

# Autoimmune Encephalitis

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# DISCLOSURE

## Relevant Financial Relationship(s)

Dr Flanagan has served on advisory boards for Alexion, Genentech and Horizon Therapeutics. He has received speaker honoraria from Pharmacy Times. He received royalties from UpToDate. Dr Flanagan was a site primary investigator in a randomized clinical trial on Inebilizumab in neuromyelitis optica spectrum disorder run by Medimmune/Viela-Bio/Horizon Therapeutics. Dr Flanagan has received funding from the NIH (R01NS113828). Dr Flanagan is a member of the medical advisory board of the MOG project. Dr Flanagan is an editorial board member of the Journal of the Neurological Sciences and Neuroimmunology Reports.

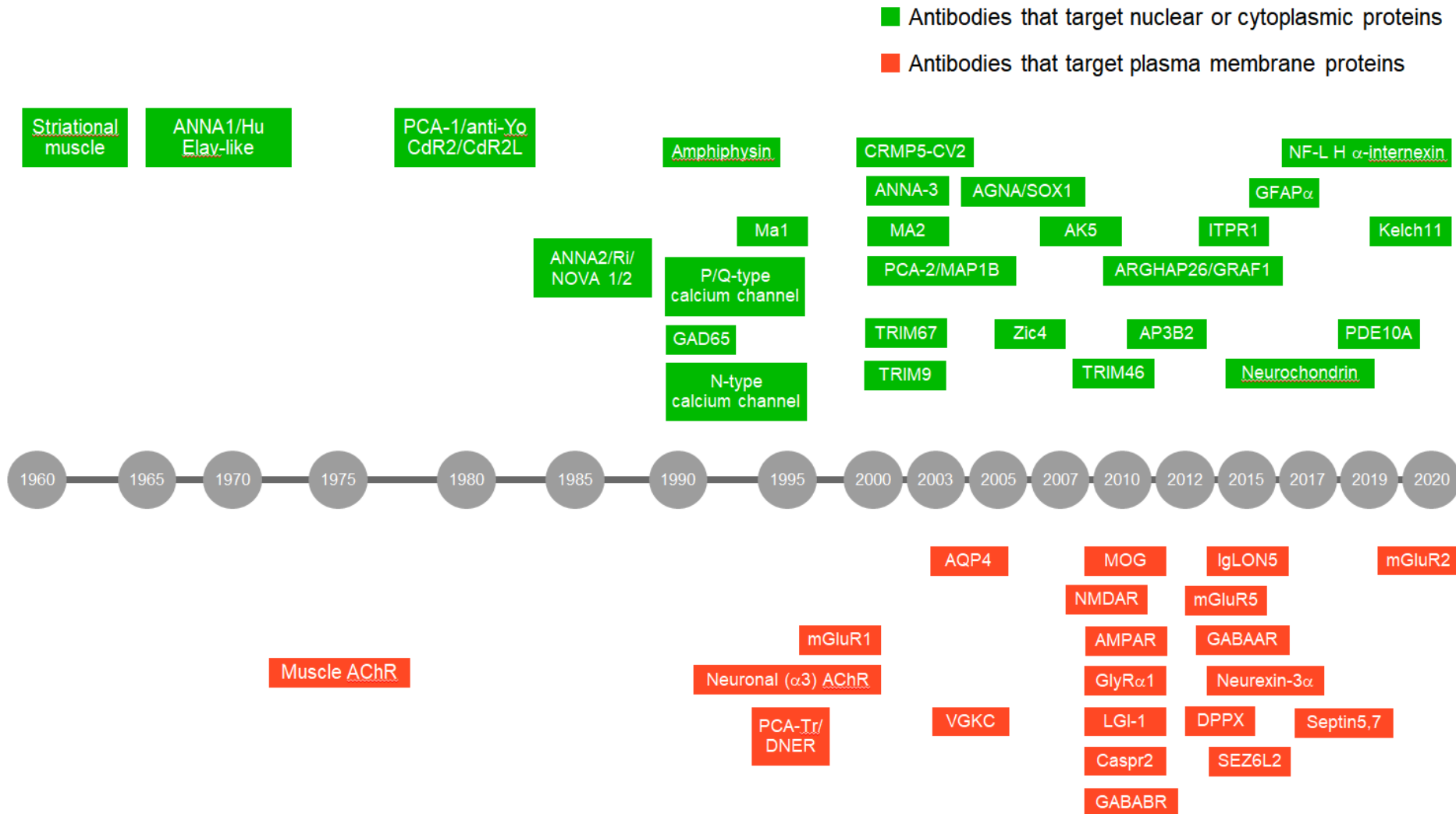
## Off Label Usage

I will discuss the off label use of a variety of immunotherapies

# Learning objectives

- Recognize the clinical manifestations of autoimmune encephalitis
- To have an appreciation of the mechanisms of neural antibody mediated autoimmune encephalitis
- To be aware of the novel settings in which autoimmune encephalitis is being encountered

# Huge Increase in Discovery of Neurologic Antibody Biomarkers in Past 20 years



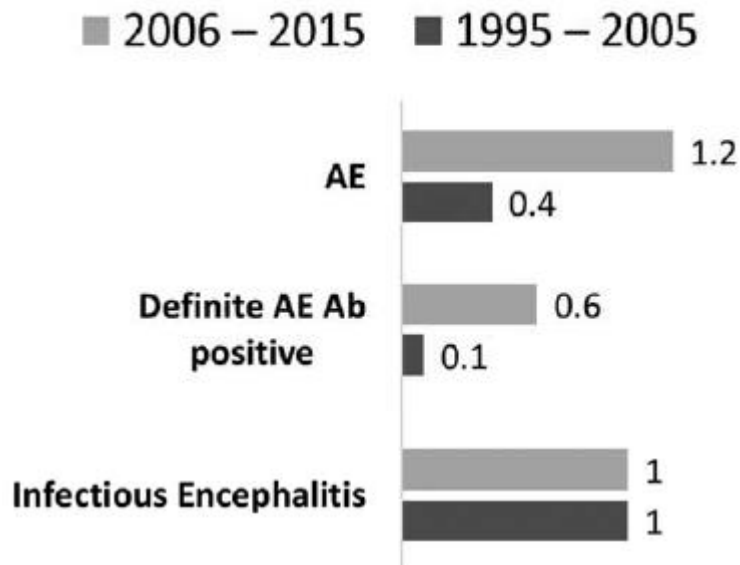
# Autoimmune Encephalitis Epidemiology and a Comparison to Infectious Encephalitis

Divyanshu Dubey, MD,<sup>1</sup> Sean J. Pittock, MD,<sup>1,2</sup> Cecilia R. Kelly, MD,<sup>1</sup>  
Andrew McKeon, MD,<sup>1,2</sup> Alfonso Sebastian Lopez-Chiriboga, MD,<sup>1</sup>  
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Sandra C. Bryant, MS,<sup>4</sup> Christopher J. Klein, MD,<sup>1,2</sup> Allen J. Aksamit, MD,<sup>1</sup>  
Michel Toledano, MD,<sup>1</sup> Bradley F. Boeve, MD,<sup>1</sup>  
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ANN NEUROL 2018;83:166–177

- Similar prevalence of autoimmune and infectious encephalitis (13.7 vs 11.6 per 100,000;  $p=0.63$ )\*

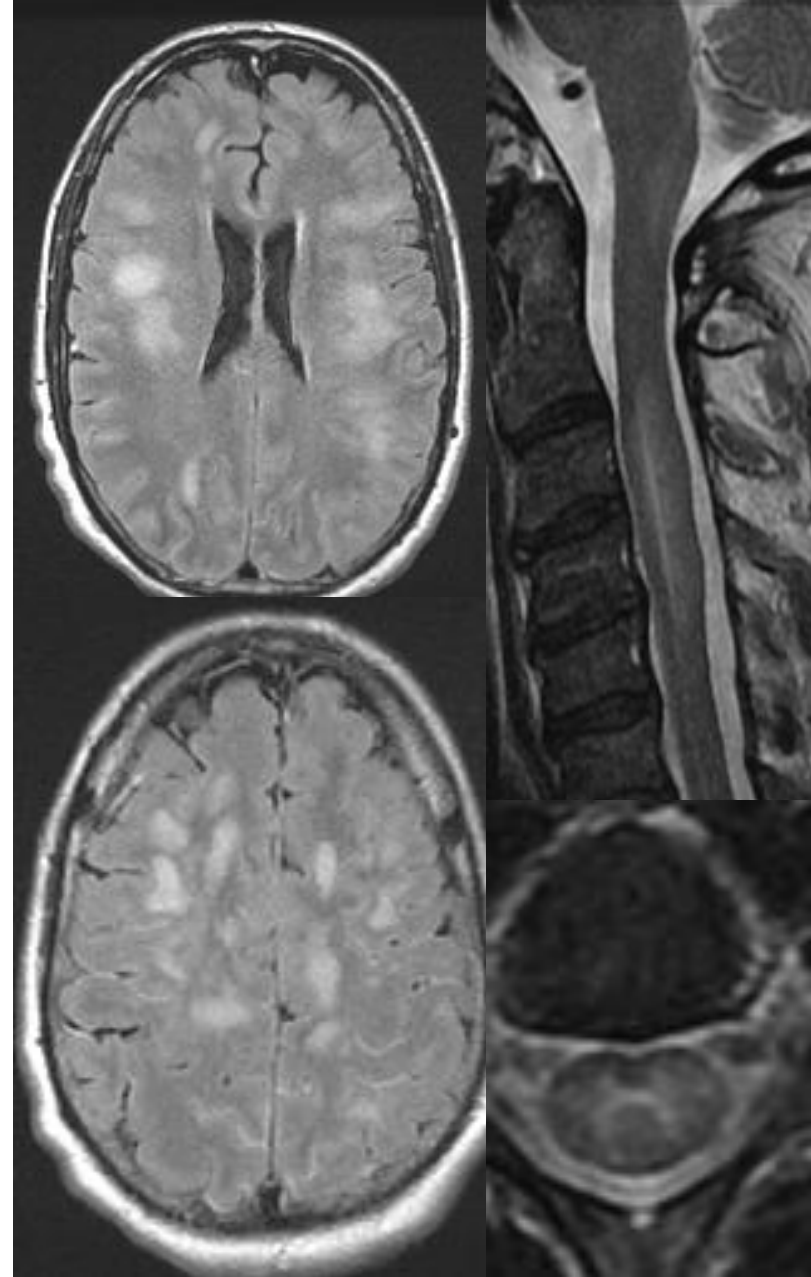
## Time trends in incidence:



*\*Next generation sequencing may change this  
Wilson et al. NEJM 2014*

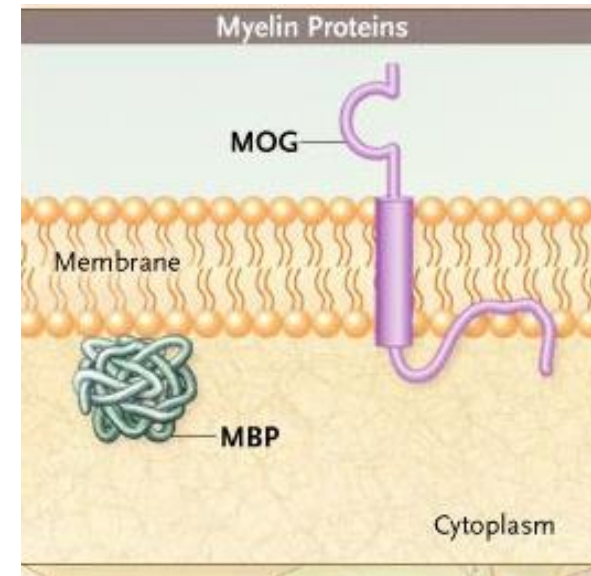
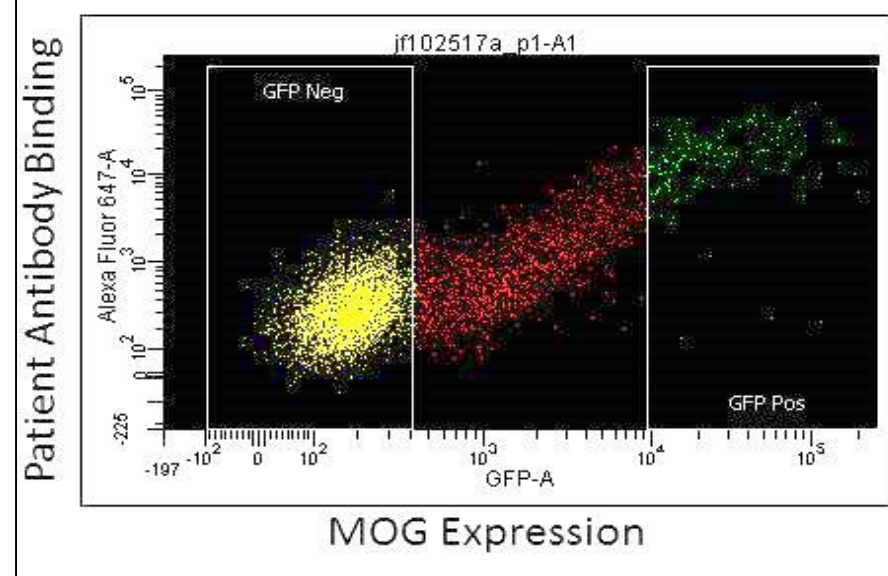
## Case 1: ADEM

- 47/M
- HPI & Exam
  - Viral prodrome
  - Subacute confusion, numbness & weakness, neurogenic bladder
  - Progressed to coma & quadriplegia
- CSF: WBC 139; Protein 109; OCB neg; No infection

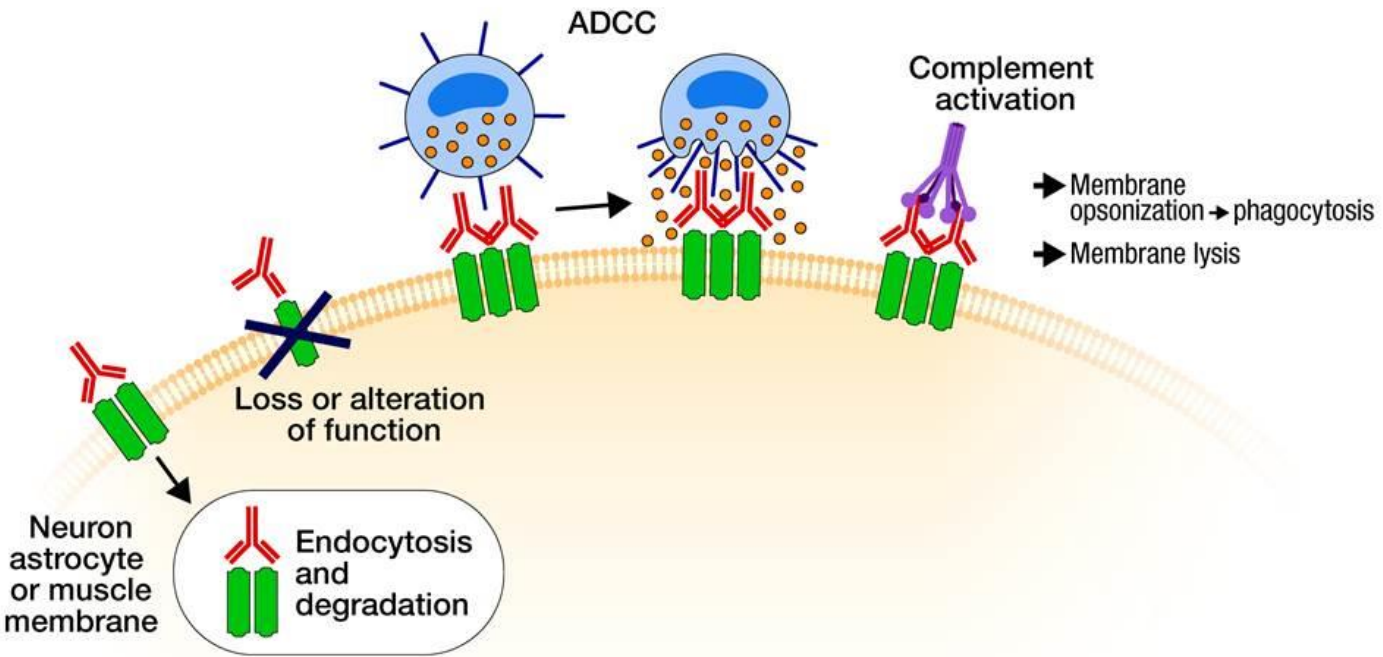


## Case 1: ADEM

- Brain biopsy - ADEM
- Serum MOG-IgG (+)
- **Diagnosis: MOG antibody associated disease**
- **Rx:** IV steroids & PLEX
  - 3 months later he was normal
  - Relapsed with optic neuritis
  - Azathioprine added



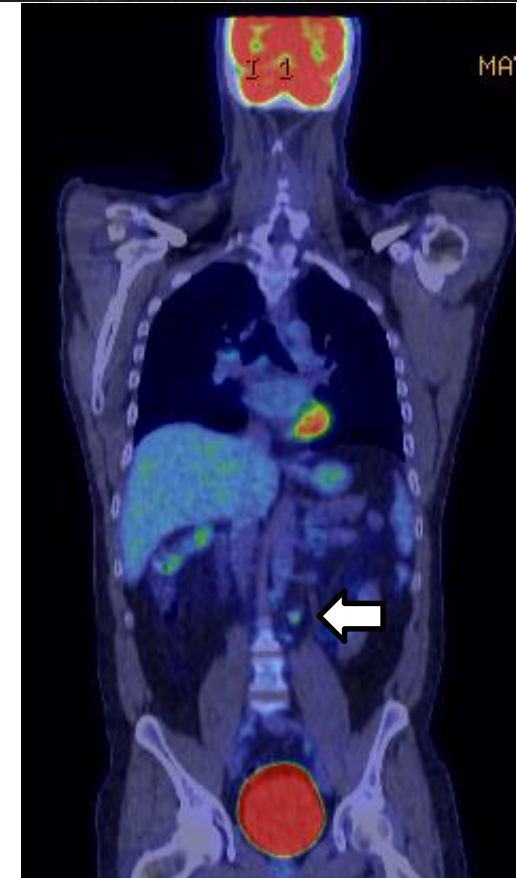
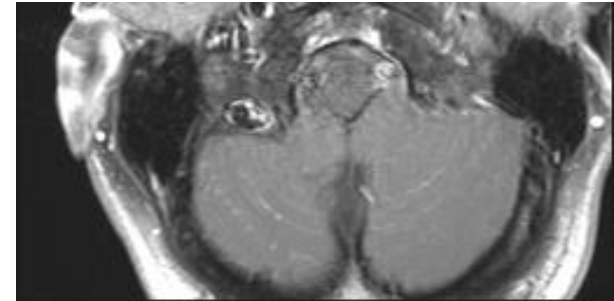
# Antibodies targeting synapses (eg, NMDAR)



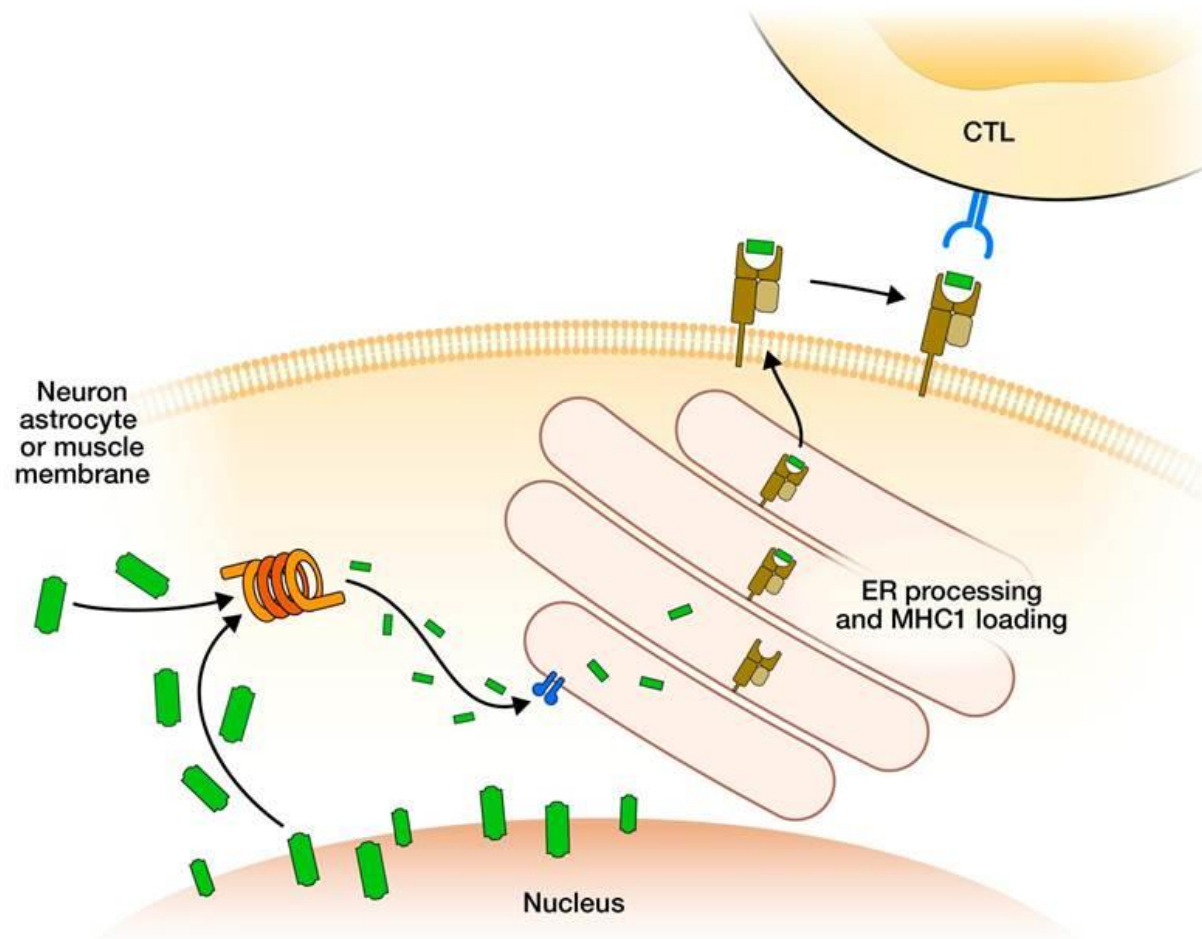


## Case 2: Subacute progressive ataxia

- 41/M with Subacute ataxia; wheelchair dependent
- CSF: WBC 71; protein 85; pos ocb
- Serum & CSF: Kelch-like protein-11
- PET/CT - Abnormal
- Biopsy: Metastatic seminoma
- Chemotherapy – bleomycin, etoposide, cisplatin
- Immunotherapy: steroids, PLEX, cyclophosphamide & rituximab but no clinical improvement



# Antibodies to intracellular antigens (eg, PCA-1/anti-Yo)



# A clinical approach to diagnosis of autoimmune encephalitis

Francesc Graus, Maarten J Titulaer, Ramani Balu, Susanne Benseler, Christian G Bien, Tania Cellucci, Irene Cortese, Russell C Dale, Jeffrey M Gelfand, Michael Geschwind, Carol A Glaser, Jerome Honnorat, Romana Höftberger, Takahiro Iizuka, Sarosh R Irani, Eric Lancaster, Frank Leypoldt, Harald Prüss, Alexander Rae-Grant, Markus Reindl, Myrna R Rosenfeld, Kevin Rostásy, Albert Saiz, Arun Venkatesan, Angela Vincent, Klaus-Peter Wandinger, Patrick Waters, Josep Dalmau

Lancet Neurol 2016; 15: 391-404

## 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<sup>3</sup>)
  - MRI features suggestive of encephalitis†
- 3 Reasonable exclusion of alternative causes (appendix)

# How to recognize autoimmune encephalitis

- **Prodrome/preceding infections**
  - Viral syndrome (MOG, others)
  - HSV encephalitis (NMDAR)
  - Weight loss ( $\approx 20$  Kg)/diarrhea (DPPX)
- **Clinical phenotype**
  - Subacute & rapid progression
    - Dementia, encephalopathy
  - Seizures
  - Multi-focal (CNS, PNS, autonomic, NMJ)

*Waters & Reindl. Nat Rev Neurol, 2019*

*Armangue et al. Lancet Neurol*

*Tobin et al. Neurol 2014*

*Hara et al. Neurol 2017*

## Other aspects on history & exam

- **Sleep disorders** (IgLON5 [parasomnia]; Ma2 [narcolepsy/cataplexy]; insomnia – Morvan's; laryngospasm – ANNA-2/Ri)
- **Hearing loss** (Kelch 11) – differential includes vasculitis, susacs, mitochondrial dx
- **PMHx:** Prior cancer; Hx of autoimmunity; transplant
- **Medications** (checkpoint inhibitors, CART)
- **Smoking history** (lung cancer risk)
- **FHx:** autoimmunity (systemic, neurologic)
- **Exam:** Quantify deficit with cognitive testing

# Demographics: Children

- ADEM
  - MOG (30-50%)
  - Aquaporin-4 (5%)
  - GABA<sub>A</sub>R: MRI is ADEM-like (thymoma)
- Psychosis, limbic encephalitis, status epilepticus, post HSV encephalitis
  - NMDAR (teratoma)
- Opsoclonus-myoclonus
  - ANNA-1/Hu  
(neuroblastoma)

*Hacohen et al. JAMA Neurol 2018*  
*McKeon et al. Neurology 2008*  
*Spatola et al. Neurology 2017*  
*Dalmau et al. Lancet Neurol 2008*  
*Berridge et al. Neurology 2018*  
*Lucchinetti et al. Neurology 1998*  
*Klaas et al. Arch Neurol 2012*

# **Characteristic clinical syndromes**

# Facio-brachial Dystonic Seizures (LGI1)



*Irani et al. Ann Neurol 2011*  
*Thompson et al. Brain 2018*



# Opsclonus-Myoclonus (ANNA-2/Ri-adults; ANNA-1: children)

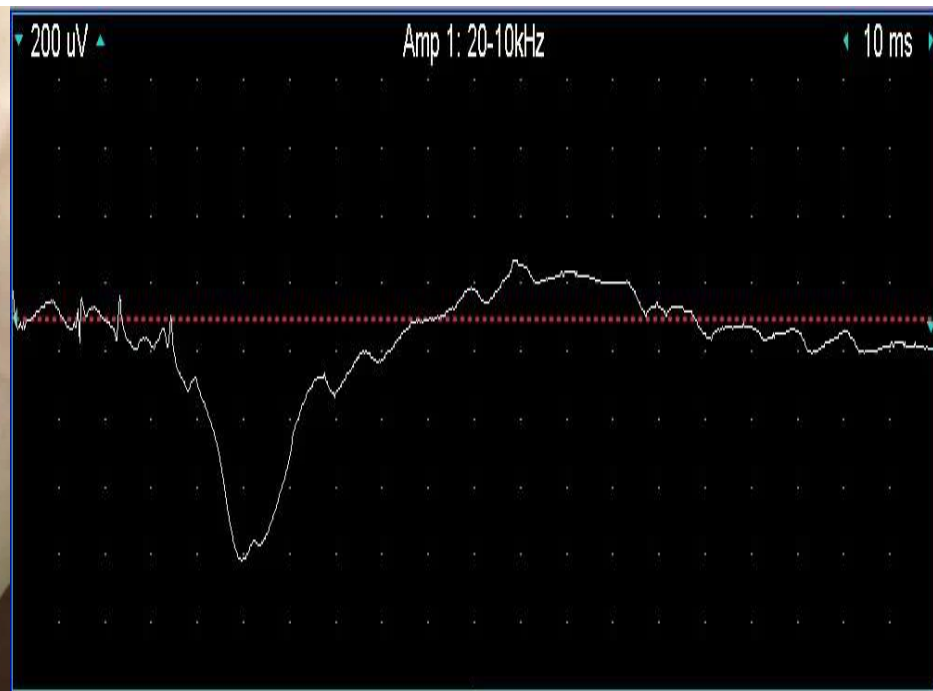
Patient 20

March 2011

# Morvan's syndrome (Caspr2)

- Encephalopathy
- Insomnia
- Hyperhidrosis
- **Peripheral nerve hyperexcitability**

Video provided by  
Dr Christopher Klein



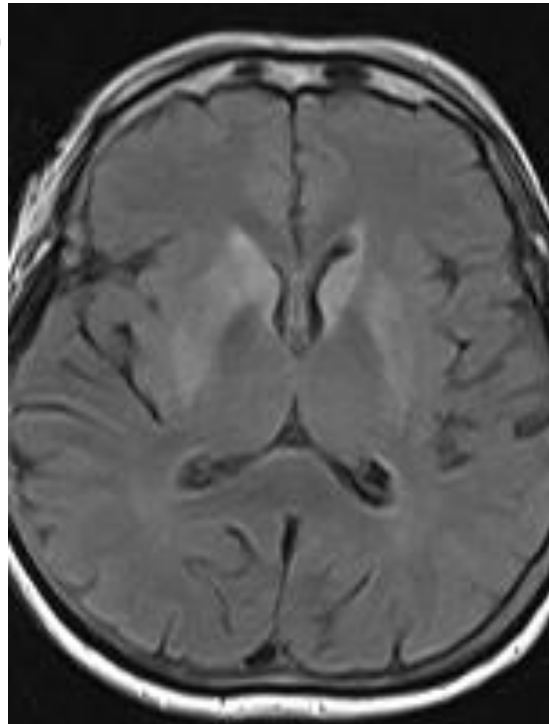
*Irani et al. Brain 2010*  
*Gadoth et al. Ann Neurol 2017*

# Dyskinesia's (eg, NMDAR)



# Hyperkinetic movement disorders

- Jaw Dystonia (ANNA-2)
- Chorea (CRMP5/anti-CV2, phospholipid/lupus anticoag, PDE10A, D2R)



*Pittock et al. Arch Neurol 2010*  
*O'Toole et al. Neurology 2013*  
*Zekeridou et al. Platform AAN Mon 5/6/19*  
*Vernino et al. Ann Neurol 2002*

# Ataxia

- Progressive (PCA1/antiYo; mGluR1, GAD65, Kelch-like protein-11)
- **Episodic (Caspr2)**

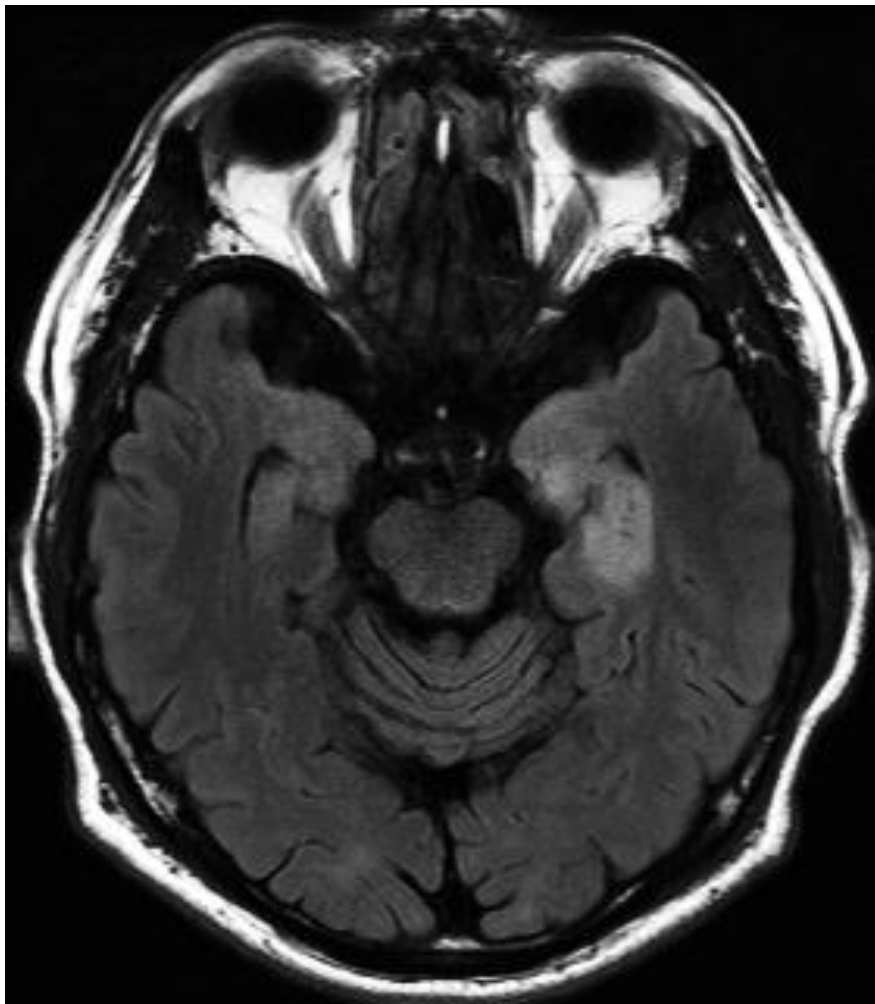


*McKeon et al. Arch Neurol 2011*  
*Lopez-Chiriboga et al. Neurology 2016*  
*Joubert et al. N2 2017*

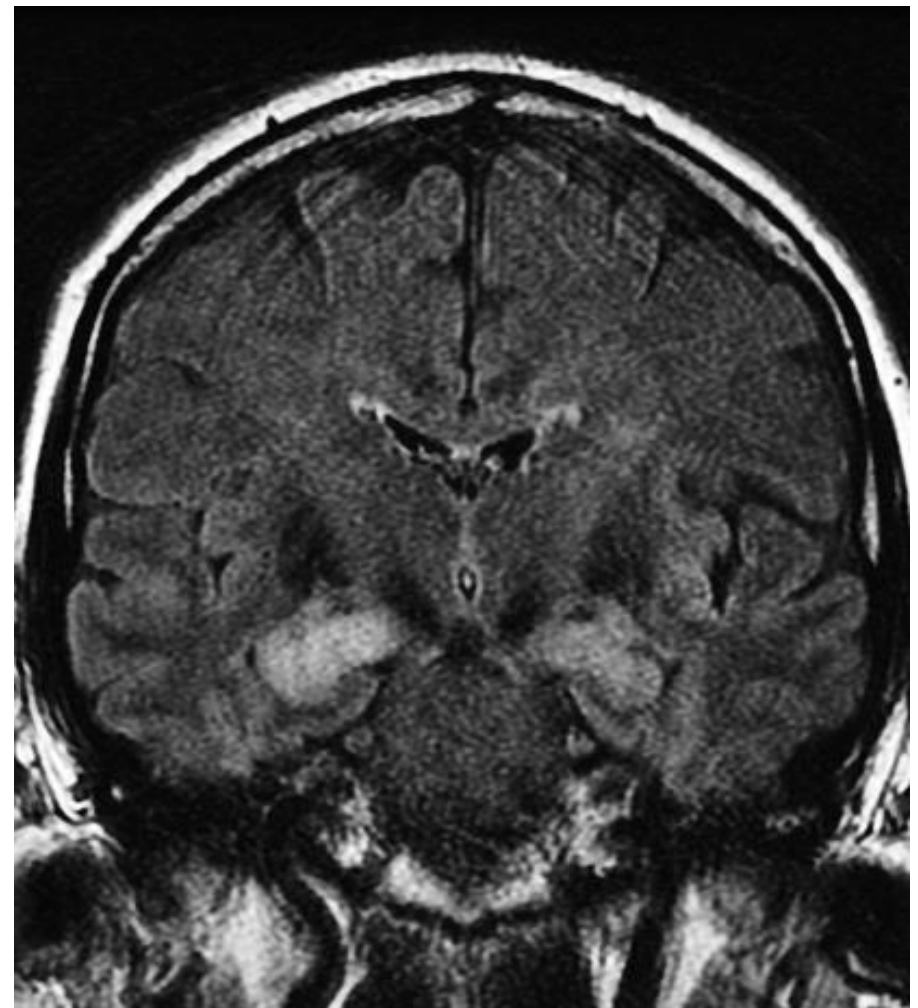
# Investigations

# MRI: Limbic Encephalitis (many antibodies)

Unilateral: LGI1 example

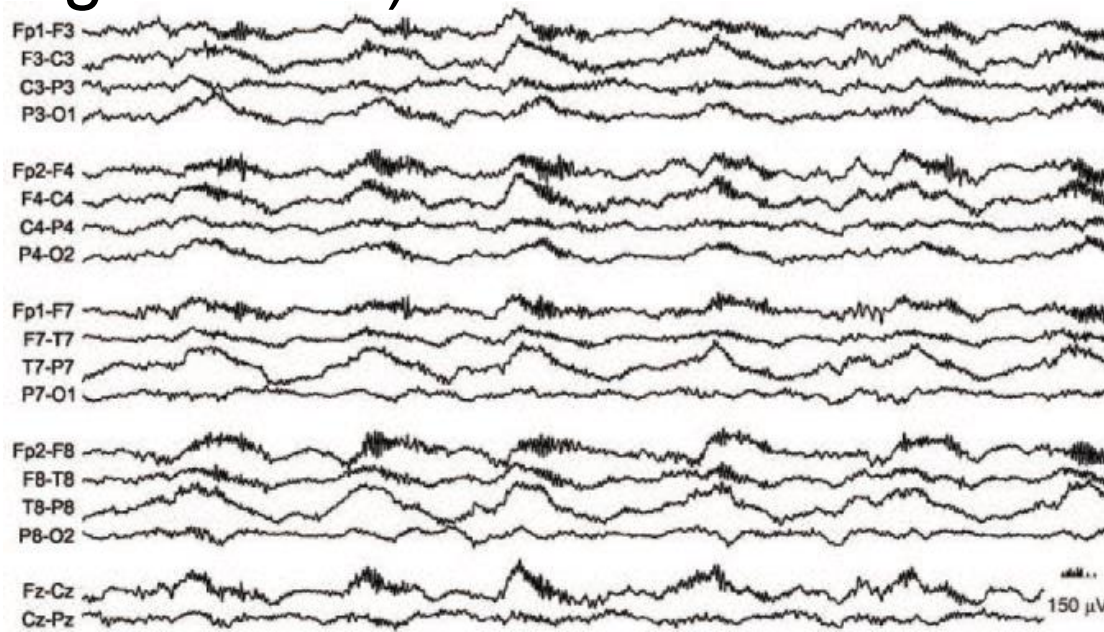


Bilateral: GABA<sub>B</sub> example



# EEG pearls in Autoimmune Encephalitis

- Epileptiform activity (sharp waves, spikes, Sz) help suggest autoimmune over degenerative
- FBDS often have no EEG correlate
- Extreme delta brush suggestive of NMDA (not pathognomonic)

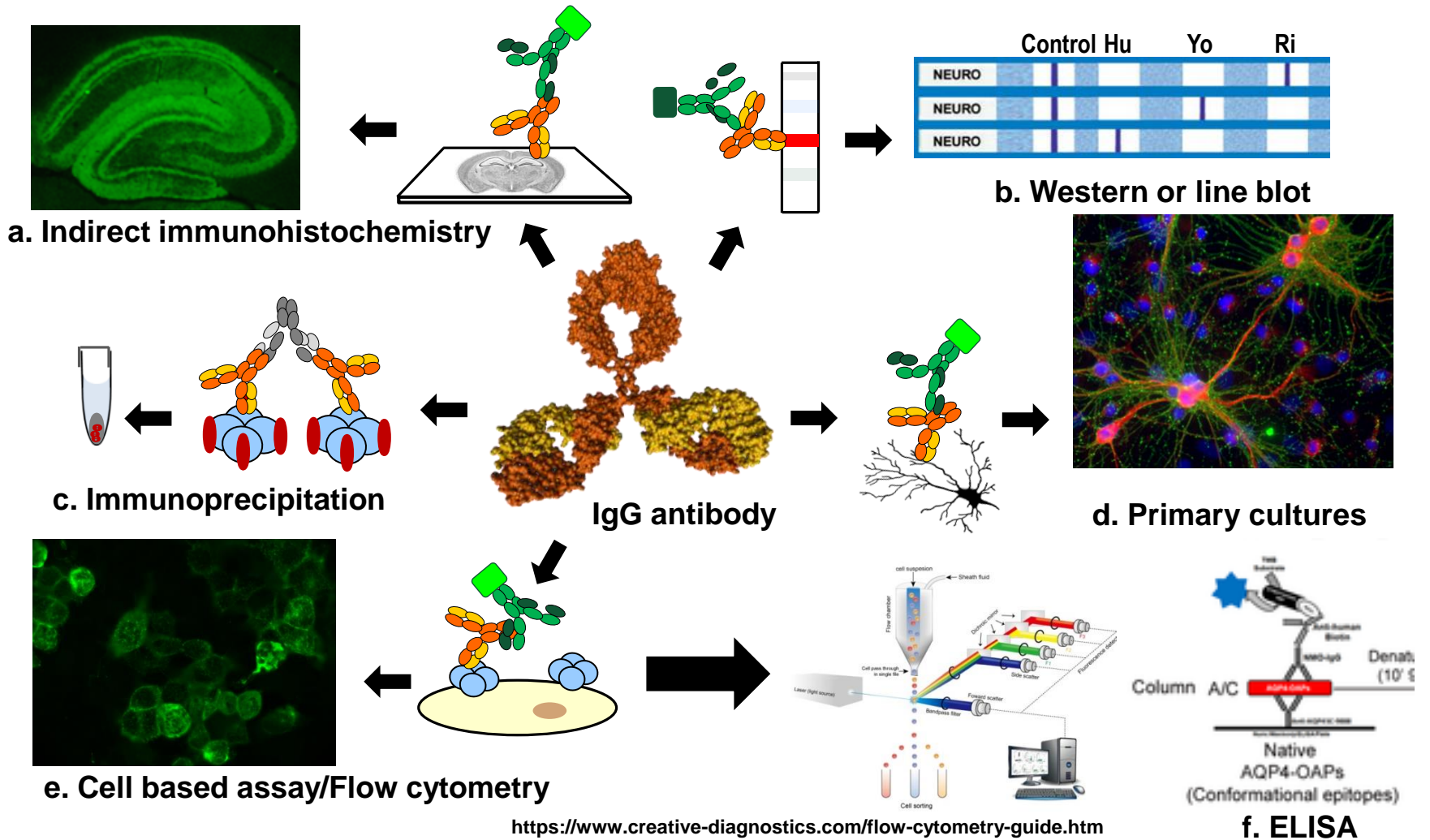




# Cerebrospinal Fluid (CSF) Analysis

- **Assess for inflammation**
  - ↑White blood cell count
  - ↑Oligoclonal bands/IgG index
- **Assess for alternative etiologies**
  - Infections (eg, HSV PCR)
  - Neoplasms/lymphoma (cytology)
- **Antibody testing**

# Neural Antibody Testing Methodology



# Neural Antibody testing (if available)

- **One antibody or a panel?**
  - For most (eg, limbic encephalitis) panel best
- **Serum or CSF?**
  - Better in CSF (NMDA-R, GFAP)
  - Better in serum (AQP4, MOG, LGI1)
- **Repeat & serial testing?**
  - Serial samples rarely useful; follow clinically
- **Pitfalls**
  - Some antibodies common in general population (e.g., TPO antibodies in 20%)

# Searching for cancer

- CT body
- Ultrasound ovaries/testicles (eg, NMDA)
- Rpt images 6 monthly if high risk antibody

# Treatment of autoimmune encephalitis

- IV methylprednisolone 1 g/day x 5 days  
(oral prednisone 1250 mg daily x 5 days)
- Follow with weekly x 6-12 weeks or oral steroid taper

## **For antibodies to cell surface antigens**

- IVIg or PLEX (if available)
- Rituximab (if available)

## **For antibodies to intracellular antigens**

- Cyclophosphamide

## **If cancer identified**

- Treat underlying tumor (e.g., teratoma resection)

# **Autoimmune Encephalitis in a Novel Setting**

# Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis

*Tháis Armangue, Marianna Spatola, Alexandru Vlăgea, Simone Mattozzi, Marc Cárceles-Cordon, Eloy Martínez-Heras, Sara Llufrí, Jordi Muchart, María Elena Erro, Laura Abreira, German Moris, Luis Monros-Giménez, Íñigo Corral-Corral, Carmen Montejo, Manuel Toledo, Luis Bataller, Gabriela Secondi, Helena Ariño, Eugenia Martínez-Hernández, Manel Juan, Maria Angeles Marcos, Laia Alsina, Albert Saiz, Myrna R Rosenfeld, Francesc Graus, Josep Dalmau, on behalf of the Spanish Herpes Simplex Encephalitis Study Group\**

*Lancet Neurol 2018; 17: 760-72*

- Autoimmune encephalitis after HSV encephalitis in 27% (NMDA>other antibodies)
- Occurs 1-3 months after HSV encephalitis onset
- Children choreo-athetosis, seizures & poor prognosis
- Adults present with psychosis & respond to treatment

# Conclusions

- Clinical clues can aid autoimmune encephalitis diagnosis
- Antibody testing is useful and its target can help determine cancer risk, treatment and prognosis
- Autoimmune encephalitis is now occurring in novel settings



# Acknowledgement:

