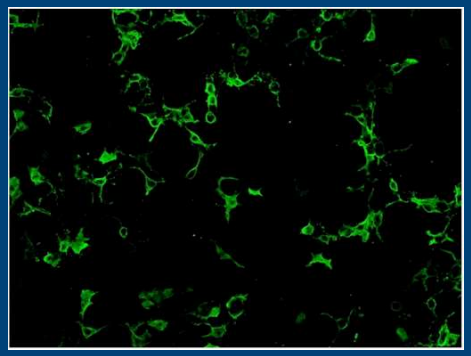
UT Southwestern
O'Donnell Brain Institute

Update on Autoimmune Neurology and Autoimmune Encephalitis



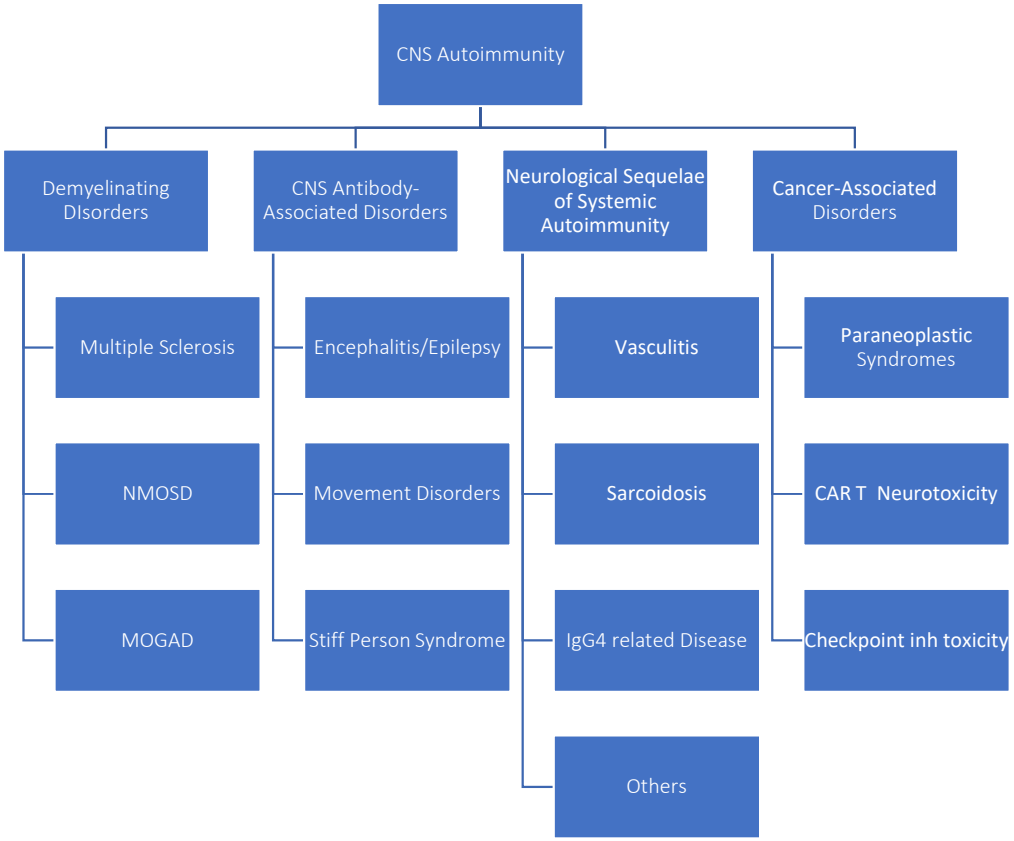
Kyle Blackburn

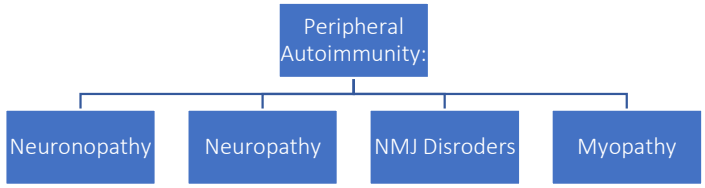
December 16, 2023

Objectives

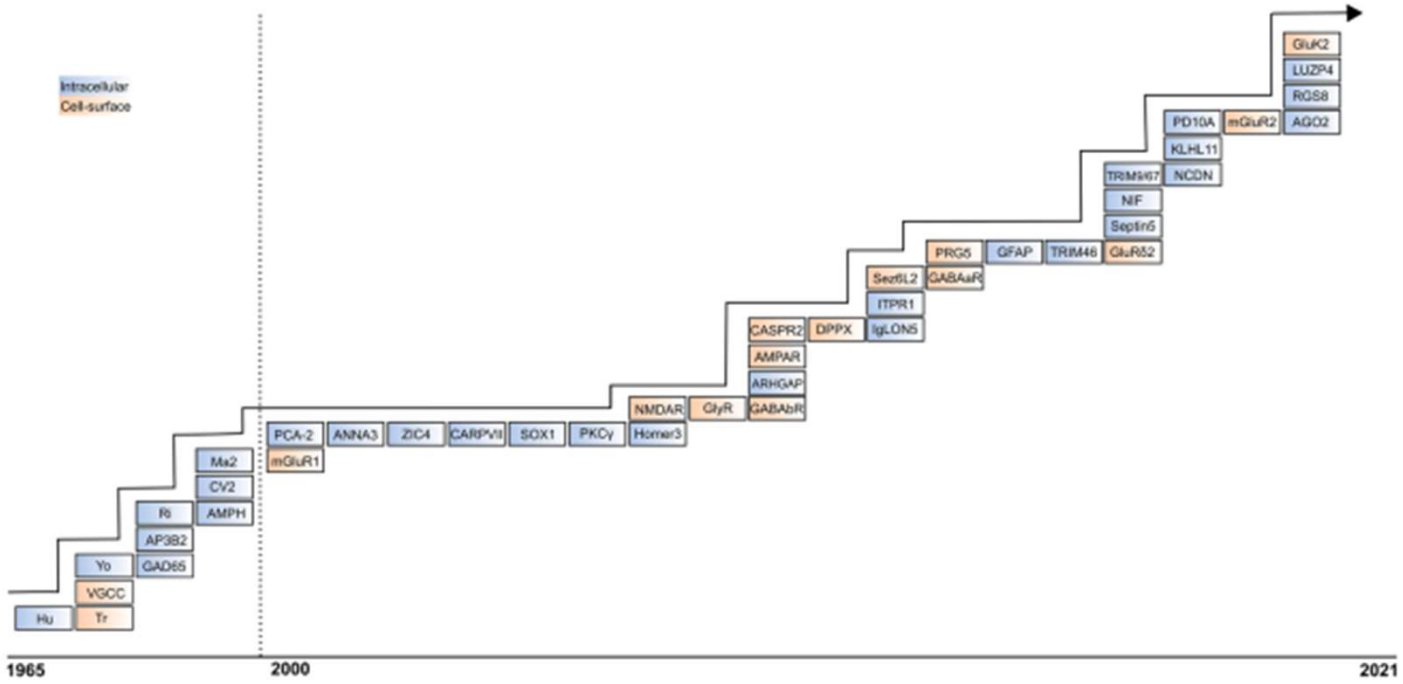
- Review the role of antibody testing in the expansion of recognized autoimmune neurological disorders. .
- Provide an overview of antibody testing, and tips to appropriate interpretation and use.
- Provide an overview of autoimmune encephalitis, including the two most common subtypes.
- Review the treatment of autoimmune encephalitis.

The field of neuroimmunology now includes many disorders beyond multiple sclerosis



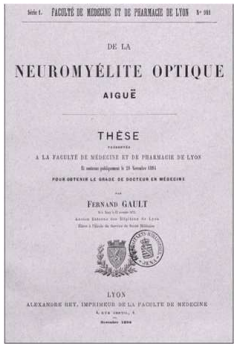


Advances in Neuroimmunology are largely fueled by discovery of autoantibodies



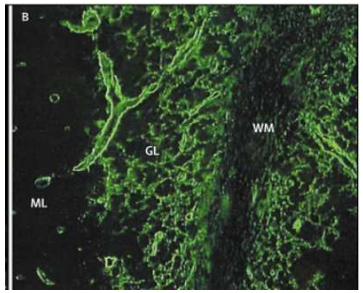
Muniz Castrillo et al. Cerebellum 2022.

NMOSD: An example of modern success



19th century:

- **Monophasic** disorder
- Optic Neuritis+ Transverse Myelitis

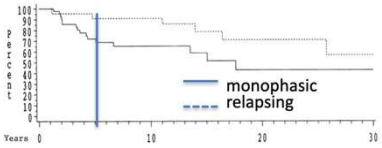


2005-2007

- Aquaporin-4 antibody
- Broadening of NMO phenotype

1990s

- Relapsing or monophasic
- 33% 5-year mortality



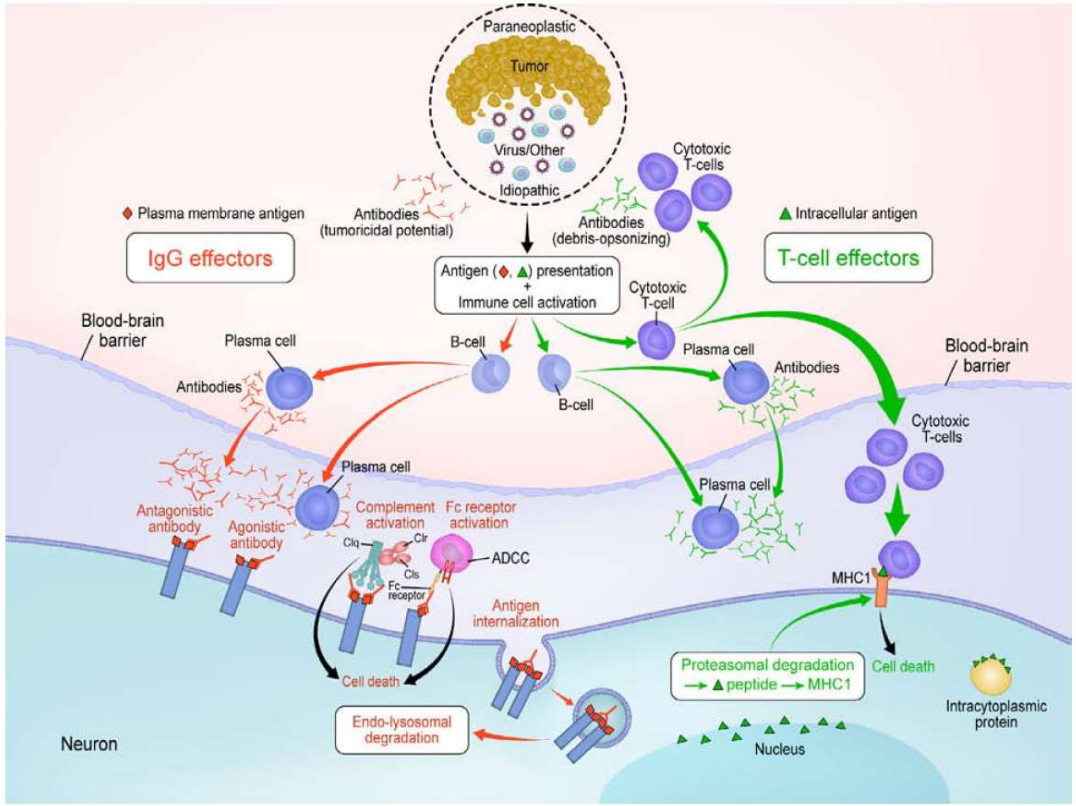
2020:

- Three FDA approved therapies

Wingerchuk et al. Neurology 1999.

Lennon et al Lancet 2004.

Antibody Testing Tip#1: Location of the target antigen provides useful information pertaining to immunology



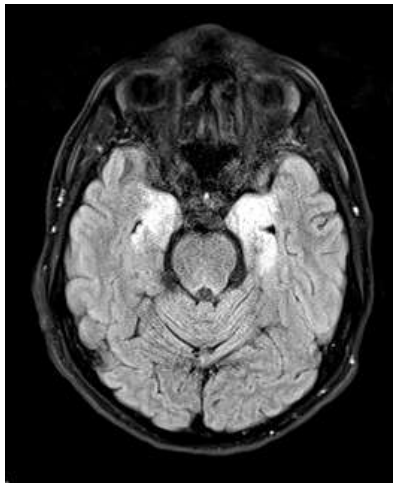
Waters P et al. Handbook Clin Neurol (2016)

Antibody Testing Tip #2: Antibody results can predict the likelihood of cancer and determine the need for surveillance.

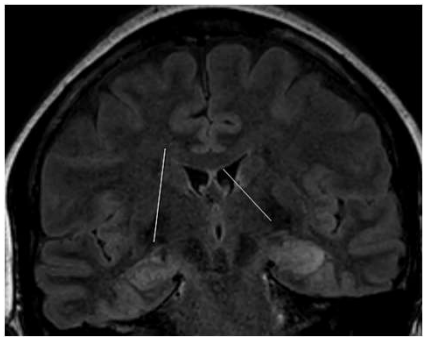
'High Risk' Paraneoplastic Antibodies	Cancer Association
Hu (ANNA-1)	Neuroendocrine tumors (mostly small cell lung carcinoma [SCLC])
CV2/CRMP5	SCLC, thymoma
SOX1	SCLC
PCA2 (MAP1B	SCLC, Breast
Amphiphysin	SCLC, Breast
Ri (ANNA-2	Breast, Lung
Yo	Ovarian, Breast
Ma/Ta	Testicular
Tr (DNER)	Lymphoma
KLH11	Testicular

'Low Risk' Antibodies (<30% risk)
mGluR1
GABA-A
CASPR2
GFAP
GAD65
LGI1
DPPX
Glycine
AQP4
MOG

Antibody Testing Tip #3: Different autoantibodies may have significant phenotypic overlap



Ma2



LGI1

It is best to send 'panels' of antibodies, rather than a random assortment.

Antibody Testing Tip #4: Certain antibodies are more likely to be found in serum, others in the CSF

	Negative	NMDA-Receptor Ab CBA
Positive		NMDA-Receptor Ab CBA CSF

Negative		GFAP IFA, S
Positive		LGI1-IgG CBA
Negative		MGLUR1 AB IFA, S
		AUTOIMMUNE
Negative	Negative	LGI1-IgG CBA, CSF

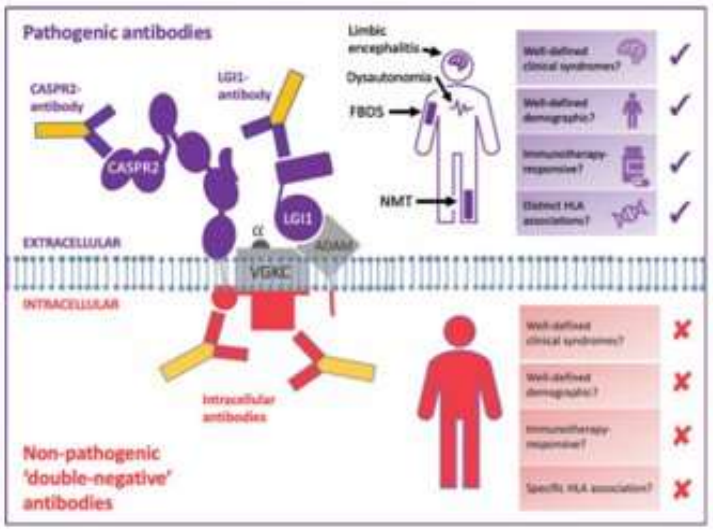
When in doubt, send the panels in both serum and CSF

Antibody Testing Tip # 5: not all positive results are 'significant'. Look at the overall clinical picture

Antibody-mediated disorders tend to prevent with **rapidly progressive, severe** neurological deficits.

Low levels of GAD, AChR, VGCC channel antibodies are common, but rarely significant (especially in CNS cases).

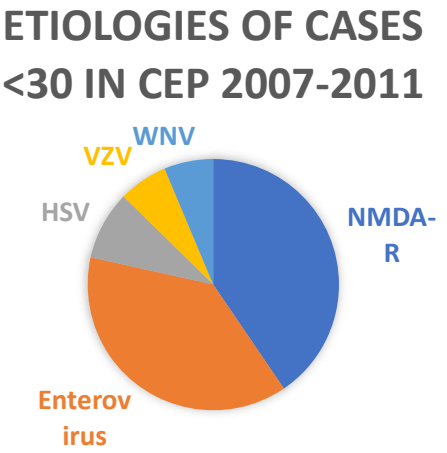
VGKC antibodies are often not significant when LGI1 or CASPR2 are negative.

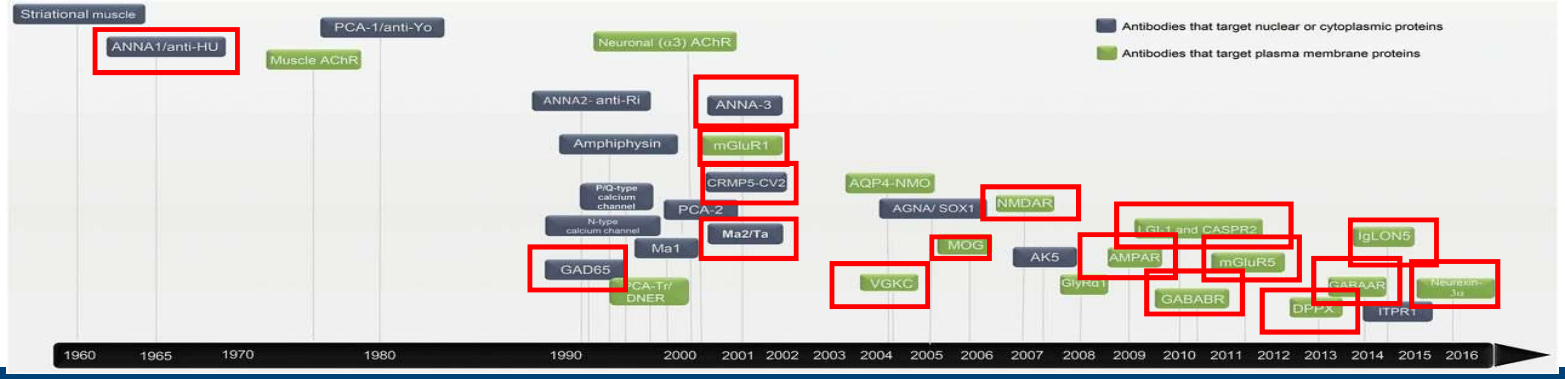


Autoimmune Encephalitis

- Estimated prevalence of 13.7/100,000 persons (MS 35.9/100,000).

- Increasing incidence, estimated at 1.2 per 100,000 persons annually (similar to infectious).





Autoimmune Encephalitis: working through the algorithm

***Panel 1:* Diagnostic criteria for possible autoimmune encephalitis**

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

1 Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms

2 At least one of the following:
- New focal CNS findings
- Seizures not explained by a previously known seizure disorder
- CSF pleocytosis (white blood cell count of more than five cells per mm^3)
- MRI features suggestive of encephalitis†

3 Reasonable exclusion of alternative causes (appendix)

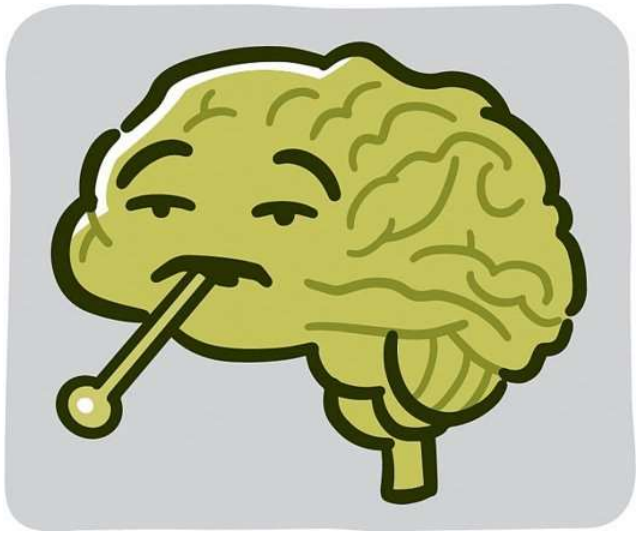
*Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change. †Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

Graus et al. Lancet Neurol 2016.

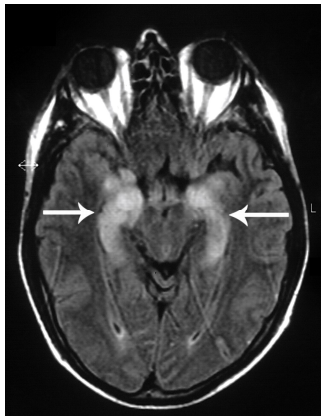
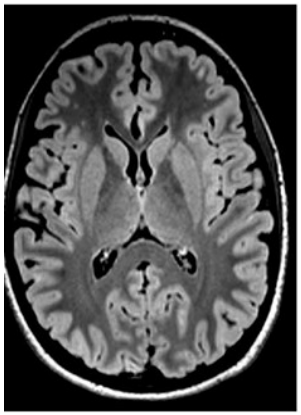
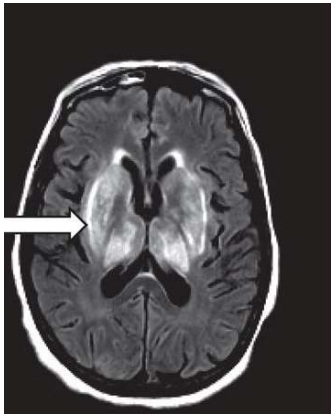
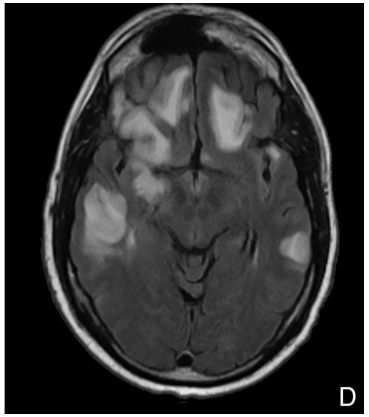
Recognizing Possible Autoimmune Encephalitis: Clinical Features

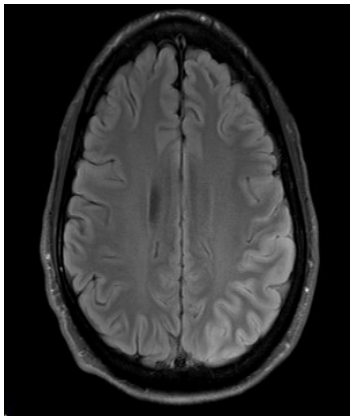
- Hallmark symptom: encephalopathy (disorientation, cognition, behavior change).

- Often accompanied by additional neurological features:
  - New onset seizures.
  - Hyperkinetic/dystonic movements, ataxia.
  - Autonomic symptoms: labile heart rate, blood pressure.
  - Other focal findings.



Recognizing autoimmune encephalitis: MRI features



Autoimmune encephalitis work-up

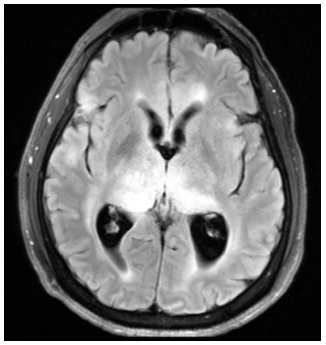
- EEG: looking for signs of subclinical seizure, signs of severe encephalopathy.

- CSF: pleocytosis, oligoclonal bands
  - Isolated protein elevation not considered specific for AIE.

- Antibody testing: panel testing is important
  - Serum and CSF!
  - Two methods of confirmation preferred

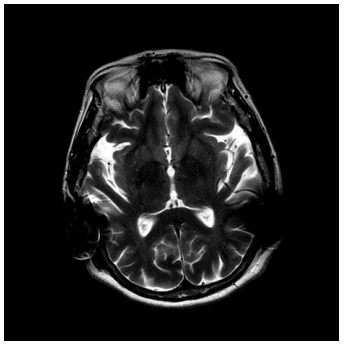
Exclude alternative diagnosis: misdiagnosis of autoimmune encephalitis is common (1/3 of referrals to tertiary referral centers)

- Disorders commonly misdiagnosed as autoimmune encephalitis:
  - Non-specific symptoms (fatigue/brain fog).
  - Functional neurological disorder
  - Psychiatric disorders (first episode psychosis).
  - Metabolic, degenerative, or neoplastic disorders.



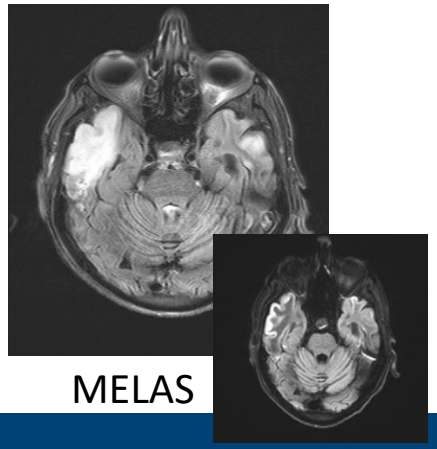
Anaplastic astrocytoma

CSF NMDAr+

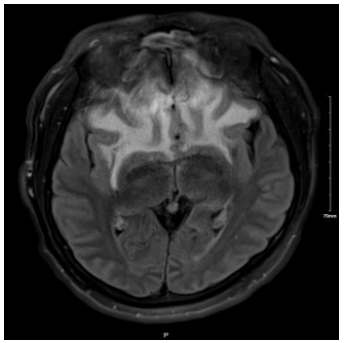


FTD with C9orf72 repeat expansion

CSF CASPR2+



MELAS



Infectious cerebritis

CSF NMDAr+

NMDA receptor encephalitis

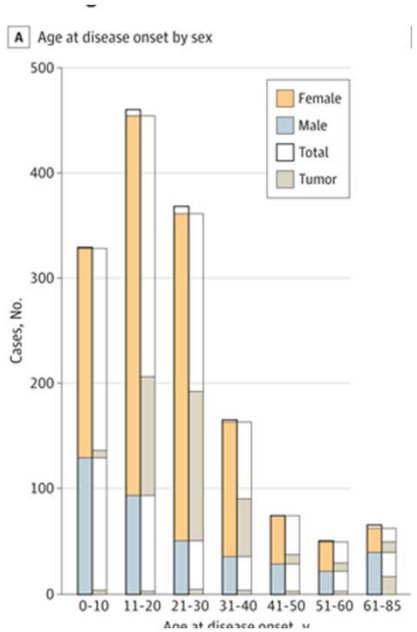
Demographics

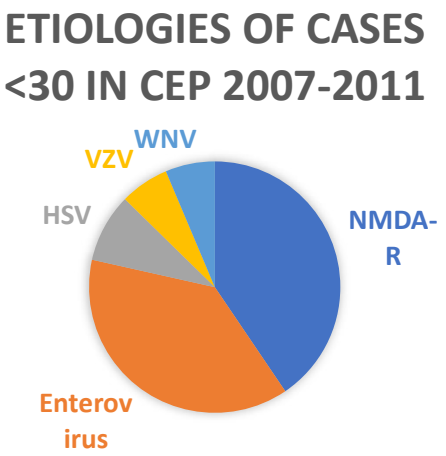
–75% female

–45% children

–25% had neoplasm (primarily ovarian teratoma).

Commonly associated with worsening after HSV encephalitis (~25% of cases)





Nosadini et al. JAMA Neurol 2021

Glazer et al. 2011

NMDA-R Encephalitis

Flu-like symptoms
Malaise, headache, nausea, URI

↓

Psychiatric Symptoms
Delusions | Hyper-religiosity | Paranoia | Mania

↓

Seizures

↓

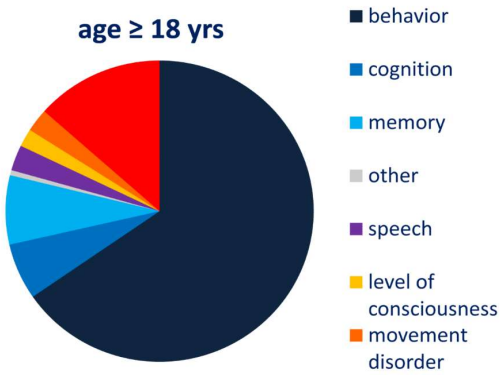
Decreased Responsiveness
Agitation | Catatonia

↓

Movement Disorders
Oro-facial Dyskinesias | Opisthotonic Postures | Choreoathetosis

↓

Coma



At nadir, 75% of patients are mRS 4-5 (unable to walk without assistance).

50% require ICU admission.

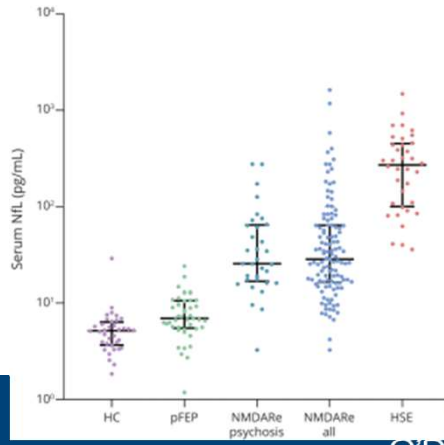
Nosadini et al. JAMA Neurol2021

Titulaer et al Ann Neurol 2013

Objective Tests in NMDA receptor encephalitis

	MRI	CSF analysis	EEG
Pro:	-Abnormalities often support a 'neurological basis' for symptoms	-More specific -Confirms diagnosis.	- Portable -Repeatable -Frequently abnormal in encephalitis.
Con	-Frequently normal (50-66% of cases) -Requires cooperation in adults.	-Invasive -68% have pleocytosis early. -NMDAr testing can take several days to return	-Can be normal early in course. -Non-specific

Candidate biomarkers: Neurofilament Light Chain (NfL)



Dalmau et al. Lancet Neurol 2019.

Guasp et al Neurology 2022.

CSF is highly sensitive for NMDA-R encephalitis, but serum can have false positive results.

Serum	CSF	Phenotype
+	+	Encephalitis
-	+	Encephalitis
+	-	consider phenotype, false positive results can occur

New onset or chronic psychosis are RARELY cause by autoimmune encephalitis

3% of first episode psychosis has a positive serum NMDAr antibody across numerous studies.

Only 1% of NMDA cases will present to a hospital with psychosis in isolation.

Large prospective longitudinal study failed to identify anyone with with fire episode psychosis with CSF positivity.

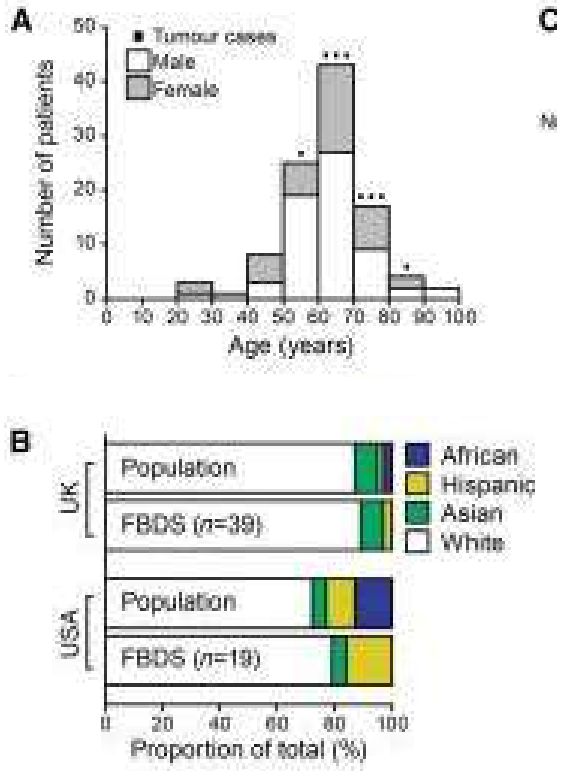
Table 5 Frequency of NMDAR IgG Antibodies in FEP

Author (Year)	Disease	Patients, n	Patients' NMDAR-abs (+), n (%)	Controls, n	Controls' NMDAR-abs (+)	Serum antibody test
De Witte et al.,[15] (2015)	FEP	55	0 (0)	(–)	(–)	Fixed CBA
Masopust et al.,[16] (2015)	FEP	50	0 (0)	50	0 (0)	Fixed CBA
Pathmanandavel et al.,[17] (2015)	FEP	43	5 (12)	43	0 (0)	Flow cytometry live cells
Jézéquel et al.,[23] (2017)	FEP	298	14 (5)	(–)	(–)	Live CBA
Lennox et al.,[18] (2017)	FEP	228	7 (3)	105	0 (0)	Live CBA
Mantere et al.,[19] (2018)	FEP or clinical high-risk psychosis	76	1 (1)	34	0 (0)	Fixed CBA
Scott et al.,[20] (2018)	FEP NMDARe	111 2	2 (2)[a] 2 (100)	(–)	(–)	Fixed CBA
Gaughran et al.,[21] (2018)	FEP	96	1 (1)	98	1 (1)	Live CBA
Hoffmann et al.,[26] (2019)	FEP	45	0 (0)	257	0 (0)	Brain tissue Fixed CBA
Kelleher et al.,[22] (2020)	FEP NMDARe	111 1	3 (3) 1 (100)	(–)	(–)	Live CBA
Engen et al.,[27] (2020)	Early-onset psychosis in adolescents	46	3 (6.5)	69	2 (3)	Live CBA

Abbreviations: CBA = cell-based assay; FEP = first episode psychosis; IgG = immunoglobulin G; NMDAR = NMDA receptor; NMDAR-abs = NMDAR antibodies; NMDARe = anti-NMDAR encephalitis.
[a] One of the 2 patients had NMDAR-abs in CSF.

LGI1 encephalitis

- Most common cause of limbic encephalitis.
- Symptom onset usually between 6-8 decade (pediatric cases rare).
- 5:1 male: female



LGI1 Encephalitis

Faciobrachial Dystonic Seizures

↓

Multifocal seizures

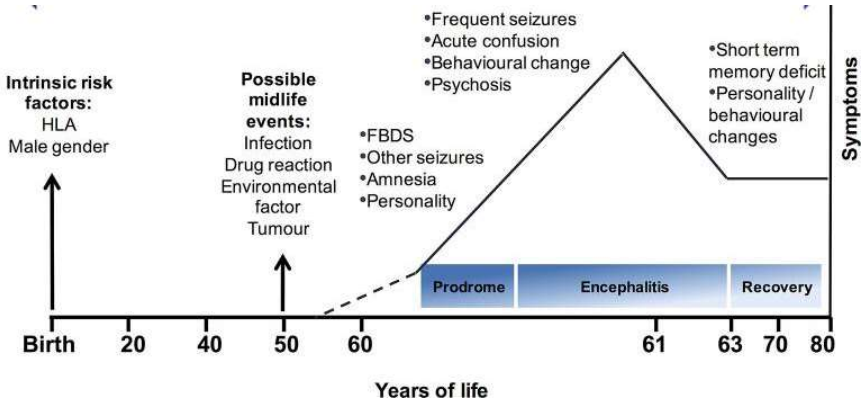
Ictal bradycardia	Gelastic seizures	Piloerection	'Paroxysmal dizzy spells

↓

Hyponatremia

↓

Short-term memory impairment



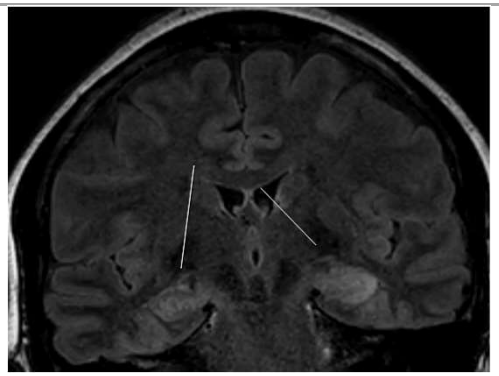
Faciobrachial Dystonic Seizures

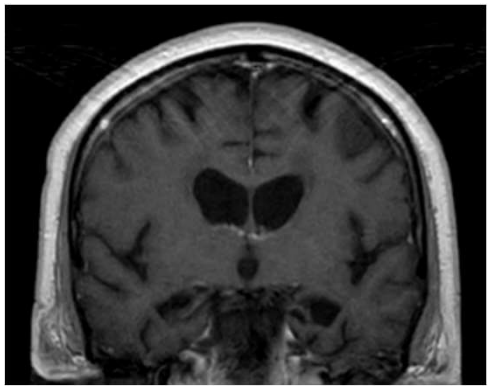
Imaging: LGI1 Encephalitis

During prodromal phases with FBDS: frequently normal

During cognitive Impairment Phase:
T2 signal in the medial temporal lobes.

Post acute phase: T2 atrophy





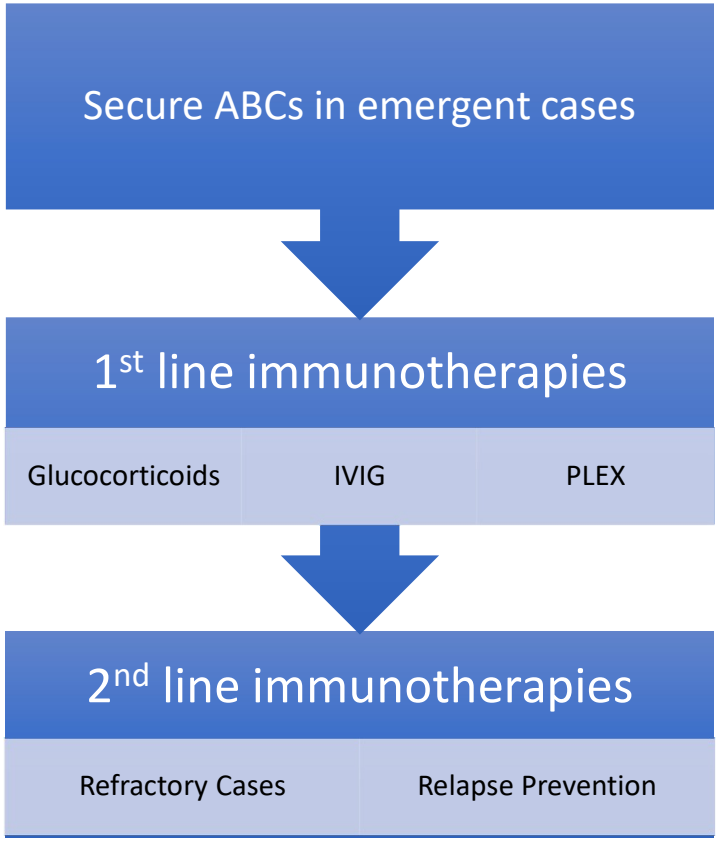
General Approach to Treatment in Autoimmune Encephalitis

First line therapies typically initiated during admission.

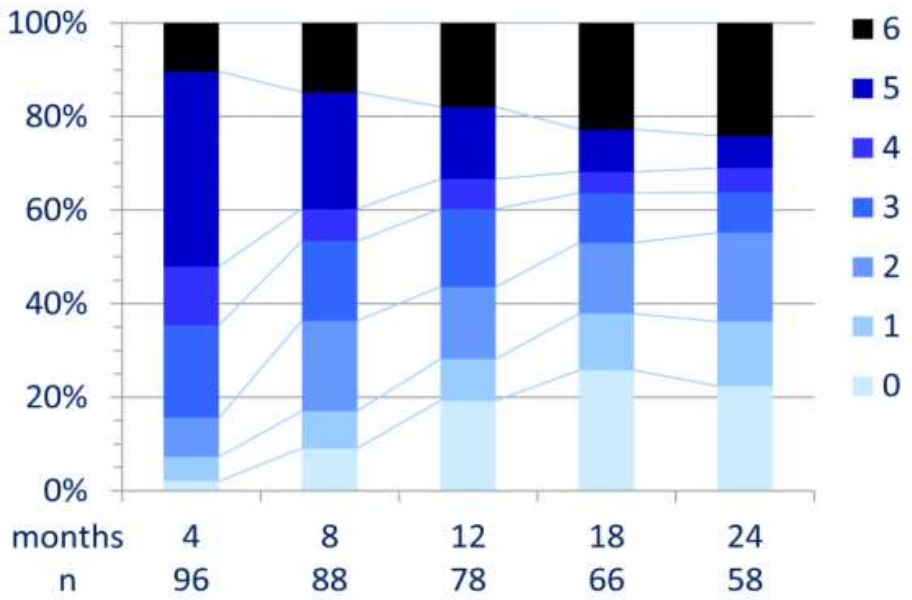
Second-line therapies: rituximab or cyclophosphamide.

Maintenance therapies: oral prednisone.

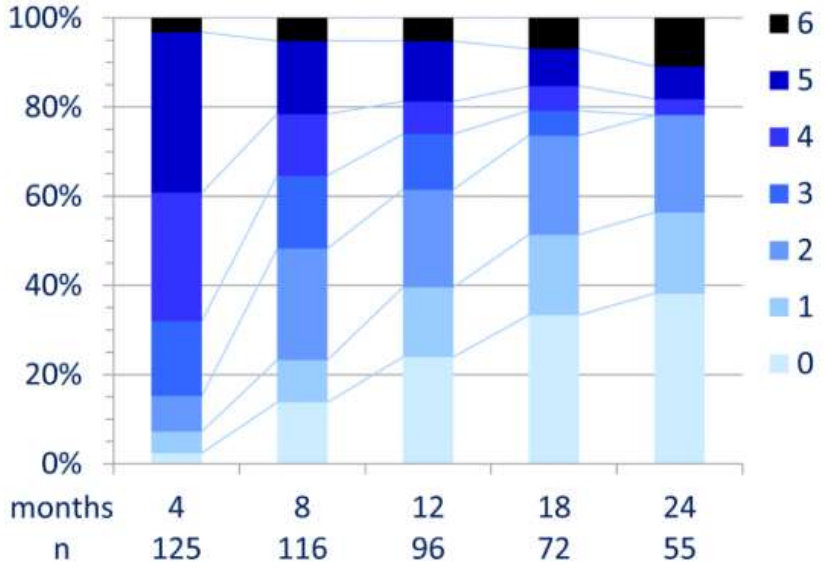
Relapse rates are variable, higher in LGI1+ cases.



Treatment: NMDA-R Encephalitis



Failed 1st line
No 2nd line treatment



Failed 1st line
Received 2nd line treatment

'Advanced treatment' of autoimmune encephalitis: do the risks outweigh benefits?

Neurotherapeutics. 2016 Oct;13(4):824-832. doi: 10.1007/s13311-016-0442-6.

Tocilizumab in Autoimmune Encephalitis Refractory to Rituximab: An Institutional Cohort Study

Woo-Jin Lee [1 2], Soon-Tae Lee [1 2], Jangsup Moon [1 2], Jun-Sang Sunwoo [1 2], Jung-Ick Byun [1 2], Jung-Ah Lim [1 2], Tae-Joon Kim [1 2], Yong-Won Shin [1 2], Keon-Joo Lee [1 2], Jin-Sun Jun [1 2], Han Sang Lee [1 2], Soyun Kim [1], Kyung-Il Park [1 3], Keun-Hwa Jung [1 2], Ki-Young Jung [1 2], Manho Kim [1 2], Sang Kun Lee [4 5], Kon Chu [6 7]

Affiliations + expand

Neurotherapeutics. 2021 Jan;18(1):474-487. doi: 10.1007/s13311-020-00921-7.

Teratoma Removal, Steroid, IVIG, Rituximab and Tocilizumab (T-SIRT) in Anti-NMDAR Encephalitis

Woo-Jin Lee [1], Soon-Tae Lee [1], Yong-Won Shin [1 2 3], Han Sang Lee [1], Hye-Rim Shin [4], Do-Yong Kim [1 5], Soyun Kim [1 5], Jung-Ah Lim [6], Jangsup Moon [1 5], Kyung-Il Park [1 5 7], Hee Seung Kim [8], Kon Chu [9 10], Sang Kun Lee [11]

Affiliations + expand

Trial to Evaluate Efficacy and Safety of Bortezomib in Patients With Severe Autoimmune Encephalitis (Generate-Boost)

THE EXTINGUISH NMDAR ENCEPHALITIS TRIAL

Recruiting patients with ACUTE presentation. Both trials have strict requirements for 1st line treatment.

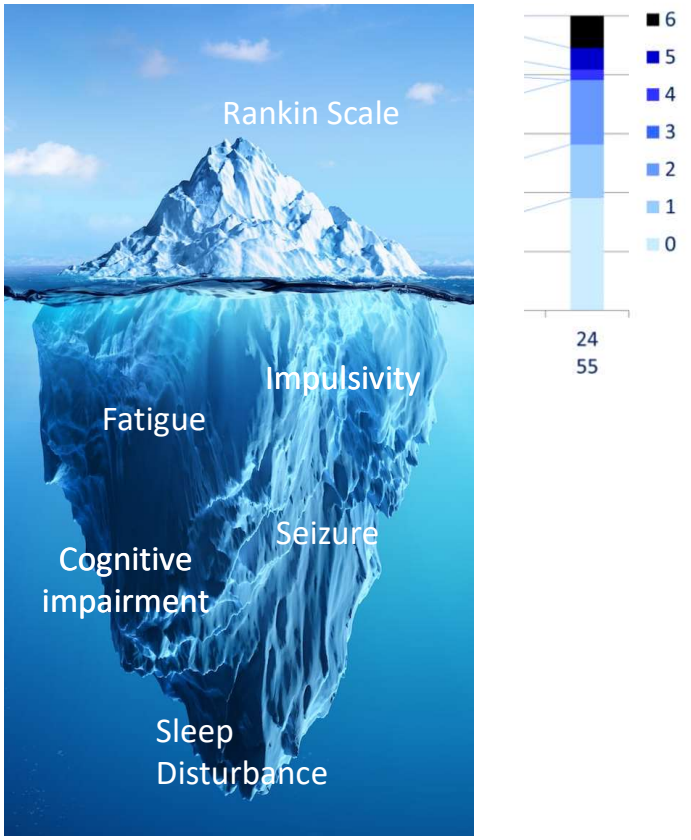
If you identify potential candidates contact me!

kyle.blackburn@utsouthwestern.edu

Post encephalitis care

- Despite ' good' outcomes and improvement, many patients left with residual cognitive impairment, behavior changes, seizures, requiring management.

- Many questions still remain in about outcomes of autoimmune encephalitis.



Autoimmune Neurology Clinic

- Encephalitis + Epilepsies
- Stiff person syndrome
- Paraneoplastic Disorders
- Neurosarcoidosis