Autoimmune encephalitis - History & current knowledge

By Finn E. Somnier, M.D., D. Sc. (Med.),
Department of Clinical Biochemistry, Immunology and Genetics,
Staten's Serum Institute, Copenhagen, Denmark

Introduction

The acute fulminating epidemic form of **encephalitis lethargica (von Economo, EL)** seems to have disappeared, since there have been no further reported epidemics after 1916-1927. During that period of time, both **rheumatic fever** (RF) and **Sydenham chorea** (SC) were associated with and later proven to be provoked by streptococcal infections. The occurrence of RF including SC has become much less frequent in the industrial world.

Unfortunately, sporadic cases of similar encephalitis are still reported and presenting with

- Neuropsychiatric symptoms, including behavioural problems, attention deficit/hyperactivity disorder (ADHD), obsessions, compulsions (OCD), anorexia, bulimia, anxiety, depression, psychosis, stupor, sleeping disorders: drowsiness, sluggishness (lethargy), sleep inversion
- Cognitive problems, memory loss or amnesia, ataxia, mutism, parkinsonism, oculogyric crises, tics, chorea, catatonia, epilepsy, myoclonus, myokymia

- These **patients range <1 and 70 years of age**, but are *most frequently children or teenagers*

At least, four key features appear to be evident	**Courses of these disorders**
➢ Idiopathic (as yet of unknown cause) ➢ Post-infectious (viral, bacterial and more) ➢ Paraneoplastic ➢ Genetic predisposition ➢ (Consider possible immunodeficiency)	➢ Monophasic ➢ Multiphasic (relapsing, recovering) ➢ Chronic - with or without relapses - with continuing problems of neuropsychiatric and movement disorders
Wide range of clinical appearances and courses ❖ Mild with a single or only a few symptoms • May mimic a psychiatric disorder and not arise suspicion of encephalitis ❖ More complex symptomatology • The patient may be seen by either a neurologist, paediatrician or a psychiatrist depending on the presenting symptoms ❖ Fulminating and maybe lethal course	

More recent discoveries appear to point towards a variety of different aetiologies of EL-like disorders and within a context of autoimmune encephalitis.

Background

The 1916-1927 epidemics of encephalitis lethargica (von Economo, EL)
The patients, mostly children of either sex, characteristically presented with headache and malaise, lethargy, insomnia, sleep inversion, ophthalmoplegia, catatonia, parkinsonism, and psychosis.

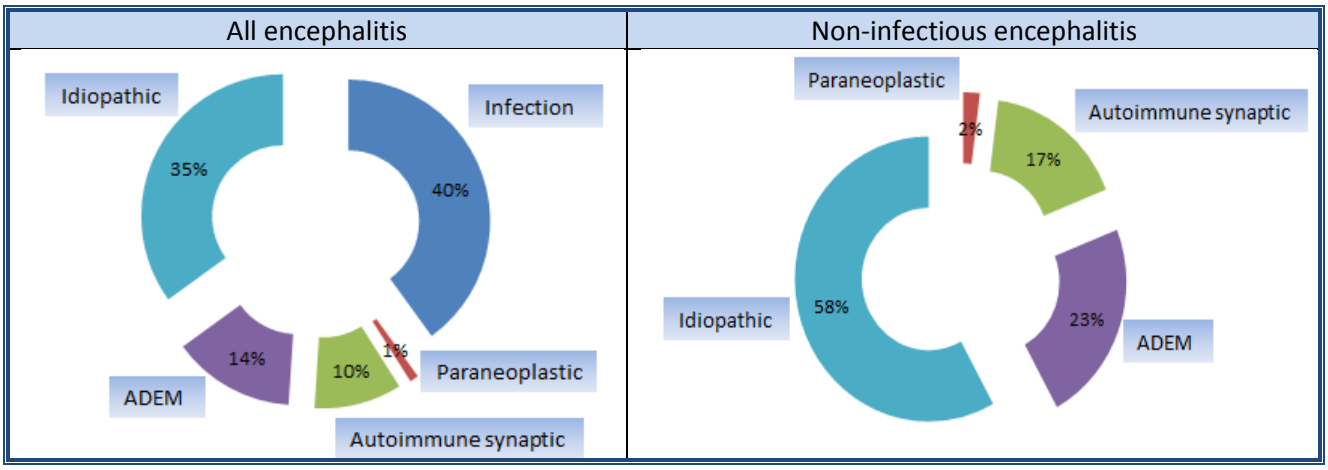
The evidence for EL as caused by flu is mostly of an associative nature, and delivery of more direct evidence has failed

- EL was associated by many observers to the influenza epidemic (Spanish flu), which expanded from America to Europe
- However, the epidemic of EL began earlier and lasted longer, and which - in contrast to the flu – spread from Europe to America
- Influenza is a known cause of viral meningoencephalitis, although extremely rare
- Post-influenza encephalitis syndrome is extremely rare
- Flu virus has not been found in archival post-mortem tissue
- Experimental infections with the reconstituted 1918 virus in mice did not identify virus outside the lung, including brain

Summary: previously, we have known very little about the aetiology of EL

It is not until the more recent decades that a concept of autoimmune encephalitis has become recognized

Epidemiology



Current knowledge

In recent years there is an increasing description of novel anti-neuronal & anti-glial antibodies that are associated with paraneoplastic and non-paraneoplastic neurological syndromes. These antibodies are useful in clinical practice to **confirm the immune-mediated origin** of the neurological disorder and are **helpful in tumour search**.

Currently, such antibodies can be classified according to the location of the recognized antigen into **three major groups:**

1. **Intracellular antigens**
   - Neuronal nuclear
     - Hu (ANNA1), Ri (ANNA2), ANNA3
   - Neuronal or muscular cytoplasmatic
     - Yo (PCA1), Tr, PCA2, Ta (Ma2), Ma1, ZIC4, Gephyrin, CARP8, ENO1, striational (Titin, RyR1, etc.)
     - Presynaptic vesicles: GAD, Amphiphysin
   - Glial
     - CV2 (CRMP-5, POP66, oligodendrocytes), Bergman (AGNA, SOX-1), ENO1

2. **Antigens located in the cell membrane**
   - Voltage- or ligand-gated CSF or plasma membrane structures
     - Ionotropic channels and receptors
       - AChR (adult, foetal, alpha3, M1-types), NMDAR (NR1, NR2), AMPAR (GluR1, GluR2), calcium- & potassium-channels (Ca-channel (P/Q-type), potassium channel K_{IR}4.1), GlyR-alpha1
     - Metabotropic channels and receptors
       - D1, D2, $GABA_B$R1, mGluR1, mGluR5
   - Other membrane structures
     - AQP4 (astrocytes), MuSK, CASPR2, myelin oligodendrocyt glycoprotein (MOG), gangliosides including lyso-GM1, ENO1

3. **Extracellular location of antigens**
   - Synaptic proteins: LGI1

Different techniques are established for detecting these antibodies:

1. Tissue-based assay (TBA), detecting most of the antibodies
2. Cell-based assay (CBA)
3. Immunoblot (IB), immunoprecipitation assay (IP)
4. ELISA

The group of disorders associated with antibodies to cell surface or synaptic proteins appears to be characterised by a more promising outcome of therapy – as opposed to those associated with autoantibodies to intracellular structures.

Neuroscience and Child & Adolescent Psychiatry / Neurology possibly analogous symptoms			
Disorder	Aliases, various diagnoses	Presenting and distinctive features	Autoantibodies and more
Autoimmune encephalitis – autoimmune psychosis			
Anti-NMDAR encephalitis: frequent in children and in a major number of cases previously categorised as of unknown aetiology	Dyskinetic encephalitis lethargica	Behaviour changes, cognitive dysfunctions, loss of memory, seizures, psychosis, dyskinesias, catatonia, sleep disorder, mutism, and sometimes, hypoventilation	Anti-NMDAR (glutamate NR1); maybe with a coexistent teratoma and also associated with mycoplasma pneumoniae infection, herpes simplex encephalitis, Guillan-Barré syndrome
PEM = paraneoplastic encephalomyelitis	Limbic encephalitis and more	Personality changes, disorientation, memory loss, anxiety, OCD	Anti-Ta (Ma2, testis tumour), anti-Tr (morbus Hodgkin), anti-LGI1, and many others
Autoimmune post-streptococcal neurological syndrome	Broad spectrum of autoimmune encephalitis: PANDAS, PANS, CANS, Sydenham chorea, Tourette syndrome, basal ganglia encephalitis, encephalitis lethargica, acute or relapsing encephalitis?	Dyskinesias: tics (motor, vocal), chorea (usually affecting limbs), facial grimacing; motoric hyperactivity, obsessive compulsive disorder (OCD); fear, anxiety; epilepsy (including multifocal myoclonus); slowed cognition; hypotonia, multifocal myokymia; gait ataxia; anorexia, bulimia; sleep disorders	Anti-lyso-GM1, anti-D1, anti-D2, anti-Tubulin, CamKII
ADEM: acute disseminated encephalomyelitis	Usually (93%) follows an infection of some kind: viral or bacterial; occasionally, a vaccination	Confusion, drowsiness, and even coma; unsteadiness and falling; trouble swallowing; weakness of arms or legs; visual blurring or double vision	Anti-MOG
CNS anti-AQP4 autoimmunity in children		Optic neuritis, transverse myelitis, or both; episodic cerebral symptoms (encephalopathy, ophthalmoparesis, ataxia, seizures, intractable vomiting, or hiccups)	Anti-AQP4
Hashimoto 's thyroiditis	Hashimoto's encephalopathy	Disorientation, psychosis, concentration and memory problems, tremors, jerks in the muscles (epilepsy)	Anti-alpha-Enolase 1, Anti-Thyreoglobulin, anti-Thyroid Peroxidase, anti-TSH receptor
Rasmussen's encephalitis		Mental deterioration, seizures, loss of motor skills and speech, hemiparesis	Unknown, since a previous report of anti-GluR3 as a feature cannot be reproduced

Overview of paraneoplastic encephalitides: autoantibodies vs. neoplasms			
Short name (alphabetical order)	Alias: anti-	Primary analysis	Associated neoplasms
AGNA	SOX1		SCLC
Anti-AMPAR	GluR1/2		SCLC, non-SCLC, thymoma, breast
Anti-Amphiphysin		Yes	Breast, SCLC
Anti-BRSK2			SCLC
Anti-CASPR2			Thymoma
Anti-CV2	CRMP5,POP66	Yes	SCLC, thymoma
Anti-EFA6A			Ovarian
Anti-GAD			SCLC, thymoma, breast
Anti-Gaba$_B$R1	GABBR1		SCLC
Anti-Hu	ANNA-1	Yes	SCLC, non-SCLC,
Anti-K-channel (anti-CASPR2, anti-LGI1)	VGKC, VGPC		SCLC, thymoma
Anti-LGI1			90% idiotypic else paraneoplastic
Anti-mGluR1			Ovarian, morbus Hodgkin
Anti-mGluR5			Morbus Hodgkin
Anti-NMDAR	NR1		Idiotypic or teratoma
Anti-Neurofilament			Neuroblastoma
Anti-PCA-2			SCLC
Anti-Ri	ANNA-2, Nova-1	Yes	SCLC, non-SCLC, breast, ovarian
Anti-Ta	Ma2, PNMA2	Yes	Testicular, ovarian
Anti-Tr	Purkinje cell (Tr)		Morbus Hodgkin
Anti-Yo	APCA-1, CDR-62	Yes	Breast, ovarian, SCLC
The true targets of antibodies previously attributed to voltage-gated potassium channels (VGKC) may in many cases by the recently reported antigens LGI1 and CASPR2 . LGI1 and CASPR2 are closely associated structures of the $K_v1.1/K_v1.2$-channel complex.			

Autoimmune epilepsy & psychiatry			
Autoantibodies	**Autoimmune disorder**	**Characteristic epileptic activity**	**Psychiatry**
Anti-NMDAR (NR1)	Encephalitis	Generalized motor Status Dystonic fits	Behavioural or personality change, psychosis
Anti-AMPAR (GluR1, GluR2)	Encephalitis	Focal motor seizures Generalized tonic-clonic seizures	Behavioural change, confusion, confabulation, agitation, combativeness, perseveration
Anti-AMPAR (GluR3)	Encephalitis	Myoclonic, maybe refractory	
Anti-LGI1	Limbic encephalitis	Faciobrachial tonic seizures; similar fits also affecting the lower extremities, slightly slower than typical myoclonus Generalized tonic-clonic seizures	Confusion, personality change or psychosis
Anti-GABA$_B$R1	Encephalitis	Complex partial seizures Partial or generalised motor Generalised tonic-clonic seizures Status.	Behavioural problems, confusion, disorientation, confabulation, agitation, paranoia, gustatory and/or visual hallucinations, psychosis
Anti-D1, anti-D2, anti-lyso-GM1	Post-streptococcal neurology	Multifocal myoclonic Multifocal myokymia	OCD, anxiety, fear
Anti-GAD	Stiff-person complex, encephalitis	Motor seizures, maybe refractory	Unspecific, resembling psychosomatic
Anti-GlyR alpha1	Stiff-person complex, encephalitis	Motor seizures	Unspecific, resembling psychosomatic
Anti-Hu	Paraneoplastic encephalomyelitis, neuronopathy	Motor seizures Epilepsia partialis continua Status	Mental status and mood changes
Anti-CV2 (CRMP5)	Paraneoplastic encephalitis	Motor seizures Status	Mental status and mood changes

Co-occurrence of autoantibodies						
Autoantibody	Anti-AMPAR	Anti-$GABA_BR1$	Anti-GAD	Anti-GlyR alpha1	Anti-ENO1	Anti-Hu
Anti-NMDAR				X		
Anti-AMPAR			X			
Anti-$GABA_BR1$			X			
Anti-GAD	X	X		X		
Anti-GlyRalpha1			X			
Anti-CV2 (CRMP5)	X					X
Anti-VGCC	X	X				X
Anti-VGKC(LGI1, CASPR3)				X		
AGNA (anti-SOX1)	X	X				
Anti-BRSK2		X				
Anti-Amphiphysin						X
Anti-Ri						X
Anti-Zic4						X
Anti-thyreoglobulin					X	
Anti-thyroid peroxidase		X		X	X	
Anti-TSH receptor					X	
Anti-M					X	
Anti-dsDNA	X					
ANA	X					
Anti-Cardiolipin	X					

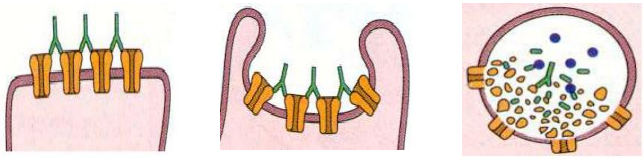
Immunological mechanisms

It is likely that T-cell mediated autoimmunity is a key factor of many of the "classical" paraneoplastic neurological disorders associated with autoantibodies directed at intracellular epitopes.

In contrast, it appears that autoantibodies associated with synaptic encephalitis operate by cross-linking their targets resulting in immunomodulation (more rapid internalization of such structures), and thereby resulting in a relative lack of receptors being attacked. *Fortunately, there are also scientific data to suggest that activated complement is not a feature of synaptic encephalitis.* Moreover, it appears that there are copious infiltrates of plasma cells/plasmablasts (antibody-secreting) in the CNS of some of these patients. Such documented mechanisms are in agreement with the reported reversibility of autoimmune synaptic encephalitis upon adequate immunotherapy provided that such remedy is initiated as soon as possible, since such structures may be synthesized and then at a rate greater than that of the loss.

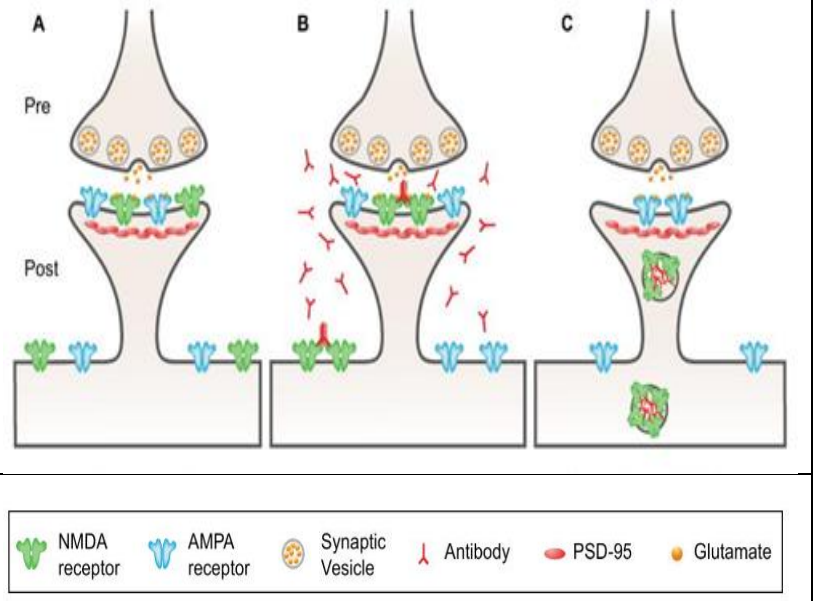
Synaptic encephalitis

Mechanisms of antibody-induced loss of receptor



Modulation of the number and density of receptors

Mechanisms underlying cellular and synaptic effects of anti-NMDA receptor antibodies



A-C: AMPA and NMDA receptors are localized in the postsynaptic membrane and are clustered at the postsynaptic density (A). Patient antibodies in the CNS bind selectively to NMDA receptors at the synapse as well as extrasynaptic receptors. This binding leads to receptor cross-linking (B). NMDA receptors that have been bound and cross-linked by antibodies are internalized, resulting in a decrease of surface, synoptically localized NMDA receptors. Other synaptic components, such as postsynaptic AMPA receptor clusters, PSD-95, as well as presynaptic terminals, dendrite branches, dendritic spines and cell viability, are unaffected (C). Thus patient anti-NMDA receptor antibodies lead to a rapid, selective excision of NMDA receptors from neuronal membranes. This effect is titer-dependent and reverses after antibody titres are reduced (not shown). J Neurosci. 2010 April 28; 30(17): 5866–5875

Experimental autoimmune encephalitis

- 2003: passive transfer of mGluR1 antibodies
- 2004: transfer of T-cells specific for the onconeural antigen Ma1
- 2005: passive transfer of anti-Amphiphysin
- 2010: passive transfer of anti-NMDAR (J Neurosci. 2010 April 28; 30(17): 5866–5875)
- 2012: Lewis rat animal model of Sydenham chorea and related neuropsychiatric disorders

Presenting symptoms of autoimmune encephalitides that frequently are not paraneoplastic

Please note that usually, fever is not a feature

Neuropsychiatric symptoms

- Behavioural problems, changed personality
- Depression, anxiety, fear, psychosis, hallucinations
- Attention deficit/hyperactivity disorder (ADHD)
- Obsessions, compulsions (OCD)
- Anorexia, bulimia

Neurological features

- Memory loss or amnesia
- Movement disorders & dystonia: motor or vocal tics, chorea, myokymia, oculogyric crises, catatonia, parkinsonism, rigidity, acute dystonia
- Epilepsy: generalized, partial, myoclonus
- Aphasia, mutism
- Nystagmus, ataxia
- Sleeping disorders: drowsiness, sluggishness (lethargy), sleep inversion
- Decreased level of consciousness, stupor, unconsciousness
- Autonomic features: instability of BT, hypoventilation, respiratory failure

Nephrologic

- Hyponatriaemia

Apart from in Hashimoto's encephalitis, Rasmussen's encephalitis and anti-GlyR encephalomyelitis, it appears that usually, **paresis is not a feature**

In an individual patient, the clinical features can vary from one or a few symptoms to a more complex combination from this palette. The severity may be from mild to very severe. An expected finding of a particular autoantibody as well as distinguishing clinical features – in other words, the likelihood of any particular type of autoimmune encephalitis versus others, is related to the more specific molecular mechanisms. *However and to speed up the diagnostic procedure, consider testing serum and often also CSF for all relevant autoantibodies at once.*

Reported presenting and subsequently occurring symptoms vs. specific type of autoimmune encephalitis

Anti-NMDAR encephalitis	○ Behavioural or personality change, psychosis ○ Cognitive dysfunctions, loss of memory ○ Dyskinesias, dystonia, or stereotyped movements, catatonia ○ Speech reduction ○ Seizures, status epilepticus ○ Sleep dysfunction, e.g. excessive daytime sleepiness (associated with decreased level of hypocretin) ○ Autonomic instability, decreased consciousness, hypoventilation (about 25%) ○ Recently, anti-NMDAR (IgA) has been reported in schizophrenia without noticeable signs of encephalitis
Anti-AMPAR encephalitis	○ Behavioural change ○ Confusion, confabulation, agitation, combativeness, perseveration ○ Short-term memory loss ○ Various types of nystagmus: down or right beating ○ Epilepsy: focal motor seizures, generalized tonic-clonic seizures ○ Dysdiadochokinesia, gait ataxia ○ Insomnia, lethargy ○ Decreased level of consciousness
Anti-LGI1 – encephalitis	○ Behavioural , personality change, psychosis ○ Cognitive dysfunctions, loss of memory ○ Faciobrachial tonic seizures; similar fits also affecting the lower extremities and slightly slower than typical myoclonus; generalized tonic-clonic seizures ○ Hyponatriaemia

anti-$GABA_BR$ 1 encephalitis	○ Behavioural problem
	○ Paranoia, psychosis, gustatory and/or visual hallucinations
	○ Confusion, disorientation, confabulation, agitation
	○ Memory impairments
	○ Abnormal orolingual movements, fluent aphasia
	○ Epilepsy
	  ○ complex partial seizures
	  ○ partial motor
	  ○ generalised, generalised tonic-clonic seizures
	  ○ status epilepticus
	○ Sleeping disorder
	○ Requiring intubation and ventilation
	○ Decline in mental status leading to coma

Anti-Aqp4 encephalitis	○ Opticus neuritis ○ Longitudinally extensive transverse myelitis ○ Encephalopathy ○ Ophthalmoparesis ○ Intractable vomiting, or hiccups ○ Seizures ○ Ataxia
Anti-MOG encephalitis	○ ADEM, clinically isolated syndrome (CIS) ○ Recurrent opticus neuritis, transverse myelitis including LETM
Anti-GAD encephalitis	○ Stiff-person syndrome (SPS) and variants including ○ PERM: progressive encephalomyelitis with rigidity and myoclonus ○ Also with anti-Glycine receptor [Neurology 2008; 71: 1291-1292] ○ Paraneoplastic limbic encephalitis with epilepsy ○ Palatal myoclonus ○ Autoimmune hyperekplexia (pronounced startle responses)
Anti-GlyR α1 encephalitis	○ Progressive encephalomyelitis with rigidity and myoclonus (PERM), Stiff person syndrome ○ Hyperekplexia
Post-streptococcal encephalitis	○ Movement disorders: tics (motor, vocal), chorea (usually affecting limbs; maybe unilateral), facial grimacing ○ Motor hyperactivity ○ Acute dystonia ○ Obsessive compulsive disorder (OCD), anxiety, episodes of unmotivated fear, psychosis ○ Epilepsy, multifocal myoclonus (maybe elicited from thalamus) ○ Multifocal myokymia ○ Slowed cognition, memory dysfunction ○ Sleep disorders, including sleep inversion ○ Gait ataxia ○ Anorexia, bulimia ?

Autoimmune encephalitis and epileptic seizures

In summary: recent studies in the field of paraneoplastic syndromes and autoimmune encephalitides provide several clues that suggest the immune aetiology of some types of epileptic disorders, including the acute presentation of symptoms, the frequent detection of CSF pleocytosis and oligoclonal bands in the context of negative viral studies, and the detection of CSF antibodies reacting with the neuropil of hippocampus and the cell surface of neurons.

These disorders can be divided into limbic and cortical extralimbic encephalitides and may have **paraneoplastic** or **non-paraneoplastic** aetiology.

Paraneoplastic autoimmune encephalitis with epilepsy

The associated antibodies include
Anti-Hu
Anti-CV2 (CRMP5)
Anti-Ta (Ma2)
Anti-Ri
Anti-Amphiphysin
Anti-mGluR5

While there is strong evidence that the first four immune responses are mediated by cytotoxic T-cells responses, there are studies indicating that amphiphysin antibodies may be directly pathogenic. Anti-mGluR5 encephalitis (Ophelia syndrome) may also be antibody-mediated [84].

Of these five immune responses, the anti-Hu antibodies are those most frequently described with seizures, epilepsia partialis continua, and status epilepticus. The underlying tumours are small-cell lung cancer (all antibodies), breast cancer (anti-Ri), germ-cell tumours of the testis (Ta/Ma2), and thymoma (CV2/CRMP5). With the exception of the encephalitis associated with Ta/Ma2 antibodies, in which approximately 30% of patients respond to tumour removal and immunotherapy, the other disorders are rarely treatment-responsive.

Autoimmune encephalitides that are not strictly paraneoplastic

There is an expanding group of autoimmune encephalitides that *may occur with or without tumour association, depending on the type of antibody*. A frequent feature of these immune responses is that the autoantigens are extracellular and therefore accessible to circulating antibodies.

The associated antibodies include	
	Extracellular
Anti-LGI1 ("anti-VGKC")	Yes
Anti-NMDAR (NR1)	Yes
Anti-AMPAR (GluR1, GluR2)	Yes
Anti-AMPAR (GluR3)	Yes
Anti-$GABA_BR1$	Yes
Anti-AQP4	Yes
Anti-D1, anti-D2, anti-lyso-GM1	Yes
Anti-Alpha-enolase (ENO1)	Yes
Anti-GAD	Yes/No#
Anti-GlyR alpha1	Yes
A finding of antibodies to extracellular epitopes would classify a disorder as **autoimmune synaptic encephalopathy** **# Located at synaptic vesicles**	

These antigens include

- **LGI1 and CASPR2,** being the true target antigens of antibodies previously attributed to voltage-gated potassium channels (VGKC).

  LGI1, a secreted neuronal protein, is a target antigen of limbic encephalitis. Interestingly, this disorder associates with frequent seizures (about 80% of such patients) along with hyponatriaemia. Moreover, mutations of LGI1 are the cause of autosomal dominant partial epilepsy with features (ADPEAF), also called autosomal dominant lateral temporal lobe epilepsy.

In contrast, CASPR2, a protein that is expressed in brain and peripheral nerve, clustering the VGKC at the juxtaparanodal regions of myelinated axons is the target antigen of encephalitis (Morvan's syndrome) and peripheral nerve hyperexcitability (Isaacs syndrome)

- **Excitatory glutamatergic receptors (NMDA, AMPA)**
  Antibodies to the NR1 subunit of the NMDAR associate with a characteristic syndrome that presents with behavioural change or psychosis and usually progresses to a decline of the level of consciousness, catatonia, seizures, dyskinesias, autonomic instability, and frequent hypoventilation. Anti-AMPAR (GluR1 and GluR2) encephalitis is not associated with neoplasia in about 30 %. Anti-GluR3 is associated with autoimmune epilepsy, including after bone marrow transplantation.

- **Inhibitory $GABA_BR1$**
  Both $GABA_BR1$ and AMPA (GluR1, GluR2) receptor antibodies associate with a clinical picture of limbic encephalitis *and with early and prominent seizures in the case of $GABA_BR1$ antibodies*

- ***Anti-AQP4***
  Associated with neuromyelitis (NMO, Devic's syndrome including LETM) and epilepsy

- **GAD antibodies** usually associate with stiff-person syndrome and cerebellar dysfunction, but there are increasing number of reports showing that these antibodies also occur with subtypes of limbic encephalitis and refractory epilepsy

  Glycine receptors antibodies (anti-GlyR alpha1) usually associate with atypical stiff-person or stiff-limb syndrome (without anti-GAD), progressive encephalomyelitis with rigidity and myoclonus (PERM), or autoimmune hyperekplexia. The GlyR are among the most widely distributed inhibitory receptors in the central nervous system. GlyRs are primarily expressed in spinal cord, brain stem, caudal brain, and retina. In adult neurons, the inhibitory chloride influx upon glycine receptor activation stabilizes the resting potential of the cell, rendering them electrically quiescent

- **Anti-D1, anti-D2, anti-lyso-GM1** are findings related to the post-streptococcal neurological syndrome

- **Anti-Alpha-enolase (ENO1)** is associated with Hashimoto's encephalitis and autoimmune thyroiditis

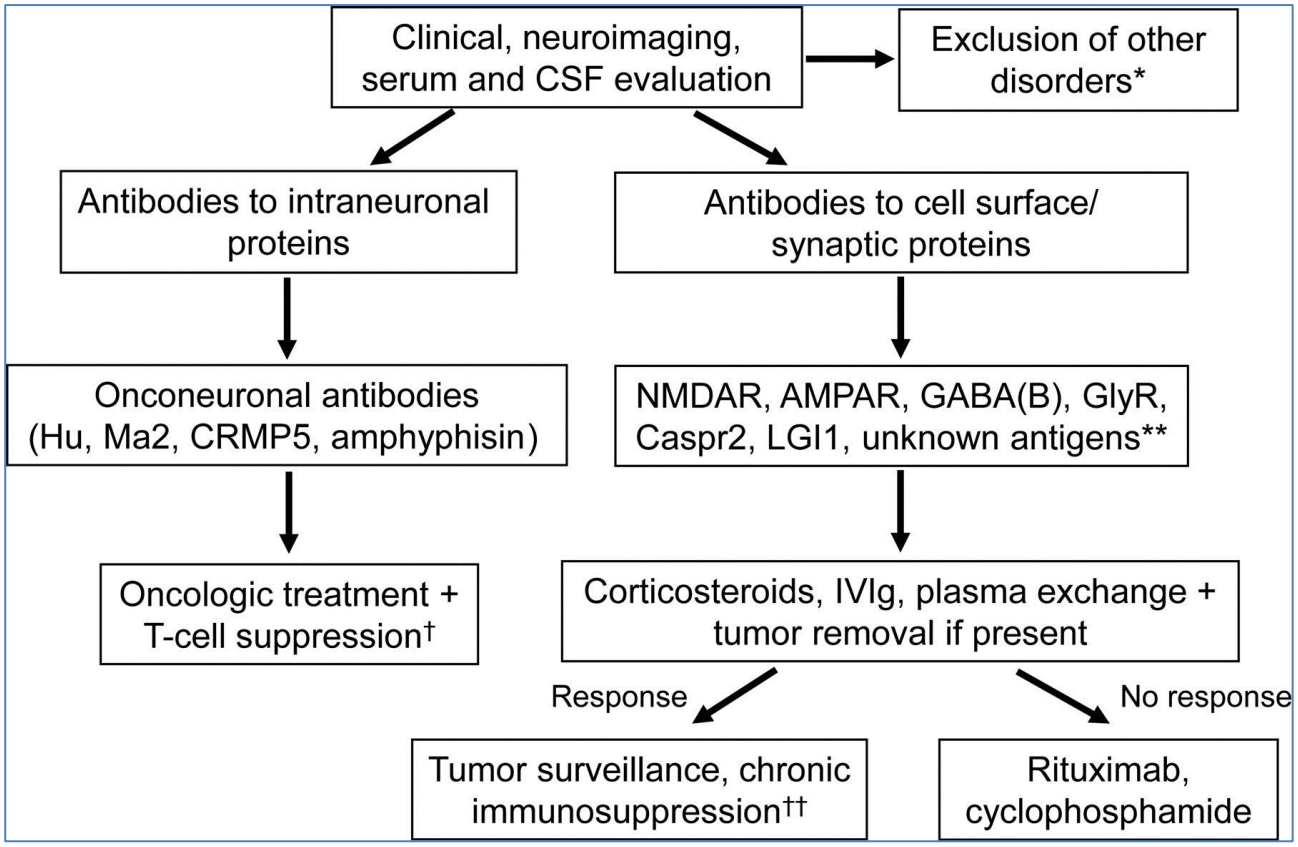
Prompt recognition of all the disorders associated with antibodies against cell surface antigens is important

- They may also affect children and young adults (typical of anti-NMDAR encephalitis)
- They are responsive to immunotherapy and/or oncological remedies when appropriate
- Unfortunately, it appears that anti-GAD associated encephalomyelitis is less treatment-responsive

General comments

Short summary
The finding of neurologic specific autoantibodies • **A cornerstone in new classifications of autoimmune encephalitides**   • **Enables a rational basis of categorization into various groups & subgroups** • **Enables a more rational therapeutic strategy**
Evaluation of autoantibodies – serum & cerebrospinal fluid (CSF) Please note that in some cases, specific autoantibodies are not a feature of serum Accordingly and if expected autoantibodies are not found in a serum sample, always include examination of CSF in the diagnostic procedures
Intrathecal synthesis of specific autoantibodies can be a feature of some autoimmune encephalitides
These disorders may be with or without association to a neoplasm
Paraneoplastic autoantibodies are always markers of neoplasia under development, although not necessarily markers of a neurological disorder – since this takes associated such symptoms to evolve as well, even though typically, this happens weeks or months before an associated tumour is diagnosed
Rapid diagnostic procedures and commencement of therapy can be of major significance

Algorithmic approach to diagnosis and treatment of encephalitis with antibodies to intracellular and cell surface neuronal antigens



From: **Lancaster E et al. Neurology 2011; 77: 179-189**

Autoimmune synaptic encephalitis - various specific disorders

Hashimoto's encephalitis and autoimmune thyroiditis

The encephalitis is associated with **anti-Alpha-enolase** (ENO1), the target being the N-terminal region (amino terminal) of alpha-enolase. The co-existent struma is associated with the following autoantibodies: anti-thyroglobulin, anti-thyroid peroxidase antibodies, anti-TSH receptor, and anti-M.

The following table summarizes a variety of findings

Demographics		Clinical manifestations	
Prevalence	2.1 / 100,000	Tremor	84 %
Median age at onset (years)	44, range 9-78	Transient aphasia	73 %
Paediatric presentation (<18 years)	22 %	Seizures	66 %
Gender (female)	81 %	Status epilepticus	12 %
Relapsing / remitting type	60 %	Myoclonus	38 %
		Hypersomnolence	63 %
		Gait ataxia	63 %
		Psychosis (paranoid, visual hallucinations)	36 %
		Stroke-like episodes	27 %
Thyroid status		**Anti-thyroid antibodies**	
Goitre	62 %	Elevated anti-TPO	100 %
Subclinical hyperthyroidism	35 %	Elevated anti-M	95 %
Euthyroid	30 %	Elevated anti-TG	73 %
Overt hypothyroidism	20 %		
Hyperthyroidism	7 %		
Cerebrospinal fluid		**Non-specific abnormalities**	
Elevated protein (range 33-228 mg)	78 %	Elevated ANA, ESR, CRP, and liver enzymes	16 %
0-3 nucleated cells / mm3	76 %		
> 100 nucleated cells / mm3	4 %		
Oligoclonal bands	27 %		

Some of the most common symptoms of Hashimoto's encephalopathy include

- **Concentration and memory problems**
- **Disorientation**
- **Psychosis**
- **Tremors**
- **Seizures, myoclonus**
- **Lack of coordination**
- **Headaches**
- **Partial paralysis on the right side**
- **Speech problems**

Sometimes, patients are mistakenly diagnosed as having had a stroke, or having Alzheimer's disease. Because most patients respond to steroids or immunosuppressant treatment, this condition is also referred to as "steroid-responsive" encephalopathy. In some cases, the condition may also be called "non-vasculitis autoimmune meningoencephalitis" (NAIM), which can include not only autoimmune thyroid problems, but also other autoimmune disorders such as Sjögren's syndrome and systemic lupus erythematosus–associated meningoencephalitis

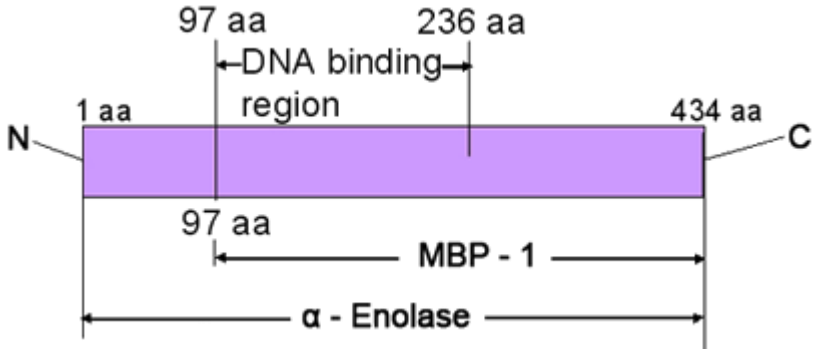
Treatment: immunotherapy

- Steroids, plasmapheresis, intravenous high-dose IgG

Function of ENO1

It is a multifunctional enzyme that, in addition to its role in glycolysis, plays a part in various processes such as growth control, hypoxia tolerance and allergic responses. This enzyme also stimulates immunoglobulin production. Moreover, it may also function in the intravascular and pericellular fibrinolytic system due to its ability to serve as a receptor and activator of plasminogen on the cell surface of several cell-types such as leukocytes and neurons.

ENO1-protein



Structure of ENO1/MBP-1 protein; N and C termini, and amino acid (aa) positions are labelled.

Expression — Alpha-Enolase is widely expressed in variety of tissues including brain, thyroid, liver, kidney, spleen, as well as adipose. In comparison with gamma-type subunit found only in neurons, type alpha subunit was also detected in astrocytes, ependymal cells, capillary endothelial cells, Schwann cells and arachnoidal endothelial cells.

Localisation — **Alpha-Enolase is most abundantly found on the cell surface and also in cytoplasm**

Characteristics of anti-NMDAR (NR1) encephalitis

Case series of anti-NMDAR patients (n=100) and info from various other sources

Epidemiology

- Median age of patients: 23 years (range 5—76 years); 90 % women
- Anti-NMDAR encephalitis is increasingly recognized in children and appears to **account for a major percentage of encephalitides cases, previously categorized as of unknown cause in such infants**

Types of autoimmune anti-NMDAR encephalitis

- Of unknown cause
- Post-infectious
- Paraneoplastic
- As a manifestation of SLE. It has been reported that up to 25 % of SLE patents may have **anti-NMDAR (NR2)** in their sera. Susceptibility to SLE has an associated gene map locus: 12p12 (GRIN2B), being the gene of MNDA glutamate receptor NR2B.

Anti-NMDAR seropositivity

In an individual patient, these autoantibodies may be to NMDAR (NR1), NMDAR (NR2) or both. Therefore, an appropriate assay testing for anti-NMDAR must cover both, although possibly, anti-NMDAR (NR2) may be more relevant in a context of SLE and neurolupus

Studies have established the cellular mechanisms through which antibodies of patients with anti-NMDAR encephalitis cause a specific, titer-dependent, and reversible loss of NMDARs J Neurosci. 2010 April 28; 30(17): 5866–5875

Complement-mediated mechanisms do not appear to play a substantial pathogenic role in anti-NMDAR encephalitis. In contrast, there are copious infiltrates of antibody-secreting cells (plasma cells/plasmablasts) in the CNS of these patients. The demonstration of these cells provides an explanation for the intrathecal synthesis of antibodies and has implications for treatment. Neurology 2011; 77 (6): 589-93

Moreover, anti-NMDA receptor encephalitis antibody binding appears to be dependent on amino acid identity of a small region within the GluN1 amino terminal domain. J Neurosci. 2012 Aug 8;32(32):11082-94.

In addition to anti-NMDAR (IgG) positive cases, also anti-NMDAR of IgA type and without co-existing IgG-type has been reported: Neurology. 2012 May 29;78(22):1743-53.

A paraneoplastic (teratoma) origin has been reported (Annals of Neurology 2007; 61 (1); The Lancet Neurology 2008 - Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies)

Onset of anti-NMDAR encephalitis may occur during an acute mycoplasma infection (Anti-NMDA receptor encephali... [Eur J Clin Microbiol Infect Dis. 2009] - PubMed - NCBI)

NMDAR antibodies of the immunoglobulin (Ig) subtypes IgA, IgG, or IgM have been reported in 13 of 44 patients (30%) **in the course of herpes simplex encephalitis**, suggesting secondary autoimmune mechanisms. Ann Neurol. 2012 Dec; 72(6): 902-11. doi: 10.1002/ana.23689.

Case history: A Young Man with Anti-NMDAR Encephalitis **following Guillain-Barré Syndrome**. Karger case reports in neurology 2011.

IgA-type NMDAR (NR1) may be a feature of **schizophrenia**. BMC Psychiatry. 2012; 12: 37.

IgA NMDA receptor antibodies are also markers of synaptic immunity in **slow cognitive impairment**. Neurology. 2012 May 29; 78(22): 1743-53. doi: 10.1212/WNL.0b013e318258300d. Epub 2012 Apr 25.

Currently, the significance of anti-NMDAR of IgM type is unclear. The literature on these antibodies is not clear and, in fact, instead of being helpful it appears to create confusion. Therefore and in cases with isolated IgM-NMDAR without further evidence of an autoimmune or inflammatory process, an approach could be not to use these antibodies to make any clinical decisions

Neuropsychiatric features (80 – 90 %)

- Behavioural or personality change, psychosis
- Cognitive dysfunctions, loss of memory
- Dyskinesias, dystonia, or stereotyped movements, catatonia
- Speech reduction
- Seizures, status epilepticus
- Sleep dysfunction, e.g. excessive daytime sleepiness (associated with decreased level of hypocretin)
  - Autonomic instability, decreased consciousness, hypoventilation (about 25%)

Reference: Dalmau J, Gleichmann AJ, Hughes EG, et al. Lancet Neurology 2008; 7: 1091-1098

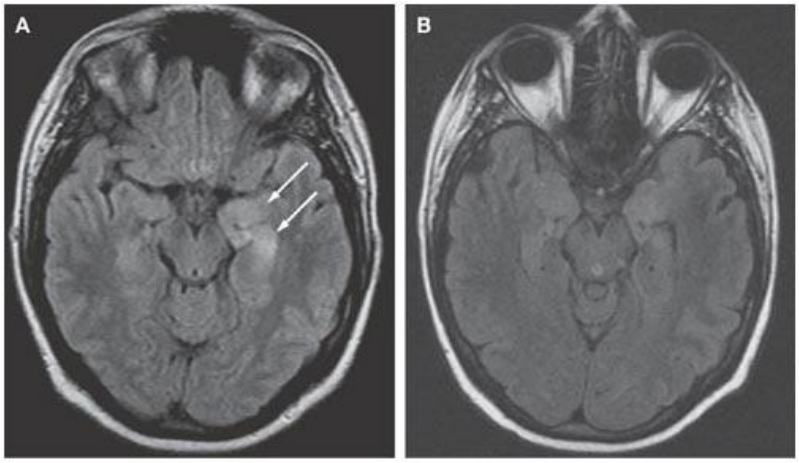
Relapses in anti-NMDAR encephalitis appear to be common (24 %). Neurology 2011; 77 (6): 589-93.

In most cases, the anti-NMDAR antibodies are of IgG-type. However, also cases with anti-NMDAR of IgA- and not IgG-type have been reported. [please see above] Consider anti-NMDAR in some cases with cognitive dysfunctions, epilepsy, schizophrenia, narcolepsy-catatonia etc.

Investigations

- **Serum**
  - **Anti-NMDAR (NR1, IgG, IgA, IgM)**
  - Mycoplasma pneumoniae antibodies
  - Herpes simplex (polymerase chain reaction
- **Throat swap, mucus from airways**
  - PCR amplification to test for mycoplasma pneumoniae genes
- **CSF**
  - **Anti-NMDAR (NR1, IgG, IgA, IgM)**
  - Herpes simplex (polymerase chain reaction)
  - Oligoclonal banding
  - Hypocretin-1 level
- **MRI**
  - More or less asymmetrical medial temporal lobe hyper intense signal

Anti-NMDAR encephalitis



MRI scan of the patient at symptom presentation and follow-up

(A) MRI fluid-attenuated inversion recovery (FLAIR) obtained at symptom presentation demonstrates bilateral medial temporal lobe hyperintense signal, predominantly involving the left hippocampus (arrows).

(B) Follow-up MRI obtained during recovery, 4 months after the initial MRI, shows considerable improvement of the FLAIR hyperintensity

Note: *CSF and MRI findings may be minimal or normal. Therefore, do consider repeated investigations later-on, if unrevealing at first examination*

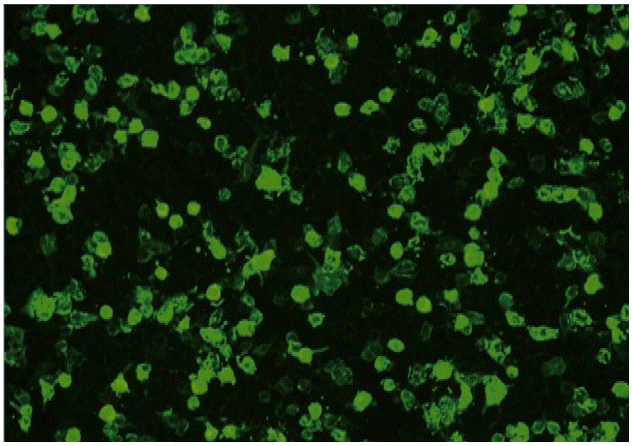
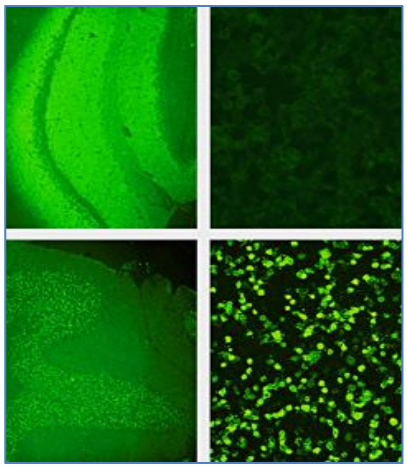
Neoplasm

- Males: only few teratomas have been reported (such neoplasm are rare in the testis, accounting for only 3-5 % of germ cell tumours)
- Females

Female patients	
Age group, years	**Frequency of teratomas**
Older than 18	56 %
14.1 – 18	31 %
Up to 14	9 %

Treatment

- **Immunotherapy**
  Intravenous high-dose IgG, steroids, Rituximab, Alemtuzumab, intrathecalMethotrexate Cyclophosphamide
- **Oncologic** (paraneoplastic type)

Incubation with anti-NMDAR positive serum	
Cell based assay (CBA): HEK293 cells transfected with recombinant NMDA receptor	**Various CNS tissues and CBA**
	

Characteristics of anti-AMPAR (GluR1, GluR2) encephalitis

Distinguishing feature: various types of nystagmus, dysdiadochokinesis, gait ataxia

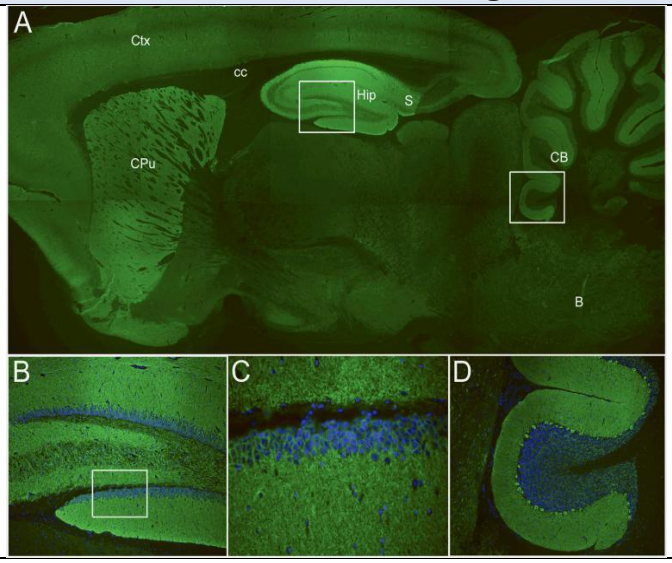
Clinical features, CSF, EEG, and MRI findings (patients n = 10, females 90 %, age range: 38 – 87 years)
From:. Lai M, Hughes EG, Peng X, et al. Ann Neurol 2009; 65(4): 424–434

Associated neoplasms: thymus, non-SCLC, SCLC, breast
No neoplasm: 30%

Frequent relapses after treatment (60 %)	Findings of additional antibodies: ANA, anti-dsDNA, anti-Cardiolipin, anti-GAD, anti-CV2 (CRMP5), anti-VGCC, AGNA (anti-SOX1)

Symptom presentation (various combinations)	Cerebrospinal fluid		Initial EEG Not available: 20% Normal: 20%	Brain MRI (FLAIR) Not available: 10% Normal: 10%	Anti- GluR1/2 (main antigen)
• **Behavioural change** • **Confusion, confabulation, agitation, combativeness, perseveration** • **Short-term memory loss** • **Various types of nystagmus: down or right beating** • **Epilepsy: focal motor seizures, generalized tonic-clonic seizures** • **Dysdiadochokinesis, gait ataxia** • **Insomnia, lethargy** **Decreased level of consciousness**	WBC (normal <4/µl)	6 – 75	Diffuse theta activity or only in posterior temporal regions Slow activity in the right temporal region or more diffuse Episodes of epileptic activity in left temporal lobe Bilateral sharp waves in temporal lobes	Mild increased signal in medial temporal lobes Or increased signal in the right medial and lateral temporal lobe, right frontal, left insular and left occipital regions	All seropositive (GluR1: 30 % GluR2: 70 %) Such antibodies alter the number and localization of AMPARs in live neurons
	Elevated protein (normal 16-46 mg/dl)	70 %			
	Oligoclonal bands	> 30 %			
	Intrathecal synthesis of anti-AMPAR	> 30%			
	Glucose levels	normal			

Immunolabeling of rat brain by patients antibodies



Sagittal section of rat brain incubated with the CSF of a patient with limbic encephalitis and novel antibodies.

Note the intense reactivity of the patient's antibodies with the neuropil of hippocampus (Hip), subiculum (S), molecular layer of the cerebellum and Purkinje cells (CB), caudate-putamen (CPu), and cerebral cortex (Ctx).

Other regions of the brain (e.g., corpus callosum (cc) and brainstem (B)) do not show significant immunolabeling. The areas boxed in A correspond to hippocampus and cerebellum and are shown at high magnification in B and D.

The box in B is located at the dentate gyrus and is shown amplified in C. In panels B-D the nuclei of the cells is demonstrated with 4',6-diamidino-2-phenylindole (DAPI).

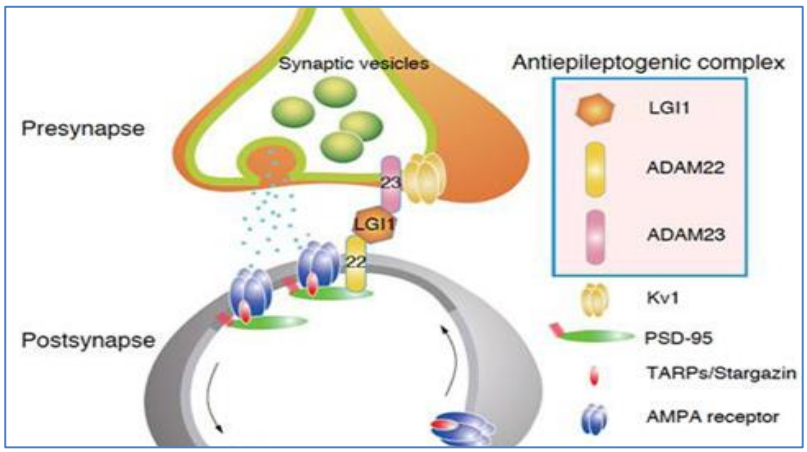
Immunofluorescent technique, A × 2.5; B and D × 200; C × 400

Treatment

- **Immunotherapy at presentation and relapses**
  - Steroids, plasmapheresis, intravenous high-dose IgG, Rituximab,
- Consider chronic treatment with azathioprine, cyclophosphamide or related drugs
- **Oncologic** (paraneoplastic type)

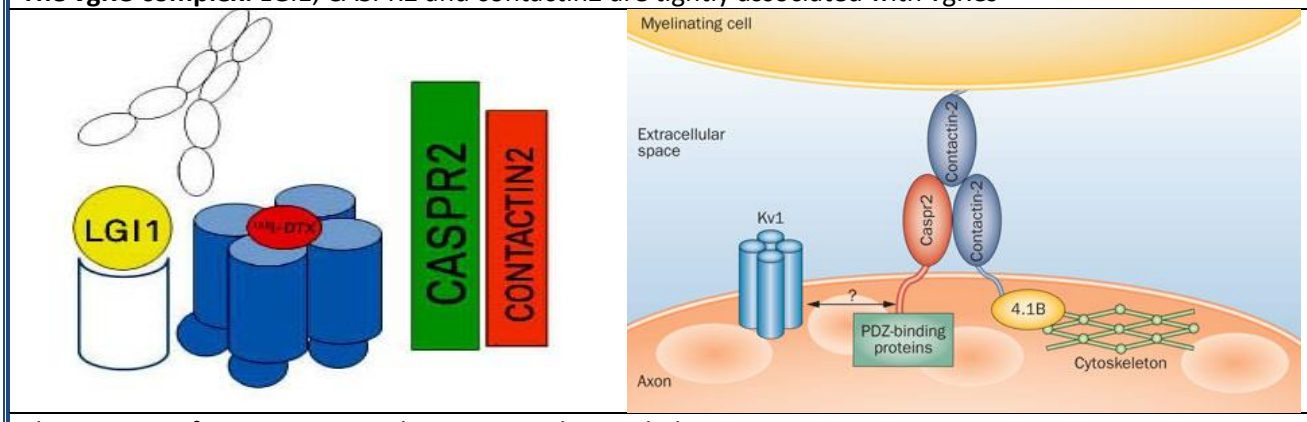
Characteristics of anti-LGI1 encephalitis (previously so-called "anti-VGKC encephalitis")

"Anti-VGKC-complex antibodies" define neurological conditions that usually are immunotherapy-responsive



Although it has been somewhat puzzling how these antibodies could cause a wide range of different clinical presentations, these antibodies have become part of investigations of cases with unexplained subacute onset of epilepsy, memory or cognitive problems, psychosis, or hyperexcitability syndromes of peripheral nerve.

The vgKC-complex: LGI1, CASPR2 and contactin2 are tightly associated with vgKCs



The concept of anti-vgKC–complex associated encephalitis

- Anti-LGI1 encephalitis
- Anti-CASPR2 encephalitis
- Anti-Contactin2 encephalitis
- **About 30 % are seropositive only using the classical RIA with dendrotoxin**

However, it appears that the majority of "VGKC-antibodies" of high titre are not directed towards the Kv subunits themselves but to two other proteins, LGI1 (leucine-rich, glioma inactivated 1**) and CASPR2** (contactin associated protein-like 2)**, both being the true targets.** LGI1 and CASPR2 are closely associated with VGKCs in brain and other tissues. The classical RIA for detection of anti-VGKC is using radiolabelled dendrotoxin and 2% digitonin extracts of VGKCs also containing complexed LGI1 and CASPR2, explaining the misenterpretation of such results as anti-VGKC.

LGI1 and CASPR2 both form part of trans-synaptic complexes and neuronal cell adhesion molecules involved in fine-tuning synaptic transmission and nerve excitability.

- LGI1 antibodies are found almost exclusively in patients with limbic encephalitis or epilepsy, 89% without and 11% with tumours, respectively [Lancet Neurol 2010; 9(8):776-85]

- CASPR2 antibodies are found in patients with limbic encephalitis, Morvan's syndrome or neuromyotonia, often co-existent with thymomas [J Thorac Oncol 2010; 5(10 Suppl 4): S277-80]. CASPR2 mediates cell–cell interactions and has a critical role in concentrating VGKCs located at juxtaparanodal regions of myelinated axons and in the hippocampus and cerebellum. The immunomodulatory effect of anti-CASPR2 causes a reduced number and decreased density of such potassium channels which is detrimental to transmission. Accordingly, the associated autoimmune disorders, acquired neuromyotonia or Isaacs's syndrome and limbic encephalitis, respectively, are explicable by such mechanisms. -- An analogue mechanism is known in anti-MuSK myasthenia gravis, since MuSK is a molecular device for the aggregation of AChRs.

LGI1 is the main target autoantigen of the limbic encephalitis previously attributed to VGKC

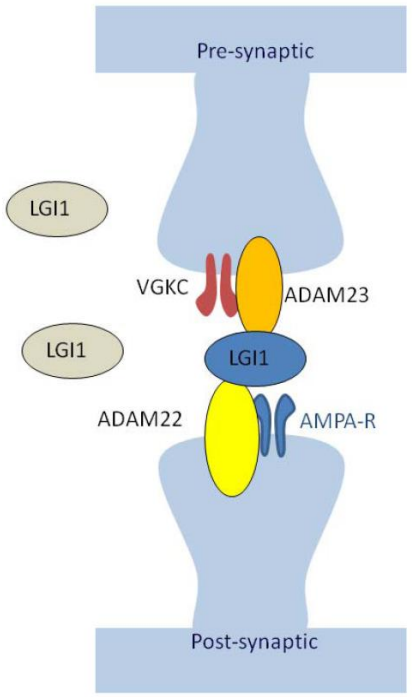
The interaction of voltage-gated potassium (Kv) channels with proteins like LGI1, calmodulin, ZIP, or PSD-95 can have dramatic effects on gating, cellular localization, and turnover of such channels

LGI1: Leucine-rich, glioma inactivated 1
Chromosome: 10q24

1. **LGI1 homo sapiens - Gene result**
2. **LGI1 Gene - GeneCards | LGI1 Protein | LGI1 Antibody**

- **Secreted synaptic protein**
- **Associates with VGKCs and AMPA receptors via the ADAM proteins**
- **LGI1-null mice have seizures and early death**
  Human mutations associate with "autosomal dominant lateral temporal lobe epilepsy" with auditory features (ADPEAF)

- **LGI1 is a ligand for ADAM22 that positively regulates synaptic transmission mediated by AMPA-type glutamate receptors (by similarity). The molecular function of ADAM22 is as a receptor, and it is highly expressed in the brain**
- **ADAM23 can bind to LGI1, and is highly expressed in the brain, prominently in the amygdala, caudate nucleus, hypothalamus, thalamus, cerebral cortex and occipital pole**
- **Regulates voltage-gated potassium channels assembled from KCNA1, KCNA4 and KCNAB1**
- **Slows down channel inactivation by precluding channel closure mediated by the KCNAB1 subunit**
- **Plays a role in suppressing the production of MMP1/3 through the phosphatidylinositol 3-kinase/ERK pathway**
- **LGI1 down-regulates glutamatergic synapses during postnatal life**



Distinguishing features: faciobrachial tonic seizures; similar fits also affecting the lower extremities, slightly slower than typical myoclonus & hyponatriaemia

The following table summarizes a variety of features (patients n=57)

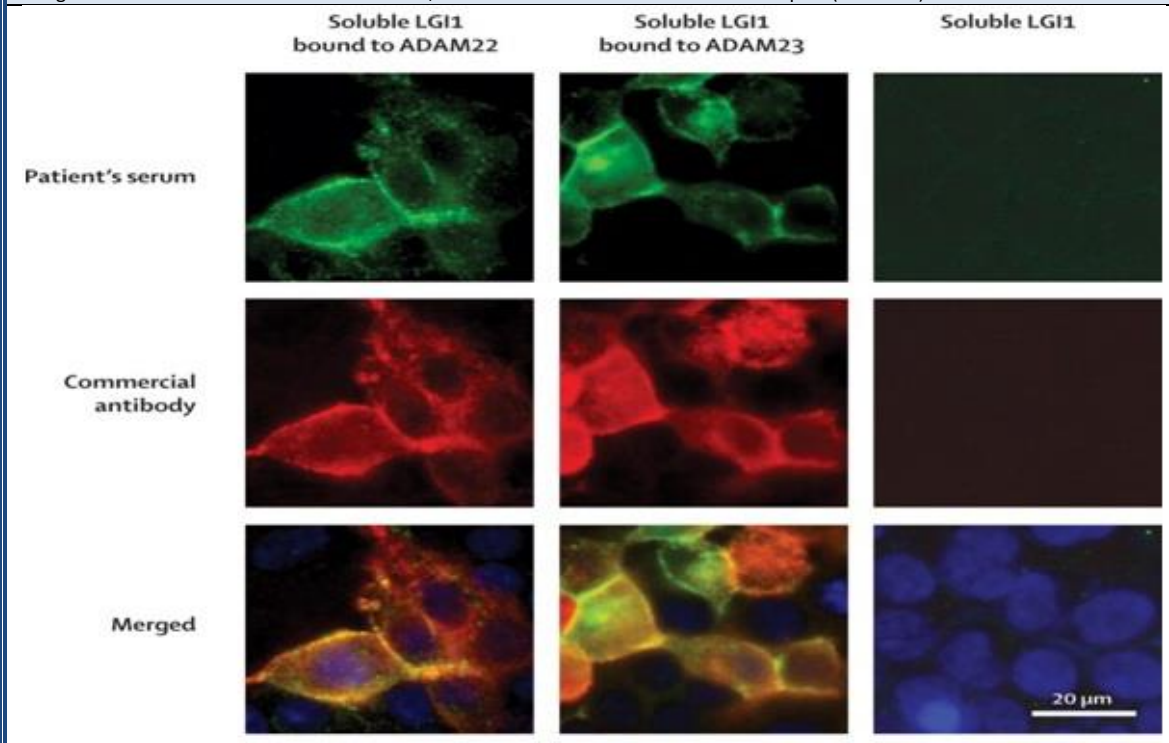
Demographics		
Men		65 %
Age (years)		60 (30-80)
Paraneoplastic background		**11 %**
Tumours present	n =	**n = 57 (6)**
Thyroid	2	4 % (33 %)
Lung	1	2 % (17 %)
Thymoma	1	2 % (17 %)
Ovarian teratoma	1	2 % (17 %)
Renal cell	1	2 % (17 %)
Relapsing course		18 %
Clinical features		
Limbic encephalitis		100 %
Memory loss		< 100 %
Seizures including generalized ones		82 %
Faciobrachial tonic seizures		40 %
Confusion, personality change or psychosis		< 100 %
Hyponatriaemia		60 %
Serum sodium (mM)		128 (118-132)
Cerebrospinal fluid		
Any abnormality		41 %
Elevated protein		28 %
Lymphocytic pleocytosis		17 %

MRI	
Increased T2 signal involving medial temporal lobe	84 %
EEG	
Any abnormality	76 %
Seizures	32 %
Epileptiform discharges	12 %
Diffuse or focal slowing	32 %
Modalities of treatment	
Steroids	84 %
Intravenous IgG	62 %
Plasma exchange	6 %
Others (rituximab, azathioprine, or cyclosporine)	12 %
Any treatment	96 %
Clinical outcomes	
Full recovery	24%
Mild disability	54%
Moderate disability	16%
Death	6%

Hyponatriaemia (60%) may be attributed to the expression of LGI1 in the hypothalamus and the kidney. From: Lai M, Huijbers MG, Lancaster E, et al. Lancet Neurol 2010; 9(8):776-85 & Irani SR, Alexander S, Waters P, et al.Brain 2010; 133 (9): 2734-2748

A patient's serum reacts with soluble LGI1 bound to ADAM22 or ADAM23

LGI1-containing media was applied to HEK293 cells expressing ADAM22 (first column) or ADAM23 (second column). Patient's antibodies recognised LGI1 bound to ADAM22 or ADAM23, but not HEK293 cells without either receptor (third row)



Characteristics of anti-GABA$_B$R1 encephalitis

GABA-receptors are probably the most common kind in the mammalian nervous system. It is estimated that close to 40% of the synapses in the human brain work with GABA and therefore have GABA-receptors.

Distinguishing features: gustatory and/or visual hallucinations, orolingual movements, fluent aphasia

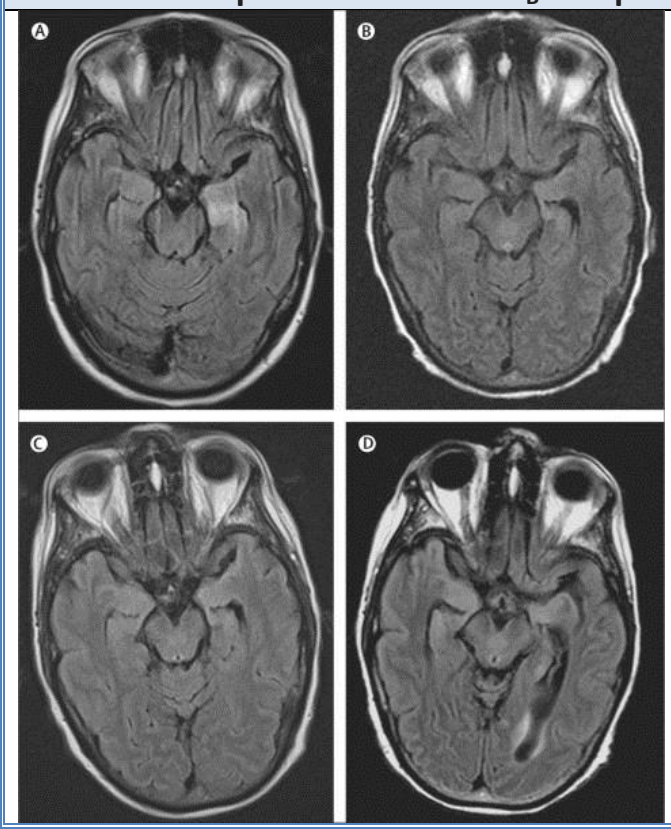
Clinical features, CSF, and MRI findings (patients n = 15, 7 females (47 %); 8 males; age range:24 – 75 years) **From:** Lancaster E, Lai M, Peng X, et al. Antibodies to the GABAB receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol* 2010; 9: 67-76.				
Associated neoplasms: SCLC, mediastinal adenopathy, neuroendocrine tumour of the lung, benign ovarian mass **No neoplasm: 47%** (five of these patients were young (median age 30 years, range 24–45), were non-smokers, and had negative cancer screening including CT/fluorodeoxyglucose-PET, and two of these patients had long-term follow-up (41 and 72 months), making the presence of cancer unlikely)				
Findings of additional antibodies: anti-VGCC (N-type), anti-GAD, AGNA (anti-SOX1, lung cancer), anti-TPO				
Symptom presentation (typically, subacute onset of various combinations)	Cerebrospinal fluid Not available: 33 % Abnormal: 90 %		Brain MRI (FLAIR) increased signal Normal: 27 % (n=4)	Anti-GABA$_B$R
• Memory impairment • Behavioural problems • Confusion, disorientation, confabulation, agitation • Paranoia, **gustatory and/or visual hallucinations**, psychosis • Sleeping disorder • **Abnormal orolingual movements, fluent aphasia** • Epilepsy: complex partial seizures, partial motor and generalised, generalised tonic-clonic seizures, status epilepticus • Requiring intubation and ventilation • Decline in mental status leading to coma	WBC (normal <4/µl)	6 – 95 (95 %)	Left medial temporal lobe Left medial temporal lobe and insula Medial temporal lobes Small area of corpus callosum	Seropositive: 75 % Else positive CSF antibody titre
	Elevated protein (normal 16-46 mg/dl)	90 %		
	Oligoclonal bands	> 45 %		

Clinical features, CSF, and MRI findings (patients n = 11, 2 females; 9 males (65 %); age range: 47 – 70 year) **From:** Boronat A, Sabater L, Saiz A, Dalmau J, Graus F. GABAB receptor antibodies in limbic encephalitis and anti-GAD–associated neurologic disorders. Neurology 2011; 76: 795-800				
Associated neoplasms: SCLC, carcinoid of thymus - **No neoplasm: 18%**				
Findings of additional antibodies: anti-VGCC, anti-GAD, AGNA (anti-SOX1, lung cancer), anti-BRSK2				
Symptom		Pleocytosis in cerebrospinal fluid Not available: 1 (9 %)	Brain MRI (FLAIR) Normal: 36 % (n=4) Temporal lesions	Anti-GABA$_B$R antibody positive
At presentation	Overall			
Seizures 82 % Memory impairment 55 % Changed behaviour 36 % Confusion 36 % Ataxia 9 %	LE 91% CA 9% # Epilepsy 82 %	Not present: n= 6 (60%) Present: n= 4 (40 %)	Bilateral: n= 5 (45 %) Left side: n= 2 (18 %)	**Seropositive**: 100 % **CSF-positive**: only 5 samples available (6 missing) **100 %**
LE = limbic encephalitis; CA = cerebellar ataxia # The patient with cerebellar ataxia was also anti-GAD seropositive				

Treatment

- **Immunotherapy: s**teroids, plasmapheresis, intravenous high-dose IgG, mycophenylate mofetil, or related drugs
- **Oncologic** (paraneoplastic type)

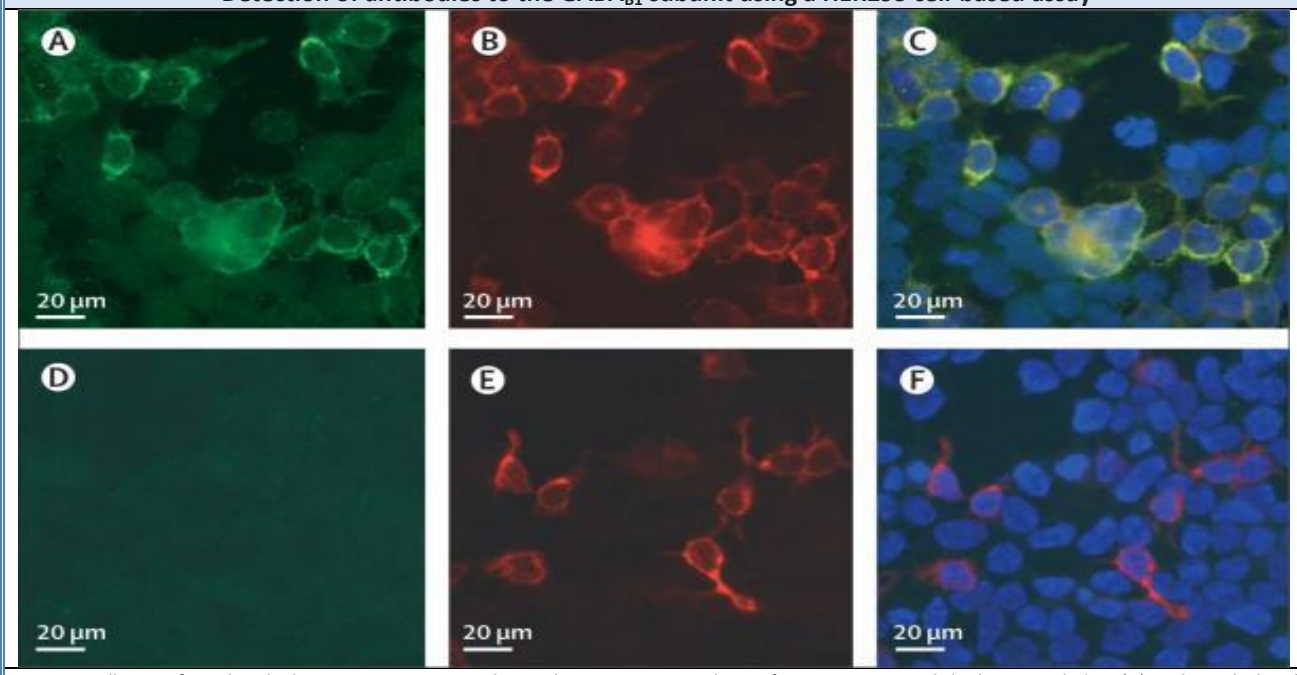
MRI of a patient with $GABA_B$ receptor antibodies and limbic encephalitis



Axial fluid-attenuated inversion recovery (FLAIR) MRI from patient 1 at presentation (A) showed increased signal in the medial temporal lobes, which was more pronounced on the left.

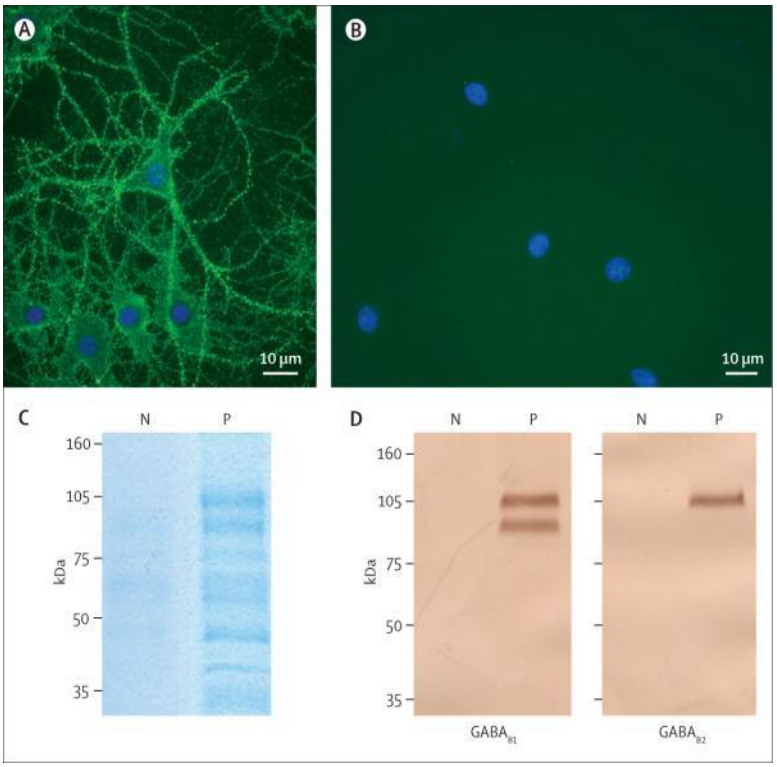
Repeat study at 1 month (B) showed improvement of the FLAIR signal that remained stable at 3 months and 9 months (C, D), with development of mild generalised atrophy (the patient received standard whole-brain radiation therapy as prophylaxis for small-cell lung cancer metastases).

Detection of antibodies to the $GABA_{B1}$ subunit using a HEK293 cell-based assay



HEK293 cells transfected with the $GABA_{B1}$ receptor subunit show reactivity with CSF from a patient with limbic encephalitis (A) and a polyclonal antibody against the B1 subunit of the $GABA_B$ receptor (B); both reactivities are merged in C. Similarly transfected cells do not react with CSF from a control individual (D) but do show reactivity with a polyclonal antibody against the B1 subunit of the $GABA_B$ receptor (E); reactivities merged in F. Immunofluorescent method.

Culture of rat hippocampal neurons incubated (live, non-permeabilised) with CSF of a patient with anti-$GABA_BR$ and limbic encephalitis versus a control individual



Note the intense punctate reactivity of patient's antibodies with cell surface antigens (A) and the absence of reactivity in the control (B); nuclei of neurons stained with 4',6-diamidino-2-phenylindole (DAPI).

The surface antigens were precipitated using the antibodies within the patient's serum, and then electrophoretically separated and visualised with EZBlue (C).

Patient's antibodies (P) precipitated two main protein bands at about 105 kDa and 90 kDa; these bands are not seen in the precipitate using serum from a control individual (N).

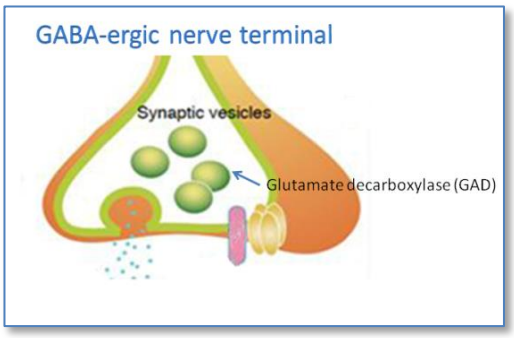
Sequencing of the 105 kDa band by use of mass spectrometry showed it contained the B1 and B2 subunits of the $GABA_B$ receptor. The 90 kDa and other smaller bands were proteolytic fragments and patient's IgG products. Subsequent transfer of the gel to nitrocellulose and immunoblotting with antibodies specific for each of the $GABA_B$ (D) subunits confirmed that patient's antibodies precipitated the B1 and B2 subunits (105 kDa) and that the 90 kDa band was a proteolytic fragment of B1.

From: Lancaster E, Lai M, Peng X, et al. Antibodies to the GABAB receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol* 2010; 9: 67-76.

Stiff-person spectrum of symptoms (SPS): characteristics of anti-GAD encephalitis (presynaptic encephalitis) and anti-GlyR alpha1 encephalomyelitis (synaptic encephalitis)

Anti-GAD is associated with

- Encephalomyelitis or limbic encephalitis with or without associated neoplasm
- Paraneoplastic cerebellar ataxia (PCD)
- Refractory seizures
- SPS including variants such as progressive encephalomyelitis with rigidity and myoclonus (PERM)
- Diabetes mellitus



A finding of anti-GAD is sometimes associated with one of the following neoplasms: **SCLC, breast, thymoma, pancreas, multiple myelomas, colon (rectum), and renal cell carcinoma.**

It appears that there are close links between autoimmunity directed against components of inhibitory synapses and neurological conditions characterized by chronic rigidity and spasms.

- **Anti-Glycine receptor** may be a feature of some cases with PERM [Neurology 2008; 71: 1291-1292], please see below
- SPS is also associated also with autoantibodies to $GABA_A$-receptor-associated protein (**anti-GABARAP**) (Brain 2006 Dec; 129 (Pt 12): 3270-6. Epub 2006 Sep 19)
- Moreover, high-titer autoantibodies directed against **gephyrin** may be a feature (Neuron. 2000 May; 26(2): 307-12)
- Some of these patients are also **anti-$GABA_B$R1-seropositive** (please see anti-$GABA_B$R1 encephalitis)

Please note

- In the paraneoplastic syndromes, the anti-GAD titre is much higher than that in diabetes mellitus (DM)
- Anti-GAD from neurological patients recognize epitopes that are different from those related to type 1 DM,
- Furthermore, patients with neurological disorders appear to have intrathecal synthesis of these antibodies

Clinical features, CSF, treatment and outcome of anti-GAD limbic encephalis (LE) with epilepsy: patients n = 9 **From:** Malter MP, Helmstaedter C, Urbach H, et al. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. Ann Neurol. 2010; 67(4): 470-8		
Compared to non anti-GAD seropositive LE, these patients were younger: median age 23 years, range: 17 – 66 years		
None had tumours		
Features	Cerebrospinal fluid (CSF)	Therapy, course
High-titer GAD antibodies define a form of non-paraneoplastic LE • Appears to be a chronic, non-remitting disorder • Should be included in the differential diagnosis of patients with temporal lobe epilepsy and mediotemporal encephalitis	**Frequent features** ○ oligoclonal bands ○ intrathecal secretion of anti-GAD	▪ Following monthly intravenous methylprednisolone pulses, GAD antibodies remained highly elevated in all patients ▪ Despite more intense anticonvulsive treatment, none of these patients became seizure free ▪ **Therapeutic trials of other immunotherapies should be undertaken**

Clinical features

The limbic encephalitis may be a gradually and slowly developing disorder with uncharacteristic cognitive symptoms – suggesting a psychosomatic nature. In such cases, later onset of unexplained epilepsy may be more revealing, and accordingly, the existence of anti-GAD-65 should be considered and preferentially using cerebrospinal fluid as material.

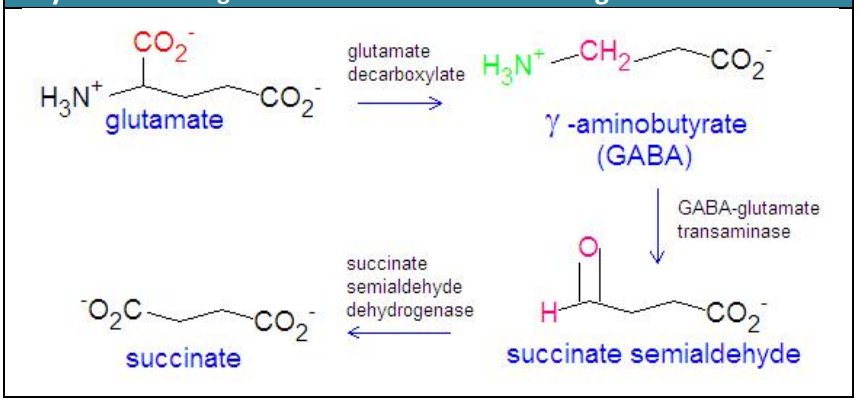
On the other hand, the disorder may be an encephalomyelitis with a more rapidly progressing symptomatology including fluctuating disorientation, delusions, and memory deficits. Respiratory failure may occur.

Short summary

In mammals, glutamate decarboxylase (GAD) exists in two isoforms encoded by two different genes		
Gene	**Molecular weight**	**Expression**
Gad-I (GAD67, Gene card 2q31	**67**	**CNS**
Gad-II (GAD65, Gene card 10p11.23	**65**	**CNS, pancreas**

- The targets of anti-GAD are located at GABA-ergic nerve terminals, which co-localizes with Amphiphysin and CV2 (CRMP5)
- GAD and Amphiphysin are non-intrinsic membrane proteins that are concentrated in nerve terminals, where a pool of both proteins is *associated with the cytoplasmic surface of* ***synaptic vesicles***
- GAD and Amphiphysin are the only two known targets of CNS autoimmunity with this distribution
- Upon incubation of nerve cells with anti-GAD serum or cerebrospinal fluid (CSF) from paraneoplastic patients, there is inhibition of the synthesis of GABA, and even **in a dose-dependent manner,** whereas this does not happen with serum or CSF from diabetics
- Furthermore, in an animal model using rats [Orphanet J Rare Dis. 2011; 6: 3.], it has been reported that intra-cerebellar administration of anti-GAD65 from a stiff-person syndrome patient impaired the NMDA-mediated turnover of glutamate, but had no effect on NMDA-mediated turnover of glycerol. By contrast, anti-GAD65 from a patient with cerebellar ataxia markedly decreased the NMDA-mediated turnover of glycerol. Both GAD65 autoantibodies increased the excitability of the spinal cord, as assessed by the F wave/M wave ratios
- In type1 diabetes, it appears that a minor fraction anti-GAD65 sera are reactive with a cross-reactive epitope found also on GAD67 [PLoS One. 2011 Apr 8; 6 (4): e18411].
- **Accordingly, these autoantibodies appear to recognize different epitopes**

Synthesis from gamma-amino butter acid and degradation of GABA

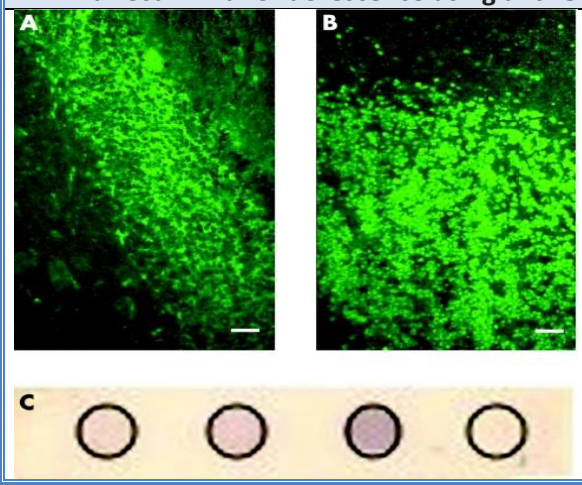


The role of γ-aminobutyric acid (GABA) and GABA receptors

- It is the major inhibitory neurotransmitter in the mammalian CNS, and mediates its effects through different classes of receptor termed $GABA_A$, $GABA_B$ and $GABA_C$
- It plays a role in regulating **neuronal excitability** throughout the nervous system
- In humans, GABA is also directly responsible for the regulation of **muscle tone**
- GABA is classified as an inhibitory neurotransmitter, as opposed to excitatory neurotransmitters, such as glutamate, which augment the nerve impulses in the neuron

- GABA-receptors mainly allow negatively charged chloride neurons to enter the neuron, thus reducing its excitability

Anti-GAD seropositive patient with epilepsy and cerebellar ataxia
Indirect immunofluorescence using anti-GAD patient serum and primate cerebellar granular cells



Indirect immunofluorescence was carried out using the patient's serum diluted to 1:10. The serum reacted positively up to a dilution of 1:8000.

(bars measure 20 µm)

(A) Cytoplasmic reactivity

(B) Anti-nuclear fluorescence was obtained with a reference anti-Hu serum (titre 1/320), diluted to 1:20. This shows the different reactivity of the patient's serum compared with anti-Hu autoantibodies.

(C) Immunoblot confirming the glutamic acid decarboxylase (GAD) reactivity. From left to right: control reaction, GAD67, GAD65, cut-off. Positivity is indicated by intensities of blue (appearing as dark rose).

The test is clearly positive for GAD65, but only weakly positive for GAD67 (reproduced by the permission of Professor J Honnorat).

Anti-GlyR alpha1 encephalomyelitis

Glycine receptors (GlyRs)

The GlyR, is the receptor for the amino acid neurotransmitter glycine. It is among the most widely distributed inhibitory receptors in the central nervous system. GlyRs are primarily expressed in spinal cord, brain stem, caudal brain, and retina. In adult neurons, the inhibitory chloride influx upon glycine receptor activation stabilizes the resting potential of the cell, rendering them electrically quiescent. Inversely, blockade of GlyRs by the competitive antagonist strychnine causes overexcitation resulting in pain, muscle cramps and exaggerated startle responses. Apart from its major transmitter function in spinal cord and brainstem, glycine also mediates substantial inhibitory neurotransmission via glycinergic amacrine cells in the mammalian retina. All four α subunits of the GlyR have been localized to specific synapses within the mammalian retina.

Anti-GlyR1 appears to be a finding in about 10 % of SPS spectrum of symptoms (with or without anti-GAD).

Glycine receptors grouped by specificity					
	Subunit	Gene	Chromosome	Genetic disorders	Acquired autoimmune disorders
Alpha	α1	GLRA1	5q32	○ Autosomal dominant hyperekplexia, ○ Autosomal recessive hyperekplexia ○ Hyperekplexia and spastic paraparesis ○ Congenital stiff-man syndrome ○ Limbic encephalitis	○ Atypical stiff-person or stiff-limb syndrome (without or with anti-GAD) ○ Progressive encephalomyelitis with rigidity and myoclonus (PERM) ○ Autoimmune hyperekplexia
	α2	GLRA2	Xp22.1-p21.3	○ Rett syndrome	
	α3	GLRA3	4q33-q34		
	α4	GLRA4	Xq22.2		
Beta	β	GLRB	4q31.3	○ Autosomal recessive hyperekplexia	

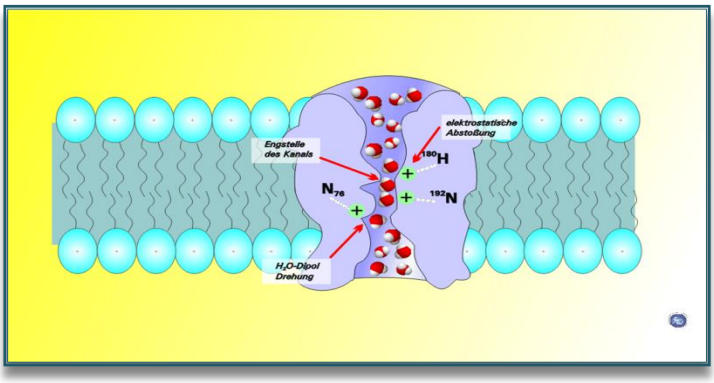
Clinical features of 18 anti-GlyR sporadic cases, studied so far: n (%)		
	First presentation	**At max severity**
Spasms / Stiffness / Rigidity (neck, trunk or limb muscles)	9 (50)	16 (89)
Excessive startle (spontaneous or triggered by noise or touch)	4 (22)	14 (78)
Limb or gait cerebellar ataxia	0	5 (28)
Limb paresis / Pyramidal signs	6 (33)	13 (72)
Walking difficulties / falls (mostly related to stiffness / rigidity / spams)	6 (33)	
Sensory symptoms/Pain	5 (28)	12 (67)
Oculomotor disturbance: nerve or gaze palsy (eyelid ptosis, diplopia, nystagmus, slow / jerky movements)	6 (33)	9 (50)
Trigeminal, facial and bulbar motor disturbance (dysphagia, dysarthria, difficulty chewing, facial numbness, trismus)	6 (33)	11 (61)
Cognitive impairment /encephalopathy /seizures /sleep disorders	4 (22)	9 (50)
Autonomic disturbances (hyper / hypohidrosis, dry mouth, brady- or tachycardia, hypo / hyper blood pressure, bladder, bowel or sexual dysfunction)	2 (11)	9 (50)
Respiratory failure (admission in ICU / ventilation)	0	6 (33)
Sudden death	0	3 (17)
Epidemiology		
Gender	5 F; 13 M	
Median age at onset (years)	51 (28-72)	
Cerebrospinal fluid		
Pleocytosis (5 - 45 lymph)	6/14 (43 %)	
Elevated protein (>1g/L)	2/14 (14 %)	
Oligoclonal banding (OCB) or elevated IgG	4/13 (21 %)	
Any abnormality	8/14 (57 %)	
MRI		
Brain: only with small vessel disease	2/17 (12 %)	
Spinal cord: with short inflammatory lesions	2/11 (18 %)	
Course of disease		
Monophasic	3/12 (25 %)	
Recurrent/relapsing	7/12 (58 %)	
Chronic progressive	2/12 (17 %)	
Follow-up too short or unknown	6/18 (33 %)	
Past medical history (PMH)		
Tumours	1 lymphoma, 2 thymoma	

Anti-GlyR alpha1 encephalomyelitis: summary of various symptomatology					Onset, course	
					Type	**Percentage**
Spinal cord involvement predominantly with later brainstem	Pain and sensory symptoms followed by brainstem and rigidity	Brainstem followed by generalised rigidity and myoclonus i.e. classical PERM	Bulbar and oculomotor dysfunction with touch sensitive myoclonus	Brain and brainstem involvement with alterations of memory, behaviour and sleep, trismus	Acute	17
					Subacute	33
					Subacute with acute exacerbations	11
					Chronic / insidious	11
					Chronic with acute exacerbations	28

The symptoms may also include neurogenic pruritus and sudden death.
Co-occurrence of neoplasms: about 17 %, see table above)
Please note that this disorder may mimic multiple sclerosis (MS)

Characteristics of anti-AQP4 (NMO) encephalomyelitis

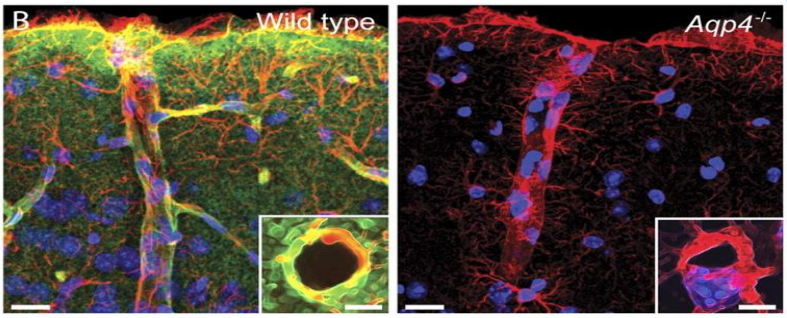
Schematic depiction of water movement through the narrow selectivity filter of the aquaporin channel
Water passes through each pore in a single file.
Estimated high water permeability: 10^9 molecules/subunit/sec



Aquaporin4 (AQP4), general aspects

Tissue expression

- In the CNS, AQP4-channels are wide-spread and partly co-localise with laminin
- They are expressed in astrocyte foot processes at the blood-brain barrier
- They are anchored at the perivascular and subpial membranes by their C terminus to alpha-syntrophin
- These channels outline CNS microvessels, pia, subpia, and Virchow-Robin space



Immunofluorescence micrographs of mouse cortex probed with primary antibodies against AQP4 (green) and GFAP (red) with DAPI-labeled nuclei (blue) for orientation.

The AQP4 immunofluorescence signal is absent in *Aqp4*$^{-/-}$ mice (right panel).
(Scale bar: 25 µm)

Insets display perivascular AQP4 and GFAP labeling at higher magnification.
(Scale bar: *Inset*, 5 µm.)

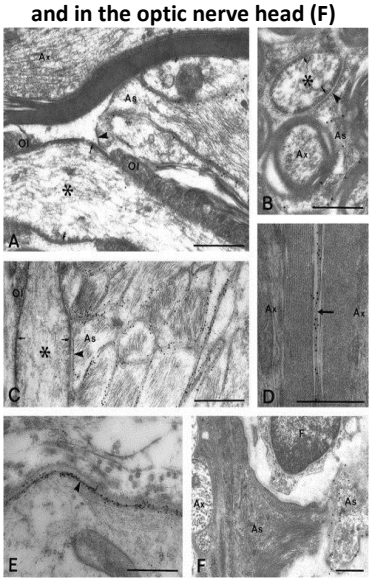
- They are also expressed in the inner ear (organ of Corti), in the retina and the optic nerve

Associated disorders

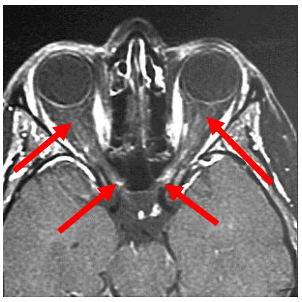
1. **AQP4s are targeted by autoantibodies in neuromyelitis optica (NMO)**
2. AQP4s are upregulated by direct insult to the central nervous system. This may result in vasogenic brain oedema
3. Upregulation may play an important role in eclampsy
4. Cytotoxic brain oedema may be an important mechanism in “idiopathic” intracranial hypertension and hepatic encephalopathy

Anti-AQP4's appear to favour symptoms at sites where the AQP4s are most accessible

AQP4 immunoreactivity in the posterior part of the optic nerve (A-E) and in the optic nerve head (F)

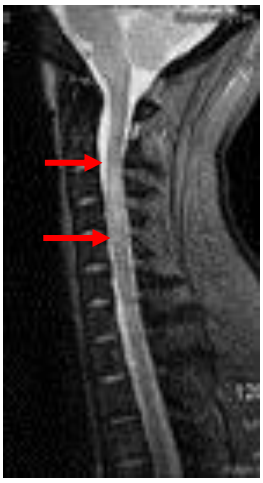


NMO, optic neuritis



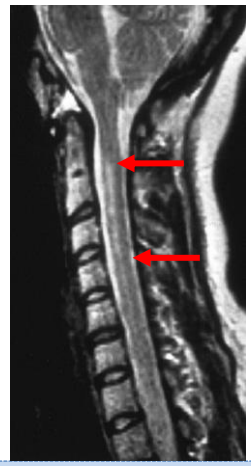
LETM

longitudinally extensive transverse myelitis



Infarction due to embolus

Spinal cord MRI visualizes expansion of a lesion from C2 to C5 levels



In about 47 % of NMO patients, there is reported serological evidence of recent viral infection when such a screening is performed during the acute phase of the neurologic illness (Koga M, Takahashi T, Kawai M, Fujihara K, Kanda T. A serological analysis of viral and bacterial infections associated with neuromyelitis optica. Journal of the Neurological Sciences 2011; 300 (1): 19-22)

Clinical features	
Neurology	**NMO (Devic's syndrome), LETM, recurrent optic neuritis**
	In children also episodic cerebral symptoms: ➢ Encephalopathy ➢ Ophthalmoparesis ➢ Ataxia ➢ Seizures ➢ Intractable vomiting, or hiccups Uncontrollable vomiting and hiccups, are now recognized as relatively "specific" symptoms of NMO that are due to brainstem involvement

In view of the abundant expression of AQP4s at perivascular and subpial membranes, more anti-AQP4 related disorders may be discovered.

The conformational epitopes of M-23 AQP4 are the primary targets of NMO-IgG Abs, whereas M-1 AQP4 Abs are developed with increasing disease duration and number of relapses (Mader et al. 2010)

DOPAMINE (post-streptococcal) related autoimmune encephalitis

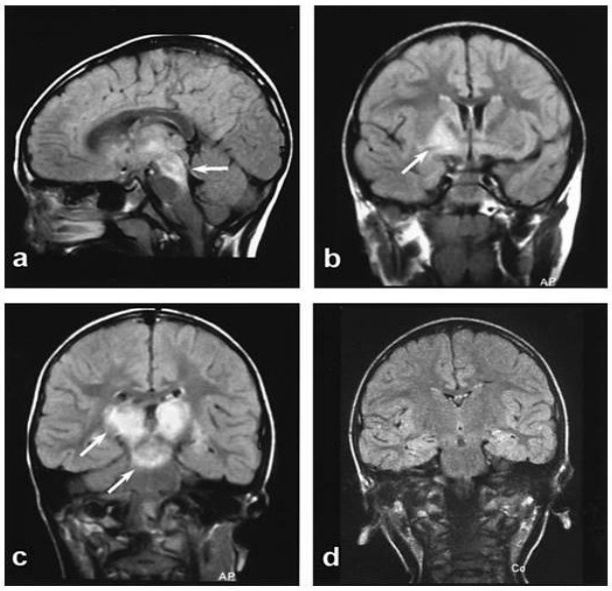
Distinguishing features: movement disorders, tics, multifocal myoclonic jerks; OCD

Onset: reported from 3-4 years and above, and rarely after teenage
Course: frequently a relapsing disorder
Usually, this disorder sets in suddenly ("overnight"), rather than gradually

Typically, the clinical picture is limited to only a few of the associated symptoms

- Movement disorders: tics (motor, vocal), chorea (usually affecting limbs; maybe unilateral), facial grimacing, parkinsonism, dystonia
- Motor hyperactivity
- Obsessive compulsive disorder (OCD)
- Anxiety, episodes of unmotivated fear, emotional lability, attention deficit, psychosis
- Behavioral (developmental) regression
- Epilepsy: multifocal myoclonus (maybe elicited from thalamus), maybe series of hiccups (myoclonic jerks of the diaphragm) – thalamic origin?
- Multifocal myokymia
- Slowed cognition, memory dysfunction
- Sleep disorders, including sleep inversion enuresis or altered urinary frequency

Streptococcal post-infectious autoimmune encephalitis



Dale R C et al. Brain 2004;127:21-33

MRI of the brain in a somnolent patient with bradykinesia and rigidity, showing inflammatory lesions (arrows) in the
(a) midbrain and periaqueductal grey matter,
(b) Right putamen and
(c) Bilaterally in thalami and midbrain.
(d) Convalescent imaging showing resolution of the inflammatory changes in the thalami and midbrain

Proposed diagnostic strategy in presumed post-streptococcal autoimmunity		
1. Diagnose a current GAS-infection		
Throat swap	Culture to show the presence of GAS	
Serum samples	➢ Anti-Streptolysin O (AST) ➢ Anti-Streptococcal DNAse B (ASDB)	
2. At later occurrence of neuropsychiatric symptoms		
Lumbar puncture	➢ Total protein (hyperproteinorachia?), IgG level ➢ Oligoclonal bands ➢ Pleiocytosis	
Serum samples, CSF samples?	➢ Anti-Lyso-GM1 (IgG) ➢ CamKII activity in culture of neuroblastoma cells incubated with such serum / CSF ➢ Anti-Dopamine-receptor 1 (D1) ➢ Anti-Dopamine-receptor 2 (D2) ➢ Anti-β-Tubulin (IgG)	Monitor consecutive samples over time to document increasing / decreasing titres

A finding of anti-Streptococcal antibodies is quite common in children – with a frequency of about 90 % being typical. Moreover, variation of such titers in an individual patient is associated with an ongoing infection and detectable long time thereafter. This is an expected feature and serves to cure the infection – and is not a biomarker of autoimmunity including in the central nervous system.

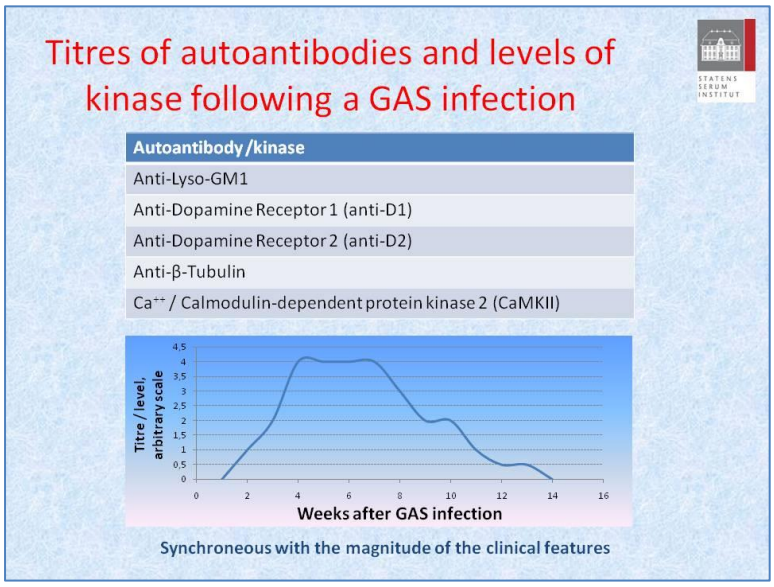


Figure to the left: in particular, children with streptococcal infections and a subsequent neurological disorder may have elevated titres of these antibodies and/or an increased percentage of activated CamKII, which in the presence of associated symptoms suggests a post-streptococcal neurological disorder.

Most frequently, one or more titres of these autoantibodies are above the reference and more rarely, all titres are elevated along with an increased concentration of CaMKII. An isolated elevated percentage of CaMKII can also be found, although sometimes together with borderline values of one or more of these autoantibodies.

Animal models suggest that these autoantibodies play a role in the disease, but they can also be biomarkers. There are of course other types of tics and OCD which are associated with other infections and are not streptococcal related.

Treatment of autoimmune post-streptococcal neurological disorders

Prophylaxis

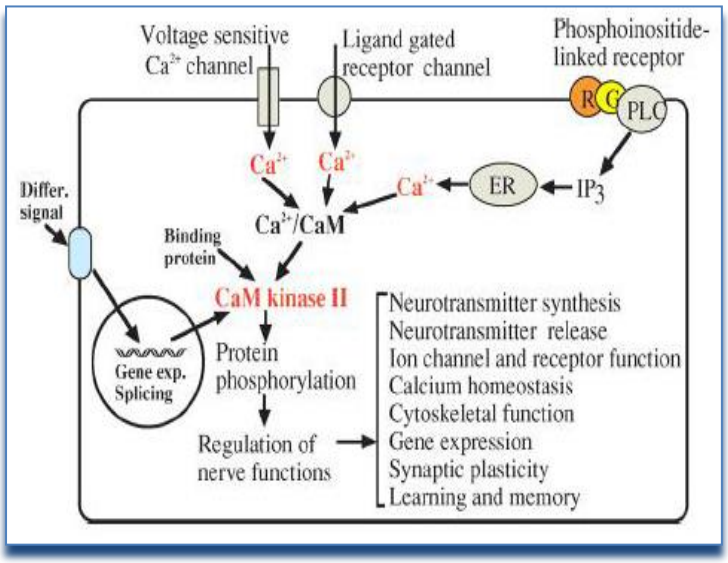
- **Primary –** V-penicillin as soon as possible on symptoms consistent with a streptococcal infection, e.g. a sore throat
- **Secondary –** long-term Azithromycin on risk of repeated infections with short intervals

Antibiotics have no effect on the neurological symptoms and are therefore given preventive or to shorten an on-going GAS-infection as much as possible. Moreover and due to variable compliance and other factors, a new GAS infection may set in anyway - and thereafter recurrence of neurological symptoms.

On neurological symptoms of a non-tolerable severity

- **Intravenous high-dose IgG –** alternatively, **plasma exchange** (IgG treatment is less traumatic for a child)
- **In combination with steroid in cases with more severe features or prolonged symptoms**
- Rituxumab

Significant scientific advances suggesting explanations for some initial steps of the pathogenic mechanisms



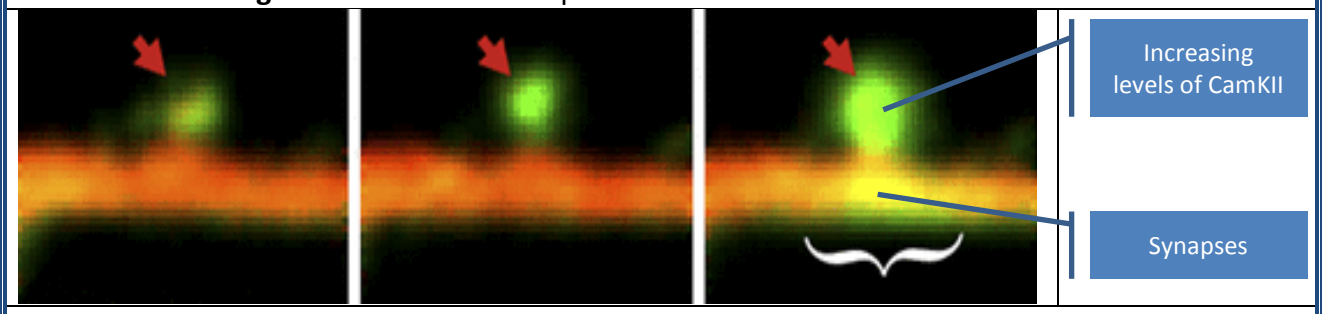
Functions of calcium/calmodulin-dependent protein kinase II (CamKII)

Due to its ability for autophosphorylation, CaMK activity can outlast the intracellular calcium transient that is needed to activate it. In neurons, this property is important for the induction of synaptic plasticity. Pharmacological inhibition of CaMKII blocks the induction of long-term potentiation. Upon activation, CaMKII phosphorylates postsynaptic **glutamate receptors** and thus changes the electrical properties of the synapse.

The **figure** provides an overview of some effects of this multifunctional kinase. Within a context of post-streptococcal pathology, synthesis and release of neurotransmitters (dopamine and serotonin) and synaptic plasticity may be the most significant ones.

Lyso-GM1, a compound of neural cell membranes, stabilizes the level of intracellular Ca^{++}. *Antibody binding to lyso-GM1 may cause an increased level of intracellular Ca^{++} and thereby* ***downstream activation of CamKII.*** However, other mechanisms of CamKII activation may also be operative as related to this type of autoimmune encephalitis.

Boosting synaptic sensitivity: CaMKII triggers nearby synapses to attract more receptors for the neurotransmitter glutamate: red arrows point to CamKII



Glutamate abnormalities contribute to the pathogenesis of OCD

Lemieux M, Labrecque S et al. The Journal of Cell Biology 2012; 198 (6): 1055-1073

Activation of CamKII also causes an increased level of neurotransmitters, whereby **DOPAMINE abnormalities appear to contribute to the pathogenesis of movement disorders** associated with post-streptococcal neurology.

These features have been confirmed by a new animal model in Lewis rats as well as in a cell model using a culture of nerve cells, **please see below.**

Animal model of autoimmune post-streptococcal neurological disorder

Behavioral, pharmacological, and immunological abnormalities after streptococcal exposure: A novel rat model of Sydenham chorea and related neuropsychiatric disorders

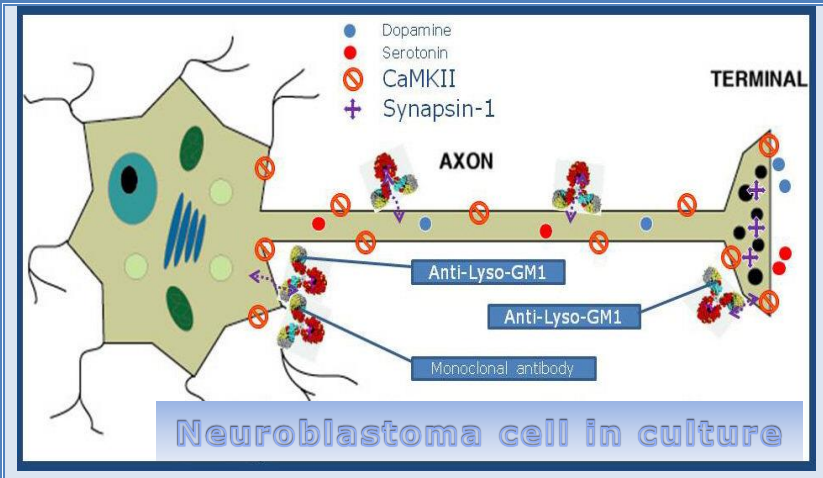
Authors: Brimberg L, Benhar I, Mascaro-Blanco A, Alvarez K, Winter C, Klein J, Moses AE, Somnier FE, Leckman JF, Swedo SE, Cunningham MW. *Neuropsychopharmacology* (2012) **37,** 2076–2087 [86]
http://www.nature.com/npp/journal/v37/n9/abs/npp201256a.html

- In streptococcal immunized rats, there were antibody deposition in the striatum, thalamus, and frontal cortex, and concomitant alterations in **dopamine** and **glutamate** [#] levels in cortex and basal ganglia
- Autoantibodies (IgG) of GAS rats caused elevated calcium/calmodulin-dependent protein kinase II signaling in SK-N-SH neuronal cells
- Discovery of autoantibodies targeted against dopamine D1 and D2 receptors
- Such immunized rats exhibited motor symptoms (impaired food manipulation and beam walking) and compulsive behavior (increased induced-grooming)

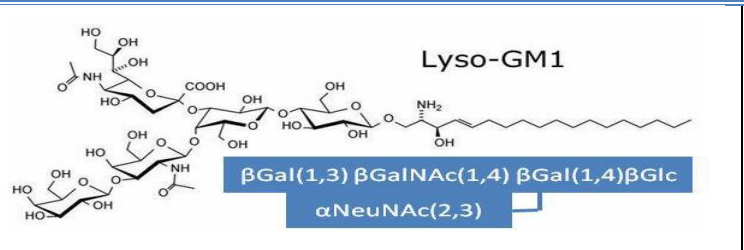
From: Department of Psychology, Tel Aviv University, Israel; Department of Biotechnology and Microbiology, Tel Aviv University, Israel; Department of Microbiology and Immunology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; Department of Psychiatry, Technical University Dresden, Germany; Department of Psychiatry, Charité University Medicine Berlin, Germany; Department of Clinical Microbiology and Infectious Diseases, Hadassah University Hospital, Israel; Department of Clinical Biochemistry and Immunology, Statens Serum Institute, Copenhagen, Denmark; Yale Child Study Center, Departments of Pediatrics and Psychiatry, Yale University School of Medicine, New Haven, CT, USA; Pediatrics and Developmental Neuroscience Branch, National Institute of Mental Health, Bethesda, MD, USA

[#]Treatment with Ketamine (a potent noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor) appears to be efficient in otherwise therapy-resistant OCD. Biol Psychiatry. 2012 Dec 1; 72(11): 964-70

Cellular model of autoimmune post-streptococcal neurological disorders



The **Figure** is a summary of reported findings after in vitro incubation of neuroblastoma cells with sera containing anti-lyso-GM1 (and maybe additional and currently unknown factors) or monoclonals with the same specificity. CamKII activates tyrosine & tryptophan hydroxylase and synapsin-1 controlling release of these two neurotransmitters. Binding of the autoantibodies causes a reduction of the inhibitory effect of lysoganglioside GM1 on CaMKII, whereby more neurotransmitters (dopamine & serotonin) are synthesised and released (synapsin 1). *Please see flow chart below.* ***Note that both dopaminergic and serotonergic pathways are affected***



Molecular mimicry

GlcNAc

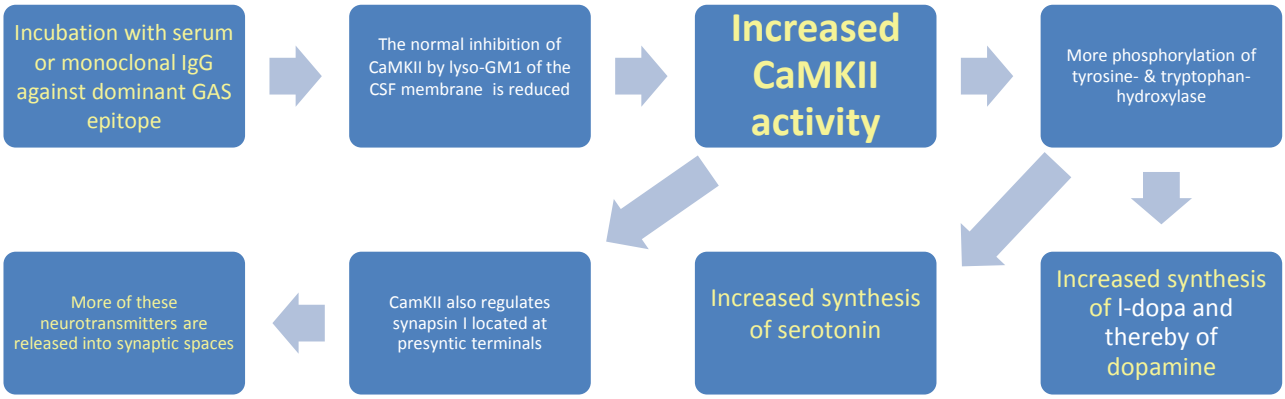
N-acetylglucosamine

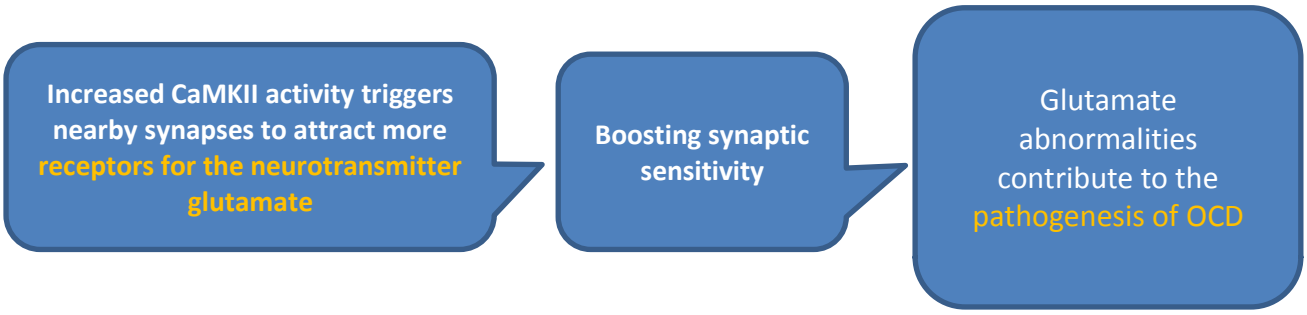
Epitope on group A streptococci and also a part of lyso-GM1.

Synapsin I and synapsin II do also contain terminal GlcNAc

Molecular mimicry - Wikipedia, the free encyclopedia; Molecular Mimicry, Bystander Activation, or Viral Persistence: Infections and Autoimmune Disease

In summary:





Anti-MOG associated encephalomyelitis

Myelin Oligodendrocyte Glycoprotein (MOG) is a glycoprotein believed to be important in the process of myelinization of nerves in the central nervous system (CNS). In humans this protein is encoded by the MOG gene (6p22.1). It is speculated to serve as a necessary "adhesion molecule" to provide structural integrity to the myelin sheath and is known to develop late on the oligodendrocyte.

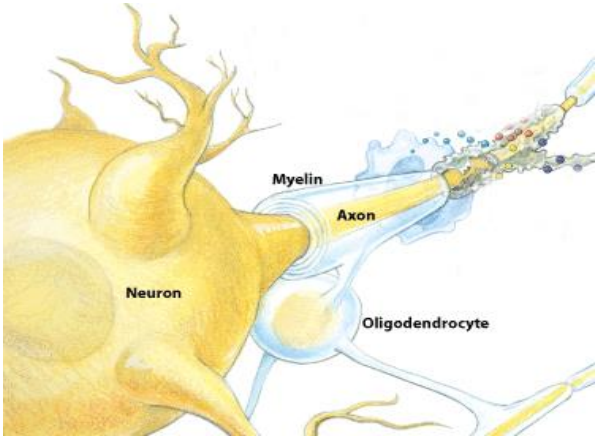
Molecular function

While the primary molecular function of MOG is not yet known, its likely role with the myelin sheath is either in sheath "completion and/or maintenance". More specifically, MOG is speculated to be "necessary" as an "adhesion molecule" on the myelin sheath of the CNS to provide the structural integrity of the myelin sheath.

MOG's cDNA coding region in humans have been shown to be "highly homologous" to rats, mice, and bovine, and hence highly conserved. This suggests "an important biological role for this protein".

Structure

The MOG gene is forming at least nine isoforms. Developmentally, MOG is formed "very late on oligodendrocytes and the myelin sheath".

MOG - myelin oligodendrocyt glycoprotein	Clinical features
	➢ **ADEM (about 40 %)** ➢ **Clinically isolated syndrome (CIS)** ➢ **Recurrent opticus neuritis** ➢ **Transverse myelitis including longitudinal extensive (LETM)**

References

1. Brilot F, Dale RC, Selter RC, Grummel V, Kalluri SR, Aslam M, Busch V, Zhou D, Cepok S, Hemmer B. **Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease.** Ann Neurol. 2009; 66(6): 833-42.
2. Brilot F, Grummel V, Kraus V, Cepok S, Dale RC, Hemmer B. Antibody responses to EBV and native MOG in pediatric inflammatory demyelinating CNS diseases. Neurology 2010; 74 (21): 1711-1715
3. Mader S, Gredler V, Schanda K, et. Al. **Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders.** *Journal of Neuroinflammation* 2011, **8**: 184 doi: 10.1186/1742-2094-8-184
4. Pröbstel AK, Dornmair K, Bittner R et al. **Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis.** Neurology. 2011 Aug 9; 77 (6): 580-8.
5. Rostasy K, Mader S, Schanda K, Huppke P, Gärtner J, Kraus V, Karenfort M, Tibussek D, Blaschek A, Bajer-Kornek B, Leitz S, Schimmel M, Di Pauli F, Berger T, Reindl M. **Anti-myelin oligodendrocyte glycoprotein antibodies in pediatric patients with optic neuritis**. Arch Neurol 2012; 69 (6): 752-6.

References (chronological listing by year of publication)

1. Corsellis JA, Goldberg GJ, Norton AR. "Limbic encephalitis" and its association with carcinoma. Brain 1968; 91: 481-496.
2. Solimena M, Folli F, Denis-Domini S, et al. Autoantibodies to glutamic acid decarboxylase in a patient with Stiff-Man Syndrome, epilepsy, and type I diabetes mellitus. N Engl J Med 1988; 318: 1012-20.
3. Burn DJ, Ball J, Lees AJ, Behan PO, Morgan-Hughes JA. A case of progressive encephalomyelitis with rigidity and positive antiglutamic acid decarboxylase antibodies [corrected]. J Neurol Neurosurg Psychiatry 1991; 54(5): 449–451.
4. De Camilli P, Thomas A, Cofiell R, et al. The synaptic vesicle-associated protein amphiphysin is the 128-kD autoantigen of Stiff-Man Syndrome with breast cancer. J Exp Med 1993; 178: 2219-2223.
5. Brown P, Marsden CD. The stiff man syndrome and stiff man plus syndromes. J Neurol 1999; 246: 648-652.
6. Helfgott SM. Stiff-man syndrome. From the bedside to the bench. Arthritis & Rheumatism 1999; 42: 1312-1320.
7. Taylor RB *et al*. Reversible paraneoplastic encephalomyelitis associated with a benign ovarian teratoma. *Can J Neurol Sci* 1999; **26**: 317–320 | PubMed | ChemPort |
8. Gultekin SH *et al*. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. *Brain* 2000; **123**: 1481–1494 | Article | PubMed | ISI |
9. Dalakas MC, Li M, Fujii M, Jacobowitz D. Stiff person syndrome. Quantification, specificity and intrathecal synthesis of GAD65 antibodies. Neurology 2001; 57: 780-784.
10. Dalakas MC, Fujii M, Li M, et al. High-dose intravenous immune globulin for stiff-person syndrome. New Engl J Med 2001; 345: 1870-1876.
11. Takenoshita H, Shizuka-Ikeda M, Mitoma H, Song S, Harigaya Y, Igeta Y, Yaguchi M, Ishida K, Shoji M, Tanaka M, Mizusawa H, Okamoto K. Presynaptic inhibition of cerebellar GABAergic transmission byglutamate decarboxylase autoantibodies in progressive cerebellar ataxia. J Neurol Neurosurg Psychiatry. 2001; 70(3): 386–389.
12. Meinck H, Faber L, Morgenthaler N, Seissler S, Maile S, Butler M, Solimena M, DeCamilli P, Scherbaum W. Antibodies against glutamic acid decarboxylase: prevalence inneurological diseases. J Neurol Neurosurg Psychiatry 2001; 71(1): 100–103.
13. Matsumoto S, Kusuhara T, Nakajima M, Ouma S, Takahashi M, Yamada T. Acute attacks and brain stem signs in a patient with glutamic acid decarboxylase autoantibodies. J Neurol Neurosurg Psychiatry 2002; 73(3): 345–346.
14. Ochi, H., Horiuchi, I., Araki, N., Toda, T., Araki, T., Sato, K., Murai, H., Osoegawa, M., Yamada, T., Okamura, K., Ogino, T., Mizumoto, K., Yamashita, H., Saya, H., Kira, J. Proteomic analysis of human brain identifies alpha-enolase as a novel autoantigen in Hashimoto's encephalopathy**.** FEBS Lett. 528: 197-202, 2002. [PubMed: 12297304, related citations] [Full Text: Elsevier Science, Pubget]
15. Antonini G, Nemni R, Giubilei F, Gragnani F, Ceschin V, Morino S, Bucci E, Accornero N. Autoantibodies to glutamic acid decarboxylase in downbeat nystagmus. J Neurol Neurosurg Psychiatry 2003; 74(7): 998–999.
16. Lawn ND, Westmoreland BF, Kiely MJ, Lennon VA, Vernino S. Clinical, magnetic resonance imaging, and electroencephalographic findings in paraneoplastic limbic encephalitis. Mayo Clin Proc 2003; 78(11): 1363-1368
17. Poliak S, Salomon D, Elhanany H et al. Juxtaparanodal clustering of Shaker-like K+channels in myelinated axons depends on Caspr2 and TAG-1. J Cell Biol 2003; 162(6): 1149-1160
18. Dale RC, Church AJ, Surtees RAH, Lees AJ, Adcock JE, Harding B, Neville BGR, Giovannoni G. "Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity". *Brain* 2004; **127** (Pt 1): 21–33. doi:10.1093/brain/awh008. PMID 14570817.
19. Vincent A *et al*. (2004) Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* **127**: 701–712 | PubMed | ISI |
20. Dalmau J, Graus F, Villarejo A et al. Clinical analysis of anti-Ma2-associated encephalitis. Brain 2004; 127(Pt 8): 1831-1844
21. Muni RH *et al*. (2004) Bilateral horizontal gaze palsy in presumed paraneoplastic brainstem encephalitis associated with a benign ovarian teratoma. *J Neuroophthalmol* **24**: 114–118 | PubMed |
22. Vincent A. Editorial - Encephalitis lethargica: part of a spectrum of poststreptococcal autoimmune diseases? Brain 2004; 127: 2-3.
23. Tumpey TM, Basler CF, Aguilar PV. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science.* 2005;310:77–80.[PubMed].
24. Takahashi Y *et al*. (2005) Autoantibodies and cell-mediated autoimmunity to NMDA-type GluRepsilon2 in patients with Rasmussen's encephalitis and chronic progressive epilepsia partialis continua. *Epilepsia* **46** (Suppl 5): S152–S158 | Article |
25. Ances BM, Vitaliani R, Taylor RA et al. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. Brain 2005; 128(Pt 8): 1764-1777
26. Mochizuki Y *et al*. (2006) Acute limbic encephalitis: a new entity? *Neurosci Lett* **394**: 5–8 | Article | PubMed | ChemPort |
27. Vitaliani R *et al*. (2005) Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. *Ann Neurol* **58**: 594–604 | Article | PubMed |
28. Fadul CE, Stommel EW, Dragnev KH, Eskey CJ, Dalmau JO. Focal paraneoplastic limbic encephalitis presenting as orgasmic epilepsy. J Neurooncol 2005; 72(2): 195-198
29. Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol 2005; 58(4): 594-604
30. Stein-Wexler R *et al*. Paraneoplastic limbic encephalitis in a teenage girl with an immature ovarian teratoma. *Pediatr Radiol* 2005; **35**: 694–697 | Article | PubMed |
31. Kirvan CA, Swedo SE, Heuser JS et al. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. Nat Med 2003; 9: 914-20.
32. Walker KG, Lawrenson J, Wilmshurst JM. Neuropsychiatric movement disorders following streptococcal infection. Dev Med Child Neurol 2005; 47: 771-5.
33. Raju R, Rakocevic G, Chen Z, Hoehn G, Semino-Mora C, Shi W, Olsen R, Dalakas MC. Autoimmunity to GABAA-receptor-associated protein in stiff-person syndrome**.** Brain 2006 Dec; 129 (Pt 12): 3270-6. Epub 2006 Sep 19
34. Kirvan CA, Swedo SE, Kurahara D et al. Streptococcal mimicry and antibody-mediated cell signaling in the pathogenesis of Sydenham's chorea. Autoimmunity 2006; 39: 21-9.
35. Kirvan CA, Swedo SE, Snider LA et al. Antibody-mediated neuronal cell signalling in behavior and movement disorders. J Neuroimmunol 2006; 179: 173-9.

36. Dalmau J *et al*. (2007) Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* **61**: 25–36 | Article | PubMed | ChemPort |
37. Tuzun E, Dalmau J. Limbic encephalitis and variants: classification, diagnosis and treatment. Neurologist 2007; 13(5): 261-271
38. Sansing LH, Tuzun E, Ko MW, Baccon J, Lynch DR, Dalmau J. A patient with encephalitis associated with NMDA receptor antibodies. Nat Clin Pract Neurol 2007; 3(5): 291-296
39. Kirvan CA, Cox CJ, Swedo SE, Cunningham MW. Tubulin Is a Neuronal Target of Autoantibodies in Sydenham's chorea. J Immunol 2007; 178: 7412-7421.
40. Shimazaki H *et al*. Reversible limbic encephalitis with antibodies against membranes of neurons of hippocampus. *J Neurol Neurosurg Psychiatry* 2007; 78: 324–325 | PubMed | ChemPort |
41. Koide R *et al*. EFA6A-like antibodies in paraneoplastic encephalitis associated with immature ovarian teratoma: a case report. *J Neurooncol* 2007; 81: 71–74 | PubMed | ChemPort |
42. Vulliemoz S, Vanini G, Truffert A, Chizzolini C, Seeck M. Epilepsy and cerebellar ataxia associated with anti-glutamic acid decarboxylase antibodies. J Neurol Neurosurg Psychiatry. 2007; 78(2): 187–189.
43. McHugh JC, Murray B, Renganathan R, Connolly S, Lynch T. GAD Antibody Positive Paraneoplastic Stiff Person Syndrome in a Patient with Renal Cell Carcinoma. *Movement Disorders 2007; 22 (9): 1343-1346.*
44. Dalmau J, Gleichmann AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurology 2008; 7: 1091-1098.
45. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol 2008; 7(4): 327-340
46. Hutchinson M, Waters P, McHugh J, Gorman G, O'Riordan S, Connolly S, Hager H, Yu C, Becker CM, Vincent A. Progressive Encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology 2008; 71: 1291-1292.
47. Geschwind MD, Tan KM, Lennon VA et al. Voltage-gated potassium channel autoimmunity mimicking creutzfeldt-jakob disease. Arch Neurol 2008; 65(10): 1341-1346
48. Iizuka T, Sakai F, Ide T et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. Neurology 2008; 70(7): 504-511
49. McKeon A, Lennon VA, Lotze T, Tenenbaum S, Ness JM, Rensel M, Kuntz NL, Fryer JP, Homburger H, Hunter J, Weinshenker BG, Krecke K, Lucchinetti CF, Pittock SJ. CNS aquaporin-4 autoimmunity in children. Neurology 2008; 71: 93 -100. http://www.neurology.org/ cgi/ content/ abstract/71/2/93
50. Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H, Matà S, Kremens D, Vitaliani R, Geschwind MD, Bataller L, Kalb RG, Davis R, Graus F, Lynch DR, Balice-Gordon R, Dalmau J. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol 2009; 65(4): 424–434.
51. Bayreuther C, Bourg V, Dellamonica J, Borg M, Bernardin G, Thomas P. Complex partial status epilepticus revealing anti-NMDA receptor encephalitis. Epileptic Disord 2009; 11(3): 261-265
52. Florance_NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, Campen CJ, Moss H, Peter N, Gleichman AJ, Glaser CA, Lynch DR, Rosenfeld MR, Dalmau J. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66(1):11-8.
53. Li W, Minohara M, Piao H, Matsushita T, Masaki K, Matsuoka T, Isobe N, Su JJ, Ohyagi Y, Kira J. Association of anti-*Helicobacter pylori* neutrophil-activating protein antibody response with anti-aquaporin-4 autoimmunity in Japanese patients with multiple sclerosis and neuromyelitis optica. Multiple Sclerosis 2009; 15 (12): 1411-1421. DOI: 10.1177/1352458509348961
54. Graus F, Boronat A, X. Xifró X, Boix M, Svigelj V, García A, Palomino A, Sabater L, Alberch J, Saiz A. The expanding clinical profile of anti-AMPA receptor encephalitis. Neurology; 2010; 74: 857-859
55. Lancaster E, Lai M, Peng X, et al. Antibodies to the GABAB receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol* 2010; 9: 67-76
56. Malter MP, Helmstaedter C, Urbach H, et al. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. Ann Neurol. 2010; 67(4): 470-8
57. Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, Peles E, Buckley C, Lang, Vincent A. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain 2010; 133 (9): 2734-2748.
58. Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R, Cowell JK, Dalmau J. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol 2010; 9(8):776-85
59. Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, Parsons TD, Lynch DR, Dalmau J, Balice-Gordon RJ. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci. 2010 April 28; 30(17): 5866–5875.
60. Ferioli S, Dalmau J, Kobet CA, Zhai QJ, Broderick JP, Espay AJ. Anti-N-methyl-Daspartate receptor encephalitis: characteristic behavioral and movement disorder. Arch Neurol 2010; 67(2): 250-251
61. Pruss H, Dalmau J, Arolt V, Wandinger KP. Anti-NMDA-receptor encephalitis. An interdisciplinary clinical picture. Nervenarzt 2010; 81(4): 396, 398, 400, passim
62. Graus F, Boronat A, Xifro X et al. The expanding clinical profile of anti-AMPA receptor encephalitis. Neurology 2010; 74(10): 857-859
63. Fukata Y, Lovero KL, Iwanaga T et al. Disruption of LGI1-linked synaptic complex causes abnormal synaptic transmission and epilepsy. Proc Natl Acad Sci U S A 2010; 107(8): 3799-3804
64. Jarius S, Wildemann B. AQP4 Antibodies in Neuromyelitis Optica: Diagnostic and Pathogenetic Relevance. Nature Reviews Neurology *2010; 6: 383-392. doi:10.1038/nrneurol.2010.72*
65. Fukata Y, Lovero KL, Iwanaga T, Watanabe A, Yokoi N, Tabuchi K, Shigemoto R, Nicoll RA, Fukata M. Disruption of LGI1–linked synaptic complex causes abnormal synaptic transmission and epilepsy. Proc Natl Acad Sci 2010; 107 (8): 3799-3804. | Abstract | Full Text | PDF–1.7M | Supplementary Material |
66. Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, Friedman D, Skeen MB, Grisold W, Kimura A, Ohta K, Iizuka T, Guzman M, Graus F, Moss SJ, Balice-Gordon R, Dalmau J. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol 2010; 9(1): 67-76.
67. Matthew P Anderson MP. Arrested Glutamatergic Synapse Development in Human Partial Epilepsy. Epilepsy Curr. 2010; 10(6): 153–158. doi: 10.1111/j.1535-7511.2010.01386.x..

68. Florance-Ryan N, Dalmau J. Update on anti-N-methyl-D-aspartate receptor encephalitis in children and adolescents. Curr Opin Pediatr 2010 Nov 1. [Epub ahead of print]
69. Moscato EH, Jain A, Peng X, Hughes EG, Dalmau J, Balice-Gordon RJ. Mechanisms underlying autoimmune synaptic encephalitis leading to disorders of memory, behavior and cognition: insights from molecular, cellular and synaptic studies [Review]. Eur J Neurosci 2010; 32(2): 298-309.
70. Kayser MS, Kohler CG, Dalmau J. Psychiatric manifestations of paraneoplastic disorders [Review]. Am J Psychiatry 2010;167(9):1039-50.
71. Vincent A, Irani SR. Caspr2 antibodies in patients with thymomas. J Thorac Oncol 2010; 5(10 Suppl 4): S277-80.
72. Haberlandt E, Bast T, Ebner A, Holthausen H, Kluger G, Kravljanac R, Kröll-Seger J, Kurlemann G, Makowski C, Rostasy K, Tuschen-Hofstätter E, Weber G, Vincent A, Bien CG. Limbic encephalitis in children and adolescents. Arch Dis Child 2010 doi:10.1136/adc.2010.183897
73. Koga M, Takahashi T, Kawai M, Fujihara K, Kanda T. A serological analysis of viral and bacterial infections associated with neuromyelitis optica. Journal of the Neurological Sciences 2011; 300 (1): 19-22
74. Manto MU, Hampe CS, Rogemond V, Honnorat J. Respective implications of glutamate decarboxylase antibodies in stiff person syndrome and cerebellar ataxia. Orphanet J Rare Dis. 2011; 6: 3.
75. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis [review]. Lancet Neurol. 2011;10(1):63-74.
76. Wandinger K-P, Saschenbrecker S, Stoecker W, Josep Dalmau J. Anti-NMDA-receptor encephalitis: A severe, multistage, treatable disorder presenting with psychosis. J Neuroimmunol 2011; 1-2: 86-91.
77. Boronat A, Sabater L, Saiz A, Dalmau J, Graus F. GABAB receptor antibodies in limbic encephalitis and anti-GAD–associated neurologic disorders. Neurology 2011; 76: 795-800.
78. Rosenfeld MR, Dalmau J. Anti-NMDA-Receptor Encephalitis and Other Synaptic Autoimmune Disorders. Curr Treat Options Neurol. 2011 Feb 5. [Epub ahead of print]
79. Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, Schott JM, Armstrong RJ, Zagami AS, Bleaset A, Somerville ER, Smith SM, Vinvent A. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol, EPub ahead of print. 17 MAR 2011; DOI: 10.1002/ana.22307
80. Irani SR, Vincent A. Autoimmune Encephalitis – New Awareness, Challenging Questions. Discov Med 2011; 11 (60): 449-458.
81. Jarius S, Jacobi C, et al. Frequency and syndrome specificity of antibodies to aquaporin-4 in neurological patients with rheumatic disorders. Mult Scler 2011, May 4. [Epub ahead of print]
82. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology 2011; 77 (2): 179-89.
83. Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y, Sangha N, Martinez-Lage M, Dalmau J. Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology 2011; 77 (6): 589-93.
84. Gabilondo I, Saiz A, Galán L, González V, Jadraque R, Sabater L, Sans A, Sempere A, Vela A, Villalobos F, Viñals M, Villoslada P, Graus F. Analysis of relapses in anti-NMDAR encephalitis. Neurology. 2011; 7 7(10): 996-9
85. Lancaster E, Martinez-Hernandez E, Titulaer MJ, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. Neurology 2011; 77: 1698-1701.
86. Vincent AS, Bien CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: new developments and future challenges [review]. *Lancet Neurol* 2011; 10: 759–72.
87. Brimberg L, Benhar I, Mascaro-Blanco A, Alvarez K, Lotan D, Winter C, Klein J, Moses AE, Somnier FE, Leckman JF, Swedo SE, Cunningham MW, Daphna Joel D. Behavioral, Pharmacological, and Immunological Abnormalities after Streptococcal Exposure: A Novel Rat Model of Sydenham Chorea and Related Neuropsychiatric Disorders. *Neuropsychopharmacology* (2012) **37,** 2076–2087; doi:10.1038/npp.2012.56; published online 25 April 2012
88. Zuliani L, Graus F, Giometto B, Bien C, Vincent A. Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition. J Neurol Neurosurg Psychiatry-2012-Zuliani-jnnp-2011-301237
89. Prüss H, Höltje M, Maier N, Gomez A, Buchert R, Harms L, Ahnert-Hilger G, Schmitz D, Terborg C, Kopp U, Klingbeil C, Probst C, Kohler S, Schwab JM, Stoecker W, Dalmau J, Wandinger KP. IgA NMDA receptor antibodies are markers of synaptic immunity in slow cognitive impairment. Neurology 2012, 78 (22): 1743-53. Epub 2012 Apr 25.
90. Tsutsui K, Kanbayashi T, Tanaka K, Boku S, Ito W, Tokunaga J, Mori A, Hishikawa Y, Shimizu T, Nishino S. Anti-NMDA-receptor antibody detected in encephalitis, schizophrenia, and narcolepsy with psychotic features. BMC Psychiatry. 2012; 12: 37.
91. Prüss H, Höltje M, Maier N, Gomez A, Buchert R, Harms L, Ahnert-Hilger G, Schmitz D, Terborg C, Kopp U, Klingbeil C, Probst C, Kohler S, Schwab JM, Stoecker W, Dalmau J, Wandinger KP. IgA NMDA receptor antibodies are markers of synaptic immunity in slow cognitive impairment. Neurology. 2012 May 29; 78(22): 1743-53. doi: 10.1212/WNL.0b013e318258300d. Epub 2012 Apr 25.
92. Prüss H, Finke C, Höltje M, Hofmann J, Klingbeil C, Probst C, Borowski K, Ahnert-Hilger G, Harms L, Schwab JM, Ploner CJ, Komorowski L, Stoecker W, Dalmau J, Wandinger KP. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis.Ann Neurol. 2012 Dec; 72(6): 902-11. doi: 10.1002/ana.23689.
93. Lancaster E, Dalmau J. Neuronal autoantigens-pathogenesis, associated disorders and antibody testing. Nat Rev Neurol. 2012;8:380-90
94. Gleichman AJ, Spruce LA, Dalmau J, Seeholzer SH, Lynch DR. Anti-NMDA Receptor Encephalitis Antibody Binding Is Dependent on Amino Acid Identity of a Small Region within the GluN1 Amino Terminal Domain. J Neurosci. 2012 Aug 8;32(32):11082-94.
95. Bloch MH, Wasylink S, Landeros.Weisenberger A, Panza KE, Billingslea E, Leckman JF, Krystal JH, Bhagwager Z, Sanacora G, Pittenger C. Effects of ketamine in treatment-refractory obsessive-compulsive disorder. Biol Psychiatry. 2012 Dec 1; 72(11): 964-70.
96. Dale RC, Merheb V, Pillai S, Wang D, Cantrill L, Murphy TK, Ben-Pazi H, Varadkar S, Aumann TD, Horne MK, Church AJ, Fath T, Brilot F. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. Brain 2012 Nov; 135 (Pt 11): 3453-68