AUTOIMMUNE ENCEPHALITIS

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DISCLOSURES

- No financial disclosure
- Evolving evidence

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OBJECTIVES

- Review the types of antibodies
- Associate antibodies with clinical syndromes and tumor associations
- Recognize the pitfalls in antibody testing

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ACUTE ENCEPHALITIS

- Brain inflammation
- < 6 weeks
- Infectious agents most common
- Non infectious – Autoimmune, paraneoplastic

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ANTIBODIES

- Neuronal intracellular antigen
- Cell surface synaptic receptors

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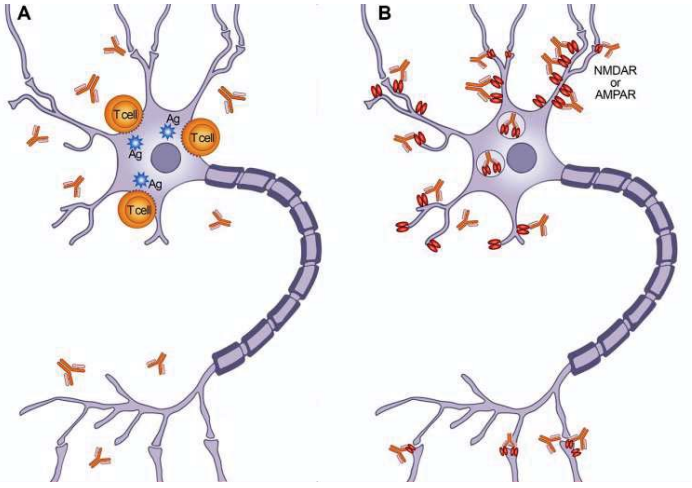
MECHANISMS OF DYSFUNCTION



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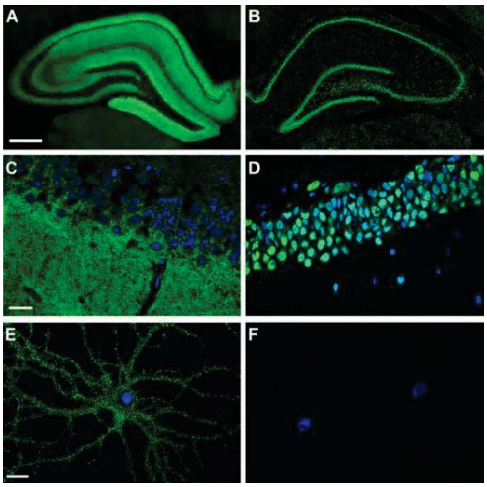
Dalmau J et al. Autoantibodies to Synaptic Receptors and neuronal Cell Surface Proteins in Autoimmune Diseases of the Central Nervous System Physiol Rev 2017

CELL SURFACE VS INTRACELLULAR

Cell surface Intracellular



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TUMOR ASSOCIATIONS

- Cell surface or synaptic proteins

Table 1. Autoimmune encephalitis with antibodies against cell surface and synaptic proteins

Antigen	Clinical syndrome	Tumor
NMDAR (GluN1)	Anti-NMDAR encephalitis: prodromal symptoms, psychiatric, seizures, amnesia, movement disorders, catatonia, autonomic instability, coma	Age-dependent 10–45% ovarian teratomas, infrequently carcinomas
AMPAR	Limbic encephalitis, psychiatric symptoms	70% (lung, breast, thymoma)
GABAbR	Limbic encephalitis, prominent seizures	50% (lung, neuroendocrine)
LGI1	Limbic encephalitis, 60% hyponatremia, occasional focal faciobrachial seizures prior to encephalitis	<10% (thymoma)
Caspr2	Encephalitis, Morvan syndrome, neuromyotonia	0–40% (thymoma)
mGluR5	Limbic encephalitis (reported in less than 10 patients)	Frequently, Hodgkin lymphoma
D2R	Basal ganglia encephalitis, Sydenham chorea	Infrequent
DPPX	Diarrhea, encephalitis with CNS hyperexcitability: confusion, psychiatric symptoms, tremor, myoclonus, nystagmus, hyperekplexia, PERM-like symptoms, ataxia	No tumor association
GABAaR	Refractory seizures, status epilepticus, or epilepsia partialis continua, stiff-person, opsoclonus	Infrequent
GlyR	Stiff-person, PERM, limbic encephalitis, cerebellar degeneration, optic neuritis	Infrequent
IgLON5	Abnormal sleep movements and behaviors, obstructive sleep apnea, stridor, dysarthria, dysphagia, ataxia, chorea (reported in less than 10 patients)	No tumor association

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Leypoldt et al. Autoimmune encephalopaties. Ann N Y Acad Sci 2014

TUMOR SCREENING

Probability depends on various factors

- Antibodies
  - Intracellular like Yo, Hu – about 95%
- Age and gender
  - 12 to 45 yr F NMDA – about 50% Ovarian teratoma
  - >45 M/F NMDA – 25% SCLC, Breast
- Clinical syndrome
  - VGCC LEMS – 50% SCLC
  - VGCC PCD – 95% SCLC

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TUMOR SCREENING

- CT chest/abdomen/pelvis
- MRI Breast
- MRI Pelvis
- US testis
- US ovaries
- FDG PET
- Tumor markers like CA 125 not sensitive

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ANTIBODY TESTING

- Usually serum testing
- CSF testing can be complementary
- Sometimes Ab may be present only in CSF - NMDAR ab, NMO ab and GFAP ab
- False positive

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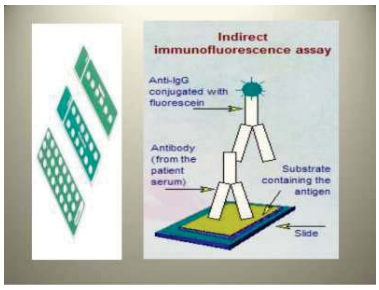
McKeon et al. CSF complements serum for evaluating paraneoplastic antibodies and NMO-IgG. Neurology 2011

ANTIBODY TESTING

- Screening
  - Indirect immunofluorescence testing
- Confirmation
  - Western Blot
  - Cell based assay
  - Immunoprecipitation



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Paraneoplastic Encephalitis, Psychiatric Symptoms, and Hypoventilation in Ovarian Teratoma

Roberta Vitaliani, MD,[1] Warren Mason, MD,[2] Beau Ances, MD, PhD,[1] Theodore Zwerdling, MD,[3] Zhilong Jiang, PhD,[1] and Josep Dalmau, MD, PhD[1]

We report four young women who developed acute psychiatric symptoms, seizures, memory deficits, decreased level of consciousness, and central hypoventilation associated with ovarian teratoma (OT) and cerebrospinal fluid (CSF) inflammatory abnormalities. Three patients recovered with treatment of the tumor or immunosuppression and one died of the disorder. Five other OT patients with a similar syndrome and response to treatment have been reported. Our patients' serum or CSF showed immunolabeling of antigens that were expressed at the cytoplasmic membrane of hippocampal neurons and processes and readily accessed by antibodies in live neurons. Immunoprobing of a hippocampal-expression library resulted in the isolation of EFA6A, a protein that interacts with a member of the two-pore-domain potassium channel family and is involved in the regulation of the dendritic development of hippocampal neurons. EFA6A-purified antibodies reproduced the hippocampal immunolabeling of all patients' antibodies and colocalized with them at the plasma membrane. These findings indicate that in a young woman with acute psychiatric symptoms, seizures, and central hypoventilation, a paraneoplastic immune-mediated syndrome should be considered. Recognition of this disorder is important because despite the severity of the symptoms, patients usually recover. The location and function of the isolated antigen suggest that the disorder is directly mediated by antibodies.

Ann Neurol 2005;58:594–604

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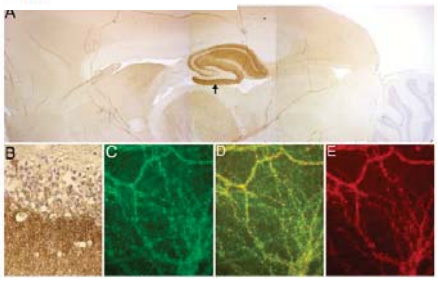
Paraneoplastic Anti–*N*-methyl-D-aspartate Receptor Encephalitis Associated with Ovarian Teratoma

Ann Neurol 2007;61:25–36



- 12 women with ovarian teratomas
- Serum/CSF Ab to cell surface of hippocampal neurons
- GluN1 subunit of NMDAR

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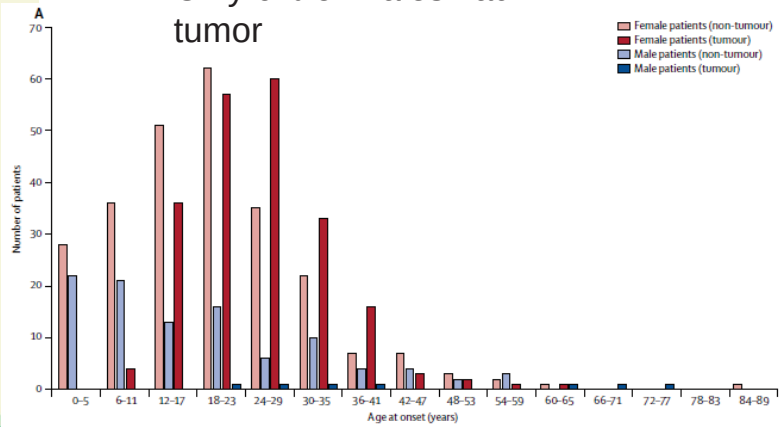
NMDAR AB: CASE SERIES OF 577 PATIENTS

- Median age: 21
- Only 6% of males had tumor



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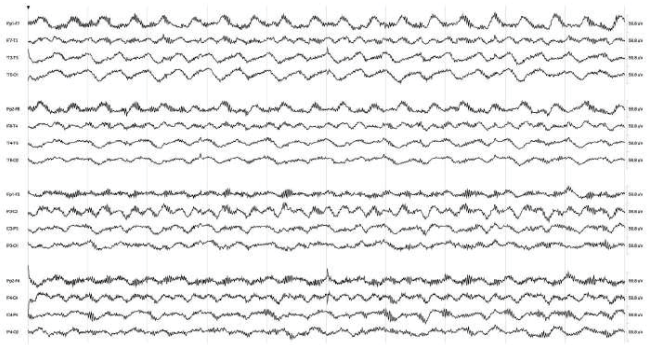
Dalmau et al; Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study, *Lancet Neurol* 2013

EXTREME DELTA BRUSH



- 30.4% patients
- Associated with prolonged hospitalization

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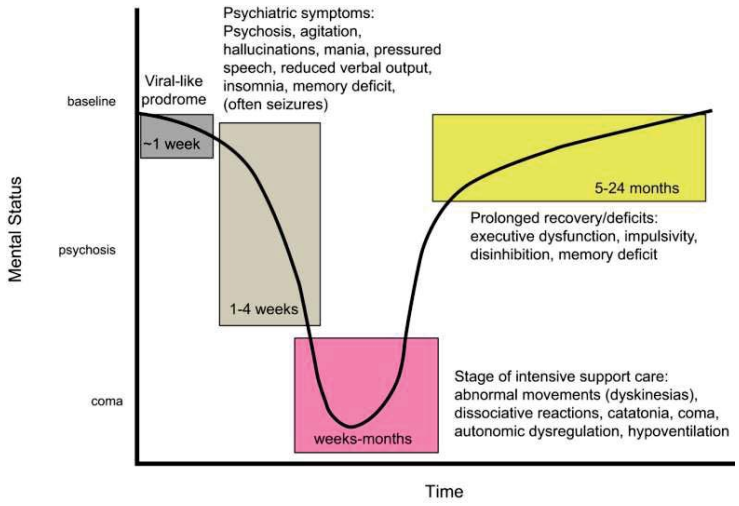
Schmitt et al. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012

NMDAR ANTIBODIES: CLINICAL COURSE



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VGKC ANTIBODIES

- Antibodies against voltage gated potassium channel
- VGKCs
  - On membrane of neurons in CNS and PNS
  - mediate repolarization after an action potential
- First associated with Isaac syndrome, Morvan syndrome

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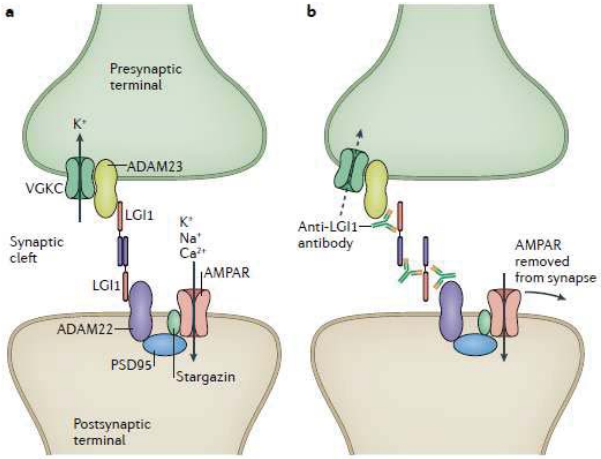
van Sonderen et al. The value of LGI1, Caspr2 and voltage-gated potassium channel antibodies in encephalitis. Nature reviews Neurology. 2017

VGKC ANTIBODIES

- Leucine-rich glioma-inactivated 1 (LGI1)



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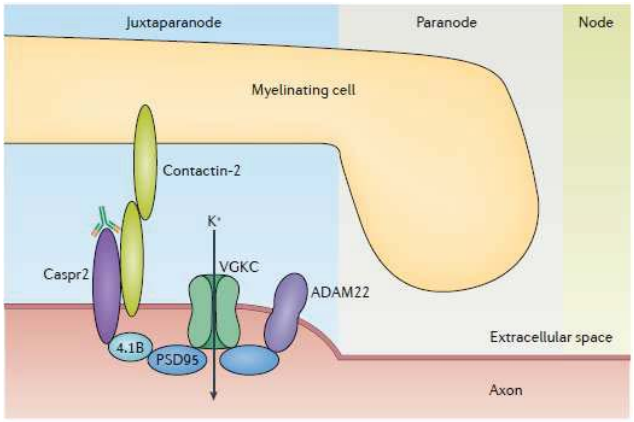
VGKC ANTIBODIES

- Contactin associated protein-like 2 (Caspr2)



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VGKC ANTIBODIES

- Anti LGI1 antibodies
- Anti Caspr2 antibodies
- VGKC Ab without above 2

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ANTI LGI1 ANTIBODIES

- Second most common etiology of autoimmune encephalitis

Box 1 | **Clinical features of anti-LGI1 encephalitis**

Patient demographics
- 67% male
- Age 50–70 years (can be younger)

Clinical syndrome: limbic encephalitis (90%)
- Seizures (90%)
  - Faciobrachial dystonic seizures (50%)
  - Subtle focal seizures (65%)
  - Tonic–clonic seizures (65%)
- Cognitive decline
  - Memory disturbance (97%)
  - Behavioural disturbance (90%)
  - Spatial disorientation (50%)
- Insomnia (65%)

Ancillary testing
- Hyponatraemia (65%)
- Brain MRI: mesial temporal lobe hyperintensity (75%)
- Cerebrospinal fluid: normal (75%)
- Tumour (<10%)

LGI1, leucine-rich glioma-inactivated 1.

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van Sonderen et al. The value of LGI1, Caspr2 and voltage-gated potassium channel antibodies in encephalitis. Nature reviews Neurology. 2017

FACIOBRACHIAL DYSTONIC SEIZURES

- Specific for anti-LGI1 encephalitis
- present in 50%
- Involuntary contractions of 1–2 seconds, affecting the unilateral arm (or leg) and face
- Occur 40 to 100 times a day
- Often not appreciated by patients and physicians
- Most have no ictal EEG correlates, but long FBDS can be preceded by electrodecremental events, which usually precede the onset of movement by ~500 ms, or a slow frontal wave that is contralateral to the FBDS

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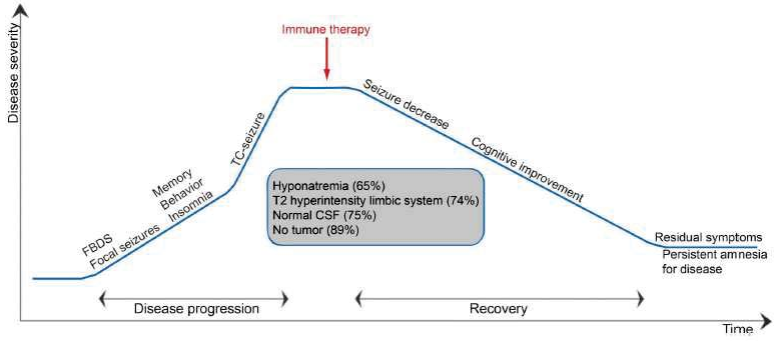
van Sonderen et al. Anti-LGI1 encephalitis Clinical syndrome and long-term follow-up. Neurology. 2016

ANTI LGI1 ANTIBODIES



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ANTI LGI1 ANTIBODIES

- AEDs not effective
- Early immunotherapy in FBDS can prevent progression to LE
- Steroids, IVIG, PE, Rituximab
- ?sustained therapy with Mycophenolate, azathioprine
- 2 yr follow up - 70% favorable outcome
- Case fatality rate - 6-19%
- > 2 yr follow up studies – 27 to 35% relapse rate

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ANTI CASPR2 ANTIBODIES

- Rare compared to anti-LGI1 ab, hence limited data
- Myokimia
- Fasciculations
- Muscle cramps
- Hyperhidrosis
- Cognitive decline

Box 2 | **Clinical features of Caspr2 disease**

Patient demographics
- 90% male
- Age 60–70 years

Caspr2 core symptoms
- Cerebral symptoms (cognition 80%, epilepsy 50%)
- Cerebellar symptoms (35%)
- Peripheral nerve hyperexcitability (55%)
- Autonomic dysfunction (45%)
- Insomnia (55%)
- Neuropathic pain (60%)
- Weight loss (60%)

Ancillary testing
- Brain MRI: normal (70%)
- Cerebrospinal fluid: normal (75%)
- Tumour (20%, mostly thymoma)

Caspr2, contactin-associated protein-like 2.

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van Sonderen et al. The value of LGI1, Caspr2 and voltage-gated potassium channel antibodies in encephalitis. Nature reviews Neurology. 2017

ANTI CASPR2 ANTIBODIES

- 70 to 90% respond to treatment
- Steroids, IVIG, PE, Rituximab
- Thymoma removal
- Favorable outcome in 73%
- 2 year case fatality rate 10%

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VGKC ANTIBODIES BUT NEGATIVE LGI1 OR CASPR2 ANTIBODIES

- Clinical significance of these is unclear
- Few have limbic encephalitis or Morvan's syndrome
- Vast majority have varied clinical manifestations - Creutzfeldt–Jakob disease, psychogenic nonepileptic seizures, REM sleep behavior disorder, MSA, peripheral neuropathy, vasculitis, seizures, mitochondrial disease, periodic paralysis, hepatic encephalopathy, FTD, Lewy body disease, Asperger syndrome and schizophrenia

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van Sonderen et al. The value of LGI1, Caspr2 and voltage-gated potassium channel antibodies in encephalitis. Nature reviews Neurology. 2017

STIFF PERSON SYNDROME

- Muscle stiffness, rigidity, and painful spams
- Paraspinal, abdominal, and lower extremity muscles
- Spontaneous or triggered by movement or sensory (tactile, auditory) and emotional stimuli.
- EMG - sustained motor unit activity leading to cocontraction of agonist and antagonist muscles.
- Improvement with sleep, diazepam, Baclofen

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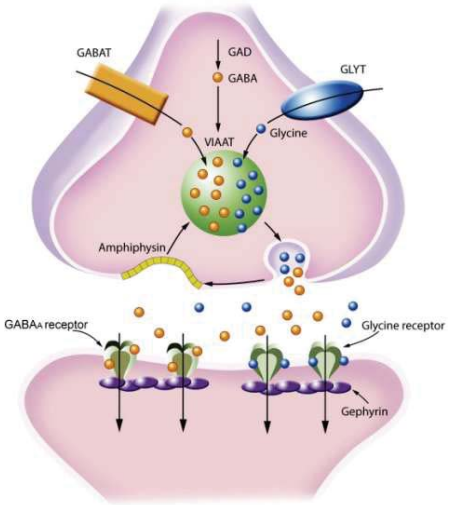
ANTIBODIES ASSOCIATED WITH STIFF PERSON SYNDROME



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ANTI GAD ANTIBODIES

- Low titres in 1% of healthy people and in 80% of people with type 1 diabetes mellitus
- High titers GAD65 antibodies associated with SPS, Cerebellar ataxia (100 to 1000 times that for type 1 DM)
- Antibodies likely not pathogenic, T-cell mediated
- Evaluate CSF for GAD antibodies

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Graus et al. A clinical approach to diagnosis of autoimmune encephalitis Lancet Neurol April 2016

ANTI THYROPEROXIDASE ANTIBODIES

- Hashimoto's encephalopathy or SREAT
- Unclear pathophysiology

***Panel 6:* Diagnostic criteria for Hashimoto's encephalopathy**

Diagnosis can be made when all six of the following criteria have been met:

1. Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes
2. Subclinical or mild overt thyroid disease (usually hypothyroidism)
3. Brain MRI normal or with non-specific abnormalities
4. Presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies*
5. Absence of well characterised neuronal antibodies in serum and CSF
6. Reasonable exclusion of alternative causes

*There is no disease-specific cutoff value for these antibodies (detectable in 13% of healthy individuals).[58]

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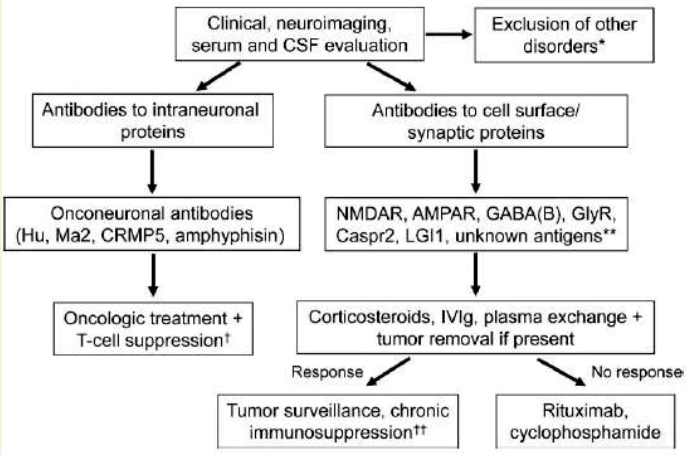
Graus et al. A clinical approach to diagnosis of autoimmune encephalitis Lancet Neurol April 2016

THERAPIES



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Lancaster et al. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. *Neurology.* 2011

SUMMARY

- Identification of clinical syndrome is very helpful
- Most antibodies have well defined clinical syndromes associated with them
- VGKC Ab without LGI1 or CASPR2 specificity likely have little value
- GAD65 ab in low titers, anti TPO ab are present in general population
- Antibodies often persist despite improvement in symptoms with treatment
- Antibody titers do not correlate with clinical course