The evolving field of autoimmune neurology

Steven Vernino M.D. Ph.D.

Professor, Vice Chair of Education and Faculty Affairs

Director of autonomic disorders fellowship

Department of Neurology

UT Southwestern Medical Center, Dallas, Texas

Disclosures: Consultant for Theravance, argenx, CSL Behring, Kyverna; Research support from Takeda, Lundbeck, Regeneron, Mission MSA and NIH

Neuroimmunology

MS

Autoimmune Neurology

diseases with a specific immune response against defined neuronal antigen(s)

Immune-mediated nerve & muscle disorders

GBS / AMAN
CIDP
Inflam. myopathy
Inflam. plexopathies
Polymyositis / DM / IBM

"Neurorheumatology"

Lupus cerebritis
CNS or PNS vasculitis
RA, SS

Neuroimmunology

Autoimmune Neurology

NMOSD & MOGAD

Autoimmune Encephalopathies

Limbic encephalitis
Brainstem enceph.
SRE
Autoimmune ataxia

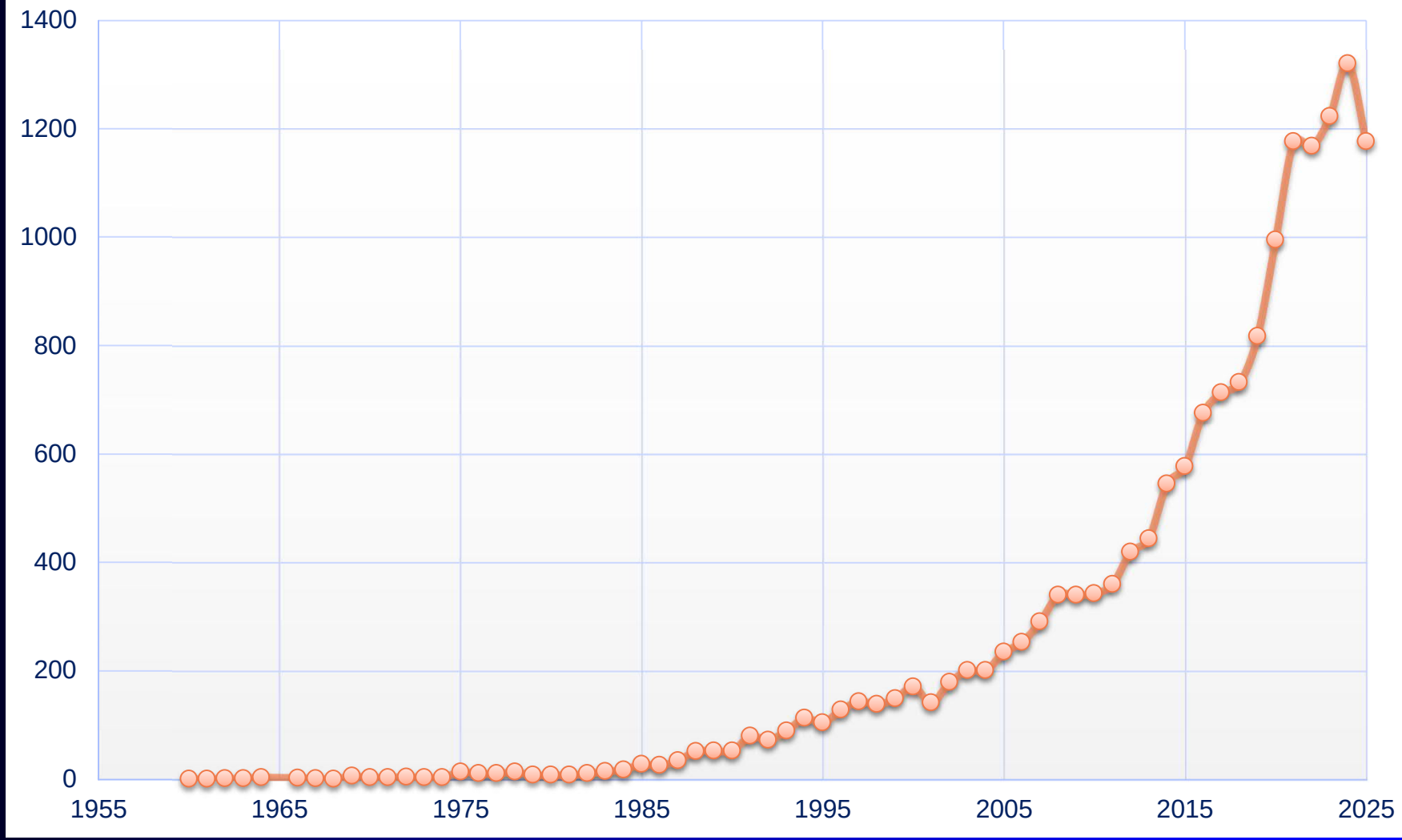
Neuromuscular Syndromes

MG
LES
Neuromyotonia
AAG

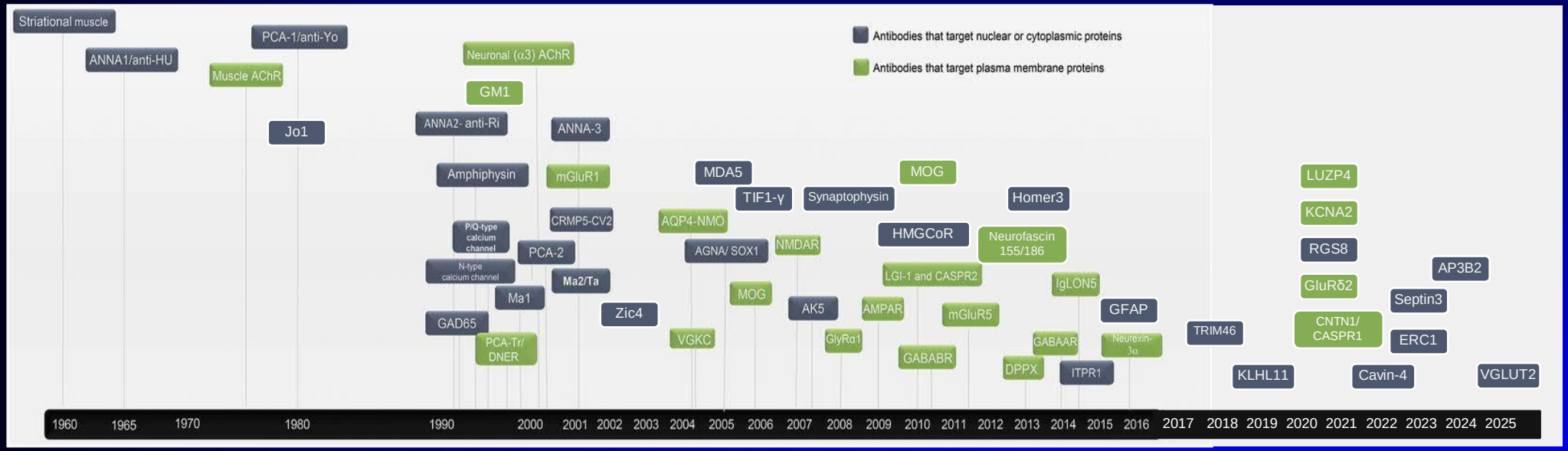
Paraneoplastic disorders

PCD
PSN
PLE
SPS

Publications per year (“autoimmune neurology”)



Autoantibody timeline

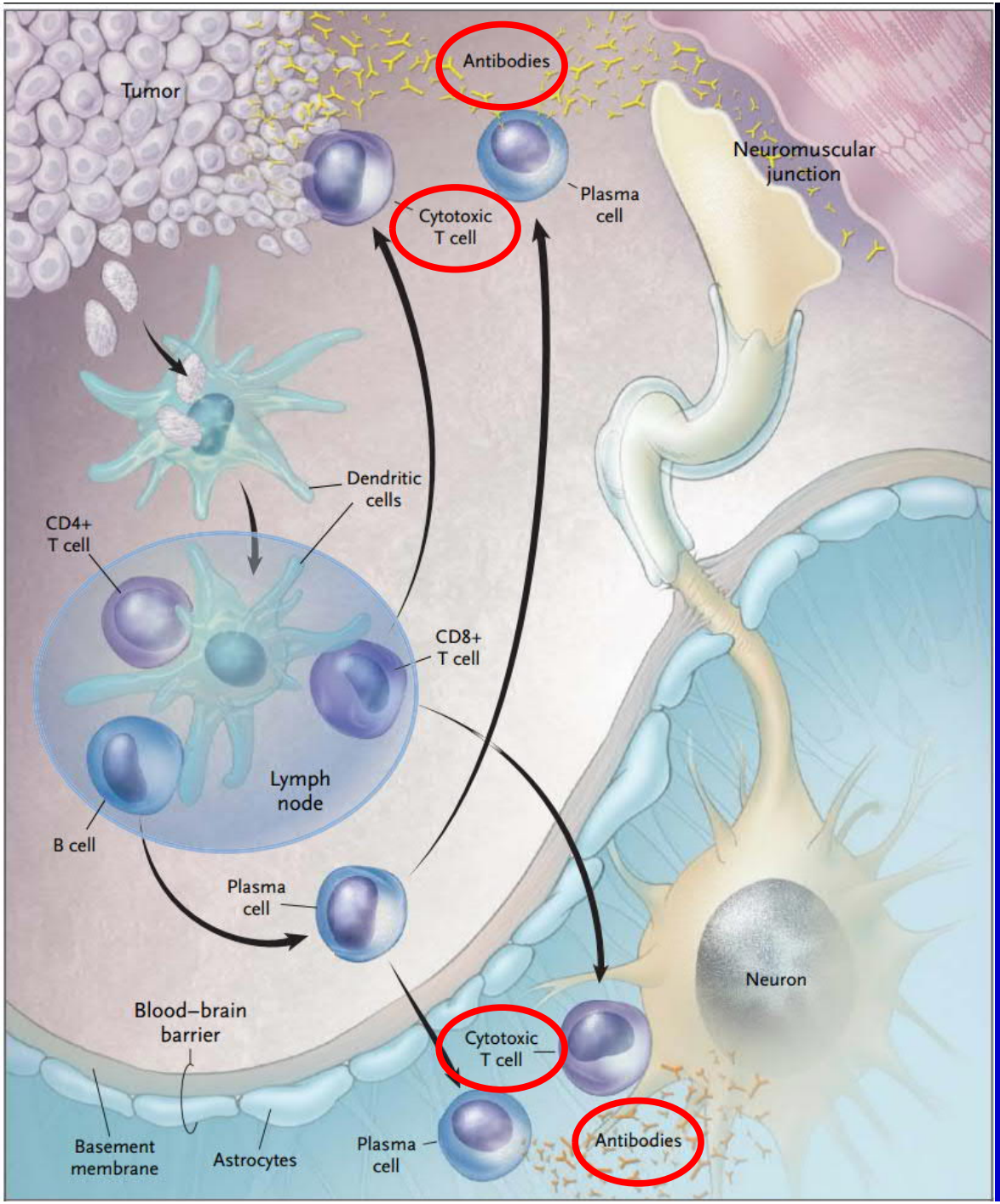


AChR Ab in MG

NMO, NMDAR, VGKC

Checkpoint inhibitor therapies

Adapted from Lopez-Chiriboga et al. Neurology 2017



Paraneoplastic Pathophysiology

Darnell and Posner NEJM 2003

One approach

Consider disorders based on antibody target

Onconeural antigens (Hu, Yo, CRMP-5)

- Intracellular - probably not pathogenic
- Surrogate of *cell-mediated* response to cancer

Surface (membrane) antigens (AQ4, AChR, NMDAR)

- May produce *direct Ab* effects (i.e. MG)
- Interact with conformational epitopes

Intracellular antigens, not neuron-specific (GFAP, GAD)

- Pathophysiology unclear
- Clinically, seem to behave like cell surface Ab

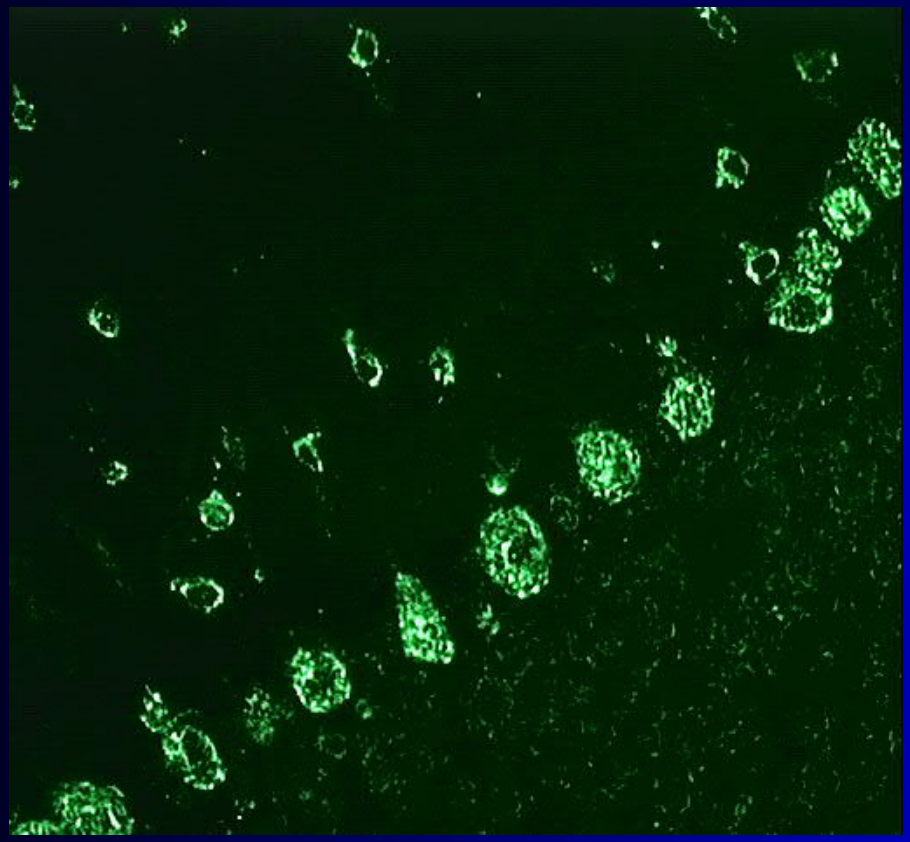
Seronegative autoimmune neurological disorders

Diagnostic testing

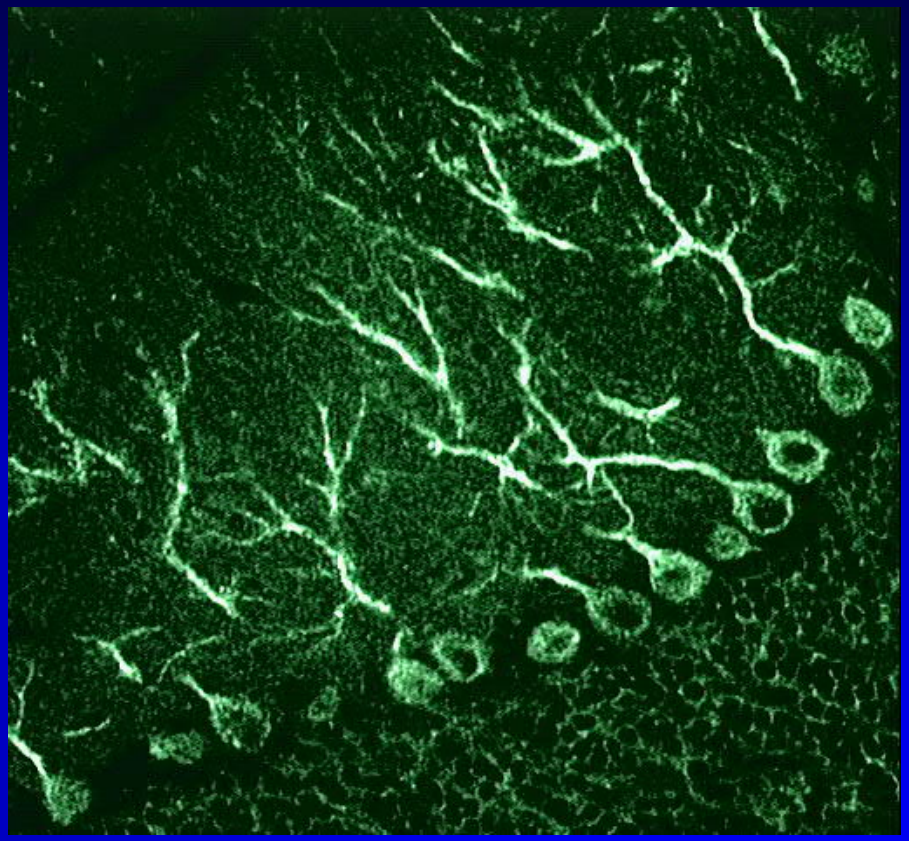
Onconeural antigens (Hu, Yo, CRMP-5)

- Neuronal or cytoplasmic antigens expressed by cancer cells and neuronal tissues
- Identified by IHC pattern in tissue and/or Western (or dot) blot
- Reported as a titer.
- High specificity (few false positives)
- Testing both CSF and serum improves sensitivity
- Testing a panel of relevant antibodies improves sensitivity

Purkinje Cell Antibodies



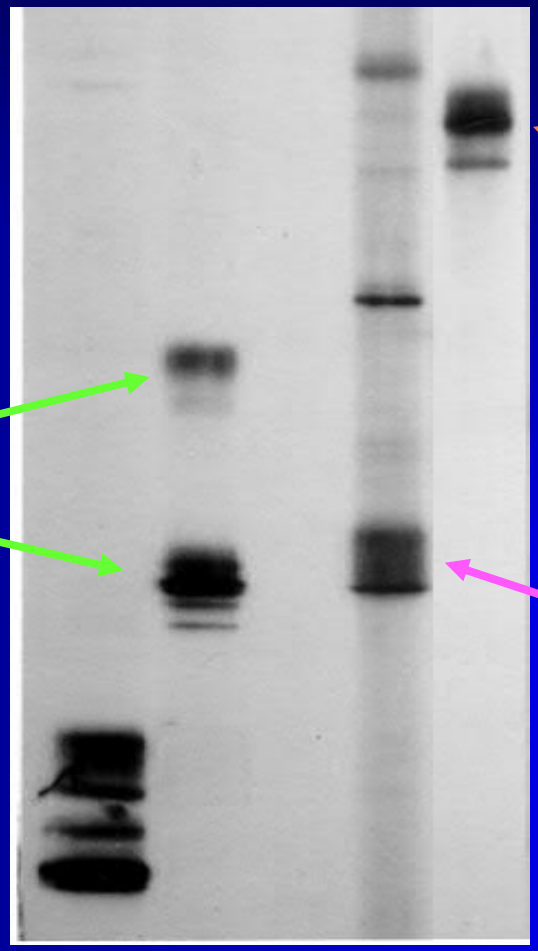
PCA-1



PCA-2

Western Blot

(Antibody binding to cerebellar proteins in a gel)



Amphiphysin

ANNA-2

PCA-1

ANNA-1

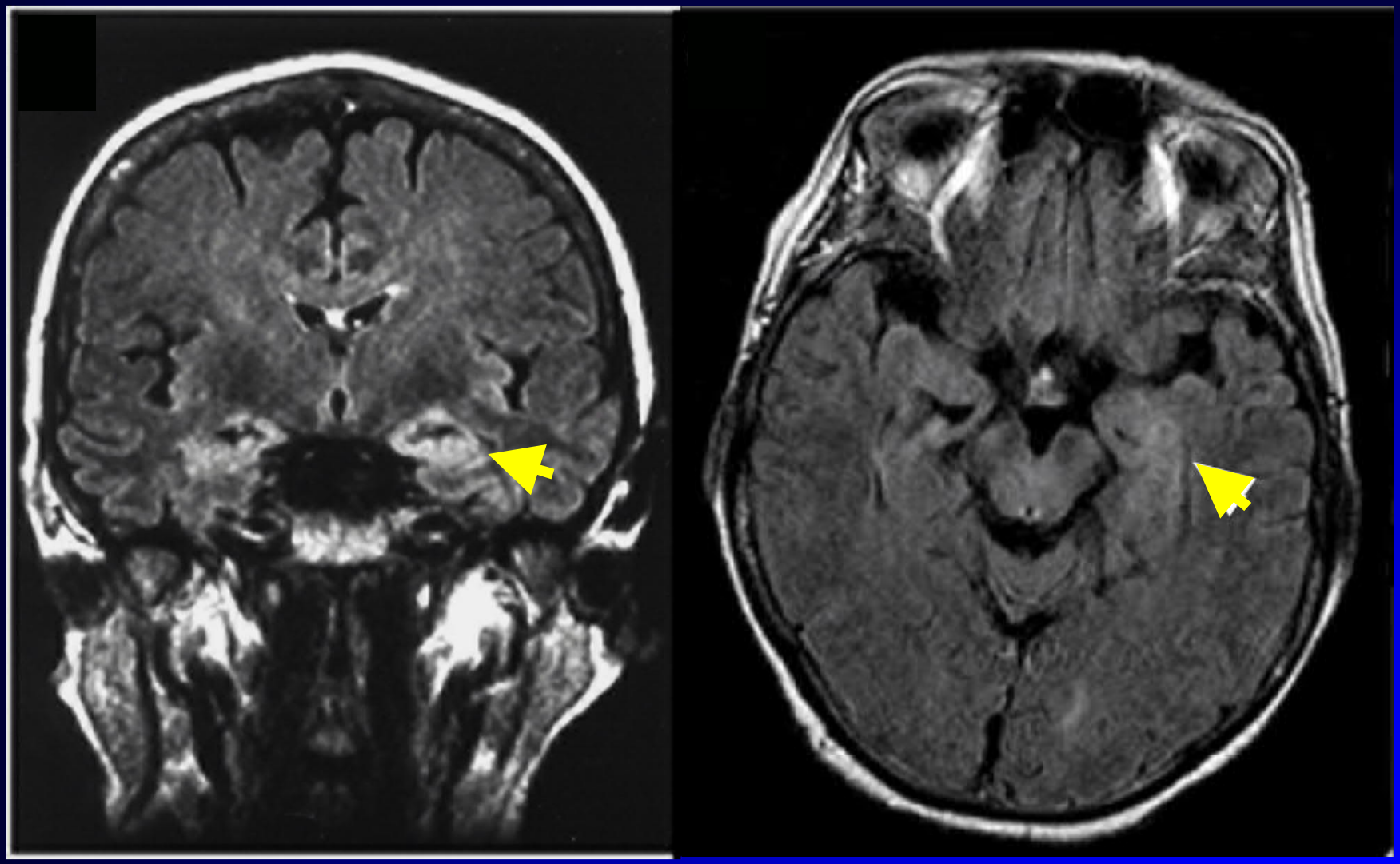
Nuclear and cytoplasmic antibodies
~2017

Name	Associations
ANNA-1 (“Hu”)	SCLC; various syndromes
ANNA-2 (“Ri”)	SCLC or breast carcinoma; POM
ANNA-3	SCLC; various syndromes
PCA-1 (“Yo”)	Ovarian or breast; PCD
PCA-2	SCLC; various syndromes
PCA-Tr (DNER)	Hodgkins lymphoma; PCD
Amphiphysin	SCLC or breast; various syndromes
CRMP-5 (“CV2”)	SCLC or thymoma; various syndromes including PN and paraneoplastic chorea.
Ma1 & Ma2	testicular (men) or breast (women); PLE
Sox-1 (AGNA)	SCLC; LEMS & other syndromes
Zic4	SCLC; PCD

Illustrative Case:

- 59 year-old woman (50 pack year smoking history)
- Develops burning and numbness of feet and hands
- Over weeks, behavioral/cognitive changes
  - Becomes a more pleasant and pliable person
  - Increasing memory loss. Cannot remember names, events or directions from day to day.
  - Good memory for events preceding her illness
  - Loses sense of smell and taste. No interest in smoking
  - 20# weight loss
- Then, she has a generalized seizure
- In addition to memory deficit, exam shows areflexia and marked asymmetric proprioceptive sensory loss

MRI - FLAIR



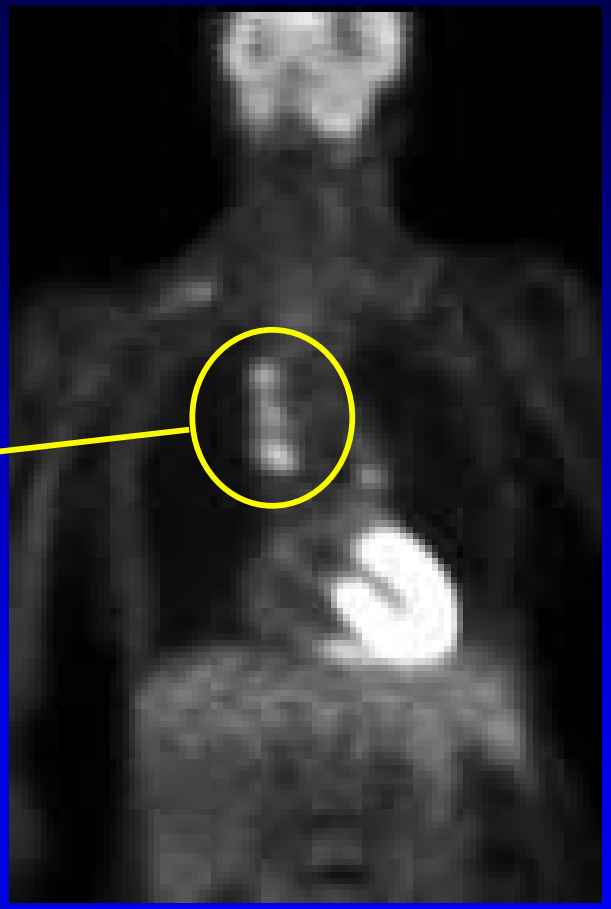
No gadolinium enhancement

- Paraneoplastic antibody testing:
  Positive for ANNA-1 (anti-Hu)

- CXR and CT body: normal.

- PET: Hypermetabolic foci in mediastinal lymph nodes

- Surgical Biopsy:
  Small-cell lung carcinoma



Treatment of classical CNS paraneoplastic neurological disorders

- These disorders are rare
- No placebo controlled trials
- Prognosis is poor; irreversible neuronal injury
- Aggressive cancer treatment and immunosuppression can lead to meaningful arrest of progression
- One small (20 patient) prospective open label trial suggested a benefit of cyclophosphamide compared to historical controls

Vernino et al. NeuroOncology 2004

Diagnostic testing

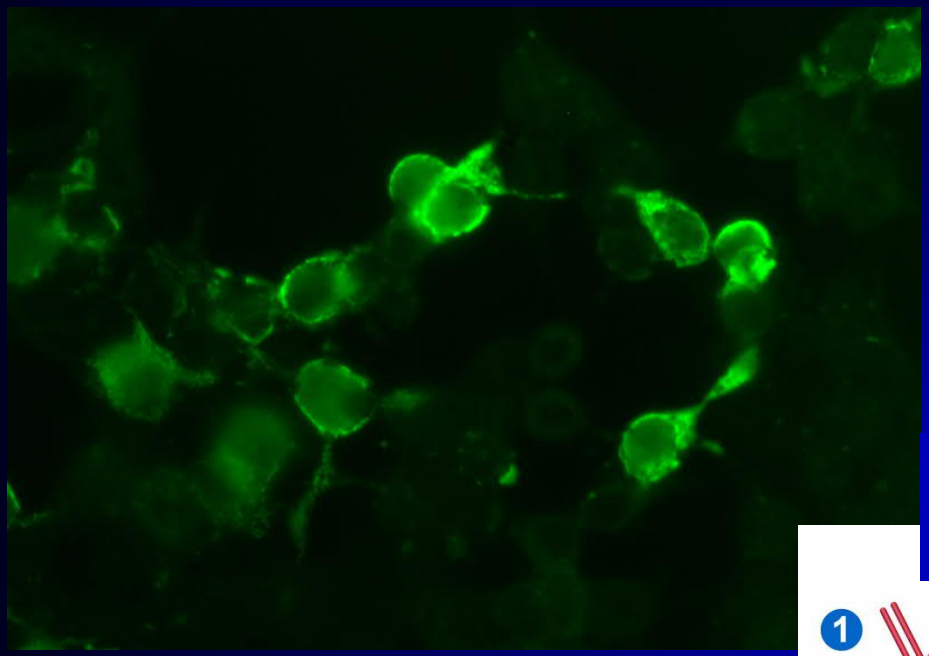
Onconeural antigens (Hu, Yo, CRMP-5)

- Identified by immunohistochemistry pattern in tissue or with Western blot
- Reported as a titer. High specificity

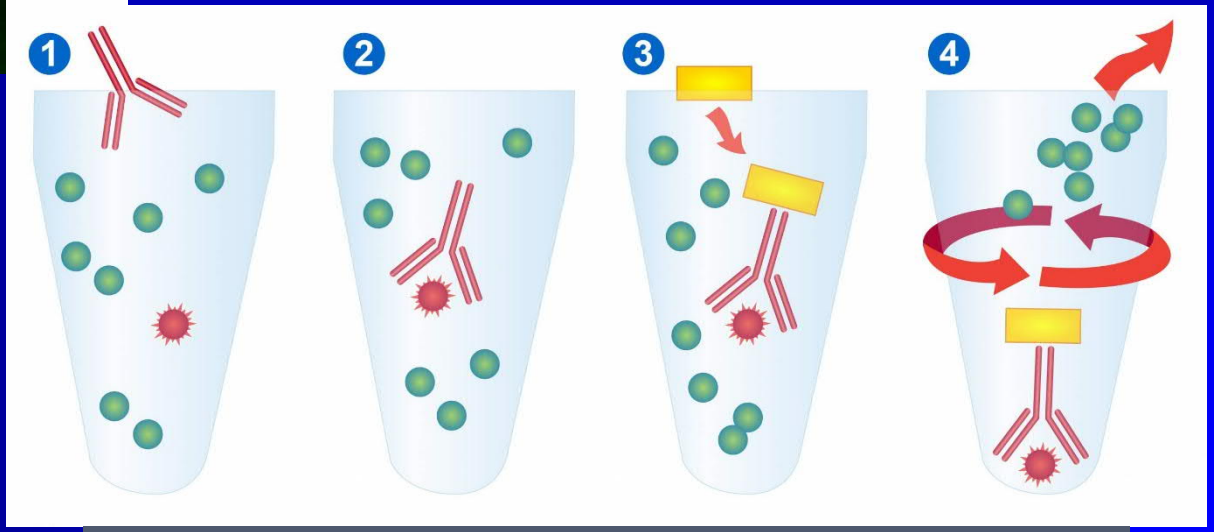
Surface (membrane) antigens (AQ4, AChR, NMDAR)

- Tested by RIA or CBA
- Reported as a level (binding capacity) for RIA
- For CBA, as pos/neg or with titer
- Higher rates of false (low nonspecific) positives
- Antibody more likely to be pathogenic
- Better treatment response targeting humoral immunity (PLEX, steroids, IVIG, anti-CD20)
- Less often associated with cancer

Cell-based assay (CBA)



Radioimmunoprecipitation assay

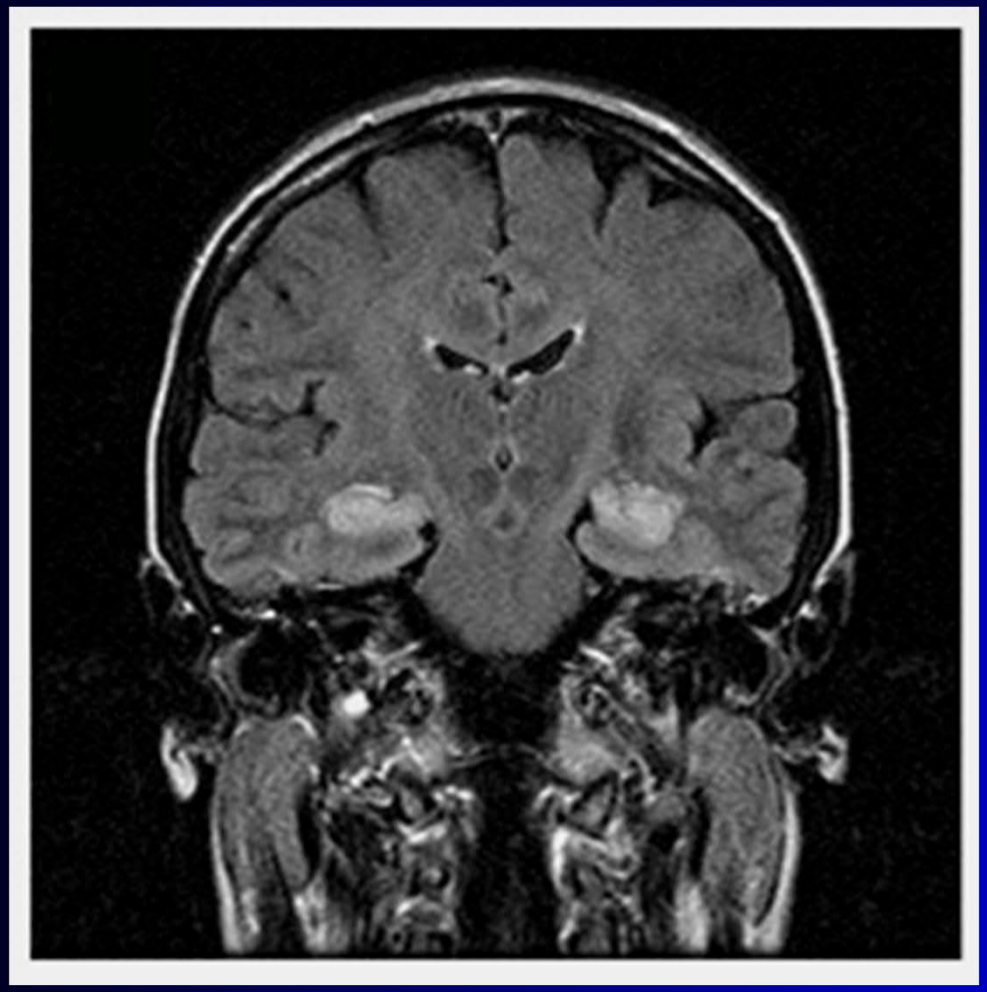


Measure radioactivity in test tube

Illustrative Case

- 62 year-old man (non-smoker)
- Over weeks, develops cognitive impairment
  - Lost in familiar places
  - Trouble managing checkbook
  - Failure to recognize friends
- Brief spells of behavioral arrest and intense sweating
- Alert, appears well
- Marked short-term memory loss
  Motor, sensory and coordination exam normal

*



EEG: generalized slowing left temporal sharp waves & short electrographic seizure

CSF: normal

Serum sodium: 125 meq/L

Paraneoplastic antibodies: Negative

Positive LGI1 antibody

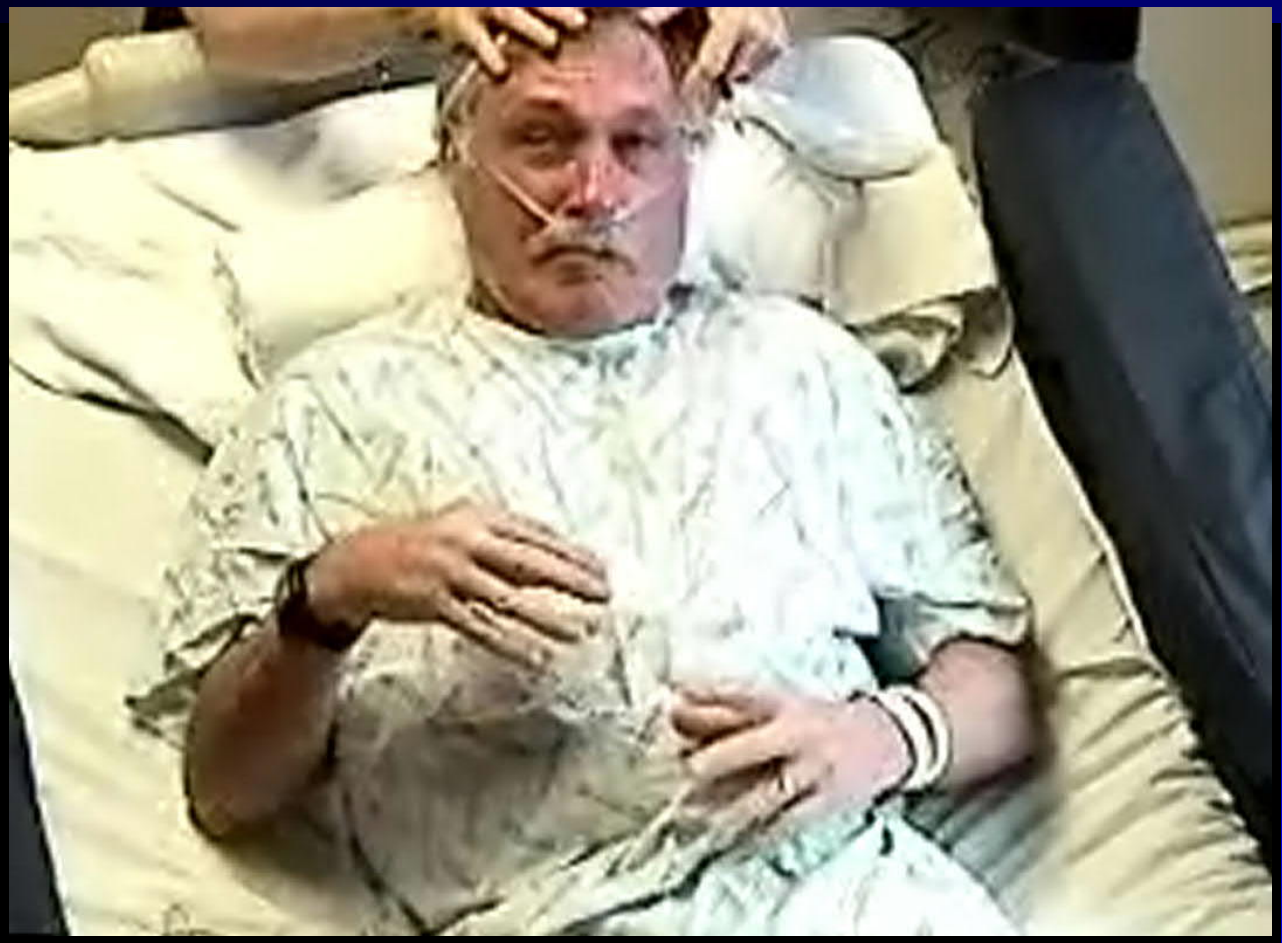
Autoimmune Limbic Encephalitis
(with VGKC/LGI1 antibodies)

- Very similar to PLE
  - Cognitive/behavioral/psych. symptoms
  - Temporal lobe CPS
  - MRI & EEG findings
- Usually not associated with cancer
- Dramatic response to high dose steroids or PLEX
- Clinical features
  - Male predominance
  - Hyponatremia (cause unknown)
  - Autonomic hyperactivity symptoms
  - Sweating and salivation
  - Faciobrachial dystonic seizures

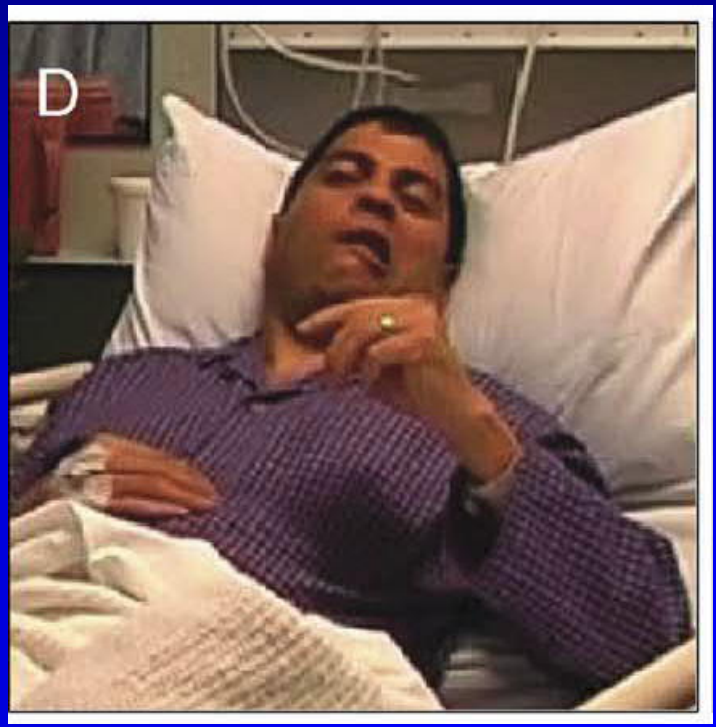
Thieben et al. Neurology 2004; Vincent et al. Brain 2004

Other features of this syndrome

"Faciobrachial dystonic seizures" may precede the onset of cognitive changes and may not respond to AED

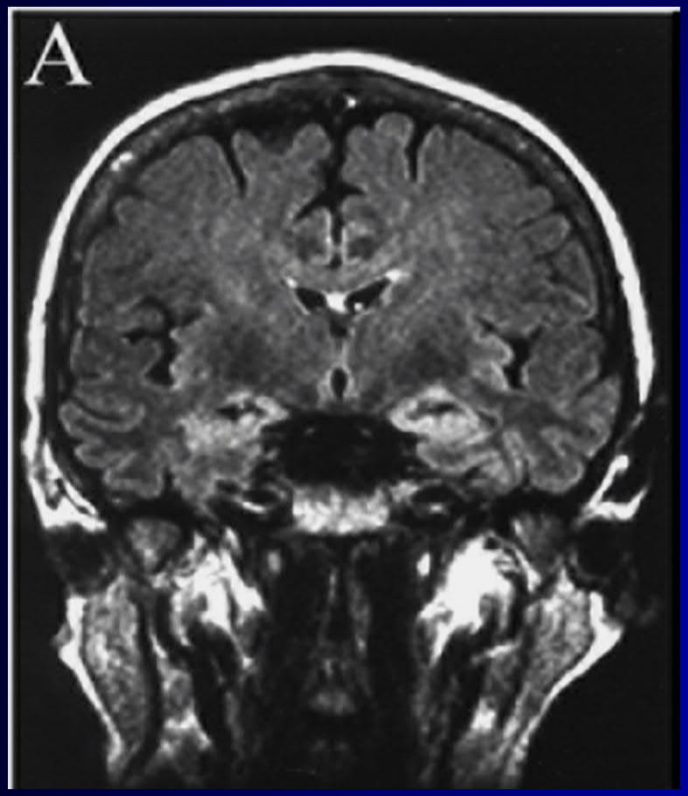


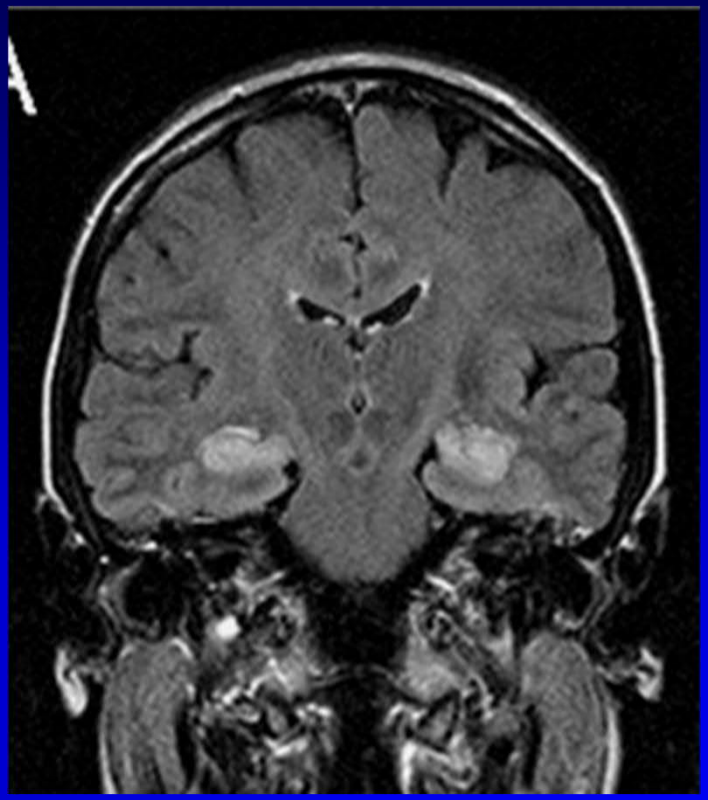
courtesy of Dr. Puneet Gupta



Irani et al., Ann Neurol 2011

A tale of two limbic encephalitides
(amnesia, confusion and seizures)





Paraneoplastic (SCLC, anti-Hu)
Pt dead within 9 mos despite Rx

No cancer (LGI1 AIE)
Excellent recovery w/ steroids & immunotherapy

Cell surface antibodies in Neurology

Disorder	Associated antibody
MG	α1 AChR, MUSK, LRP4
AAG	α3 ganglionic AChR
Lambert-Eaton	VGCC
NMT (Isaacs/Morvan)	VGKCc (Caspr2)
Autoimmune encephalitis	VGKCc (LGI1), NMDA-R AMPA-R, GABA-R, DPPX
SPS	Glycine-R
Rasmussen encephalitis	α7 AChR, GluR3
NMO	aquaporin-4, MOG
PCD	VGCC, mGluR1

Antibodies against neuronal membrane Ag

- Not highly predictive of cancer
  - e.g. about 10-15% of MG patients have thymoma
  - A minority of NMDAR patients have ovarian tumors
  - Cancer association varies according to Ab
- Antibodies may be pathogenic
  - Antibody level correlates roughly with disease severity
  - Disease can be transferred in passive transfer animal models
  - Antibody effects may be reversible
  - Treatments that reduce antibody levels may improve disease
- Beware of low specificity at low Ab levels
  - VGKC Ab 2-3% false positive (? significance if LGI1/CASPR2 neg)
  - 40% of patients with ganglionic AChR < 0.1 had no neurological dx

Diagnostic testing

Onconeural antigens (Hu, Yo, CRMP-5)

- Identified by immunohistochemistry pattern in tissue or with Western blot
- Reported as a titer. High specificity

Surface (membrane) antigens (AQ4, AChR, NMDAR)

- Tested by RIA or CBA
- Higher rates of false (low nonspecific) positives

Intracellular antigens, not neuron-specific (GFAP, GAD)

- Can be tested by many methods (including ELISA)
- Reporting depends on assay. Different labs with different values
  - N.B. GAD-65 can be reported as IU or as nmol/L with different normal
- Treatment approach more similar to cell-surface Ab

GAD-65 antibodies

- Glutamic acid decarboxylase is synthetic enzyme for GABA (and also present in pancreas islet cells)
- ~ 60% Stiff-person syndrome (> 20.0)
- 7% positive rate in normals (low level < 0.5)
- 100% type 1 diabetes (low level < 20.0)
- Autoimmune epilepsy (> 100) *personal experience*
- Limbic encephalopathy
- Autoimmune ataxia
- Antibody level is important

Autoimmune encephalopathy
UT Southwestern experience

- 64 cases in 6 years (>10 per year)

  likely an underestimate based on retrospective review

Antibody	number	Clinical Features	Cancer
No antibody	20	Immunotherapy responsive limbic encephalitis. Age range 5-66 yrs	25% (adenocarcinomas)
NMDA-R	16	More than half in children (median age 15) 50% with normal MRI	12% (ovarian teratomas)
VGKCc	9	7/9 male. Typical limbic features	40% (various)
Thyroid	9	"Hashimoto" cases, plus others	0
GAD-65	6	Memory loss and seizures (median age 40)	0
$GABA_B$	3		1 (SCLC)
Hu (ANNA-1)	1	Typical limbic encephalitis	Probable SCLC

Dubey et al. J Neuroimmunol 2015

Lessons learned about the misdiagnosis of autoimmune encephalitis

- **Functional / nonspecific symptoms represent a high proportion of misdiagnoses.**
- Psychiatric disorders (first psychosis) may be misclassified as autoimmune encephalitis.
- Non-immune neurological disorders misdiagnosed as autoimmune encephalitis.
- False positive or misinterpretation of antibody testing.

Alternative diagnoses	No (%)
Functional Neurological Disorder	**27 (25)**
Psychiatric Disorder	19 (18)
Neurodegenerative Disorder	22 (20.5)
Neoplasm	10 (9.5)
Seizure Disorder	5 (4.5)
Other Neurological Disorder	13 (12.5)
Nonspecific symptoms (fibromyalgia, medication effect, sleep disturbance)	**11 (10)**

Flanagan et al. Autoimmune Encephalitis Misdiagnosis in Adults. JAMA Neurol. 2023

Autoimmune neurology

- Wide diversity of clinical presentation
- Different antibodies are interpreted differently
- Clinicians need to consider immunopathophysiology to better select therapies

- Still clinically underrecognized?

Key advancements emerging trends

- **Ongoing autoantibody discovery**
  Accessibility and standardization of autoantibody testing
- **Understanding of disease mechanisms**
  Role of complement, Plasma cell regulation, immune tolerance
- **Successful Treatment trials**
  Particularly for Ab-mediated diseases like MG, NMOSD
- **New treatment modalities**
  CAR T-cell therapy, FcRN targeted treatments
- **Comprehensive multidisciplinary care**

Thank you

Dr. Div Dubey

- UT Southwestern neurology resident
- Fellowship training at Harvard and Mayo
- Mayo Rochester Autoimmune Neurologist
- Professor of Neurology / Laboratory Medicine
- Co-Director, Neuroimmunology Laboratory