AUTOIMMUNE ENCEPHALOPATHY

DEFINITIONS:

- Autoimmune encephalitis (or encephalopathy) (AIE) is a syndrome that involves encephalopathy of acute-subacute onset & related to antibodies either of paraneoplastic or non-paraneoplastic etiology.
- Paraneoplastic syndromes are combinations of symptoms and signs resulting from damage to organs or tissues that are remote from the site of a neoplasm or its metastases.
- Non-paraneoplastic encephalitis is either primary (Ab mainly affecting the nervous system) or secondary to other systemic autoimmune disease (SLE, Sjogren..).

HISTORY:

PARANEOPLASTIC ENCEPHALITIS:

- First paraneoplastic syndrome mentioned in the medical literature was the Trousseau syndrome (venous thrombosis in patients with gastric and pancreatic cancer) in 1825.
- Hermann Oppenheim in 1888 suggested that some of the neurological manifestations in cancer patients could be directly related to the underlying tumor. In 1948 Denny Brown reported degeneration of the dorsal root ganglia (sensory neuronopathy) in patients with bronchogenic lung carcinoma. In 1965, Lambert, Eaton & Rooke described a novel presynaptic neuromuscular transmission syndrome in patients with small cell lung cancer, In 1968 Coresllis was the first one to define limbic encephalitis in 3 patients with subacute memory impairment and lung cancer. In 1985, Graus et al. reported the presence of the first paraneoplastic antibodies (ANNA-1) in patients with subacute sensory neuropathy and small cell lung cancer.

- Why paraneoplastic syndromes usually target the nervous system? because normally the nervous system is immune-privileged zone that is not exposed to the immune system. Expression of neuronal antigens by the tumor will incite an immune response that results in an immune response against either the nervous system, the tumor itself or both.

- Why paraneoplastic & autoimmune encephalitis are usually grouped together? Most paraneoplastic syndromes can cause autoimmune encephalitis, also many of autoimmune mediated encephalitis can be a part of paraneoplastic syndrome.

PRIMARY AUTOIMMUNE ENCEPHALITIS:

- Needs to be added

EPIDEMIOLOGY:

- Autoimmune encephalitis: 5-10 per 100,000
- Most common AIE is ADEM followed by NMDA encephalitis ($2/10^6$)
- Burden of encephalitis associated hospitalization: 20,000 hospitalization per year in US – costing 2billion dollars.
- 60% of cases, we can't reach the etiologic agent of autoimmune encephalitis.

CLASSIFICATION:

ACCORDING TO LOCATION OF ANTIGEN:

1. **NUCLEAR & CYTOPLASMIC ANTIGENS, KNOWN AS "ONCONEURAL AB":**
   - *INCLUDES:* Hu, Ri, Yo, CV2, Ma, PCA, CRMP5, GAD65, GFAP, Recoverin and Tr/DNER. All are considered classic Paraneoplastic antibodies (highly associated with cancer, that's why they are called collectively as onconeural antibodies) except GAD65.
   - *CANCER ASSOCIATION:* Strongly associated with cancer
   - *IMMUNE RESPONSE:* Cell-mediated immune response. In cancer patients there is up-regulation of MHC-I molecules which tend to represent the peptides byproducts from the breakdown of these antigens to cytotoxic T cells initiating the immune response.
   - *RESPONSE TO TREATMENT:* Poor because of the cell-mediated mechanism and the already established damage to the neuronal cells.
   - Called onconeural antibodies; because antigens are specifically present in both tumor cells and neurons.

2. **NEURONAL SURFACE (CELL MEMBRANE & SYNAPTIC) ABBREVIATED "NSABS":**
   - *INCLUDES:*
     - **Against receptors**: NMDA, AMPA, GABA-A, GABA-B, Glycine, Dopamine receptor, Muscle AChR, Ganglionic AChR, P/Q & N type VGCC, mGluR1, mGlur5.
     - **Against ion/water channel:** LGI1, Caspr2, DPPX, aquaporin
     - **Against other cell membrane proteins:** GQ1b, MOG, Amphiphysin
   - *CANCER ASSOCIATION*: highly variable (Ex. 50% with NMDA, 10% with Glycine)
   - *IMMUNE RESPONSE:* direct effect through Ab-mediated immune response.
   - *RESPONSE TO TREATMENT:* usually excellent response with full remission possible.

3. **ENCEPHALITIS WITH AB OF UNCLEAR SIGNIFICANCE:**
   - *INCLUDES:* Hashimoto's encephalopathy (the role and mechanism of anti-TPO/thyroglobulin is not known)
   - *CANCER ASSOCIATION:* not associated with cancer
   - *RESPONSE TO TREATMENT:* Variable

- NB: Amphiphysin is a synaptic protein present on cytoplasmic surface of synaptic vesicles and gets exposed during fusion of vesicles with cell membrane, so it is grouped with membrane rather than cytoplasmic antigens. as it is membrane bound not free cytoplasmic protein and mechanism of involvement is Ab mediated.

ACCORDING TO RELATION TO CANCER:

1) **NOT ASSOCIATED WITH CANCER:** GQ1b – MOG – Aquaporin – Dopamine receptor
2) **USUALLY NOT ASSOCIATED WITH CANCER:** LGI1 – DPPX – GABA-A – AchR – Glycine
3) **MAY BE ASSOCIATED WITH CANCER (AROUND 50% ASSOCIATION WITH CANCER):** NMDA – AMPA – GABA-B – mGluR5 – CASPR2 – GAD
4) **ALMOST ALWAYS ASSOCIATED WITH CANCER:** Hu – Yo - Ri– Ma2- CV2

DIAGNOSTIC CRITERIA:

APPROACH FOR WORKUP AND TREATMENT:

- **REMEMBER**: 50% of patient with autoimmune encephalitis are Ab-negative.
- **APE2 SCORE** (Antibody Prevalence in Epilepsy and Encephalopathy) published by Mayo clinic is a beneficial screening tool to decide which patients to screen for autoimmune encephalopathy:

APE2 Score	
New onset rapidly progressive mental status change over 1-6 weeks or new onset seizure activity (with in past year)	+1
Neuropsychiatric changes, agitation, aggressiveness, emotional lability	+1
Autonomic dysfunction	+1
Viral prodrome (low grade fever, rhinorrhea, sore throat), only scored in absence of history of malignancy within 5 years of onset	+2
Faciobrachial dystonic seizures	+3
Facial dyskinesia, only scored in absence of faciobrachial dystonic seizures	+2
Seizures refractory to 2 AED	+2
CSF consistent with inflammation	+2
Brain MRI suggesting encephalitis	
Systemic cancer diagnosed within 5 years of onset (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor or brain metastasis)	+2

- APE2 score > or = 4 indicates higher possibility of autoimmune disease (98% sensitive, 84% specific)
- If neural specific Ab positive -> definite autoimmune encephalopathy/epilepsy
- If neural specific Ab negative -> immunotherapy trial -> favorable outcome indicates probable (if APE2 >= 7) or possible autoimmune disease (if APE2 = 4:6).
- Immunotherapy trials definition:
    - 12-weeks of IVMP: 1gm daily for 3 days then weekly for 5 weeks then biweekly for 6 weeks (total 11 doses).
    - 6-week of IVMP: 1gm daily for 3 days then weekly for 5 weeks (total of 8 doses).
    - 12-weeks of IVIG: 0.4gm/kg daily for 3 days then weekly for 6 weeks then biweekly for 6 weeks (total of 12 doses)
    - 6-weeks of IVIG: 0.4gm/kg daily for 3 days then weekly for 6 weeks (total of 9 doses)
- Favorable outcome definition: improvement or seizure reduction > 50%

POSSIBLE AUTOIMMUNE ENCEPHALITIS

Diagnosis can be made when all three of the following criteria have been met:

1- Subacute onset (< 12 weeks) of working memory deficits , altered mental status, or psychiatric symptoms
2- At least one of the followings:
    - 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 mm3)
    - MRI features suggestive of encephalitis†
3- Reasonable exclusion of alternative causes

DEFINITE LIMBIC ENCEPHALITIS:

Diagnosis can be made when all four of the following criteria have been met:

1- Subacute onset (< 12 weeks) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system.
2- Bilateral brain abnormalities on T2-weighted FLAIR MRI highly restricted to the medial temporal lobes.
3- At least one of the following:
    - CSF pleocytosis (white blood cell count of more than five cells per mm3)
    - EEG with epileptic or slow-wave activity involving the temporal lobes
4- Reasonable exclusion of alternative causes

DEFINITE ACUTE DISSEMINATED ENCEPHALOMYELITIS:

Diagnosis can be made when all five of the following criteria have been met:

1- A first multifocal, clinical CNS event of presumed inflammatory demyelinating cause
2- Encephalopathy that cannot be explained by fever
3- Abnormal brain MRI:
    - Diffuse, poorly demarcated, large (>1–2 cm) lesions predominantly involving the white matter
    - T1-hypointense lesions in the white matter in rare cases
    - Deep grey matter abnormalities (eg, thalamus or basal ganglia) can be present
4- No new clinical or MRI findings after 3 months of symptom onset
5- Reasonable exclusion of alternative causes

PROBABLE ANTI-NMDA RECEPTOR ENCEPHALITIS

Diagnosis can be made when all three of the following criteria have been met:

1- Rapid onset (< 12 weeks) of at least four of the six following major groups of symptoms:
    - Abnormal (psychiatric) behavior or cognitive dysfunction
    - Speech dysfunction (pressured speech, verbal reduction, mutism)
    - Seizures
    - Movement disorder, dyskinesias, or rigidity/abnormal postures
    - Decreased level of consciousness
    - Autonomic dysfunction or central hypoventilation
2- At least one of the following laboratory study results:
    - Abnormal EEG (focal or diffuse slow activity, epileptic activity, or extreme delta brush)
    - CSF with pleocytosis or oligoclonal bands
3- Reasonable exclusion of other disorders.

DEFINITE ANTI-NMDA RECEPTOR ENCEPHALITIS:

One or more of the six major groups of symptoms:

- Abnormal (psychiatric) behavior or cognitive dysfunction

- Speech dysfunction (pressured speech, verbal reduction, mutism)
- Seizures
- Movement disorder, dyskinesias, or rigidity/abnormal postures
- Decreased level of consciousness
- Autonomic dysfunction or central hypoventilation

Positive IgG anti-NMDA antibodies

Reasonable exclusion of other disorders

Probable Bickerstaff's brainstem encephalitis

Diagnosis can be made when both of the following criteria have been met:

1 Subacute onset (> 4 weeks) of all the following symptoms:
- Decreased level of consciousness
- Bilateral external ophthalmoplegia
- Ataxia

2- Reasonable exclusion of alternative causes

Definite Bickerstaff's brainstem encephalitis

Decreased level of consciousness with Positive IgG anti-GQ1b antibodies (even if bilateral external ophthalmoplegia is not complete or ataxia cannot be assessed).

Steroid-responsive encephalopathy with autoimmune thyroiditis (Hashimoto's Encephalopathy):

Diagnosis can be made when all six of the following criteria have been met:

1- Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes
2- Subclinical or mild overt thyroid disease (usually hypothyroidism)
3- Brain MRI normal or with non-specific abnormalities
4- Presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies
5- Absence of well characterized neuronal antibodies in serum and CSF
6- Reasonable exclusion of alternative cause

>> Thyroid antibodies alone are not diagnostic since it is present in 13% of healthy individuals. No disease-specific cut-off value has been identified. Since the underlying mechanism is still unclear, There is a tendency now to call it "probable autoimmune encephalitis".

Criteria for autoantibody-negative but probable autoimmune encephalitis

Diagnosis can be made when all four of the following criteria have been met:

1- Rapid progression (< 12 weeks) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms.
2- Exclusion of well-defined syndromes of autoimmune encephalitis.
3- Absence of well characterized autoantibodies in serum and CSF, and at least two of the following criteria:
- MRI abnormalities suggestive of autoimmune encephalitis
- CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index.
- Brain biopsy showing inflammatory infiltrates.

4- Reasonable exclusion of alternative causes

WORKUP:

1- ANTIBODY TESTING:

- **ANTIBODY PANEL OR SEPARATE TESTS?**
  - Panels are always a better decision and economically wiser. Only if you're very confident about a diagnosis then a single Ab test may be more economic.
  - Panel may detect more than one Ab which may point to a specific cancer. Ex; If CRMP5 positive and AChR positive then it is more specific for thymoma.
  - If you have broad-differential (a patient with rapidly progressive dementia, unexplained encephalopathy and seizure) then a panel make more sense.
  - Two panels are usually available in different laboratories, Autoimmune CNS panel and paraneoplastic panels, both of them use algorithmic approach (they don't run all the tests on the sample, rather they use certain algorithms to be more cost efficient).

- **BLOOD OR CSF?**
  - Sending **both serum and CSF** will decrease false positive & false negative results.
  - Some Antibodies can be non-specific for CNS autoimmunity as anti-GAD, to confirm CNS involvement intrathecal Ab synthesis rate may be helpful (will need both CSF and serum Ab levels)
  - **CSF is more sensitive for NMDA, AMPA, GFAP & CRMP5.**
  - **Serum is more sensitive for VGKC, NMO & MOG**
  - Advantage of adding CSF testing:
    - CSF titers were found to correlate more with disease activity
    - A positive serum with negative CSF will need additional testing method to rule out false positive result.
    - NMDA: CSF is better (100% of seropositive patients are CSF positive, while only 87% had positive serum cell-based assay and 94% had positive immunohistochemistry)

- **Laboratory methods to detect antibodies:**
  - 3 main methods are used, tissue-based assay, cell-based assay & immunoprecipitation (immunoblotting).

    TISSUE-BASED IMMUNOFLUORESCENT ASSAY (TISSUE-IFA): used as a screening method. Sections of mouse brain are stained with patient's serum or CSF using an indirect immunofluorescence technique. Once Ab in patient's blood reacts to the brain section, it will lighten up under fluorescent microscopy. This will detect any antibody even unknown ones, antibodies are identified based on their staining pattern.
    - Limitations:
      - Mouse brain is different from human brain, the target antigen may not be present which may give false negatives.
      - Antibodies are identified based only on staining pattern which may give false positives.
    - Advantage:
      - Can detect autoimmune reactions that are not identified yet.
      - Used mainly as a screening for autoimmunity. If a reaction was found, a confirmatory test should be done (more specific test).

    CELL-BASED IMMUNOFLUORESCENT ASSAY (CELL-IFA): used for detection of **cell-surface Abs.** A plasmid coding for the specific antigen is inserted into a vector (cell line) then the vector is exposed to the patient's blood. An indirect florescent reaction indicates positivity.
    - Limitations:

        - Only detects what it tests for (VGKC CBA can't detect NMDA Ab), so, it is used mainly for confirmation not for screening.
    - Advantage:
        - More specific than Tissue-based assay (test-cells and control-cells are different only in the introduced antigen, a reaction against test-cells means Ab is directed against the introduced antigen).
        - Antigens are in their natural forms

IMMUNOBLOTTING TECHNIQUE (WESTERN BLOT): used for Abs against **intracellular Ag.** Mouse brain proteins are extracted and purified then using electrophoresis, specific antigens are obtained and placed on membrane strips. A sample of the patient's serum and the control (specific Ab) are applied to the membrane. Reactivity with patient's serum is detected by using enzyme linked (ELISA) or radioisotope techniques (RIA).

- Limitations:
    - Only detects what it tests for (VGKC CBA can't detect NMDA Ab), so, it is used mainly for confirmation not for screening.
    - Antigens are not in their natural forms
- Advantage:
    - Very sensitive, can detect a pico or nano concentrations of tested Ab.
    - Very specific

>> All nuclear, cytoplasmic and synaptic antibodies are typically tested by Western blot.
All surface antibodies should be tested by cell-based assay.

- **Ab-negative patients:**
  Can patient still have autoimmune encephalopathy if autoimmune encephalopathy panel (including tissue based assay) is negative?
    - Tissue-based assay is very sensitive for any antibody directed against the nervous system, however it is not 100% sensitive for some reasons:
        - Antigen denaturation during fixation.
        - Small amount of Ab causing false negative result
        - Difference between human and mouse protein
        - And presence of T-cell dominant autoimmune encephalitis.
    - About 50% of patients who meet criteria for autoimmune encephalopathy will have negative Ab panels, 50% of these Ab-negative patients will still respond to rituximab therapy.
- **Ab-positive patients:**
  Are all patients with positive Ab, symptomatic?
    - No, some patients with SCLC test positive for anti-Hu without developing symptoms.
    - VGKC Ab can be positive in patients with Miller-Fischer syndrome and Bickerstaff encephalitis.
    - NMDA Ab can be positive in some patients with MS and NMO.

- **AVAILABLE PANELS ARE INCLUDED AT THE END OF THIS CHAPTER.**

2- CSF INFLAMMATORY MARKERS:

- **CSF cell count:** Mild pleocytosis is usually found but CSF can be also be normal
- **Intrathecal IgG synthesis rate:**
  - Calculates the amount of IgG synthesized in the CNS by calculating the IgG diffused from blood to CSF based on the amount of increased albumin in CSF then subtracts this amount from total IgG in CSF resulting in the synthesized IgG.
  - Value: indicative of intrathecal inflammatory process, especially if Ab is present in both serum and CSF (as anti-GAD) and you want to make sure it is a relevant finding; Anti-GAD IgG intrathecal synthesis rate will be helpful.
  - Equation: CSF synthesis rate = 5 [{CSF IgG - (Serum IgG/369)} – {(CSF albumin - serum albumin/230)} x 0.43 (serum IgG/serum albumin)]
  - Normal value: -9.9 to +3.3 mg/24 hours
  - Limitation: high false positive results in conditions with BBB disruption
- **CSF IgG Index**:
  - Value: ratio between IgG in the CSF to IgG in the blood
  - Equation: [CSF IgG / Sr IgG] / [CSF Alb / Sr Alb]
  - Normal value: 0.34-0.70
- **Tau, phospho-Tau and Aβ**: Increased Tau with normal phosphor-Tau and amyloid indicates a process involving cell death (not neurodegenerative disease)

3- BRAIN IMAGING:

- **MRI BRAIN:**
  - *ONCONEURONAL AUTOIMMUNE ENCEPHALITIS, SPECIALLY LIMBIC ENCEPHALITIS:* Medial temporal T2-hyperintensities are common and usually followed by hippocampal atrophy in chronic cases.
  - *NMDA ENCEPHALITIS:* MRI is usually normal, only 20-40% of patients may show T2 hyperintensities in various areas of the brain.
  - *VGKC ENCEPHALITIS:* 70% of patients show medial temporal hyperintensities which again may progress to medial temporal atrophy.
  - *GABA-B:* majority of patients have medial temporal hyperintensities
  - *GABA-A:* multiple cortical/subcortical T2-hyperintensities.
- **FDG-PET SCAN:** can be helpful in patients with normal MRI.
  - *LIMBIC ENCEPHALITIS:* may show medial temporal hypo/hypermetabolism
  - *NMDA ENCEPHALITIS:* diffuse (whole brain) or focal (frontal, temporal or occipital) abnormalities.
  - *LGI1 ENCEPHALITIS:* basal ganglia and medial temporal hypermetabolism

4- EEG:

- 90% of patients had non-specific patterns including NCSE, PLEDS or slowing. Extreme delta brush (generalized delta slowing with superimposed fast activity) was seen in NMDA patients who required prolonged hospitalization.

5- CANCER SCREENING:

- Start with MRI chest, abdomen & pelvis with contrast
- Women: gynecological examination, mammography
- Men: prostate & testicular examination and US
- > 60 years old with positive Ab: Whole body PET scan.

CLINICAL PEARLS:

AGE AND GENDER MAY GUIDE DIAGNOSIS:

NMDA Encephalitis:

- Fertile women: 50% associated with ovarian teratoma
- In elderly: 25% associated with somatic cancers
- In children: not associated with cancer

Opsoclonus-Myoclonus syndrome:

- In children: associated with neuroblastoma and Hu antibodies
- In young adults: associated with ovarian teratoma without antibodies
- In elderly: associated with breast cancer and Ri antibodies.

Age of the patient:

- NMDA constitute around 65% of all autoimmune encephalitis with age peak in the 3rd decade.
- LGI1 is the second most common autoimmune encephalitis with age peak in the 7th decade.

CLINICAL MANIFESTATIONS MAY HELP NARROWING THE DIFFERENTIALS:

- Although there is marked overlap between syndromes, the following pearls may ease the differentiation.
  - **Seizures**: more with NMDA, GABA-A, GABA-B, GAD65, LGI1
  - **Faciobrachial dystonic seizures** (very brief intermittent slow movement involving the arm or the face, may resemble a choreic movement specially when the patient tries to put a semi-purposeful component to it, however it is slower than chorea): pathognomonic to LGI1
  - **Psychosis**: NMDA or AMPA
  - **Cerebellar signs:** Yo, Hu, VGCC, GABABR, Caspr2 or GAD65
  - **Diarrhea & weight loss**: DPPX
  - **Rigidity, myoclonus & startle**: Glycine, DPPX, GAD

TREATMENT:

- *RESPONSE*: Neuronal surface Ab (NSAbs) usually respond well to immunotherapy except amphiphysin, DNER and IgLON-5
- *FIRST LINE THERAPY:* steroids, IVIG and PLEX
- *SECOND LINE THERAPY:* Rituximab. Start in 2-3 weeks if no response.
- *CANCER SCREENING* and frequency of repeat screening varies with syndromes.
- *TREATMENT DURATION:* mainly based on clinical judgement. No data available. Titers will remain positive for longtime after the attack and shouldn't be used to guide treatment (can be used to evaluate for relapses though).
- *RELAPSES:* follow up of antibody titer helps to confirm relapse versus fluctuation in disease course.

NUCLEAR & CYTOPLASMIC ANTIBODIES (CLASSIC PARANEOPLASTIC ANTIBODIES)

Antibody	Antigen	Cancer association	Clinical presentation	
ANNA-1 (Hu)	Hu (ELAVL) Drosophila embryonic lethal abnormal visual like protein	90% cancer association • Small cell lung cancer (80%) • Neuroblastoma – thymoma	**Paraneoplastic cerebellar degeneration** **Limbic encephalitis** Brainstem encephalitis Encephalomyelitis **Peripheral neuropathy** (mainly sensory & autonomic)	Usually in older subjects with history of smoking.
ANNA-2 (Ri)	Ri (NOVA)	90% cancer association • Small cell lung cancer • Breast adenocarcinoma (50%) • Ovarian, uterine cancer	Limbic encephalitis **Brainstem encephalitis** **Paraneoplastic Opsoclonus-Myoclonus Ataxia syndrome (POMA)** Cerebellar ataxia Myelopathy Peripheral neuropathy	
ANNA-3	Unknown	90% cancer association • Small cell lung cancer • Digestive system carcinomas	Limbic encephalitis Brainstem encephalitis Myelopathy Peripheral neuropathy	
Ma1 – Ma2	PNMA-1 PNMA-2	95% cancer association • Ma2: Testicular seminoma • Ma1: Testicular, breast & colon	**Hypothalamic disorders** **Limbic encephalitis** Brainstem encephalitis	Usually in younger men < 45 years Seminoma is usually microscopic
PCA-1 (Yo)	CDR2	90% cancer association • Ovary, Mullerian or breast adenocarcinoma	**Paraneoplastic cerebellar degeneration** Brainstem encephalitis Myelopathy Peripheral neuropathy	
PCA-2	MAP1B	90% cancer association • Small cell lung cancer	**Paraneoplastic cerebellar degeneration** Limbic encephalitis Brainstem encephalitis Peripheral neuropathy **LEMS**	
CRMP-5 (CV2)	Collapsin response-mediator protein	90% cancer association • Small cell lung cancer • Thymoma, thyroid or renal carcinoma	**Encephalopathy (Subacute dementia), Depression** **Cerebellar ataxia, Chorea** **Optic Neuropathy** Myelopathy, Radiculopathy, Neuropathy **LEMS**	
Amphiphysin	Amphiphysin (Protein present on cytoplasmic surface of synaptic vesicles)	90% cancer association • Small cell lung cancer • Breast adenocarcinoma	**Encephalopathy (Subacute dementia)** **Aphasia** Limbic encephalitis **Stiff person syndrome** Myelopathy Neuropathy	
GAD65	GAD65 (Glutamic acid decarboxylase)	10% cancer association • Thymoma, Renal cell carcinoma, Breast or colon adenocarcinoma	**Cerebellar ataxia** **Seizures** **Limbic encephalitis (Usually with tumors)** Brainstem encephalitis **Parkinsonism** **Ophthalmoplegia**	**Low titer:** present in 80% of type-1 diabetics. **High titer**: associated with neuro-immunological disorders (RIA>1:1000 – ELISA > 1:10,000 – CBA +ve – immunohistochemistry +ve)

			Myelopathy **Stiff person syndrome** **Stiff Person Syndrome Plus (PERM; progressive encephalopathy, rigidity & myoclonus)**	**Borderline titer**: intrathecal antibody production & oligoclonal bands support immune neurological disorder.
GFAP	GFAP	Teratoma	Meningoencephalitis – Myelitis - Bilateral optic disc edema	Mainly in CSF
GRAF1 (Ca)	Purkinje cells (GTPase regulator associated with focal adhesion kinase)	Ovarian cancer	Cerebellar ataxia	
Recoverin	Recoverin	Small cell lung cancer Neuroendocrine carcinomas	Retinopathy	
AGNA(anti-glial nuclear)	SOX-1	90% cancer association • Small cell lung cancer	Limbic encephalitis **LEMS** Peripheral neuropathy	
Zic4	Zic gene encodes for Zinc finger proteins	Small cell lung cancer	Cerebellar ataxia	
AK5	Adenylate kinase 5	Not known yet	Limbic Encephalitis	Common in elderly (55-80)

ANNA: anti-neuronal nuclear antibody – AGNA: anti-glial nuclear antibodies - ELAVL: Drosophila Embryonic lethal abnormal visual like protein – LEMS: Lambert Eaton Myasthenic syndrome

Steps to memorize clinical manifestations of classical Paraneoplastic antibodies:

- **There are 12 cytoplasmic/nuclear antibodies, 11 are classic and only one (GAD65) is not classic.** Classic means associated with cancer and poor response to immunotherapy.
- **Antibody-based memorization:**
  Out of the 12, 2 are associated with single characteristic Paraneoplastic syndrome (GFAP – Recoverin), while the other 10 may present with multiple syndromes.
  The other 10, all can cause limbic encephalitis, myelopathy and neuropathy plus the following:
  - ANNA2: Opsoclonus-myoclonus
  - Ma: hypothalamic dysfunction
  - PCA1: cerebellar ataxia
  - PCA2: ataxia and LEMS
  - CRMP: ataxia, LEMS and Subacute dementia
  - Amphiphysin: Stiff person syndrome, aphasia & Subacute dementia
  - GAD65: Stiff person syndrome, parkinsonism, seizures, ataxia, Ophthalmoplegia
  - AGNA: LEMS
- **Syndrome-based memorization:**
  - Paraneoplastic Limbic encephalitis (LE): Almost all classic antibodies can cause it, big ones are ANNA1, ANNA2, Ma2, CRMP5.
  - Paraneoplastic cerebellar degeneration (PCD): PCA1, PCA2, ANNA2, Ma, CRMP5, AGNA, DNER (surface Ab).
  - Paraneoplastic Opsoclonus myoclonus syndrome (POMS/POMA): ANNA1 in children (with neuroblastoma), ANNA2 in adults (with breast cancer).
  - Paraneoplastic Encephalomyelitis: ANNA1, CRMP5, Ma2, Amphiphysin
  - Paraneoplastic Subacute sensory neuropathy (SSN): ANNA1, CRMP5
  - Paraneoplastic Stiff person syndrome: Amphiphysin

NEURONAL SURFACE ANTIBODIES (CELL MEMBRANE & SYNAPTIC)

	Antibody	Antigen	Cancer association	Clinical presentation	Sample
Autoimmune Channelopathies					
VGKC Complex	LGI1	Leucine-rich, glioma Inactivated protein 1 Part of VGKC complex that interacts with other epilepsy-related proteins.	10% (Thymoma)	**Limbic encephalitis** (focal seizures followed by memory loss, disorientation and behavioral abnormalities) **Focal seizures** may be dyscognitive, dysautonomic or facio-brachial dystonic seizures (FBDS) **Facio-brachial dystonic seizures**: very brief repetitive dystonic contraction of the arm and face, refractory to AED treatment. **Insomnia and RBD** (REM behavior disorder) **Hyponatremia** in 60%. **Bradycardia** that may require pacemaker Ab positive in: serum > CSF CSF with lymphocytosis and OCB only in 50% of patients (50% will have normal CSF) MRI with T2 hippocampal hyperintensity in 74% of patients MRI/CSF negative in 1/3 of patients Response to immunomodulation: quick and marked response Residual deficits: amnesia for the disease period in 86% Relapses: third of patients develop relapses, can be as far as 8 years after initial episode. *N.B: mutation in LGI1 protein results in autosomal dominant lateral temporal lobe epilepsy*	**Serum**
	CASPR2	Contactin associated protein type 2 Part of VGKC complex in the brain & myelinated axons.	10:30% (Thymoma)	**Neuromyotonia (Isaac Syndrome)** **Morvan syndrome:** more in patients with thymoma. Presents with diffuse hyperexcitability involving autonomic (hyperhidrosis & dysautonomia), peripheral (neuromyotonia, hyperexcitability) and central nervous systems (limbic encephalitis) **Limbic encephalitis** (focal seizures followed by memory loss, disorientation and behavioral abnormalities) in few cases. Good response to treatment, but relapses in 35% of patients. *N.B: CASPR2 mutation is seen in patients with autism*	**Serum**
	DPPX	Dipeptidyl-peptidase–like protein 6 Part of VGKC complex in the brain and myenteric plexus, prevents back-propagation of action potentials.	< 10% (Lymphoma)	**Triad of GI symptoms (diarrhea-weight loss), cognitive dysfunction, CNS hyperexcitability** Starts with diarrhea, weight loss (average 20Kg) followed by CNS hyperexcitability (myoclonus, seizures, hyperekplexia) and cognitive dysfunction (memory loss, hallucinations, agitation) over a few months period. By the time neurological symptoms appear, the GI symptoms have resolved.	**CSF & Serum**
	Contactin2	Contactin2 protein Part of VGKC complex in myelinated axons, forms bridges between the axon surface and myelin .	None	Although Contactin2 Ab were detected in a small number of patients with multiple sclerosis, it is not associated with disease activity and not associated with specific set of symptoms.	
	LGI1/CASPR2/DPPX negative VGKC	Antibodies against other parts of the VGKC complex.	No specific cancer association	Uncertain clinical significance. Can be seen in normal individuals with no symptoms.	
	VGCC P/Q & N	P/Q & N type VGCC	15% (SCLC, breast or gynecological cancers)	**Lambert Eaton Myasthenic Syndrome** (proximal weakness, dry mouth, constipation) Patients with LEMS should be screened with CXR every 6 months for lung cancer. **Cerebellar ataxia**	**Serum**
	NMO-IgG	Aquaporin-4	None	NMO Spectrum Disorders (NMOSD), may present with encephalitis in children.	**Serum**

Autoimmune Receptoropathies					
	NMDA	GluN1 receptor	50% cancer association • Fertile women: Ovarian teratoma • Elderly: other cancers • Children: no cancer	Sometimes symptoms are preceded by headache and flu like symptoms that can persist for weeks/months then patients developed psychiatric symptoms (agitation, paranoia, psychosis), later on confusion, memory impairment and seizures proceed. Ab positive in: CSF > Serum MRI with variable T2 hyperintensities (percent) Response to immunomodulation: responsive but may take 1-2 years for full recovery – very sensitive to neuroleptics (may develop NMS) Residual deficits: 20% may attain residual deficits Relapses:	**CSF**
	AMPA	GluR1,2 receptor	70% (SCLC, breast, thymus)	**Limbic encephalitis** in 50% of patients – Tend to relapse Symptoms may vary from a single symptom (Confusion, disorientation – memory impairment – seizures) to multi-symptoms (similar to limbic encephalitis) to fulminant encephalitis. Patients may have coexisting other onconeural antibodies	**CSF**
	Metabotropic glutamate 1	mGluR1	70% (Hodgkin lymphoma)	Cerebellar ataxia (idiopathic or paraneoplastic)	
	Metabotropic glutamate 5	mGlur5	Hodgkin lymphoma	**Ophelia Syndrome** (Limbic encephalitis with memory, cognitive and psychiatric symptoms in patients with Hodgkin lymphoma) Usually respond well to treatment.	
GABA Receptor	GABA-B	GABA-B receptor	70% (SCLC, neuroendocrine neoplasms)	**Limbic encephalitis with marked refractory seizures** Patients may have coexisting other onconeural antibodies MRI: bilateral medial temporal SI	**CSF**
	GABA-A	GABA-A receptor	None	**Limbic encephalitis with marked refractory seizures or status epilepticus** MRI: multifocal cortical/subcortical or diffuse SI, can be associated with some enhancement	**CSF**
	Dopamine-2	Dopamine-2 receptor	None	**Sydenham chorea** **Basal ganglia encephalitis (parkinsonism, chorea, dystonia)**	
	Muscle AChR	Muscle AChR	10% cancer association	Myasthenia gravis	
	Ganglionic AChR	Ganglionic AChR	10% (thymoma – other cancers)	**Dysautonomia**	
	Glycine	α1 subunit of GlyR (Present in brainstem & Spinal cord)	10% cancer association	**Stiff person syndrome** **PERM**: progressive encephalopathy, rigidity and myoclonus – more severe form of stiff person syndrome **Hyperekplexia**	
Cell Adhesion Proteinopathies					
	IgLON-5 associated tauopathy	Cell adhesion protein IgLON (LAMP, OBCAM, Ntm)	None	**Parasomnias – REB and non-REM behavior disorder – Chorea – Dementia – Ataxia – Vertical gaze palsy** **Poor response to treatment** Pathology shows tauopathy that is different in distribution from all known tauopathies– so it is autoimmune disease causing neurodegenerative disease which is unique. Usually doesn't respond to steroids.	
	Neurexin-3 α	Cell adhesion protein	None	Prodrome of headache, fever, GI upset followed by seizures and altered mental status.	
	DNER (previously known as Anti-Tr)	Delta/notch-like epidermal growth factor-related receptor	Hodgkin lymphoma in 90%	Paraneoplastic cerebellar degeneration -> nystagmus, dysarthria, limb ataxia and gait ataxia **History**: Hodgkin disease patients with cerebellar degeneration were found to have their sera react against Purkinje cells in a specific pattern, named "Anti-Tr Ab pattern". In 2015, the target of Anti-Tr was found to be DNER. **Protein**: transmembrane protein carrying extracellular EGF-like repeats, DNER is upregulated in various cancers and knocking this protein down decreased cell proliferation and invasion.	

Add: Anti-Tr – Anti-Zic4 – GFAP – MOG - SREAT

Systemic autoimmune diseases associated with autoimmune encephalitis:

Lupus: Bilateral medial temporal involvement – CSF pleocytosis

Sjogren: unilateral – unknown CSF

Behcet: bilateral – pleocytosis

Infection-related autoimmune encephalitis:

HSE: HSV may trigger an autoimmune encephalitis which will manifest with psychiatric symptoms in adults and choreoathetosis in children – Some patients test positive for NMDA Ab.

ANTIBODY-ASSOCIATED SYNDROMES:

Anti-NMDA ENCEPHALITIS:

PROTEIN: **(a brief introduction on location and function of protein)**

EPIDEMIOLOGY:

- Second most common cause of AE (after ADEM), incidence about 2 per million.
- Median age of incidence is 20 with a wide age range (2month to 93 years). Youngest reported age was 2 months.
- Most common cause of AE associated with psychosis (many patients get admitted to psychiatric wards).

CANCER ASSOCIATION: not associated with cancer in children and middle-aged men, 50% associated with ovarian teratoma in fertile women, 25% associated with other somatic cancers in elderly.

CLINICAL PICTURE:

- Classic presentation (in middle aged individuals):
  - **Prodrome** (flue like symptoms with headache, fever & malaise) -> presence of fever may make the diagnosis more challenging.
  - **Early stage**: Behavioral changes (agitation, anxiety) & psychiatric manifestations (hallucinations, paranoid delusions) along with memory impairment and sleep impairment (insomnia, RBD).
  - **Advanced stage** (weeks later): impaired consciousness, abnormal movement, seizures & autonomic instability. Some patients may require mechanical ventilation.
- In Children: presents with seizures and altered mental status -> idiopathic seizure-like picture
- In Elderly: presents with memory deficits and abnormal behavior -> rapidly progressive dementia like picture
- Rare: may present with isolated psychosis in 4% of patients
- Controversial: whether NMDA Abs have a role in patients with schizophrenia (a study found NMDA Ab present in 19% of patients with schizophrenia and only 3% of normal individuals, there were no Ab in CSF though).

TESTING:

- **Routine CSF**: elevated protein and mild pleocytosis in 90%
- **Antibodies**: NMDA Ab tested in CSF (more sensitive than serum) using CBA which is 90% sensitive and 100% specific.
- **EEG**: abnormal (focal slowing or epileptogenic activity)
- **MRI**: Normal in 70%

TREATMENT:

- Usually responsive to immunomodulating therapy however recovery may be slow and may take 1-2 years for full recovery. (don't be disappointed if patient doesn't recover quickly after PLEX or IVIG).
- Patients are sensitive for antipsychotics with tendency to develop reactions including NMS.

ANTI-LGI1 ENCEPHALITIS:

PROTEIN: Leucine-rich, glioma Inactivated protein 1. Part of VGKC complex that interacts with other epilepsy-related proteins. *Off note, mutation in LGI1 protein results in autosomal dominant lateral temporal lobe epilepsy*.

EPIDEMIOLOGY:

- More common in HLA-DR7 and HLA-DRB4 in non-paraneoplastic patients, paraneoplastic etiology is more likely if patient is not HLA-DR7 or DRB4.

CANCER ASSOCIATION: 90% are not associated with cancer – only 10% are associated with thymoma.

CLINICAL PICTURE:

- **Early stage**:
  - **Seizures**: either faciobrachial dystonic seizures (FBDS in 45%) or focal tonic seizures (in 65%). Faciobrachial dystonic seizures are very brief (seconds), involve face and arm and are usually very frequent (tens to hundreds per day). It can mimic chorea (very brief, patient may try to give it a purpose). FBDS usually doesn't show up on EEG and is usually refractory to AED.
  - **Memory loss**: shortly after the beginning of seizures, patient will develop memory impairment.
  - **Bradycardia, hyponatremia (in 60%), Insomnia and RBD**
- **Advanced stage** (weeks later):
  - Generalized tonic clonic seizures
  - Limbic encephalitis: Marked memory loss, disorientation and behavioral abnormalities.

- Rare:
- Controversial:

TESTING:

- **Routine CSF**: usually normal, some patients may have pleocytosis or positive OCB.
- **Antibodies**: LGI1 seen in serum better than CSF
- **EEG**: usually unremarkable
- **MRI**: hippocampal hyperintensity seen in 74% of patients, bilateral basal ganglia signal hyperintensities are seen in some patients.

TREATMENT:

- Quick and marked response to immunomodulating therapy however many patients will continue to suffer from cognitive dysfunction.
- Seizures usually subside completely with immunotherapy (no long-term AED)
- Cognitive dysfunction, amnesia to the active disease period and spatial disorientation are seen in 86% of patients.
- The earlier the treatment with immunotherapy, the less cognitive dysfunction.
- 30% of patients will develop future relapses (as far as 8 years after initial episode)

ANTI-CASPR-2 ENCEPHALITIS:

PROTEIN: Contactin associated protein type-2. Part of VGKC complex, present in the brain & juxta-paranodal regions of myelinated axons. Responsible for local differentiation of the axons at node of Ranvier.

EPIDEMIOLOGY:

CANCER ASSOCIATION: 80% are not associated with cancer, 20% have thymoma.

CLINICAL PICTURE:

- Usually subacute (weeks) or chronic (months) onset.
- Usual presentation is limbic encephalitis, Morvan syndrome or another picture in-between.
- Symptoms include confusion, cerebellar symptoms, dysautonomia, peripheral hyperexcitability (neuromyotonia, exaggerated startle response).
- Half of patients will have seizures, but usually not prominent feature.

- Rare:
- Controversial:

TESTING:

- **Routine CSF**: normal in 65% of patients
- **Antibodies**: Caspr2 is seen more in blood than CSF
- **EEG**: usually normal
- **MRI**: Normal in 70%
- **EMG**: neuromyotonia may be seen.

TREATMENT:

- Good response to treatment in most patients.
- The earlier the treatment with immunotherapy, the less cognitive dysfunction.
- 35% of patients will develop future relapse

ANTI GABA-B ENCEPHALITIS:

PROTEIN:

EPIDEMIOLOGY:

CANCER ASSOCIATION: 50% of patients have SCLC, most of them are not discovered before encephalitis.

CLINICAL PICTURE:

- Seizures and status epilepticus that is refractory to AED.
- Some patients may show opsoclonus, myoclonus or ataxia.

TESTING:

- **Routine CSF**:
- **Antibodies**: GABA-B Ab seen more in CSF than in serum
- **EEG**:
- **MRI**: Temporal signal hyperintensity in 65% of patients

TREATMENT:

- Responds very well to immunotherapy and chemotherapy
- Prognosis depends on tumor respectability.

ANTI GABA-A ENCEPHALITIS:

PROTEIN:

EPIDEMIOLOGY: All age have been involved, from 3 to 65 years.

CANCER ASSOCIATION: not associated with cancer

CLINICAL PICTURE:

- Memory loss, seizures and status epilepticus that is refractory to AED.

TESTING:

- **Routine CSF**:
- **Antibodies**: GABA-A Ab seen more in CSF than in serum
- **EEG**:
- **MRI**: non-specific signal hyperintensities

TREATMENT:

- Tends to respond to immunotherapy and chemotherapy

Clinical Syndromes (By presenting symptoms):

Acute Psychosis and Behavioral changes:

- **Clinical Picture**: acute development of psychosis (delusions, hallucinations) and behavioral changes in patients with no past history of psychiatric illness and no systemic cause. Such patients should be tested for both infectious and autoimmune etiology.
- **Association:**
    - All cell surface AE can present with psychosis and behavioral changes. Psychosis is an early feature of NMDA AE, can also be seen as a late manifestation of other cell-surface AE.
    - Most common AE associated with psychosis: NMDA encephalitis
    - Other AE associated with psychosis include: AMPA, DPPX, LGI1, CASPR2
- **Under investigation**: Whether NMDA Abs have a role in patients with schizophrenia (a study found NMDA Ab present in 19% of patients with schizophrenia and only 3% of normal individuals, there were no Ab in CSF though).

Seizures:

- Clinical Picture:
- **Association:**
    - All cell surface AE can present with seizures. Seizures is an early and prominent feature in LGI1, Caspr2, GABA-B, GABA-A and GAD65.
    - GAD65 Ab are non-specific if present in low titers, usually associated with neurological symptoms if the titer is high > 1:1000 in RIA - > 1:10,000 in ELISA or positive in CBA).
- **Under investigations**:
    - Incidence of AE antibodies in patients with chronic epilepsy and status epilepticus.
    - A recent study showed incidence of antibodies in 11% of patients (double negative VGKC, GlyR, NMDA & GAD65). The results were controversial given the non-specificity of double negative VGKC and GAD65 which can be seen in normal individuals.
    - A recent study had found that 37% of patients with status epilepticus with negative workup have probable autoimmune encephalitis (25% of those patients had positive antibodies).

Autoimmune Cerebellar Ataxia (ACA):

- **Clinical Picture:**
- **Association**:
    - Paraneoplastic: Anti-Hu, ANNA3, Yo, CV2, Tr, Zic4, GRAF, PKCγ, PCA2, CARP, ITPR1, VGCC
    - Autoimmune: mGluR1

Limbic encephalitis:

- **Clinical Picture:** rapidly progressive cognitive decline with memory deficits, psychiatric disturbance and possible seizures.
- **Association:**
    - **Intracellular:** Ma2 – Hu – CV2 – AK5 – Amphiphysin
    - **Surface:** LGI1 – CASPR2 – DPPX – GABA A – GABA B – AMPA -

Neuromyotonia:

- Serology: Most patients are antibody-negative while some of them are CASPR2 positive
- Symptoms: cramps, fasciculations, hypertonia
- Differential: Can be confusing with ALS (due to presence of fasciculations and hypertonia)
- Cancer association:
-

MORVAN SYNDROME:

- Serology: some patients are CASPR2 positive
- Symptoms:
- Differential: rapidly progressive dementias
- Cancer association: thymoma

DIFFERENTIAL DIAGNOSIS:

Rapidly progressive dementia or encephalopathies:

- Autoimmune: Morvan syndrome, limbic encephalitis, DPPX encephalitis
- Infectious: CJD
- Metabolic: hypothyroidism, Vitamin B deficiency (B1,6, 12)

Autoantibodies that can be positive in sera of normal individuals:

- GAD65
- GABA-A

Antibodies that can be positive with other diseases:

- NMDA: in some patients with MS and NMO
- VGKC: in some patients with Miller-Fischer syndrome

Autoimmune encephalitis with poor response to immunotherapy: IGLON – Post-HSE

Notes from AAN:

- GAD 65, 67: presynaptic to glycine receptor – present with SPS or PERM –
- Autoimmune encephalitis : likely caused by B-cells itself rather than Ab which can't cross BBB.
- HSV encephalitis can developed choreoathetosis post-herpes encephalitis few weeks later (6-7 weeks) – seen in 27% of patients which is autoimmune encephalitis. Some patients develop NMDA encephalitis after completing ttt for HSV encephalitis that require cyclophosphamide or other immunomodulators.

- **Types of Rcs: blockers – internalization - …. Types of immunity, B cell or T cell or Ab. – Response to treatment – association with cancer.**

Questions need answers:

- NMDA Ab are present in 10% of population, however it is not symptomatic except in a small proportion of those who test positive. The questions is why some people are symptomatic and others are not?
    - Answer: immunoglobulins in asymptomatic people are usually IgA and IgM which doesn't reach the brain. In patients with NMDA AE, it is usually IgG that found in CSF that is directed against GluN1.
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AVAILABLE AUTOIMMUNE/PARANEOPLASTIC PANELS

Laboratory – Test name - *sample (Abbrev)*	Always performed	Reflexely performed	Not performed
Mayo Clinic – Paraneoplastic – *Serum* (PAVAL)	**Tissue IFA**: ANNA1,2,3 – PCA1,2 – PCA Tr – AGNA1 – Amphiphysin, CRMP5 **RIA**: VGCC – AChR binding – AChR ganglionic – VGKC ELISA – Striational Ab	**If AChR +ve ->** modulating Ab & CRMP-5 **If VGKC +ve ->** CASPR2 & LGI1 CBA **Based on Tissue-IFA pattern, may add ->** NMO FACS, NMDA CBA, AMPA CBA, GABA-B CBA, GAD Ab assay **If Tissue IFA +ve for specific Ab ->** confirmed with western blot	Ma/Ta DPPX, Recoverin, GFAP, Zic4
Mayo Clinic - Paraneoplastic – *CSF* (PAC1)	Only Tissue IFA is performed		Ma/Ta DPPX - Recoverin – GFAP Ganglionic AChR – VGCC
Mayo Clinic – Autoimmune encephalopathy – *Serum* (ENS1)	**Tissue IFA**: ANNA1,2,3 – PCA1,2 – PCA Tr – AGNA1 – Amphiphysin, CRMP5 **RIA**: VGCC – AChR binding – AChR ganglionic – VGKC ELISA – GAD65 **Cell-based assay:** NMDA – AMPA – GABA-B – CASPR2 – LGI1	**If Tissue IFA +ve ->** western blot confirmation	DPPX, Recoverin, GFAP, Zic4
Mayo Clinic – Autoimmune encephalopathy – *Serum* (ENS2)	**Tissue IFA**: ANNA1,2,3 – PCA1,2 – PCA Tr – AGNA1 – Amphiphysin, CRMP5, DPPX, GFAP, mGluR1 **RIA**: VGCC (CCN & CCPQ) – AChR binding – AChR ganglionic – VGKC ELISA – GAD65 **Cell-based assay:** NMDA – AMPA – GABA-B – CASPR2 – LGI1	**If CRMP5, AMPA, CASPR2 +ve =>** AChR binding/modulating – CRMP5 WB **If ANNA, PCA, CRMP5 or Amphiphysin indeterminate =>** paraneoplastic WB panel **If IFA DPPX, GFAP, mGluR1 or Amphiphysin are positive =>** confirmed with CBA or WB	
Mayo Clinic – Autoimmune encephalopathy – *CSF* (ENC1)	**Tissue IFA**: ANNA1,2,3 – PCA1,2 – PCA Tr – AGNA1 – Amphiphysin, CRMP5 **RIA**: VGKC– GAD65 **Cell-based assay:** NMDA – AMPA – GABA-B – CASPR2 – LGI1	**If Tissue IFA +ve ->** western blot confirmation	Ganglionic AChR – VGCC DPPX - Recoverin - GFAP
Mayo Clinic – Autoimmune encephalopathy – *CSF* (ENC2)	**Tissue IFA**: ANNA1,2,3 – PCA1,2 – PCA Tr – AGNA1 – Amphiphysin, CRMP5, DPPX, GFAP, mGluR1 **RIA**: VGKC– GAD65 - AChR ganglionic – CCN (N type) – CCPQ (P/Q type) **Cell-based assay:** NMDA – AMPA – GABA-B – CASPR2 – LGI1	AChR binding – AchR modulating – AMPA-R – Paraneoplastic western blot Doesn't include CRMP5 WB – Ma1,2 (substitute with testicular US for males) CRMP5 western blot for highly suspicious cases (chorea, visual loss, myelopathy, cranial neuropathy) can be added if requested (CRMP5 low titers may not show on IFA)	
Athena – Paraneoplastic Neurological Initial Assessment - *Serum* (4500)	Ma/Ta, CV2, Amphiphysin, ANNA1,2 , PCA1	**Brief, limited panel with quick turn-around (3-5 days)**	Narrow spectrum panel
Athena - NeoComplete Paraneoplastic Evaluation - *Serum* (467)	LGI1, CASPR2, VGKC, NMDA, GAD65 Ma/Ta, CV2, Amphiphysin, ANNA1,2 , PCA1, Zic4, Recoverin, VGCC, AChR ganglionic		ANNA3, PCA2, PCATr, AGNA, AChR binding, Striational Ab

Athena - NeoEncephalitis Paraneoplastic Evaluation - *Serum* (447)	LGI1, CASPR2, VGKC, NMDA, GAD65 Ma/Ta, CV2, Amphiphysin, ANNA1	**N.B: only for autoimmune encephalitis of paraneoplastic origin (in cancer patients)**	ANNA2,3, PCA1,2,PCATr, AGNA, VGCC, AChR, AChR ganglionic, NMDA, AMPA
Athena - NeoCerebellar Degeneration paraneolastic eval - *Serum* (438)	GAD65, Ma/Ta, CV2, Amphiphysin, ANNA1,2 , PCA1, Zic4		PCA2, PCATr
Athena - NeoSensory neuropathy paraneoplastic eval - *Serum* (436)	CV2, Amphiphysin, ANNA1		
Athena – Autoimmune Rapidly Progressive Demenita with Recombx - *Serum* (1711)	VGKC - CASPR2 – LGI1 – GAD65 – NMDA – Amphiphysin – CV2 – ANNA1 – Ma/Ta		DPPX, PCA, AChR Ganglionic

- **CBA:** cell-based assay **– FACS:** fluorescence-activated cell sorting – **IPA**: immunoprecipitation assay
- Panels usually require 2ml sample, most paraneoplastic panel turnaround time is 28 days. Athena tests are all serum, not CSF.