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:
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MORVAN SYNDROME:

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