Viral and auto-immune Encephalitides

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Encephalitis: inflammation of the brain parenchyma with neurologic dysfunction

Infectious, postinfectious, and noninfectious causes.

A heterogenous group of disorders.

Their global prevalence is uncertain.

Causes remain unknown (60%)

Infectious: 50% of identifiable cases and the most common etiology.

21% Immune mediated cause (ab against neuronal cell surface or synaptic proteins)

Venkatesan A. Curr Opin Neurol. 2015
GBD 2016 Neurology CollaboratorsLancet Neurol. 2019
Introduction

- Improvement in prognosis in the last two decades: -27% in mortality since 1990.
- Prompt recognition and treatment can be lifesaving.
- Mortality rates still too high around 5–15%, with marked physical and cognitive morbidity among survivors.

Venkatesan A. Curr Opin Neurol. 2015
GBD 2016 Neurology CollaboratorsLancet Neurol. 2019
Case n°1 : Patient Y.Z.

- 20 years – old male.
- Influenza – like syndrome during a week.
- Behavioural disorders and tonic – clonic seizures.
- On neurological examination:
  - T°:39, **confusion**.
  - **contamination delusion**.
  - **pyramidal syndrome**.
T2/FLAIR and diffusion hyperintensities in insula
Case n°1 : Patient Y.Z.

Delta slow waves on the right hemisphere with right cerebral dysfunction
Case n°1 : Patient Y.Z.

- Lumbar puncture:
  - WBC : 120/mm³ (90% lymphocytes).
  - CSF glucose and CSF albumin : normal.
  - HSV (1 + 2) serology in CSF : positive for IgM.

- Herpes simplex virus meningo – encephalitis.
Case n°1 : Patient Y.Z.

- Our patient received:
  - **Aciclovir 10 mg/kg every 8 hours for 21 days in ICU.**
  - **Valproic acide 500mg/j (15mg/kg daily).**

- no recurrence of seizures.
- no cognitive sequelae: MMSE = 30/30.
- presence of psychiatric sequelae:
  - anxiety.
  - hyperphagia.
  - attention disorder.
Herpetic encephalitis: History

- Herpetic infections recognized since the time of ancient Greece.
- The word herpes translates as “creeping” or “crawling”: reference to herpetic skin lesions.
- 1920s, the Mathewson commission suggested HSV caused encephalitis.
- 1944: 1st adult case, a 25-y man with headache, fever, aphasia, and left pupillary dilatation.
- Postmortem: petechiae and ecchymoses with perivascular lymphocytic cuffing in the left temporal lobe, midbrain, and pons.

Michael J. Bradshaw 2016
Herpetic encephalitis: Prevalence

- HSV-1 infection is common, with seropositivity among older adults 60–90%.
- HSV-1 is consistently the single most common cause of sporadic encephalitis.
- Incidence: between 2 and 4 cases/1,000,000.
- Bimodal distribution: up to 3 years of age, and adults aged > 50 years.

Smith JS, Robinson NJ. J Infect Dis. 2002
Granerod J et al. Lancet Infect Dis 2010
Mechanisms by which HSV gains access to (CNS): unclear

- Retrograde transport through the olfactory or trigeminal nerves, or via hematogenous dissemination.
- Olfactory nerve pathways do not route through the thalamus but connect directly to the frontal and mesiotemporal lobes.
- Virions can spread to the contralateral temporal lobe via anterior commissure.
Herpetic encephalitis: Diagnosis

- Prodromal symptoms: upper respiratory tract or other systemic infection.

- Most common manifestations:
  - Altered mental status (typically for ≥ 24 h)
  - fever
  - seizures, headaches
  - focal neurological deficits.

Rozenberg F. 2020
Herpetic encephalitis: Diagnosis

- MRI: contrast-enhancing lesions
- (CSF) pleocytosis ($\geq 5$ nucleated cells/ml)

Diffusion restriction on diffusion weighted imaging (DWI) in the left mesial temporal lobe and (FLAIR) hyperintensity

Rozenberg F. 2020
Herpetic encephalitis: diagnosis

- **EEG**: periodic discharges, focal or generalized slowing, and electrographic seizures, including status epilepticus.

Stahl JP, Mailles A. Curr Opin Infect Dis. 2019
Management

First line treatment, before microbiological results:

► Acyclovir 10 mg/kg every 8 hours

► Amoxicillin (200 mg/kg/day as 4 infusions minimum, or as a continuous administration)

► a reevaluation is performed at 48 hours.

► the acyclovir dose must be increased to 15 mg/kg every 8 hours in case of skin vesicles or imaging signs of vasculopathy (VZV).

Stahl JP. Rev Neurol. 2019
Corticosteroids:

- clinical evidence in humans is scant
- reserved for patients in whom there is significant edema and mass effect.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Typical dosing/administration</th>
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| HSVE                             | Aciclovir, 10 mg/kg i.v. q8h for 14–21 days  
Renal insufficiency  
CrCl 25–50 ml/min/1.73 m²: 10 mg/kg q12h  
CrCl 10–25 ml/min/1.73 m²: 10 mg/kg q24h  
CrCl <10 ml/min/1.73 m²: 5 mg/kg q24h  
Thrice-weekly hemodialysis: 2.5–5.0 mg/kg q24h (given after dialysis)  
Peritoneal dialysis: 10 mg/kg q24h  
Hepatic impairment: no adjustment needed, use caution |
| Aciclovir resistance             | Foscarnet 90 mg/kg i.v. q12h or 60 mg/kg i.v. q8h                                                                                                           |
| Aciclovir shortage               | Ganciclovir 5 mg/kg q12h                                                                                                                                      |
| Cerebral edema                   | Mannitol 0.25–1 g/kg bolus q4–6 h  
Dexamethasone 10 mg q6h  
Hypertonic saline  
Active brain herniation, 23 % saline (30-ml bolus via central venous access)  
Maintenance, 2–3 % saline (250–500-ml boluses or continuous venous infusion; 3 % saline via central venous access) |

Seizures and SE
First line, initial dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg i.v. up to 4 mg per dose</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.25 mg/kg i.m. up to 10 mg maximum</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.15 mg/kg i.v. up to 10 mg per dose</td>
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Second line, initial dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Fosphenytoin loading dose</td>
<td>20 mg PE/kg (maximum rate of administration 150 mg PE/minute); if necessary, an additional 5 mg PE/kg 10 minutes after the loading dose Levetiracetam 1000–3000 mg i.v.</td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>20–40 mg/kg i.v.</td>
</tr>
</tbody>
</table>

Third line, loading dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>1–2 mg/kg</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>20 mg/kg i.v.</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>5–15 mg/kg i.v.</td>
</tr>
</tbody>
</table>
Outcomes

Mortality of untreated HSV encephalitis is roughly 70%, and 97% of survivors will not return to their previous level of function.

**Acute complications:**
- cerebral edema
- status epilepticus

**Chronic complications:**
- Autoimmune encephalitis associated with antibodies to the N-MDA receptor and other neuronal cell surface and synaptic epitopes (trigger synaptic autoimmunity)
Most significant negative prognostic factors

- Older age
- Coma/lower level of consciousness at presentation
- Restricted diffusion on DWI
- Delay in aciclovir administration

Singh TD 2016
Case n° 2 : Patient N.S.

- 54 years – old female.

- Acute onset of: fever, tonico – clonic seizures, behavioural disorders and walk disturbance

**Neurological Examination:**
- GCS : 13/15.
- Kernig sign.
- Brudzinski sign.
diffusion hyperintensities of cerebellar peduncles with normal ADC
Lumbar puncture:

- CSF – WBC : 100/mm³.
- CSF glucose and CSF albumin : normal.

West nile virus serology : positive for IgM and IgG.

- West nile Virus meningo – encephalitis.
Case n°2 : Patient N.S.

our patient recieved support therapy in ICU for 10 days.

- No recurrence of seizures.

- Persistance of neuropsychiatric symptoms :
  
  - NPI : FxG = 33 and R = 14.
Box. Diagnostic Criteria

West Nile Meningitis

A. Clinical signs of meningeal inflammation, including nuchal rigidity, Kernig or Brudzinski sign, or photophobia or phonophobia

B. Additional evidence of acute infection, including 1 or more of the following: fever (>38°C) or hypothermia (<35°C); cerebrospinal fluid pleocytosis (≥5 leukocytes/mm³); peripheral leukocyte count >10000/mm³; neuroimaging findings consistent with acute meningeal inflammation

West Nile Encephalitis

A. Encephalopathy (depressed or altered level of consciousness, lethargy, or personality change lasting ≥24 hours)

B. Additional evidence of central nervous system inflammation, including 2 or more of the following: fever (≥38°C) or hypothermia (≤35°C); cerebrospinal fluid pleocytosis (≥5 leukocytes/mm³); peripheral leukocyte count >10000/mm³; neuroimaging findings consistent with acute inflammation (with or without involvement of the meninges) or acute demyelination; presence of focal neurologic deficit; meningismus (as defined in A); electroencephalography findings consistent with encephalitis; seizures, either new onset or exacerbation of previously controlled
West Nile virus Encephalitis

- West Nile virus is a member of the Japanese encephalitis serocomplex.
- Mosquito salivary components introduced to target cells such as keratinocytes and dendritic cells.
- Infected cells or migrate through lymph nodes to serum to the central nervous system.

Less than 1% of patients develop a neuro invasive disease.

Preferentially affects the basal ganglia and cerebellum.

- can present with movement disorders and/or cerebellar syndrome.

West Nile virus Encephalitis: treatment

- There is **no specific treatment**; clinical management is supportive.

- Severe meningeal symptoms: pain control for headaches, antiemetic therapy and rehydration for associated nausea and vomiting.

- Encephalitis: close monitoring for the development of elevated intracranial pressure and seizures.

- Various drugs have been evaluated or empirically used: IVIG, corticosteroids, interferon and ribavirin: **None have shown specific benefit to date.**
Parents infected with Covid – 19 a week earlier.

Abdminal pain, vomiting, fever > 4 days.

48 hours later: hypersomnia, insteady gait and behavioural disorders.

On examination:
- Ataxia
- Upper limb tremor
- Perioral dyskinesia
- Bilateral subconjunctival hemorrhage
- Cutaneous eruption.
Corpus callosum T2/FLAIR hypertensity with diffusion hypertensity and ADC restriction
Case n°3: 9 years – old girl

Laboratory tests:

- **CRP 130** with normal CBC.
- **D-Dimers**: 2077.
- CSF analysis: normal.
- HSV – PCR, EBV serology and anti – NMDA in CSF: NEGATIVE.
- **SARS – Cov2 serology**: negative for IgM and **positive for IgG**.
Case n°3: 9 years – old girl

**Acute encephalitis**: probable infectious origin
**SARS-Cov2?**: positive serology

**Multisystemic attack**: Digestive, Dermatological and Neurological Manifestations
**Biological markers of inflammation**

→ **Multisystemic inflammatory syndrome in children (MIS-C) due to SARS Cov2**
Multisystem Inflammatory Syndrome In Children

- **MIS-C**: Inflammation caused by *excessive immune response* after *acute COVID-19* infection in children

- Clinical findings appear within **2-3 weeks after previous infection**.

- RT-PCR or **serology positivity for SARS-CoV-2**, indicating that infection was passed

- **Wide range** of clinical symptoms according to the system affected

- Neurological symptoms: Seizure, neck stiffness, and inability to walk
Multisystem Inflammatory Syndrome In Children

Imaging

Most common cause of transient splenial lesions in children:

- **Mild encephalopathy with a reversible splenial lesion** (MERS), secondary to focal intramyelinic edema due to inflammation

ADEM Like lesions

Palabiyik F. 2021
<table>
<thead>
<tr>
<th>Case Definitions for MIS-C (Obtained From WHO)</th>
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</thead>
<tbody>
<tr>
<td>Children and adolescents aged 0–19 years with fever ≥3 days AND two of the following:</td>
</tr>
<tr>
<td>1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet)</td>
</tr>
<tr>
<td>2. Hypotension or shock</td>
</tr>
<tr>
<td>3. Features of myocardial dysfunction pericarditis, valvulitis or coronary abnormalities (including echocardiographic findings or elevated troponin/NT-proBNP)</td>
</tr>
<tr>
<td>4. Evidence of coagulopathy (based on PT, PTT, and elevated D-dimer levels)</td>
</tr>
<tr>
<td>5. Acute gastrointestinal problems (diarrhea, vomiting or abdominal pain) AND Elevated markers of inflammation, such as ESR, CRP and procalcitonin AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes AND Evidence of COVID-19 (RT-PCR assay, antigen test or serology positivity) or possible contact with a patient with COVID-19</td>
</tr>
</tbody>
</table>
MIS-C: Pathophysiology

Phase I: asymptomatic or pauci-symptomatic

Respiratory phase (phase II): severe in adult patients, usually absent in children: activation of macrophages and lymphocytes T helpers.

Cytokines' secretion, macrophages' activation, lymphocytes B and plasmocytes' activation.

Hyperimmune response: (phase III)

Inflammatory response.
Hypoxia, hypotension and coagulopathy induce ischemic lesions.

Inflammation and immune reactions induce cytokine storm.

According to pathological studies: neuronal degeneration and oedema.

Vulnerability of Corpus callosum to hyperinflammatory state and cytokines

High concentration of glutamate receptors → cytotoxicity of Covid – induced inflammation to the splenium of Corpus callosum.

Case n° 4 : Patient A.Z.

- 31 years – old female.
- **Acute onset of psychosis** (delusion, hallucinations, behavioural disorders).
- All routine laboratory tests were normal.
- Hospitalized in psychiatry department, **resistance to Antipsychotics**.
- A few days later, she developed depression symptoms.
- An organic cause was suspected.
MRI: NORMAL.
Case n° 4 : Patient A.Z.

- First psychotic event.
- **Atypical**: mood disorder appearing secondarily and resistance to antipsychotics.
- MRI: Normal.
- EEG: diffuse slow waves.
- Lumbar puncture: CSF – **WBC**: 100/mm3.
- CSF glucose and CSF albumin: normal.
- CSF – **anti NMDAr antibodies**: POSITIVE.
Case n°4 : Patient A.Z.

- thoraco abdominopelvic ct scan revealed an **ovarian teratoma**.

- Tumor resection: improvement of psychiatric symptoms.
Auto immune encephalitides are non infectious and mediated by 2 types of Ab:
- against neuronal cell-surface antigens.
- against the intracellular antigen.
Anti – NMDAr Encephalitis : main characteristics

- **Most common** cause of nonviral encephalitis.

- At onset, about 90% of patients have prominent **psychiatric symptoms** difficult to differentiate from a psychiatric disease.

- Female: 80%.

- Median Age: 21 years.

- Frequently associated to **tumors** (mostly ovarian teratoma).

Lynch DR et al Adv Pharmacol. 2018
Anti – NMDAr Encephalitis: a syndrome

In 2005: 4 women

► **Prodromal symptoms:**
Headache, fever, vomiting, diarrhoea, or upper respiratory-tract symptoms.

► <2 weeks: **psychiatric symptoms, memory deficits, decreased consciousness, and hypoventilation**

► **ovarian teratomas.**

► **anti-N-methyl-D-aspartate receptor detected**

Vitaliani R. 2005, Dalmau 2007
Anti–NMDAr Encephalitis: pathophysiology

- NMDAR is the main postsynaptic ionotropic glutamate receptor.
- Postsynaptic NMDARs are protective against neuronal toxicity.
- But NMDAR overactivation leads to neurotoxicity.

Saurabh S. et al. Behavioural Brain Research, 2020,
**Anti – NMDAr Encephalitis : pathophysiology**

*Figure 6: Clinical correlates of antibody-mediated decrease of NMDAR*

The figure is based on data from animal models of pharmacological or genetic decrease of NMDAR

Dalmau 2011
Absence of history of psychiatric disease, rapid onset.

Sleep dysfunction: severe insomnia.

Excitement, disinhibition, or manic behaviour alternating with depressive behavior, manic and bizarre behaviour, hypersexuality.

Fluctuating catatonia.

Negative and positive symptoms at presentation: in schizophrenia, positive symptoms are disproportionally more frequent than negative symptoms at disease onset.

Antipsychotic intolerance.

Dalmau J et al Lancet Neurol. 2019
Anti – NMDAr Encephalitis: Other symptoms

- Short term Memory loss
- **Seizures**, status epilepticus
- Language disintegration (from reduction of verbal output and echolalia to frank mutism)
- Movements disorders (**Oro-lingual-facial dyskinesias**++ choreoathetosis, oculogyric crisis, dystonia, rigidity, and opisthotonic)
- **Autonomic dysfuction** (hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, urinary incontinence, and erectile dysfunction)
- **breathing instability**

Dalmau J et al Lancet Neurol. 2019
Anti-NMDAr Encephalitis: Diagnosis

- Normal MRI: 70%. (hyperintensity: hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem)
- EEG: abnormal in most patients, usually showing non-specific, slow, and disorganised activity
- CSF:
  - Moderate lymphocytic pleocytosis
  - Normal or mildly increased protein concentration
  - CSF-specific oligoclonal bands (60%).
  - Intrathecal synthesis of NMDAR ab

Dalmau J et al Lancet Neurol. 2019
Anti – NMDAr Encephalitis : a paraneoplastic syndrome

► Evaluation for an **underlying malignancy** (ovarian teratoma++)

► Males, younger and white patients are less likely to have tumors.

► Tumors should **be removed without delay**.

► With **immunotherapy and/or tumor removal**, most patients **recover** (recovery can take as long as 18 months).

► Other neural autoantibodies are also associated with AE

Bradshaw et al Semin Neurol2018
Anti – NMDAr Encephalitis: Management.

- Escalation of immunotherapy:
  - 1st line therapies (steroids, IVIG, or plasma exchange).
  - 2nd-line therapies (rituximab or cyclophosphamide) for patients who did not improve at 4 weeks of initiation of first-line therapies.
  - 3rd-line treatment: bortezomib (a proteasome inhibitor) or tocilizumab (IL-6 receptor antagonist) have been suggested.

Dalmau J et al Lancet Neurol. 2019
Case n° 5: Patient H.A.

- **65 years** – old male, vitamine B12 deficiency.
- **Rapid progressive cognitive impairment** over 6 months.
- 4 generalized **seizures**.
- Visual hallucinations.
- **Behavioural disorders** (aggressiveness).
Case n° 5: Patient H.A.

- On examination: confusion, reflex pyramidal syndrome.
- Biology: Hyponatremia Na+ = 125
- EEG: slow basic rhythm: 6 – 7Hz, no epileptic abnormalities.
- Cerebral MRI: normal.
- Lumbar puncture: the family did not give consent.
- Anti-neuronal Ab in serum were positive for anti–VGKC: 892 mol/l with positive anti LGI – 1.
Case n° 5: Patient H.A

- Our patient received 1000mg/d of Intravenous methylprednisolone for 3 days then oral prednisone.
- Partial cognitive recovery.
- No recurrence of seizures.

van Sonderen A, et al Nat Rev Neurol. 2017
Auto immune encephalitides are non infectious and mediated by 2 types of Ab:
- against neuronal cell-surface antigens.
- against the intracellular antigen.
Anti – LGI - 1 encephalitis

- 2nd most frequent cause of autoimmune encephalitis.
- Age 50 – 70 years. (tumors are rare: Thymoma)
- 3 clinical epileptic syndromes:
  - Facio brachial dystonic seizure.
  - Focal seizures.
  - Tonic – clonic seizures.
- Cognitive decline (symptoms of limbic dysfunction) (97%).
- Hyponatraemia (65%).
- CSF: normal (75%).

van Sonderen A, et al Nat Rev Neurol. 2017
Anti-LGI1 encephalitis

First-line pulse therapy: intravenous methylprednisolone, intravenous immunoglobulins or plasma exchange

Effective in 2–3 weeks?*

Yes: Consider adding oral prednisone (in patients with moderate or severe disease), and azathioprine or mycophenolate mofetil

No: Taper down prednisone after 4 weeks

No: Alternative first-line pulse therapy

Effective in 2–3 weeks?*

Yes: Taper down prednisone after 4 weeks

No: Second-line therapy: rituximab

Effective in 6 weeks?*

No: B-cell depletion?

No: Rituximab for an additional 2 weeks

Yes: Alternative second-line therapy: cyclophosphamide

van Sonderen A, et al Nat Rev Neurol. 2017
Take – home messages

► Encephalitides should be considered in patients with **acute/subacute onset**: Seizures, neuropsychiatric symptoms, movement disorders, decrease level of consciousness

► **Infectious causes**: eliminated firstly including rare causes

► Prompt recognition and treatment can be lifesaving

► **Auto – immune** encephalitis still rare
  
  ► **can resemble infectious encephalitis**, and sometimes are triggered by infectious disorders.
  
  ► Detection of antibodies to cell surface or synaptic proteins often associates with **response to immunotherapy**.
  
  ► Detection and treatment of tumor in some specific cases is recommended for the patient improvement
Thank You