Viral and auto-immune Encephalitides

IMEN KACEM, MAJOUL SLIM, GOUIDER RIADH
Department of Neurology, Razi Universitary Hospital ,Tunisia

Introduction

- Encephalitis: i**nflammation 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

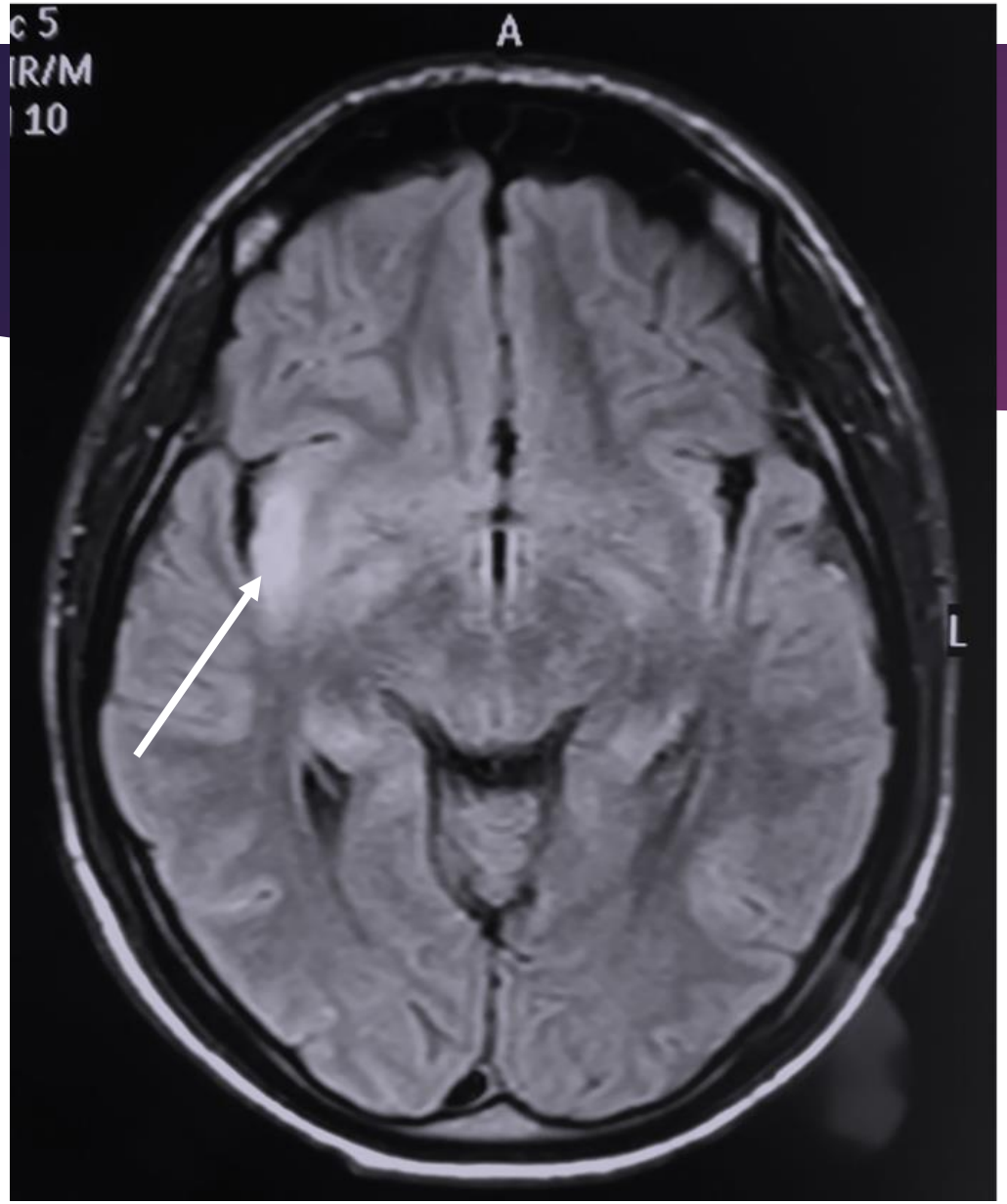
Introduction

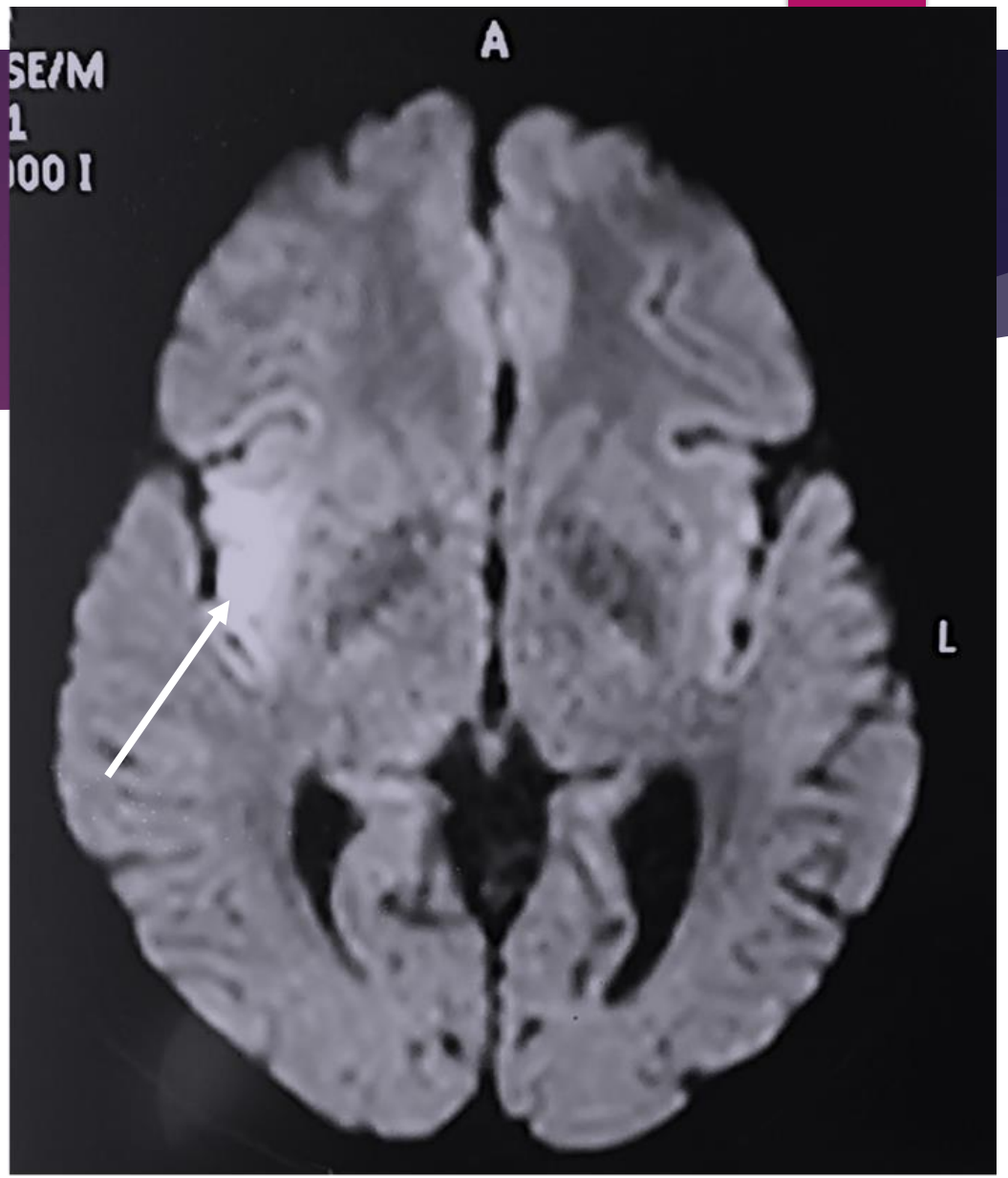
- Improvement in prognosis in the last two decades : -27% in mortality since 1990.
- Prompt recognition and treatment can be lifesaving
- Mortality rates still too high around 5–15%, with marked physical and cognitive morbidity among survivors.

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

Case n°1 : Patient Y.Z.

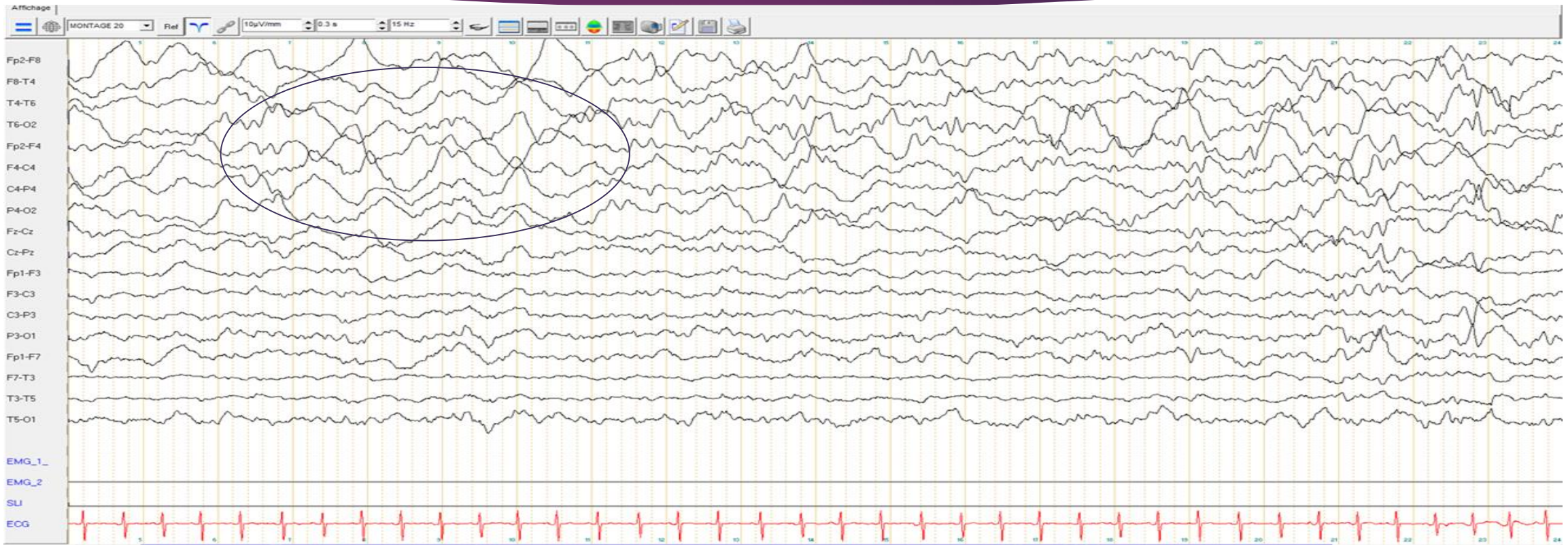
- 20 years – old male.
- Influenza – like syndrome during a week.
- behavioural disorders and tonic – clonic seizures.
- On neurological examination :
  - T°:39, **confusion.**
  - **contamination delusion.**
  - **pyramidal syndrome.**





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).**

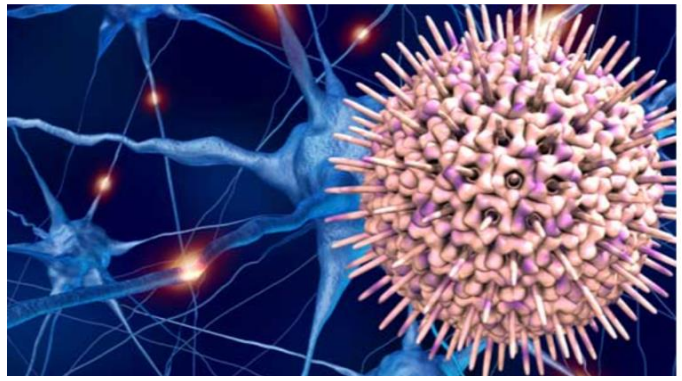
- no recurrence of seizures.
- no cognitive sequelae : MMSE = 30/30.
- presence of psychiatric sequelae :
  - anxiety.
  - hyperphagia.
  - attention disorder.

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.

Herpetic encephalitis : Prevalence

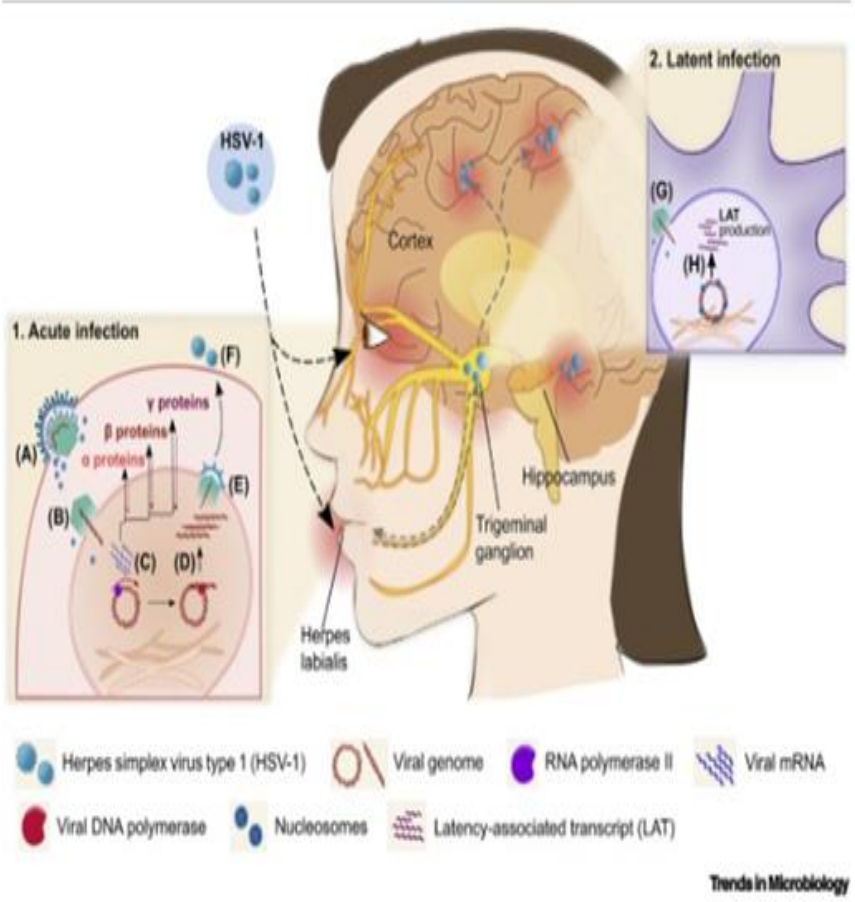
- HSV-1 infection is common, with seropositivity among older adults 60–90 %
- HSV-1 is consistently the single **most common cause of sporadic encephalitis**
- Incidence: between 2 and 4 cases/1,000,000.
- bimodal distribution:up to 3 years of age, and adults aged > 50 years.



Smith JS, Robinson NJ. J Infect Dis. 2002
Granerod J et al. Lancet Infect Dis 2010

Herpetic encephalitis : Pathophysiology

- 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

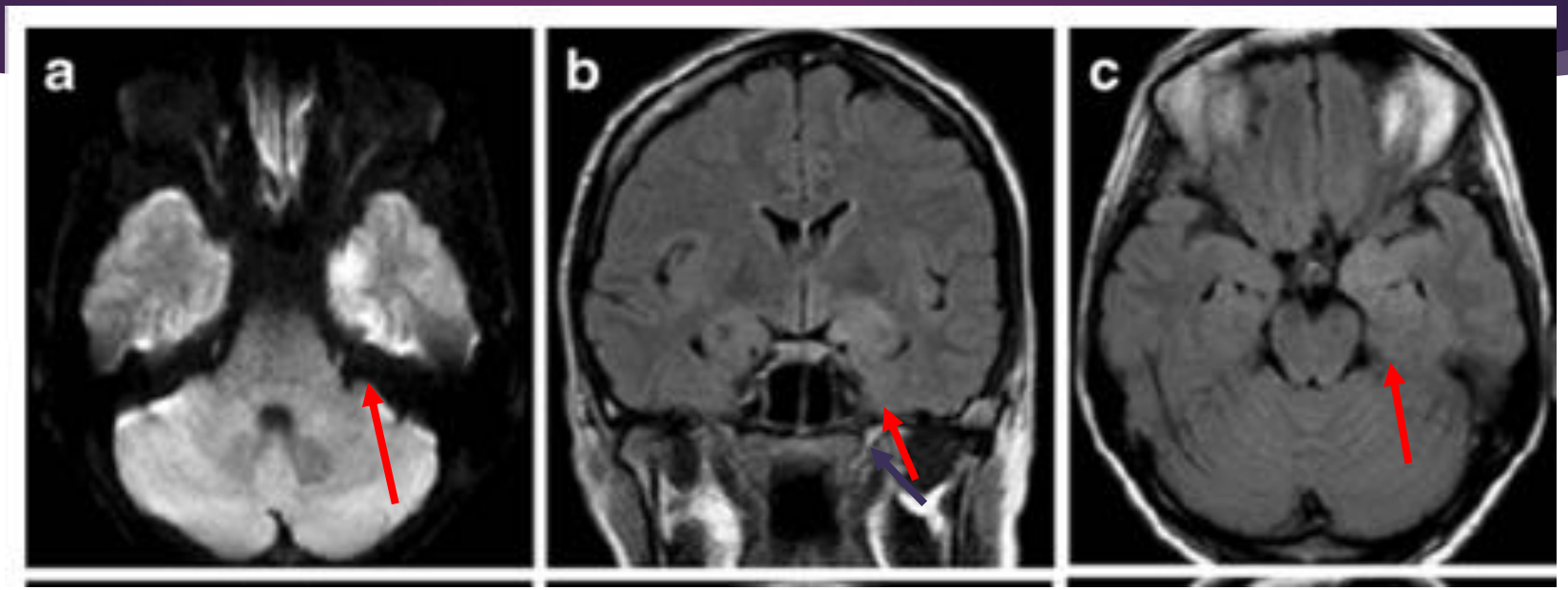


Herpetic encephalitis : Diagnosis

- 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



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

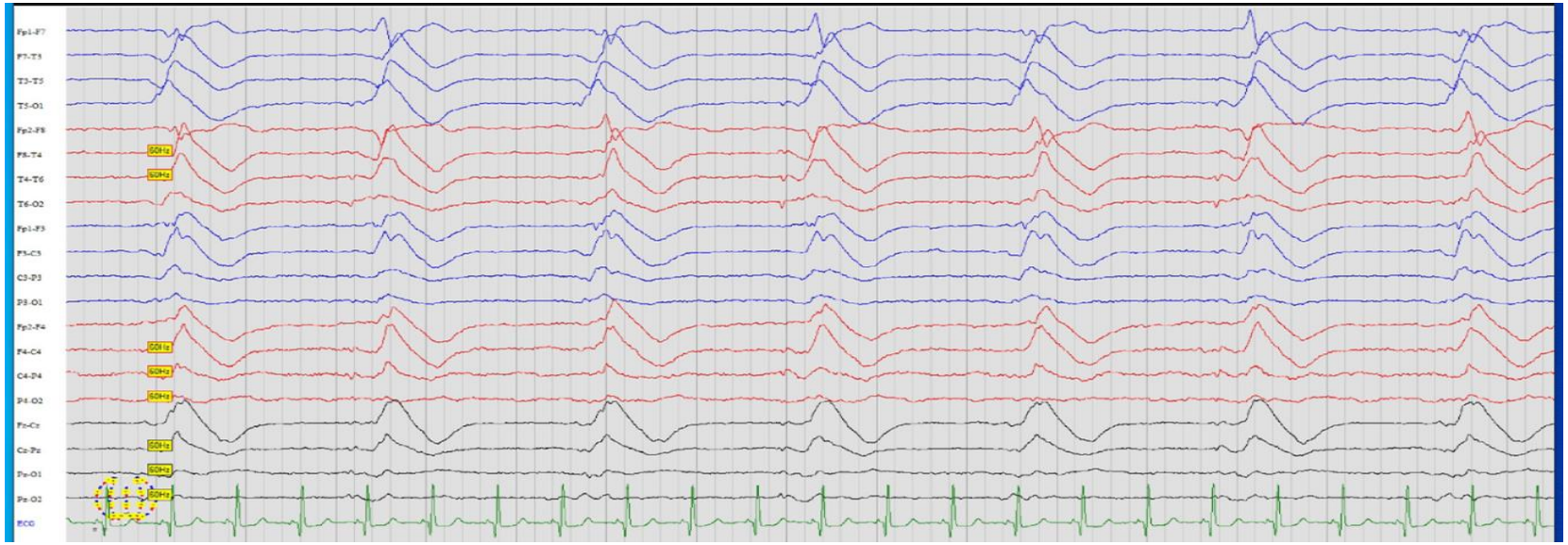
- **MRI: contrast-enhancing lesions**
- (CSF) pleocytosis (**≥5 nucleated cells/ml)**

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



EEG showing classical triphasic waves with burst suppression pattern. (Algahtani 2017)

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

Management

Corticosteroids:

- clinical evidence in humans is scant
- reserved for patients in whom there is significant edema and mass effect.

Stahl JP. Rev Neurol. 2019

Table 2 Therapeutics used in the treatment of herpes simplex virus-1 encephalitis (HSVE) and its complications

Indication	Typical dosing/administration
HSVE	Aciclovir, 10 mg/kg i.v. q8h for 14–21 days
	Renal insufficiency
	CrCl 25–50 ml/min/1.73 m^2: 10 mg/kg q12h
	CrCl 10-25 ml/min/1.73 m^2: 10 mg/kg q24h
	CrCl <10 ml/min/1.73 m^2: 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	Lorazepam 0.1 mg/kg i.v. up to 4 mg per dose
	Midazolam 0.25 mg/kg i.m. up to 10 mg maximum
	Diazepam 0.15 mg/kg i.v. up to 10 mg per dose
Second line, initial dosing	
	Fosphenytoin loading dose: 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.
	Valproate sodium, 20–40 mg/kg i.v.
Third line, loading dose	Propofol 1–2 mg/kg
	Phenobarbital 20 mg/kg i.v.
	Pentobarbital 5–15 mg/kg i.v.

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)

Prognosis

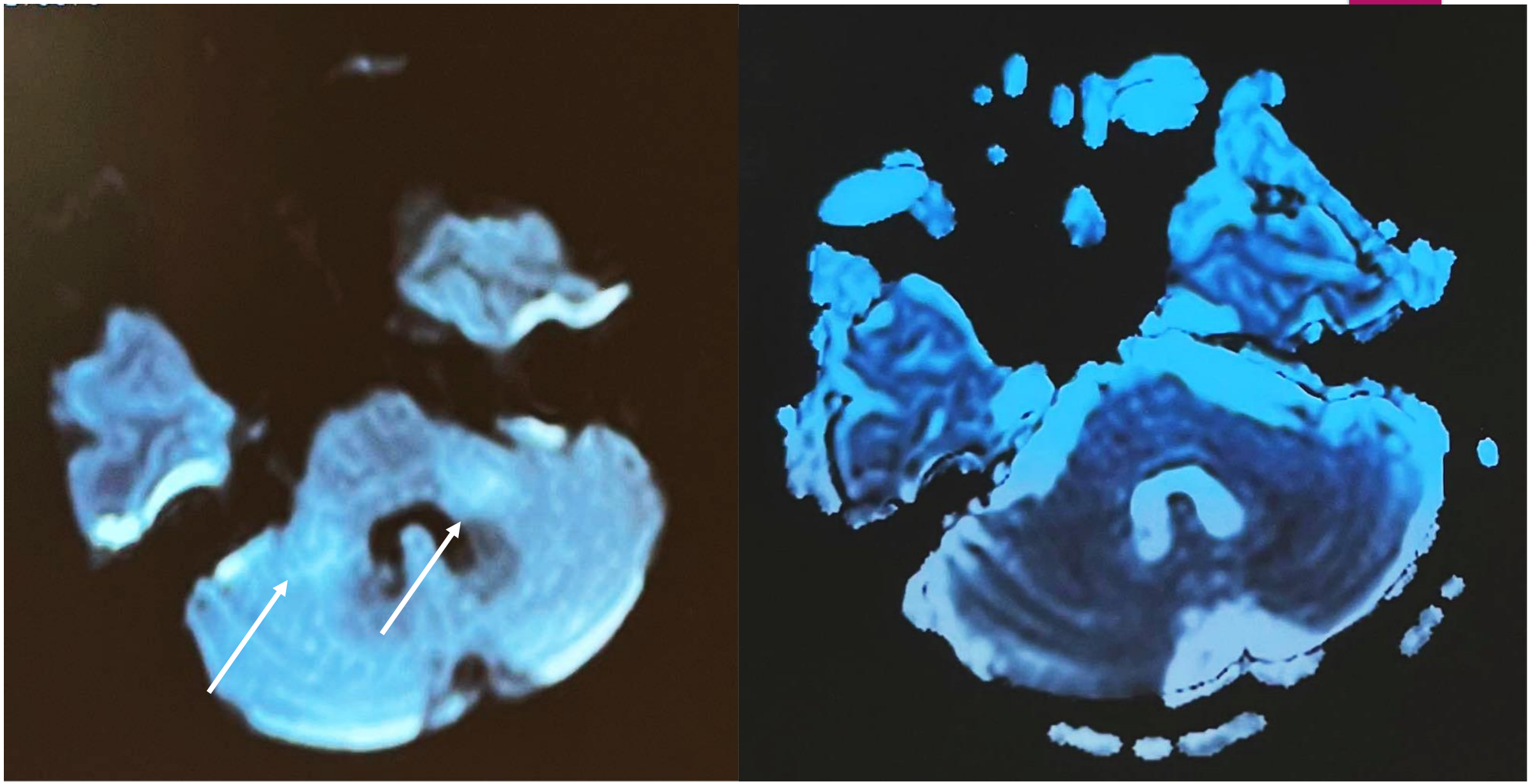
Most significant **negative prognostic factors**

- 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

Case n° 2 : Patient N.S.

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.

West Nile virus Encephalitis

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

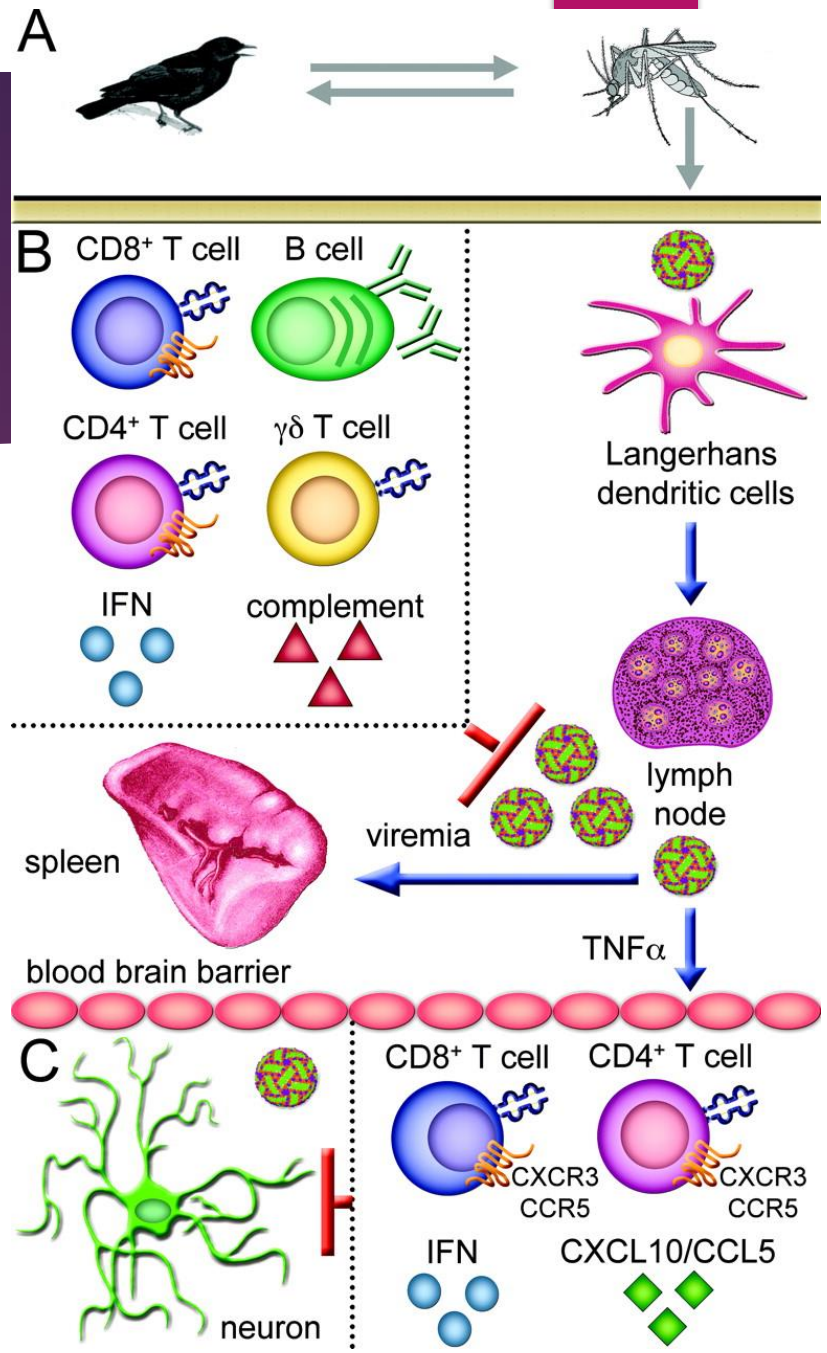
A. Encephalopathy (depressed or altered level of consciousness, lethargy, or personality change lasting ≥24 hours)

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

Sejvar JJ, et al JAMA. 2003

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.



Samuel MA, Diamond MS.J Virol. 2006, Sejvar JJ, et al JAMA. 2003

West Nile virus Encephalitis

- **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.

Sejvar JJ, et al JAMA. 2003

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.

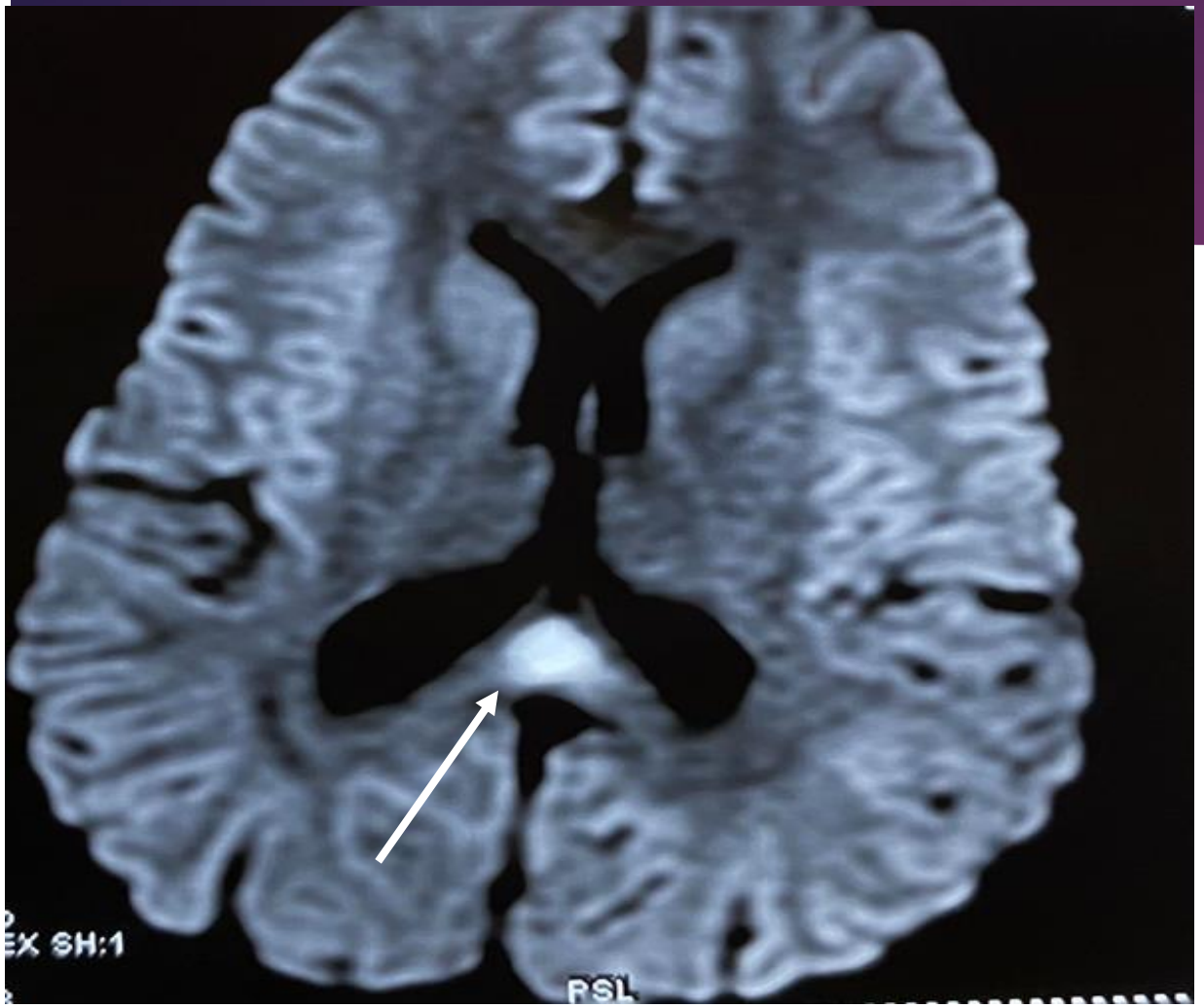
- Encephalitis: close monitoring for the development of elevated intracranial pressure and seizures.

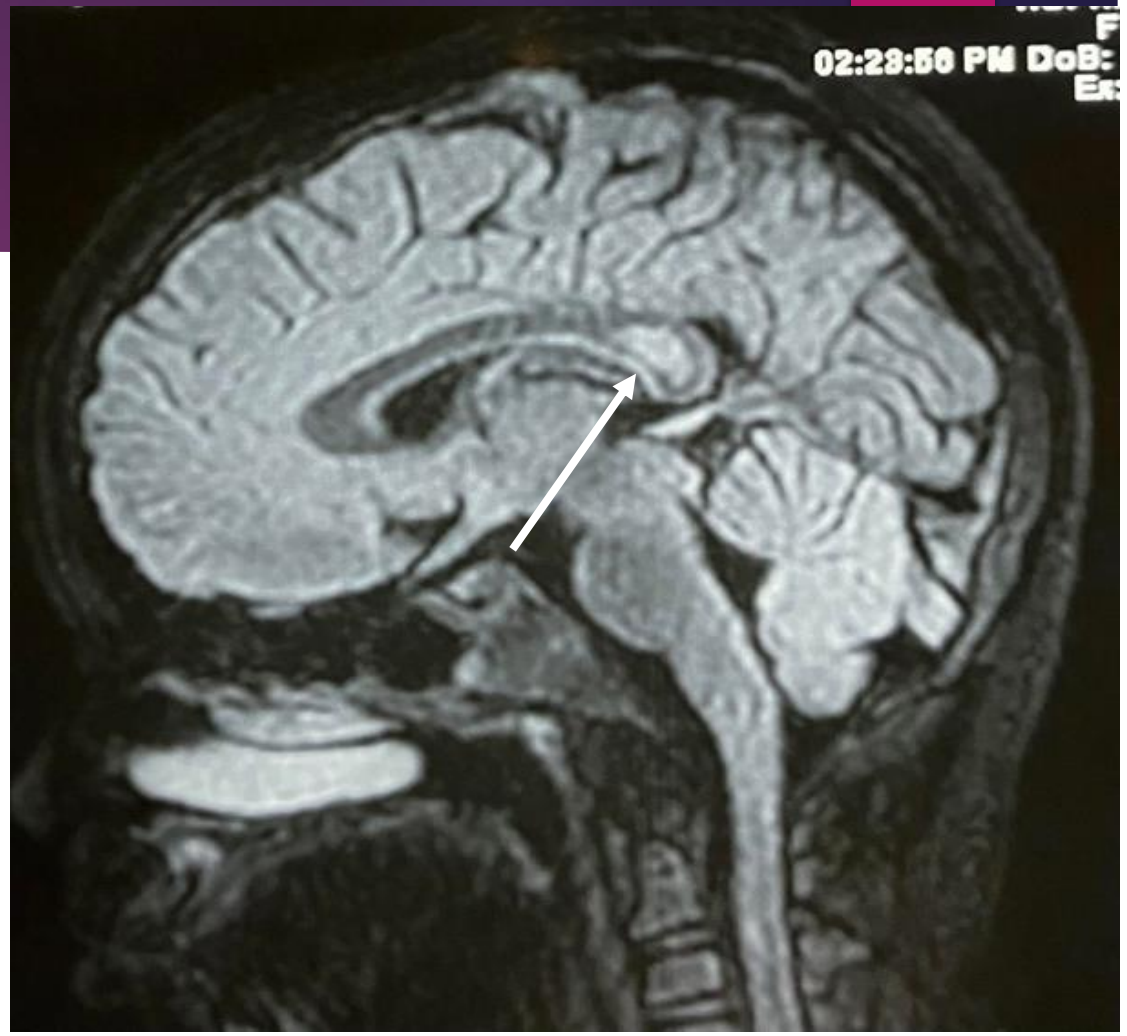
- Various drugs have been evaluated or empirically used : IVIG, corticosteroids, interferon and ribavirin: **None have shown specific benefit to date.**

Diamond 2009; Beasley 2011; Lim 2013

Case n°3 : 9 years – old girl

- 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

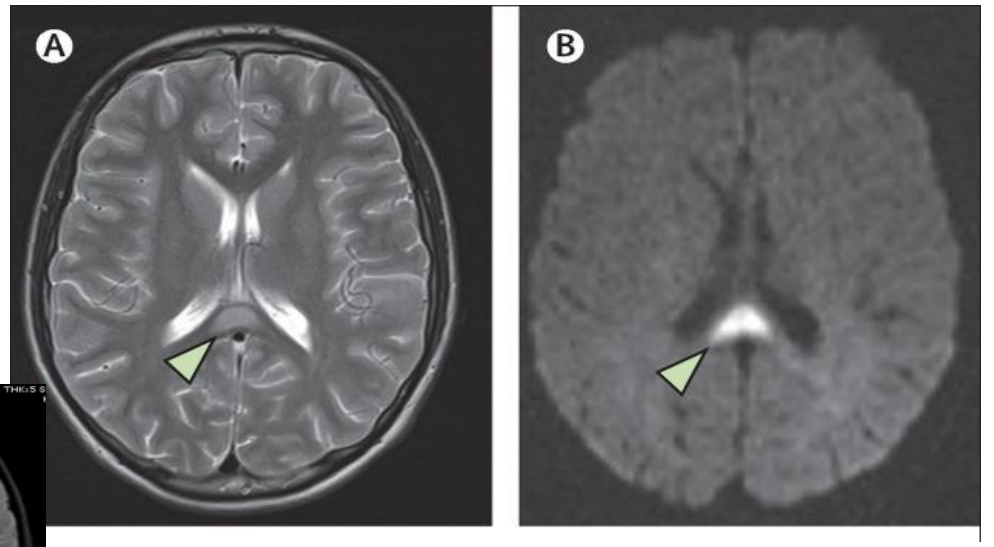
- **MIS-C:** Inflammation caused by excessive immune response after acute COVID-19 infection in children
- Clinical findings appear within **2-3 weeks after previous infection**.
- RT-PCR or **serology positivity for SARS-CoV-2**, indicating that infection was passed
- **Wide range** of clinical symptoms according to the system affected
- Neurological symptoms: Seizure, neck stiffness, and inability to walk

Multisystem Inflammatory Syndrome In Children

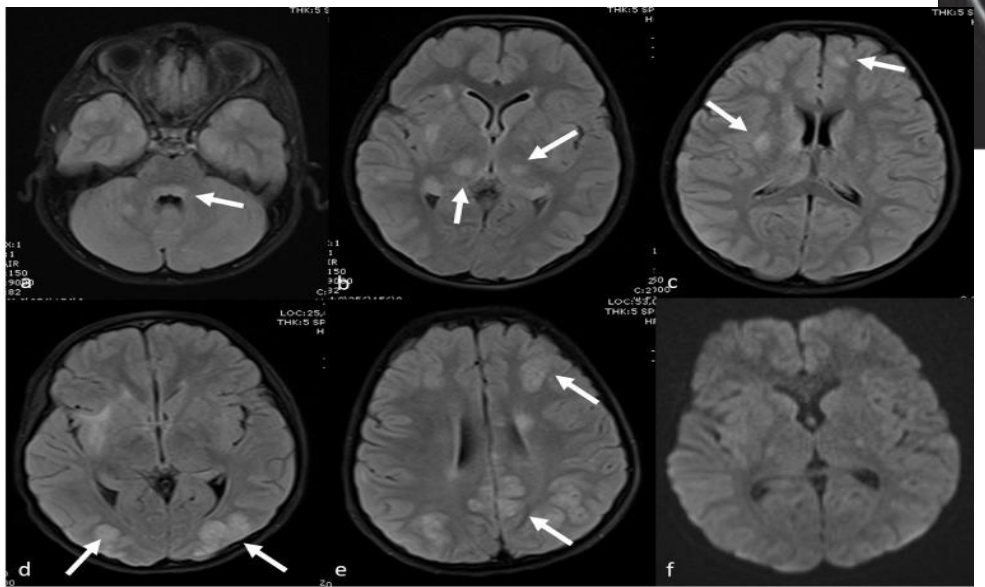
Imaging

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 1. Case Definitions for MIS-C (Obtained From WHO)

Children and adolescents aged 0–19 years with fever ≥3 days
AND two of the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
2. Hypotension or shock
3. Features of myocardial dysfunction pericarditis, valvulitis or coronary abnormalities (including echocardiographic findings or elevated troponin/NT-proBNP)
4. Evidence of coagulopathy (based on PT, PTT, and elevated D-dimer levels)
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

MIS-C: Pathophysiology

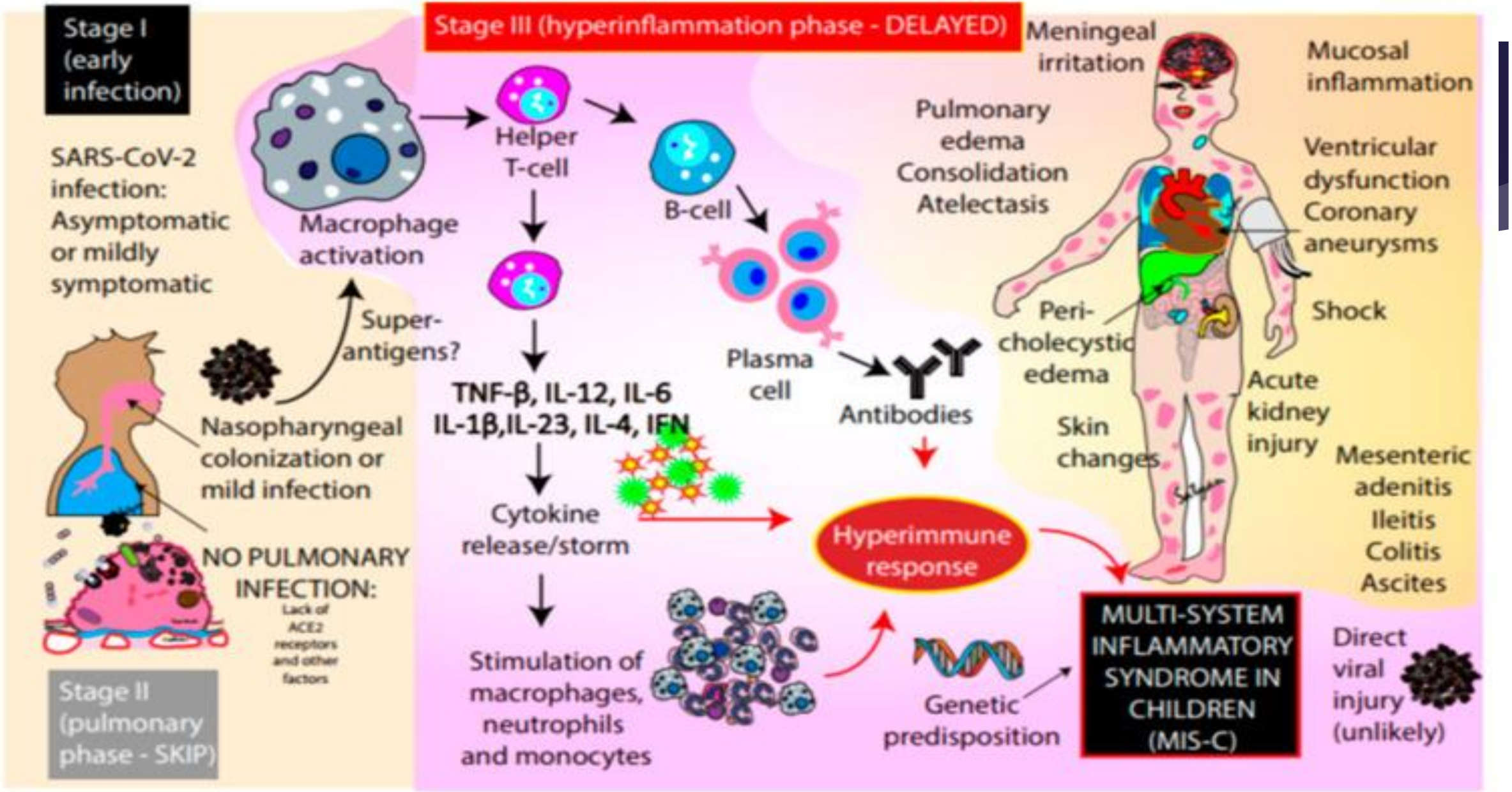
Phase I: asymptomatic or pauci – symptomatic

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's activation.

Hyperimmune response : (phase III)

Inflammatory response.

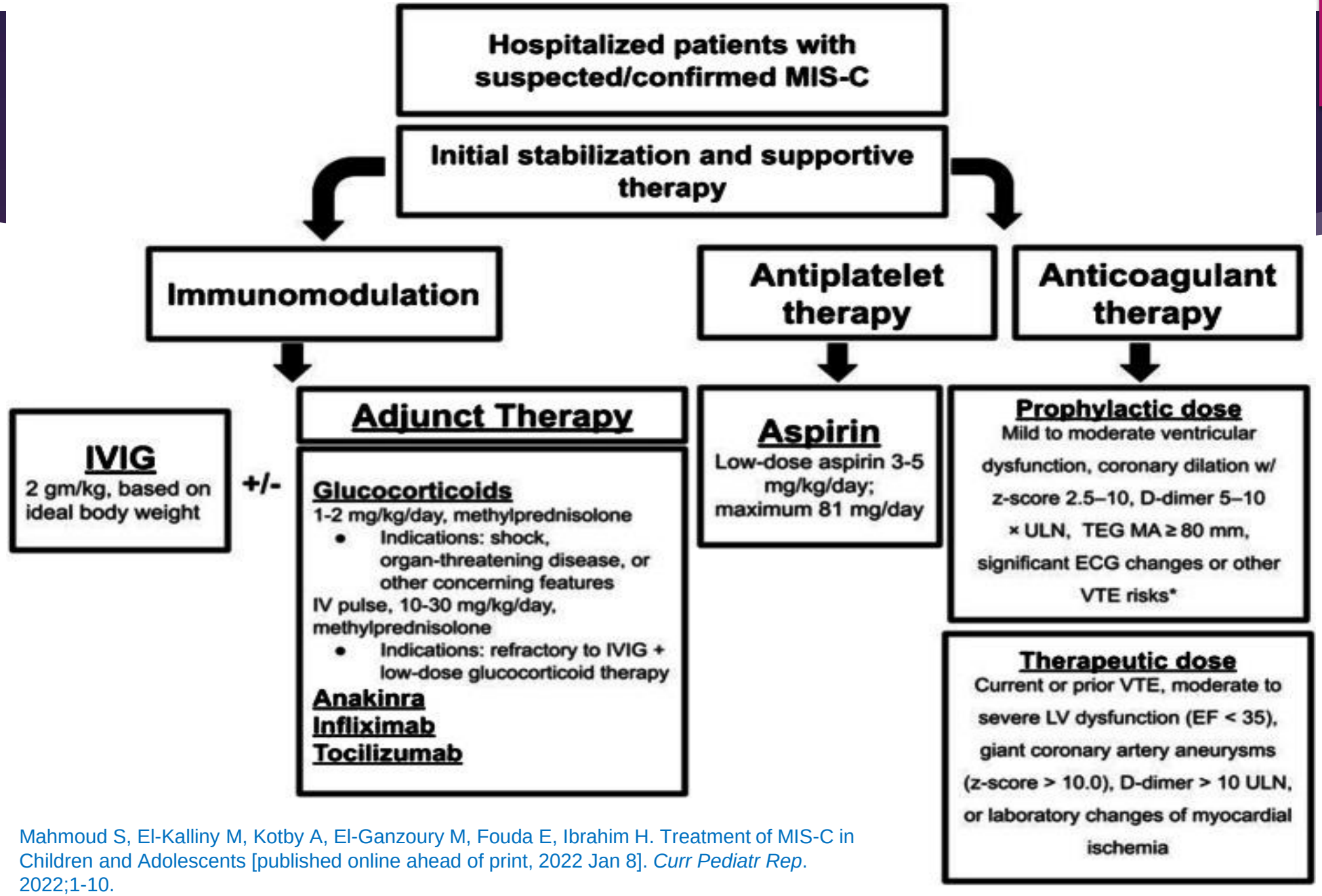


Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-System Inflammatory Syndrome in Children (MIS-C) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed Management. *Children (Basel)*. 2020;7(7):69. Published 2020 Jul 1. doi:10.3390/children7070069

MIS-C : Pathophysiology of neurologic involvement

- 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.

Farooq A, Alam F, Saeed A, e al. 2021

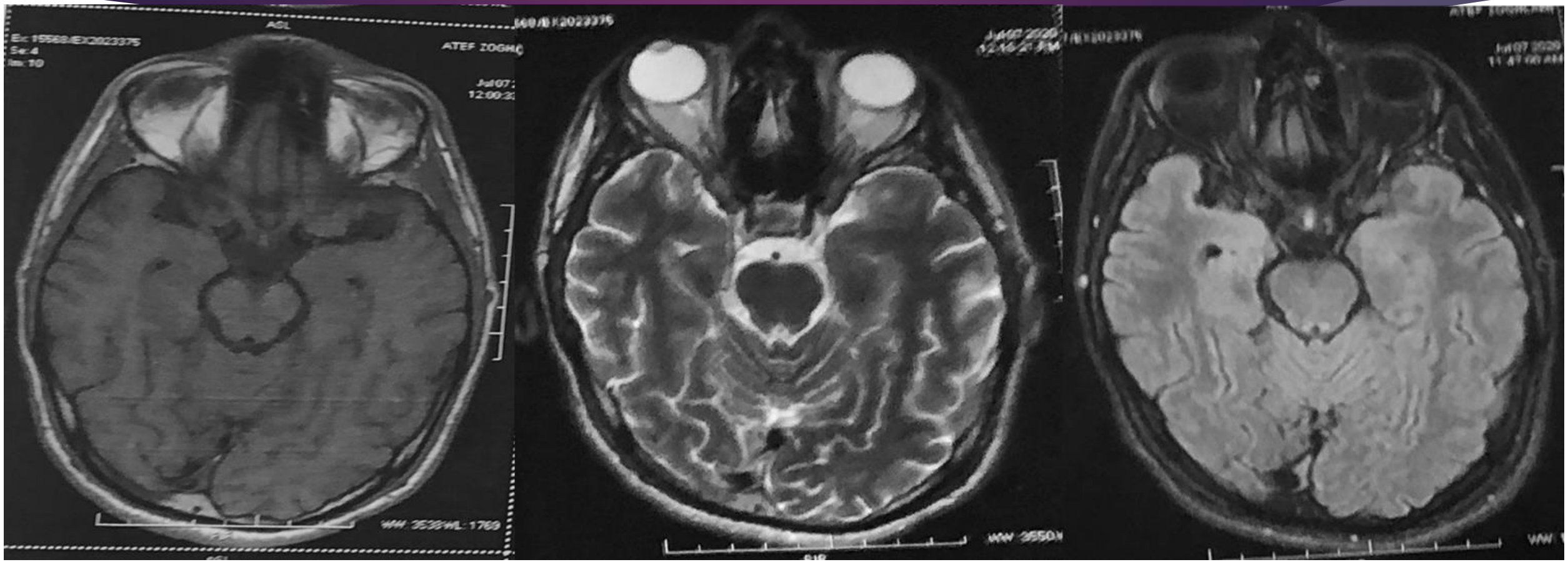


Mahmoud S, El-Kalliny M, Kotby A, El-Ganzoury M, Fouda E, Ibrahim H. Treatment of MIS-C in Children and Adolescents [published online ahead of print, 2022 Jan 8]. *Curr Pediatr Rep*. 2022;1-10.

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 developped depression symptoms.
- An organic cause was suspected.

MRI : NORMAL.

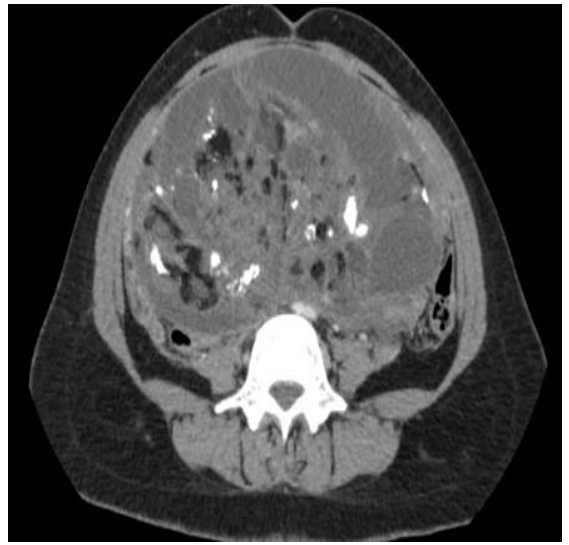


Case n° 4 : Patient A.Z.

- 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**.



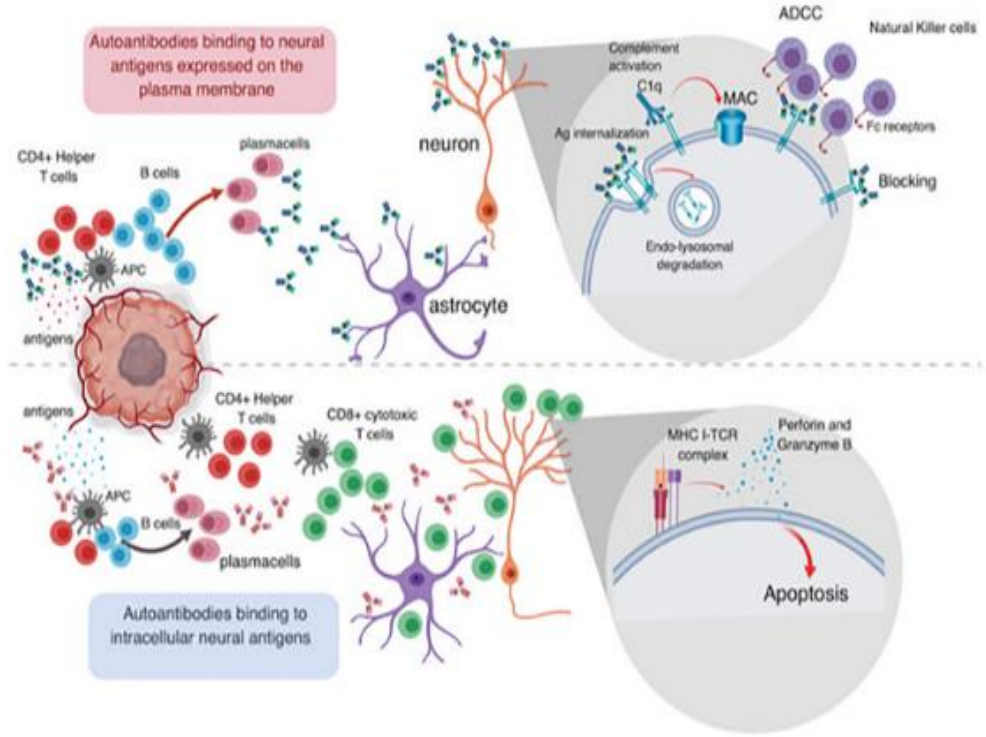
- Tumor resection: improvement of psychiatric symptoms.

Auto – immune encephalitides

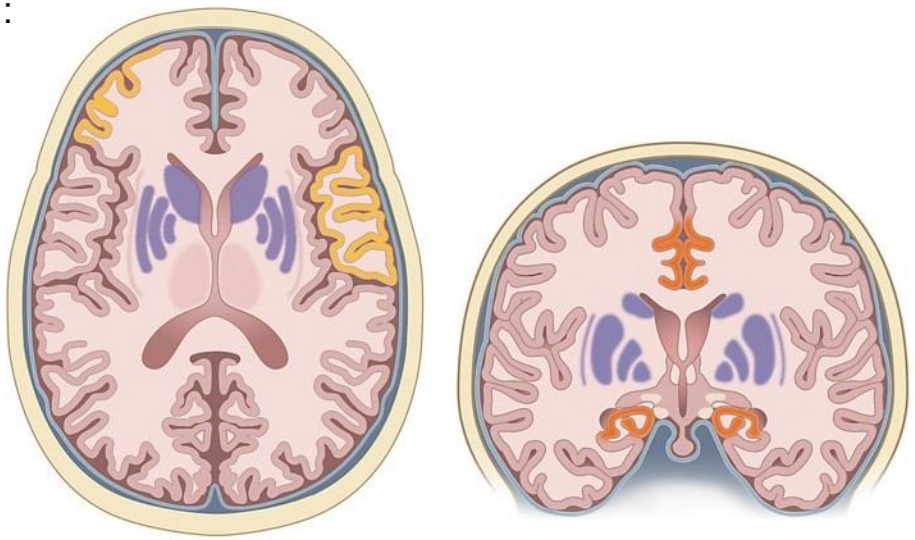
Auto immune encephalitides are non infectious and mediated by 2 types of Ab :

- against neuronal cell-surface antigens.
- against the intracellular antigen.

NMDA
AMPA
CASPR2
DPPX
mGluR
GABA
LGI1
VGCC



Yo
Ri
Ma2
SOX1
Amphiphysin
CV2



Limbic System	Extra-limbic Cortices	Basal Ganglia	Cerebellum	Brainstem
Anti-Hu **Anti-VGKC** **Anti-GAD65** **Anti-GABA B** **Anti-AMPAr** Anti-LGI1 Anti-VGCC	**Anti-NMDAr** **Anti-VGCC** **Anti-GABA-A** **Anti-GLuR3**	**Anti-CV2** **Anti-D2** Anti-NMDAr	**Anti-Yo** **Anti-GLuR1** Anti-Hu Anti-GAD65 Anti-VGCC	**Anti-Ma** **Anti-Ri** Anti-Hu Anti-Yo

Ball C, Fisicaro et al. Clin Imaging. 2022

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

- **Prodomal symptoms** :

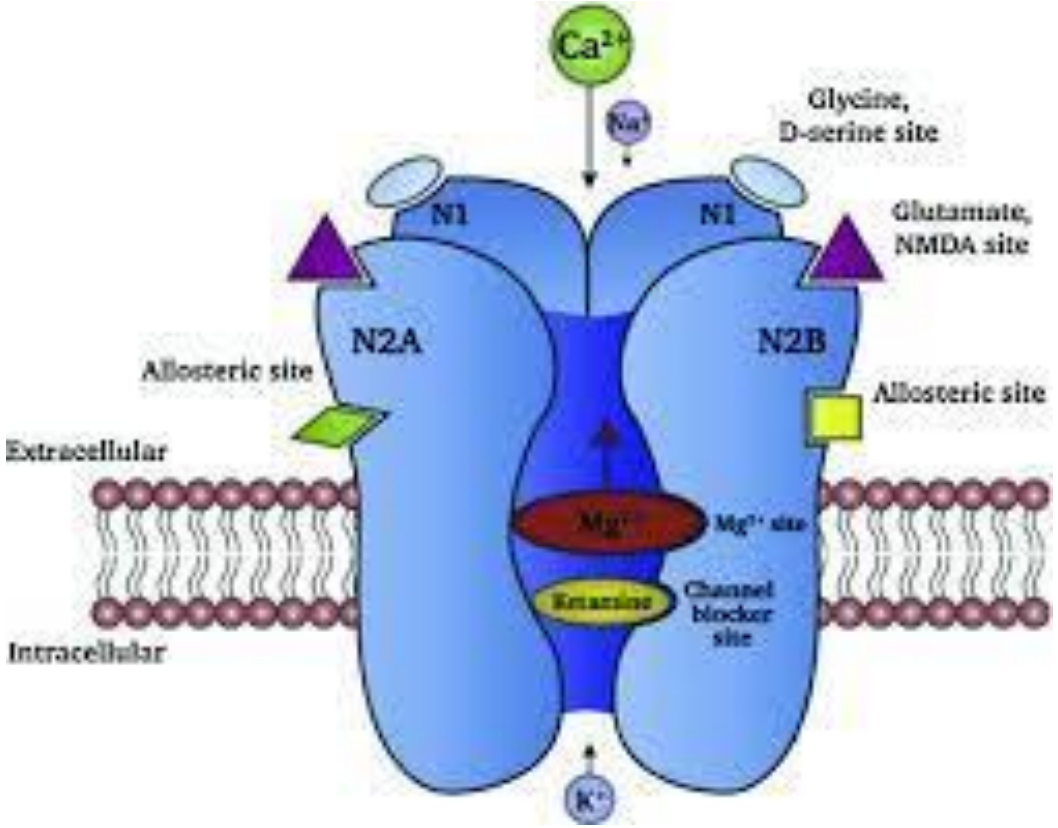
Headache, fever, vomiting, diarrhoea, or upper respiratory-tract symptoms.

- <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

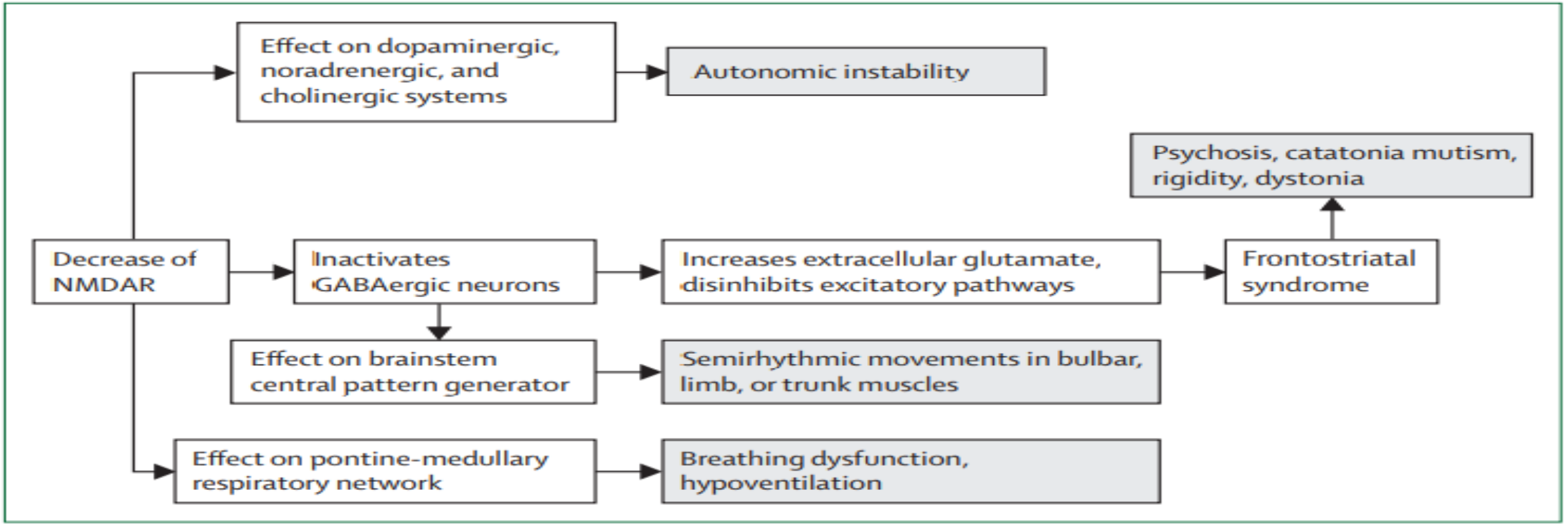


***Figure 6:* Clinical correlates of antibody-mediated decrease of NMDAR**
The figure is based on data from animal models of pharmacological or genetic decrease of NMDAR

Dalmau 2011

Anti – NMDAr Encephalitis : psychiatric features

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

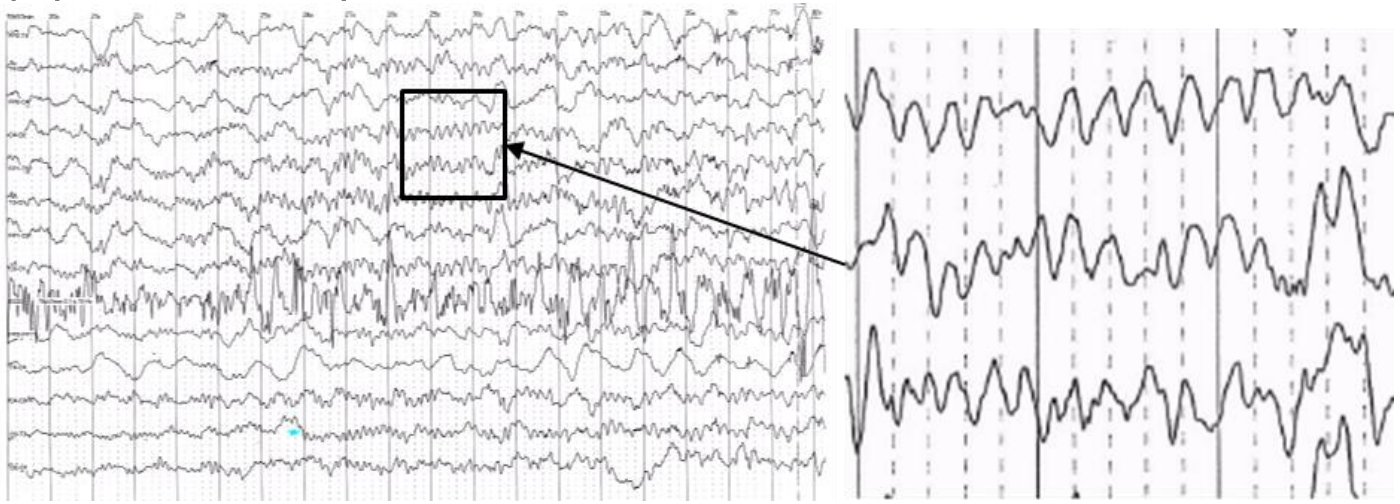
Dalmau J et al Lancet Neurol. 2019

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** (agressiveness).

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

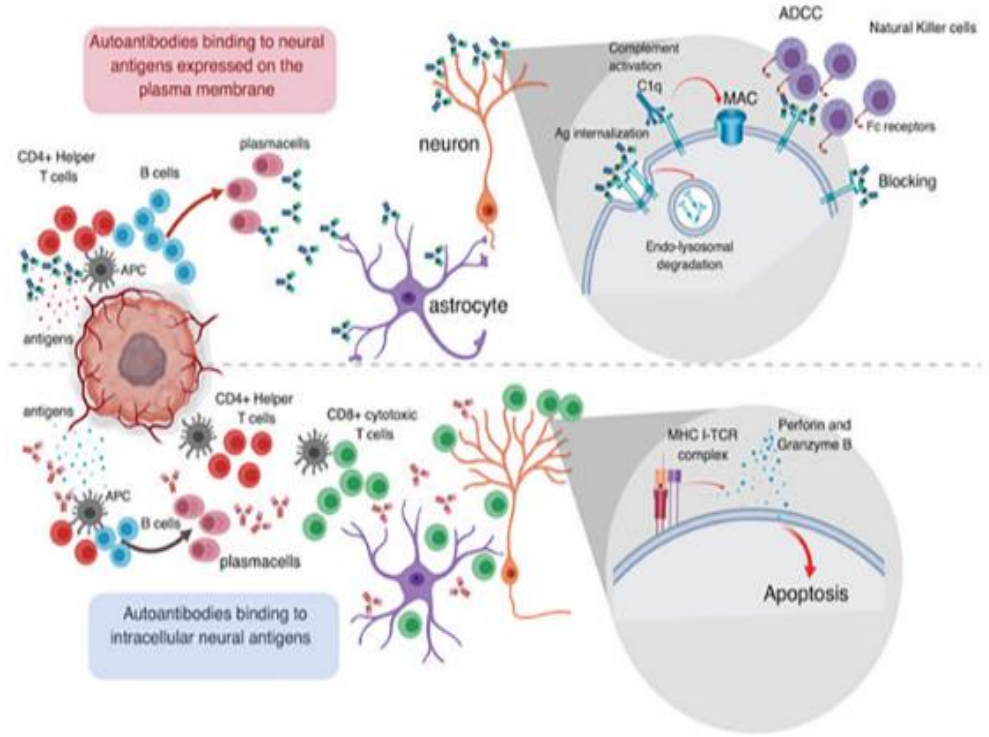
van Sonderen A, et al Nat Rev Neurol. 2017

Auto – immune encephalitides

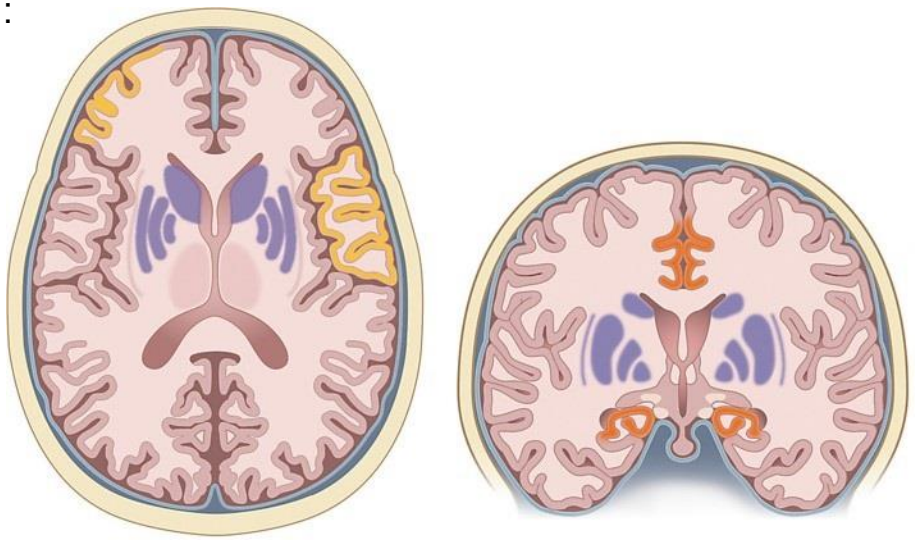
Auto immune encephalitides are non infectious and mediated by 2 types of Ab :

- against neuronal cell-surface antigens.
- against the intracellular antigen.

NMDA
AMPA
CASPR2
DPPX
mGluR
GABA
LGI1
VGCC



Yo
Ri
Ma2
SOX1
Amphiphysin
CV2



Limbic System	Extra-limbic Cortices	Basal Ganglia	Cerebellum	Brainstem
Anti-Hu **Anti-VGKC** **Anti-GAD65** **Anti-GABA B** **Anti-AMPAr** Anti-LGI1 Anti-VGCC	**Anti-NMDAr** **Anti-VGCC** **Anti-GABA-A** **Anti-GLuR3**	**Anti-CV2** **Anti-D2** Anti-NMDAr	**Anti-Yo** **Anti-GLuR1** Anti-Hu Anti-GAD65 Anti-VGCC	**Anti-Ma** **Anti-Ri** Anti-Hu Anti-Yo

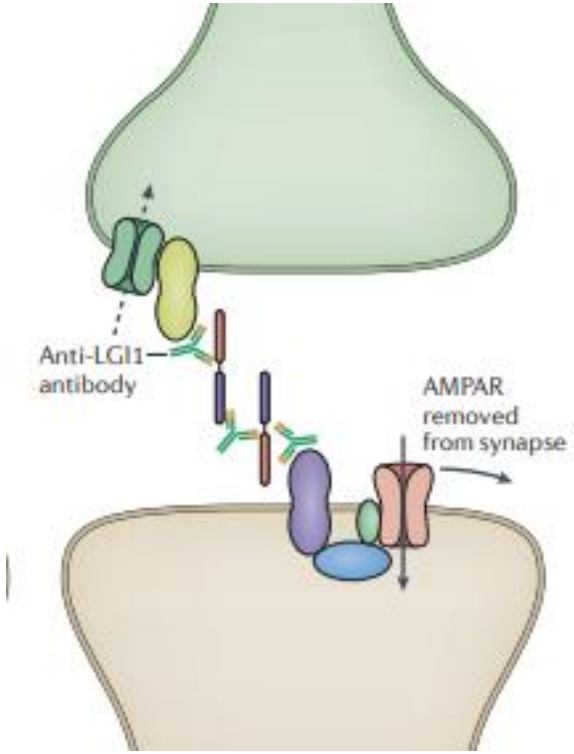
Ball C, Fisicaro et al. Clin Imaging. 2022

Anti – LGI - 1 encephalitis

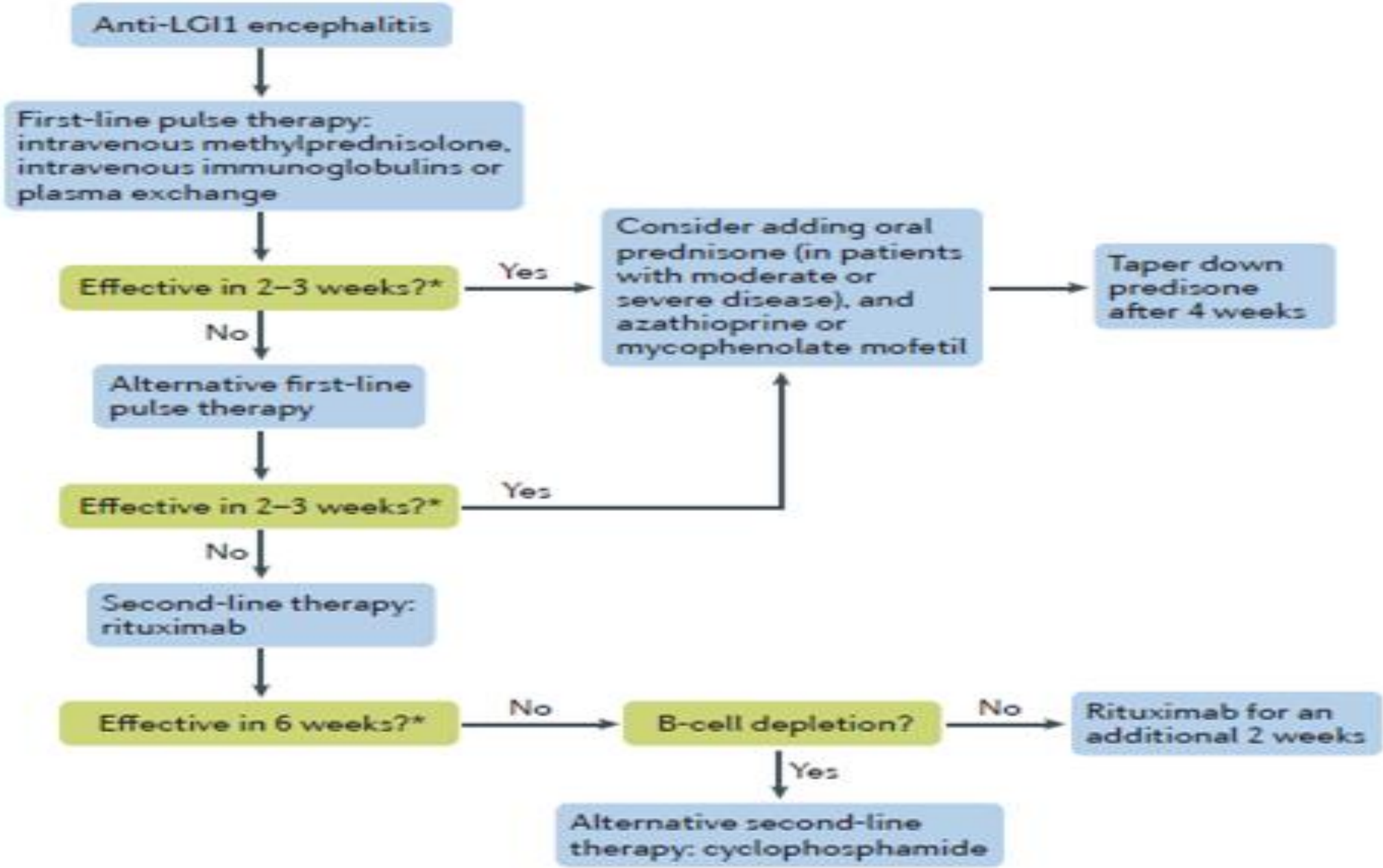
- 2nd most frequent cause of auto – immune encephalitis.
- Age 50 – 70 years. (tumors are rare: Thymoma)
- 3 clinical epileptic syndromes :

- **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



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 consciousenss

- **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