# AUTOIMMUNE ENCEPHALITIS

## DEFINITION:

- Autoimmune encephalitis (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 ($2/10^6$)

# 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:

- Remember that 50% of patient with autoimmune encephalitis are Ab-negative.

## 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 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 <u>all four of the following</u> 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 <u>all five of the following</u> 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 cerebral 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 <u>all three</u> of the following criteria have been met:

1- Rapid onset (< 12 weeks) of at least <u>four</u> 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 or disorganized 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-GluN1 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).

# WORKUP:

## ANTIBODY TESTING:

- **ANTIBODY PANEL OR SEPARATE TESTS?**
  - If you suspect only one or two Ab, then separate test orders should be the right decision.
  - If you have broad-differential (a patient with rapidly progressive dementia, unexplained encephalopathy and seizure) then a panel testing may be more efficient.
  - 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.
  - 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 patients are CSF positive, while only 87% had positive serum cell-based assay and 94% had positive immunohistochemistry)
- **Laboratory methods:**
  - 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. 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).

*IMMUNOBLOTTING TECHNIQUE (WESTERN BLOT):* used for Abs against intracellular Ag. The specific antigen protein is obtained by electrophoresis then transferred onto a membrane. 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.
- Advantage:
  - Very sensitive, can detect a pico or nano concentrations of tested Ab.
  - Very specific

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

- Ab-negative autoimmune encephalitis: Why we still think the 50% Ab-negative patients are still having autoimmune encephalitis if 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.
  - 50% of these 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.

## CSF INFLAMMATORY MARKERS:

- **INTRATHECAL IGG SYNTHESIS RATE:**
  - Calculates the amount the 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: Similar to IgG synthesis rate
  - Equation: [CSF IgG / Sr IgG] / [CSF Alb / Sr Alb]
  - Normal value: 0.34-0.70

### BRAIN IMAGING:

- **MRI BRAIN:**
  - *ONCONEURONAL AUTOIMMUNE 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

### 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.

### 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 3$^{rd}$ decade.
- LGI1 is the second most common autoimmune encephalitis with age peak in the 7$^{th}$ 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.