Autoimmune Causes of Epilepsy?

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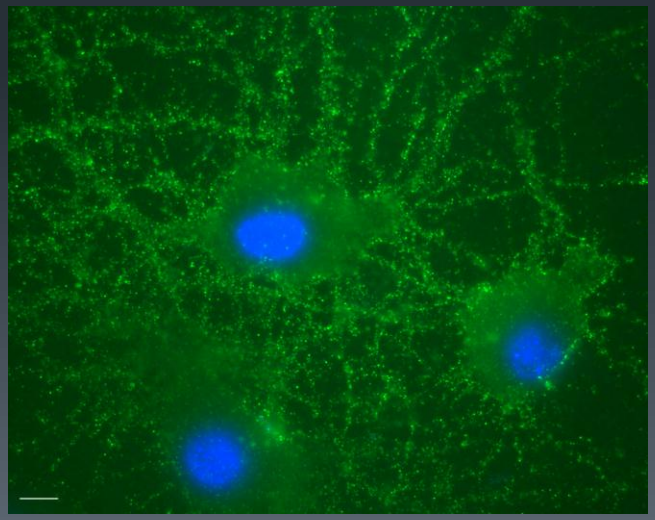


Epilepsy Center of Excellence
SAN FRANCISCO VA MEDICAL CENTER

Objectives

- 1) Understand the relationship between autoimmune encephalitides and seizures.
- 2) Understand the role of autoantibodies in “uncomplicated” epilepsy.
- 3) Understand rational approaches to autoantibody testing in the epilepsy population.

Case presentation

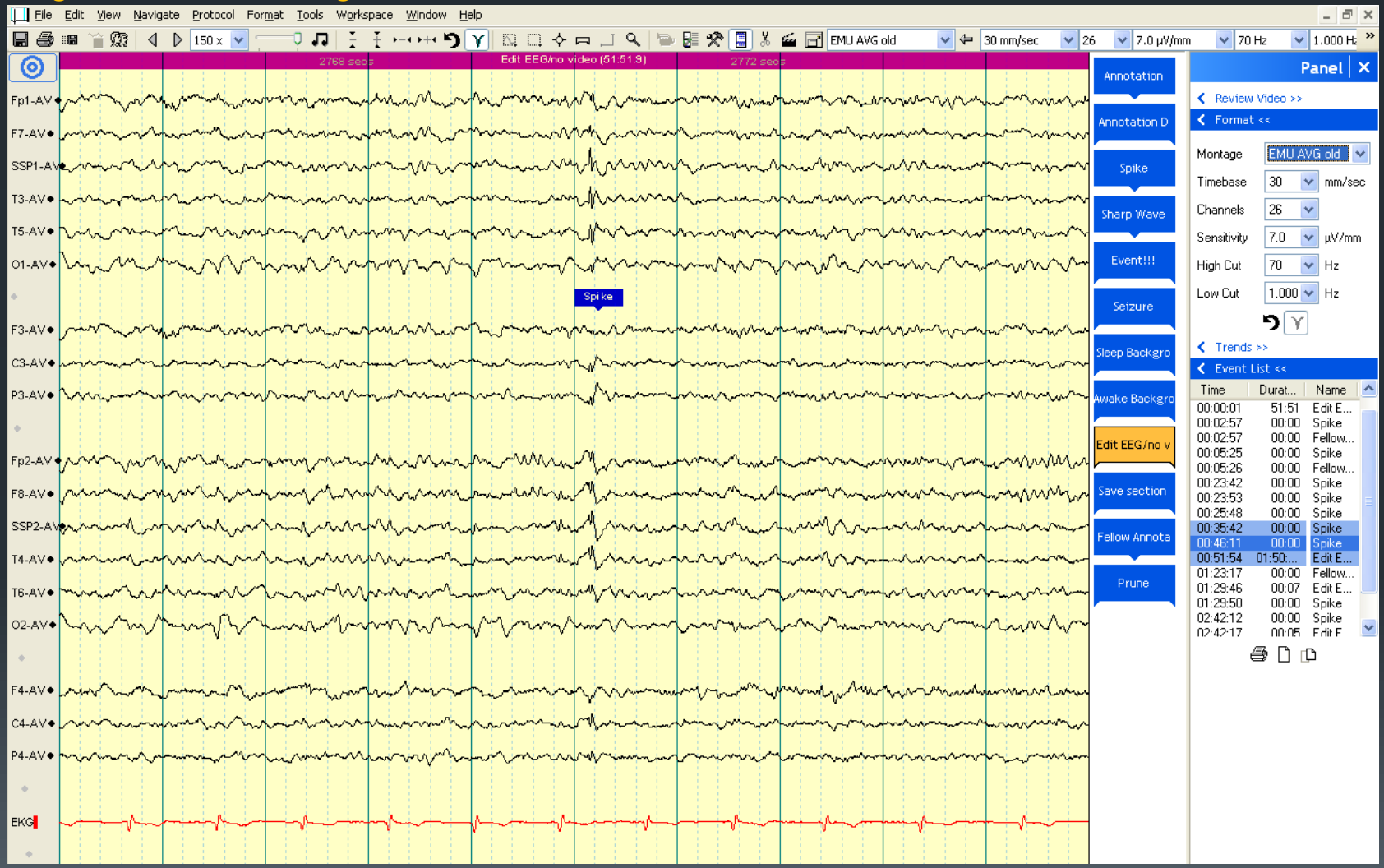
- HPI: 47 RHM with 6 months of spells involving an unusual smell, nausea, dizziness, visual distortions, disorientation, and unresponsiveness.
- He had developed cough, dyspnea, and asthenia several months prior to spell onset, coinciding with his moving from Florida to Stockton, CA.
- PMH: Depression, remote alcohol abuse; no seizure risk factors
- Meds: Albuterol, tiotropium, B12, levetiracetam 500 mg BID
- Allergies: None
- Family Hx: No known history of epilepsy
- Social Hx: Former security alarm technician, now on disability; non-smoker, occasional alcohol, no illicits
- Neuro Exam: Normal

Prior Workup

- Chest CT: axillary/mediastinal lymphadenopathy, RML tree-in-bud opacities
- Lung biopsy: chronic inflammation, no malignancy, mycobacterial stains neg
- Lumbar puncture: **12 WBC** (88% lymphs, 11% monos), 13 RBC, Glc 55, TP 33, CSF ACE neg, cytology negative
- Serum studies:
  - Cocci Ab neg
  - HIV Ab neg
  - ACE neg
  - Galactomannan neg
  - ESR 100, CRP 7.28
- Routine EEG: normal
- Brain MRI (1.5T): normal (cervical lymphadenopathy noted)

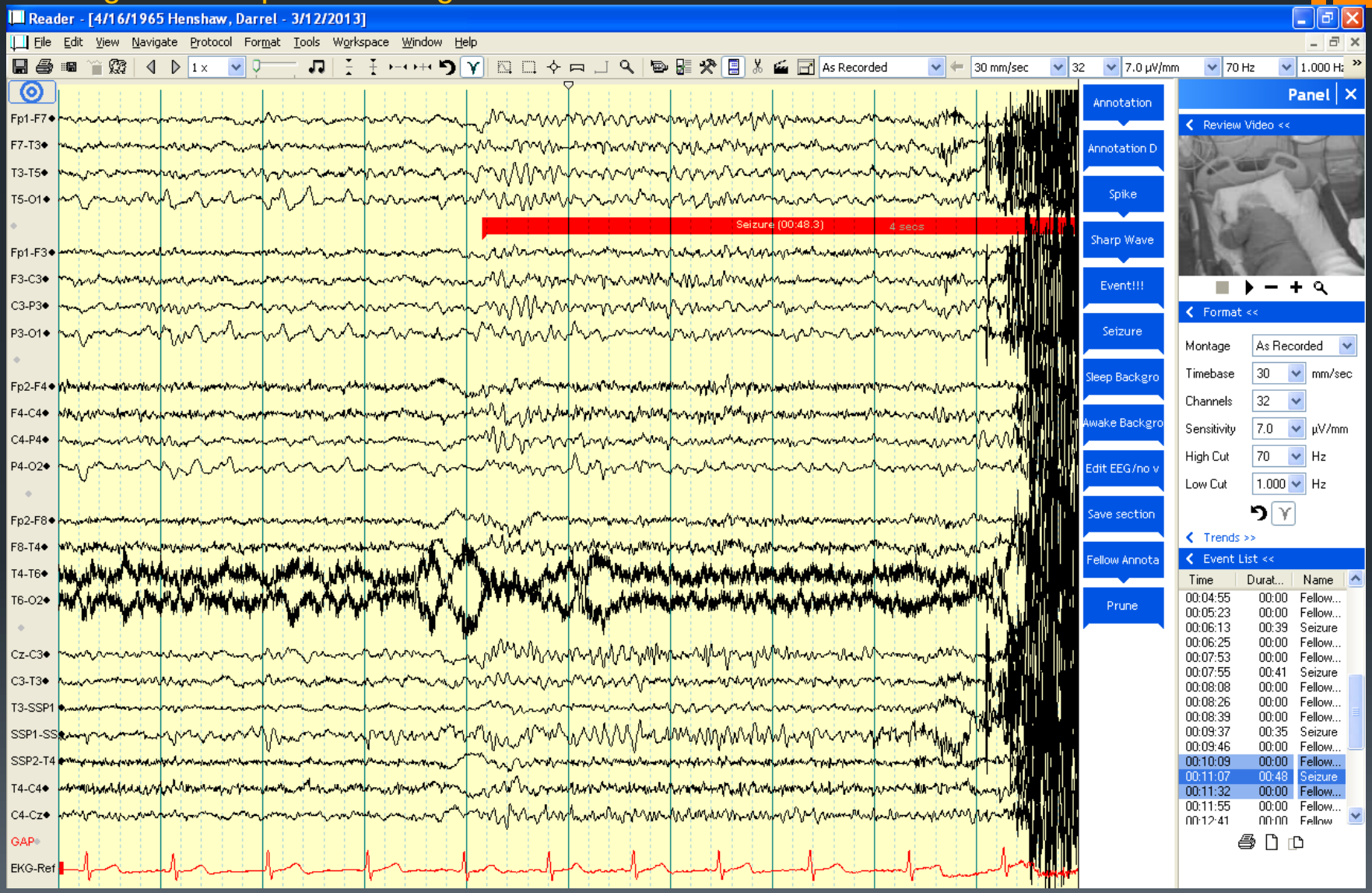
Interictal EEG

Avg reference montage

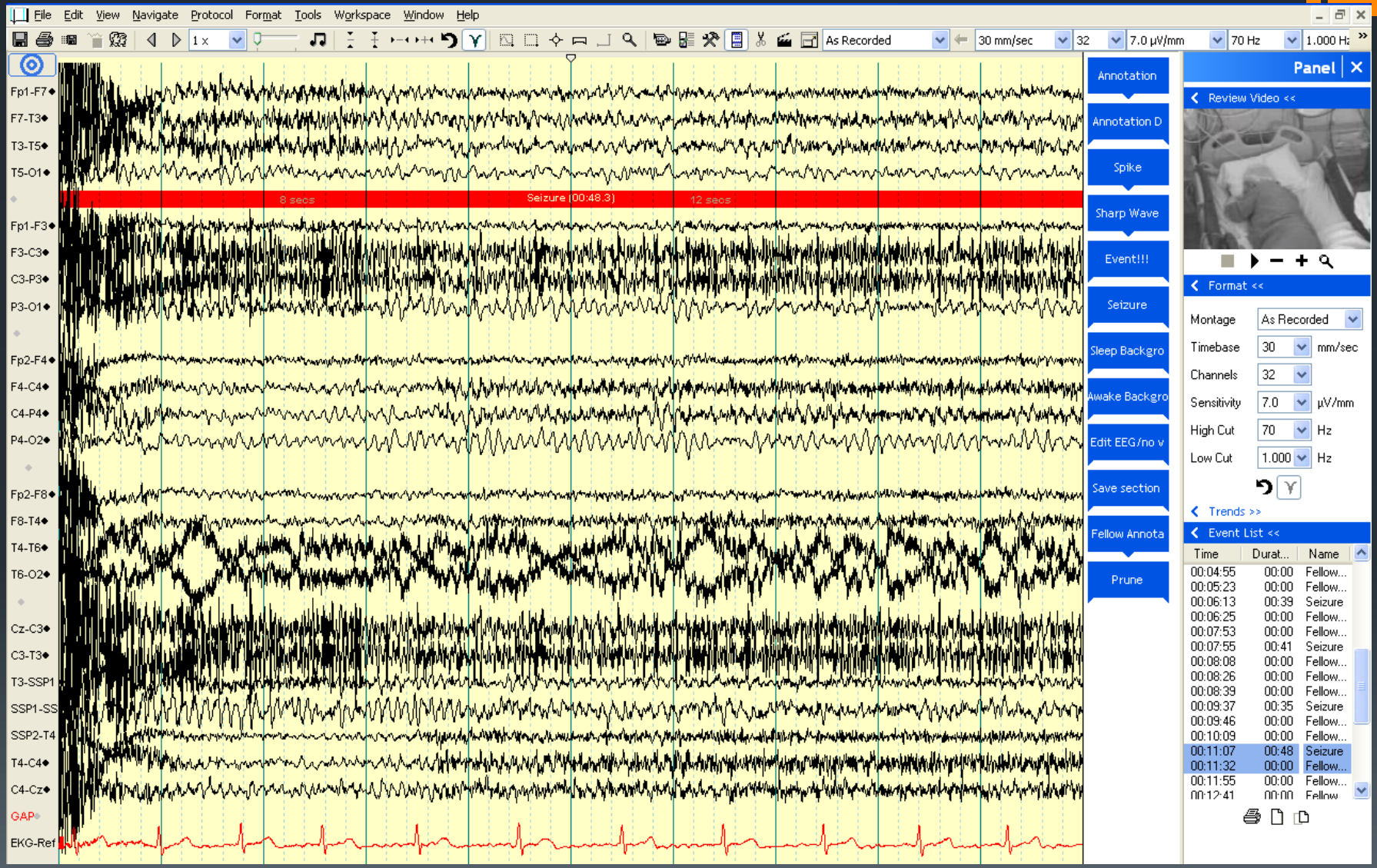


Ictal EEG – 1

Longitudinal bipolar montage



Ictal EEG – 2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As Recorded
30 mm/sec
32
7.0 µV/mm
70 Hz
Fp1-F7
F7-T3
T3-T5
T5-O1
8 secs
Seizure (00:48.3)
12 secs
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
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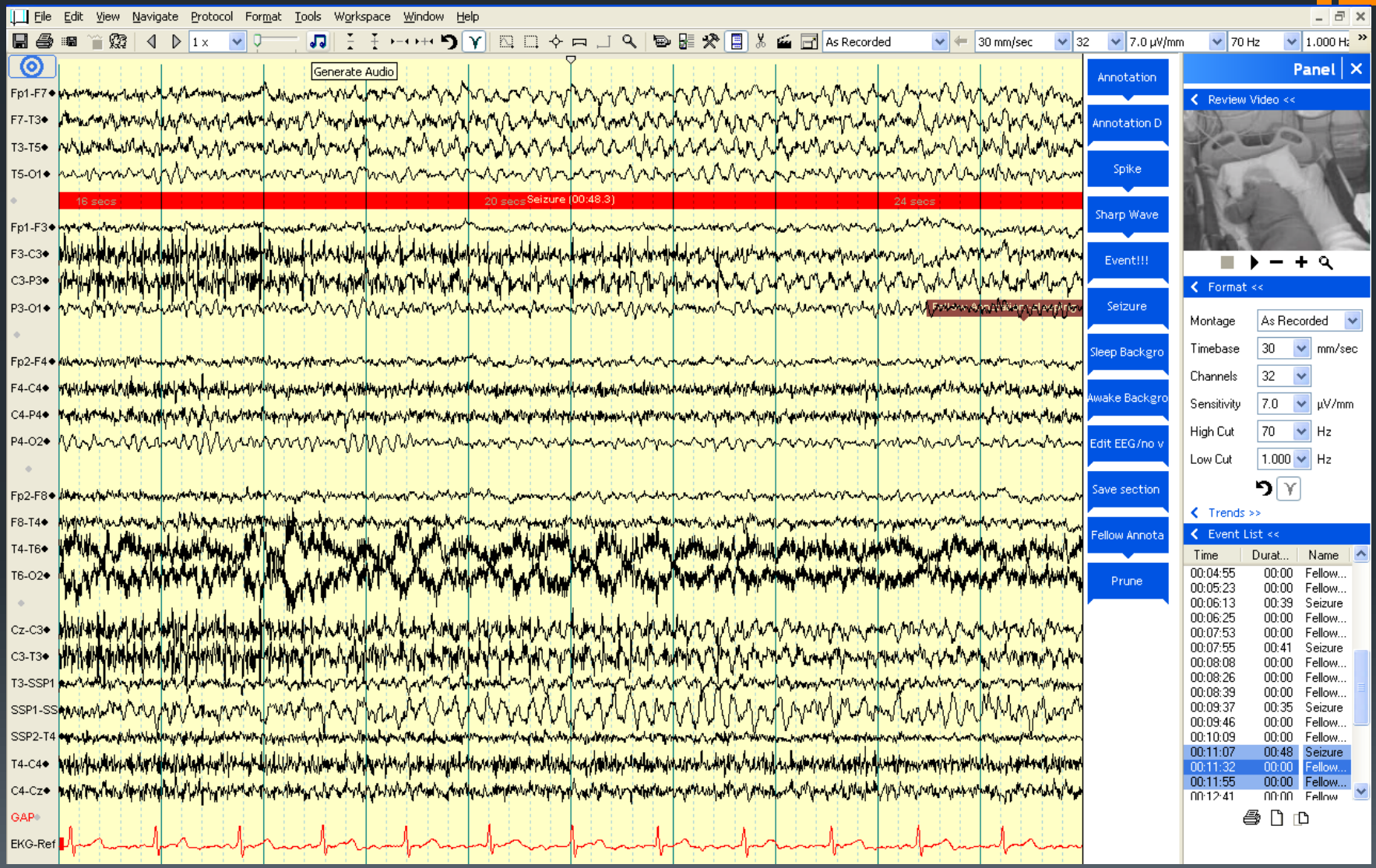
00:07:55 00:41 Seizure
00:08:08 00:00 Fellow...
00:08:26 00:00 Fellow...
00:08:39 00:00 Fellow...
00:09:37 00:35 Seizure
00:09:46 00:00 Fellow...
00:10:09 00:00 Fellow...
00:11:07 00:48 Seizure
00:11:32 00:00 Fellow...
00:11:55 00:00 Fellow...

Ictal EEG – 3


File Edit View Navigate Protocol Format Tools Workspace Window Help
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T3-T5
T5-O1
16 secs
20 secs
Seizure (00:48.3)
24 secs
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Cz-C3
C3-T3
T3-SSP1
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Event List <<
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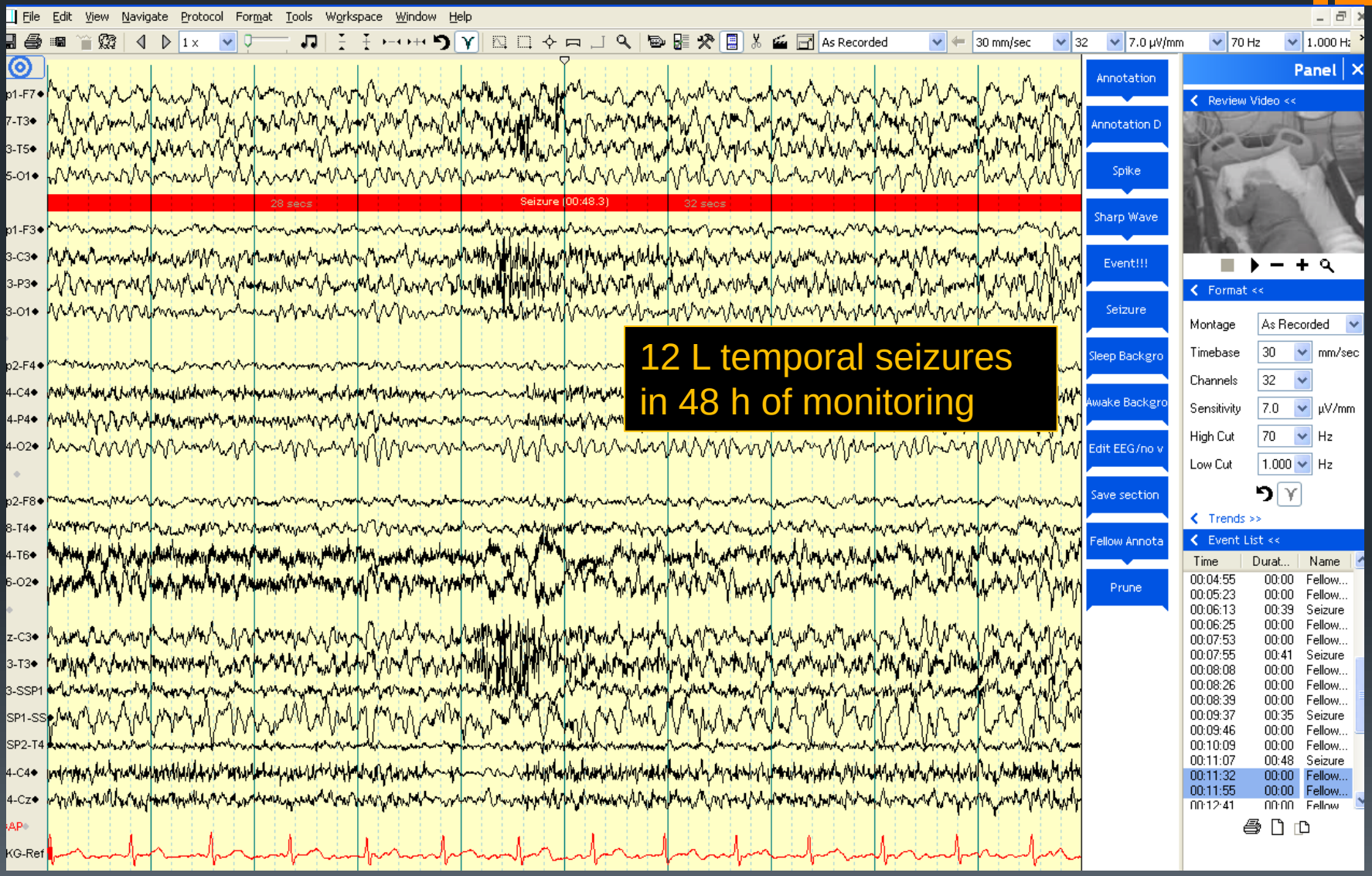
00:10:09 00:00 Fellow...
00:11:07 00:48 Seizure
00:11:32 00:00 Fellow...
00:11:55 00:00 Fellow...

Ictal EEG – 4


File Edit View Navigate Protocol Format Tools Workspace Window Help
As Recorded
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Seizure (00:48.3)
28 secs
32 secs
12 L temporal seizures
in 48 h of monitoring
Annotation
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Spike
Sharp Wave
Event!!!
Seizure
Sleep Backgro
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Montage As Recorded
Timebase 30 mm/sec
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00:08:08 00:00 Fellow...
00:08:26 00:00 Fellow...
00:08:39 00:00 Fellow...
00:09:37 00:35 Seizure
00:09:46 00:00 Fellow...
00:10:09 00:00 Fellow...
00:11:07 00:48 Seizure
00:11:32 00:00 Fellow...
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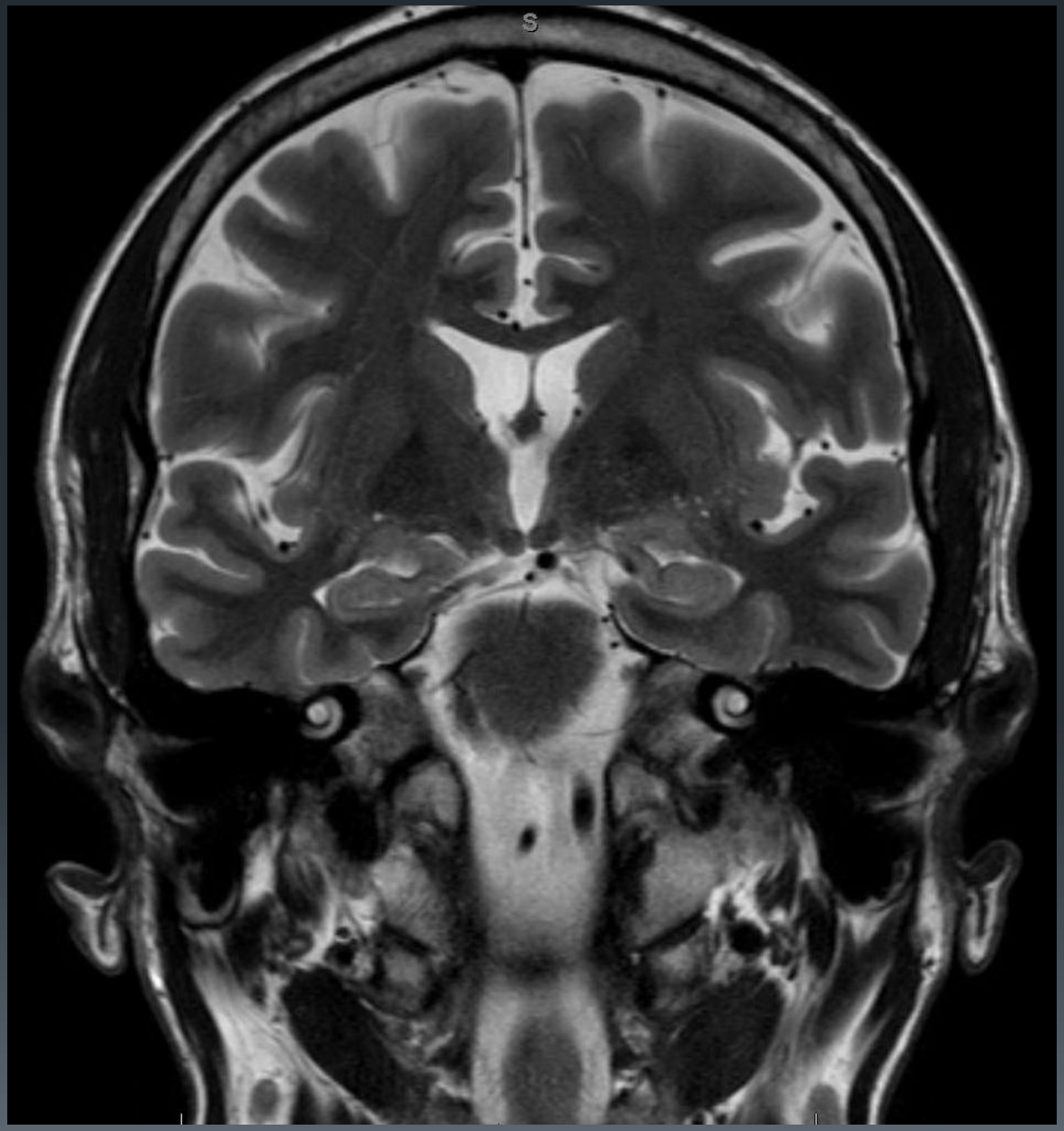
3T Brain MRI



Additional labs

- Anti-NMDAR and anti-GAD65 Abs neg
- Serum HHV8 IFA neg
- Repeat HIV neg
- HBV / HCV labs neg
- ***Anti-VGKC Ab positive (titer 850; ref range 31-88)***
- **Now what?**

Overview

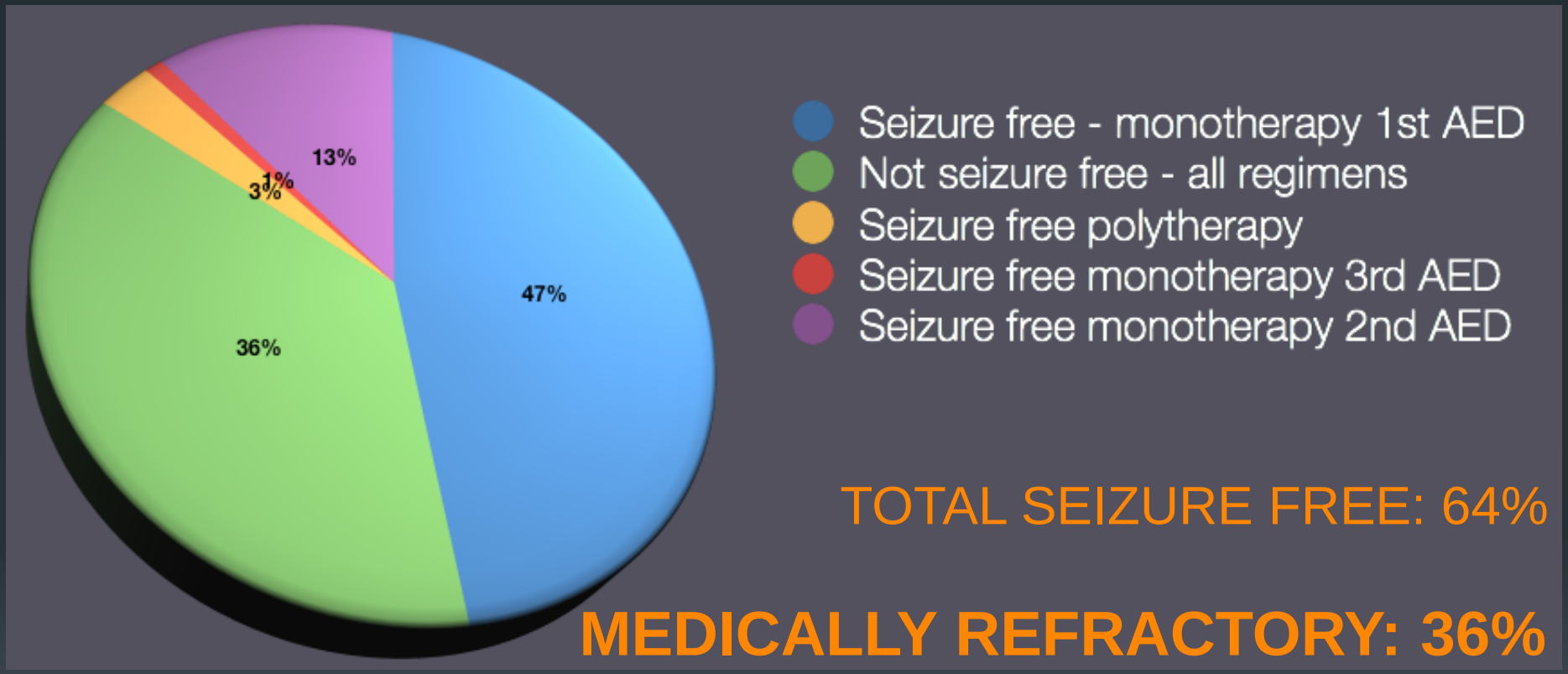
- Clinicians and scientists have long debated whether immune or inflammatory factors are important in epilepsy
- Autoimmune neurological disease is often unrelated to any particular antibody (i.e. MS)
- However, autoantibodies to neuronal antigens have been associated with a number of clinical syndromes, especially limbic encephalitides (LE), in the past decade
- These syndromes often have seizures as a prominent clinical feature

Overview

- This raises several questions:
- ***Could autoantibodies to CNS antigens be responsible for "uncomplicated" epilepsy (seizures without classic LE symptoms)?***
- ***What is the prevalence of such autoantibodies in the epilepsy population?***
- ***Are the autoantibodies pathogenic?***
- ***Are patients with these autoantibodies more likely to become medically refractory?***
- ***Do such patients need a different approach to treatment?***

Why is this important?

AEDs and Seizure Freedom:

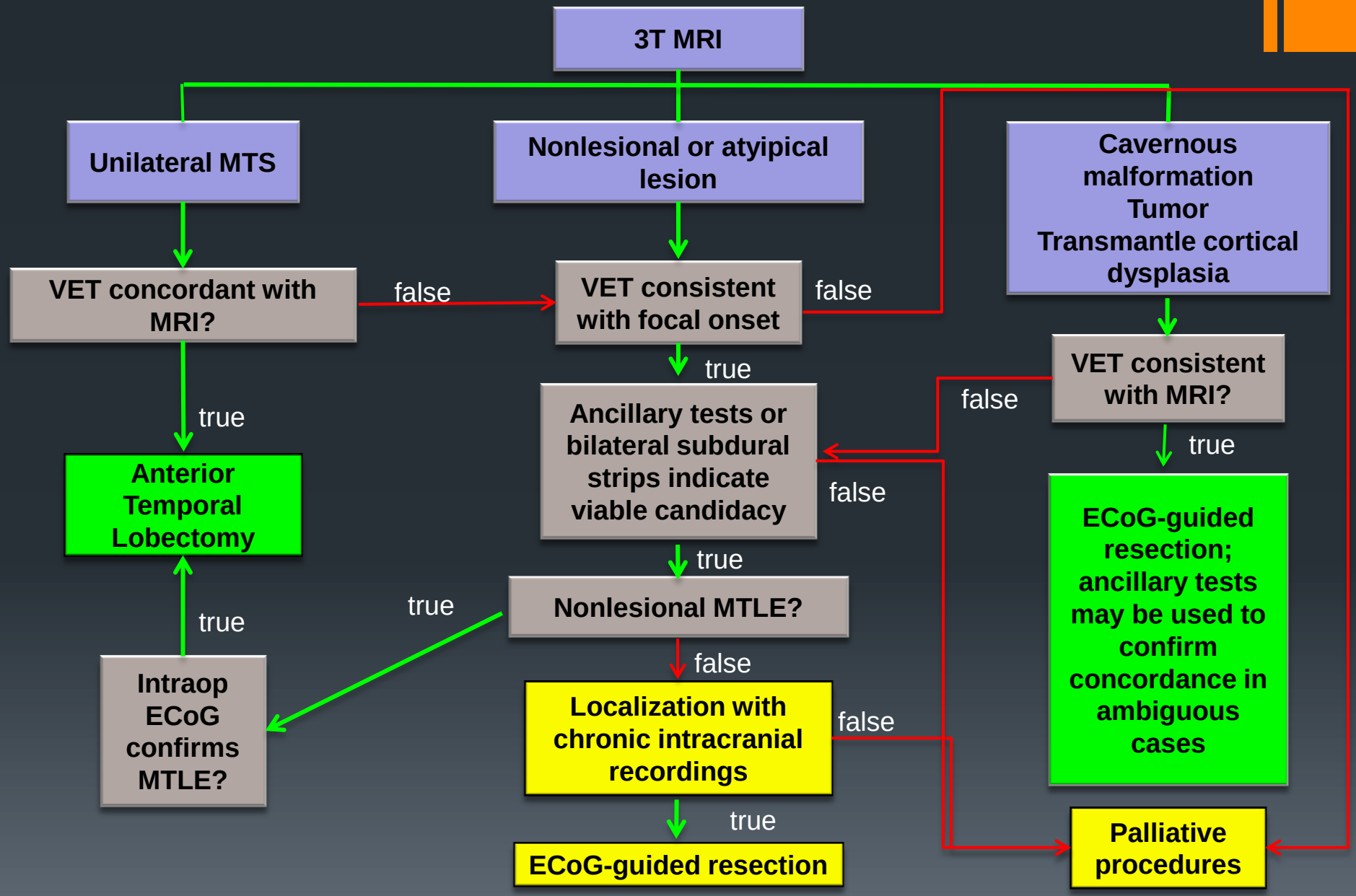


TOTAL SEIZURE FREE: 64%

MEDICALLY REFRACTORY: 36%

Kwan and Brodie, NEJM 2000

UCSF Pathway for Resective Surgery in Adults with Medically Refractory Focal Epilepsy



Overview

- Efforts to define new phenotypes or subpopulations among those with “medically refractory focal epilepsy” are critical to improving treatments
- Autoantibodies are one step in this direction
  - Disclaimer: autoimmunity is more than autoantibodies!
- Antibodies to 2 targets are of particular interest:
  - *N*-methyl-d-aspartate (**NMDA**) glutamate receptor
  - Voltage-gated potassium channel complex (**VGKCC**)
    - LGI1
    - Caspr2

Prevalence I

- Several series have studied autoantibody prevalence in epilepsy populations
- Marked differences in inclusion criteria
  - New onset vs chronic vs medically refractory
  - Age, gender
  - Selection biases (“suspected autoimmune epilepsy”)
- In a study of 139 epilepsy patients **McKnight et al 2005** found that 12% had VGKCC antibodies, and 4% had GAD antibodies
  - Subgroup (n=67) with medically refractory epilepsy:
    - 2: VGKCC
    - 3: GAD
    - 1: ganglioside GM1

Prevalence II

- **Majoie et al 2006:** 106 women age 14-45 with long standing drug resistant epilepsy
  - 7% had + VGKC Ab
  - 1 patient had equivocal GAD Ab test
  - None had other autoimmune dz
- **Quek et al 2012** studied 32 patients with "suspected autoimmune epilepsy"
  - 91% had neuronal autoantibodies
    - 56% VGKCC
    - 22% GAD65
    - 6% CRMP
    - NMDA, Ma2, ACHR – 1 patient each
  - 81% improved and 67% seizure free with immunotherapy

Prevalence III

- **Brenner et al 2013** studied cohorts with newly diagnosed and chronic focal epilepsy.
- 46/416 tested positive for serum antibodies to VGKCC (5%), glycine receptors (3%), GAD (1.7%) or NMDA receptors (1.7%)
- Significantly higher than for the controls.
- Titers significantly higher in “cryptogenic” patients
- Autoantibody+ groups: nonsignificant trend towards poor initial anticonvulsant response
- No significant difference in autoantibody prevalence between longstanding epilepsy versus recently diagnosed (argues against epiphenomenon)

Prevalence IV

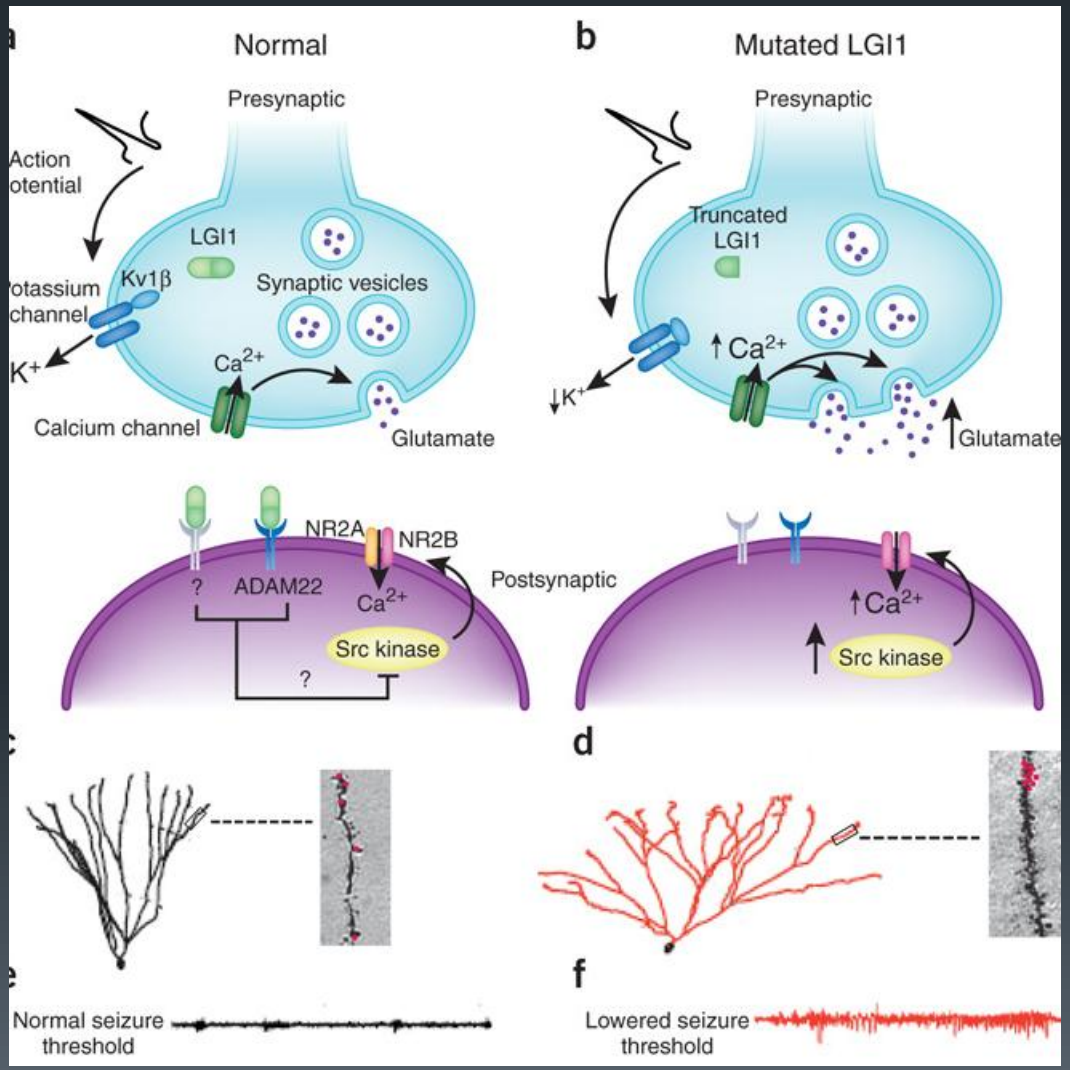
- **Suleiman et al 2013**: 12 children with suspected autoimmune epilepsy:
  - 3 NMDA receptor antibodies
  - 3 VGKC antibodies
  - 1 GAD.
- All five autoantibody-positive children improved with immunomodulatory therapy.

Autoantibody prevalence in adult epilepsy subpopulations

Study	N	Antibody type and prevalence			
		VGKCC	NMDA-R	GAD	Other
Brenner 2013	**416**	**5%**	**1.7%**	**1.7%**	**Glycine receptor 3%**
McKnight 2005	139	12%	-	4%	<1% GM1
Majoie 2006	106	7%	-	0	VGCC 1%
Quek 2012	32	56%	3%	22%	CMRP 6% Ma 3% AchR 3%

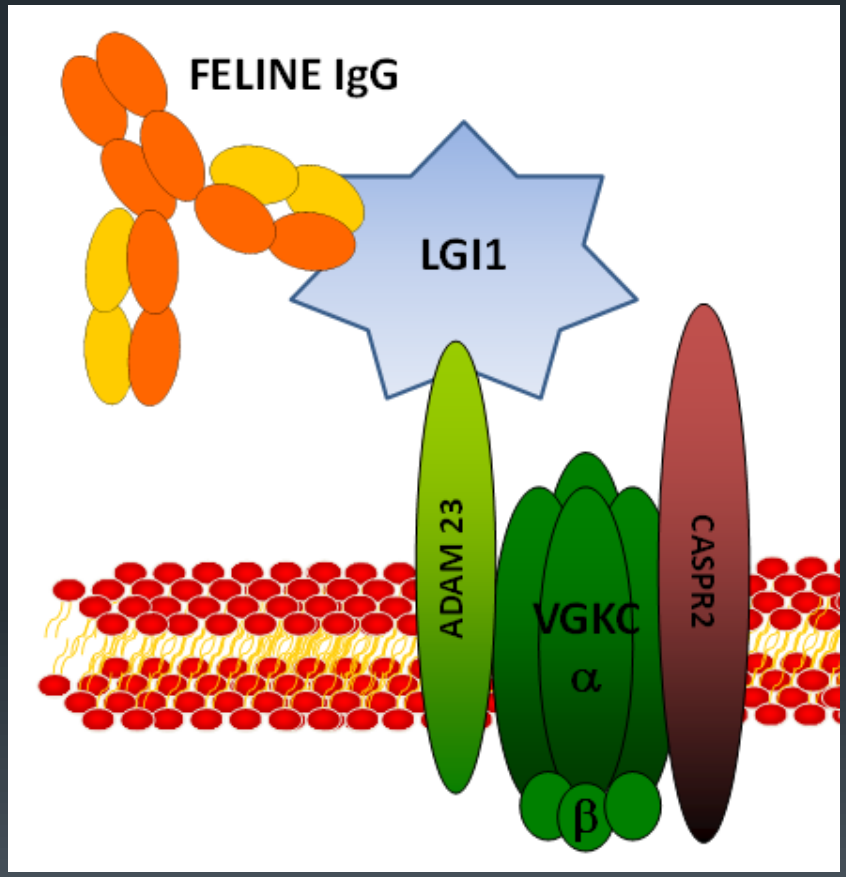
VGKCC Antibodies

- VGKC critical in modulating excitability at the presynaptic terminal
- Mutations associated with benign familial neonatal seizures.
- Previously, antibodies to VGKC described, but precise antigen unclear
- Now, distinct VGKCC epitopes found with different phenotypes



VGKCC Antibodies

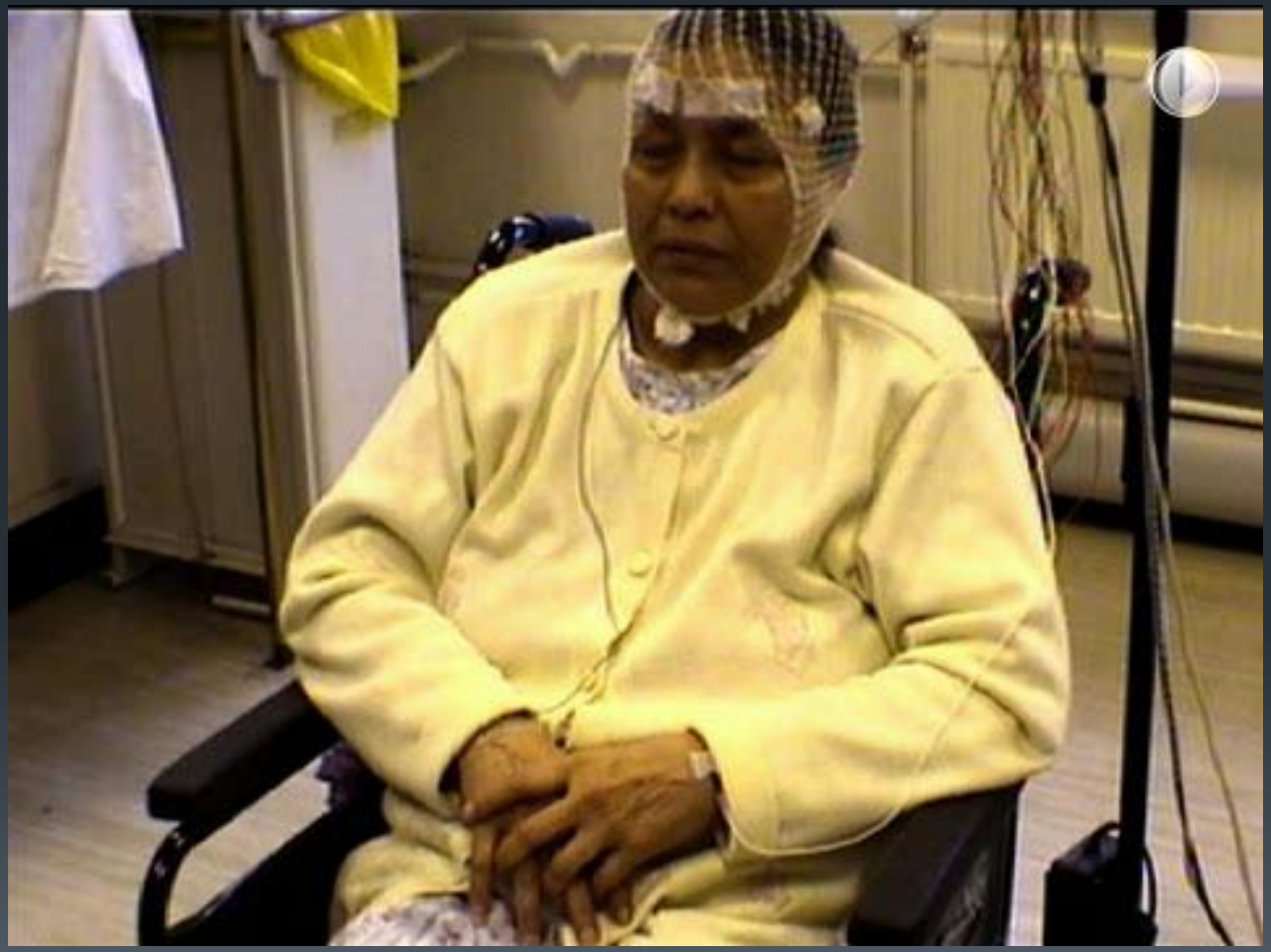
- LGI1: extracellular matrix protein associated with the pre- synaptic potassium channel
  - Mutations seen in observed in autosomal dominant temporal lobe epilepsy with auditory features
  - Antibodies to LGI1 have also been associated with LE.
  - More recently, a novel seizure phenotype has been associated with this condition: faciobrachial dystonic seizure.
- Caspr2: antibodies more typically associated with Morvan's syndrome or neuromyotonia, +/- LE and seizures



Feature	NMDA Receptor	AMPA Receptor	GABA B Receptor	VGKCC: LGI1	VGKCC: Caspr2
Age	23 months to 76 years (median 19)	38 to 87 years (median 60)	24 to 75 years (median 62)	30 to 80 years (median 60)	46 to 77 years (median 60)
Sex	80% female	90% female	50% female	65% male	85% male
Syndrome	Psychiatric symptoms, language dysfunction, abnormal movements, seizures, decreased consciousness, breathing and autonomic instability	Classic limbic encephalitis[a], isolated psychiatric symptoms	Classic limbic encephalitis, early and prominent seizures	Classic limbic encephalitis, hyponatremia (60%), brief tonic-myoclonic seizures (40%)	Encephalitis, peripheral nerve hyperexcitability, or both (Morvan syndrome)
MRI	~50% abnormal; cortical or subcortical transient increase of fluid-attenuated inversion recovery (FLAIR) signal Occasional cortical-meningeal contrast enhancement, signs of intracranial hypertension or demyelination	~90% medial temporal lobe increase of FLAIR signal	~66% medial temporal lobe increase of FLAIR signal	~84% medial temporal lobe increase of FLAIR signal	~40% with encephalitis: medial temporal lobe increase of FLAIR signal
CSF	94% abnormal[b]; almost always intrathecal synthesis of antibodies	90% abnormal[b]; frequent intrathecal synthesis of antibodies	90% abnormal[b]; frequent intrathecal synthesis of antibodies	41% abnormal[b]; infrequent intrathecal synthesis of antibodies	~25% abnormal[b]; limited information regarding intrathecal synthesis of antibodies
Tumor	Age, sex, race dependent (9% to 55%) Mostly ovarian teratoma	70% tumors of the lung, breast, thymus	60% small cell lung cancer	<20% tumors (lung, thymus, other)	Limited experience, likely <20% (tumors of the thymus)

Rosenfeld and Dalmau Neuro-Onc Continuum 2012;18(2):366

Faciobrachial Dystonic Seizures



FBDS and LGI1 antibodies

- **Irani et al 2011** found 29 patients with this syndrome
- All were positive for VGKCC antibodies
- 89% had antibodies specific for LGI1
- 77% went on to develop typical LE symptoms

- **Irani et al 2013**: follow-up study of 10 of these patients
- 9 were refractory to AEDs
- All had favorable response to steroids
- Outcome correlated with time to immunotherapy, but not time to AED therapy

Anti-NMDA Receptor Encephalitis

- Seizures, neuropsychiatric disturbances, dysautonomia and choreoathetosis
- Previously, thought to be a paraneoplastic phenomenon restricted to women < 45 with ovarian teratomas.
- Both genders may be affected in the absence of a detectable tumor
- Niehusmann et al 2009 studied 19 women (aged 15–45 years) with unexplained new-onset epilepsy
  - 5/19 +NMDAR ab
    - Shorter time to presentation
    - more psych sxs,
    - CSF pleocytosis,
    - extratemporal sz,
    - no mesial temporal MRI findings
    - 1/16 was paraneoplastic
- Prolonged nonconvulsive status epilepticus has also been reported in patients with anti-NMDA encephalitis

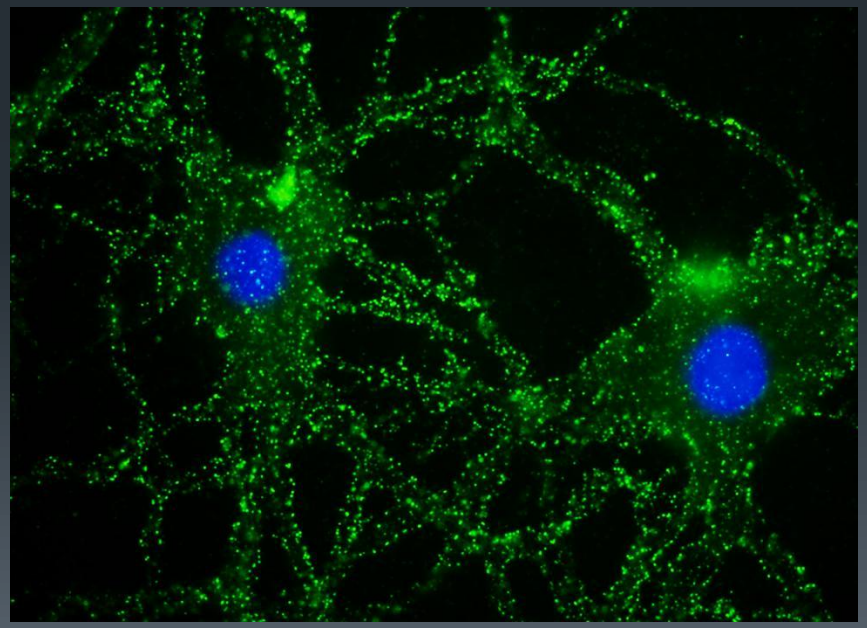
Clinical features of anti-NMDA receptor encephalitis

Two stages:
Early: neuropsychiatric sx (psychosis, behavior change, amnesia, dysphasia), seizures in 70%
Late: dyskinesias, altered consciousness, dysautonomia, central hypoventilation

Tumor association:
Paraneoplastic in 38% (46% of women, 6% of men), usu. ovarian teratoma (94%)

Diagnostic workup:
Clinical syndrome, MRI, EEG, serum and CSF (intrathecal Ab production) for anti-NMDAR Ab

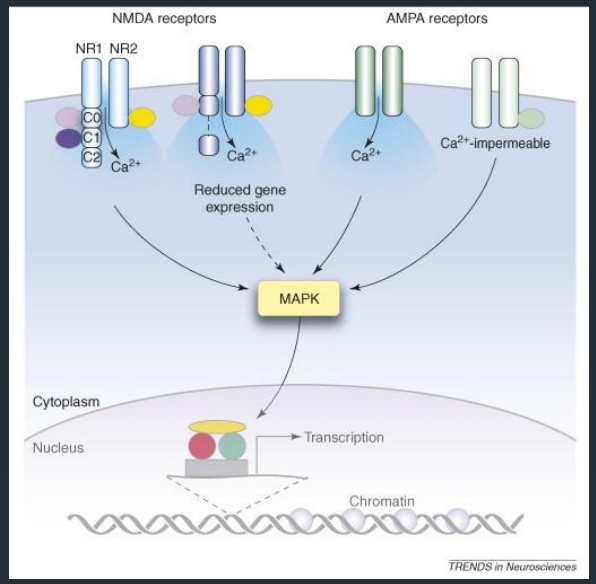
(n = 577)		number	%
MRI abnormalities	Yes	180	33%
	No	360	67%
	Unknown	37	
EEG	Abnormal	432	90%
	Slow pattern *	398	83%
	Epileptic features *	115	24%
	No abnormalities	50	10%
	Unknown	95	
CSF	Abnormal	418	79%
	Pleocytosis *	402	76%
	High protein *	93	17%
	No abnormalities	114	21%
	Unknown	45	
Sensitivity antibodies # (250 random patients)	CSF	250	100%
	Serum	213	85%



Irani et al. *Brain* (2010) & Titulaer et al. *Lancet Neurol* (2013)

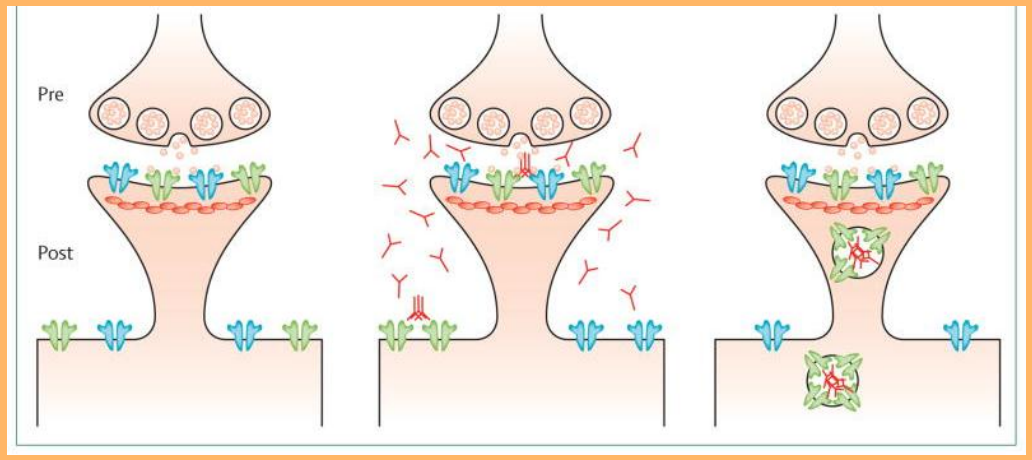
Potential pathogenic mechanisms of anti-NMDAR Ab's

Signal transduction (gene expression)



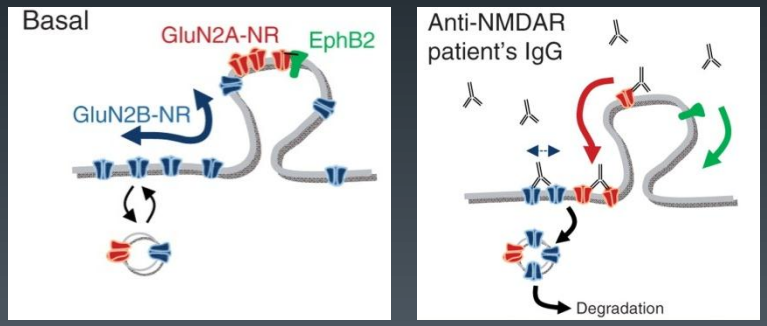
Rao and Finkbeiner, *TINS* (2007)

NMDAR internalization (hypofunction)



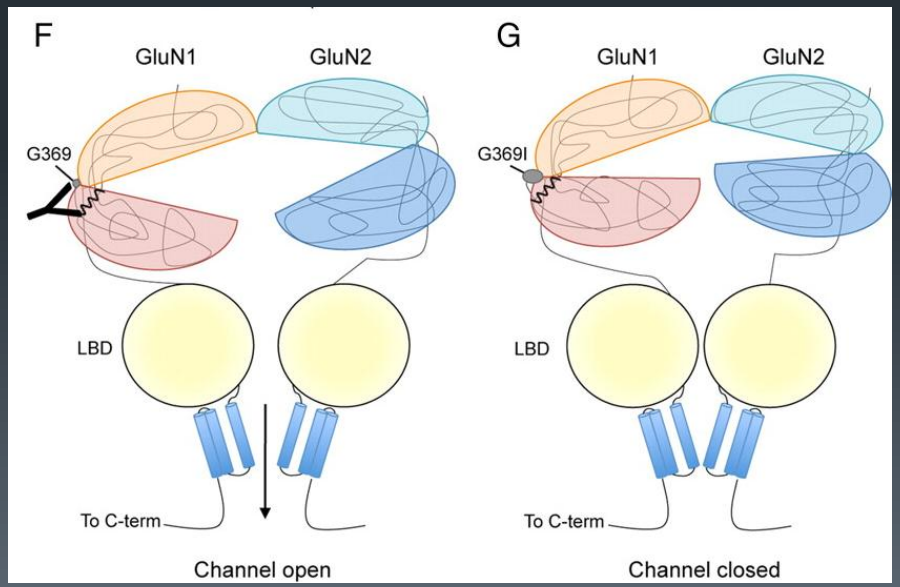
Dalmau et al, *Lancet Neurol* (2011)

Surface trafficking/synaptic retention (plasticity)



Mikasova et al. *Brain* (2012)

Channel conformation (hyperfunction)



Gleichman, *J Neurosci* (2012)

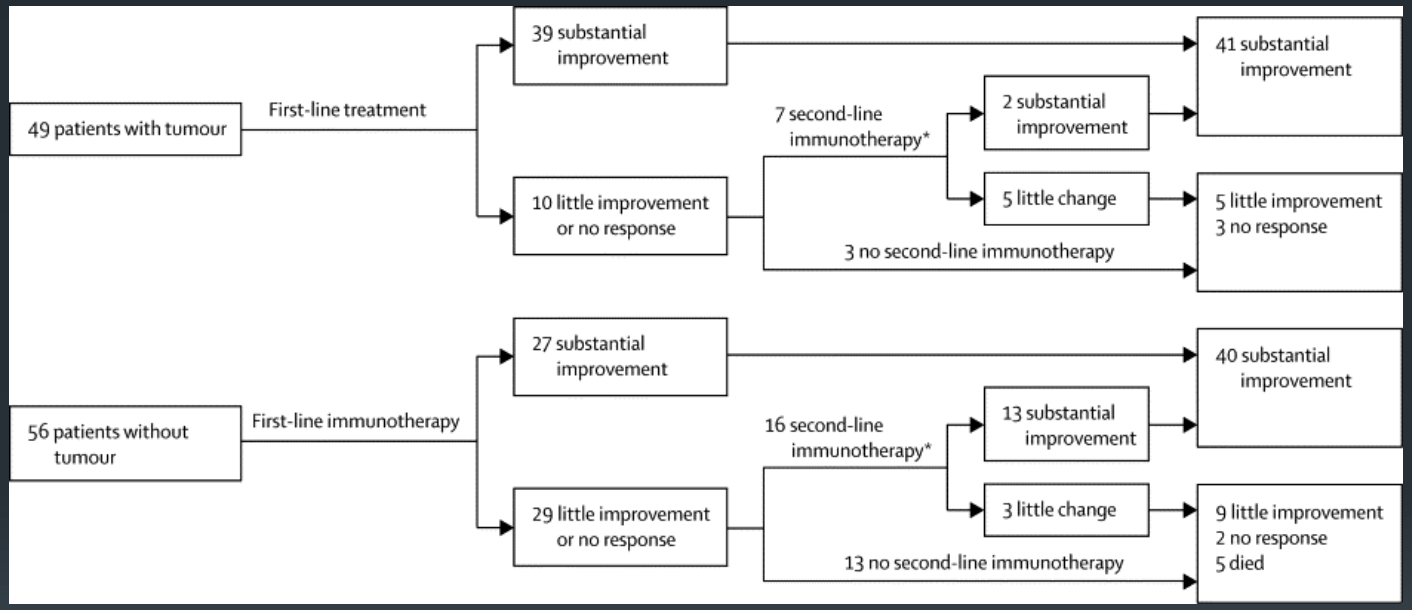
Immunosuppressive treatment for anti-NMDAR encephaliitis

Treatment:

Tumor removal (if applicable)

First-line immunosuppression – IV Ig, corticosteroids, PLEX

Second-line immunosuppression – rituximab, cyclophosphamide



Prognosis:

75% recover (reverse order of symptom onset); 25% death / severe disability

Patients without tumors need 2nd-line immunotherapy more often but have similar recovery

Early treatment predicts better recovery, which can be protracted (<24 months)

Dalmau *Lancet Neurol* (2011) & Titulaer et al. *Lancet Neurol* (2013)

HOT OFF THE PRESSES!

Anti-$GABA_A$ Receptor Encephalitis

Anti-$GABA_A$ Receptor Encephalitis

- **Petit Pedrol et al, 2014** studied serum and CSF from 140 patients with encephalitis, seizures or status epilepticus, and antibodies to unknown neuropil antigens
- 6/140 had high titers of antibodies to the GABAA receptor
- Another 12 had low titers
- Clinical presentation ranged from seizures alone (rarely) to a typical limbic encephalitis picture
- Some had features of Stiff-Person or Opsoclonus-Myoclonus syndromes
- 12/15 responded to a mix of AED and immunomodulatory therapies; 3 died

The scant evidence club

Molecule	Role	Notes
Anti-AMPA receptor antibodies	Produces LE with prominent seizures	Few case series
Anti-$GABA_B$ receptor antibodies	RPD or LE with prominent seizures	Few (one?) case series
Anti-GAD antibodies	Seen in epilepsy patients, but also seen in IDDM, Stiff Person syndrome.	Intracellular, nonspecific, unlikely to be pathogenic. However, might be associated with lower cortical GABA levels in epilepsy patients (MRS data; Stagg et al 2010)
CRMP antibodies Antineuronal antibody type 1 VGCC antibodies Ganglionic achR antibodies		

EVEN HOTTER OFF THE PRESSES!

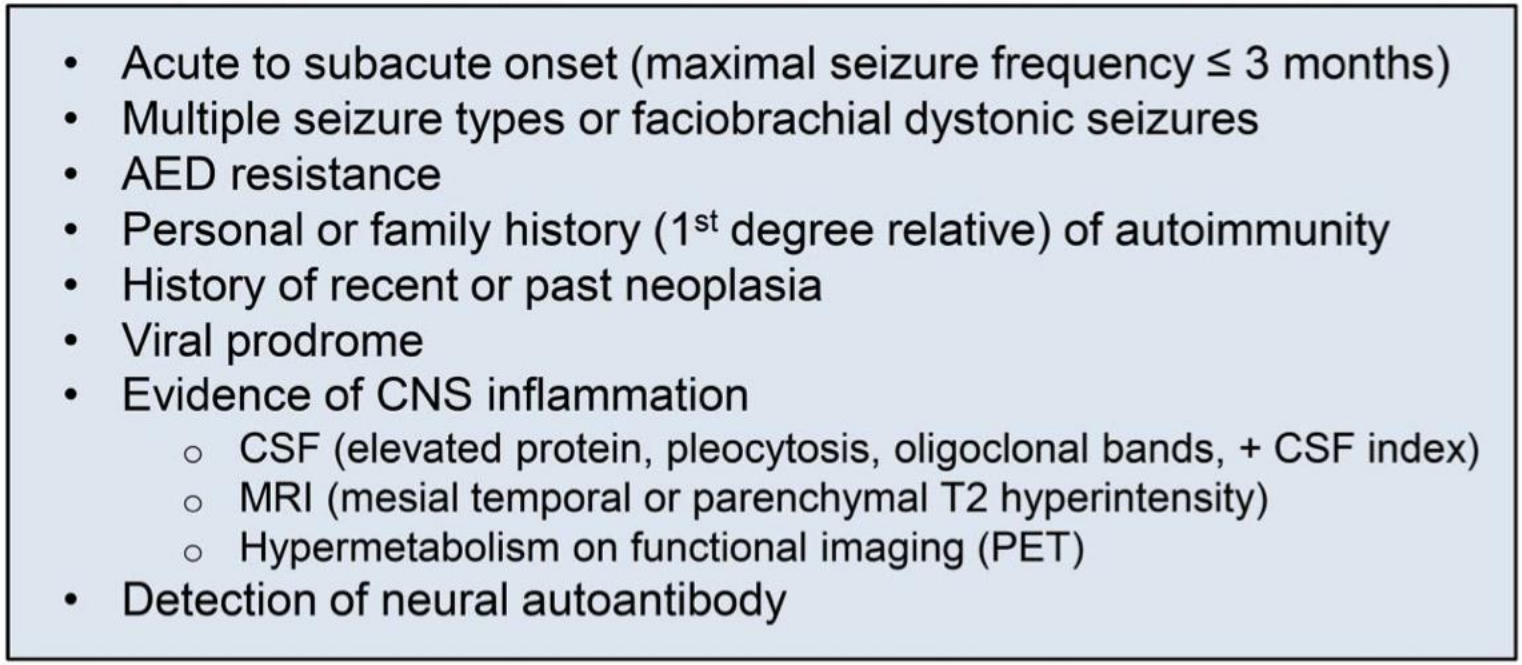
Treatment

Treatment: Toledano et al 2014

- ***Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy***
- Class IV evidence
- Inclusion:
  - Presence of at least 1 neural autoantibody (n=23) OR
  - Personal or family history or physical stigmata of autoimmunity AND
  - Frequent or medically intractable seizures
- Treatment: 6-12 weeks of IV methylprednisolone or IVIg
- Retrospective categorizations of seizure frequency
  - Daily, weekly, monthly

Treatment: Toledano et al 2014

Figure 1 **Clinical features suggestive of autoimmune epilepsy**



AED = antiepileptic drug.

Treatment: Toledano et al 2014

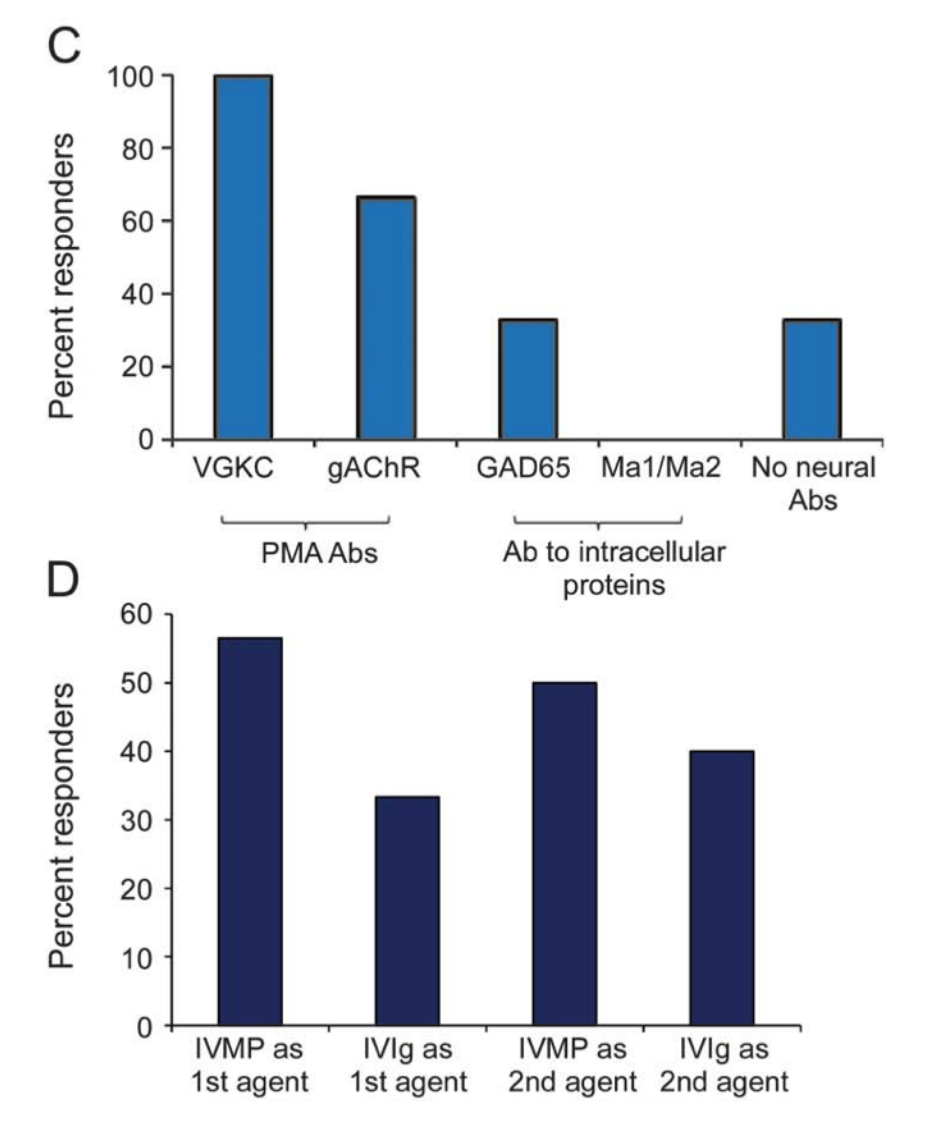
- Identified 29 patients in Mayo autoimmune neurology clinic with a chief complaint of seizures

Antibody	N	Responders
VGKCC	**12**	**12**
gAChR	3	2
CC P/Q	1	0
GAD65	6	2
Ma1/Ma2	1	0
None	6	2

Treatment: Toledano et al 2014

- 62% favorable response
  - 10/18 -> seizure free
  - Remainder had >50% reduction in seizure frequency
- Half of initial non-responders responded to second immunotherapy agent
- All remained on AEDs
- 89% of responders took long-term maintenance immunotherapy

Treatment: Toledano et al 2014

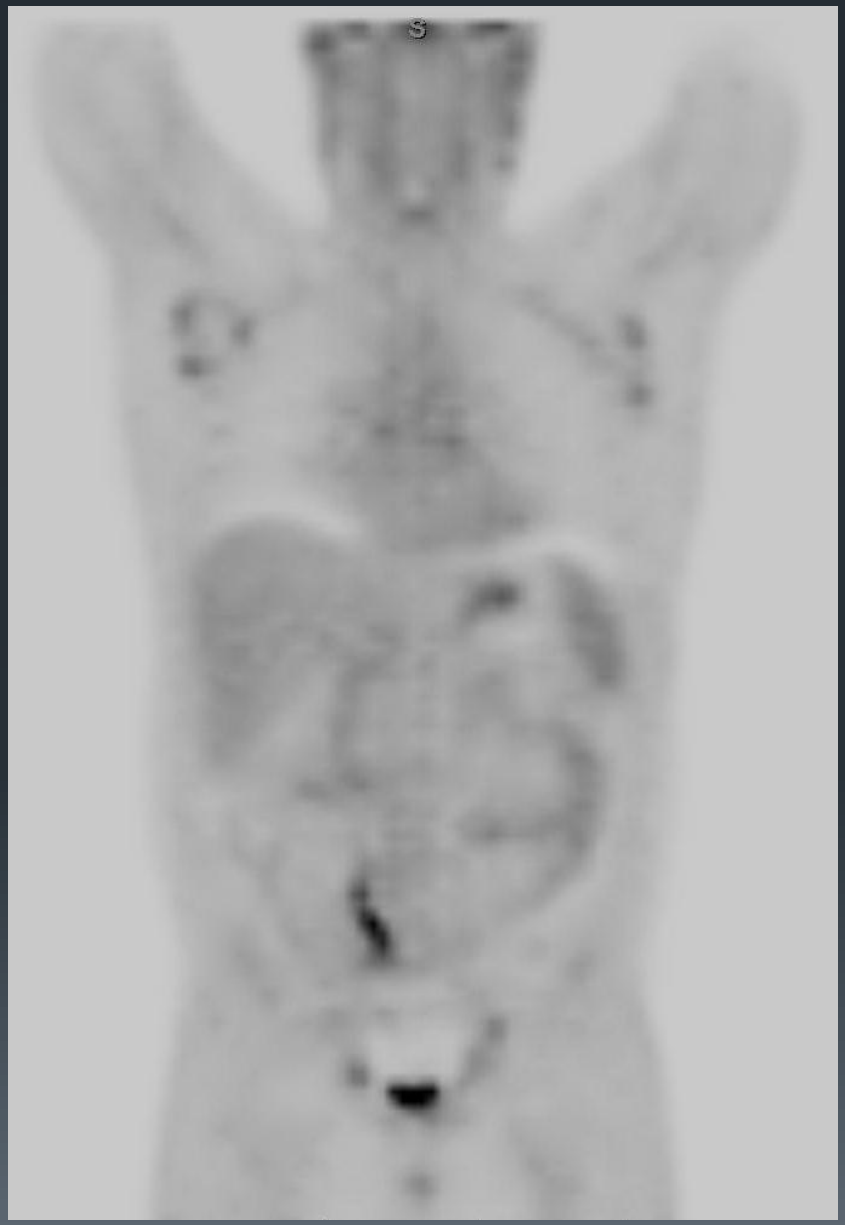


So, who should we test?

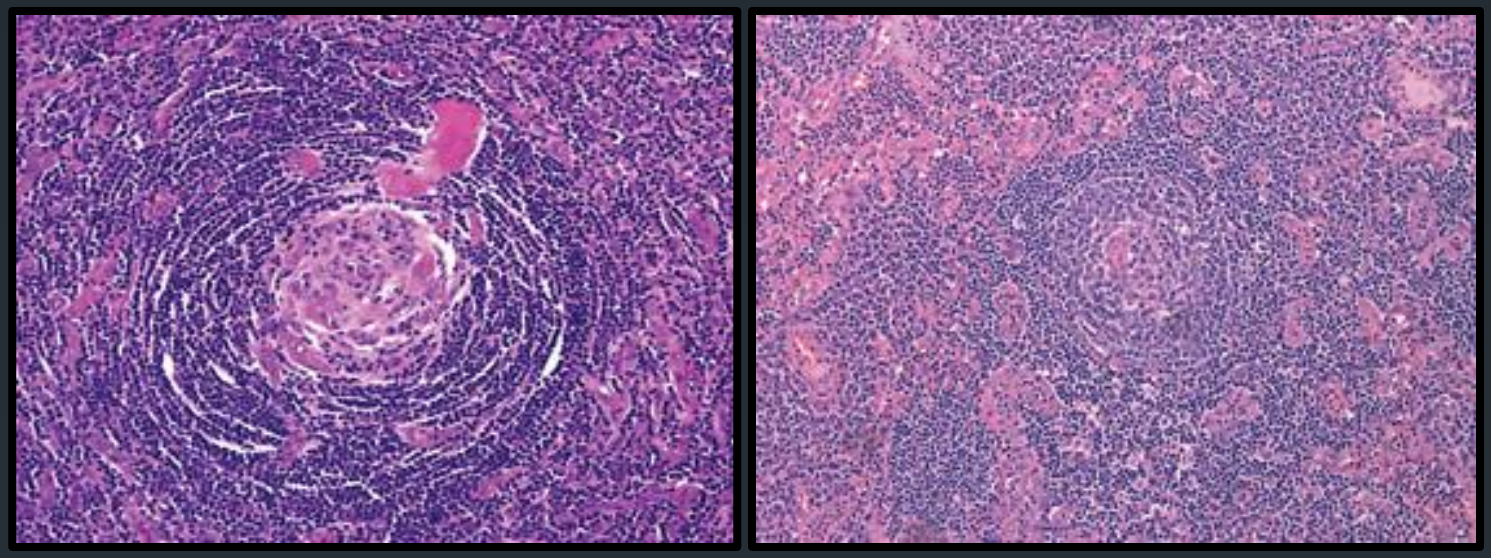
- We need large prospective observational studies to determine true autoantibody prevalence, prognostic value (regarding drug resistance), and to determine risk factors for autoantibody presence
- In the absence of such data, consider testing patients in which some elements of the anti-VGKCC or anti-NMDA syndrome are present to suggest high pretest probability
- Additional factors that may influence your decision include:
  - Younger women or older men
  - Explosive onset, frequent seizures, multiple seizure types
  - Medically refractory
  - Family or personal autoimmune history
  - Hyponatremia, SIADH, prominent neuropsychiatric sxs, cerebellar signs, or movement disorder
  - *Medically refractory, poor surgical candidacy*
- LP for CSF may be a useful screening tool if unsure

Back to our case…

Whole-body PET-CT



Cervical Lymph Node Biopsy



N.B. images not from patient, c.f. Schulte and Talat (2010) Nat Rev Clin Oncol

Histology: nodular pattern of ‘onion-skinned’ follicles, abundance of interfollicular CD138+ plasma cells, no lymphoma, HHV8 stain negative

Flow cytometry: no clonal lymphoid populations

Dx: Multicentric Castleman’s Disease, plasma cell variant

Castleman's Disease

- Angiofollicular lymph node hyperplasia: **Rare lymphoproliferative disorder with increased risk of lymphoma;** unicentric (UCD) and multicentric (MCD) forms; UCD associated with paraneoplastic pemphigus; MCD often associated with HIV and HHV8
- Clinical:
- -UCD: young adult, often asymptomatic, mass can cause compression sx
- -MCD: middle-aged patient, non-specific 'B' symptoms, peripheral lymphadenopathy, cough/dyspnea related to pulmonary infiltrates
- Diagnosis: imaging, labs (anemia, hypoalbuminemia, ↑ESR), lymph node bx (pathology: hyaline vascular variant (90%), plasma cell variant, mixed)
- Treatment:
- -Resection curative in unicentric disease and prognosis favorable
- -MCD is more aggressive, course variable but prognosis usu. worse (median survival 8-14 mo); rituximab first-line, chemo if fails (etoposide vs. CHOP)
- Significance:
- <15 reported cases of CD with CNS involvement (all UCD with mass lesions, MRI similar to meningiomas), 8 patients had seizures
- Paraneoplastic limbic encephalitis has been rarely reported with malignant hemopathies (AML, HL, NHL), sometimes with anti-VGKC Ab's, but no reports in Castleman's

Follow-up

- Seizures well-controlled on Depakote XR 1000 mg BID
- Rituximab treatment initiated
- Plan to follow with serial PET-CT and anti-VGKC Ab titers

Conclusions

- Think about autoantibody testing in patients with new-onset refractory focal epilepsy without a clear etiology
- Antibodies to the VGKCC, NMDA receptor, and possibly $GABA_A$ receptor are likely highest-yield
- The full spectrum of these phenotypes is not yet known
- More data is needed to determine autoantibodies' prognostic significance in epilepsy
- A number of other immune/inflammatory mediators are under active investigation for their roles in epilepsy

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References

- Brenner et al, Epilepsia 54, 1028–1035 (2013).
- Hegde & Lowenstein, Biomarkers Med. 8(3), 413–427 (2014)
- Irani et al, Ann. Neurol. 69(5), 892–900 (2011).
- Irani et al, Brain. 2013 Oct;136(Pt 10):3151-62
- McKnight et al, Neurology 65(11), 1730–1736 (2005).
- Niehusmann et al, Arch. Neurol. 66(4), 458–464 (2009).
- Petit-Pedrol et al, Lancet Neurol 2014; 13: 276–86
- Quek et al, Arch. Neurol. 69(5), 582 (2012).
- Suleiman et al. Epilepsia 54(6),1036–1045 (2013)
- Toledano et al. Neurology, published online April 4, 2014