



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

Adenoviridae
 Arenaviridae
 Bunyaviridae
 Filoviridae
 Flaviviridae
 complex
 Herpesviridae
 Paramyxoviridae
 (Paramyxovirus)
 (Morbillivirus)
 Picornaviridae
 Reoviridae
 Retroviridae
 (Lentivirus)
 Rhabdoviridae
 Togaviridae
 (Alphavirus)

Specific viruses

Adenovirus
 LCMV (lymphocytic choriomeningitis virus), Lassa
 La Crosse, Rift Valley
 Ebola, Marburg
 St. Louis, Murray Valley, West Nile, Japanese B, Tick-borne
 HSV-1, HSV-2, VZV, HHV-6, EBV, CMV, Herpes B
 Mumps
 Measles, Hendra, Nipah
 Poliovirus, Coxsackie virus, Echovirus
 Colorado tick fever
 HIV
 Lyssavirus, Rabies
 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)

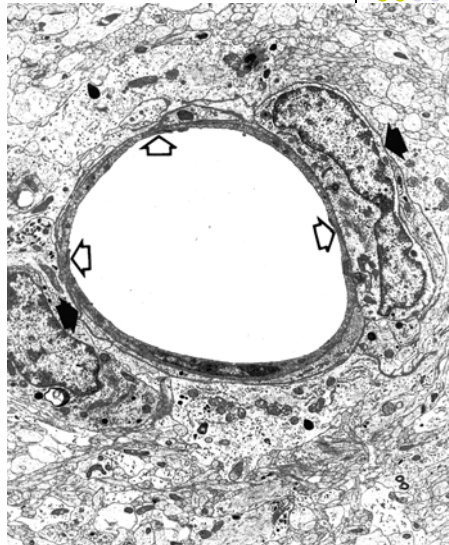


- Entry
 - Respiratory, GI, GU, skin, ocular conjunctiva, blood
- Invasion
- Entry into central nervous system
 - Hematogenous dissemination
 - Neural dissemination
- Neurovirulence and Immunopathology

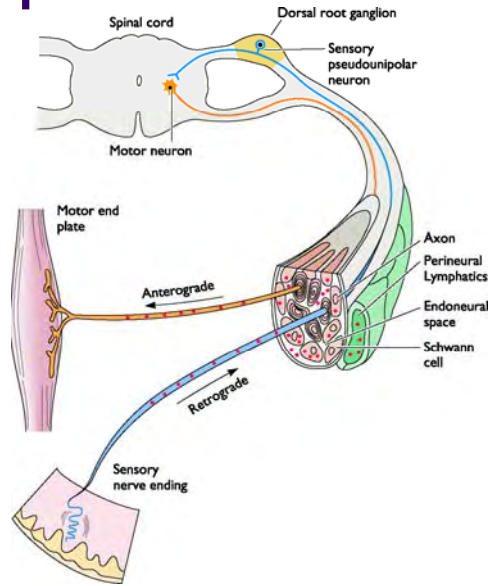
Hematogenous Spread



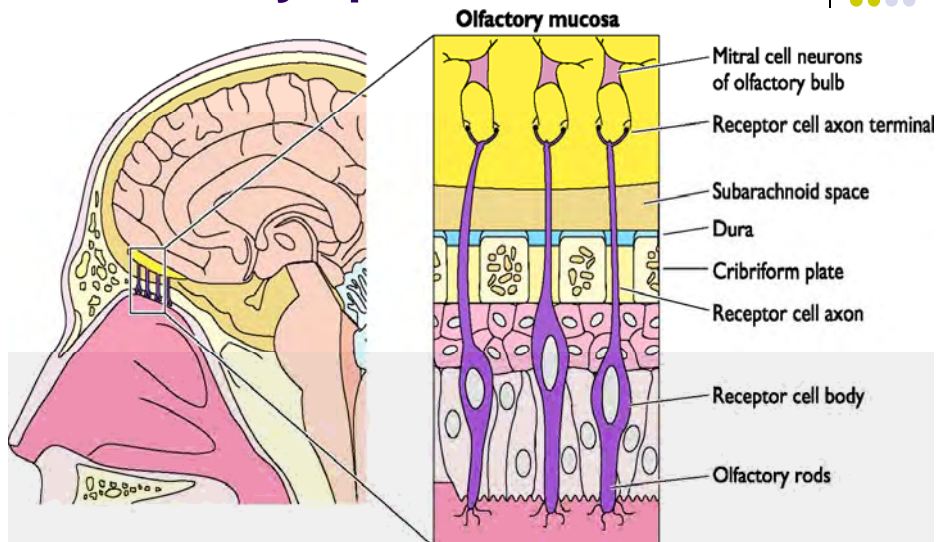
- Occurs despite blood brain barrier with tight junctions
- Via choroid plexus
- Via infection of cerebral capillary endothelial cells
- Via diapedesis



Neural spread



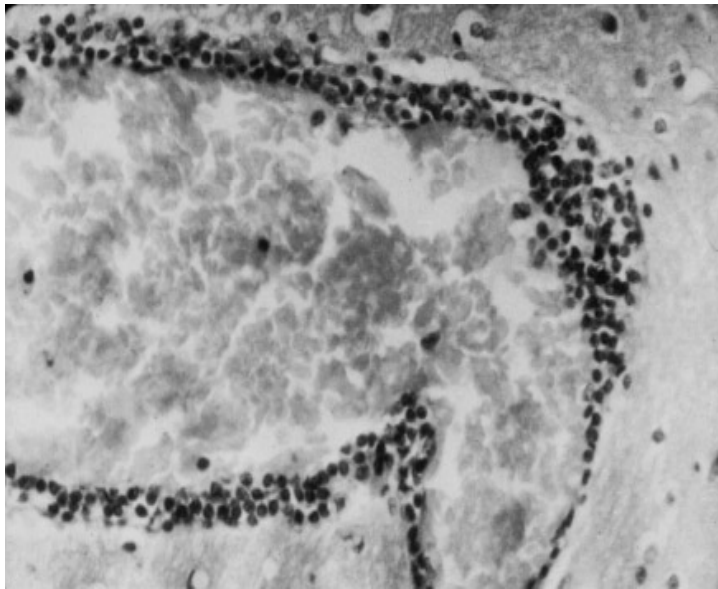
Olfactory spread



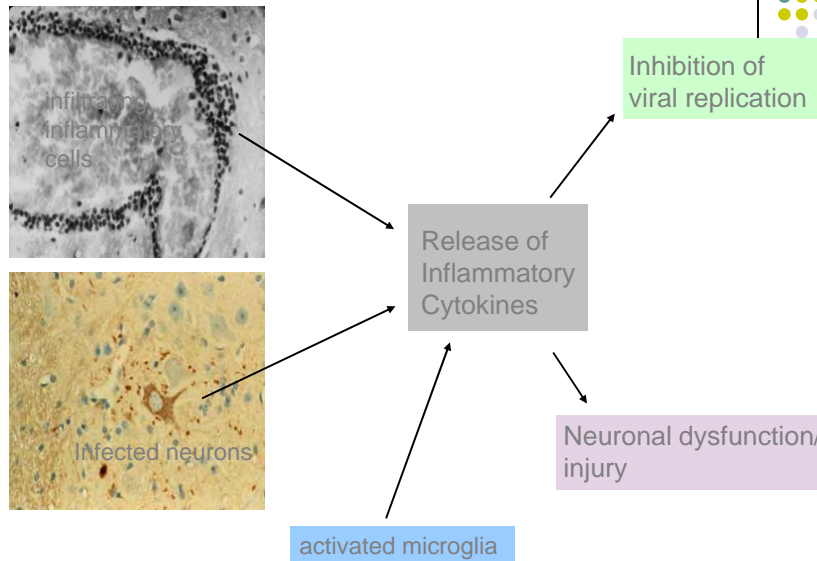
Pathogenesis (III)



- 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



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 ₂ O)	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 A:



- 63 year old accountant from Riverdale awakens from a Saturday afternoon nap in December, puts on her swimsuit, and begins to fill the bathtub with shredded pieces of that day's newspaper. Her daughter is concerned.

Clinical Scenario (continued)



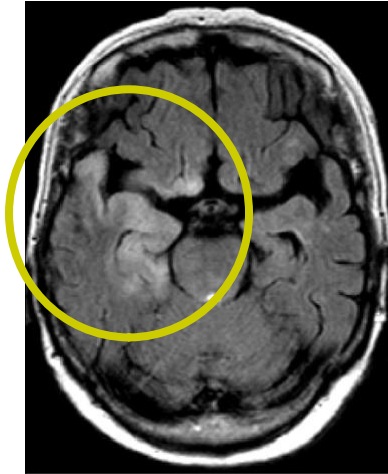
- She finds nothing odd about her behavior but complains of a headache.
- Her daughter convinces her to go to the E.R., where she is found to be febrile (102.4), smelling of urinary incontinence, extremely lethargic, paraphasic and combative with the evaluation.

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 (84% of cases)
 - 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

HSV Encephalitis - Prognosis



- 236 Patients diagnosed with HIV-1 Encephalitis in Sweden
- 14% mortality
- Among survivors:
 - 24% with epilepsy
 - 22% neuropsychiatric sequelae

Hjalmarsson, A, et al. Herpes simplex encephalitis in Sweden, 1990-2001: incidence, morbidity and mortality. CID 2007; 45:875

Clinical scenario B



- 66 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

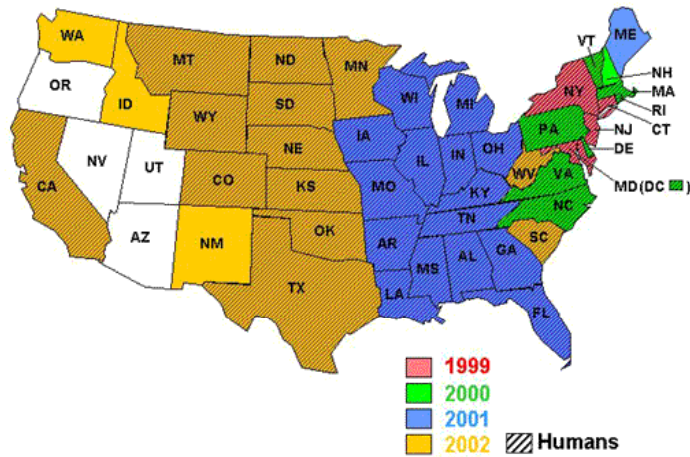
Scientists Begin to Crack the Mysteries of West Nile

Transmitting the Virus
West Nile virus is transmitted by mosquitoes, primarily the Culex species, or certain house mosquito species, which are attracted to the host on mosquito blood. For about two weeks after the virus enters the mosquito's sensory glands and can be transmitted to humans and animals whose mosquitoes bite them to take blood.

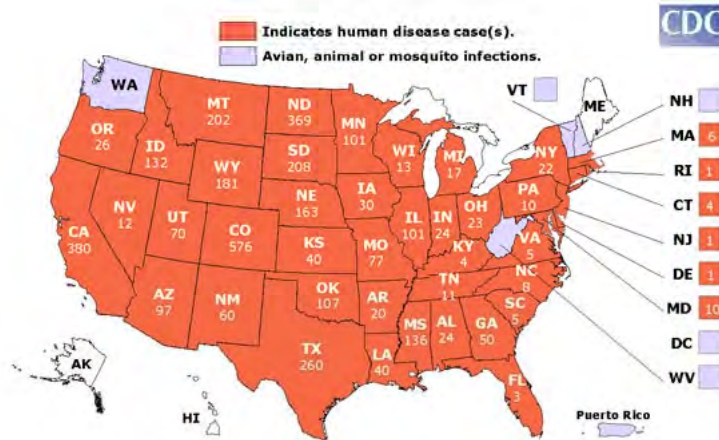
The Host
At least 17 animal and avian species, including the house sparrow, have been found to be hosts. Other species, some birds, can pass on the disease to mosquitoes for up to five days.

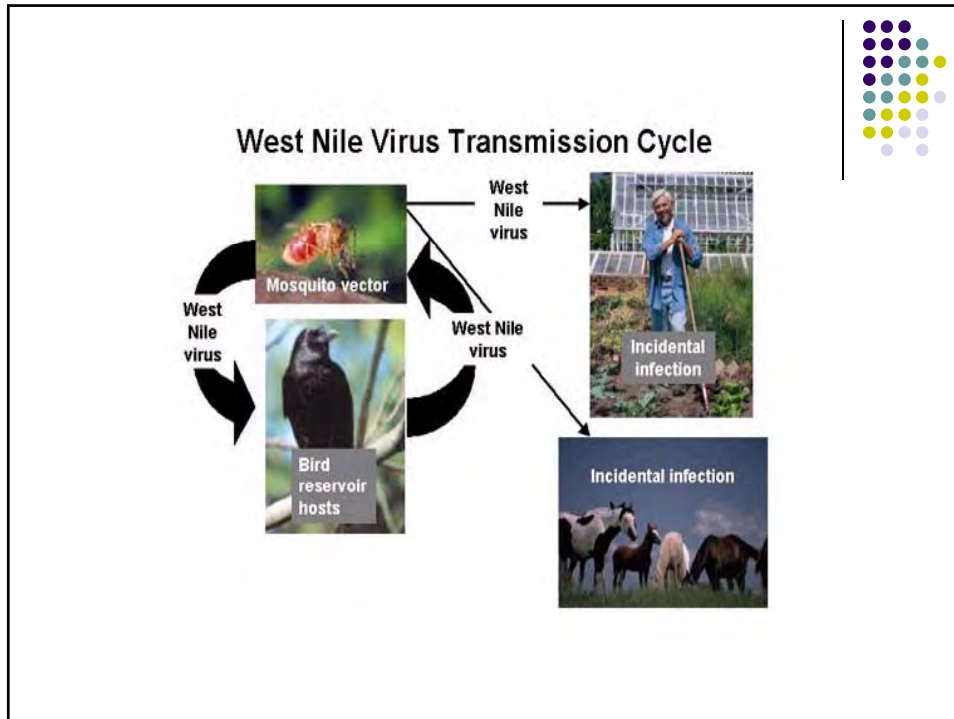


West Nile Virus in the United States, 1999 - 2002



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



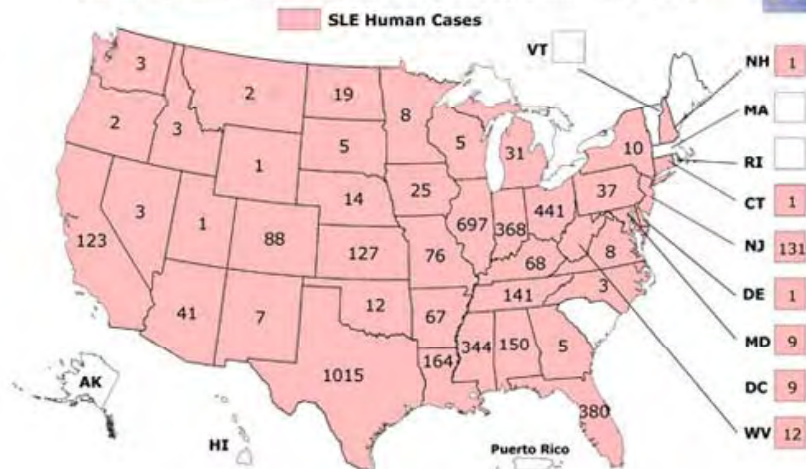
- Diagnosis
 - Most sensitive screening test is IgM ELISA in CSF and/or serum
 - NYSDOH PCR panel on CSF includes arboviruses, enteroviruses, HSV, CMV, VZV, EBV
- Treatment
 - Supportive; experimental interferon, ribavirin, immunoglobulin
- Reporting to DOH
- Prognosis

Arboviral encephalitis: classification

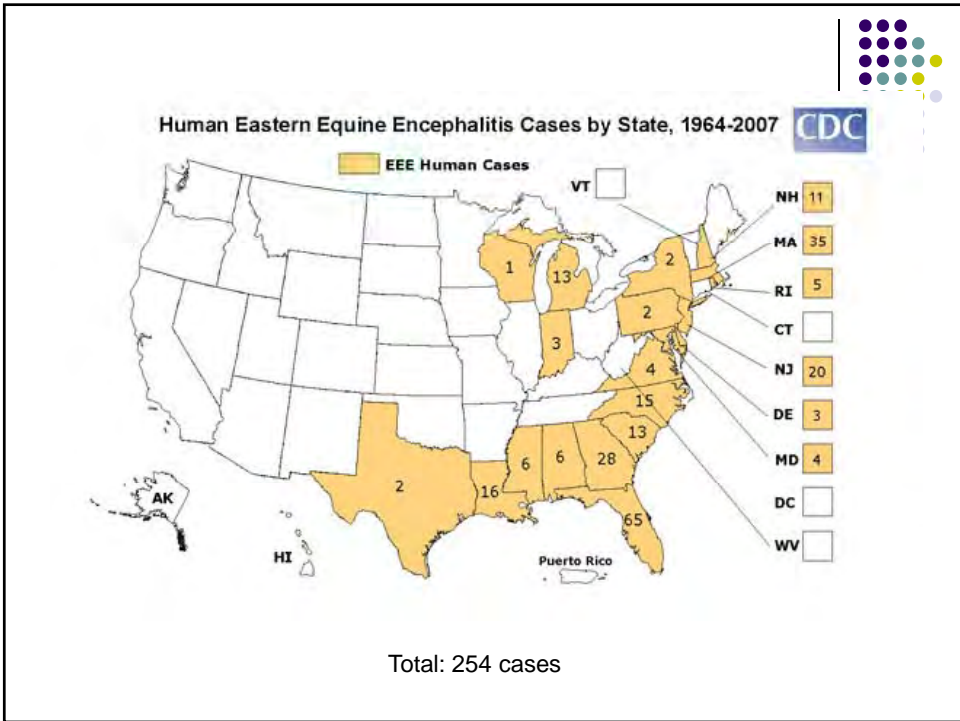
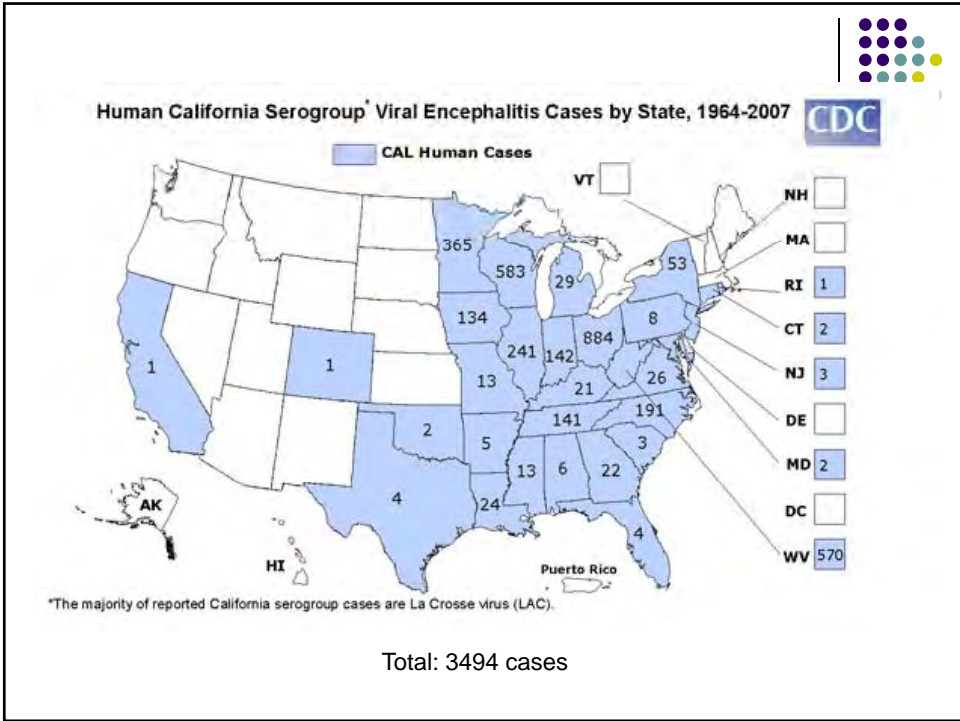


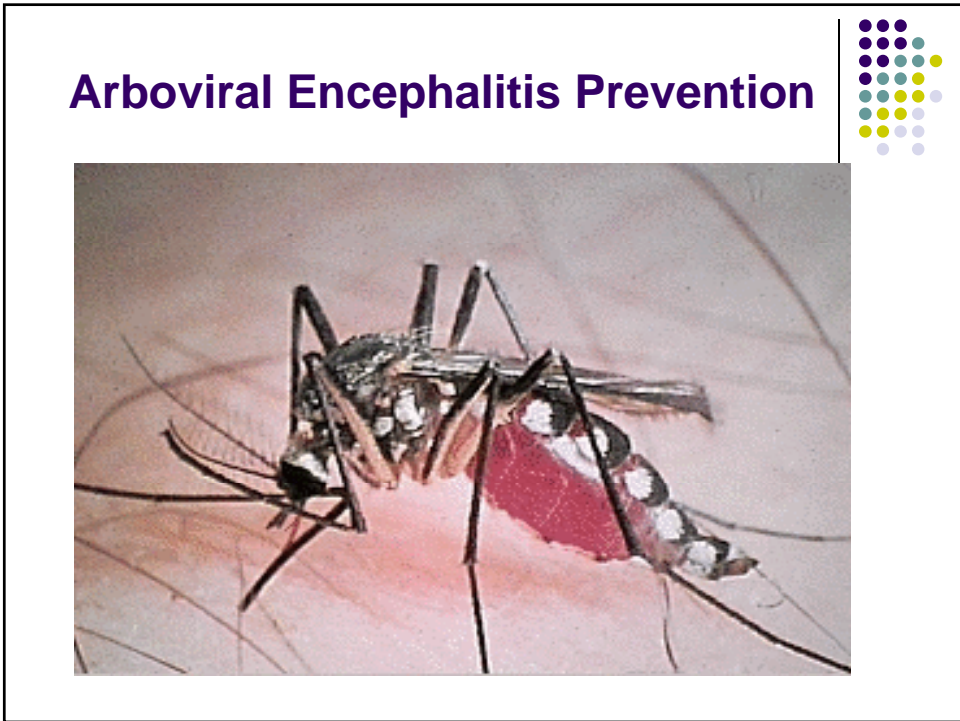
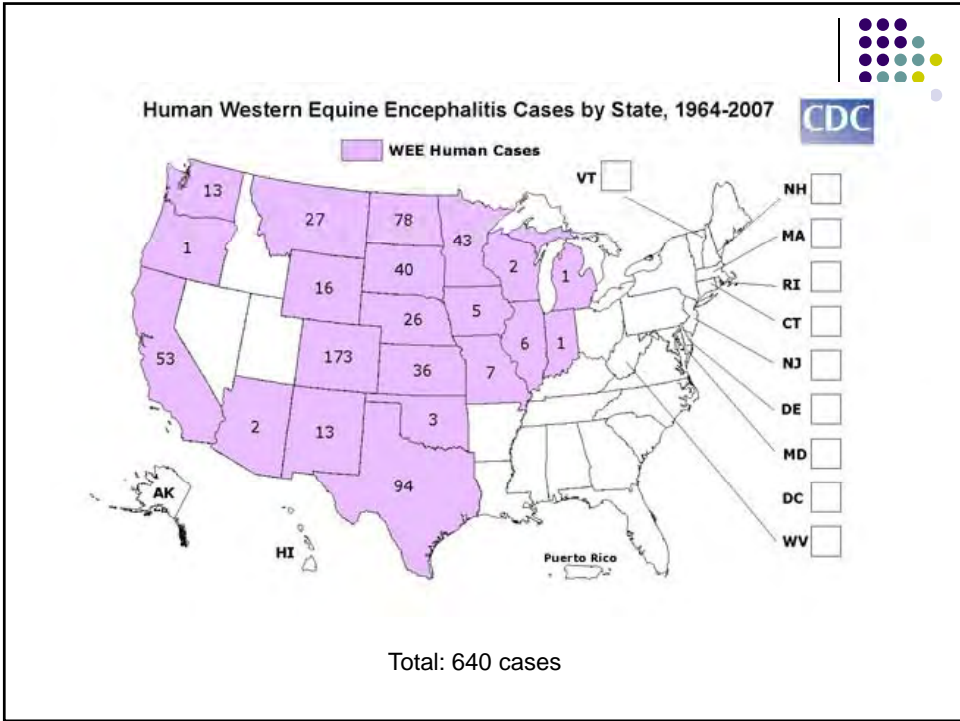
Family	Genus	Species
Togaviridae	Alphavirus (ssRNA+, env)	Western Equine Eastern Equine Venezuelan Equine
Flaviviridae	Flavivirus (ssRNA+, env)	Japanese B antigenic complex Tick-borne antigenic complex Dengue, Yellow Fever
Bunyaviridae	Bunyavirus (ssRNA-, segmented env)	LaCrosse California encephalitis

Human Saint Louis Encephalitis Cases by State, 1964-2006



Total: 4658 cases





Clinical scenario C:



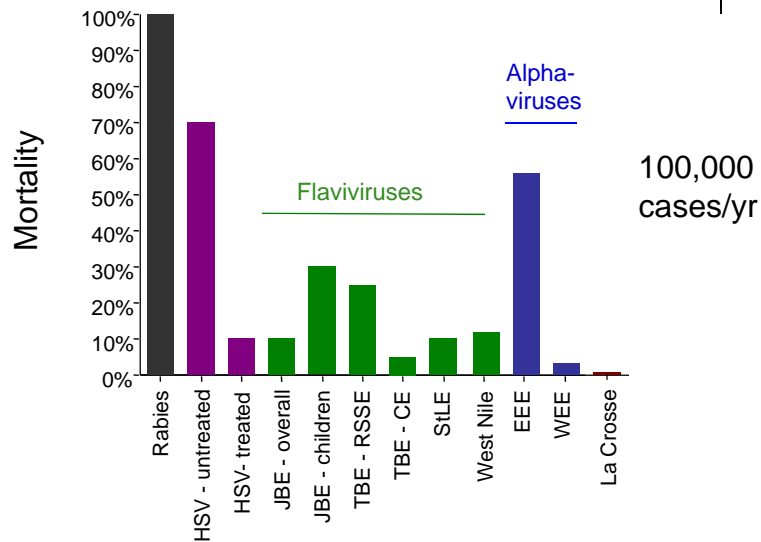
- 32 yo woman returns to NYC in June after traveling to India, Nepal, Thailand, Vietnam
- In July, brought to ER by boyfriend because intermittent periods of extreme agitation and aggressive behavior x 1 day
- She is lucid, complains of headache, malaise, paresthesias in hand at site of old dog bite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

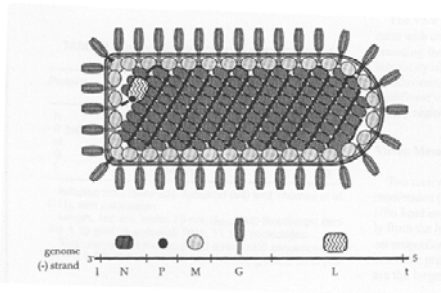


Rabies epidemiology



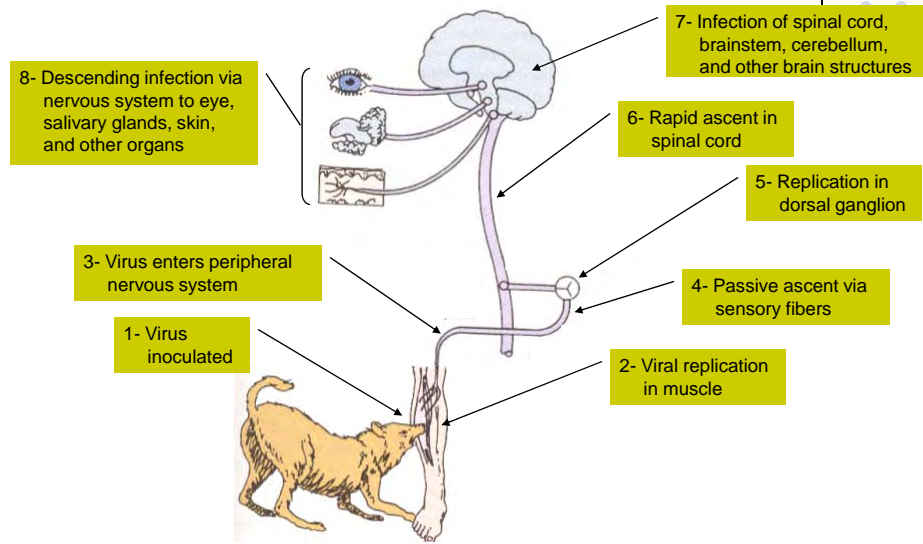
- 60,000 estimated human deaths annually worldwide
- 1-3 deaths per year in U.S.
- Dogs in developing countries
- Wild animals in developed countries (bat, skunk, raccoon, fox)
- Bites, inhalation, transplant
- U.S., major source is bat (often no history of a bite)

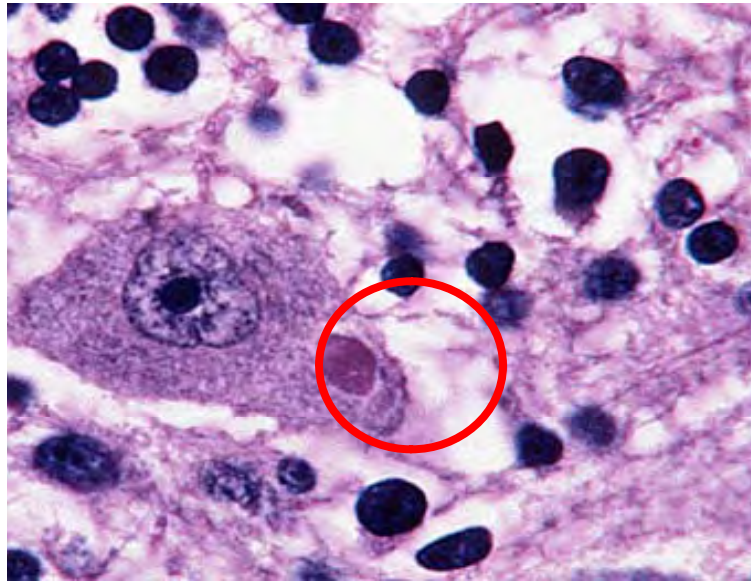
Rhabdovirus structure/proteins



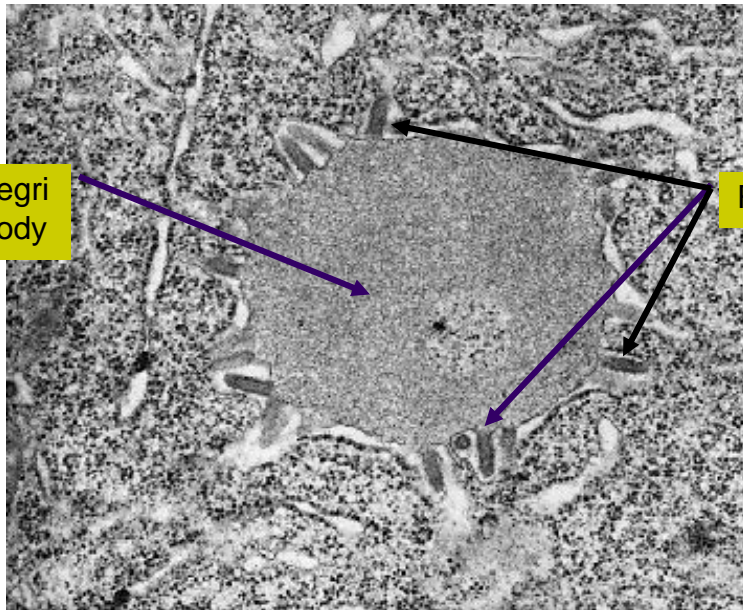
- L,P serve as RNA-dependent RNA polymerase
- N wraps the template (naked RNA not used) – Ribonucleoprotein core
- M – viral assembly and budding; host species
- G – glycoprotein; target for neutralizing antibodies

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



Negri
Body

Rabies



Rabies - Clinical features



- Incubation period 1 week to 1 year
- \pm 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 (passive), rabies vaccine (active)
 - +/- 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