
بسم الله الرحمن الرحيم

دکتر غلامرضا خادمی

فلوشیپ مراقبت های ویژه کودکان
بیمارستان تخصصی و فوق تخصصی کودکان اکبر
مشهد

Dr. Gholamreza Khademi
Pediatrics Intensivist
Mashhad university of medical sciences

Encephalitis Update

Viral Meningitis and Encephalitis Update

Boris Garber[1] · Johnathan Glauser[2]

Accepted: 2 May 2024 / Published online: 14 May 2024

Encephalopathy

altered consciousness lasting for more than 24 hours including lethargy, irritability or a change in personality or behavior

per se can complicate many serious systemic infectious and inflammatory conditions, can result from local or systemic circulatory issues, or it can be a sign of degenerative brain disorders.

Encephalitis

- The International Encephalitis Consortium:
- encephalopathy for 24h plus two of the following:
- 1) fever;
- 2) seizures;
- 3) focal neurological findings;
- 4) CSF (cerebrospinal fluid) pleocytosis;
- 5) characteristic brain MRI or electroencephalogram (EEG) findings.

cause of encephalitis

- unknown in over half the cases despite extensive diagnostic workup

- Fortunately, incidence of **bacterial meningitis** has been **decreasing**

due to ;

effective target **immunizations**

Aseptic meningitis

- is a somewhat misleading term for meningeal inflammation from causes **other than pus-producing bacteria** [14]. Those causes include infectious agents, such as
- "**atypical" bacteria**
- (*Borrelia burgdorferi*,
- *Leptospira spp*.,
- *Mycobacteria*,
- or *Treponema pallidum*),
- fungi (such as *Cryptococcus neoformans*),
- or a free-living ameba (*Naegleria fowleri*).

Mechanisms of virus migration through BBB

1- viremia develop

2-viruses can either directly infect brain microvascular endothelium or pass through them via transcytosis in endocytic vesicles

3- infection of monocytes or macrophages (diapedesis)

"Trojan Horse" mechanism

4- via inflammatory cytokine production by viruses, West Nile,HIV

5-using specialized proteins [COVID-19 and Rabies virus

6- directly infect glia cells (part of the BBB), Nipah virus

LP

- **In immunocompetent patients**

  Without

- focal neurological abnormalities,
- prior neurosurgery,
- recent trauma,
- or papilledema,

lumbar puncture can be done without head CT first

Suggests bacterial meningitis

- CSF not clear,
- increased opening pressure,
- WBC count > 500 cells/mL >80% of neutrophils,
- glucose CSF/blood ratio <0.4,
- CSF protein > 1g/L,
- visible microorganisms

Diagnosis

- CSF lactic acid above 4.2 mmol/L is also strongly associated with bacterial infection

➡Second LP

➡ Eliza

➡PCR,…

Viral suggested

- On the other hand , **CSF:**
- pleocytosis <300 cells/mL with lymphocytic predominance,
- clear fluid
- normal opening pressure,
- normal or only slightly decreased glucose,
- normal protein

all suggest viral etiology

Encephalitis Etiology

- US 2000–2010, unknown etiology in 50%
- viral etiologies (48.2%),
- HSV, *toxoplasma gondii*, and West Nile Virus, with co-morbid HIV present in 7.7% of hospitalizations.
- Autoimmune encephalitis among other specified causes was reported in 32.5% of cases with known etiology (George et al., 2014

In Mashhad,

- Detects 4 virus

- VZ
- Enterovirus
- HSV
- CMV

Our specialists believe

- diagnosis of arboviruses(CCHF, WNV,…)
- is serologic base.

HSV

- most common cause of sporadic encephalitis
- 90% HSV-1
- ----------
- Initially similar bacterial meningitis with

fever,

headache,

neck stiffness

at extremes of age,

focal seizures (temporal lobe abn)

RBC in a non-traumatic tap

New born HSV

:shock, status epilepticus, DIC,..

HSV Tx

- High-dose IV acyclovir 14–21 days in immunocompetent and immunosuppressed patients, respectively
- ….significantly reduce mortality

HSV (CS& Acyclovir combination therapy)

- limited clinical data for CS therapy
- beneft in mouse
- pre-clinical models, ,(human study)

  reduction in the severity of infection
-

HSV Tx cont,

- beneficial long-term effects,
- no increase in viral burden

- concern of potentially increasing viral replication

-

- Front Cell Infect Microbiol. 2020; 10: 592017.
- Published online 2020 Nov 23. doi: 10.3389/fcimb.2020.592017
- PMCID: PMC7719626
- PMID: 33330135
- The Use of Adjunctive Steroids in Central Nervous Infections

HSV (C S& Acyclovir

combination therapy research)

➡Japan :

beneficial impact on clinical outcome and reduction in the extent of HSE infection, without inhibition of the antiviral action of acyclovir (Kamei et al., 2005)

(C S& Acyclovir combination therapy)

- Although corticosteroid adjunctive therapy must be studied further

Adjunctive **dexamethasone** might be considered for patients with HSV encephalitis and severe **brain edema** or **vasculitis**

Viral Neural infection presentations

- stroke,
- mono neuropathies,
- polyneuropathies,
- Guillain-Barre syndrome myelitis,
- meningitis,
- encephalopathy,
- encephalitis,
- neuromyelitis optica,
- optic neuritis,
- Hemorrhagic encephalitis (AHLE),
- ADEM
- ANEC.

West Nile Virus Encephalitis

- arthropod-borne infection that is most commonly transmitted by a mosquito bite
- virus migrates to lymph tissue and CNS
- Incubation 2 days to 14
- 80% of cases remain asymptomatic, 20% have a febrile
- And wide spectrum CNS symptoms.
- no FDA approved vaccine
- CS therapy in controversy!

PCR

- There are two rapid multiplex PCR-based panel tests on the market for the detection of multiple viral, bacterial, and fungal in CSF

- In Iran there is rapid multiplex PCR-based panel tests just for TB

2 type PCR

- **Traditional PCR**→ electrophoresis-→vision of protein bands

- **Real time PCR** is expensive the result following and observe with florescent and

the monitoring is completely by technology equipment.

Tests are:

I. Qualitative

II. Quantitative more expensive

- **rapid test** →Eliza objective , Hepatitis , Influanza. Covid..

Encephalitis comlications

today about,

- **ADEM**
- **AHLE**
- **ANEC**
- **Autoimmune Encephalitis**

Cause of pediatrics CNS demyelization

- include acute disseminated encephalomyelitis (ADEM);
- multiple sclerosis (MS);
- optic neuritis;
- transverse myelitis;
- myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD);
- neuromyelitis optica spectrum disorder (NMOSD);
- and various infectious, metabolic, and rheumatologic conditions

---

- peripheral demyelization : GBS

ADEM

- typically presents with encephalopathy and multifocal brain lesions
- often a monophasic illness with good functional recovery
- postulated to be an autoimmune disorder
- demyelination of white matter typically following a recent (1-2 weeks prior) viral infection or vaccination
- . Grey matter is also, as is the spinal cord.

ADEM cont,

- from a cross-reactivity in immunity to viral antigens, triggering a subsequent autoimmune attack
- half of all confirmed cases, anti-MOG (myelin oligodendrocyte glycoprotein) immunoglobulin G antibodies

Markers:

CSF

- pleocytosis
- show an increase in myelin basic protein
- anti-MOG antibodies

ADEM cont,

- Some conditions can be fatal,
- including acute hemorrhagic leukoencephalitis (also known as Weston–Hurst syndrome) and
- acute necrotizing encephalitis of childhood

These have been associated with specific inciting infections and genetic mutations

ADEM
DDx

- multiple sclerosis or
- neuromyelitis optica
- 1-Unlike MS, symptoms are more systemic rather than focal and include fever, headache, decreased level of consciousness (varying from lethargy to coma), seizure, and multifocal neurologic symptoms including hemiparesis,

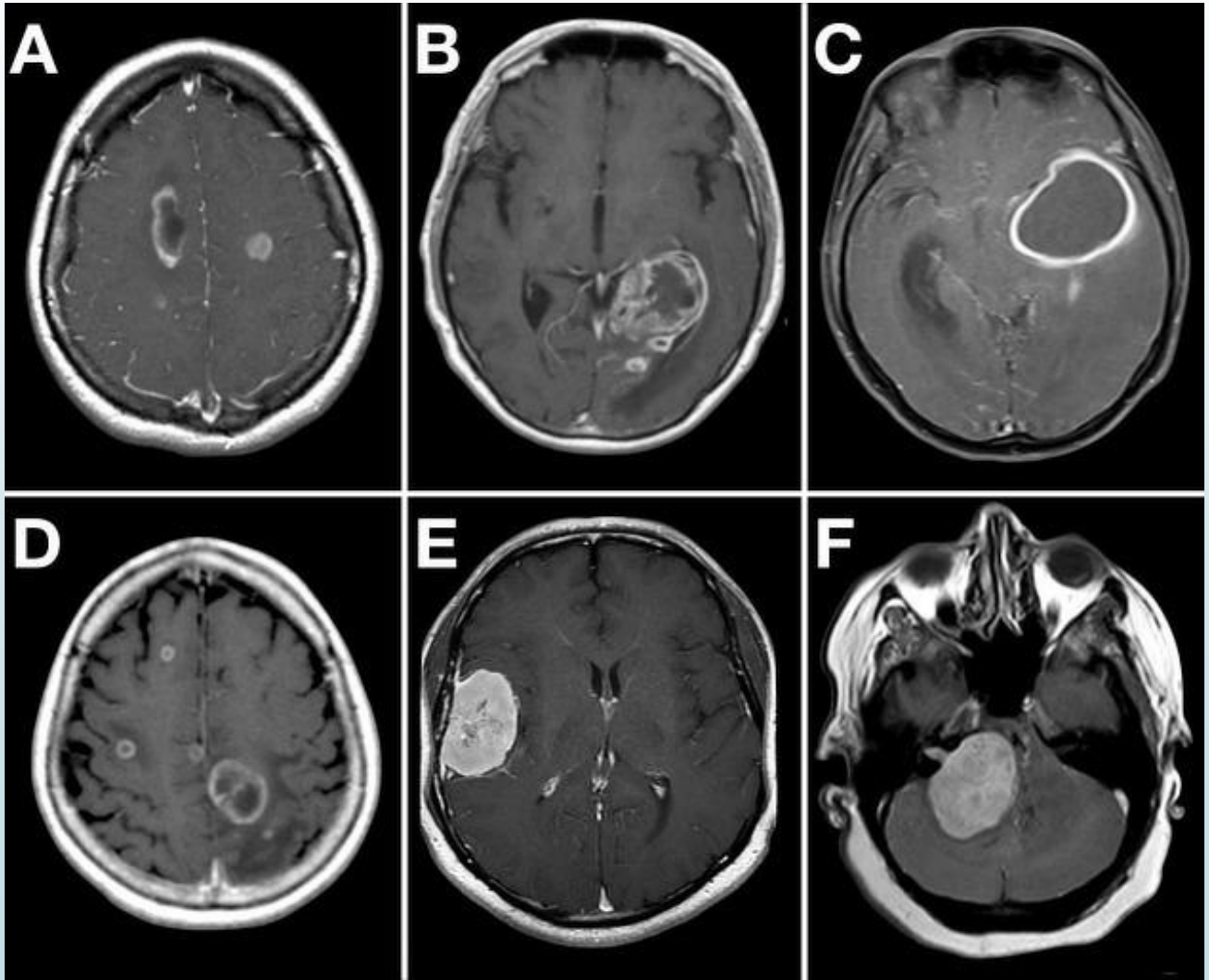
  lesion may demonstrate hemorrhage AHLE (Hurst disease)
- 2- ADEM Firstly with viral infection Sn& Sx

- ADEM progression to MS is not uncommon (35%).

ADEM

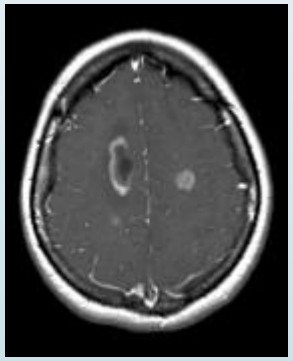
- The International Pediatric Multiple Sclerosis Study Group defined ADEM as follows [21]:
- A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause.
- Encephalopathy that cannot be explained by fever.
- No new clinical and magnetic resonance imaging (MRI) findings emerge ≥3 months after the onset.
- Brain MRI is abnormal during the acute (3-month) phase.

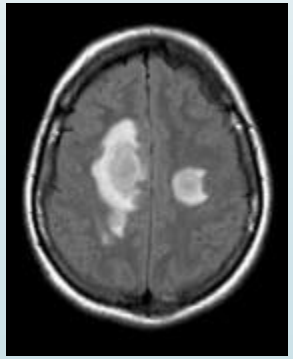
Which one is most similar to ADEM?

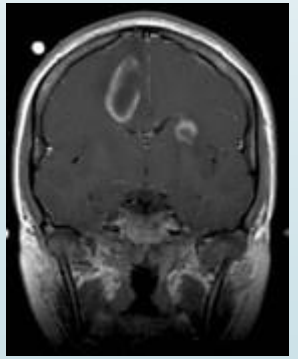


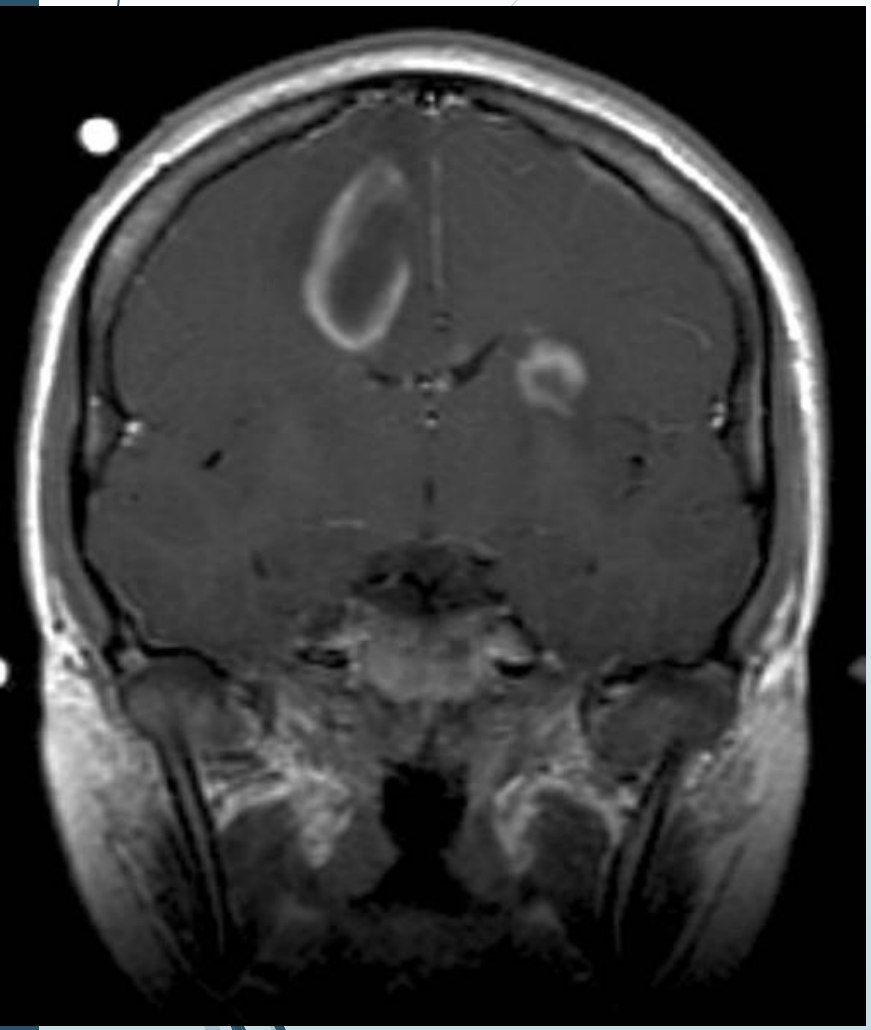
ADEM

This young woman presented with progressive left hemiparesis after having had a viral infection a week earlier





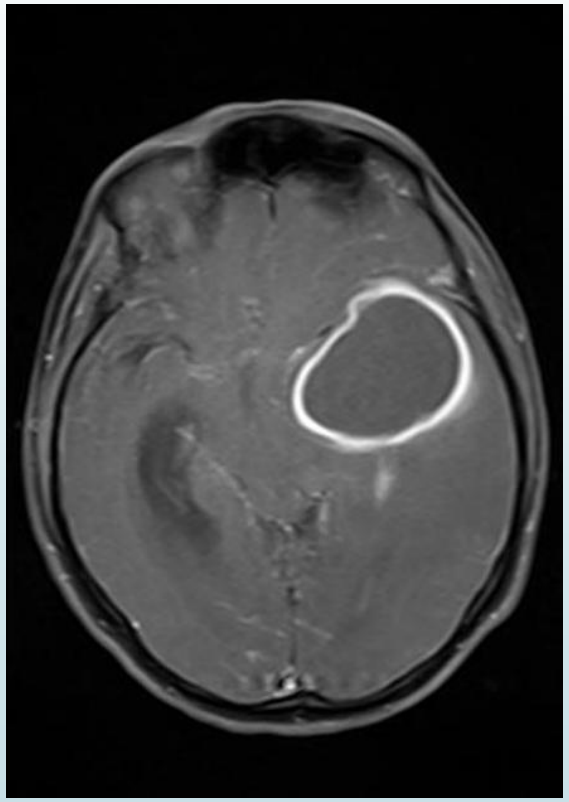




bilateral asymmetric lesions with open ring enhancement charact eristic of demyelination. Note that restricted diffusion is not seen centrally (usually seen in cerebral abscesses), but at the advancing rim of demyelination

Brain abscess CT

Cerebral abscess



ADEM Tx

- Treatment typically consists of methylprednisolone, with immunoglobulin and cyclophosphamide reserved for patients refractory to steroids [4].
- Monoclonal target antibody (in research)
- Recovery 1-3 mo

Pharmacological Recruitment of Endogenous **Neural** Precursors to Promote Pediatric White Matter Repair: Establishing Correlations Between Visual Outcomes, Saccadic Function and MEG Oscillations in Children With **Demyelinating** Disorders in Comparison to Healthy Control Children

ClinicalTrials.gov ID NCT03010826

Sponsor The Hospital for Sick Children

Information provided by E. Ann Yeh, The Hospital for Sick Children (Responsible Party)

Last Update Posted 2020-01-07

Hemorrhagic encephalitis(AHLE)

- closely mimic HSE in both CSF and in MRI
- **The absence of oligoclonal bands exclud fulminant MS** .
- difficult to Dx other causes of ADEM from AHLE based on clinical and MRI, diagnosis via biopsy.
- **rare ,fatal ,acute onset , hemorrhage in the white matter**
- **categorized in group of ADEM (progression to hemorrhage)**

hemorrhagic encephalitis(AHLE)

- majority of the cases are the parietal lobes
- but the lesions can be seen in the subcortical white matter, mid brain, pons, corpus callosum, basal ganglia, medulla, cerebellum, and even spinal cord

Acute necrotizing encephalopathy (ANEC)

- Children
- Genetic cause??
- rapidly progressive at first
- previously healthy child
- following a viral infection & viral Sn &Sx
- **symmetric** lesions in the basal ganglia, thalamus and brainstem, reminiscent of those seen in mitochondrial disorders, e.g. in Leigh syndrome or AHLE
- CSF pleocytosis is usually absent

Figure 1(A and B): (A) Axial FLAIR and (B) gradient echo (GRE) MR images at the level of basal ganglia show multifocal FLAIR hyperintense lesions at gray-white matter junction and in bilateral basal ganglia. None of the lesions shows evidence of hemorrhage (B)

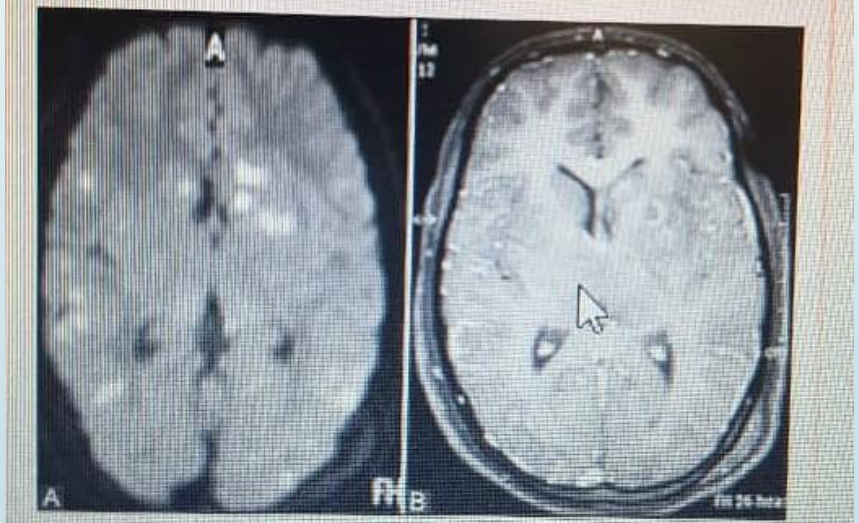
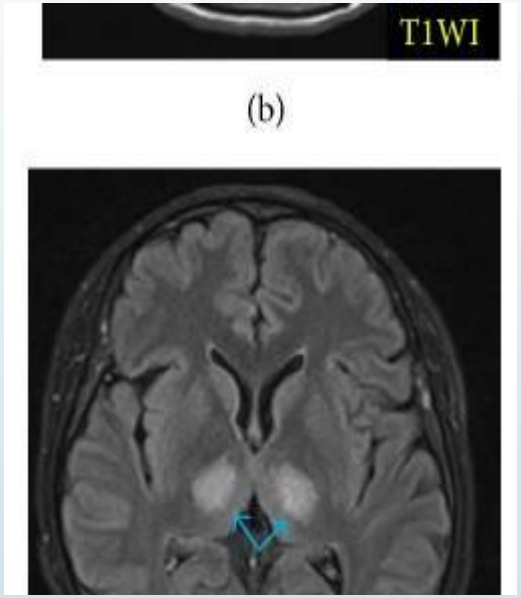
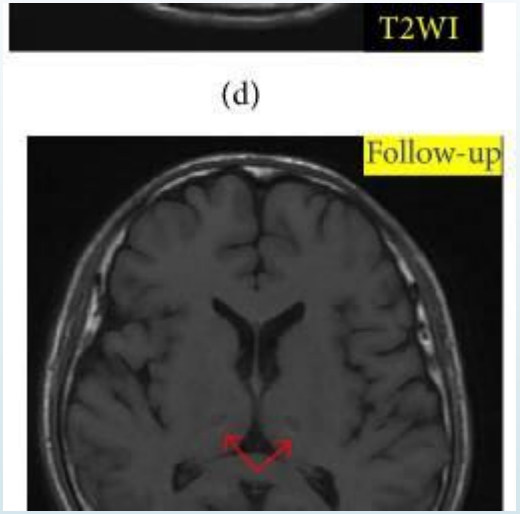


Figure 2 (A and B): (A) Axial DWI MR image at the level of basal ganglia shows restricted diffusion within these lesions. (B) Contrast-enhanced T1W MR image shows peripheral ring enhancement of the lesions

ANEC cont,

- etiology and the pathogenesis unclear
- most hypothesis is the hypercytokinemia---->liver dysfunction, acute renal failure, shock, and DIC
- development independent of the type of infectious agents.
- **edema to petechial hemorrhage and then to necrosis**
- familial episodes reported


T1WI
(b)


T2WI
(d)
Follow-up

ANEC Tx

Not clear

- Immunotherapy
- IVIG

- 2022 Taiwan Pulse prednisolone plus IVIG with good outcome

Autoimmune encephalitis

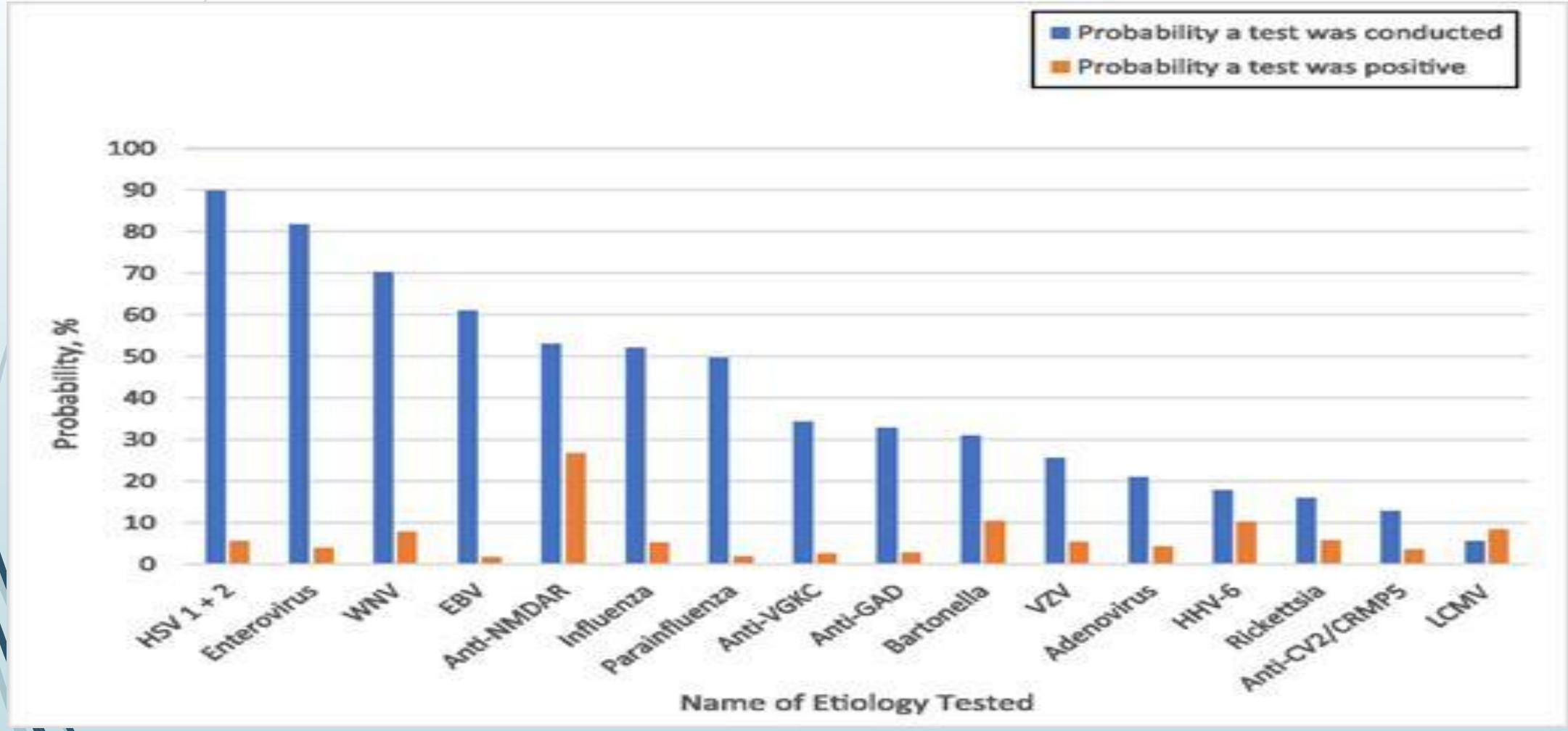
- 20% of all cases of encephalitis,
- developed countries it is more common
- can follow viral encephalitis or vaccinations,
- Be paraneoplastic(less in chidren) or cryptogenic

- NMDA-R encephalitis is now more commonly identified
- Female predominance
- Young adult

JUNE 01 2020

Infectious and Autoimmune Causes of Encephalitis in Children

American academy of pediatrics



autoimmune encephalitis

- **Early** immunotherapy, with either corticosteroids or IVIG, improves outcomes

can have a relapsing course

neurological deficits rather than psychiatric manifestations.

autoimmune encephalitis

cont,

- Tumor is uncommonly identified in children; however, ovarian teratomas occur in about 30% of women younger than 18 years
- 94% lymphocytic pleocytosis (>5 CSF
- EEG is abnormal 90%
- recovery up to two years after initial presentation.

autoimmune encephalitis

cont,

- Long term Tx Rituximab, monthly IVIG, cyclophosphamide
- Prognosis is Good
- ----------
- CSF -→often NL

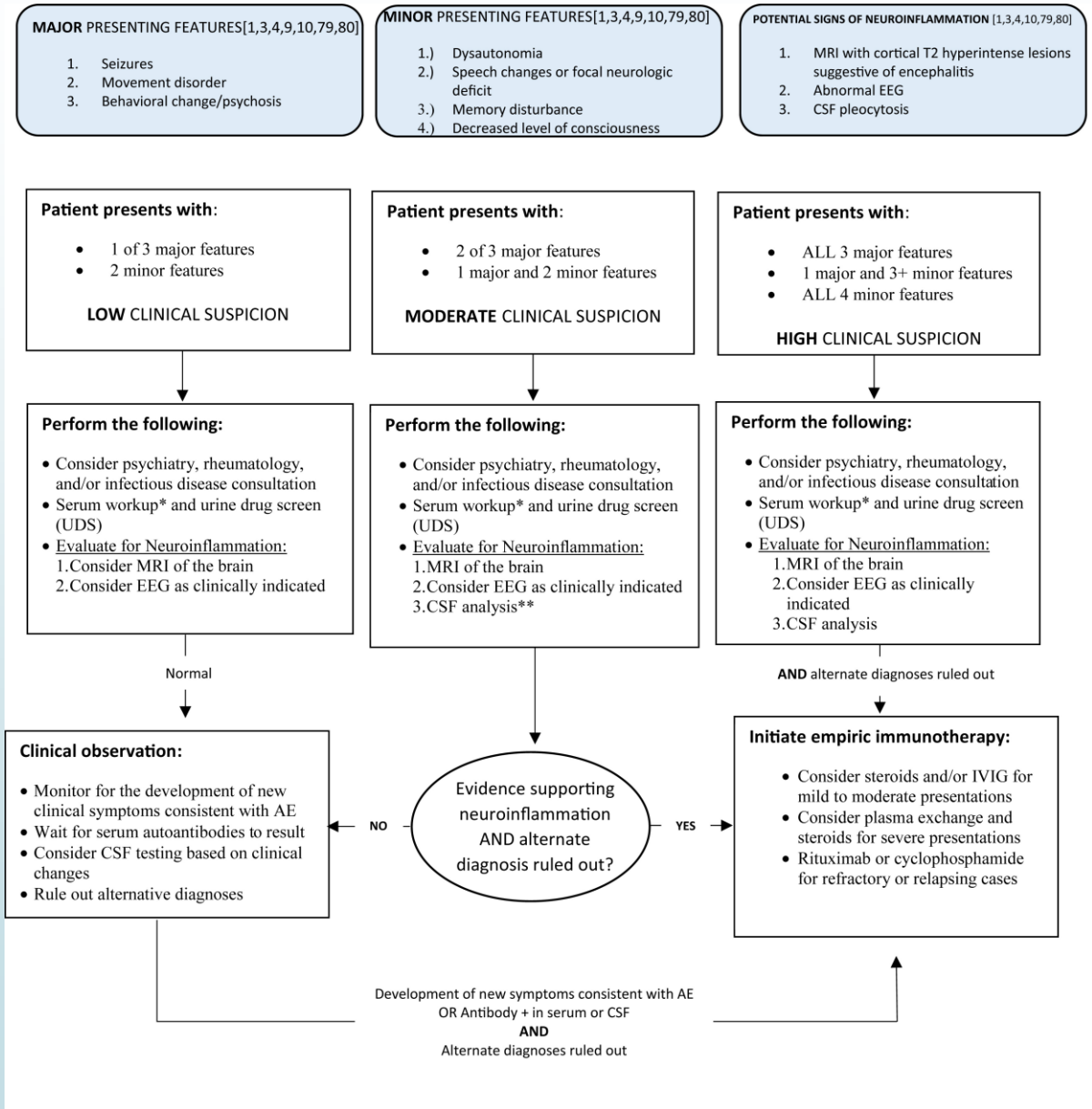
autoimmune encephalitis

- Dx **cont,**
- **# csf Ab**
- **# blood Ab**
- **# MRI**
- **# Cn finding**
- testing can take days to weeks to result,
- **empirical treatment is recommended for high index of suspicion**

start empirical IVMP, IVIG, or PLEX

- **Immunotherapy should be escalated to second-line therapies such as rituximab or cyclophosphamide in refractory cases.**

autoimmune encephalitis



AE types

- **Leucine-rich, glioma-inactivated 1 (LGI-1) and contactin-associated protein-like 2 encephalitis**
- Cn is similar

- Rx: IVMP, IVIG, and/or PLEX with most children improving with immunotherapy
- **Glycine receptor antibody encephalitis**
- muscle rigidity, debilitating muscle spasms, and myoclonus
- Often nl MRI

AE types

- **Gamma-aminobutyric acid type A & B receptor encephalitis**
- Some tomes tumor related
- **Ophelia syndrome**
- Hodgkin related
- good outcomes with tumor Tx
- **Myelin oligodendrocyte glycoprotein (MOG**
- Myelin oligodendrocyte glycoprotein (MOG) is a myelin protein
- Behavior: is like ADEM, optic neuritis, and transverse myelitis
- 30% relaps ,
- more affect children
- Sometimes MOG Ab finded in patients with NMDA-R

AE types

- **Hashimoto encephalopathy**

most common presenting symptoms in children include psychosis, confusion, abnormal movements, cognitive deterioration, and seizure.[54] Diagnostic criteria for HE in adults proposed by Graus et al. was based on clinical presentation; the presence of elevated anti-thyroid antibodies, namely, thyroid peroxidase antibodies and/or thyroglobulin antibodies; MRI findings; absence of well-characterized neuronal antibodies in the serum or CSF; and presence of subclinical or mild overt thyroid disease.[55] However, more recently, a study with 17 pediatric patients with HE revealed that adult diagnostic criteria lacked sensitivity when applied to children, given that the

Some differences

- Hashimoto
- CSF -→protein increasing
- Long term Tx -→Rituximab
- majority of did not have thyroid disease.
- Px-→ good
- IVIG or PLEX with good effect.
- Rituximab had favorite outcome for relapsing

AE types

- Rasmussen encephalitis
- unihemispheric focal cortical atrophy
- Tx: CS. IVIG.
- but definitive treatment remains surgical hemispherectomy

Antibody-negative autoimmune encephalitis

- One of the more difficult types of AE

But

- Cn& pCn like AE
- had poorer cognitive outcomes at 1-year follow-up compared with children with NMDA-R encephalitis.[79] This study also demonstrated that postencephalitic epilepsy was more common

AE
Diagnostic approach

- discussions between neurologists, rheumatologists, psychiatrists, and infectious disease physicians. In children, the differential diagnosis includes infection, vascular etiologies, demyelinating disorders, metabolic and/or mitochondrial disorders, malignancies, drug intoxications, neurorheumatologic disorders, genetic leukoencephalopathies, and psychiatric disorders

-

AE diagnostic W/U

- neuroinflammatory studies
- autoimmune encephalopathy panel,
- myelin oligodendrocyte glycoprotein antibodies,
- aquaporin-4 antibodies,
- oligoclonal bands),
- neurorheumatologic studies
- angiotensin converting enzyme,
- anti-nuclear antibody testing,
- anti-neutrophil cytoplasmic antibody testing,
- double-stranded DNA testing),

AE diagnostic W/U

- metabolic and mitochondrial testing (
- lactate/pyruvate ratio,
- comprehensive metabolic panel,
- plasma amino acids,
- ammonia level,
- copper,
- ceruloplasmin,
- vitamin B_{12},
- vitamin B_1),
- thyroid studies (thyroid stimulating hormone, thyroxine, thyroglobulin antibodies, thyroid peroxidase antibodies),
- and serum drug screens.
- **Cerebrospinal fluid (CSF) for all…

AE diagnostic W/U

Diagnostic Study Categories	Serum Studies	Cerebrospinal Fluid Studies	Urine Studies
Infectious studies	• CBC • ESR • CRP • HSV • HIV • VZV • Viral encephalitis panel/meningitis panel	• Routine studies (WBC, protein, glucose) • HSV	• Urinalysis • Urine cul

AE diagnostic W/U

Neuroinflammatory studies	• MOG antibodies • AQP-4 antibodies • Autoimmune encephalopathy panel • Paraneoplastic panel • Oligoclonal bands	• Oligoclonal bands	• None
Neurorheumatologic studies	• ACE • ESR • ANCA • ANA antibody panel • dsDNA	• ACE	• None

AE diagnostic W/U

Mitochondrial, metabolic, & malignancy studies	• Comprehensive metabolic panel • Lactate/pyruvate ratio • Plasma amino acids • Acylcarnitine profile • Ammonia • Copper • Ceruloplasmin • Vitamin B_{12} • Vitamin B_1	• Cytology • Flow cytometry	• Urine organic acids
Thyroid studies	• TSH • T4 • Thyroglobulin antibodies • Thyroid peroxidase antibodies	• None	• None

Mitochondrial, metabolic, & malignancy studies	**Comprehensive metabolic panel** **Lactate/pyruvate ratio** **Plasma amino acids** **Acylcarnitine profile** **Ammonia** **Copper** **Ceruloplasmin** **Vitamin B_{12}** **Vitamin B_1**	• **Cytology** • **Flow cytometry**	• **Urine organic acids**
Thyroid studies	**TSH** **T4** **Thyroglobulin antibodies** **Thyroid peroxidase antibodies**	• **None**	• **None**

AE diagnostic W/U

- Neuroimaging and EEG
- Tumor evaluation **F/U at least 2 y after**

SARS-CoV-2

- SARS-CoV-2 virus infection symptoms are highly variable, and most infected people remain asymptomatic or only develop mild symptoms
- In symptomatic patients the respiratory and digestive systems involvement predominate.
- Multiple neurological complications have been reported

Autoimmune Encephalitis

TOPICAL REVIEW Volume 132P56-66July 2022

Autoimmune Encephalitis in Children

Duriel Hardy, MD Duriel.Hardy@austin.utexas.edu

Noninfectious meningitis

- Noninfectious meningitis can have an autoimmune cause triggered by certain medications [14], may be due to autoimmune diseases such as systemic lupus erythematosus, or can result from malignant invasion of the meninges

Transverse myelitis

- is defined by inflammation of the spinal cord itself, which can be triggered either by viral invasion or by an autoimmune process

- It presents with acute or subacute symmetric motor and sensory deficits in extremities, usually in combination with neurogenic bowel and bladder dysfunction which can progress to respiratory muscle dysfunction, but without meningeal signs or encephalopathy.

Rhombencephalitis

- Inflammation in the brainstem and, which can manifest as an onset of ataxia and cranial nerve abnormalities, followed by hemodynamic instability and respiratory failure

- ----------

Tick-borne encephalitis

- virus can also cause encephaloradiculitis, where pain in radicular distribution is a prominent symptom

Thailand journal ٢٠٢٤

- Outcome and Prognostic Factors of Pediatric
- Encephalitis in Thailand
- Vitchayaporn Emarach Saengow1 Natnicha Praphaphanthasak1
- 1Department of Pediatrics, Maharat Nakhon Ratchasima Hospital,
- Nakhon Ratchasima, Thailand
- J Child Sci 2024;14:e13–e18

پایدار و سربلند باشید

Extra comment

- most analyses have concluded that short courses of high-dose steroids seem neither to benefit nor to harm patients with septic shock.

- medsape

Extra comment

- Some data support the concept of low-dose hydrocortisone for a longer duration in combination with fludrocortisone in patients with sepsis, particularly those with relative adrenal insufficiency.[34] Recent reports suggest that such steroid treatment might be best reserved for patients with vasopressor-refractory hypotension.

- medscape