My first case as a CC3…

- 75yo woman admitted for chest pain
  - Back from an island off the coast of Cape Cod where she'd been on vacation x3 weeks
  - Generally not feeling well
  - Sub-xiphoid pressure, transient, completely resolved by the time I saw her
  - "Ruled out" for myocardial infarction
  - By the time I was presenting her, the intern was writing her discharge orders

First case (con't)

- In AM of hospital day #1, temperature 101.1
- Vomited once
- Attending went to discharge her, and she couldn't remember the name of her island vacation spot

She had…

Viral Encephalitis

- Definitions
- Pathogenesis
- Epidemiology
- Clinical findings/diagnosis/treatment
- Specific examples:
  - HSV-1
  - Arboviruses/West Nile
  - Rabies

Definitions/Descriptions

- Viral meningitis
  - Fever, headache, n/v, malaise, stiff neck, photophobia
  - Enteroviruses, herpes viruses, “arboviruses,” acute HIV
- Viral encephalitis
  - Fever, headache, altered mental status, decreased consciousness, focal neurological findings
  - Herpes viruses, “arboviruses,” enteroviruses (U.S.)
- Aseptic meningitis
- Meningoencephalitis
- Myelitis

Viral causes of acute encephalitis/encephalomyelitis

Virus Family	Specific viruses
Adenoviridae	Adenovirus
Arenaviridae	LCMV (lymphocytic choriomeningitis virus), Lassa
Bunyaviridae	La Crosse, Rift Valley
Filoviridae	Ebola, Marburg
Flaviviridae complex	St. Louis, Murray Valley, West Nile, Japanese B, Tick-borne
Herpesviridae	HSV-1, HSV-2, VZV, HHV-6, EBV, CMV, Herpes B
Paramyxoviridae	
(Paramyxovirus)	Mumps
(Morbillivirus)	Measles, Hendra, Nipah
Picornaviridae	Poliovirus, Coxsackie virus, Echovirus
Reoviridae	Colorado tick fever
Retroviridae	
(Lentivirus)	HIV
Rhabdoviridae	Lyssavirus, Rabies
Togaviridae	
(Alphavirus)	Eastern equine, Western equine, Venezuelan equine

Pathogenesis (I)

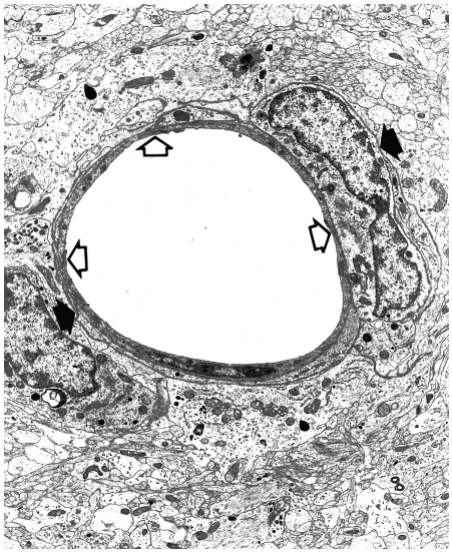
- Neurotropism
- Neuroinvasiveness
- Neurovirulence
- Outcome dependent on:
  - Viral factors
    - Above plus site of entry, size of inoculum
  - Host factors
    - Age, sex, immune status, genetic factors

Pathogenesis (II)

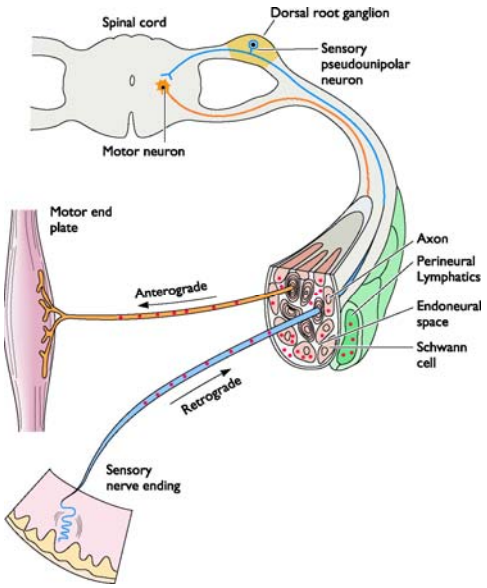
- Entry
  - Respiratory, GI, GU, skin, ocular conjunctiva, blood
- Invasion
- Entry into central nervous system
  - Hematogenous dissemination
  - Neural dissemination
- Neurovirulence and Immunopathology

Hematogenous Spread

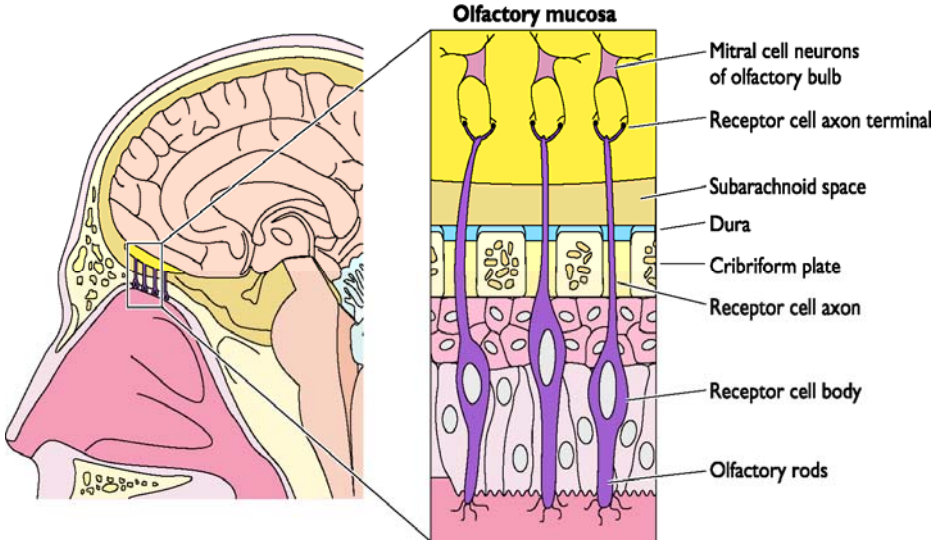
- Occurs despite blood brain barrier with tight junctions
- Via choroid plexus
- Via infection of cerebral capillary endothelial cells
- Via diapedesis



Neural spread

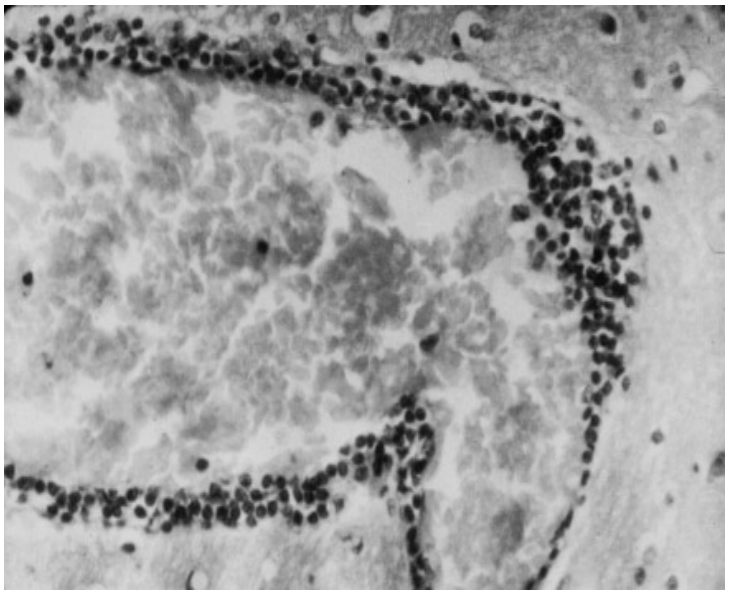


Olfactory spread

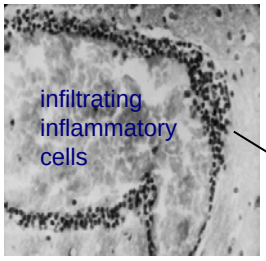


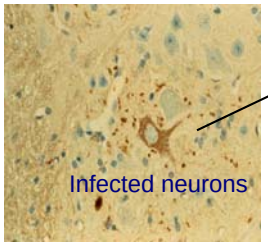
Pathogenesis (III)

- Neurovirulence
  - Neuronal infection
    - Latency, subtly altered function, apoptosis, necrosis
    - Anatomic location affects manifestations
  - Oligodendroglial cells
    - JC virus, PML (progressive multifocal leukoencephalopathy)
- Immunopathology
  - Inflammatory reaction in meninges and in perivascular distribution within brain
  - Acute disseminated encephalomyelitis (ADEM)



Immune Activation Plays a Protective and Pathologic Role





Release of Inflammatory Cytokines

Inhibition of viral replication

Neuronal dysfunction/ injury

activated microglia

Epidemiology

- 20,000 cases annually in U.S.
- Worldwide incidence unknown
  - 10,000 deaths due to Japanese encephalitis
  - 60,000 deaths due to rabies
- Geographic and temporal niches
- Iceberg phenomenon
- Extremes of age and the immunocompromised
- Altered by +/- routine vaccinations

Clinical Features

- Headache
- Fever
- Altered consciousness
- Confusion, cognitive impairment, personality changes
- Seizures
- Weakness and movement disorders

Focal neuro findings + fever + HA => encephalitis!!!

- Prognosis

Diagnosis and Treatment

- Diagnosis
  - History and Physical
  - CSF profile
    - Mild-mod lymph pleocytosis, normal or slightly elevated protein, normal glucose
  - Rule out other causes
  - Viral cultures, detection of viral nucleic acid, serology of CSF and serum
  - MRI, EEG
- Treatment supportive except acyclovir for HSV

Typical CSF findings in CNS infections

Condition	Pressure (cm H_2O)	Cell Count (WBC/mm^3)	Cell Type	Glucose (mg/dL)	Protein (mg/dL)
Normal	9-18	0-5	Lymph	50-75	15-40
Bacterial meningitis	20-50	100-10,000	>80% PMN	<40 (may be normal early)	100-1000
Viral meningitis/ encephalitis	9-20	10-500	Lymph (early PMN)	Normal; (Low in LCM, HSV, mumps)	50-100
TB meningitis	18-30	<500	Lymph	<50 (may be normal early)	100-300
Cryptococcal meningitis	18-30	10-200	Lymph	<40 (may be normal early)	50-300

Clinical scenario #2

- 50 yo M in Riverdale awakens from a Saturday afternoon nap in December, puts on his swimsuit, and begins to fill the bathtub with shredded pieces of that day's newspaper.

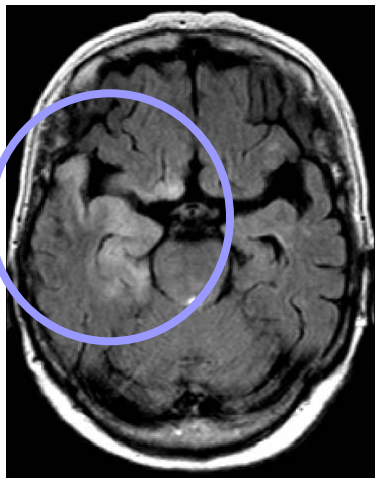
Clinical Scenario #2 (con't)

- He finds nothing odd about his behavior but complains of a headache.
- His wife convinces him to go to the E.R., where he is found to be febrile (102.4) and extremely lethargic.

HSV encephalitis

- The major treatable viral encephalitis
- Most common cause in U.S. of sporadic, fatal encephalitis
- Usually HSV1 (HSV 2: meningitis)
- Occurs year-round, kids and adults
- Reactivation > primary but can be either
- Retrograde transport into CNS via olfactory or trigeminal nerves
- Necrotizing encephalitis and hemorrhagic necrosis, particularly temporal lobe

HSV encephalitis -- MRI



Resident and Staff Physician, v52i1(2006)

HSV encephalitis

- Clinical
  - Personality changes and bizarre behavior, amnesia, hypomania
  - Sudden onset, no prodrome
- Diagnosis
  - as above, plus sometimes RBCs in CSF
  - MRI and EEG with temporal lobe findings
  - PCR of CSF 98% sensitive, 94% specific
- Treatment
  - Acyclovir is well-tolerated and reduces mortality from 70% to 19% and should be started EARLY

Clinical scenario #2

- 60 yo man from Queens admitted in August with fever, weakness, nausea x 3 days
- HD4:
  - confusion, proximal muscle weakness, decreased DTRs, respiratory difficulty requiring ventilatory support
- 7 other patients, similar, flaccid paralysis

"ARBOVIRUSES"

(arthropod-borne viruses)

West Nile virus -- a flavivirus, ssRNA, enveloped

Science Times

The New York Times

Clues to an Alien Virus

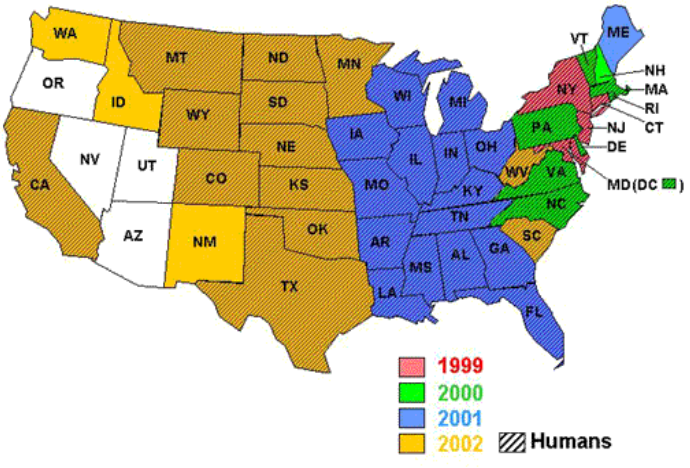
Scientists Begin to Crack the Mysteries of West Nile

Transmitting the Virus

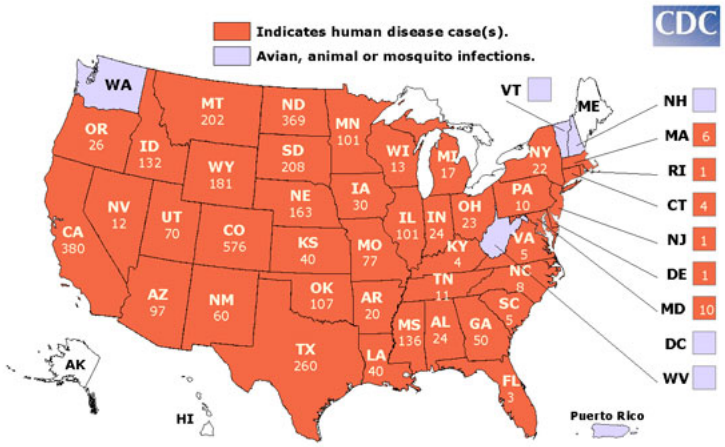
West Nile virus is transmitted by mosquitoes, primarily the Culex pipiens species, or common house mosquito, which are infected when they feed on infected birds. Ten days to two weeks later, the virus reaches the mosquito's salivary glands and can be transmitted to humans and animals when mosquitoes bite them to take blood.

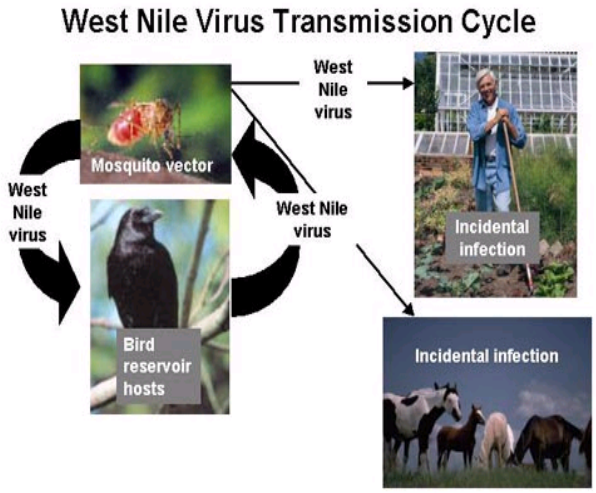
The Host

At least 17 native bird species, including the house sparrow, have tested positive for the virus. Once infected, some birds can pass on the disease to mosquitoes for up to five days.



U.S. WNV Activity 2007





Arboviral encephalitis: Pathogenesis

- Non-cytopathic in mosquito vectors
- Cytopathic in most mammalian cells
- Hematogenous entry into CNS
  - Arthropod bite -> replication in peripheral sites -> viremia -> CNS invasion
- Neuron is primary CNS target
  - Neurovirulence from neuronal dysfunction and death induced directly by virus
- Age of host
  - primary factor in neuroinvasion/neurovirulence

West Nile virus - clinical

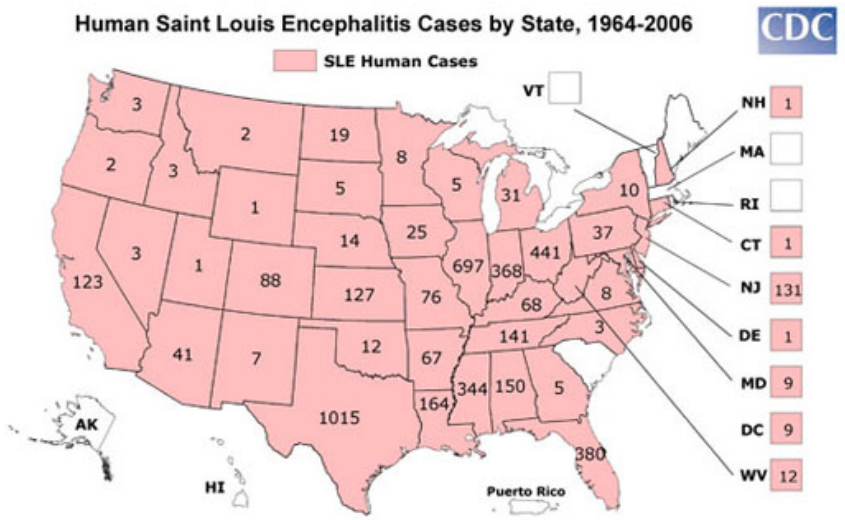
- Most human infections clinically inapparent
  - 1/5 febrile illness; 1/150 CNS involvement
  - Elderly at increased risk for neuro sx and death
  - Rash and lymphadenopathy common
- 2-15 day incubation period
- Neuroinvasive features (enceph > meningitis)
  - Acute flaccid paralysis (anterior horn cells)
  - Seizures, cranial nerve findings, ataxia
  - Movement disorder – myoclonus, parkinsonism

West Nile encephalitis

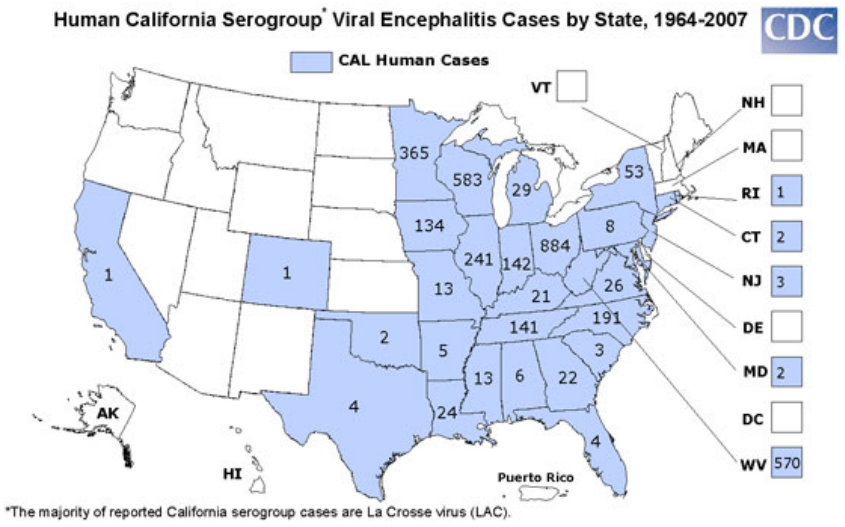
- Diagnosis
  - Most sensitive screening test is IgM ELISA in CSF and/or serum
  - NYSDOH PCR panel on CSF includes arboviruses, enteroviruses, HSV, CMV, VZV, EBV
- Treatment
  - Supportive; experimental interferon, ribavirin, immunoglobulin
- Reporting to DOH
- Prognosis

Arboviral encephalitis: classification

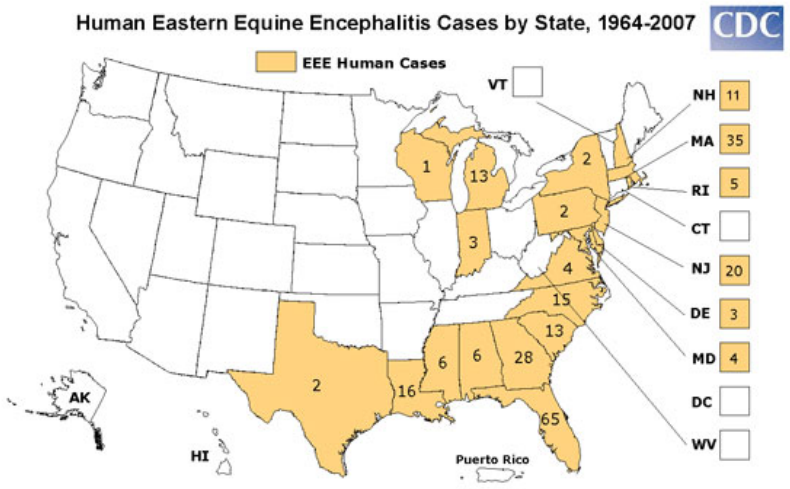
Family	Genus	Species
Togaviridae	Alphavirus (ssRNA+, env)	Western Equine Eastern Equine Venezuelan Equine
Flaviviridae	Flavivirus (ssRNA+, env)	Japanese B antigenic complex Tick-borne antigenic complex
Bunyaviridae	Bunyavirus (ssRNA-, segmented env)	LaCrosse California encephalitis



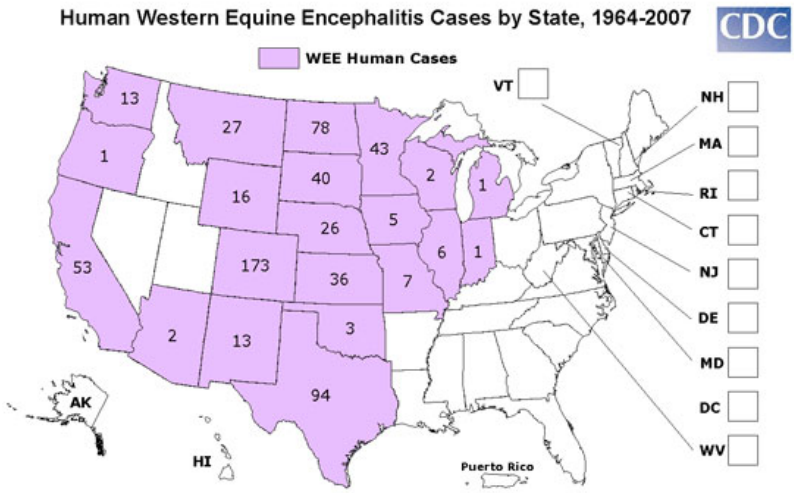
Total: 4658 cases



Total: 3494 cases

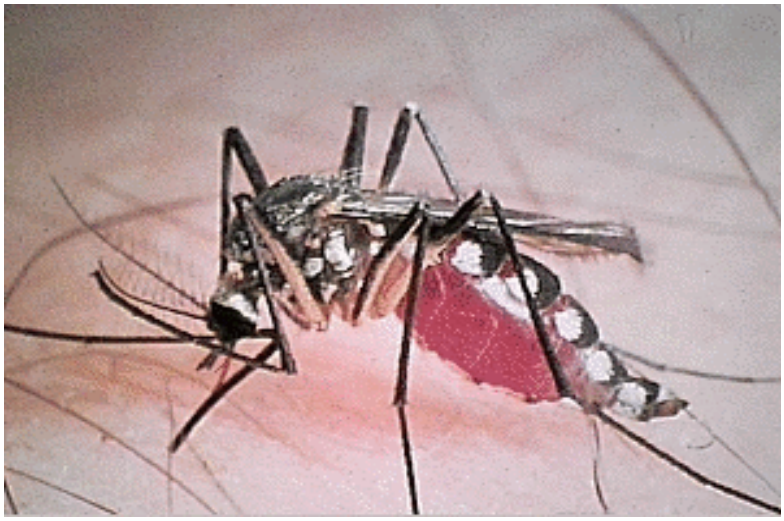


Total: 254 cases



Total: 640 cases

Arboviral Encephalitis Prevention



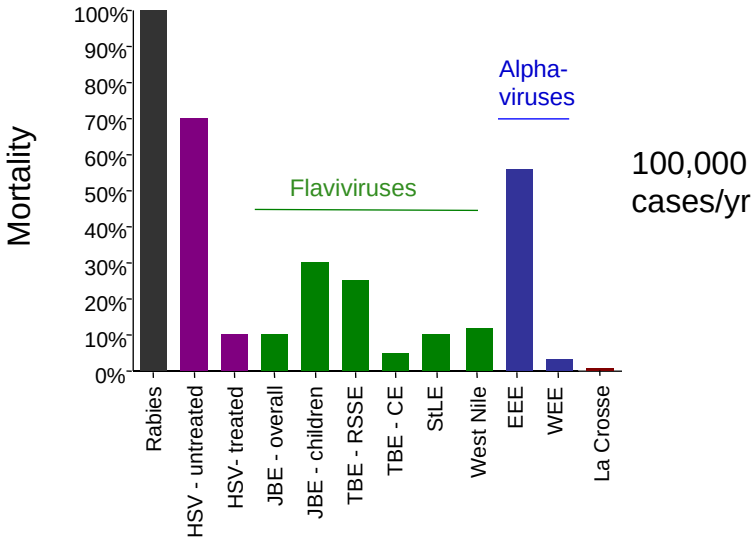
Clinical scenario #3

- 32 yo woman returns to NYC in June after traveling to India, Nepal, Thailand, Vietnam
- In July, brought to ER by boyfriend because intermittent periods of extreme agitation and aggressive behavior x 1 day
- She is lucid, complains of headache, malaise, paresthesias in hand at site of old dog bite x 2 days
- Later that day, agitation, hypersalivation, hydrophobia
- Coma and death five days later

Rabies Virus

- Rabies
  - Sanskrit “to rage”
  - Latin “to rave”
- Rhabdoviridae family, Lyssavirus genus
  - Greek “frenzy”
- Isolated by Pasteur in 1880s
- Nonsegmented negative sense, single-stranded RNA, enveloped
  - Bullet-shaped

Mortality in Patients with Symptomatic Encephalitis

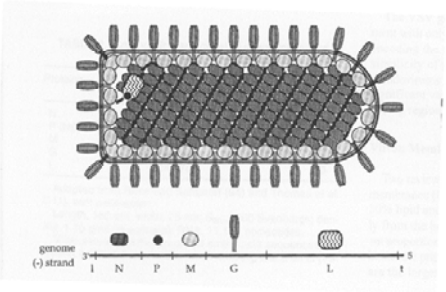


100,000 cases/yr

Rabies epidemiology

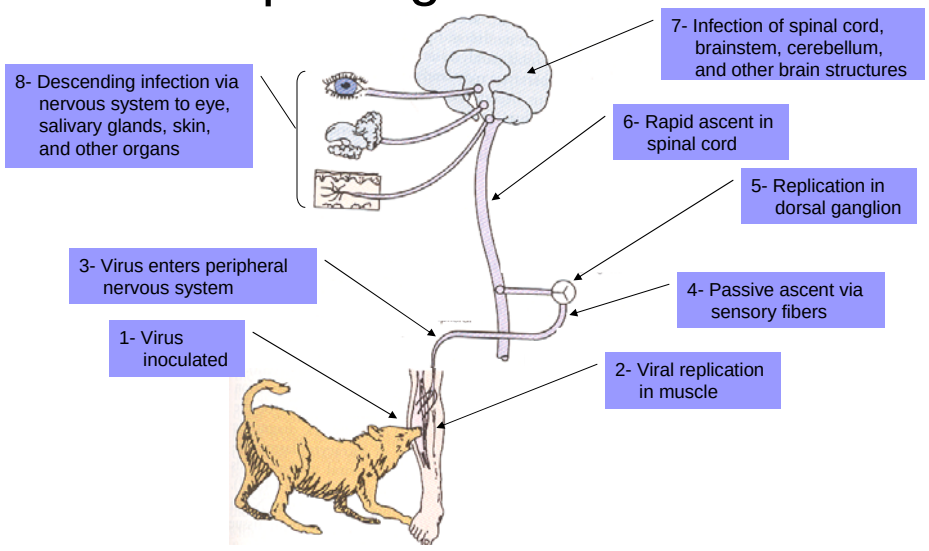
- 60,000 estimated human deaths annually worldwide
- 1-3 deaths per year in U.S.
- Dogs in developing countries
- Wild animals in developed countries (skunk, raccoon, fox, bat)
- Bites, inhalation, transplant
- U.S., major source is bat (often no history of a bite)

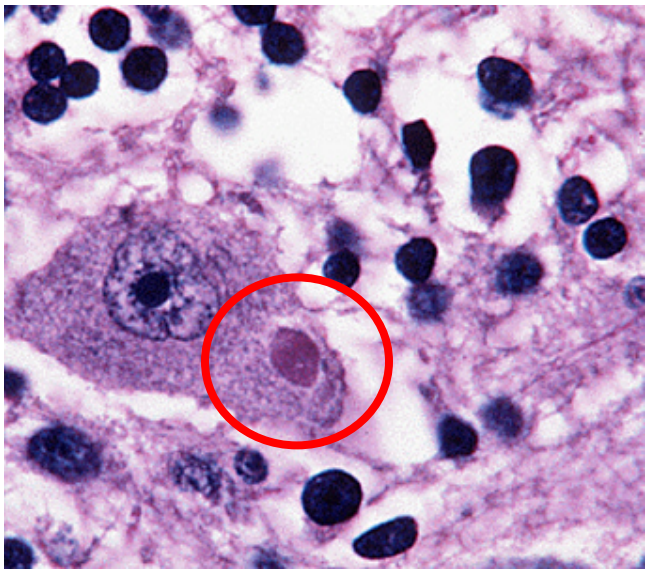
Rhabdovirus structure/proteins



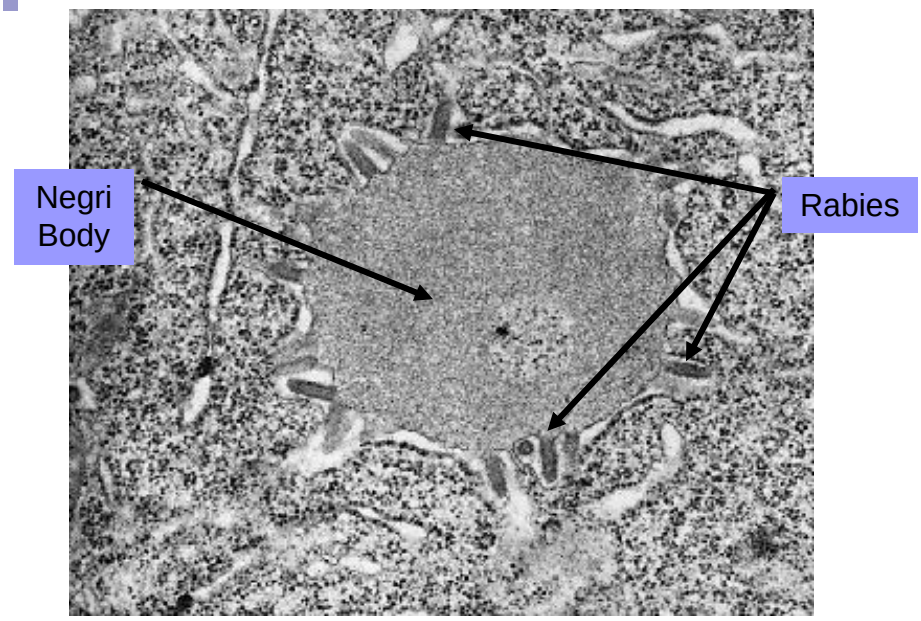
- L,P serve as RNA-dependent RNA polymerase
- N wraps the template (naked RNA not used) – Ribonucleoprotein core
- M – viral assembly and budding; host species
- G – glycoprotein; target for neutralizing antibodies

Rabies pathogenesis





Micrograph from http://www.ncbi.nlm.nih.gov/ICTVdb courtesy of Dr. Frederick A. Murphy, School of Veterinary Medicine, University of California Davis



Rabies - Clinical features

- Incubation period 1 week to 1 year
- ± 100% fatality rate
- Prodromal phase – 2-10 days
  - Fever, sore throat, headache, paresthesias, pain at site of bite
- Acute neurologic phase (encephalitic/furious) – 2-10 days
  - Agitation, delirium, stiffness, hypersalivation, hydrophobia
- Coma, flaccid paralysis, seizures, respiratory and vascular collapse
- Less commonly, pure ascending paralysis (paralytic)

Rabies diagnosis, treatment, prevention

- Diagnosis
  - Isolate virus or detect antigen or nucleic acid in saliva, skin biopsies, CSF
  - Serology
- Treatment
  - No effective treatment once symptoms arise
  - Exception in Wisconsin teenager
- Prevention
  - Pre-exposure prophylaxis (rabies vaccine)
  - Post-exposure prophylaxis
    - Wound care, rabies immune globulin, rabies vaccine
    - +/- animal observation x 10 days

A few take home points

- Recognize encephalitis vs. meningitis and know potential etiologic agents
- Hematogenous vs. neural spread into CNS
  - "arboviral" vs. rabies/HSV
- Early administration of acyclovir for possibility of HSV encephalitis
- Beware of BATS

Back to my first case…

- She was not discharged
- Over the course of the next 6 hours, her word-finding difficulties increased, as did her fever, headache and nausea
- A diagnostic procedure (or two) was performed

What did she have?