*World congress Neurology 2013*

# *Autoimmune Neurology of the CNS*

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# DISCLOSURE

**Dr. Pittock receives no royalties from the sale of tests performed in the Neuroimmunology Laboratory at Mayo Clinic; however, Mayo Collaborative Services Inc. does receive revenue for conducting these.**

**Mayo Clinic and Dr. Pittock have a financial interest in technology associated with:**

1. **"Aquaporin-4 AutoAntibody as a Cancer Marker".**
2. **"Aquaporin-4 Binding Autoantibodies in Patients with Neuromyelitis Optica Impair Glutamate Transport by Down-Regulating EAAT2."**
3. "Peripherin-Specific Autoantibodies as a Marker for Neurological and Endocrinological Disease"

**Dr. Pittock receives research support from Alexion Pharmaceutical, Inc., the Guthy-Jackson Charitable Foundation, and the National Institutes of Health (NS065829).**

**Dr. Pittock has provided consultation to Alexion Pharmaceutical, MedImmune LLC, and Chugai Pharma, but has received no personal fees or compensation for these consulting activities. All compensation for consulting activities is paid directly to Mayo Clinic.**

**<u>Off Label Usage</u>**

- **I will mention use of a variety of immunotherapies.**

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Hypothalamus

Cerebellum

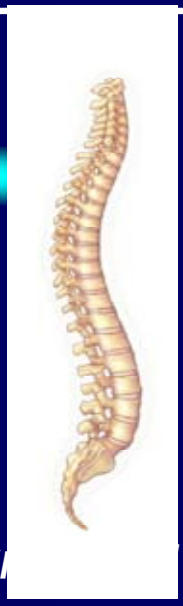
Basal ganglia

Brain stem

Cortex

Optic nerve/retina

# Autoimmune neurology



*Peripheral nervous system*

*Sp*

Neuromuscular junction

Autonomic

Somatic

Muscle

Spinal cord

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# Outline

- What are Autoimmune Neurological Disorders?
- How do patients present?
- Why do they occur?
- How do I evaluate further?
    - Basic serum/CSF testing
    - Neural antibody (Ab) testing
    - Treatment trial in suspected cases ‘The diagnostic test’

# Autoimmune Neurological Disorders

- Nervous system disorders caused by *aberrant immune response* to self antigen
- May be *paraneoplastic, parainfectious or idiopathic*
- Often unified by *Ab marker* detected in serum or cerebrospinal fluid (CSF)

# How do patients present?

- Subacute onset symptoms
- Fluctuating course
- Can affect any neurological domain
- Often multifocal
- Think rostrocaudal

# What are the risk factors?

- Occur in all age groups
- Occur in women and men
- Coexisting autoimmune disease, e.g. thyroid disease, type 1 diabetes mellitus
- Smoking history
- Family history of autoimmune disease or cancer

# How do I evaluate further?

- Determine extent of neurological involvement:
  - Neurological examination
  - Mental status testing
  - Neuropsychometric testing
  - MRI imaging
  - Electrophysiology (EEG, EMG, SSEPs)

# How do I evaluate further?

- ***Ab testing, serum***:

  - **Non-neural Abs: e.g. thyroid peroxidase Abs, connective tissue cascade**

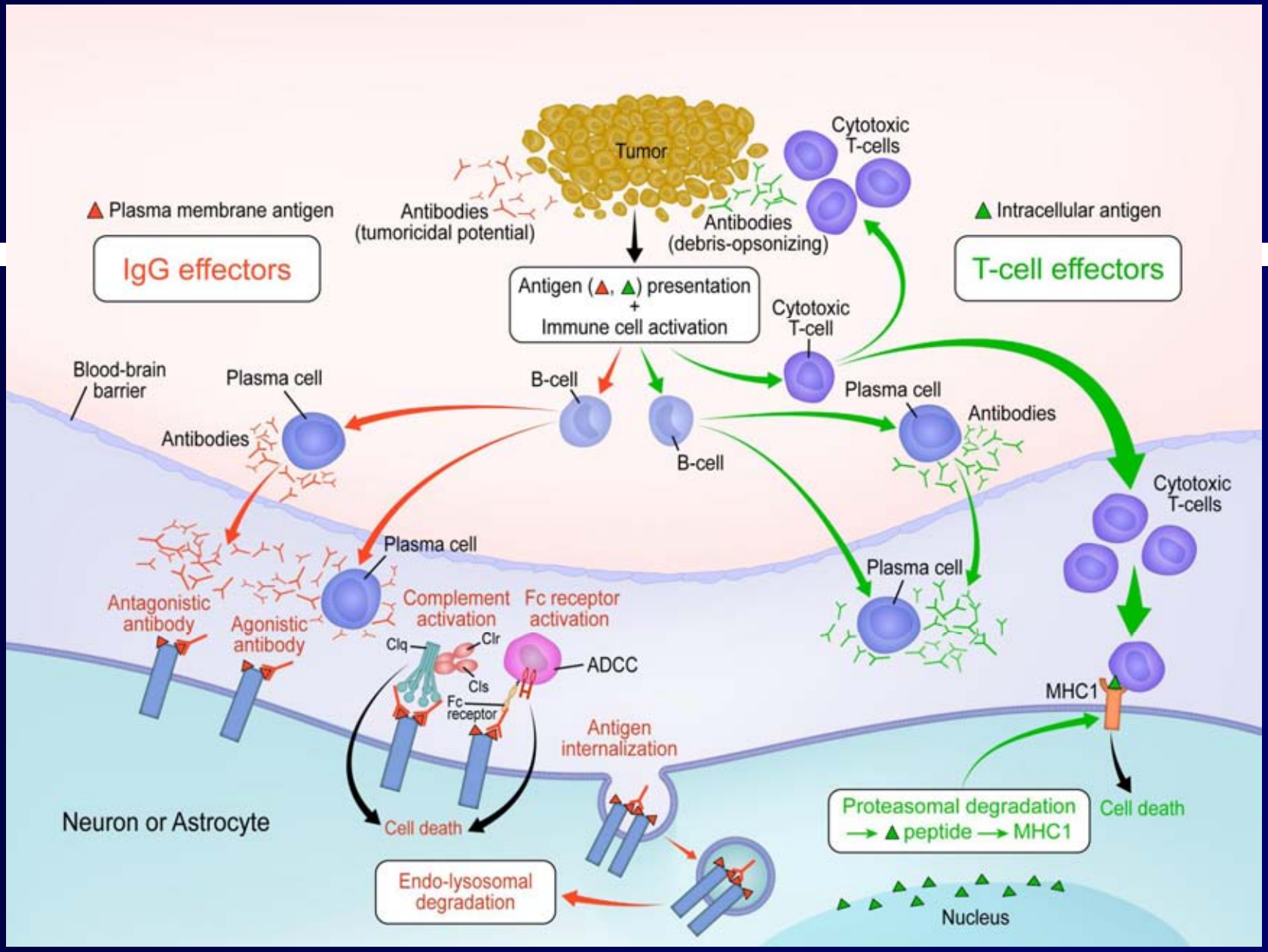
  - **Neural Abs: main subject of this talk**

- **CSF testing: protein, white cell count, IgG index and synthesis rate, oligoclonal bands, neural Abs**

# Neural Autoantibodies and Cancer

| | |
|---|---|
| ***Lung*** | **ANNA-1 (Hu),2 (Ri),3, CRMP-5 (CV2), amphiphysin, PCA 2, striational, recoverin, Zic4, VGCC (N-type and P/Q-type),VGKC comlex, ganglionic/muscle AChR, AGNA, Ma2, GABAB, AMPAR, NMO-IgG** |
| ***Thymoma*** | **Muscle/ganglionic AChR, striational, GAD65, CRMP-5, VGKC, ANNA-1, GABAB, AMPAR** |
| ***Breast*** | **ANNA-2, amphiphysin, VGCC (N-type), muscle AChR, VGKC complex, Ma, NMO-IgG AMPAR,** |
| ***Ovarian/ Mullerian duct*** | **PCA-1(Yo), VGCC (N-type > P/Q type), muscle AChR, NMDAR (teratoma)** |
| ***Testicular*** | **Ta-Ma2** |
| ***Hodgkin's lymphoma*** | **PCA-Tr** |
| ***Neuroblastoma*** | **ANNA-1, muscle AChR, VGCC (N-type), striational** |

# Why do autoimmune neurological diseases occur?

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***McKeon & Pittock, Acta Neuropath 2011***

# Neural Abs Overview

IgG Antibodies targeting

Neural cell surface antigens

(ion channels, receptors, synapses)

e.g. VGKC complex Ab, NMDA-R Ab, gAChR

Immunotherapy

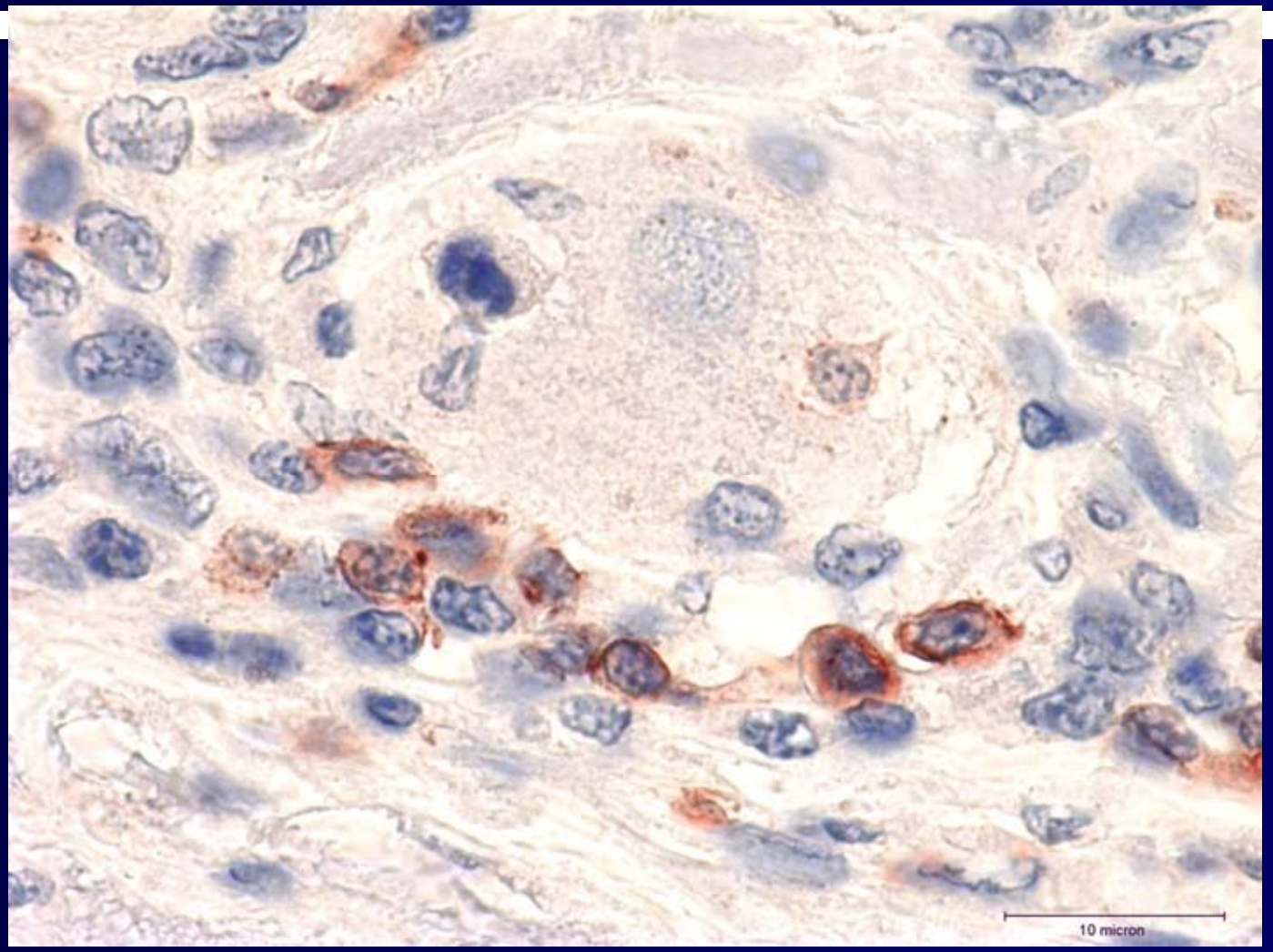
Neuronal nuclear, cytoplasmic antigens

e.g. ANNA-1 (hu), PCA-1CRMP-5 IgG

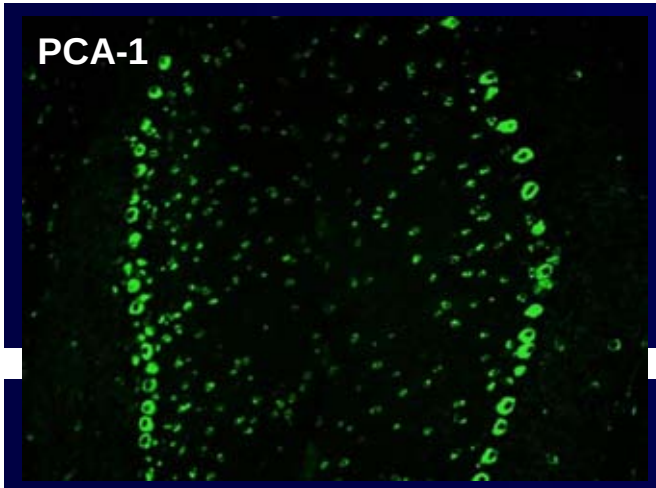
Oncological therapy

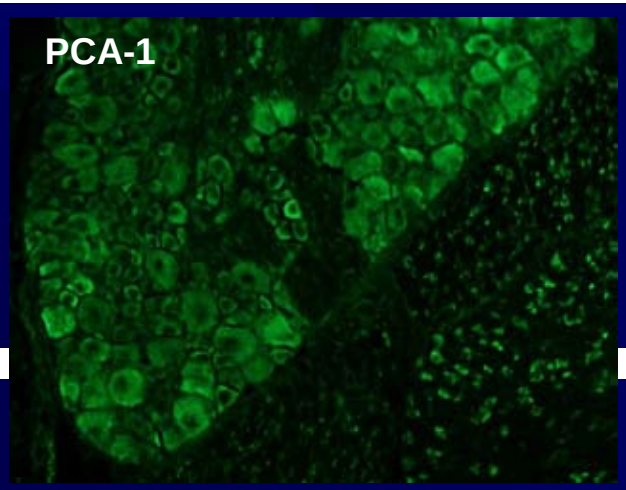
# *Cytotoxic T Cell Killing?*

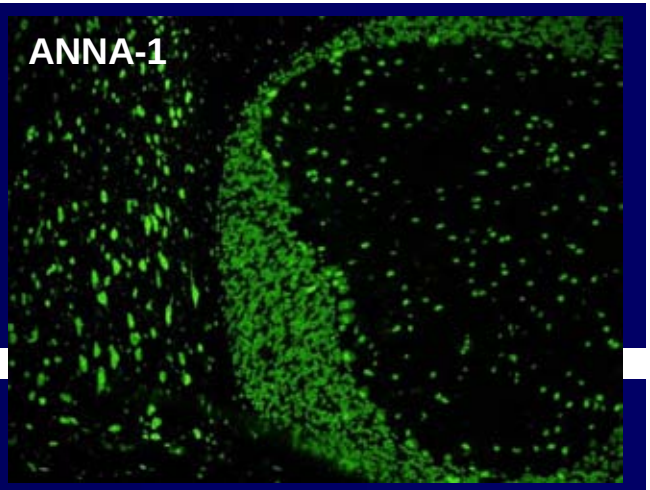
**CD8+ T-cells**



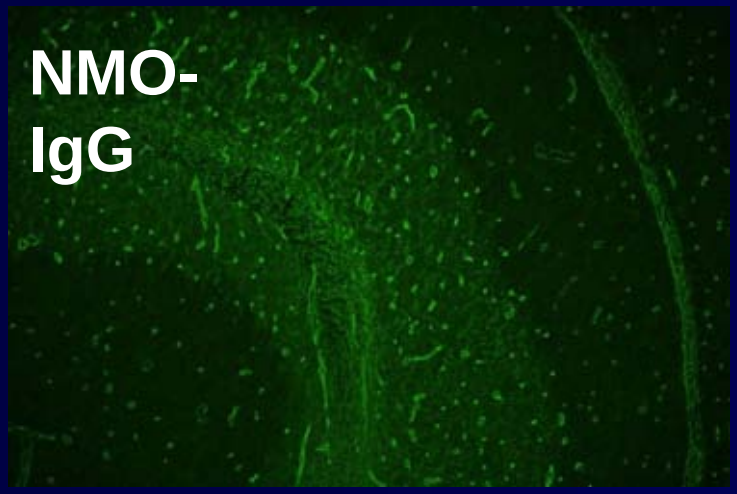
# How Are Patients Evaluated in the Laboratory?

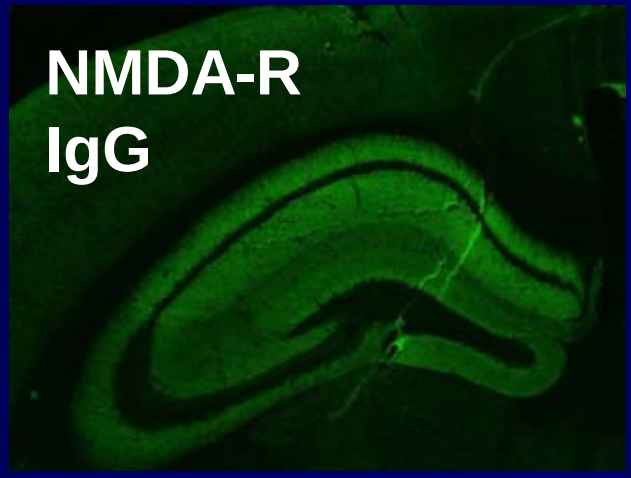



## Tissue-based Immunofluorescence

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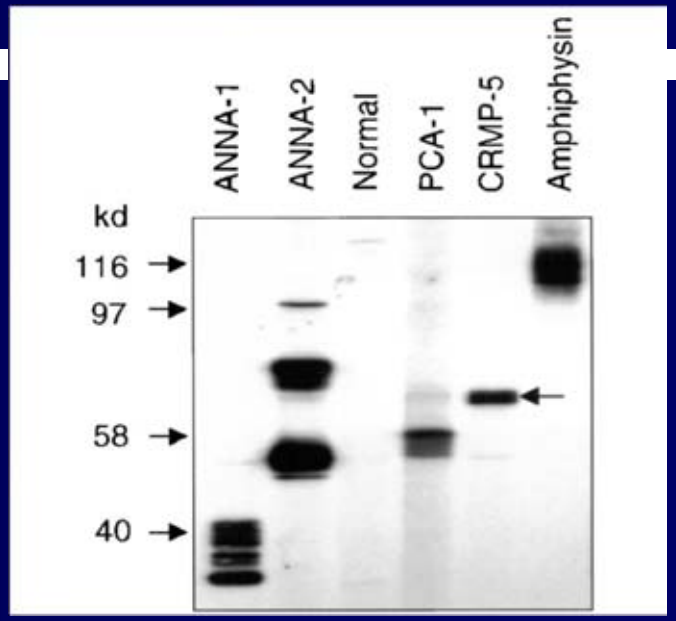
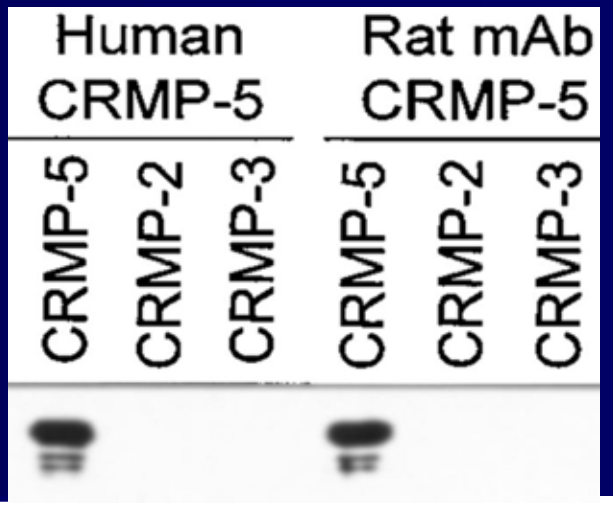
# Western blot

Western blot




*Yu, Kryzer Ann Neurol 2001*

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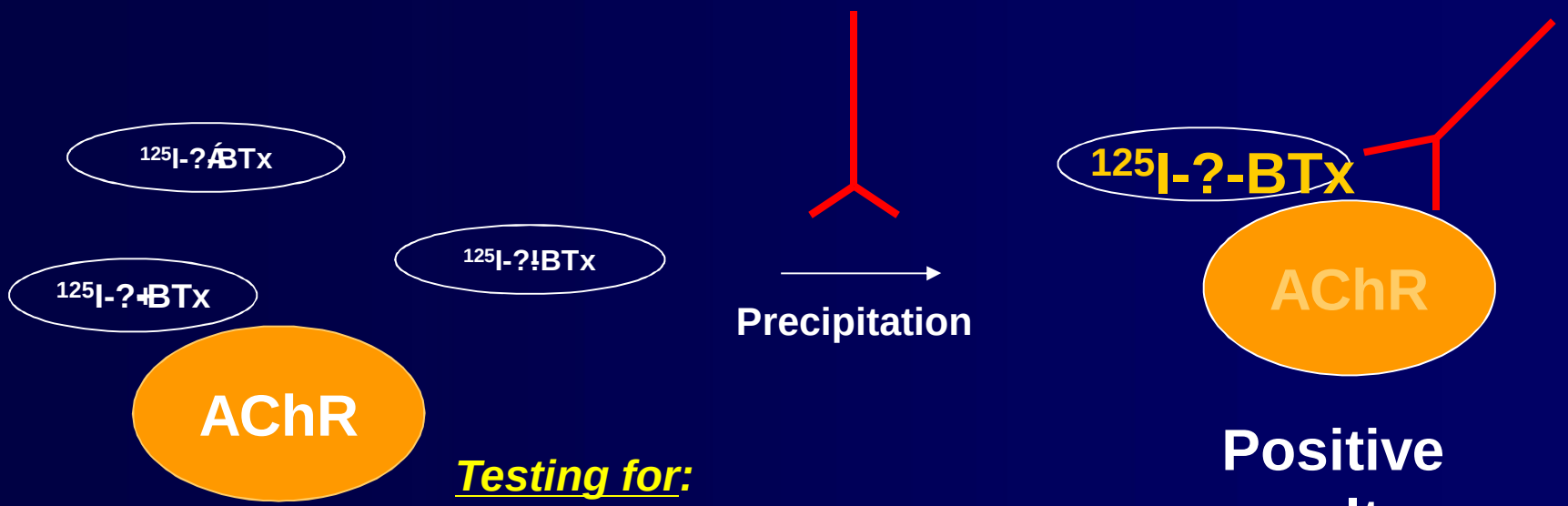
# Immunoprecipitation

## Auto Ab to AChR




Positive result

***Testing for:***

- Muscle AChR Abs
- Neuronal AChR Abs (?3)
- Calcium channel Abs (N or P/Q types)
- VGKC complex Abs
- GAD65 Ab

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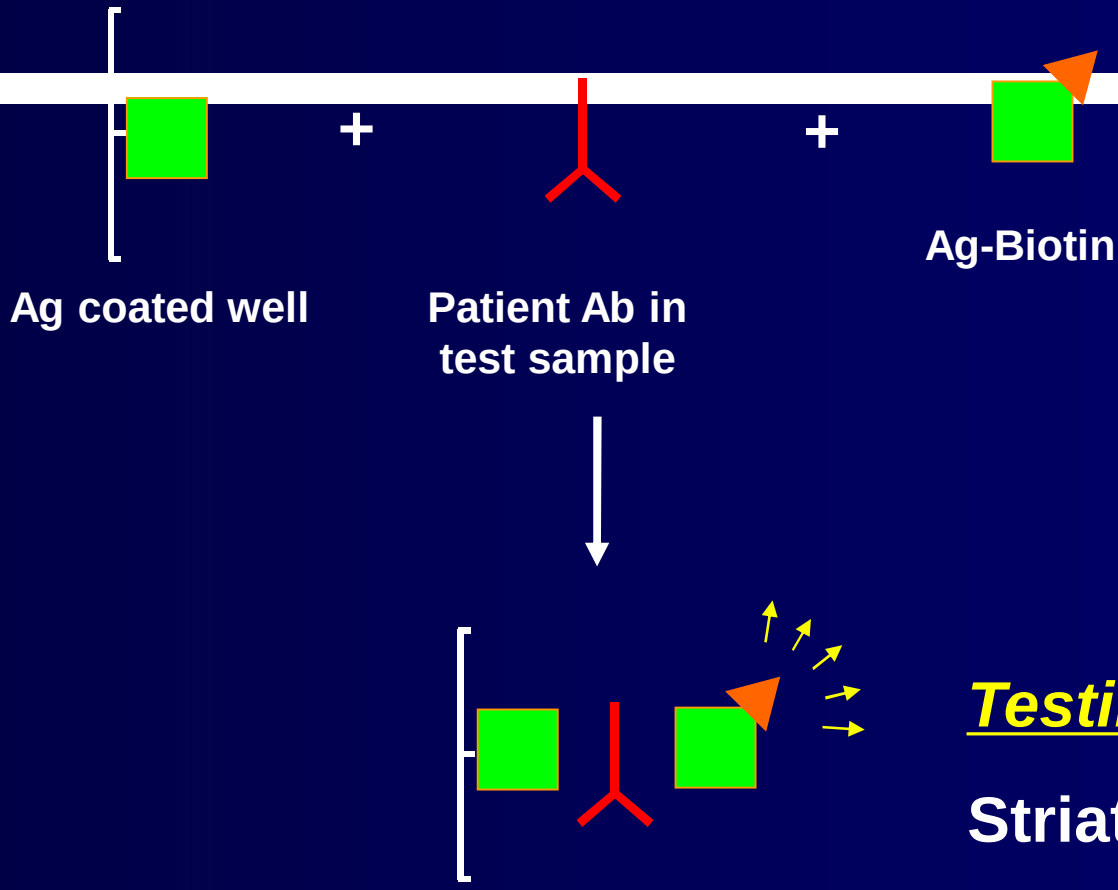
# ELISA



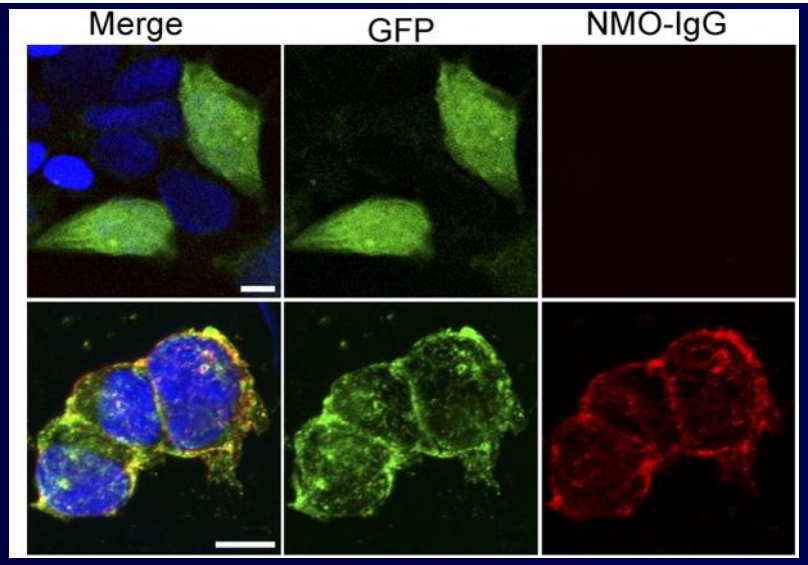

***Testing for:***

**Striational Abs**

**AQP4-IgG**

**Detect Ag-Biotin bound by addition of streptavidin peroxidase and colorogenic substrate.**

# Cell-based Immunofluorescence




*Lennon et al J Exp Med 2005*

**HEK-293 cells transfected with GFP-tagged aquaporin-4**

***Testing for:***

**AQP4-IgG (NMO-IgG)**

**NMDA-R Ab**

**AMPA-R Ab**

**GABA-B R Ab**

**Glycine receptor Ab**

# Some Examples of Autoimmune Neurological Disorders

# In general…

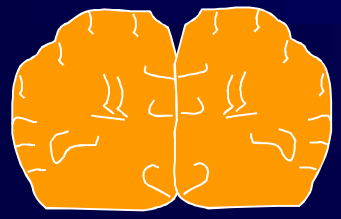
- Some neurological contexts are classic

**BUT**

- Neural Abs are detected in diverse neurological contexts
- Neurological disorders are often multifocal
- Cancer positive predictive values vary
- Ab profiles are informative of cancer type

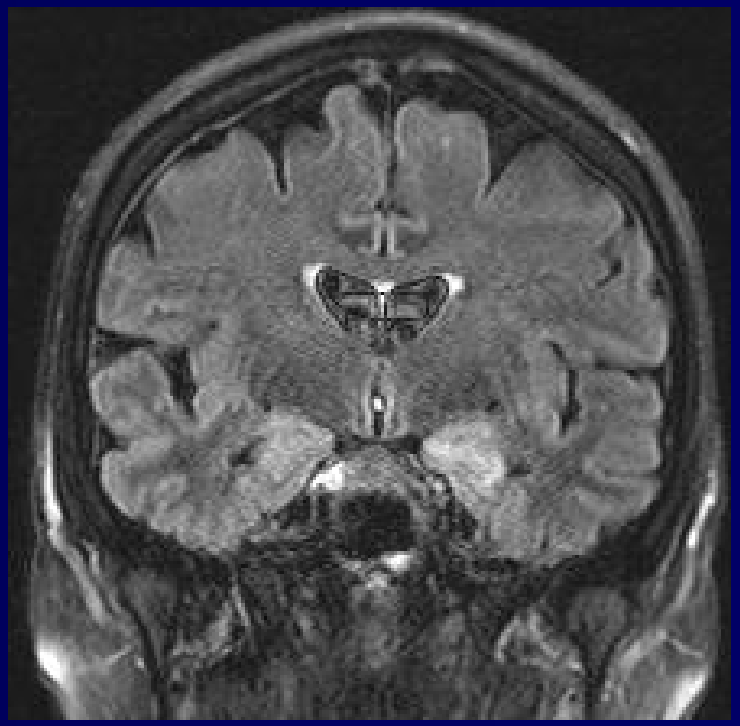
# Changing concepts

- ANNA-2 (anti-Ri) is *not* most frequently associated with Opsoclonus Myoclonus
  - Opsoclonus/myoclonus in 32%
    - Multifocal neurological disorder in most
- Amphiphysin-IgG is *not* most frequently associated with Stiff Man Syndrome
  - Stiff man, 6% Stiff limb, 16%;
  - Neuropathy, 50%; Encephalopathy, 24%; Myelopathy, 19%; Cerebellar syndrome, 15%
- CRMP5-IgG is *not* uncommon
  - CRMP-5=ANNA-1(Hu)>PCA-1(Yo)>PCA-2>Amphiphysin>ANNA-2(Ri)>ANNA-3
- Gad 65-IgG is *not* most frequently associated with Stiff man Syndrome
  - Stiff limb 26%; Stiff man syndrome 3%
  - Cerebellar ataxia 63%; Brainstem syndrome 29%; Seizures/encephalopathy 31%;
  - Myelopathy 8%; Extrapyramidal (parkinsonism) 16%;
- VGKC Complex-IgG is *not* most frequently associated with Morvan's syndrome or Isaac syndrome
  - Morvan syndrome <1%; Isaac syndrome/PN hyperexcitability 15%;
  - Dysautonomia 30%; Cognitive impairment 20%; neuropathy 20%; Seizures 10%

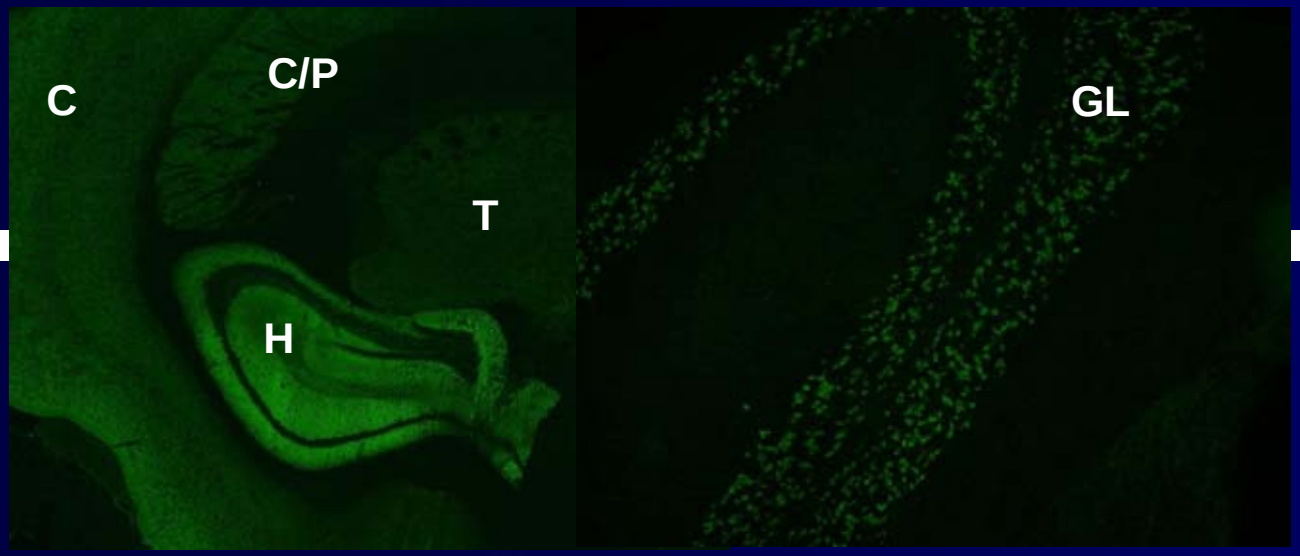


# Encephalitis

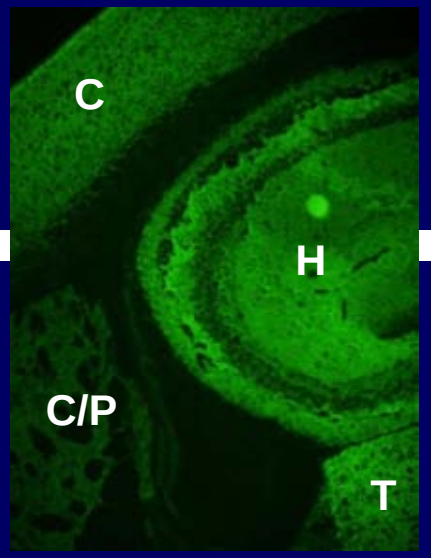
- Memory, mood, personality changes, seizures: limbic encephalitis
- ***<u>Diverse autoantibody associations:</u>***
  - ANNA-1, 2 (anti Hu, Ri)
  - CRMP-5 IgG
  - VGKC complex IgGs
  - GAD65 Ab (High titer)
  - AMPA, GABA B receptor Abs
- Anti-NMDA-R encephalitis



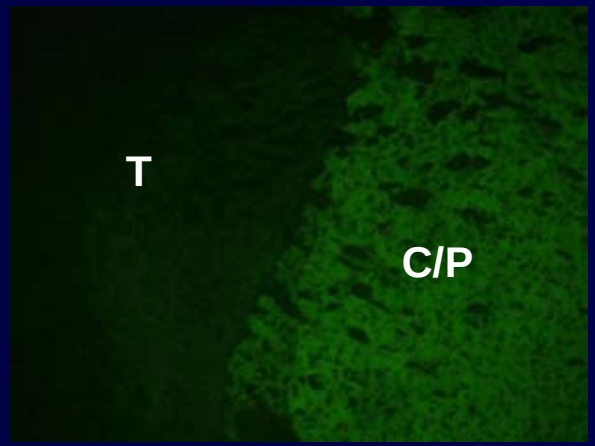
## NMDA-R



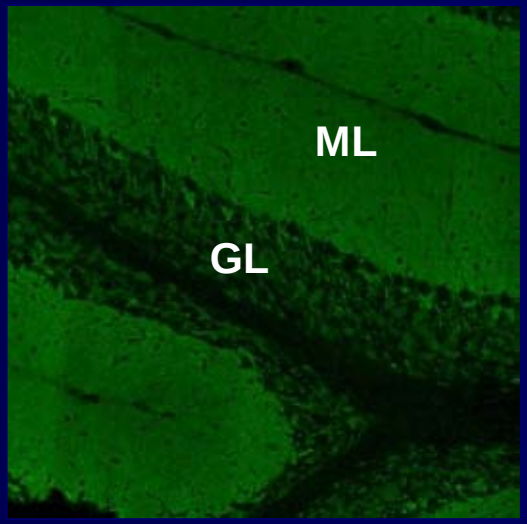

## GABAB-R

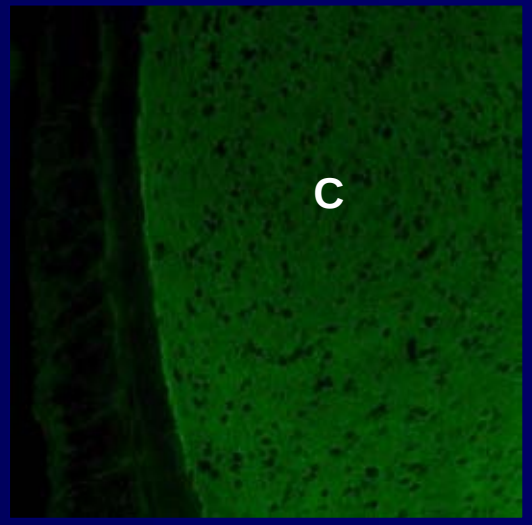



## AMPA-R




## VGKC complex

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# Anti-NMDA Receptor Encephalitis

- Females (5 – 76)
- **History**
  - Seizures
  - Psych symptoms
  - Cognitive decline
- **Exam**
  - Catatonia
  - Dyskinesias
  - Autonomic
  - Hypoventilation
- **MRI and EEG**
  - Temporal Lobe
- **Cancer**
  - Teratomas (usually ovarian)
- **Serology**
  - CSF > Serum



*Dalmau et al., 2008*

# Anti-$GABA_B$ Receptor Encephalitis

- Age (24 – 75 yrs)
- History/Exam
  - Seizures
  - Confusion
  - Memory loss
- CSF
  - Inflammatory
- MRI
  - Limbic encephalitis
- EEG
  - Temporal lobe onset
- Cancer
  - Small cell lung (33%)
- Serology
  - CSF > serum

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*Lancaster et al., 2010*

# Anti-AMPA Receptor Encephalitis

- Females (38 – 87) yrs
- History/Exam
  - Seizures
  - Memory loss
  - Confusion
- CSF
  - Inflammatory
- MRI and EEG
  - Temporal lobe
- Cancer
  - Lung
  - Breast
  - Thymus
- Serology
  - Serum or CSF



*Lai et al., 2009*

## Cortex

- Autoimmune dementia
- Autoimmune epilepsy
- Autoimmune encephalopathy

### Major Antibodies

VGKC complex
NMDA-R, GABAB-R, AMPA-R
GAD 65
ANNA-1 (hu), CRMP5
AQP4


# Autoimmune neurology

Menu

*Peripheral nervous system*

*Sp*

Neuromuscular junction | Autonomic | Somatic | Muscle | Spinal cord

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# Autoimmune Encephalopathy and Dementia

- Considered only in context of “limbic encephalitis”
- Reluctance to consider in absence of delirium
- Recent reports of a broader spectrum
- May mimic neurodegenerative disease

# Autoimmune Encephalopathy and Dementia
## Evolving Spectrum of VGKC complex autoimunity

OBSERVATION

### Potassium Channel Antibody–Associated Encephalopathy Presenting With a Frontotemporal Dementia–like Syndrome

*Andrew McKeon, MB, MRCPI; Michael Marnane, MB, MRCPI; Martin O'Connell, FFR, RCSI; John P. Stack, FFR, RCSI; Peter J. Kelly, MD, FRCPI; Timothy Lynch, MD, FRCPI*

ORIGINAL CONTRIBUTION

### Voltage-Gated Potassium Channel Autoimmunity Mimicking Creutzfeldt-Jakob Disease

*Michael D. Geschwind, MD, PhD; K. Meng Tan, MD; Vanda A. Lennon, MD, PhD; Ramon F. Barajas Jr, BS; Aissa Haman, MD; Christopher J. Klein, MD; S. Andrew Josephson, MD; Sean J. Pittock, MD*

**Background:** Rapidly progressive dementia has a variety of causes, including Creutzfeldt-Jakob disease (CJD) and neuronal voltage-gated potassium channel (VGKC) autoantibody–associated encephalopathy.

**Objective:** To describe patients thought initially to have CJD but found subsequently to have immunotherapy-responsive VGKC autoimmunity.

**Design:** Observational, prospective case series.

**Setting:** Department of Neurology, Mayo Clinic, and the Memory and Aging Center, University of California, San Francisco.

**Patients:** A clinical serologic cohort of 15 patients referred for paraneoplastic autoantibody evaluation. Seven patients were evaluated clinically by at least one of us. Clinical information for the remaining patients was obtained by physician interview or medical record review.

**Main Outcome Measures:** Clinical features, magnetic resonance imaging abnormalities, electroencephalographic patterns, cerebrospinal fluid analyses, and responses to immunomodulatory therapy.

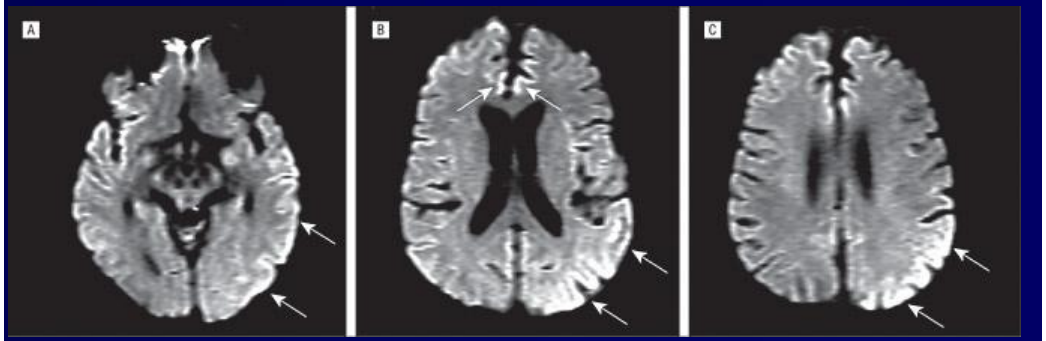
**Results:** All the patients presented subacutely with neurologic manifestations, including rapidly progressive dementia, myoclonus, extrapyramidal dysfunction, visual hallucinations, psychiatric disturbance, and seizures; most (60%) satisfied World Health Organization diagnostic criteria for CJD. Magnetic resonance imaging abnormalities included cerebral cortical diffusion-weighted imaging hyperintensities. Electroencephalographic abnormalities included diffuse slowing, frontal intermittent rhythmic delta activity, and focal epileptogenic activity but not periodic sharp wave complexes. Cerebrospinal fluid 14-3-3 protein or neuron-specific enolase levels were elevated in 5 of 8 patients. Hyponatremia was common (60%). Neoplasia was confirmed histologically in 5 patients (33%) and was suspected in another 5. Most patients' conditions (92%) improved after immunomodulatory therapy.

**Conclusions:** Clinical, radiologic, electrophysiologic, and laboratory findings in VGKC autoantibody–associated encephalopathy may be confused with those of CJD. Serologic evaluation for markers of neurologic autoimmunity, including VGKC autoantibodies, may be warranted in suspected CJD cases.

*Arch Neurol. 2008;65(10):1341-1346*

**Diffusion-weighted magnetic resonance images in a patient with immunotherapy-responsive VGKC complex autoimmunity**

**Note signal in the left temporo-occipital cortex (A and C, arrows) and the bilateral mesial frontal cortex (B, arrows)**



# Diagnosis of Possible Autoimmune Neurological Disorder

Not evidence based

***Objective baseline measurements***

***Acute treatment, "Diagnostic Test"***

**IV methylprednisolone**
**or**
**IVIg**
**or**
**Plasma exchange**

**Consider alternative acute therapy or no further therapy**

**No improvement**

**Improvement**

**Chronic treatment**
**Continue acute IV therapy, and taper**
**or**
**Oral prednisone taper**
**and**
**Oral azathioprine or Oral mycophenolate mofetil**
**or**
**Other options**

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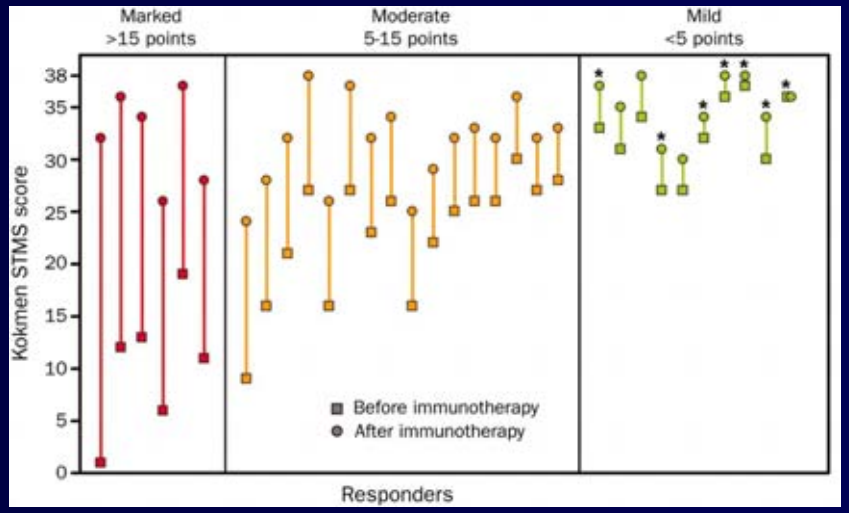
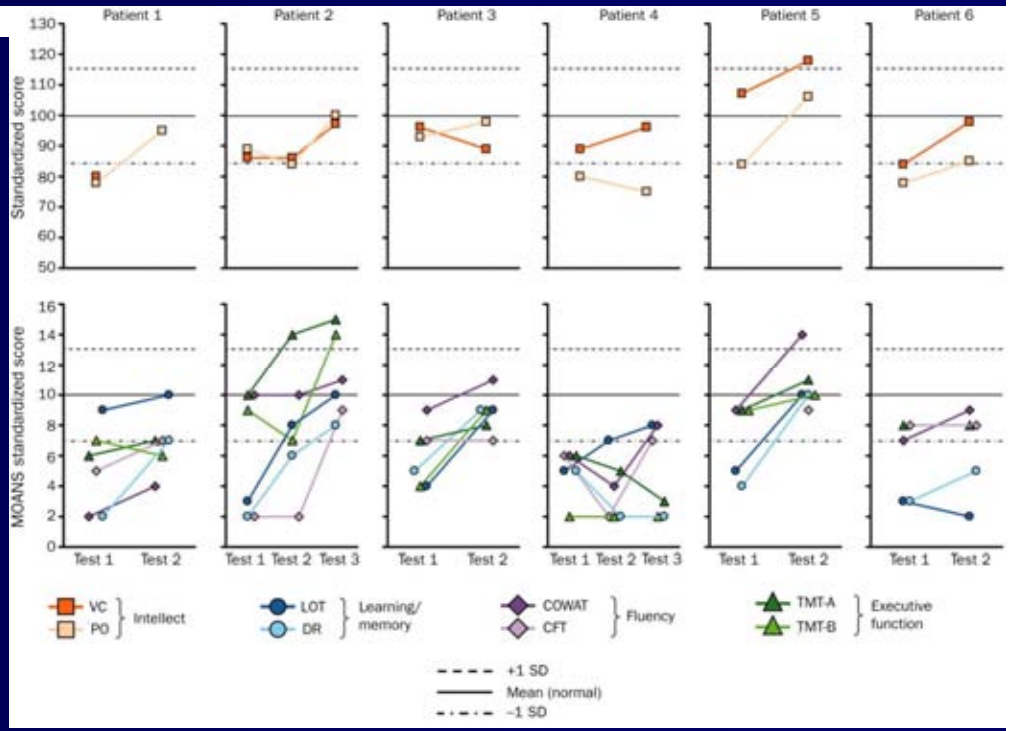
# Evaluations before and after treatment in patients positive for VGKC complex antibody with dementia.

## MMTS




## Neuropsychological tests




Flanagan E P et al. Mayo Clin Proc. 2010;85:881-897

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Mayo Clinic Proceedings

## Predictors of Immunotherapy Response in Autoimmune Dementia

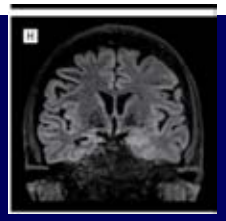
| | Responders | Non-responders | P value | Odds Ratio |
|---|---|---|---|---|
| Subacute onset | 93% | 35% | <0.001 | 27.1 |
| Fluctuating course | 91% | 19% | <0.001 | 44.1 |
| Headache | 24% | 4% | 0.06 | 7.9 |
| Tremor | 43% | 8% | 0.0013 | 8.4 |
| CSF protein (>100 mg/dL) or pleocytosis | 35% | 9% | 0.036 | 6.9 |
| Neuronal ion channel Ab | 41% | 10% | 0.009 | 8.1 |
| Mean time to treatment (months) | 11 | 25 | <0.001 | 0.95 |

# Autoimmune Epilepsy

- May have seizure predominant presentation
- Scan may be normal at onset in half
- *Dx:* EEG, CSF, Ab testing
- VGKC complex Abs > GAD65 Ab > CRMP-5 IgG > Ma2 = NMDA receptor Ab

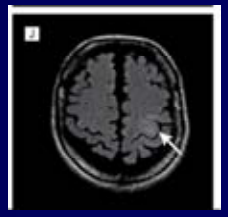
*Quek et al, Arch Neurol 2012.*

*Localizations*

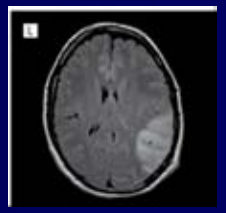


Mesial temporal

Neocortical temporal



Precentral



Frontoparietal

# *Clues to Autoimmunity*

## Neural Autoantibodies, 91%

- VGKC-complex, 56%

  ***Lgi1 (44%), Caspr2 (3%), neither (9%)***

- GAD-65, 22%

- Other, 16%

  ***CRMP-5, Ma-1/Ma-2, NMDAR,***
  ***neuronal ganglionic AChR***

# *Seizure Characteristics*

- Type
  - Complex partial, 81%
  - Simple partial, 69%
  - Generalized tonic clonic, 44%
- Medically intractable
  - Failed 2+ antiepileptic drugs, 81%
  - Daily, 81%
- Other findings
  - Cognitive deficits, 63%
  - Personality changes, 25%
  - Depression / anxiety, 19%
  - None, 34%

# *Immunotherapy (n=27)*

IVMP, 12; IVIG,3; IVMP + IVIg, or other,12

- Improved, 82%
  - Seizure free, 64%
    - ***Median 9 months (2-48)***
  - Seizure frequency ?á18%
- No response, 18%

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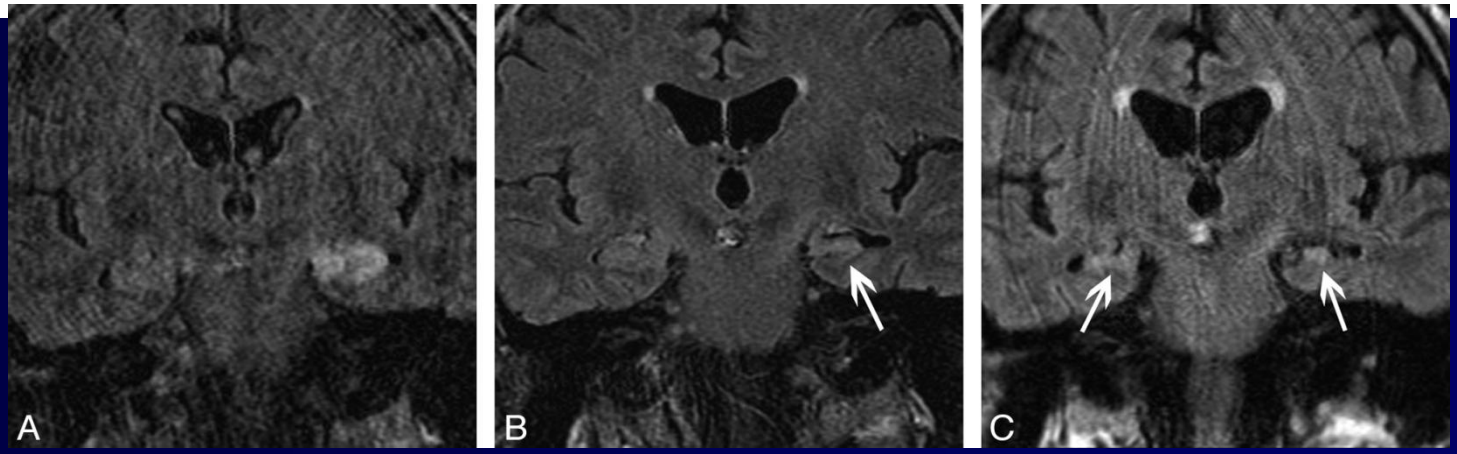
# MRI Findings in Autoimmune VGKC Complex Encephalitis with Seizures: One Potential Etiology for Mesial Temporal Sclerosis

Kotsenas et al. AJNR 2013

## A 66-year-old man with autoimmune VGKC epilepsy.




Presentation signal and enlargement L hippocampus

7-months L MTS

46 month bilateral MTS

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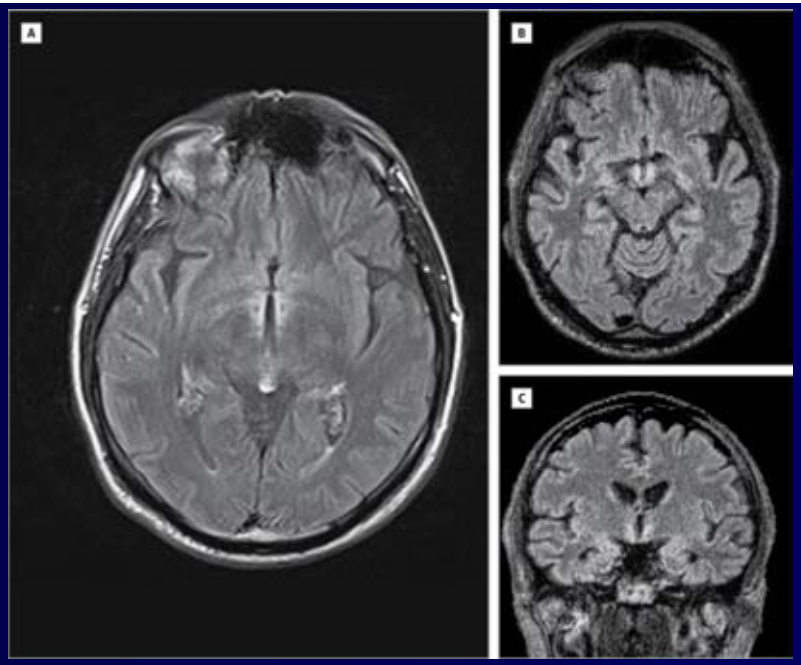
# Ma (anti-PNMA1+PNMA2): Ta (anti PNMA2)

published data so far: Hoffman et al, 2008

| | Ma | Ta |
|---|---|---|
| F:M | 1.6:1 | 1:3.5 |
| Neurologic manifestations | Cbl/BS>LE<br>PN/cord/BG | LE>Cbl/BS<br>PN/cord/BG |
| Tumor | Varied | Germ cell 75%;lung 9%; breast 9% |
| PNS before tumor | 66% (2-14 mo) | 82% (2-36mo) |
| MRI head abnormal | 86% | 82% |
| CSF abnormal | 77% | 81% |
| Outcome | 75% progression | 31% progression |

# Hypothalamic Immunopathology in Anti-Ma–Associated Diencephalitis With Narcolepsy-Cataplexy. Dauvilliers et al. JAMA Neurology 2013




- Exclusive inflammation and tissue injury in the hypothalamus
- Cytotoxic $CD8^+$ T lymphocytes
- Inflammation-complete loss of hypocretinergic neurons

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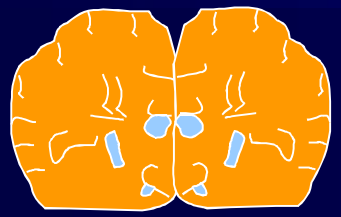
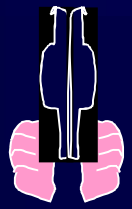


# Chorea

- Paraneoplastic or idiopathic autoimmune
- ***Paraneoplastic:***
  - CRMP-5 IgG
  - ANNA-1
  - GAD65
- ***Idiopathic autoimmune:***
  - Lupus, APL Ab syndrome
  - CASPR2

*O' Toole et al, AAN 2012*

- ***Paraneoplastic patients more likely:***
  - Older
  - Male
  - More frequent weight loss
  - More frequent coexisting peripheral neuropathy
  - Some improved with immunotherapy/cancer therapy
- ***Idiopathic***
  - Often milder course
  - Improved/resolved with steroids



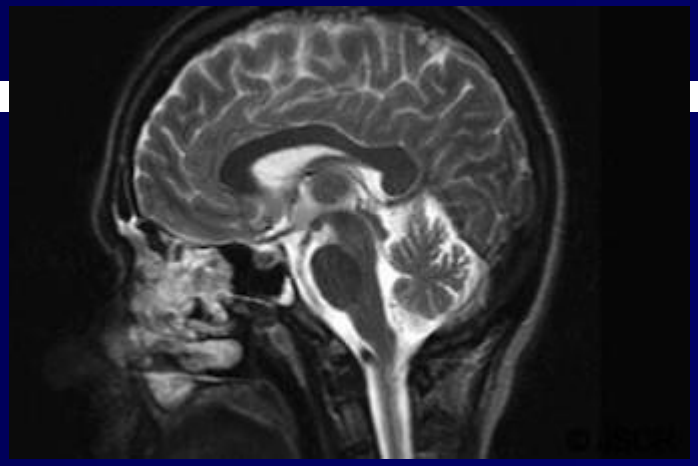
# Cerebellar ataxia

- Symptoms frequently overlap with brainstem disorders
- Rapid-onset dysarthria, incoordination, gait disturbance, vertigo
- ***Prototypic disorder:***

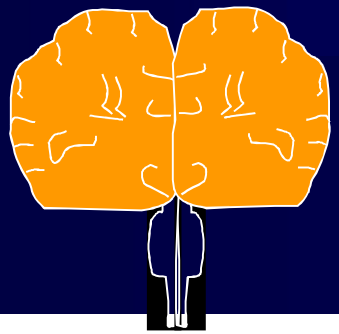
  PCA-1 (anti-Yo) associated cerebellar degeneration in women with mullerian or breast adenocarcinoma
- ***Other Abs***: P/Q-type calcium channel Ab, GAD65 Ab, PCA-Tr

*Peterson et al, Neurology 1992*

*McKeon et al, Arch Neurol 2010*



*Cerebellar atrophy*



# Opsoclonus-myoclonus

- ***Children***
- Neuroblastoma
- ANNA-1 in a minority
- ***Adults***
- 15% paraneoplastic
- ANNA-2 > ANNA-1 = NMDA-R Ab
- Frequently idiopathic autoimmune (immunotherapy responsive)

*Klaas et al, Arch Neurol 2012*

***Whole body tremor***

- Small amplitude generalized polymyoclonus
- No opsoclonus
- 25% have autoimmune cause
- Occult cancer possible
- VGKC, Alpha 3 ganglionic, CRMP-5 IgG

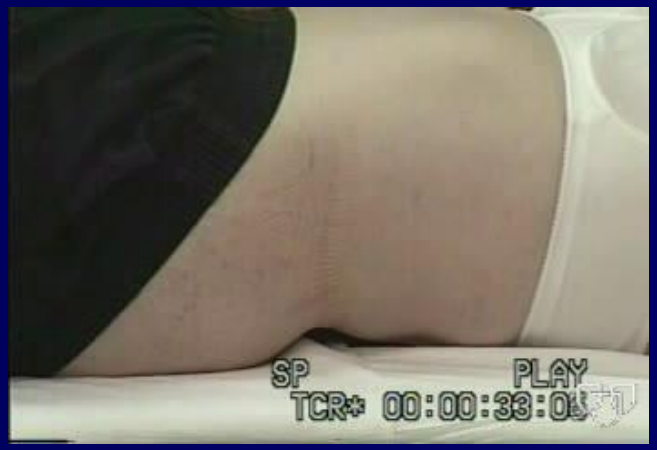
*McKeon et al, Arch Neurol, 2007*

# Stiff-man syndrome

- First case recognized 1924

*Moersch, Woltman*

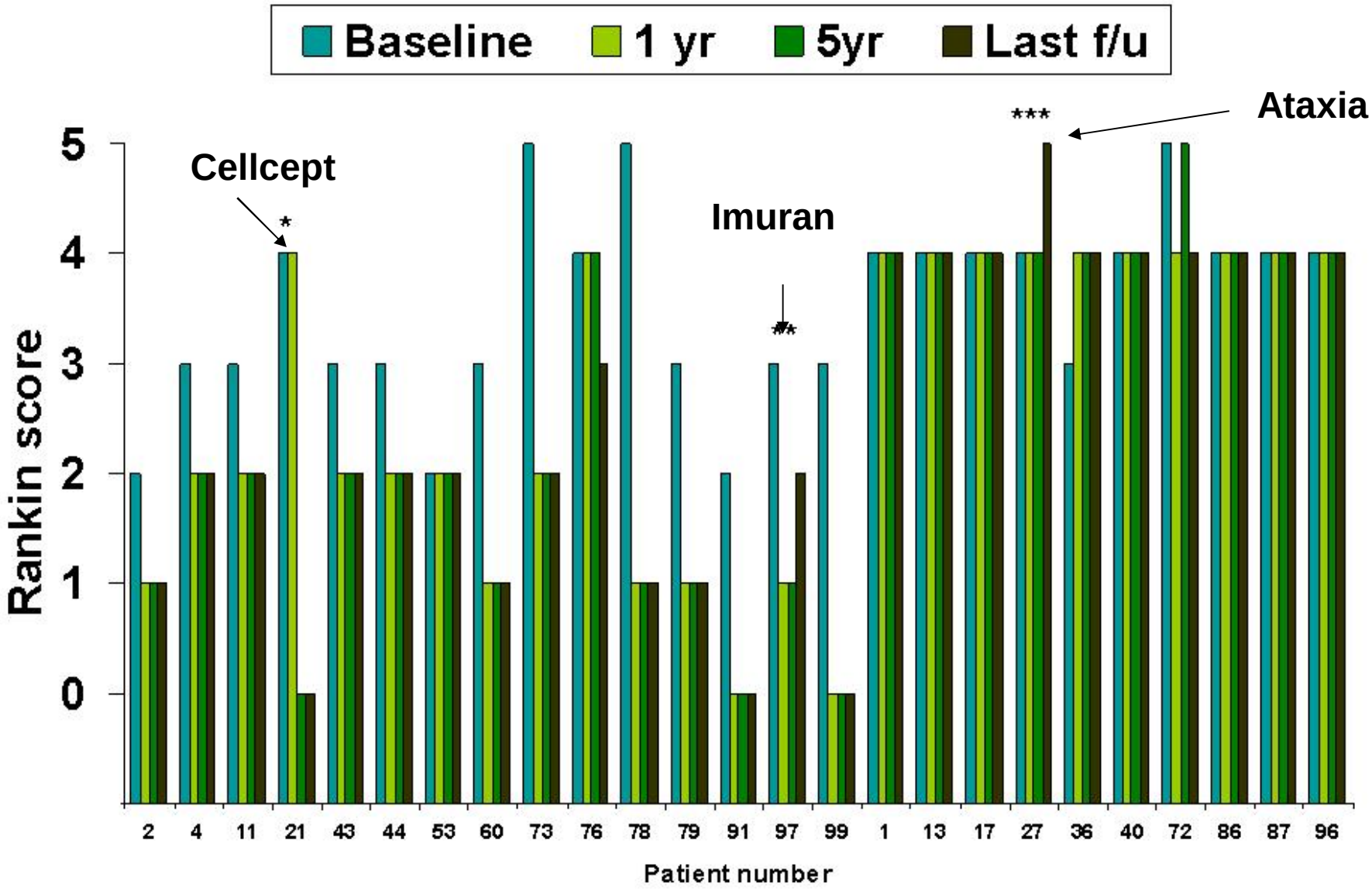
- Stiffness, spasms proximal lower extremities and low back
- Classic and variant forms (including PERM)
- Autoimmune disease common: Type 1 DM & Thyroid disease
- GAD65 IgG values, median value 163 nmol/L (N< 0.02)




*McKeon et al, Arch Neurol, 2012*

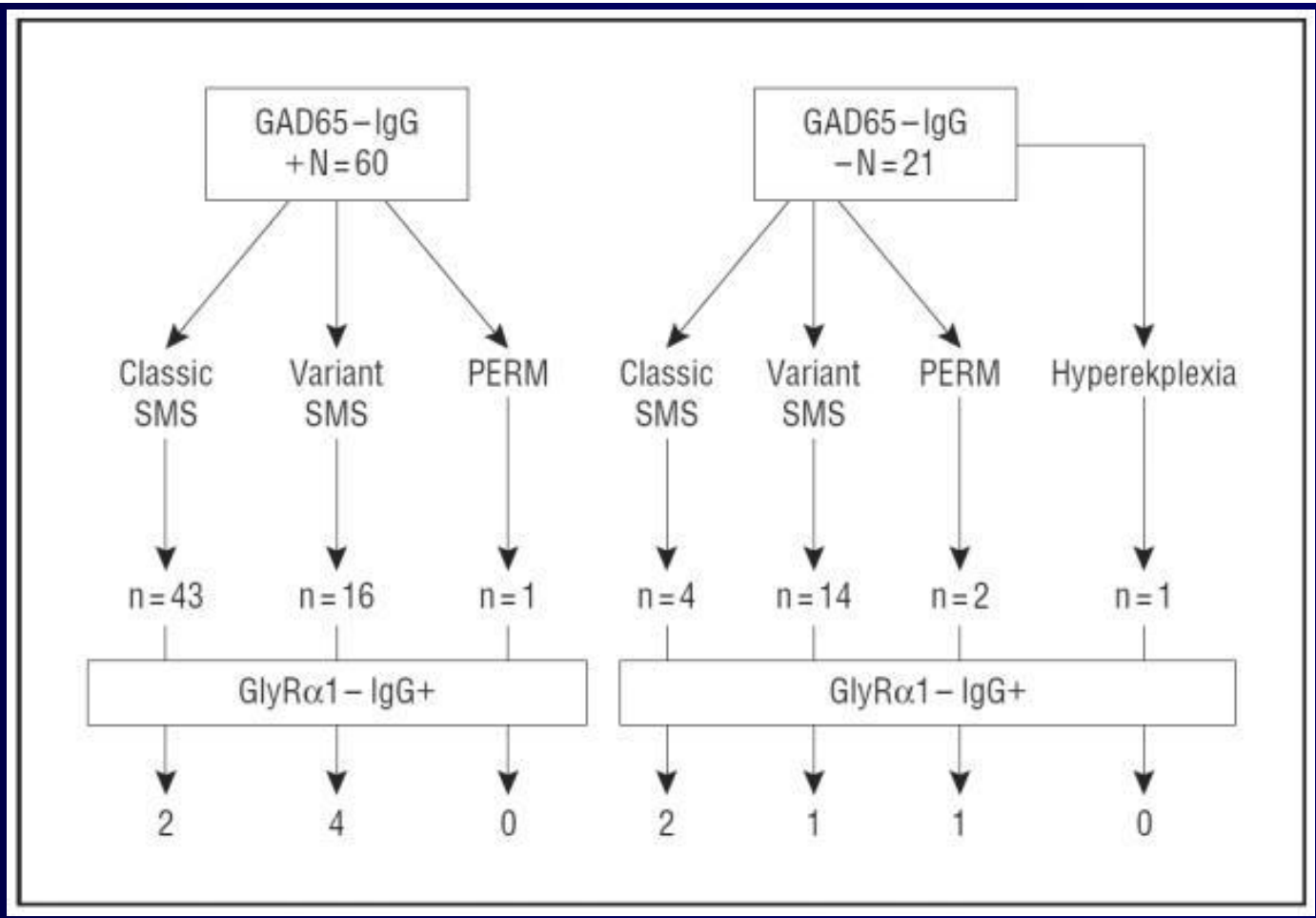
# Outcome in 25 SMS patients with ?ì5 years follow-up

McKeon et al. Archives Neurol 2012



# Glycine Receptor Autoimmune Spectrum With Stiff-Man Syndrome Phenotype. McKeon et al. JAMA Neurology 2013

1st report:
Hutchinson et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. *Neurology*. 2008.

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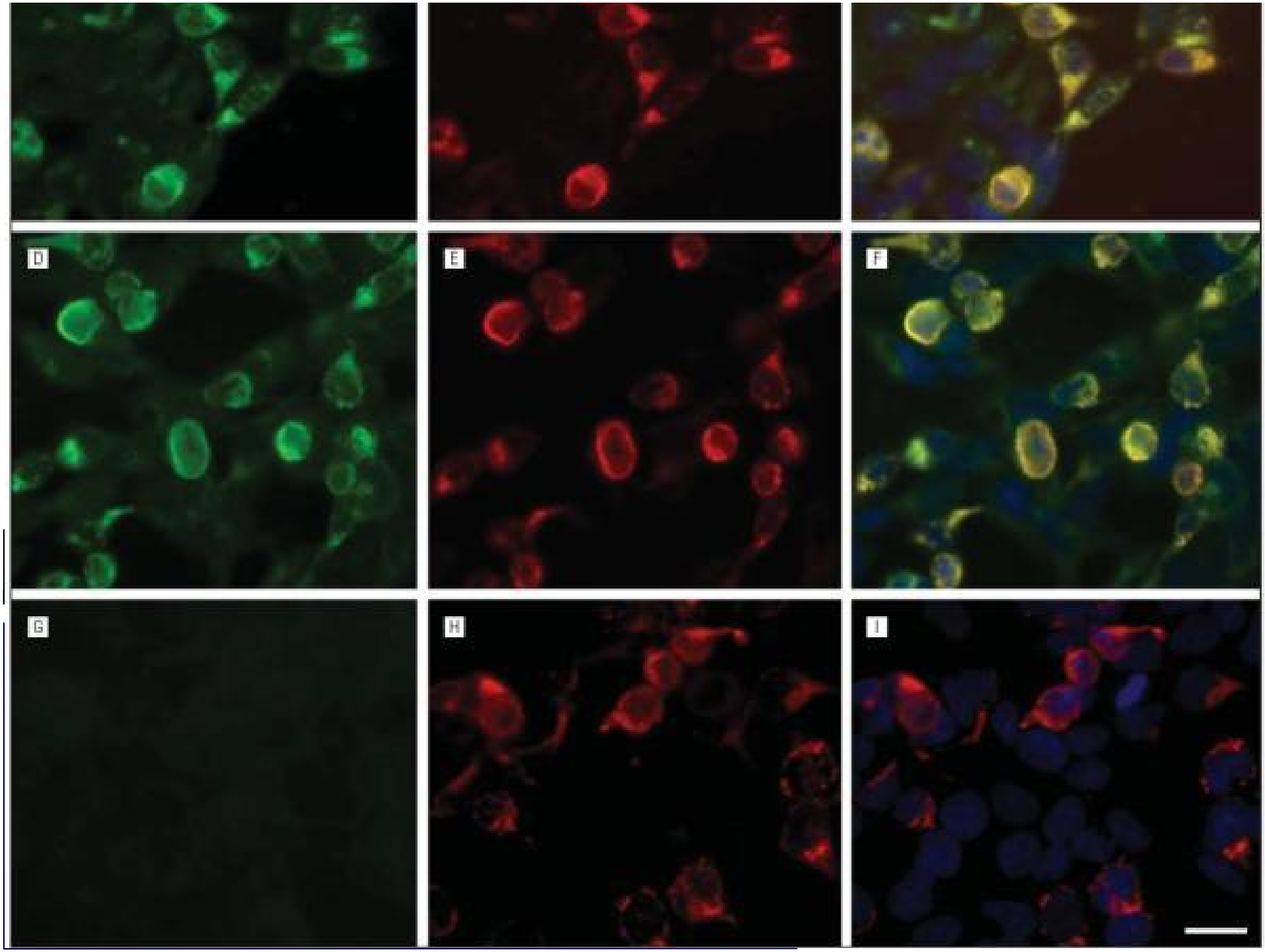
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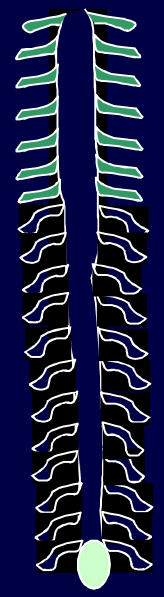
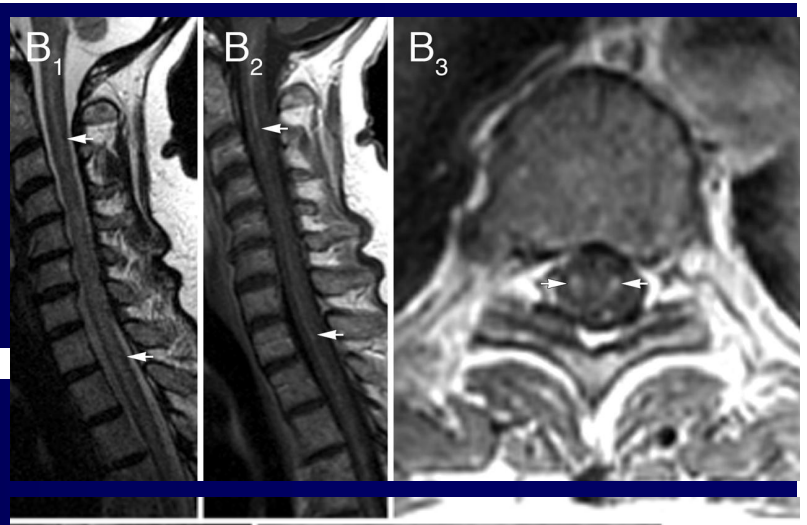
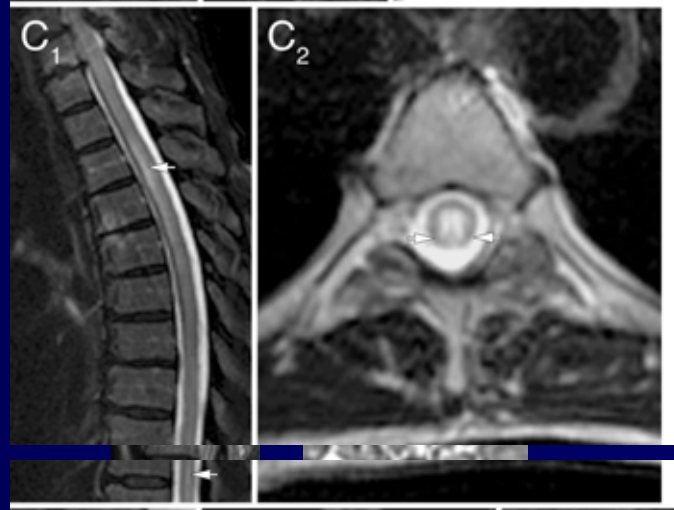
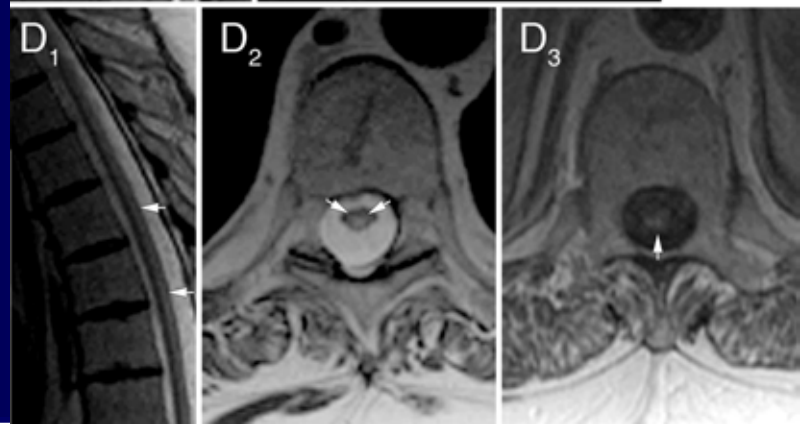
# Paraneoplastic Myelopathy



- Subacute or insidious onset
- Lung, breast, kidney, thyroid,ovary/endometrium, melanoma, or other.
- Amphiphysin IgG, CRMP-5 IgG, ANNA-1, PCA-1, ANNA-3
- Minority improve with treatment
- 50% Wheelchair bound

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# Evaluation for cancer

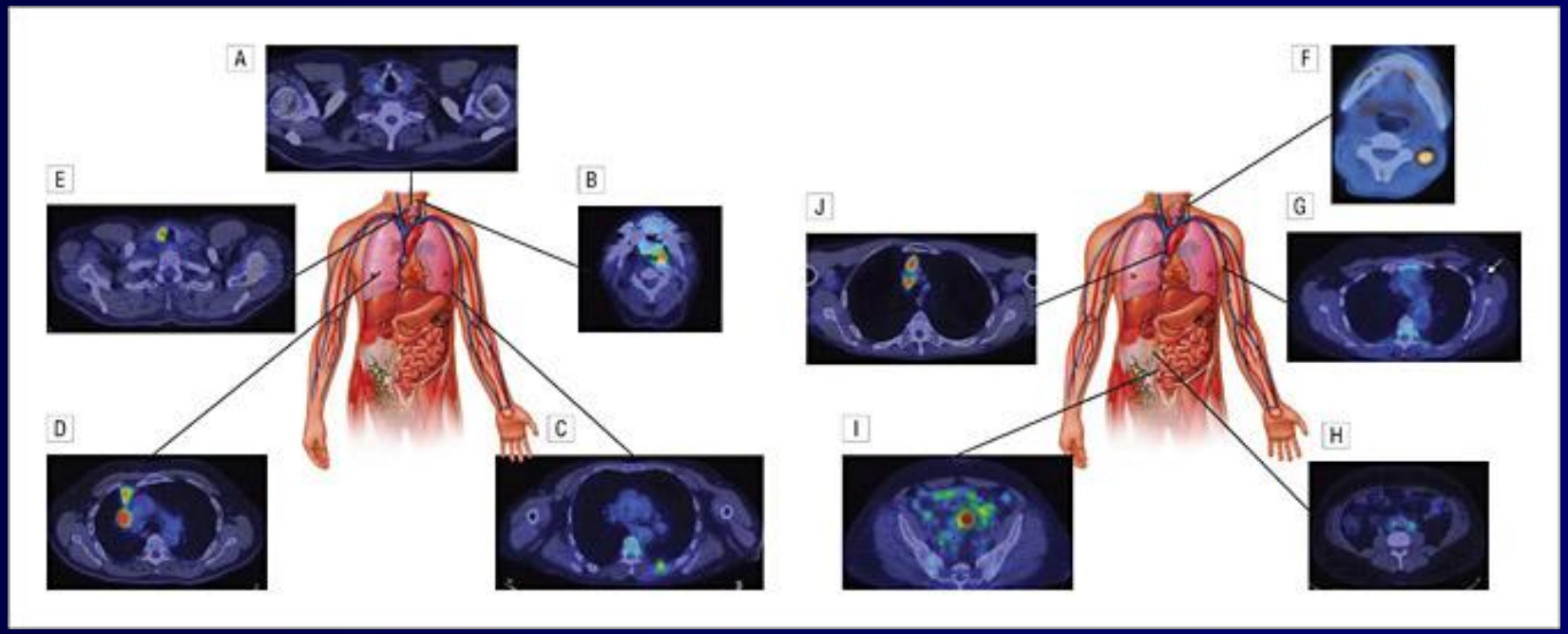
- Based on: specific Ab finding(s)

OR

- Age, sex, family history

- CT chest, abdomen, pelvis
- Pelvic ultrasound (incl. transvaginal views)
- Testicular ultrasound
- Mammogram
- Exploratory surgery

# PET-CT




*Increased cancer detection rate ~ 20%

***McKeon et al, Arch Neurol, 2010***

# Treatment: principles

- Trials of immunotherapy
- Measure improvement objectively
- Determining if short-term or long term treatment required
- Consider steroid-sparing agent

# Cytotoxic T cell mediated disorders

- Paraneoplastic disorders
- Do not generally have good responses to steroids, IVIg or plasma exchange
- General approach:
- Oncological therapy (surgery, chemotherapy, radiation therapy)
- Cyclophosphamide

*Vernino et al, Neuro Oncol. 2004;6:55-62*

# Antibody-mediated disorders (definite or possible)

- Acute (early important)
- Corticosteroids
- Intravenous immune globulin (IVIg)
- Plasma exchange
- Chronic
- Mycophenolate mofetil
- Azathioprine
- Rituximab, cyclophosphamide

# Diagnosis of Possible Autoimmune Neurological Disorder

Not evidence based

***Objective baseline measurements***

***Acute treatment, "Diagnostic Test"***

**IV methylprednisolone**
**or**
**IVIg**
**or**
**Plasma exchange**

**Consider alternative acute therapy or no further therapy**

**No improvement**

**Improvement**

**Chronic treatment**
**Continue acute IV therapy, and taper**
**or**
**Oral prednisone taper**
**and**
**Oral azathioprine or Oral mycophenolate mofetil**
**or**
**Other options**

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# Summary

- Autoimmune neurological disorders are important to consider
  - Potentially treatable
  - May be indicative of occult cancer
- Clues may emanate from
  - history
  - examination
  - serum & CSF Ab evaluations
  - response to treatment