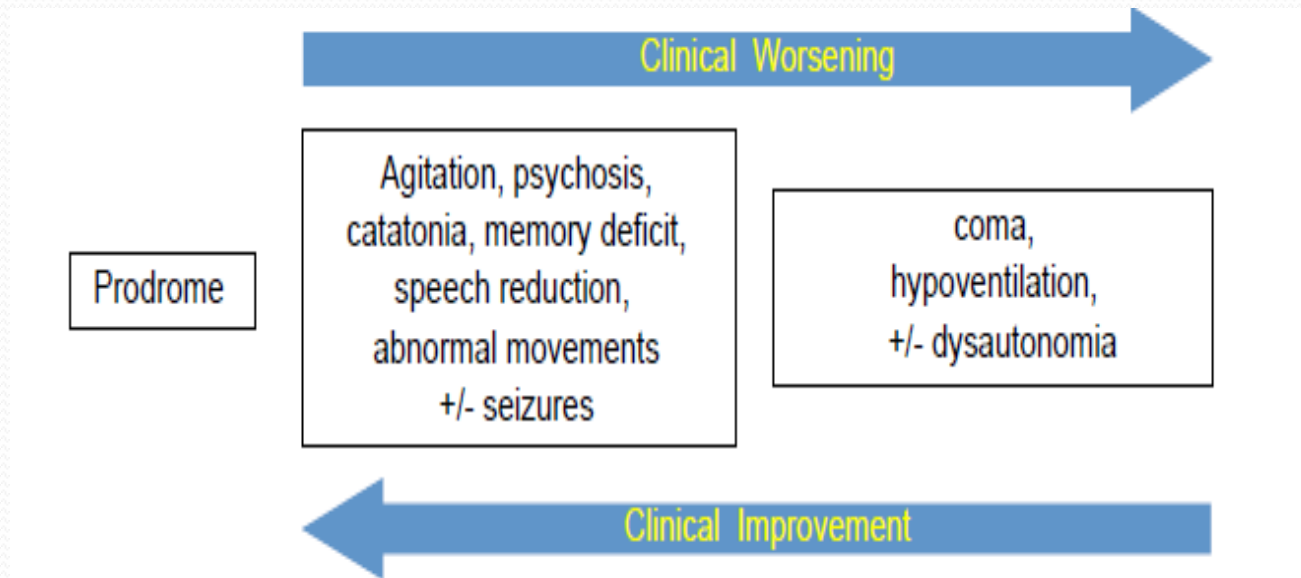
Tumour distribution by age and sex



Tumour types

- Ovarian teratoma
 - 94% of tumours *Titulaer et al 2013*
 - Tumours show intense expression of NR2 subunit of the NMDAR
- Extraovarian teratomas
 - mediastinum, testis
- Other tumours
 - neuroblastoma, Hodgkin's, sex cord-stromal tumour, SCC of lung, pancreas, thymic carcinoma, breast, ovarian

Clinical Features



Clinical Features

- Prodrome:
 - 70%
 - headaches, fever, vomiting, URT symptoms
 - Inflammatory event causing temporary or localised disruption of the blood-brain barrier
 - Allows antibodies to gain entry to the CNS
- Reported after vaccination
- Reported after Herpes Simplex Encephalitis (HSE)

Clinical Features

- Psychiatric Symptoms
 - Within 2- 3 weeks
 - Anxiety, paranoia, delusions, agitation, bizarre behaviour, grandiosity, mania, hyper-religiosity
- Short term memory loss
- Loss of language
- Children
 - Temper tantrums, irritability, hyperactivity

Clinical Features

- Seizures
- Movement disorders
 - Tremor, writhing, rigidity, abnormal eye movements, abnormal posture, elaborate motions of arms and legs
 - More common in children
 - Atypical features: hemiparesis, cerebellar ataxia also commoner in children

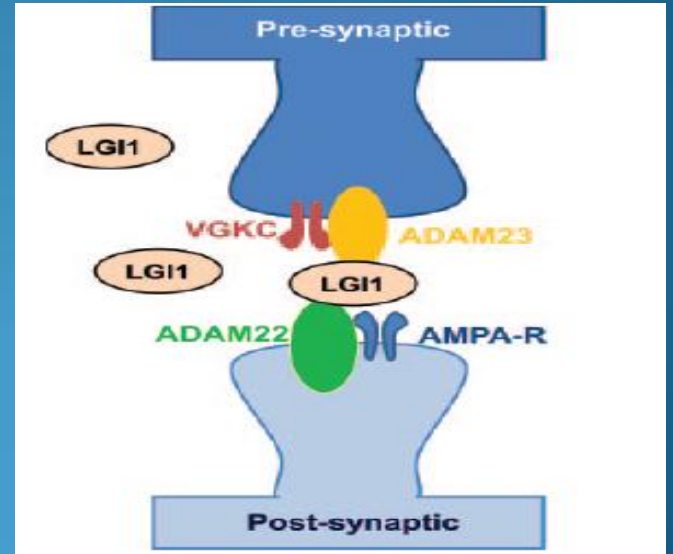
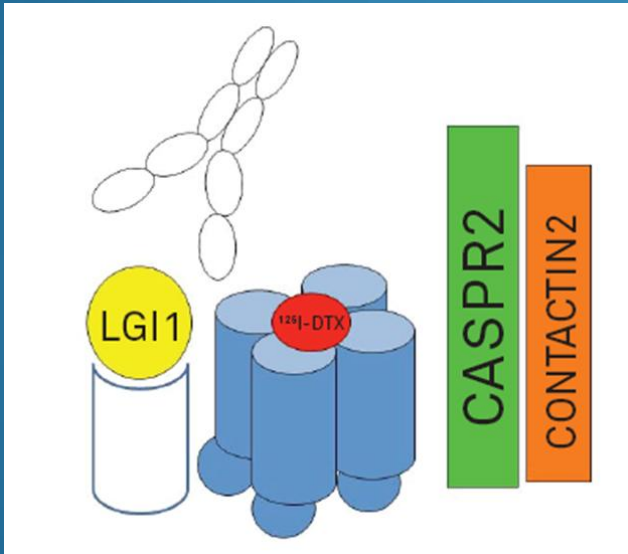
Clinical Features

- Autonomic Dysfunction
 - Hyperthermia, tachycardia, hypertension, hypersalivation, bradycardia, hypotension, urinary incontinence, erectile dysfunction
- Hypoventilation requiring ventilation

Treatment & Outcomes

- Tumour removal
- Steroids, IVIg, Plasma exchange, Rituximab, cyclophosphamide, MMF
- Recovery or mild disease: 75-80%
- Relapse 12-25%
- Mortality 4-6%
- Prolonged recovery

VGKC-associated encephalitis



VGKC antibodies: Associated conditions

- Limbic encephalitis
- Acquired neuromyotonia
 - Peripheral nerve hyperexcitability
 - Muscle cramps & stiffness, slow relaxation, twitching
- Morvan's Syndrome
 - Neuromyotonia, autonomic dysfunction, insomnia

LGI1 antibody-associated Disease

- Limbic encephalitis: amnesia, confusion, neuropsychiatric disturbance, seizures
- Hyponatraemia (SIADH)
- Males: 65%
- Age 30-80 (median 60)
- <20% tumour: thymoma, lung

Irani et al Brain 2010

Caspr2-associated disease

- Morvan's Syndrome
 - Neuromyotonia
 - Autonomic dysfunction: sweating, cardiovascular instability, constipation, urinary complaints
 - Encephalopathy: confusion, hallucinations, agitation, infrequent seizures, insomnia
 - Neuropathic pain
 - Weight loss
 - Thymoma: 40%
 - Male: 85-93%
 - Age 19-80 years (median 57)

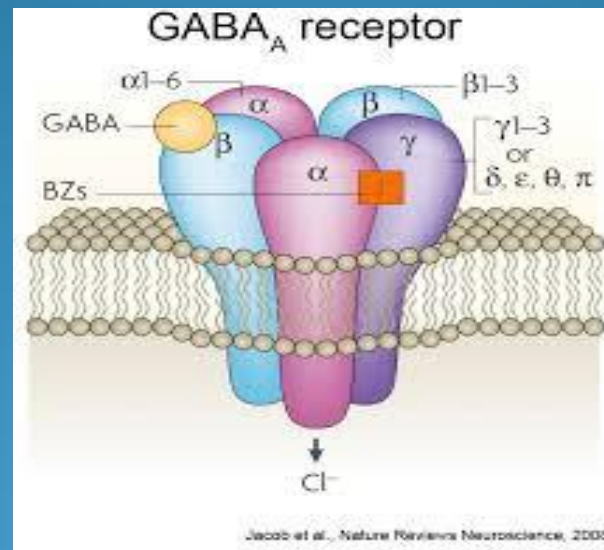
Caspr2-associated disease

- Neuromyotonia only
- Encephalitis only
- Cerebellar ataxia
 - 9 /88 cases positive
 - Tremor, abnormal gait
 - Subacute or insidious onset
 - 1 patient also had encephalitis and was positive for VGKC antibodies

Becker et al JNNP 2012

- Both LGI1 and Caspr2 antibodies
 - Encephalitis
 - Neuromyotonia
 - Neuropathic pain
- *Klein et al 2013*
 - 26% VGKC positives were positive for LGI1 or Caspr2
 - Low positive VGKC antibodies were clinically significant
- Contactin 2 antibodies
 - Found in 3 patients with Caspr2 antibodies and cardiovascular instability
 - Expressed in cardiac conduction tissue

GABAR encephalitis



GABA-B R encephalitis

- 16-77 years
- Male:Female 3:2
- Limbic encephalitis: Seizures, memory loss, confusion, Hallucinations, personality change
- *Hoftberger et al 2013*
 - Status epilepticus
 - Ataxia
 - Opsoclonus-myoclonus: rapid eye movements, twitching

GABA-B R encephalitis

- 50% Tumours
 - SCLC
 - Male
- Neurological symptoms respond to immunotherapy or cancer treatment
- Poorer prognosis
 - Presence of other antibodies: Amphiphysin, SOX1, Ri
 - Those with SCLC

Hoftberger et al 2013

GABA-A R encephalitis

- 6 patients
- 3-63 years, 5 males
- Encephalitis with refractory seizures and status epilepticus
- Hodgkin's: 1 patient
- CSF & serum
- Low titre, Serum only:
 - other autoantibodies: GAD65, NMDAR, ANA
 - Encephalitis, stiff-person syndrome, opsoclonus-myoclonus

AMPA encephalitis

AMPA encephalitis

- 2/3 Female
- 7-92 years
- Encephalitis: memory loss, behaviour change, agitation
- Seizures less common
- Tumours: 50-70% (lung, breast, thymic carcinoma, thymoma, ovarian)
- Cerebral atrophy: 20%

mGluR5 encephalitis

mGluR5 antibody-associated disease

- Ophelia Syndrome
- Limbic encephalitis
 - Depression
 - Personality change
 - Memory deficits
 - Delusions, hallucinations
 - Seizures
- Myoclonus
- Hodgkin's Lymphoma



GlyR encephalitis

Glycine receptor antibody-associated disease

- Age 1-75 years (median 50)
- 2/3 females
- Progressive encephalomyelitis
- Rigidity
- Myoclonus: Brief involuntary twitching
- Hyperekplexia: Pronounced startle responses
- Malignancy: uncommon
 - Thymoma, lymphoma, breast

DPXX encephalitis

DPXX encephalitis

- 4 cases
 - 2 males
 - 45-76 years
 - 3: prodromal diarrhoea and weight loss
 - Encephalitis
- 3 cases
 - PERM: progressive encephalomyelitis, rigidity and myoclonus
 - 2 had GIT symptoms

GAD65 encephalitis

GAD65 encephalitis

- Stiff-person syndrome
- Limbic encephalitis
- Cerebellar ataxia
- Tumours: lung, thymic
- Epilepsy
 - Young women
 - Non-malignant

Dopamine 2 (D2) receptor encephalitis

D2 receptor encephalitis

- 12 children
- Movement disorders
 - Dystonia, tremor, parkinsonism, chorea
- Agitation, anxiety, psychosis, sleep disorders
- Responds to immunotherapy but residual deficits seen
- Subset of patients with Sydenhams' chorea
 - Rheumatic fever

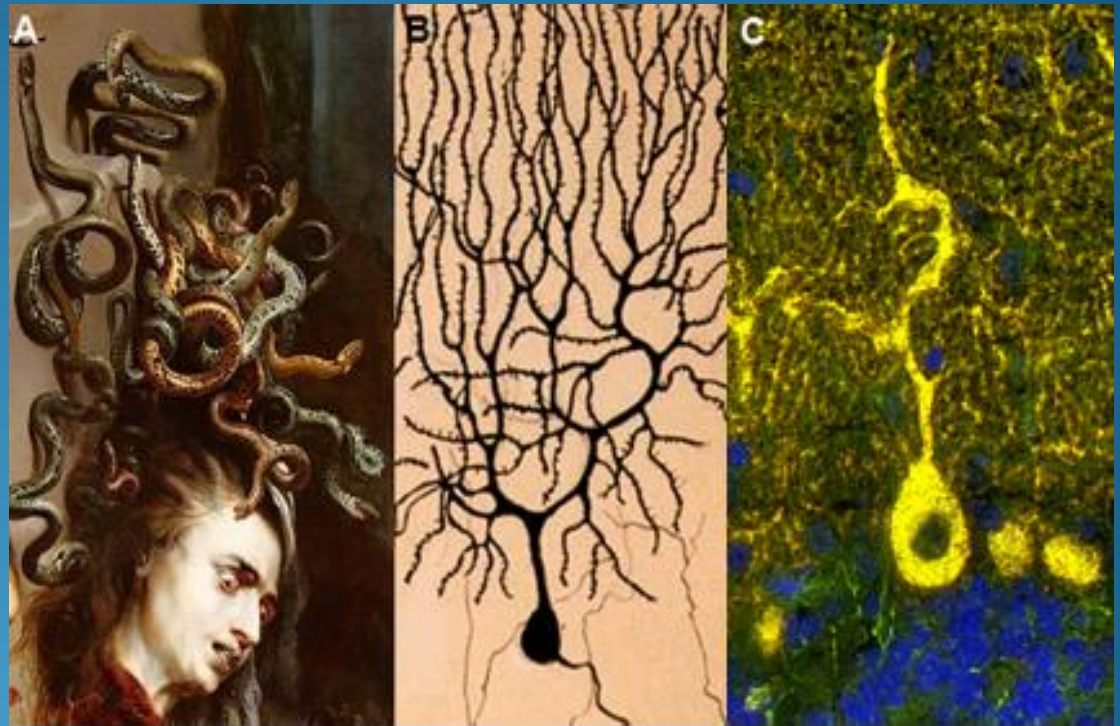


IgLON5 encephalitis

IgLON5 encephalitis

- *Sabateur et al Lancet Neurol 2014*
 - 8 patients
 - 52-76 years
 - 5 females
 - Subacute/prolonged presentation: 6 months-12 years
 - Sleep disorders
 - Abnormal movements, OSA, stridor
 - Dysarthria, dysphagia, ataxia, chorea
 - No response to immunotherapy
 - 6 dead at time of publication
 - Neuronal loss, extensive deposition of hyperphosphorylated tau

Autoimmune Cerebellar Ataxia



Cerebellar ataxia

- Unsteady gait, falls, swaying
- Tremor
- Difficulty with rapid movements
- Inaccurate movement: pass-pointing
- Speech abnormalities
- Nystagmus: abnormal eye movements
- Paraneoplastic & non-paraneoplastic
- 12 antibodies: staining resembles a Gorgon's head

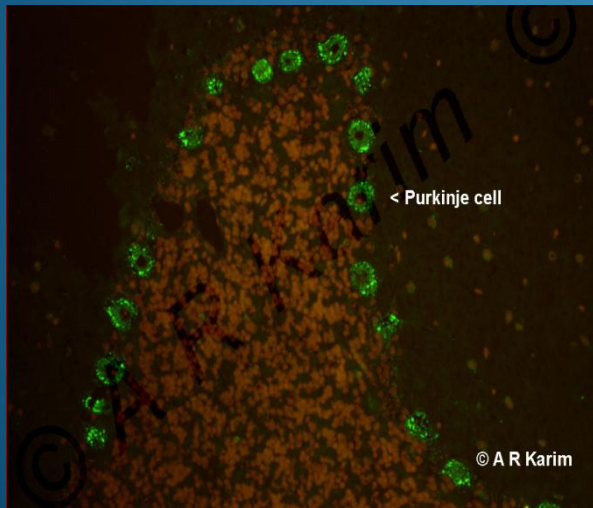
Autoimmune cerebellar ataxia

Antibody	Features	Tumour
Yo	Ataxia Poor prognosis Rare in men	Ovary, breast, uterus, fallopian tubes, cervix
Tr/DNER	Ataxia Cerebellar atrophy	Hodgkin's Lymphoma
mGlyR ₁	Ataxia Encephalitis	3/5: Hodgkin's, prostate
VGCC	Ataxia, LEMS	SCLC, prostate, NHL, non-paraneoplastic
PCA-2	Ataxia, encephalitis, neuropathy: non-specific	SCLC

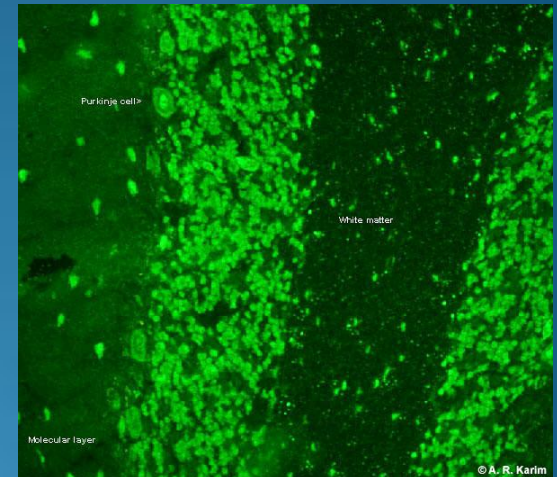
Autoimmune cerebellar ataxia

Antibody	Features	Tumour
Homer-3	Ataxia, encephalitis (1)	1/4 : lung
Sj/ITPR ₁	No response to steroids	None yet
CARP VIII	2 patients. Poor prognosis	Melanoma, ovary
PKC-gamma	Symptoms precede tumour x 2-3 months	2/2: Non-small cell lung, liver
Ca/ARHGAP26	MRI: progressive atrophy 50%: post-infection	1/6: Ovary
Nb/AP ₃ B ₂	1 patient: ataxia,	None
GluR σ ₂	Ataxia, encephalitis (GluR ϵ ₂) Associated with infection or vaccination	None

Paraneoplastic neuronal antibodies



Amphi-physin	
CV2	
PNMA2 (Ma2/Ta)	
Ri	
Yo	
Hu	
Recoverin	
SOX1	
Titin	
Zic4	
GAD65	
Tr (DNER)	
Control	



Encephalitis associated with Paraneoplastic antibodies

Antibody	Tumour	Associated conditions
Ma1	Breast, other tumours	Brainstem encephalitis
Ta/Ma2	Testicular	
CV2/CRMP5	Small Cell lung Cancer (SCLC), thymoma	Polyneuropathy, optic neuritis, cerebellar degeneration
Hu	SCLC, neuroblastoma	Cerebellar degeneration, neuropathy
PCA2	SCLC	Polyneuropathy, LEMS, ataxia
ANNA3	SCLC	Neuropathy, cerebellar degeneration

Other paraneoplastic antibodies

Antibody	Disease	Tumour
Yo	Cerebellar degeneration	Breast, ovarian
Ri	Opsoclonus-myoclonus, cerebellar degeneration	Breast
Amphiphysin	Stiff person syndrome	Breast, SCLC
GAD	Stiff person syndrome	Breast, SCLC, colon
MAG	Peripheral neuropathy	MM, Waldenstrom's
VGCC	LEMS	SCLC
Tr1	Cerebellar degeneration	Lymphoma
Recoverin	Retinopathy	SCLC
SOX1	LEMS	SCLC
ZIC4	Cerebellar degeneration	SCLC



Any Questions?