



Encephalitis Including West Nile and Rabies

Allan R. Tunkel, MD, PhD, MACP
Professor of Medicine and Medical Science
The Warren Alpert Medical School of Brown University



Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Encephalitis Definitions

- Encephalitis
 - Inflammation of brain parenchyma with neurologic dysfunction
 - Gold standard is pathologic examination and testing of brain tissue
 - Usually based on clinical, laboratory, and imaging
- Encephalopathy
 - Altered consciousness (confusion, disorientation, behavioral changes, cognitive impairment) + inflammation
 - Usually metabolic or toxic conditions

Encephalitis Epidemiology

- ~5 cases/100,000 population annually in US from 1990-2017
- >1 million cases annually worldwide
 - Rabies
 - Measles
 - Japanese encephalitis virus

Encephalitis Etiology

- California Encephalitis Project (CEP) reviewed 1,570 cases over 7-year period (CID 2006;43:1565)
- Confirmed or probable etiology in 16%
 - 69% viral
 - 20% bacterial
 - 7% prion
 - 3% parasitic
 - 1% fungal
- Possible etiology in 13%

Encephalitis Etiology

- Australian Childhood Encephalitis Study (CID 2020;70:2517)
- 287 children with confirmed encephalitis
- 57% infectious (confirmed/probable)
- 25% immune-mediated
- 17% unknown

Reasons Etiology not Identified

- Undiscovered pathogens
- Uncommon presentation by common pathogens
- Common presentation by uncommon pathogens
- Wrong test
- Wrong sample
- Wrong timing
- Not an infection

General Approach

- Can't test for everything
- Epidemiologic and clinical clues
- General diagnostic studies
- Neuroimaging clues
- Consider noninfectious etiologies

Tunkel et al. Clin Infect Dis 2008;47:303
Bloch et al. Clin Infect Dis 2023;doi.org/10.1093/cid/ciad306
El Zibairi et al. Curr Op Infect Dis 2026;39:206
Binks, et al. Lancet 2026;407:1968

Question #1

- 50-year-old man presents with a several day history of fever, headache, and personality change with progression to confusion
- On exam, temperature is 101oF; he is disoriented and unable to follow commands
- CT scan of the head without contrast is negative
- CSF analysis reveals a WBC of 80/mm3 (95% lymphs), glucose 70 mg/dL (serum 100 mg/dL), protein 120 mg/dL; Gram stain is negative
- Acyclovir is initiated
- MRI with gadolinium reveals enhancement in the left temporal lobe
- Results of initial cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for HSV-1 and HSV-2 return negative
- After 3 days, the patient is now oriented to name and follows simple commands

Question #1

What is the next step in the management of this patient?

- A. Perform a brain biopsy of the left temporal lobe
- B. Obtain new CSF for HSV PCR testing
- C. Send serum for HSV IgG antibodies
- D. Repeat brain MRI
- E. Discontinue acyclovir

Question #2

Which of the following is the most likely reason for his second presentation of encephalitis?

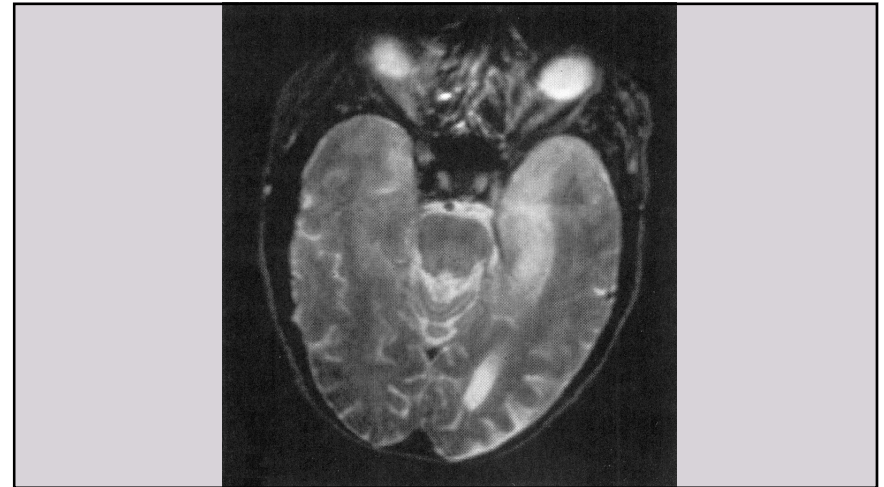
- A. Relapse of herpes simplex encephalitis
- B. Development of acyclovir-resistant herpes simplex encephalitis
- C. Development of autoimmune encephalitis
- D. Acyclovir neurotoxicity

Herpes Simplex Encephalitis

- Epidemiology
 - Among the most severe of all human viral infections of brain; >70% mortality with no or ineffective therapy
 - Accounts for 10-20% of encephalitis viral infections
 - Occurs throughout the year and in patients of all ages
 - Described following whole brain irradiation or following a neurosurgical procedure
 - Majority in adults caused by HSV-1
- Clinical features
 - Fever, personality change, dysphasia, autonomic dysfunction

Herpes Simplex Encephalitis

- Electroencephalography
 - Sensitivity of ~84%
 - Periodic lateralizing epileptiform discharges (PLEDs)
- Neuroimaging
 - Computed tomography (lesions in 50-75% of patients)
 - Magnetic resonance imaging (>90% of cases)
- Brain biopsy
 - Inflammation with widespread hemorrhagic necrosis
 - Intracellular inclusions (50% of patients)
 - Reserve for patients not responding to acyclovir therapy



Herpes Simplex Encephalitis

- Cerebrospinal fluid (CSF) findings
 - Lymphocytic pleocytosis (mean of 100 cells/mm³)
 - Presence of red blood cells (25% never have RBCs)
 - Elevated protein
 - Absent pleocytosis (<5/mm³) in up to 25% of patients on initial evaluation*
- CSF Polymerase Chain Reaction
 - Sensitivity 98%
 - Specificity 94%
 - Positive predictive value 95%
 - Negative predictive value 98%
 - If negative, may need new CSF sample in 3-7 days

*Habis et al. Clin Infect Dis 2025;81:179

Herpes Simplex Encephalitis

- Acyclovir is the antiviral agent of choice
 - Mortality of 19% at 6 months
 - Mortality of 28% at 18 months
 - Morbidity ~50%
- Dosage in adults is 30 mg/kg/day in 3 divided dosages (in those with normal renal function) for 14-21 days
- No clear benefit of adjunctive dexamethasone
- No added benefit on oral valacyclovir (3-month course) after standard course of acyclovir

Other Herpesviruses

- Varicella-zoster virus
 - Can occur without rash (zoster sine herpete)
 - Focal neurologic deficits and seizures
 - CSF PCR; lower sensitivity in those with vasculopathy so also check CSF antibodies
 - MRI/MRA large vessel vasculitis and ischemia
 - Acyclovir (however, no controlled studies) + ?corticosteroids (if vasculopathy)
- Epstein-Barr virus
 - Encephalitis and/or transverse myelitis
 - Serologic testing; CSF PCR (may have false-positives)

Other Herpesviruses

- Human herpesvirus 6
 - Immunocompromised patients, but seen in children
 - CSF PCR (sensitivity >95%); high rate of detection in healthy adults (PPV only 30%)
 - Ganciclovir or foscarnet
- Cytomegalovirus
 - Immunocompromised (especially HIV)
 - Evidence of widespread disease
 - CSF PCR (sensitivity 82-100%; specificity 86-100%)
 - MRI may reveal subependymal gadolinium enhancement and non-specific white matter changes
 - Ganciclovir + foscarnet

Question #3

- 72-year-old man presents in late August with complaints of fever, chills, and weakness beginning 1 week earlier; on the day of admission, he becomes confused
- He lives in central New Jersey, where he and his wife have a horse farm; they often noted mosquito and tick bites
- No significant past medical history
- On presentation, he is somnolent and unable to provide a complete history, although denies headache and stiff neck

Question #3

- T 103.1oF, P 110, RR 16, BP 110/70 mmHg
- No rash or petechiae, neck supple, no adenopathy, lungs clear, heart without murmurs, abdomen normal
- On neurologic exam, he is oriented to person only. Cranial nerves intact. Motor strength 4/5 UE, and 3/5 LLE and 2/5 RLE. Sensation intact. Reflexes diminished in LE

Question #3

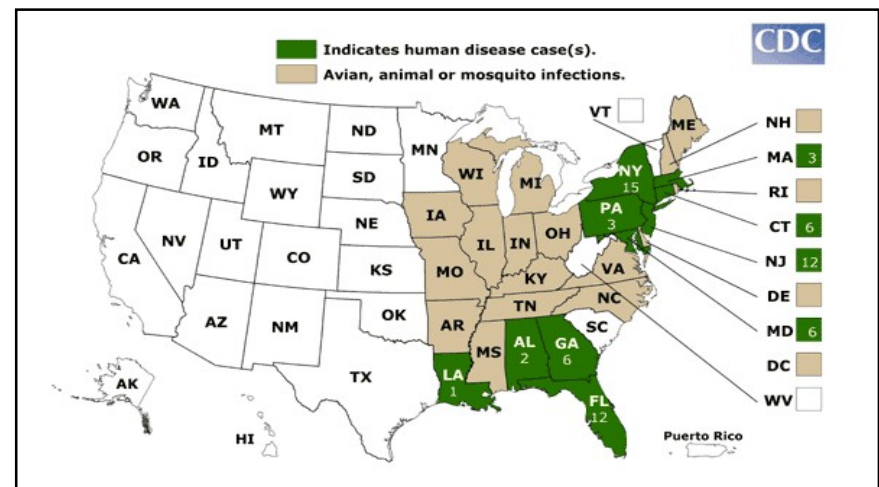
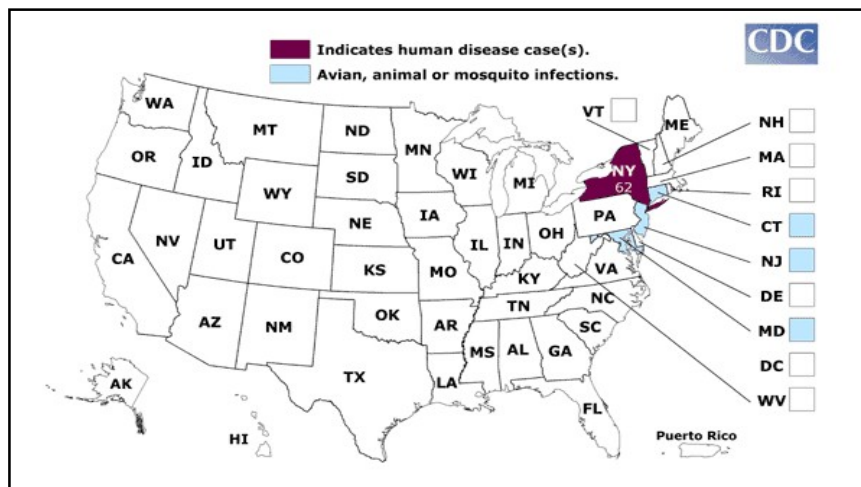
Which of the following tests is most likely to establish the etiology of this patient's encephalitis?

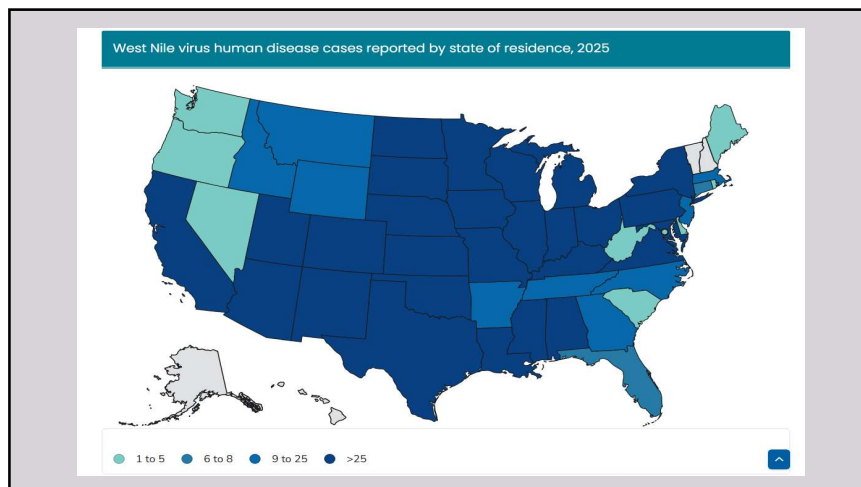
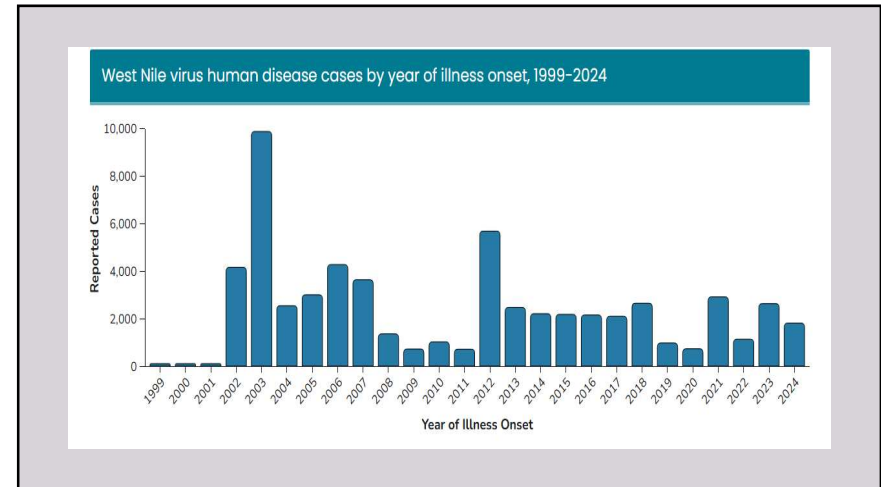
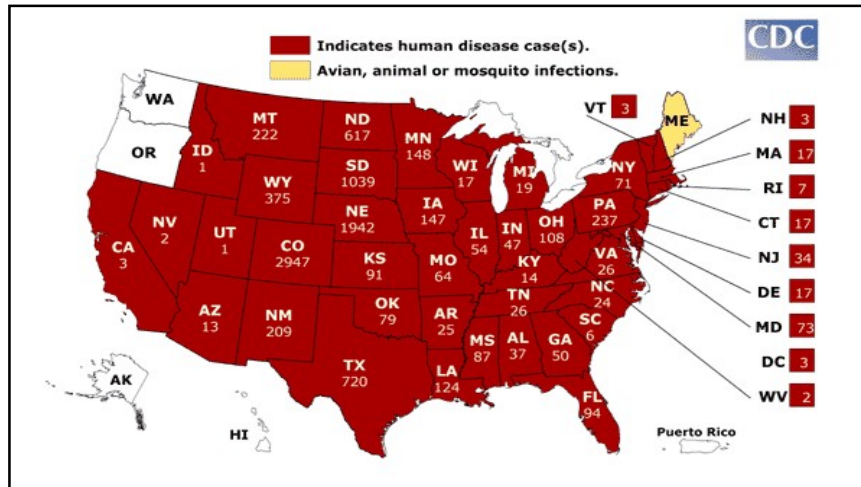
- A. Serum IgM
- B. Serum polymerase chain reaction
- C. Cerebrospinal fluid IgM
- D. Cerebrospinal fluid polymerase chain reaction
- E. Brain MRI

West Nile Virus (WNV) Encephalitis

- First US cases reported in 1999 in New York City
- Birds are main reservoirs
- Mosquito vector
- Other modes of transmission
 - Transplanted organs
 - Blood transfusions
 - Breast milk
 - Transplacental
 - Occupational

Gould et al. JAMA 2025;334:618



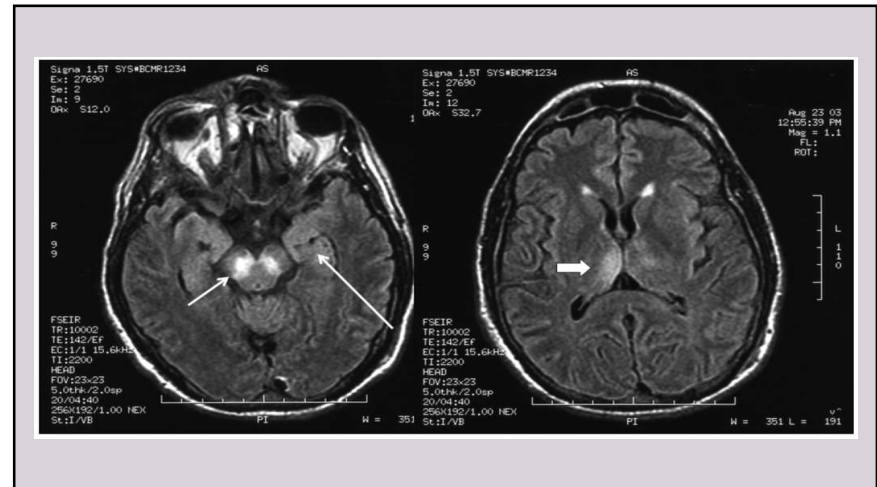


West Nile Virus Clinical Syndromes

- No clinical illness or symptoms (~80%)
- West Nile Fever (~20%)
- Severe WNV Disease (1 in 150)
 - Meningitis (37%)
 - Encephalitis/Meningoencephalitis (53%)
 - Poliomyelitis-like flaccid paralysis (7%)

West Nile Virus Encephalitis

- Diagnosis
 - Serum IgM antibody (8-14 days of illness onset)
 - CSF reveals lymphocytic pleocytosis and elevated protein; glucose is normal
 - CSF IgM (positive in >90%)
 - CSF PCR (<60% sensitivity overall, but may be more sensitive in immunocompromised patients)
- Neuroimaging



West Nile Virus Encephalitis

- Therapy
 - Supportive
 - Ribavirin, interferon alpha, and IVIG don't work

Other Arboviruses

- St. Louis encephalitis virus
 - Mosquito vector; bird reservoir
 - Endemic in western US; periodic outbreaks in eastern US
 - Urinary symptoms early; SIADH (one-third of cases)
 - Serology; CSF IgM
- Japanese encephalitis virus
 - Most common cause of mosquito-borne encephalitis worldwide (SE Asia, China, India, Nepal, Korea, Japan)
 - Mainly children; rice fields where vectors breed
 - Seizures and parkinsonian features; poliomyelitis-like flaccid paralysis
 - Serology; CSF IgM

Other Arboviruses

- Powassan virus
 - Tick vector (*Ixodes scapularis* in NE); rodent reservoir; New England
 - Prevalence among animal hosts and vectors increasing
 - Parkinsonism, involvement of basal ganglia and thalamus, as well as lower brainstem, cerebellum and spinal cord
 - Serology; CSF IgM; PCR if immunocompromised; metagenomic sequencing
- Tickborne encephalitis virus
 - Tick vector, rodent reservoir; drinking unpasteurized milk or cheese; solid organ transplantation; rituximab
 - Eastern Russia, central Europe
 - Poliomyelitis-like paralysis
 - Serology; CSF IgM
 - Anti-TBE immune globulin for post-exposure prophylaxis

Other Arboviruses

- La Crosse virus
 - Mosquito vector; chipmunk and squirrel reservoir
 - Midwest and eastern US; woodlands
 - 2nd most common arbovirus in US
 - Serology; CSF IgM; SIADH (~20%)
- Eastern equine encephalitis virus
 - Mosquito vector; bird reservoir in North America; organ transplantation
 - Primarily Atlantic and Gulf coast states
 - Abrupt onset with fulminant course; seizures common
 - High case-fatality rate (50-70%)
 - Serologic testing
 - High CSF WBC count (>1000 cells/mm³)

Measles Virus

- Primary encephalitis
 - Up to 1 per 1,000 infections
 - Usually appears within a few days (typically 5 days) of rash
 - Fever, headache, stiff neck, drowsiness, convulsions, coma
 - Rapidly progressive and fatal in ~15%
- Acute disseminated encephalomyelitis
 - Up to 1 per 1000 infections
 - Usually appears ~2 weeks after exposure
 - Demyelinating disease; post-infectious autoimmune response
 - Fever, fatigue, headache, nausea, vomiting
 - 10-20% mortality

Measles Virus

- Inclusion body encephalitis
 - Unvaccinated children and adults; immunocompromised
 - Symptoms 1-6 months after exposure;
 - Decreased consciousness, focal signs, seizures
- Subacute sclerosing panencephalitis
 - Acquisition of measles before 2 years of age
 - 6-10 years after infection (range 3-35 years)
 - Behavioral changes, cognitive impairment at presentation
 - Myoclonus, seizures, neurologic deterioration (coma and death) later

BioFire® FilmArray® Meningitis/Encephalitis Panel

Bacteria	Viruses	Fungi
<i>Escherichia coli</i> K1	Cytomegalovirus	<i>Cryptococcus neoformans/gatti</i>
<i>Haemophilus influenzae</i>	Enterovirus	
<i>Listeria monocytogenes</i>	Herpes simplex virus 1	
<i>Neisseria meningitidis</i>	Herpes simplex virus 2	
<i>Streptococcus agalactiae</i>	Human herpesvirus 6	
<i>Streptococcus pneumoniae</i>	Human parechovirus	
	Varicella zoster virus	

Metagenomic Next-generation Sequencing

- Allows unbiased or agnostic pan-species molecular diagnostics
- 204 patients (58 with meningitis or encephalitis), NGS identified an infectious cause in 22% not identified by clinical testing*
- 220 CNS infections, 40% identified by conventional methods and NGS, 22% by NGS alone and 36% only by conventional methods**
- Possible role in testing of enigmatic cases

*Wilson et al. NEJM 2019;380:2327
**Benoit et al. Nature Med 2024;30:3522

Question #4

- 36-year-old man is on a hiking trip in northern California and is bitten on his lower leg by a skunk
- Upon presentation, he is afebrile and has several puncture wounds on his right lower extremity
- You irrigate with wounds with soap and povidone iodine, and administer a tetanus booster
- He has never been vaccinated against rabies

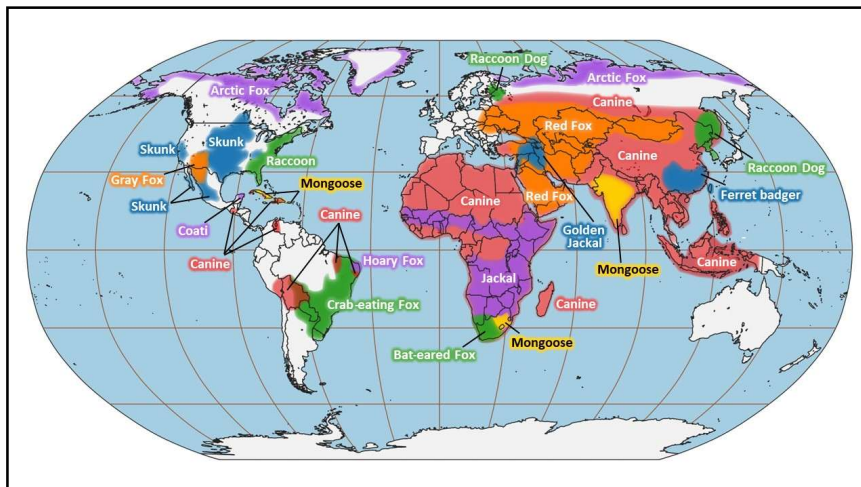
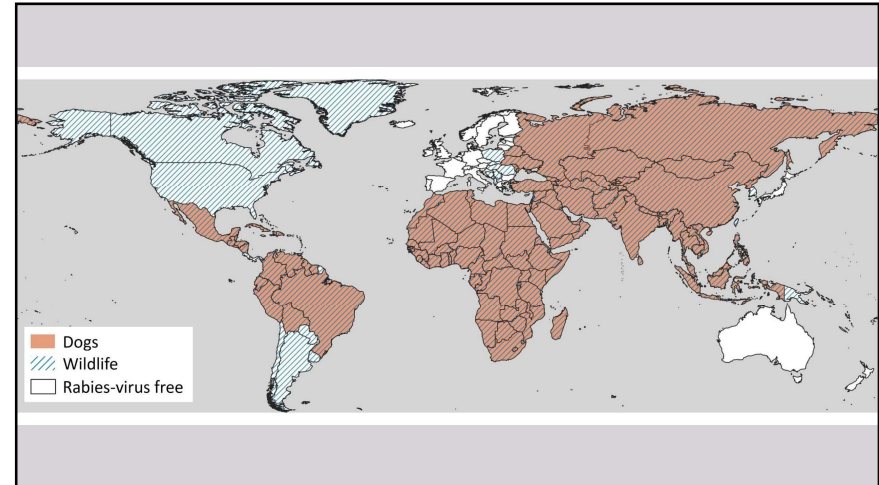
Question #4

In addition to administration of rabies vaccine, what is the most appropriate management?

- Rabies immune globulin at the bite site
- Rabies immune globulin in the deltoid muscle
- Rabies immune globulin in the buttocks
- Rabies immune globulin intraperitoneally
- Nothing further is indicated

Rabies

- Transmitted by bite of infected animal
 - Dogs are principal vector (98% of cases) worldwide
 - May be transmitted after unrecognized bites by bats
- Rare and sporadic in US – 125 cases from 1960-2018
 - 36 (28%) attributed to dog bite during international travel
 - 89 acquired in US; 62 (70%) attributed to bats
- Worldwide in distribution (50,000-100,000 annual deaths)
- Incubation period 20-90 days



Rabies

- Encephalitic (furious) form (80%)
 - Agitation alternating with lucidity
 - Hypersalivation
 - Hydrophobia
 - Bizarre behavior
 - Disorientation, stupor, coma, death
- Paralytic (dumb) form
 - Ascending paralysis; early muscle weakness
 - Later cerebral involvement

Rabies

- **Diagnosis**
 - Culture and RT-PCR of saliva
 - Immunofluorescent detection of viral antigens and RT-PCR in nuchal biopsy
 - CSF antibodies and RT-PCR
 - Brain biopsy (antigen detection/Negri bodies)
- **Therapy**
 - Supportive (especially critical care)
 - Milwaukee Protocol has failed in at least 64 cases
 - Post-exposure prophylaxis (rabies immune globulin at bite site and vaccine)

Question #5

- 22-year-old woman with no significant past medical or psychiatric history develops headache and low-grade fever followed by confusion and hallucinations
- On presentation, she is afebrile and disoriented; she has evidence of abnormal movements of her mouth and face
- CSF analysis reveals a WBC count of 20/mm³, with normal glucose and protein
- Brain MRI is normal

Question #5

- EEG reveals diffuse slowing
- CSF Gram stain and cultures, and PCR for HSV are negative
- A diagnosis of autoimmune encephalitis is considered, and appropriate studies sent
- CSF returns positive for antibodies to the NR1 subunit of the N-methyl-D-aspartate receptor
- Corticosteroids and IV immune globulin are initiated

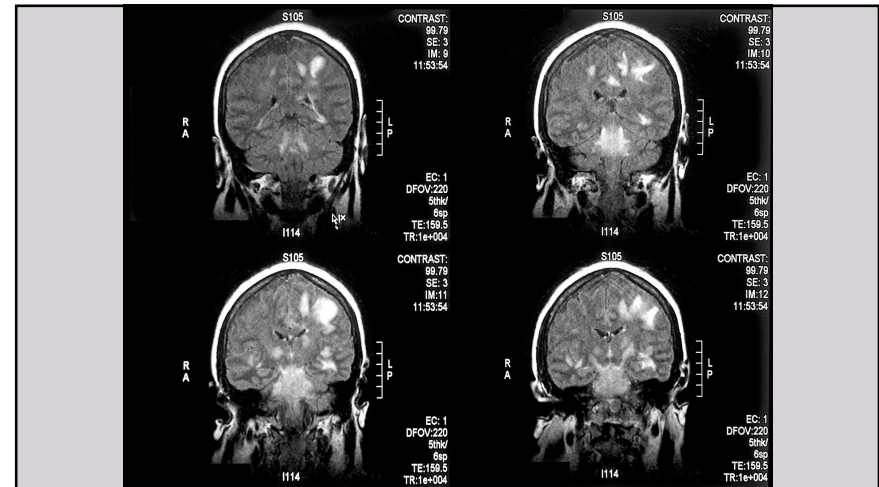
Question #5

Which of the following studies should now be performed?

- A. CT scan of the chest
- B. CT scan of the abdomen
- C. Carotid ultrasound
- D. Renal ultrasound
- E. Transvaginal ultrasound

Encephalitis Noninfectious Etiologies

- Acute disseminated encephalomyelitis (ADEM)
 - 10-15% of encephalitis cases in US
 - Post-infectious
 - Symptoms 2-4 weeks after trigger
 - MRI bilateral asymmetric T2 hyperintensity in subcortical and deep white matter
- Approximately 20-30% of encephalitis cases are due to autoimmune conditions (e.g., anti-N-methyl-D-aspartate receptor [Anti-NMDAR] encephalitis)



Anti-NMDAR Encephalitis

- Neuronal antibody-associated encephalitis
- In California Encephalitis Project, this entity exceeded that of any single viral entity in children and was also seen in adults
- Female to male ratio of about 8:2
- 37% of patients younger than 18 years at presentation

Anti-NMDAR Encephalitis

- Abnormal behavior (psychiatric symptoms)
- Cognitive dysfunction
- Seizures
- Movement disorders (orofacial dyskinesias)
- Decreased level of consciousness
- Autonomic instability
- May be associated with ovarian teratoma (in ~50% of patients older than 18 years)

Anti-NMDAR Encephalitis

- CSF analysis
 - Mild pleocytosis (median WBC 23/mm³); normal glucose and protein
 - Specific IgG antibodies to GluN1 subunit of the NMDAR in CSF and serum
 - Viral causes of encephalitis (e.g., HSV) are associated with development of NMDAR antibodies*

*Armangue et al. Brain 2023;146:4306

Anti-NMDAR Encephalitis

- Neuroimaging
 - Abnormal in 50%, but nonspecific
 - T2 and FLAIR hyperintensity (hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem)
- EEG
 - Diffuse or focal slowing
 - Occasional superimposed epileptic activity

Anti-NMDAR Encephalitis

- Therapy
 - First-line
 - Corticosteroids
 - Intravenous immunoglobulin
 - Plasma exchange
 - Second-line
 - Rituximab or cyclophosphamide
 - Female patients should be evaluated for ovarian teratoma; if present, remove
- 75% of patients have mild sequelae or fully recover; relapse in up to 24%



Questions

Allan R. Tunkel, MD, PhD, MACP

Email: allan_tunkel@brown.edu