AACC Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

Pearl Title: Autoimmune Neurology: Paraneoplastic Disorders & Beyond

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DOI: 10.15428/CCTC.2020.316604

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Presentation Outline

- Define Autoimmune Neurology
- Recognize different disorders
- Recognize key clinical features
- Testing modalities
- Select evaluations

Autoimmune neurological disorders

- Neurological disorders caused by aberrant immune response
- Antigen-specific
- May be paraneoplastic, parainfectious, or idiopathic
- Unified by IgG marker detected in serum or cerebrospinal fluid (CSF)

How do patients present?

- Subacute onset symptoms
- Rapid progression
- Fluctuating course
- Can affect any neurological domain
- Classic phenotypes
- Atypical phenotypes
- Multifocal disorders

Cortex: encephalopathy
Visual System: optic neuritis

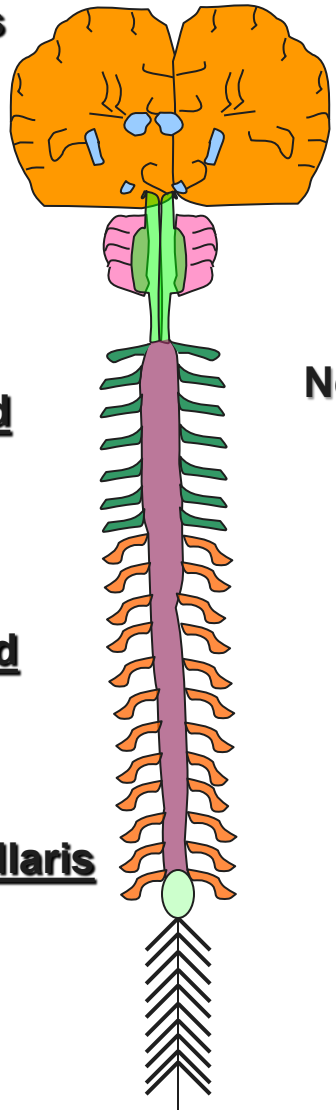
Basal ganglia:

movement disorders

Cerebellum: ataxia

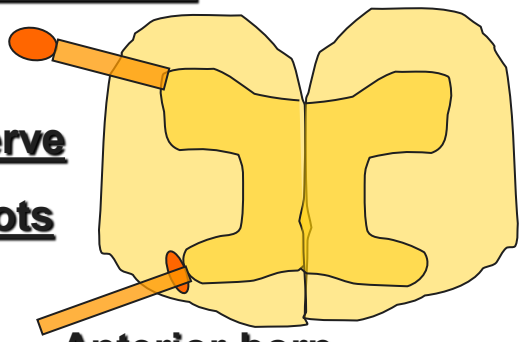
Brainstem: ataxia, diplopia

Myelopathy
- **Cervical cord**
- **Thoracic cord**
- **Conus medullaris**



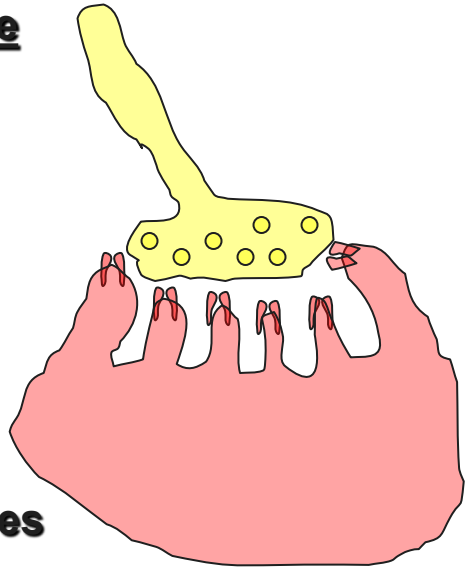
Lumbosacral roots:
radiculopathies

Neuropathies
- **Dorsal horn**
- **Nerve roots**
- **Anterior horn**
- **Nerve**



NMJ: myasthenia

Muscle: myopathies



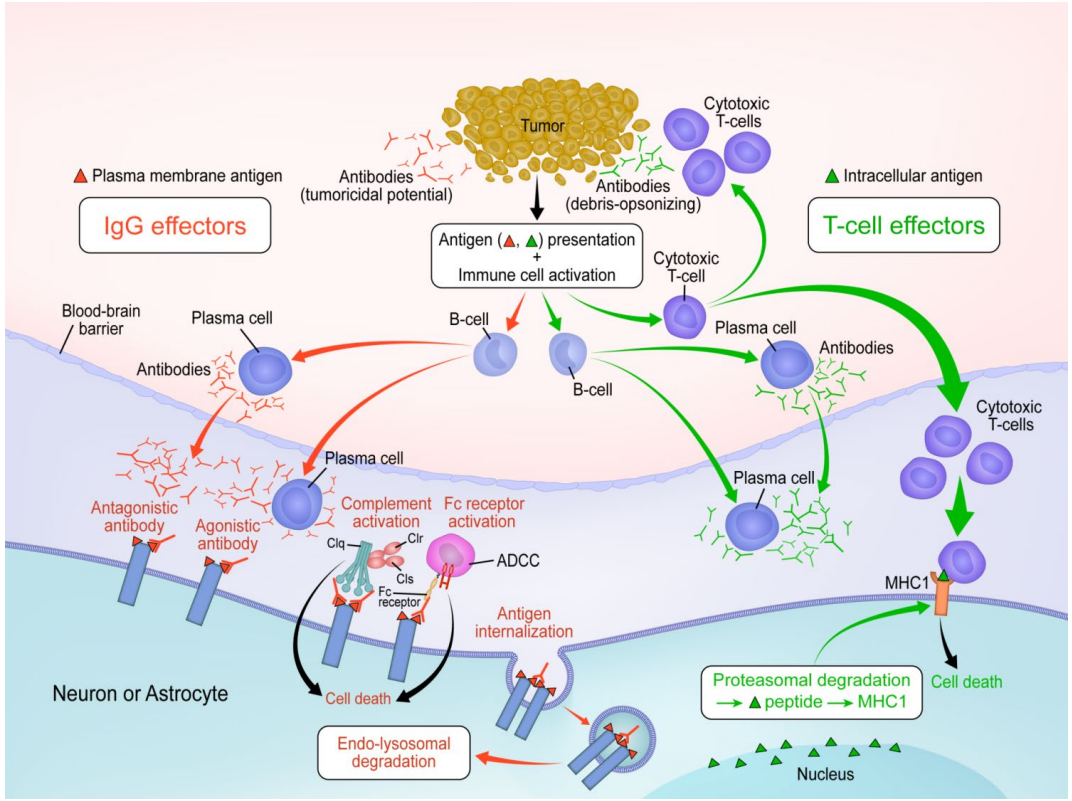
What are the risk factors?

- Sometimes none
- Coexisting autoimmune disease, e.g. thyroid disease, type 1 diabetes mellitus
- Cancer history
- Smoking history
- Family history of autoimmune disease or cancer
- Recent infection

How to evaluate further?

Serum testing	CSF testing
Thyroid Abs	Protein
Connective tissue Abs	Cell count
Neural Abs	IgG index/synthesis rate
	Oligoclonal bands
	Neural Abs

Why do autoimmune neurological diseases occur?



McKeon A, **Pittock** SJ. Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol 2011;122:381-400. Reproduced with permission from: Wolters Kluwer.

Neuronal nuclear or cytoplasmic Abs

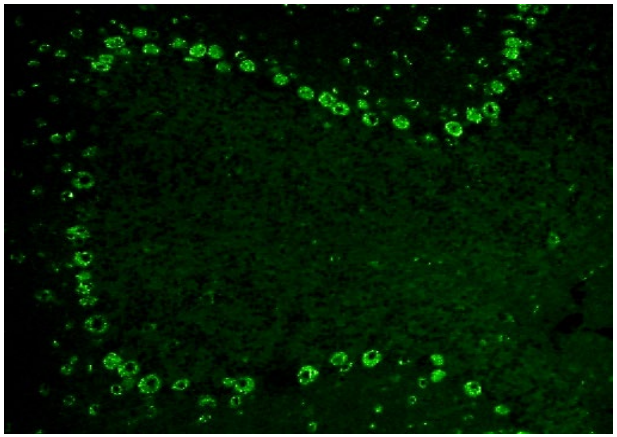
Antibody	Oncological association
ANNA-1 (anti-Hu)	Small-cell carcinoma
ANNA-2 (anti-Ri)	Small-cell carcinoma Breast adenocarcinoma
ANNA-3	Aerodigestive carcinomas
AGNA (SOX-1)	Small-cell carcinoma
PCA-1 (anti-Yo)	Gynecological adenocarcinomas Breast adenocarcinoma
PCA-2 (MAP1B)	Small-cell carcinoma
CRMP-5 IgG (anti-CV2)	Small-cell carcinoma Thymoma
Amphiphysin IgG	Small-cell carcinoma Breast adenocarcinoma
GFAP-IgG	Teratoma, other
NIF-IgGs	Neuroendocrine (small cell, Merkel cell, other)
Septin 5	None
AP3B2	None

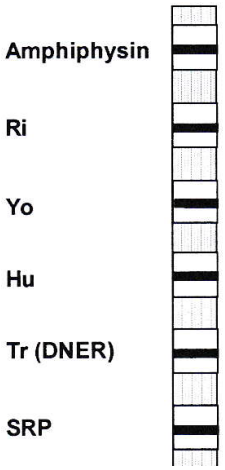
Synaptic Autoantibodies

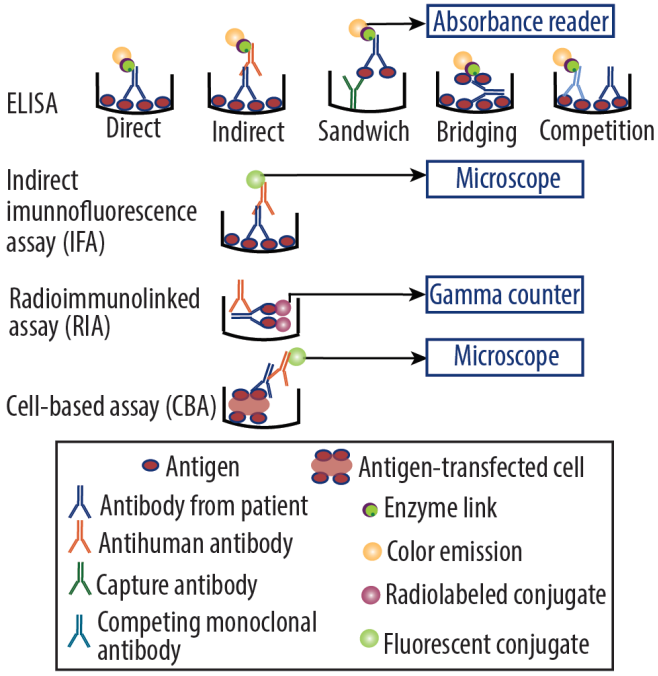
Antibody	Oncological association
Lgi1/CASPR2	Thymoma, other
NMDA receptor	50% Ovarian teratoma
AMPA receptor	70% Thymoma, lung carcinoma, breast carcinoma
GABA-B receptor	50% Small-cell lung carcinoma
P/Q & N type calcium channel	Small-cell carcinoma, breast or gynecological adenocarcinoma
GlyR	Thymoma
DPPX	Occasional B cell neoplasm
IgLON5	None
PCA-Tr (DNER)	70%: Hodgkin lymphoma

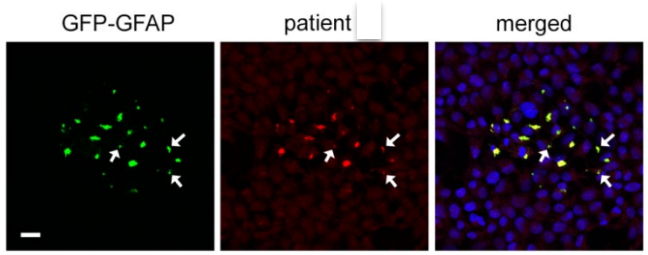
How are Abs detected?

Test	Linear epitopes	Conformational epitopes
ELISA	+	
Tissue-based IFA	+	+
Immunoprecipitation (RIA)	+	+
Cell-based IFA	+	+
Flow cytometry		+
Immunoblot	+	

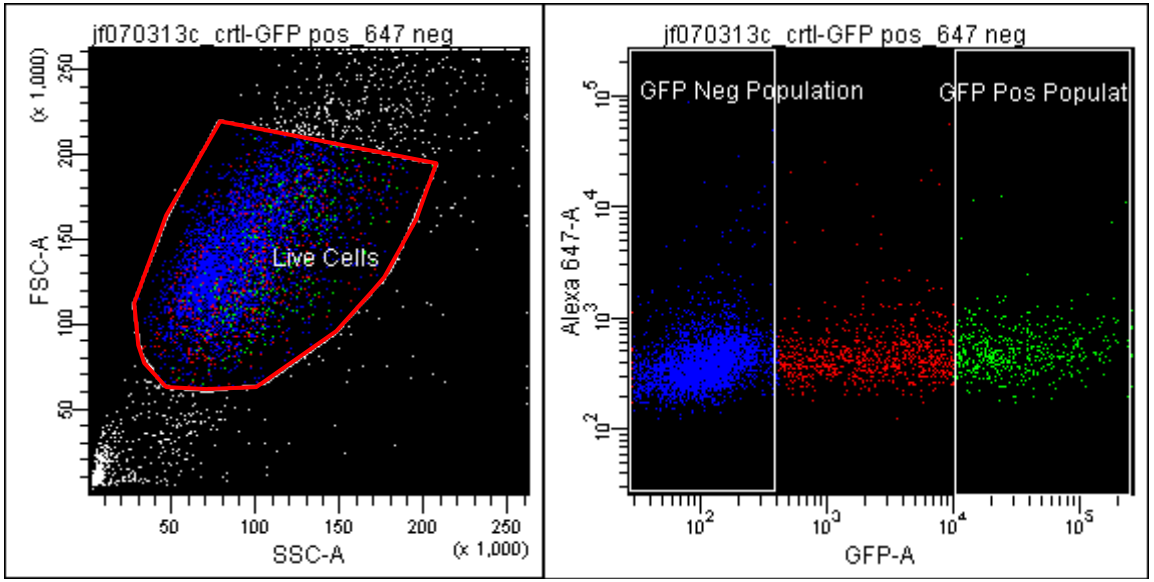






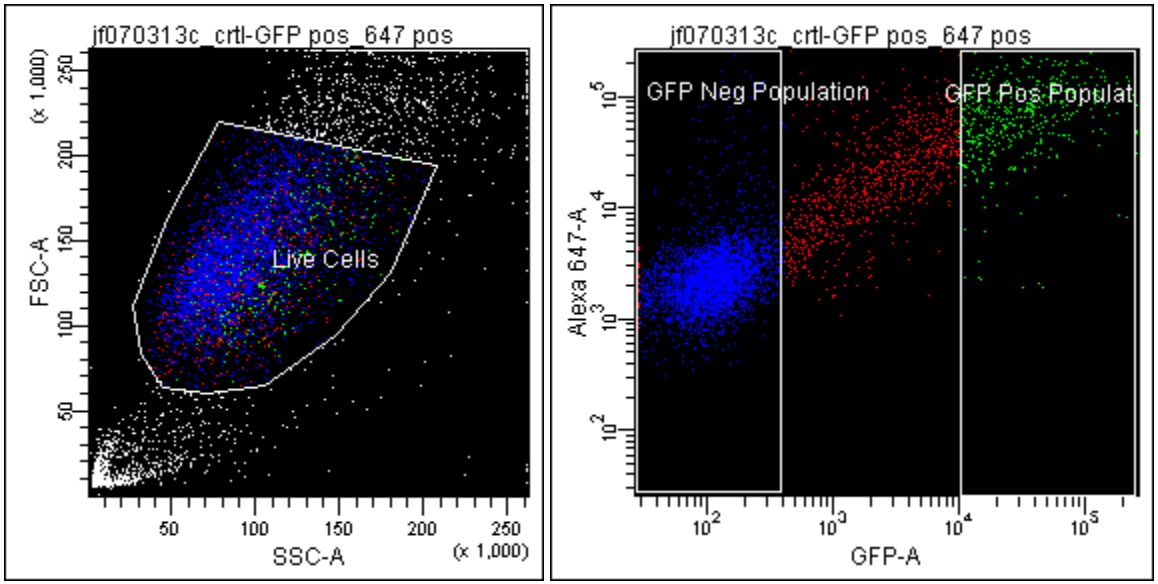


AQP4-IgG evaluation: FACS



Negative Control Serum

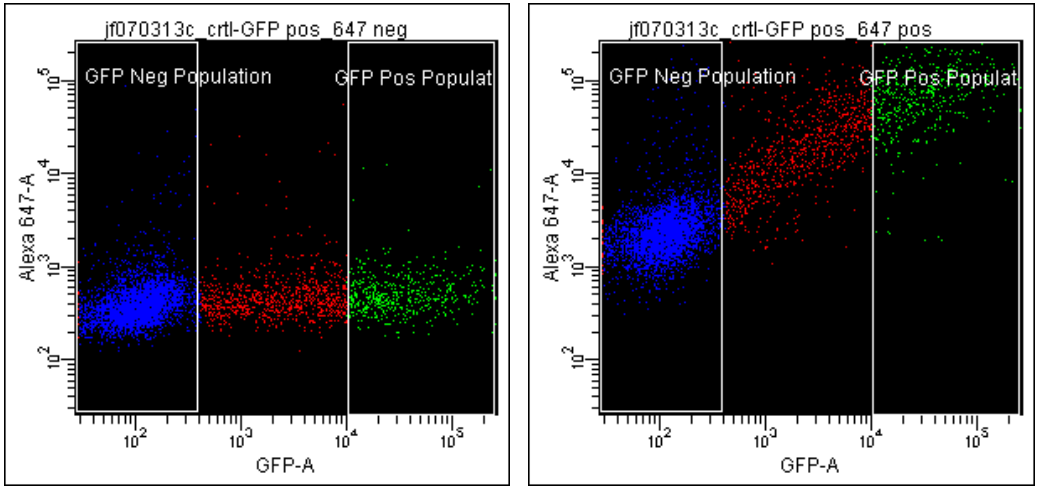
AQP4-IgG evaluation: FACS



Positive Control Serum

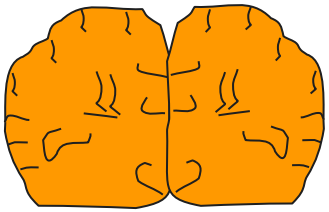
AQP4-IgG evaluation: FACS

IgG Binding Index = $\frac{\text{MFI GFP}^{+}\text{ Population}}{\text{MFI GFP}^{-}\text{ Population}}$



For example,

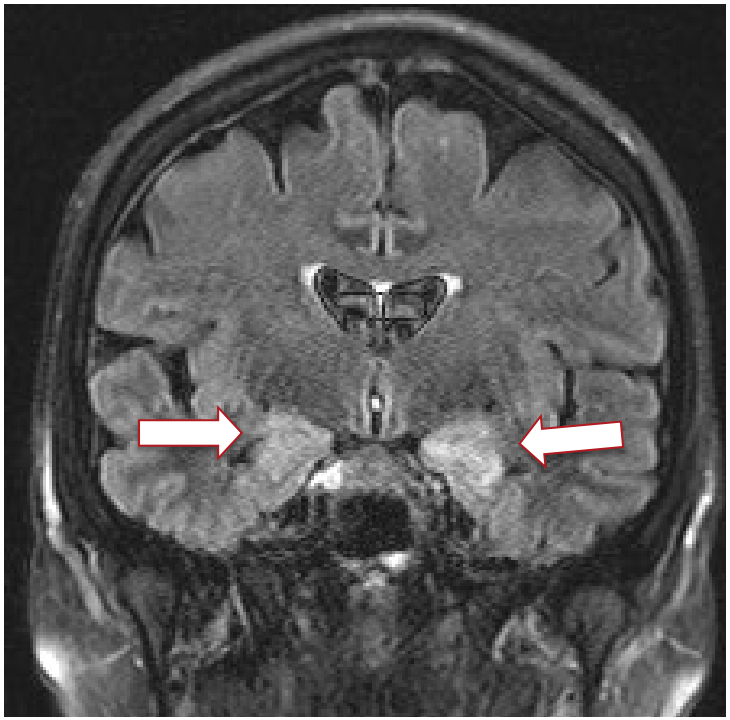
IgG Binding Index of negative sample; 468/376 = 1.24
IgG Binding Index of positive sample; 72,031/2,384 = 30.2
Binding Index ≥2 = positive



Limbic encephalitis

- Memory, mood, personality changes, seizures
- ***Diverse autoantibody associations:***
  - ANNA-1, 2 (anti-Hu, Ri)
  - CRMP-5 IgG
  - Lgi1, CASPR2 IgGs
  - GAD65 Ab (High titer)
  - AMPA, GABA-B receptor Abs
  - mGluR5 Ab
- ***Restricted forms:***

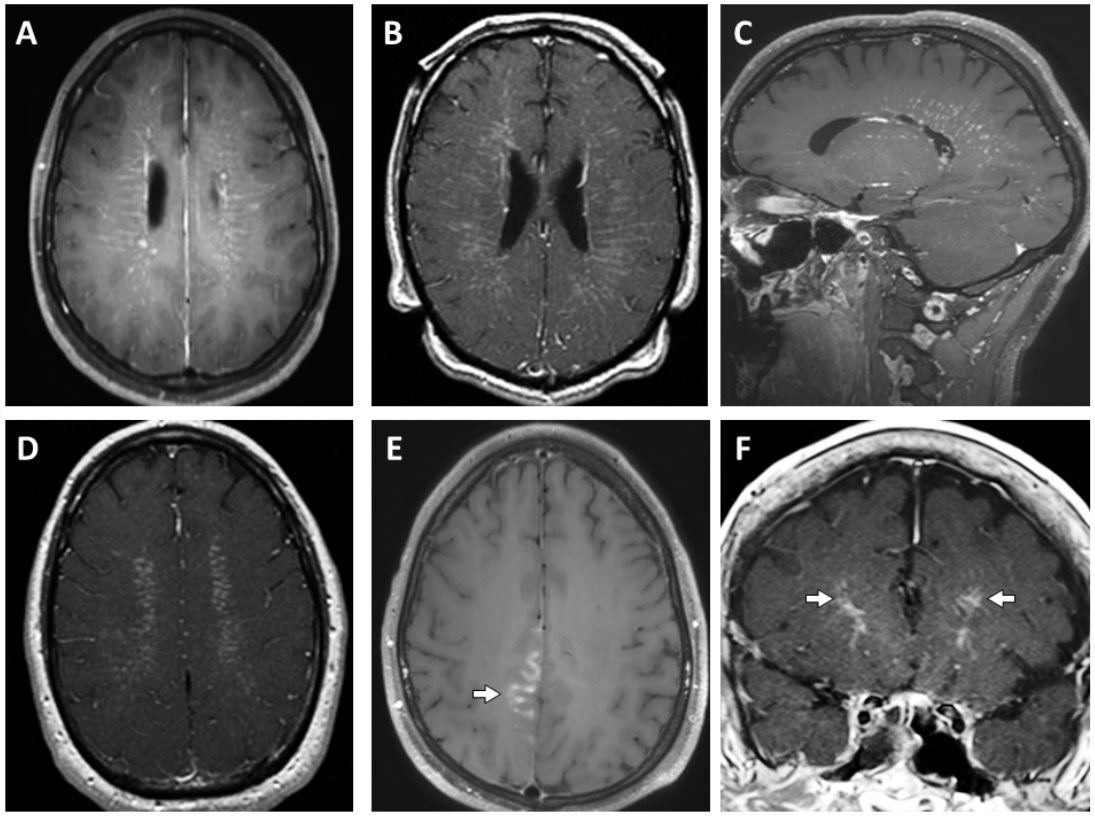
Autoimmune epilepsy, dementia



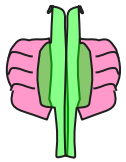
Non-limbic encephalitis

Targets

- **NMDA-R**
- **GABA$_A$R**
- **NIFs**
- **GFAP**



Flanagan EP, Hinson SR, Lennon VA, Fang B, Aksamit AJ, Morris PP. Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: Analysis of 102 patients. Ann Neurol 2017;81:298-309. Reproduced with permission from: Wiley.



Movement disorders: Ataxia

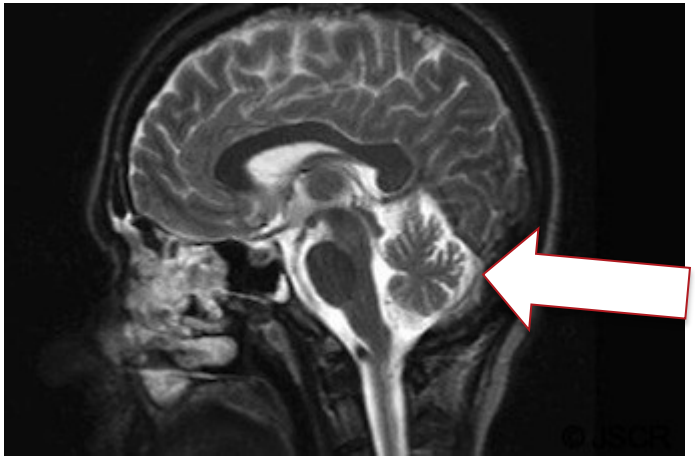
- **Rapid-onset dysarthria, incoordination, gait disturbance, vertigo**
- ***Prototypic disorder:***

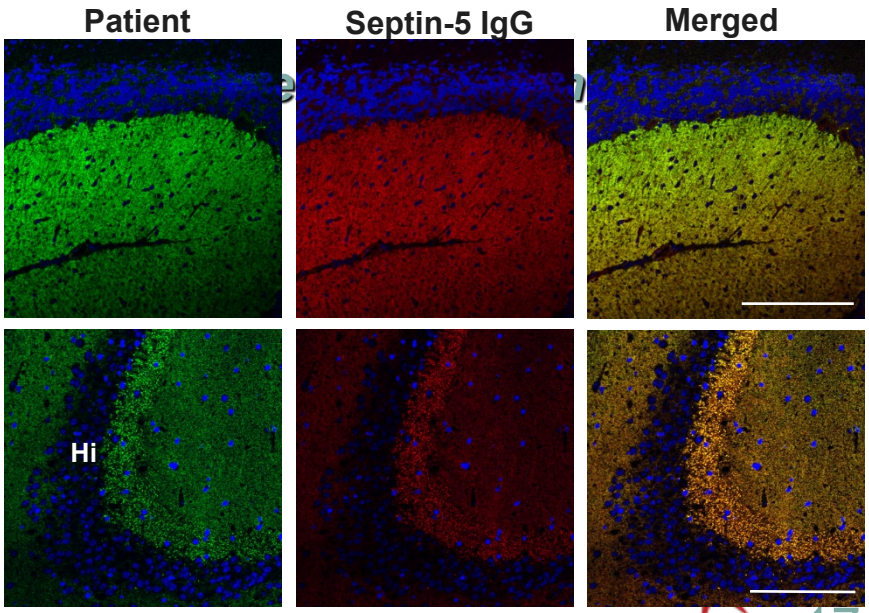
  PCA-1 (anti-Yo):bad outcome

But…

***Other Abs*:**

e.g. mGluR1 Ab, Septin-5: better prognosis

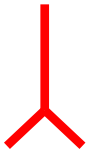




Honorat JA, Lopez-Chiriboga AS, Kryzer TJ, Fryer JP, Devine M, Flores A, et al, Autoimmune septin-5 cerebellar ataxia. Neurol Neuroimmunol Neuroinflamm 2018; 9:e474 (reproduced with permission from Wolters-Kluwer).

Disease categories to consider

- Encephalopathy
- Dementia
- Epilepsy
- Movement Disorders
- Myelopathy
- Neuropathy
- Myasthenia gravis & Lambert Eaton syndrome
- Myopathy



	PLASMA MEMBRANE SPECIFICITIES																NUCLEAR AND CYTOPLASMIC SPECIFICITIES																	
	NMDA-R	LGI1	CASPR2	AMPA-R	GABA-B-R	DPPX	mGluR1	VGKC-Complex	P/Q Type VGCC	N-Type VGCC	AChR Binding	AChR Ganglionic	PCA-TR	AQP4	MOG	IgLON5	ANNA-1 (Hu)	ANNA-2 (Ri)	ANNA-3	AGNA (SOX1)	PCA-1 (Yo)	PCA-2	CRMP-5 (CV2)	Amphiphysin	Striational	GAD65	GFAP	GRAF1	ITPR1	NIF
CENTRAL NERVOUS SYSTEM EVALUATIONS																																		
Encephalopathy, Serum	•	•	•	•	•	•	•		•	•		•	•			•	•	•	•	•	•	•	•	•		•	•			•				
Encephalopathy, CSF	•	•	•	•	•	•	•						•			•	•	•	•	•	•	•	•	•		•	•			•				
Dementia, Serum	•	•	•	•	•	•	•		•	•		•	•			•	•	•	•	•		•	•	•		•	•			•				
Dementia, CSF	•	•	•	•	•	•	•						•			•	•	•	•	•		•	•	•		•	•			•				
Epilepsy, Serum	•	•	•	•	•	•	•		•	•		•	•				•	•	•	•		•	•	•		•	•							
Epilepsy, CSF	•	•	•	•	•	•	•						•				•	•	•	•		•	•	•		•	•							
Movement Disorders, Serum	•	•	•			•	•		•	•		•	•			•	•	•	•	•	•	•	•	•		•		•	•	•				
Movement Disorders, CSF	•	•	•			•	•						•			•	•	•	•	•	•	•	•	•		•		•	•	•				
Pediatric CNS Disorders, Serum	•	•	•		•	•	•		•	•		•	•	•	•		•									•	•							
Pediatric CNS Disorders, CSF	•	•	•		•	•	•						•	•			•									•	•							
Myelopathy, Serum						•	•		•	•			•	•	•		•	•	•	•	•	•	•	•		•	•			•				
Myelopathy, CSF						•	•						•	•			•	•	•	•	•	•	•	•		•	•			•				
CNS Demyelinating Disease, Serum														•	•																			
PARANEOPLASTIC EVALUATIONS																																		
Paraneoplastic, Serum								•	•	•		•	•				•	•	•	•	•	•	•	•	•									
Paraneoplastic, CSF													•				•	•	•	•	•	•	•	•	•									
PERIPHERAL NEUROPATHY EVALUATIONS																																		
Autoimmune Axonal, Serum		•	•									•					•		•	•	•	•	•	•									
Autoimmune Dysautonomia, Serum						•		•	•	•	•	•					•								•	•								

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

References

1. Flanagan EP, Hinson SR, Lennon VA, Fang B, Aksamit AJ, Morris PP. Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: Analysis of 102 patients. Ann Neurol 2017;81:298-309.
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4. Autoimmune Encephalopathies and Dementias. **McKeon** A.Continuum (Minneap Minn) 2016;22:538-58.

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: No disclosures
- **Consultant or Advisory Role:** No disclosures
- **Stock Ownership:** No disclosures
- **Honoraria:** No disclosures
- **Research Funding:** Euroimmun, Medimmune
- **Expert Testimony:** No disclosures
- **Patents:** pending for the following IgGs as biomarkers of autoimmune neurological disease: septin-5, septin-7, Kelch-like-11, PDE10A, LUZP4, GFAP, MAP1B.

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