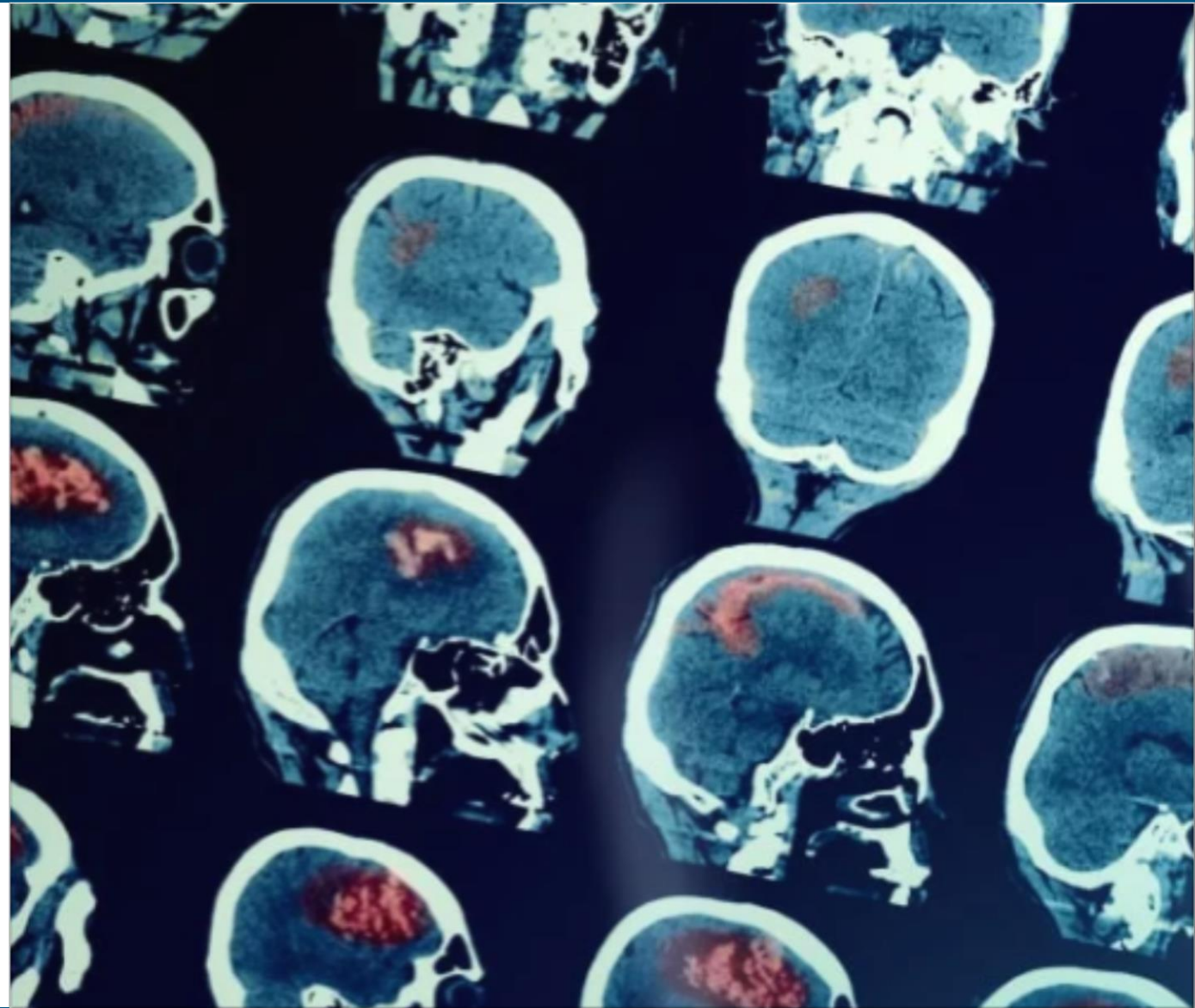


Encephalitis in the Pediatric Patient

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Disclosure

- *This presentation is for educational purposes only and should not be used as a substitute for clinical judgement.*
- *The presenter assumes no responsibility or liability resulting from the use of information contained herein.*

I do not have any disclosures.

Objectives

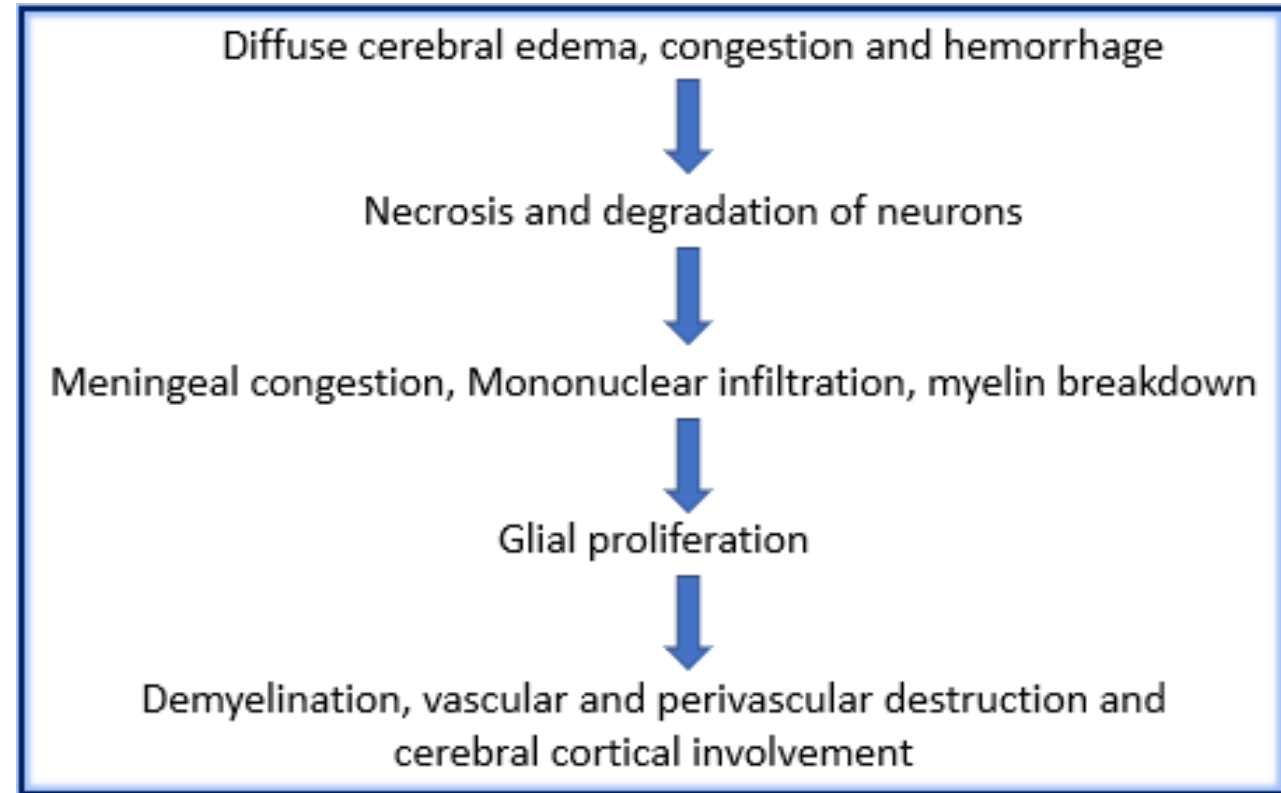
- Define encephalitis and its many forms
- Recognize emerging/endemic encephalitis in Nebraska
- Understand key presenting symptoms of encephalitis
- Work up encephalitis based on best practice guidelines
- Learn to treat encephalitis

What is Encephalitis?

- Encephalitis: infection or inflammation of the brain
- Meningitis: infection or inflammation of the meninges which is a thin membrane that surrounds brain and spinal cord
- Myelitis: infection or inflammation of the spinal cord
 - Meningo-encephalitis
 - Encephalo-myelitis
 - Meningo-encephalo-myelitis
- Demyelination – loss of myelin (protective covering around axons/nerves in brain and spinal cord)

Pathophysiology

- Encephalitis is primarily defined by CNS dysfunction
 - Infections and other disorders activate the immune system leads to inflammation of brain
- Wide range of symptoms including permanent sequelae and death
 - Morbidity > Mortality
- ~1000 new cases reported/year
- Often etiology unknown
 - Specific diagnosis can be made ~30% of the time



Barriers to Diagnosis

- Timing is key!
 - Delay is symptom onset to evaluation/diagnosis
- Lack of available sensitive tests
 - improved since advent of PCR in 1990s
- Lack of sample
- Limited capacity for pediatric patients to describe symptoms
- Confounding comorbid illnesses

Complications

- Morbidity
 - Hearing difficulty
 - Speech difficulty
 - Memory impairment
 - Intellectual disability
 - Depression
 - Weakness
 - Epilepsy
- Mortality
 - Death (case-fatality rate in USA is >5%)

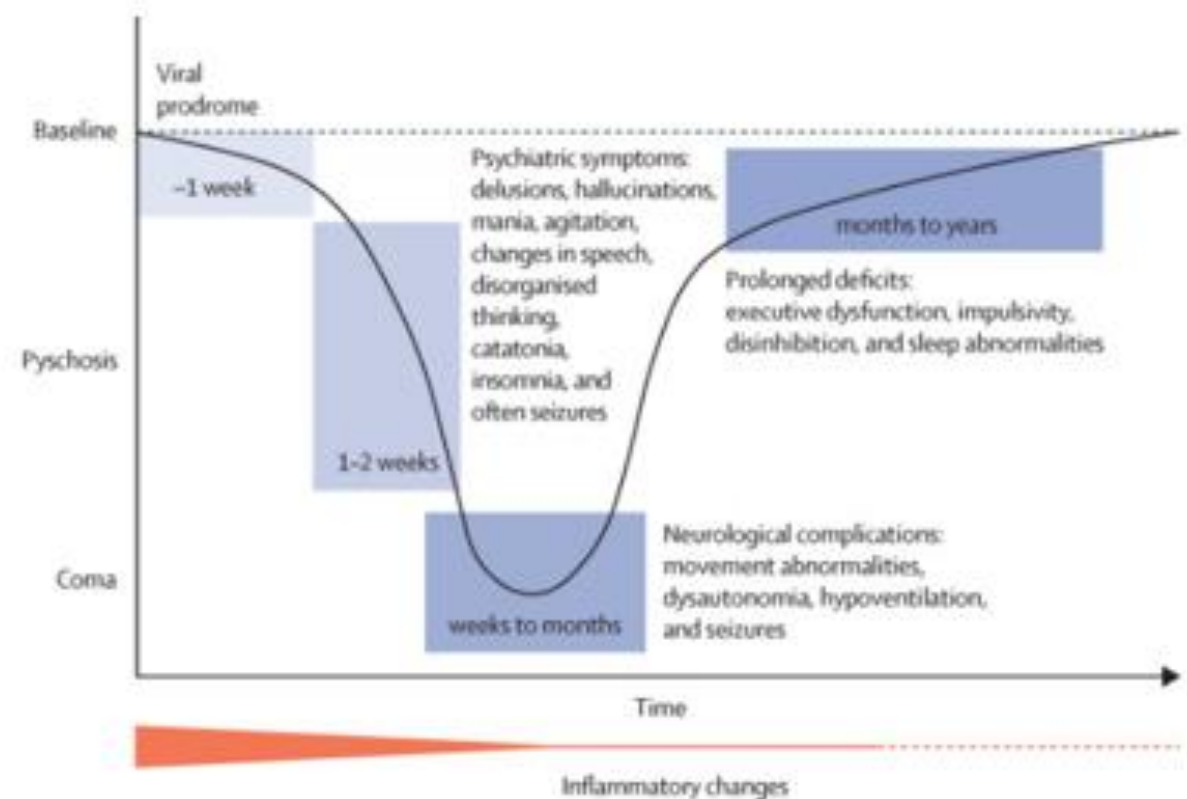
Encephalitis Caregiver Tips

After surviving a severe case of encephalitis, patients are very often forced to deal with complications that may last the rest of their lives. Although the disease is gone, its lingering effects can make everyday difficult, and caregivers can help sufferers to return to their normal daily routines as much as possible.

- ❑ Learn as much as you can about the disease and its long-term effects. The sufferer may need help with ongoing therapies, such as physical therapy, occupational therapy, speech therapy, or psychotherapy.
- ❑ Understand that although your loved one may look as if everything is fine, he or she may be struggling with subtle, unseen complications. Depression and anxiety often are a result of these struggles, and daily tasks such as paying bills may be difficult, a situation that can lead to financial missteps. As a caregiver, be aware that these apparently unrelated problems are a result of the disease and be alert for warning signs.
- ❑ Create an environment that's free of distraction and confusion to help the sufferer cope with any problems with concentration or focus.
- ❑ Find a support group for both the sufferer and yourself as a caregiver. It always helps to know that you're not alone in what you're going through.

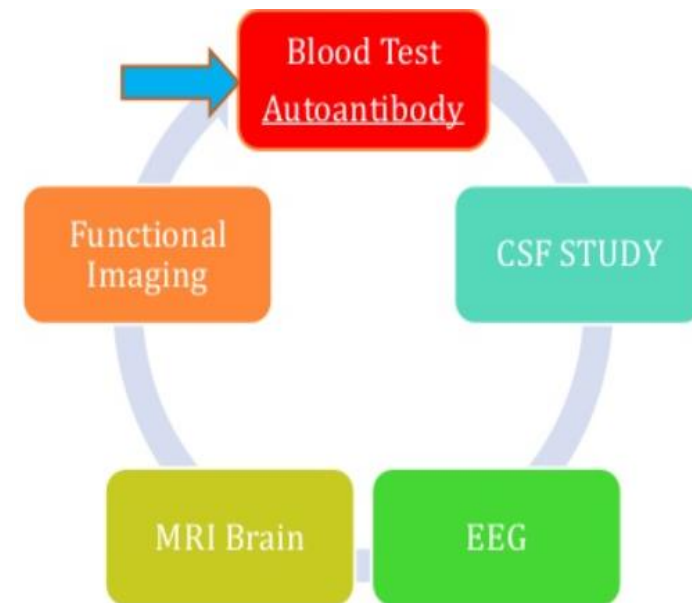
How to Recognize Encephalitis

- ACUTE (sudden) onset symptoms
- Headaches
- Personality change
- Hallucinations, paranoia
- Abnormal movements (fast or slow)
- Fatigue, excessive sleepiness
- Encephalopathy, confusion
- Seizures



Work-up

- Lumbar puncture
 - Glucose, protein, cell count, culture
 - Oligoclonal bands (must compare with serum oligoclonal bands)
 - CSF autoimmune encephalitis panel*
 - CSF meningoencephalitis panel
- Serum labs
 - Serum autoimmune encephalitis panel, Anti-TPO antibodies
 - HSV, EBV, CMV, West Nile virus, Enterovirus, Respiratory Viral Panel
 - Immunoglobulin panel, TB, HIV
- EEG
- MRI brain w/wo contrast
- UA/Urine/Serum toxin screen



CSF

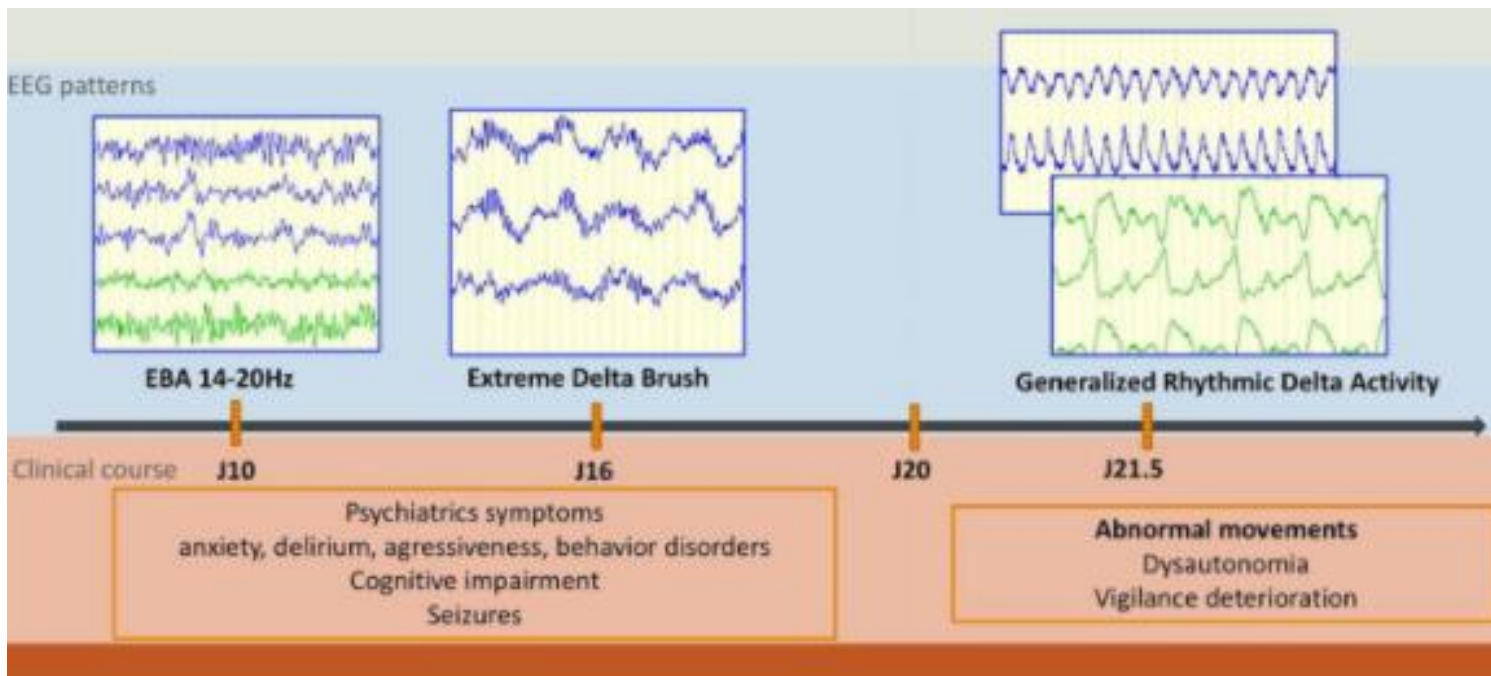
- Abnormal CSF findings in ~80% of patients
- CSF lymphocytic pleocytosis in >90% of cases
- Protein increase in ~33% cases
- Oligoclonal bands in ~25% of cases
- Glucose in mostly normal

Antibodies	Antibodies
In CSF	85.6% also had them in serum
In Serum	100% also had them in csf

Autoantibodies are almost always present in CSF
The serum can be negative in ~10% of patients

EEG

- Sensitive test (90%) but not specific (40%)
- See signs of encephalopathy/slowning (most often) or seizures (50%)
- Improves with treatment



- Delta Brush
- PLEDS
- Temporal seizures
- Facio-Brachial dystonic seizure

MRI

- At presentation 50% of patients have abnormal MRI
- Most commonly increased signal T2-FLAIR (40%)
 - Medial temporal lobe
 - Insular region
 - Brainstem
 - Corpus callosum
- Brain atrophy
 - Some cases there is mild improvement in atrophy with treatment
- Contrast enhancement

Treatment

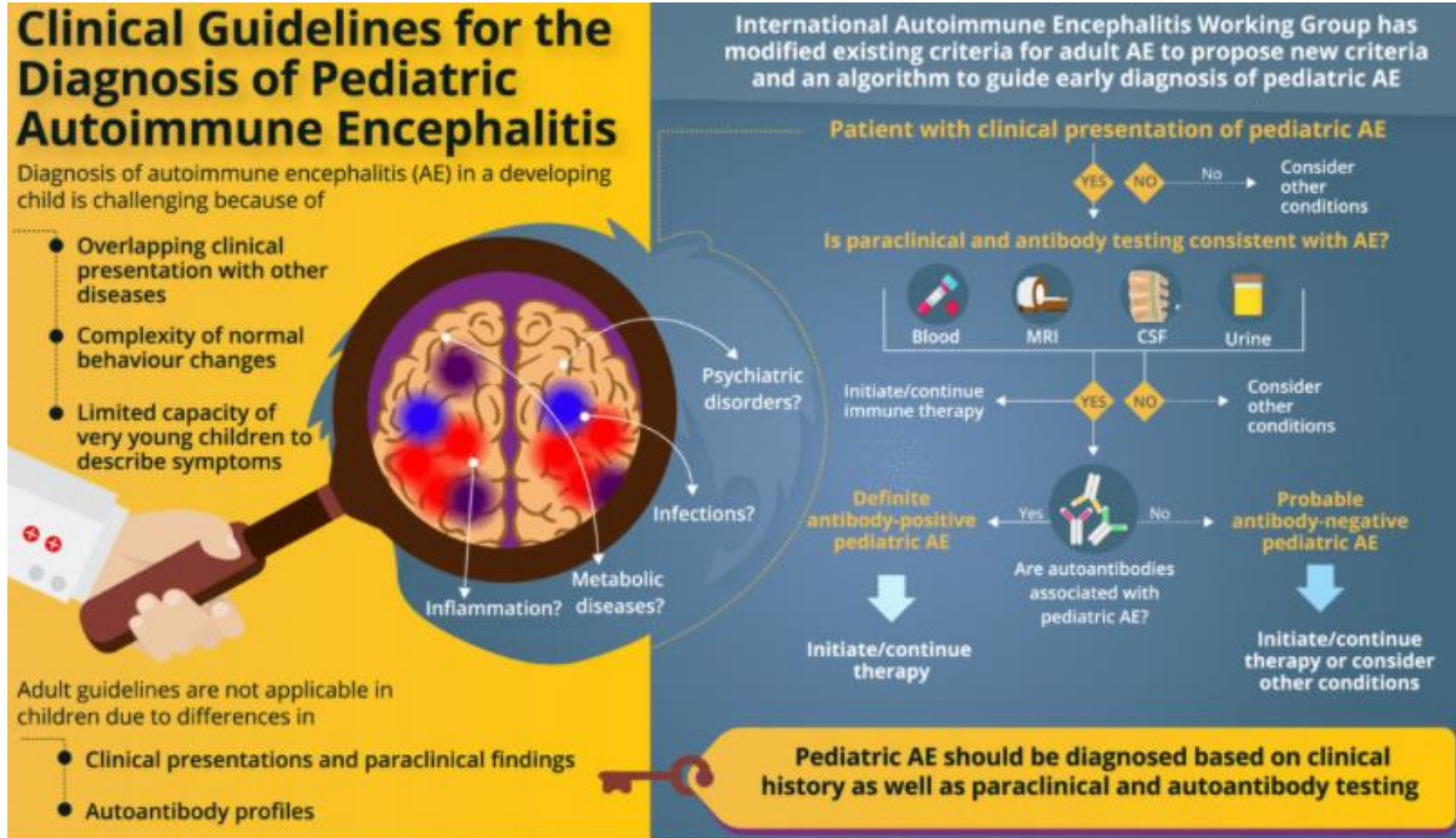
*draw labs and can “hold” sample before treatments

- IVMP
 - 30mg/kg/day (max 1g/day) x 5-7days
 - Prednisolone taper (Bactrim/PPI/Vit D/CA)
- IVIG*
 - 1g/kg/d x 2days vs 400mg/kg/d x 5days
- PLEX
- Rituximab <-> Cyclophosphamide
- Methotrexate <-> Aziothioprine



**Antibody-Mediated
Inflammatory Brain Disease
Treatment Protocols**

Best Practice Guidelines



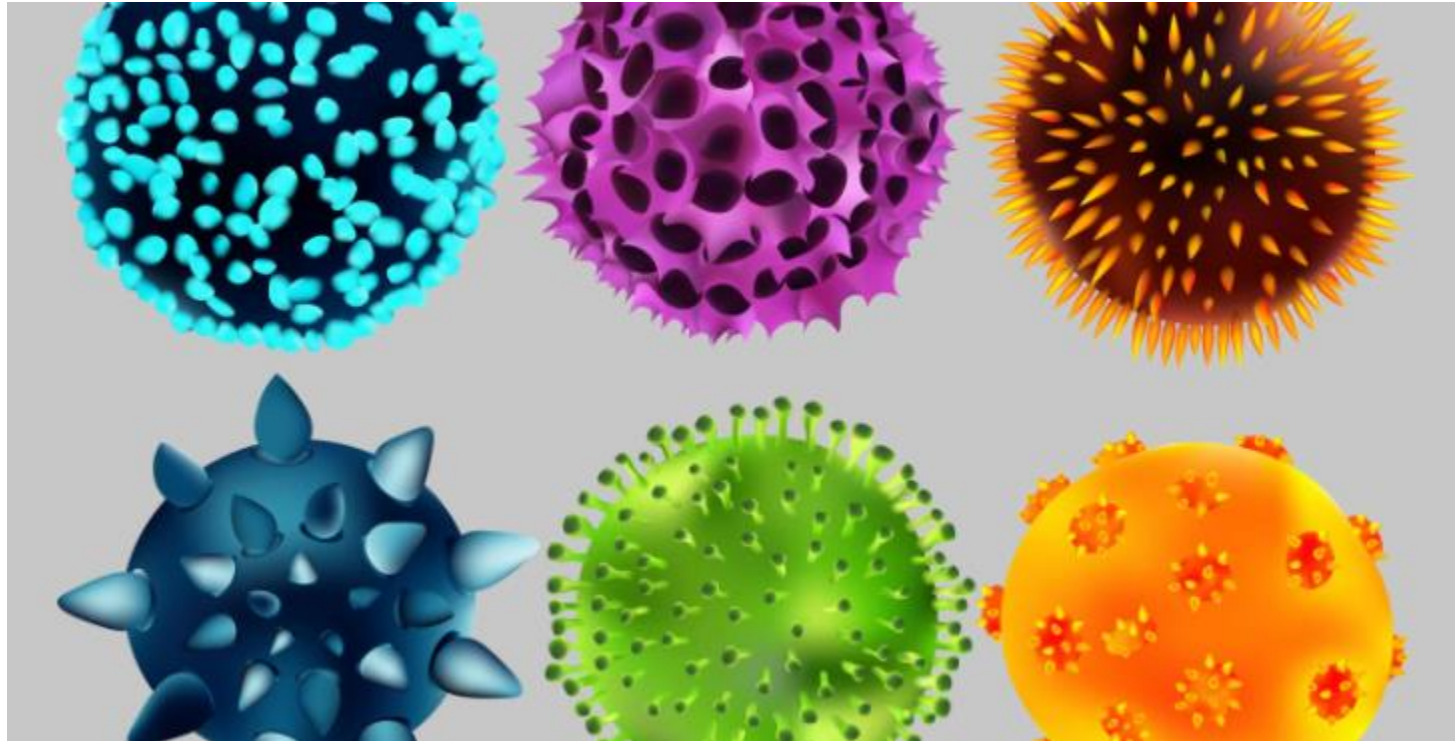
doi:10.1212/NXI.0000000000000663

Neurology

What are the different types?

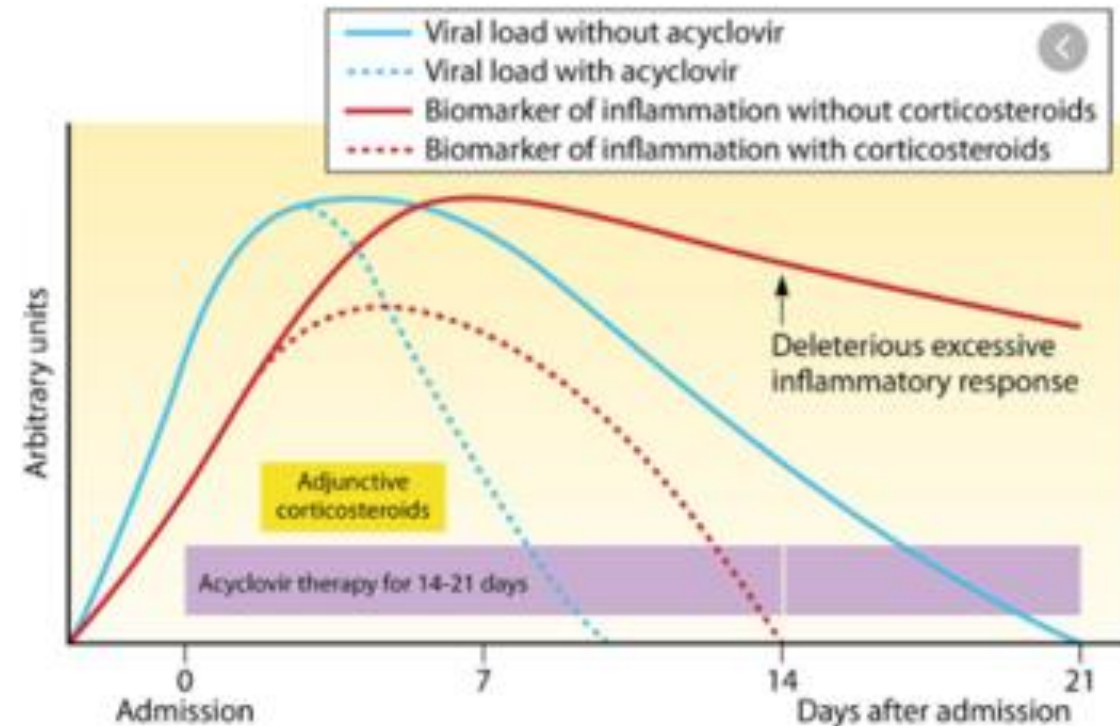
- Infectious
 - Bacterial (Lyme encephalitis)
 - Viral (HSV, West-Nile virus, Enterovirus, EBV, Measles/SSPE)
 - Prion (Bovine Spongiform Encephalitis Encephalopathy – “Mad Cow Encephalitis”)
- Post-infectious
 - ADEM
 - Post-Covid encephalitis
- Autoimmune
 - Hashimoto’s
 - Limbic
- Para-neoplastic
 - Anti-NMDAr-encephalitis
 - Opsoclonus Myoclonus syndrome

Infectious



HSV

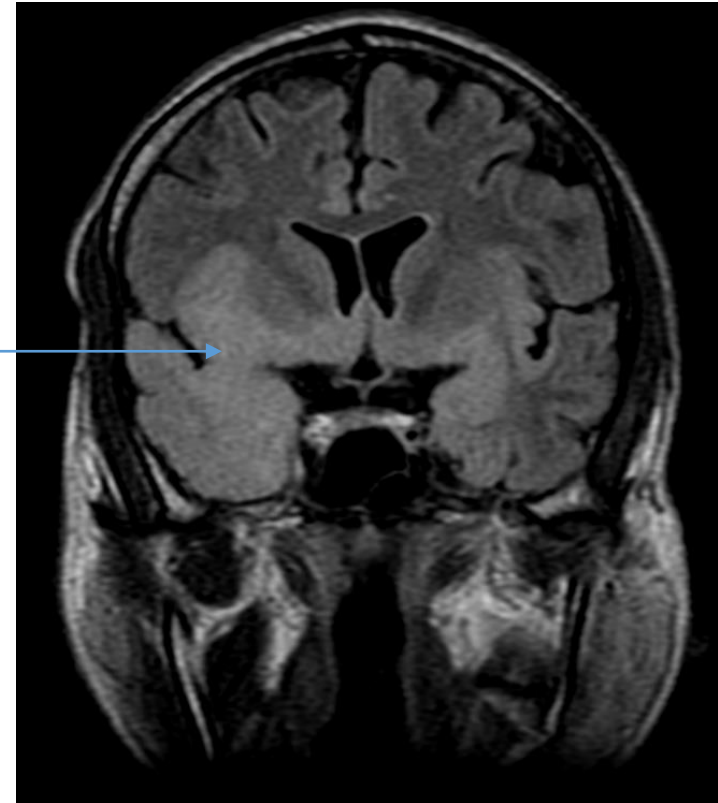
- Most common form of sporadic, focal encephalitis in US
 - Accounts for 10% of all encephalitis cases
 - It is HSV until proven otherwise
- 30% of cases result from initial infection with HSV, rest all from reactivation (hides in trigeminal ganglion)
 - Most acquire during childhood
 - HSV1 (cold sores) 90%
 - HSV2 (genital) 10%
- 50-70% fatality rate if untreated
 - 25% mortality in previously healthy children with mild symptoms
 - Majority have sequelae (2.5% make full recovery)



HSV

- Presentation
 - Seizures
 - Personality changes
 - Memory/Speech difficulty
 - Focal exam findings
- Diagnostics
 - RBC in CSF
 - Temporal seizures/PLEDS on EEG
 - Positive HSV 1/2 PCR
 - MRI showing classic pattern
- Treatment
 - Treat with Acyclovir

T2-C



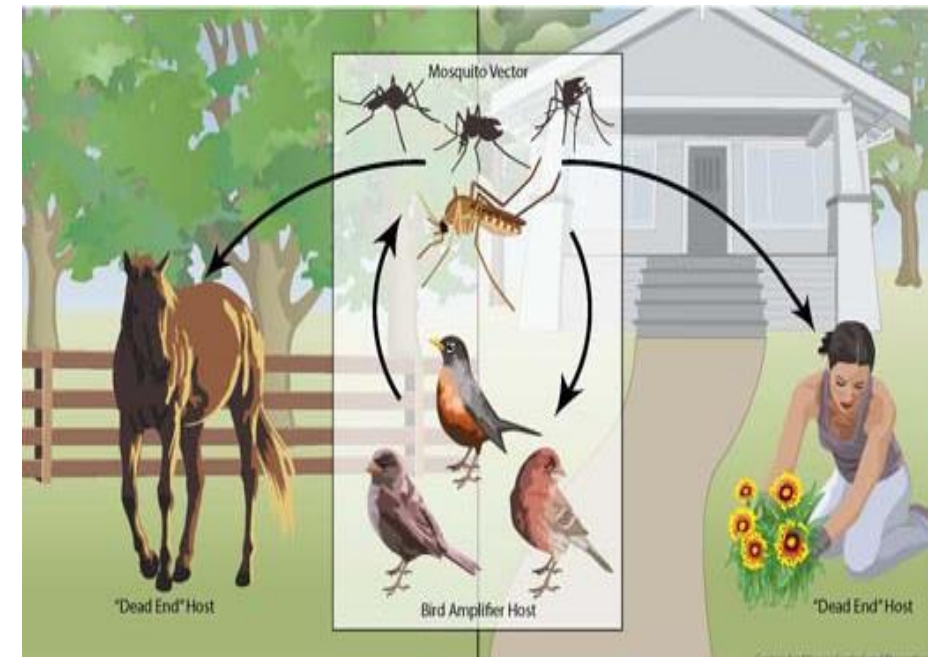
B/L Asymmetric involvement of ...

- **limbic, medial temporal, insular, inferolateral frontal lobes**
- **In children can also see parietal lobe involvement**
- **Can see frontal or temporal hemorrhage (rare/dangerous)**
- **SPARING basal ganglia (differentiate it from stroke)**

West-Nile Virus

- West Nile Virus was first discovered in 1937
- The virus can infect horses and humans
- Transmitted by mosquitoes (endemic to NE)
- Approximately 1 in 100 people infected with the virus will develop neurological symptoms
 - Most commonly causes myelitis (Polio-like)
 - Can also mimic Multiple Sclerosis-like picture
- Often see encephalitis, tremors, bowel/bladder dysfunction in conjunction
 - Myalgia and sensory disturbance less common

Life-cycle of West Nile Virus



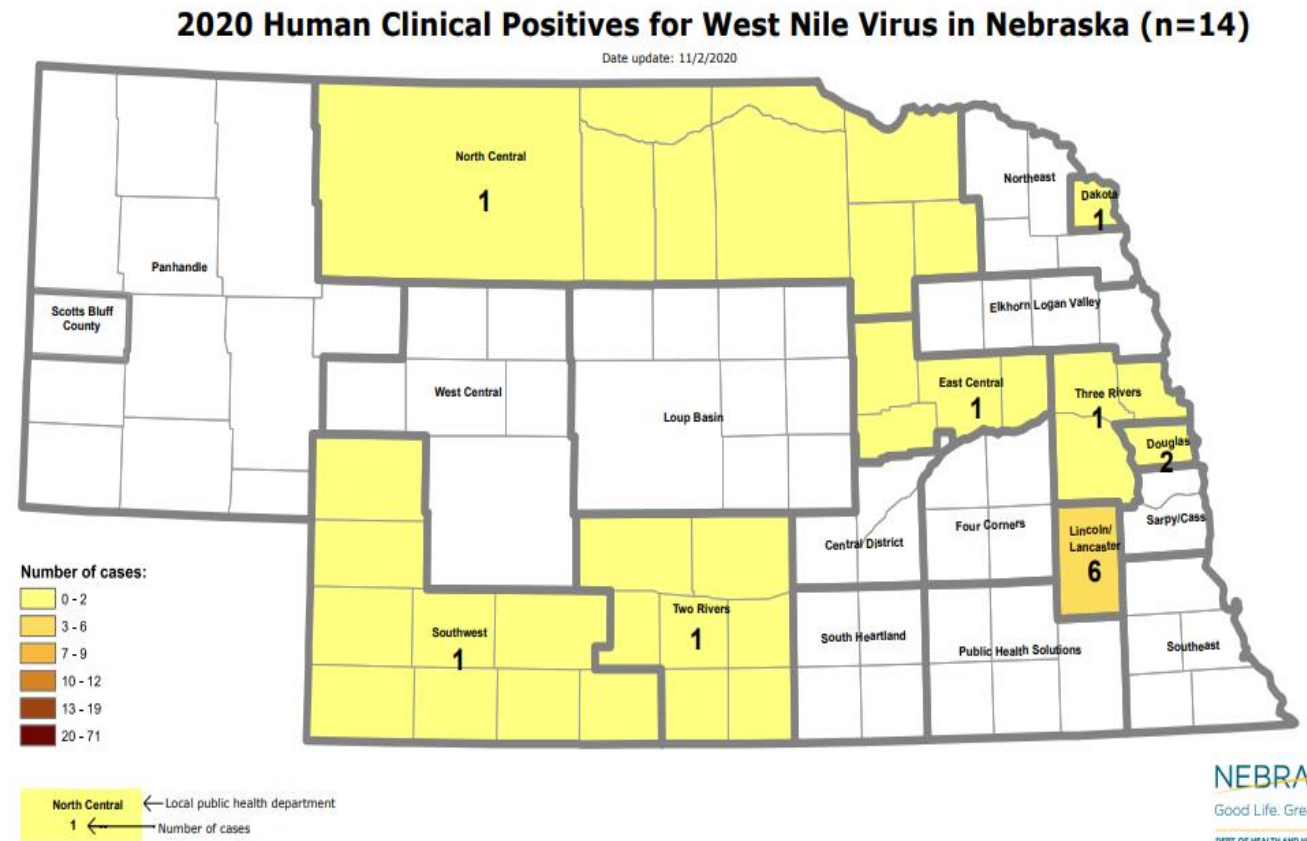
West Nile Epidemiology

*Courtesy of the DHHS West Nile Virus Surveillance Program

2020 Nebraska statistics (n=14):

- 8 neuro-invasive
- 13 cases were male
- 1 case 14-25yr age range
- 6 cases 25-50yr age range

**in 2018 Nebraska leading the nation in deadly cases of WNV

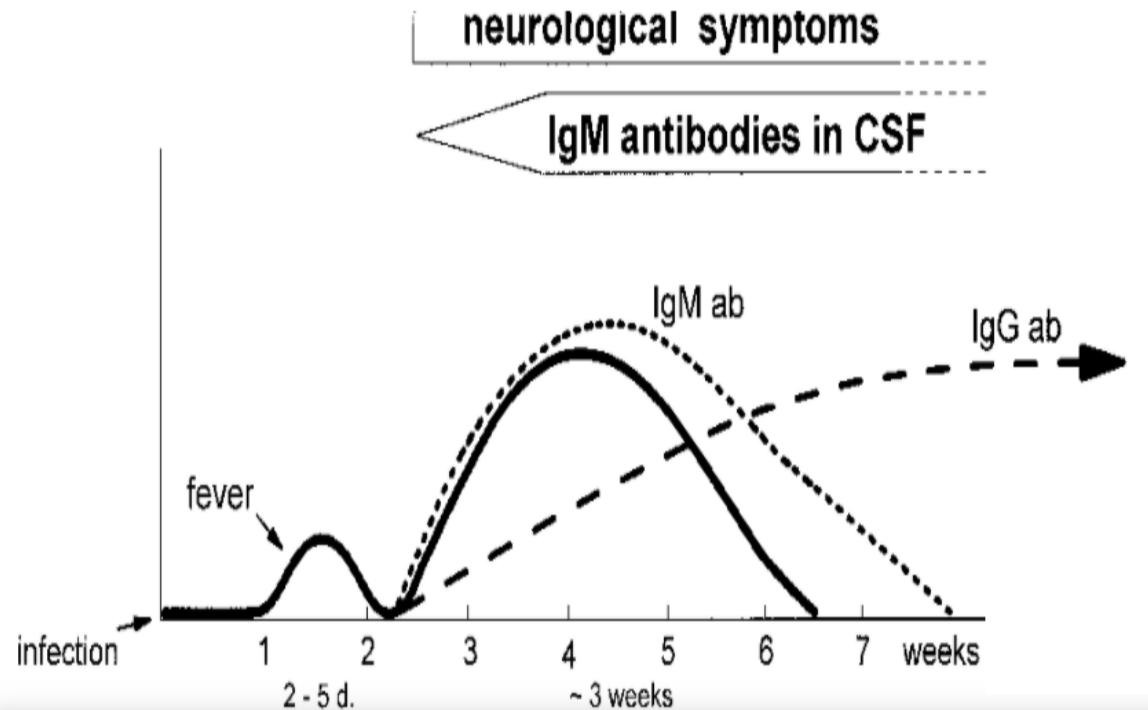


Enterovirus

- Enters the human host through the GI or respiratory tract
 - First reported case in 1950
- The incidence of encephalitis is reported to be about 3%
 - Peak cases often in summer/autumn months → increasing
- Unfavorable outcomes of enteroviral encephalitis have been associated with...
 - younger age (<4yr)
 - high peak leukocyte counts (>13 000/mm³)
 - Seizures
 - EV 71 infection (particularly aggressive → also cause acute flaccid myelitis)
- Treatment with Pleconaril (blocks viral attachment to cell) shows promise
- Fluoxetine may have role in treatment of CHRONIC enterovirus encephalitis in patient's with X-linked Agammaglobulinemia

Lyme Disease

- Most often leads to meningitis but can also cause encephalitis
- Caused by *Borrelia burgdorferi*
- Transmitted by the black-legged/deer tick
- Increased incidence of tick since 2019 in Douglas, Sarpy, and Saunders counties



Measles/SSPE

- Subacute sclerosing panencephalitis (SSPE) is a rare progressive and FATAL encephalitis caused by a persistent infection of measles virus
 - Reports of Measles infection goes back 700yr (spread through air particles)
 - Very serious condition per WHO
- Often affect young children with symptom onset at 9-13yr of age
- 1 in 100,000 people infected with measles will develop SSPE
 - The marked decline of SSPE due to widespread measles vaccination
 - The MMR vaccine is very safe and effective. Two doses of MMR vaccine are about 97% effective at preventing measles; one dose is about 93% effective
- Symptoms include seizures, eye abnormalities, coma, progressive decline → fatal

Information for Healthcare Providers:

Notices to Healthcare Providers:

[Measles: Additional exposure location identified \(3/27/2017\)](#)

[Measles Exposures in Omaha, Papillion, and La Vista \(3/23/2107\)](#)

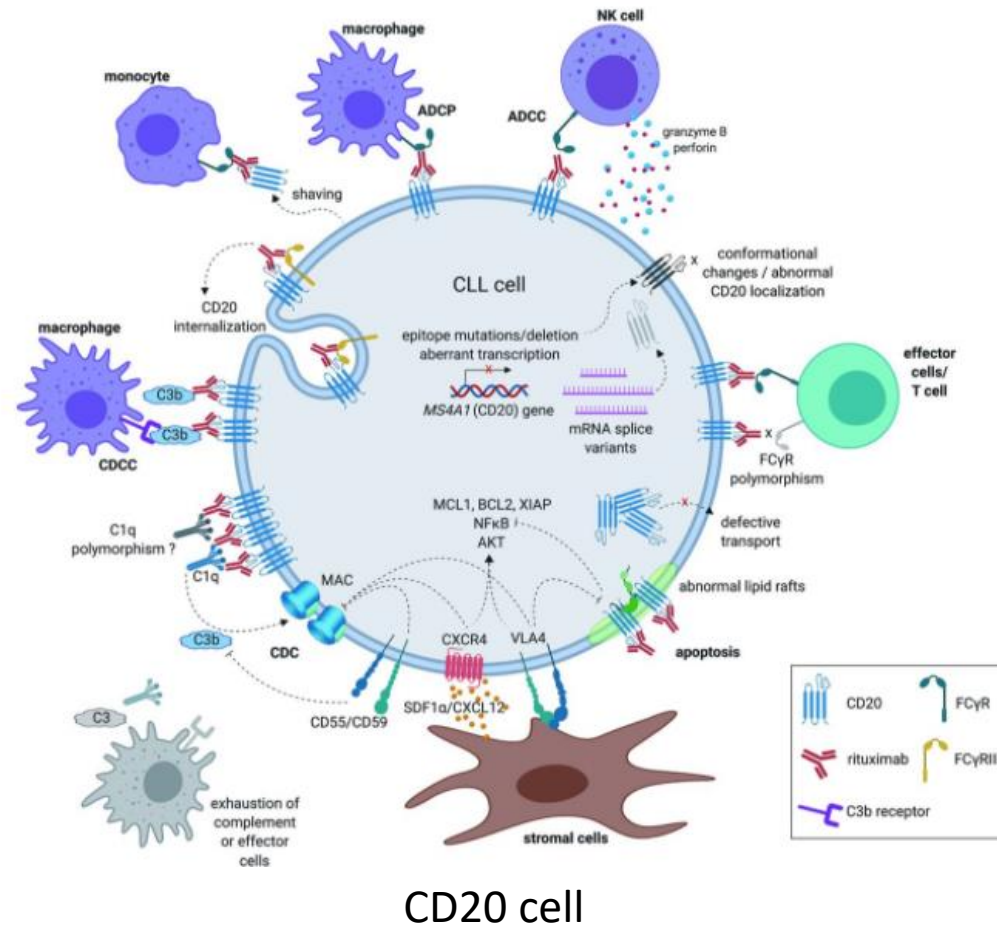
[Measles Alert #2: Second Case of Measles Confirmed in Three Rivers Public Health District Child \(1/29/2015\)](#)

[Nebraska / CDC Health Advisory: U.S. Multi-state Measles Outbreak, December 2014-January 2015 \(1/23/2015\)](#)

[Measles Alert: Exposures in Omaha and Blair \(1/21/2015\)](#)

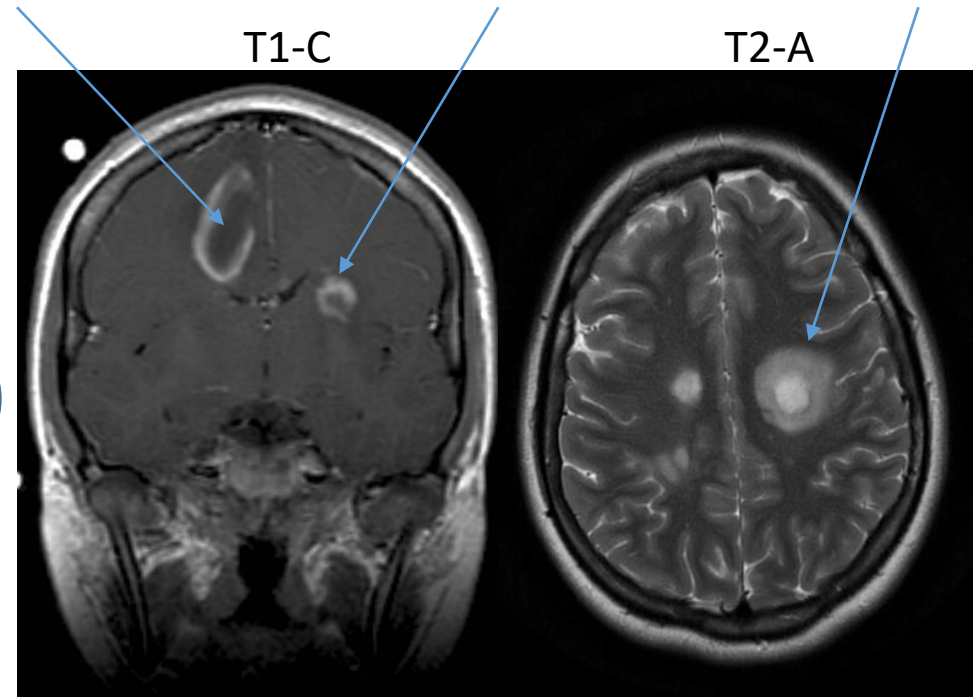


Post-infectious



ADEM (Acute Disseminated Encephalomyelitis)

- Monophasic (different from MS)
 - brief/single/one-time attack (10% will relapse in 3mon)
- Inflammation + demyelination
- Onset ~2weeks post infection (Peak at 6-15yr of age, ?M>F)
 - Cross reactivity (anti-MOG - 50%)
- Generalized symptoms (MS has more focal symptoms)
 - multiple cranial nerve abnormalities, fever, lethargy
- Mostly affects brain > spinal cord
 - can involve basal ganglia



- Does not involve calloseptal area (as in MS)
- Tumefactive lesions with mass effect
- U shaped – not often seen in tumor

Callen MS-ADEM criteria
for first attack

Table III. Criteria to distinguish MS from ADEM*

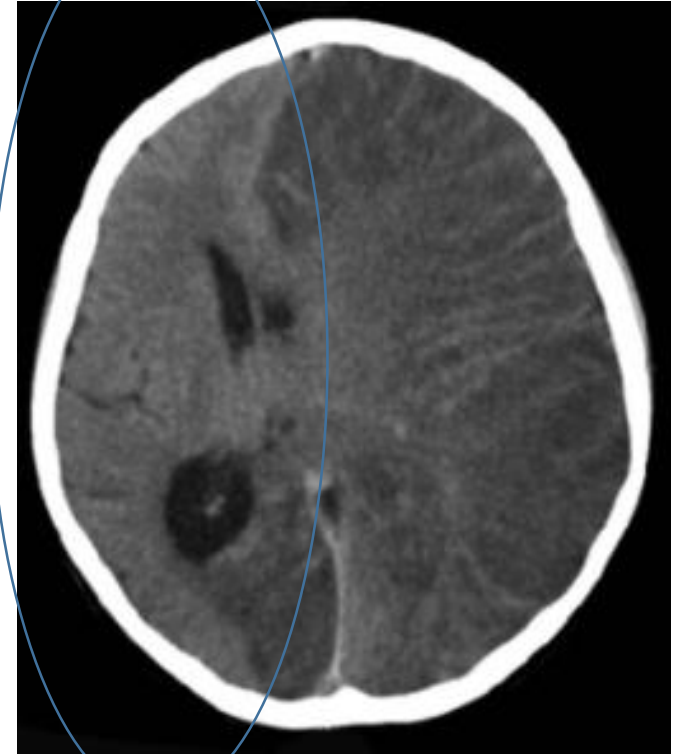
Any 2 of:

- Absence of a diffuse bilateral lesion pattern
- Presence of black holes
- Presence of 2 or more periventricular lesions

*Callen, et al. Role of MRI in differentiation of ADEM from MS in children. Neurology 2009;72(11):968-73.

Rasmussen's Encephalitis

- Etiology unknown (suspect post infectious vs autoimmune)
- Chronic inflammation of brain by T lymphocytes
- Average age of onset 6yr of age
- Encephalitis - Typically affects one hemisphere of brain
 - Refractory epilepsy
 - epilepsia partialis continua, focal motor seizures
 - Hemiparesis
 - Dementia
- Treat surgically with Corpus Callasotomy vs Hemispherectomy
- Treat medically with IVMP/IVIG/AED
 - Less role for PLEX



Post-Covid Encephalitis

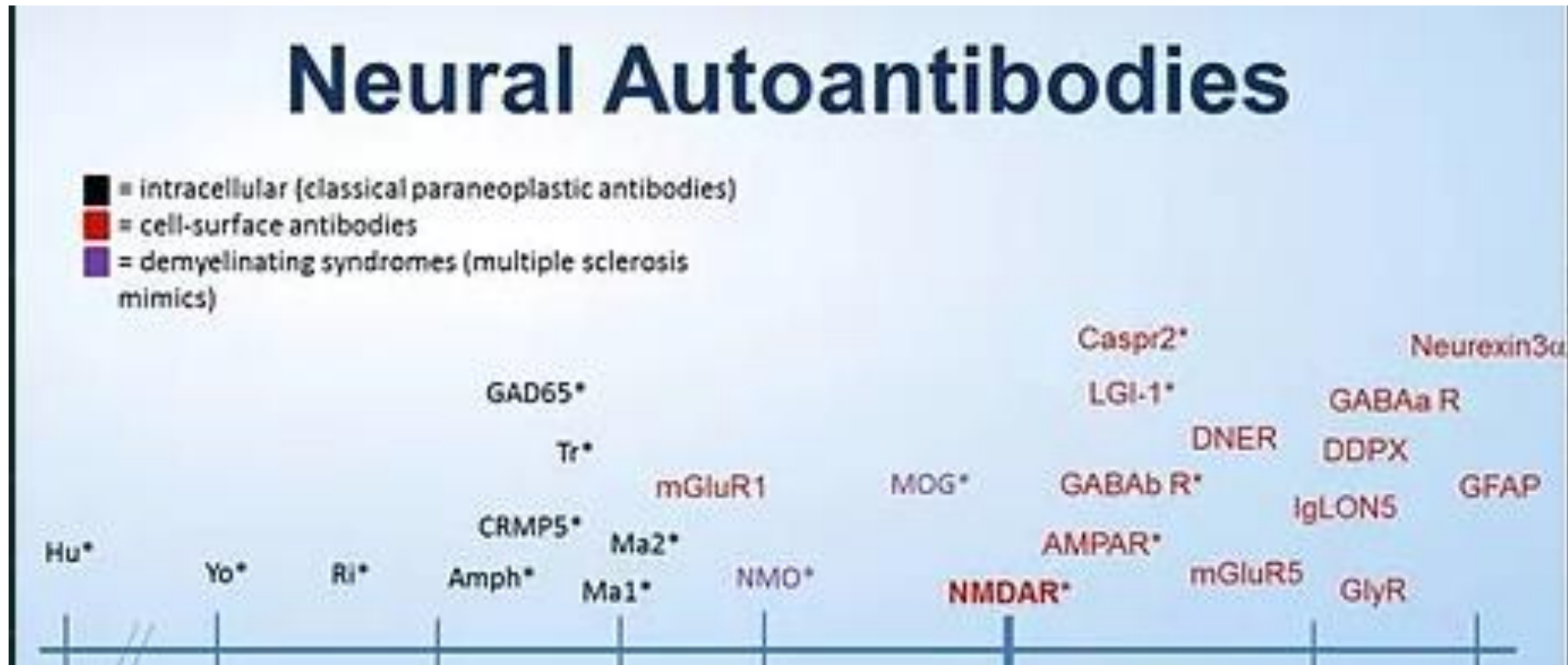
- Increasing reports of neurological and neuropsychiatric complications of COVID-19
- from direct encephalitic effects (seizure as presenting sign of infection)
- indirect effects from post-inflammatory responses, elevated risk of stroke, hypoxia, and additional psychiatric factors that can affect cognition
- Boystown pioneering care for young children with post-Covid-19 encephalitis
- Treatment with Rituximab q6mon has shown promise

Autoimmune

Antibodies towards neuronal surface or synaptic proteins

Para-neoplastic

Antibodies towards intracellular neuronal antigens



Limbic Encephalitis

- Ab to LG1 >>> CASPR2
- Facio-brachial dystonic seizures and myoclonus (40%)
- Mainly affects the hippocampus
 - Short-term memory impairment
 - Hallucinations, paranoia, aggression
- Hyponatremia (50%)

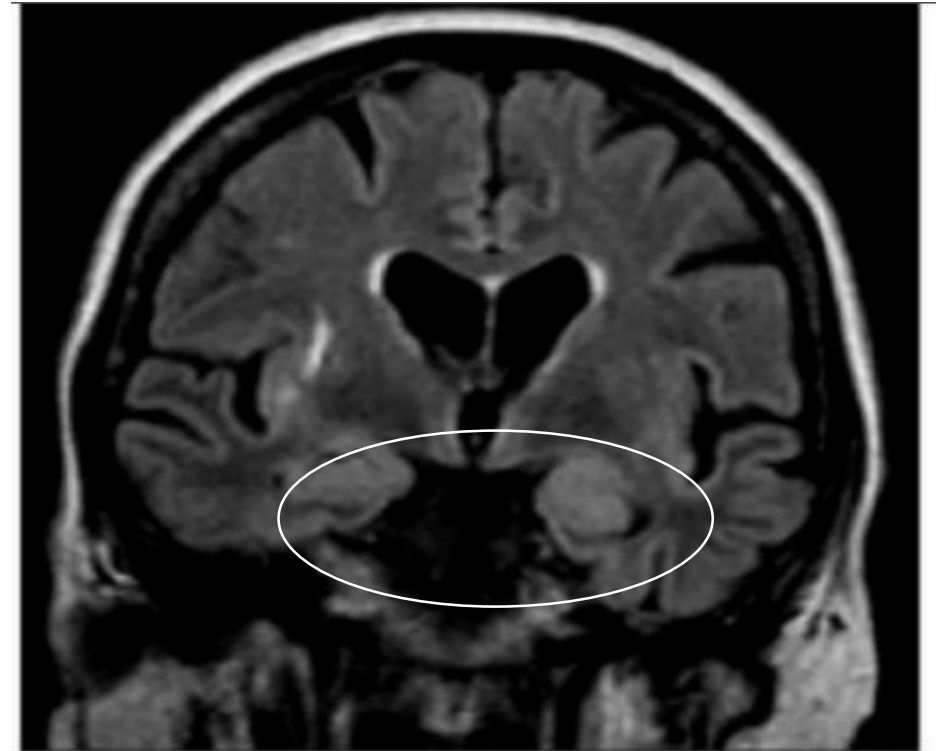


Figure 2. MRI FLAIR sequence coronal view showing bilateral high-signal changes in mesial temporal lobes and insular cortices.

Often symmetric hippocampal/insular involvement (compared to HSV)

Hashimotos Encephalitis

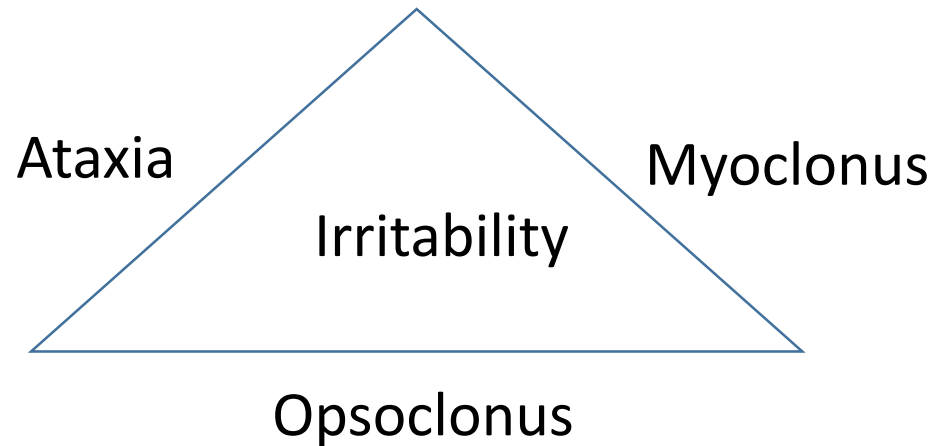
- Rare complication of thyroid disease
 - Anti-TPO (more reliable), thyroid function tests
- Independent of serum thyroid status
 - Most often thyroid function tests normal at time at attack (false reassurance)
- Relapsing-Remitting encephalopathy, depression and seizures
- Steroid responsive
- MRI typically normal
- EEG shows encephalopathy or seizures

Anti-NMDAr Encephalitis

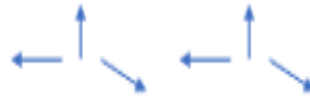
- Most common in young females
- 60% of time associated with Ovarian teratoma (stem cell tumor)
 - MUST do ovarian ultrasound (hunt for cancer)
 - 80% response rate to tumor removal and immunosuppression
- Antibodies to NDMAr (titers correlate with disease severity)
- Characteristic phases
 - Phase 1: flu-like symptoms
 - Phase 2: psychiatric symptoms, mutism
 - Phase 3: altered sensorium (88%) and seizures (76%), dysautonomia (70%)
 - Phase 4: movement disorder (oral dyskinesia, chorea, catatonia)
 - Phase 5: recovery, sequelae such ADHD
- MRI brain typically normal



Opsoclonus Myoclonus Syndrome



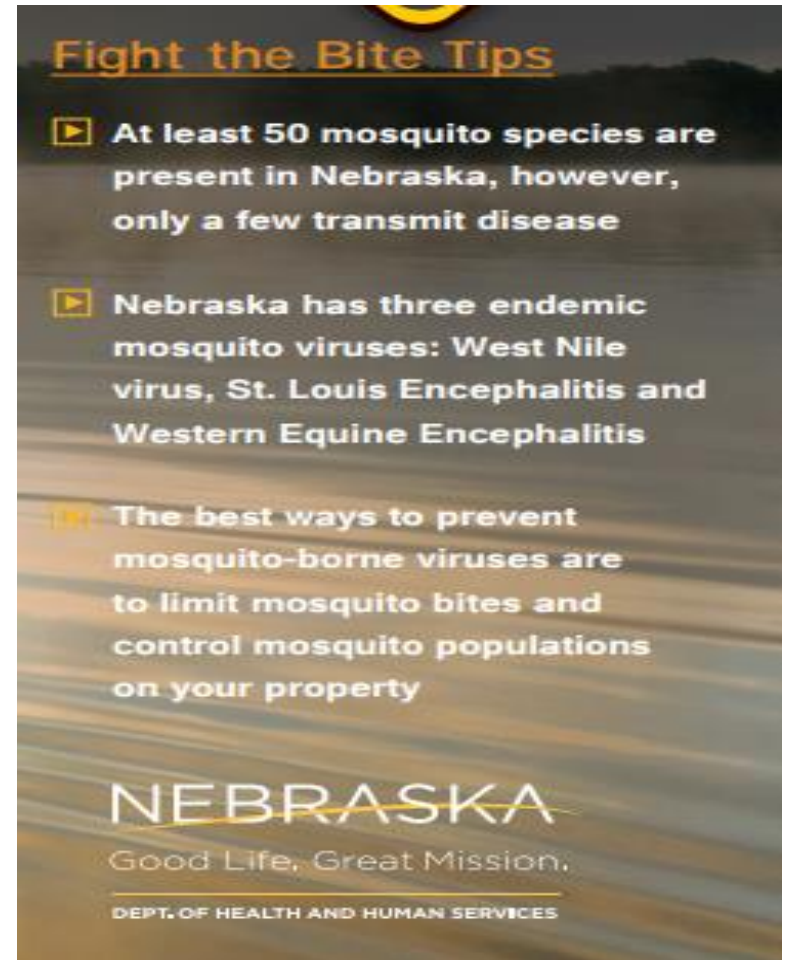
- Ataxia (drunk walk)
- Irritability (inconsolable)
- Myoclonus (limb jerking)
- Opsoclonus (multi-directional nystagmus)



- Associated with Neuroblastoma (benign tumor of nerve tissue)
 - MRI brain + spine + abdomen + chest (most common locations)
- Peak in children 1-3yrs of age
- Treat by removing tumor, IVMP (sometimes ACTH)

Encephalitis Prevention

- Prevent infections
- Vaccinate
- Hand wash
- Avoid tick and mosquito bites
 - Wet long sleeves and long pants when you're outside, especially in areas of tall grass and between dusk and dawn.
 - Use insect repellents and insecticides
 - Avoid wet areas where mosquitos are common and don't allow standing water to collect around your home



Is Encephalitis Hereditary?

- In general, there seems to be little connection between family health history and the development of encephalitis
- possible role of genetics in susceptibility to HSV encephalitis
- In the study, scientists focused on blood cells from two French children with a deficiency for UNC-93B, an endoplasmic reticulum protein involved in the recognition of pathogens. When infected with herpes simplex virus-1, the UNC-93B-deficient cells were unable to produce natural interferons alpha, beta, and gamma (IFNs α , β , and γ). Interferons are produced by the immune system to fight infections and tumors.
- This deficiency resulted in high rates of herpes simplex virus-1 proliferation and cell death. Assuming these findings extend to neurons, they provide a plausible mechanism for herpes simplex encephalitis.

Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency: A Fast Procedure for the Detection of Defects in Toll-Like Receptor Signaling

Section Editor(s): Leggiadro, Robert J. MD

The Pediatric Infectious Disease Journal: August 2007 - Volume 26 - Issue 8 - p 770

doi: 10.1097/INF.0b013e318064f1bd

Latest Research

Safety and Immunogenicity Study of the Western Equine Encephalitis (WEE) Vaccine, Efficacy of Ocrelizumab in Autoimmune Encephalitis, and Venezuelan Equine Encephalitis Monovalent Virus-Like Particle Vaccine (VEEV)

The ExTINGUISH Trial of Inebilizumab in NMDAR Encephalitis (ExTINGUISH)

Dexamethasone in Herpes Simplex Virus Encephalitis (DexEnceph)

Resources

- autoimmune-encephalitis.org
- antinmdafoundation.org
- americanbrainsociety.org
- dhhs.ne.gov
- encephalitis.info

