



Encephalitis Including West Nile and Rabies

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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 Zibair 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 101°F; 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

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Question #1

- Repeat CSF analysis on day #4 reveals that the PCR is now positive for HSV-1
- The patient continues to improve and completes a 14-day course of acyclovir
- One month later, he presents again with fever and confusion
- CSF analysis reveals a WBC count of 30/mm³ (all lymphocytes) with normal glucose and mildly elevated protein; CSF PCR tests for HSV-1 and HSV-2 are negative

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

Question #2

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

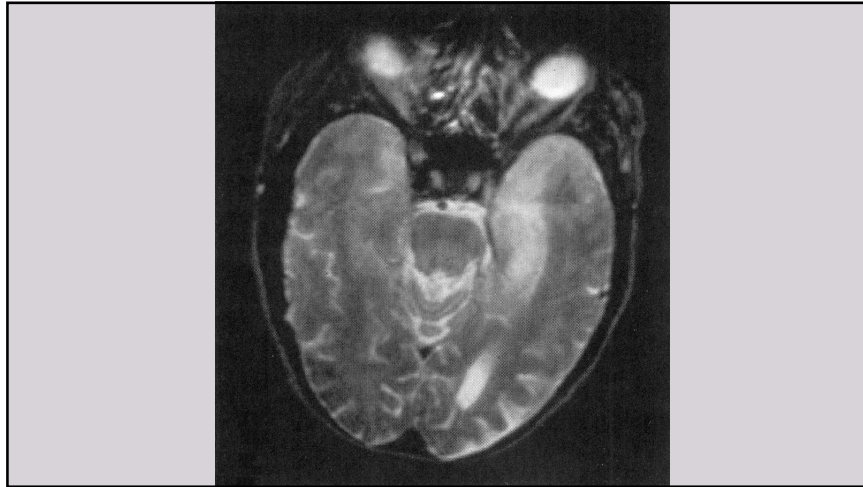
- A. Relapse of herpes simplex encephalitis
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- C. Development of autoimmune encephalitis*
- D. Acyclovir neurotoxicity

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
 - Intranuclear 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

Question #3

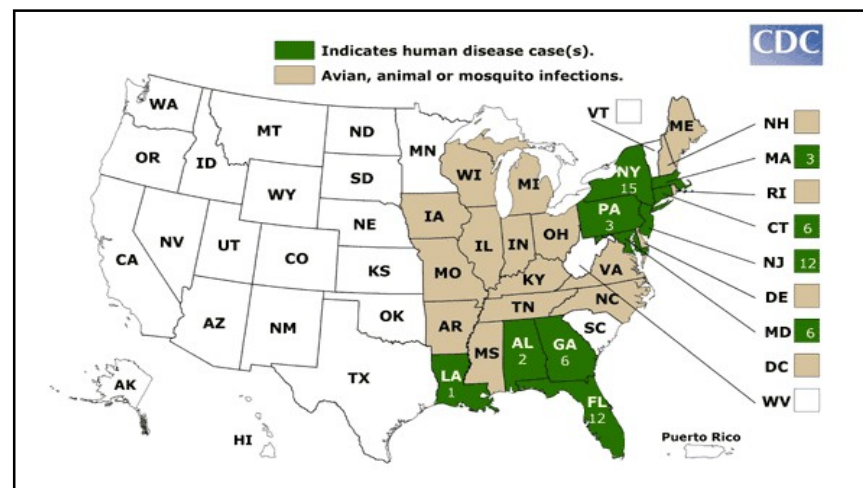
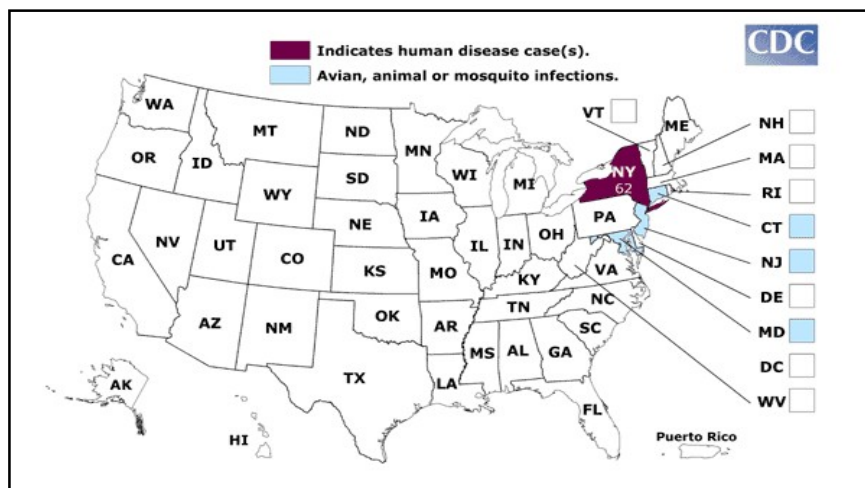
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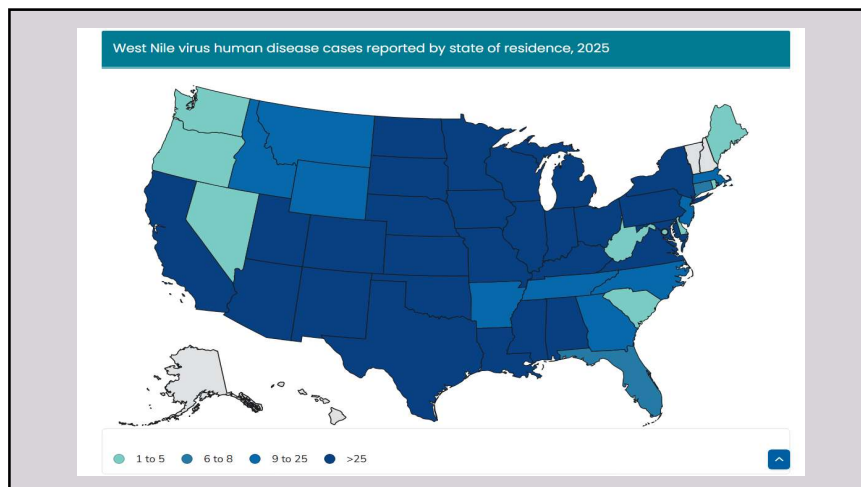
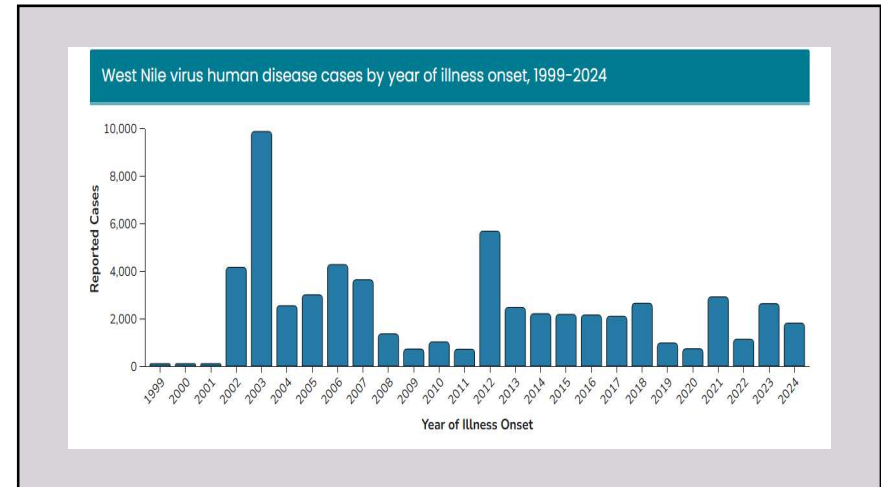
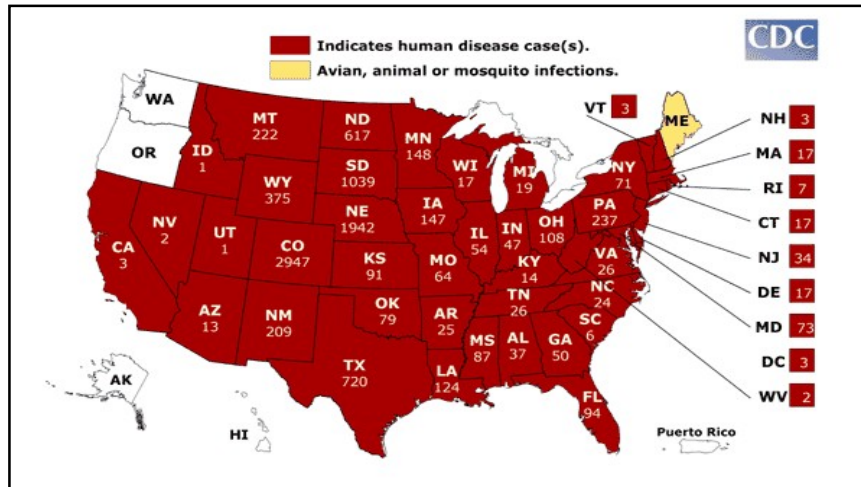
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- C. Cerebrospinal fluid IgM***
- D. Cerebrospinal fluid polymerase chain reaction
- E. Brain MRI

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



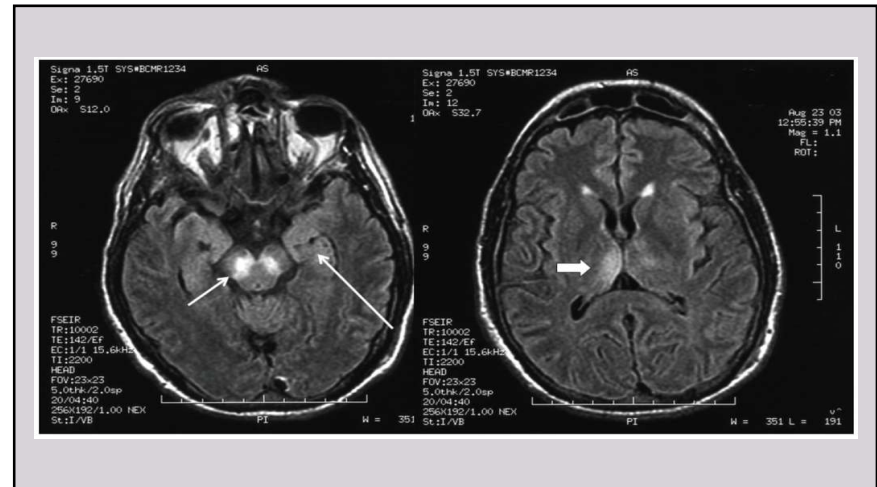


West Nile Virus Clinical Syndromes

- 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

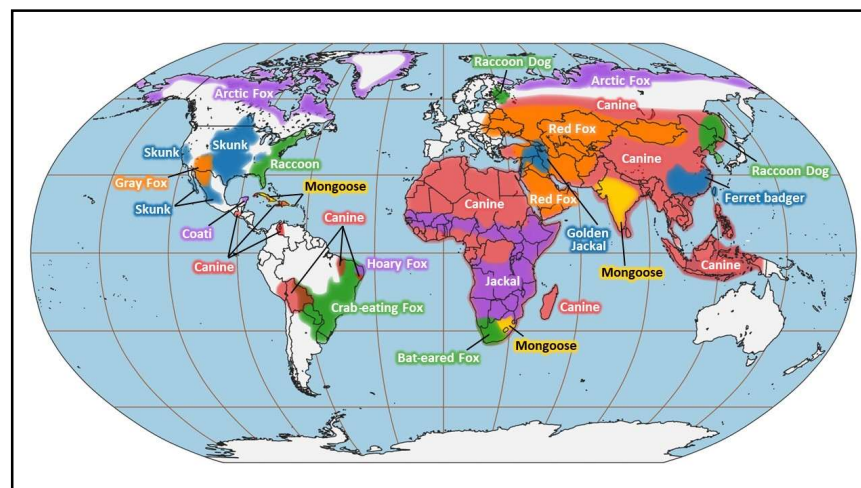
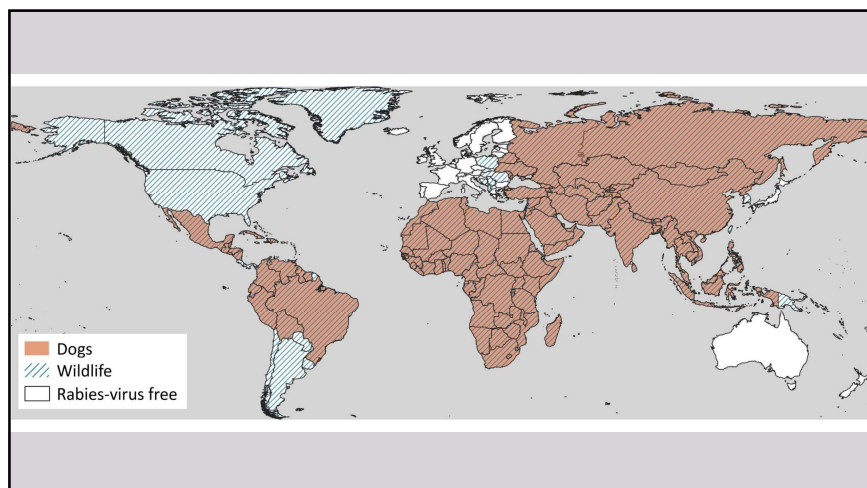
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- E. Nothing further is indicated

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

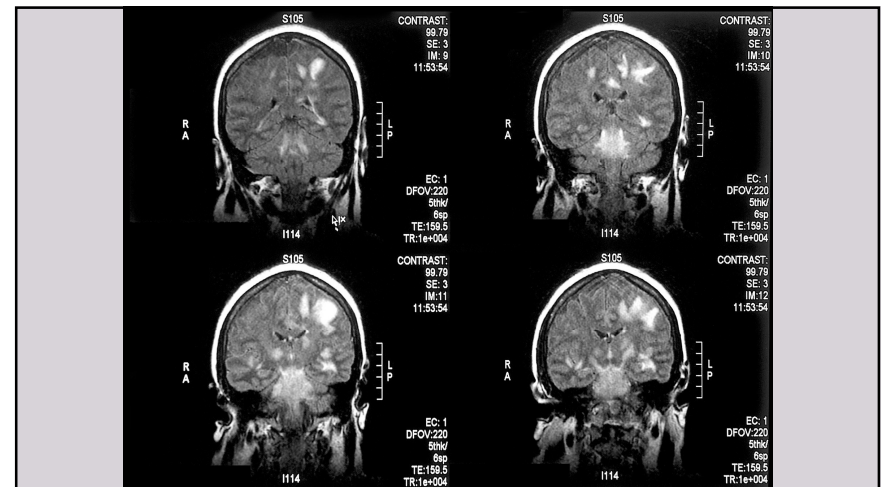
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Encephalitis Noninfectious Etiologies

- 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)



14 Encephalitis including West Nile and Rabies

Speaker: Allan Tunkel, MD, PhD

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

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