

Viral Encephalitis

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

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

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

Pathogenesis (II)

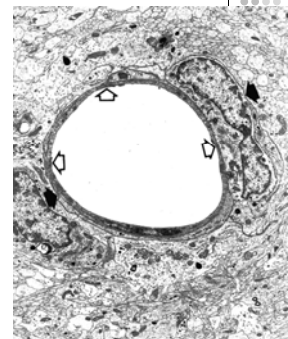
- Entry
 - Respiratory, GI, GU, skin, ocular conjunctiva, blood
- Invasion
- Entry into central nervous system
 - Hematogenous dissemination
 - Neural dissemination
- Neurovirulence and Immunopathology

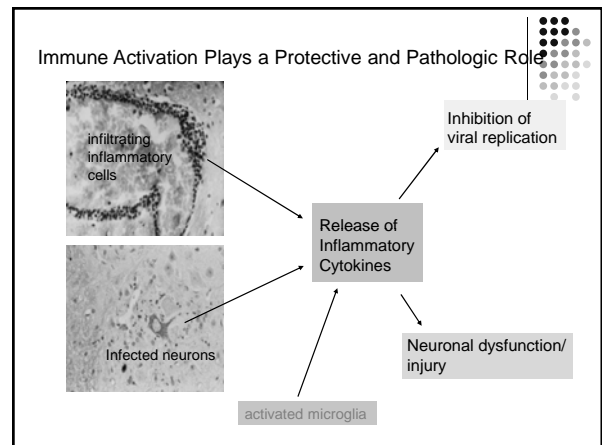
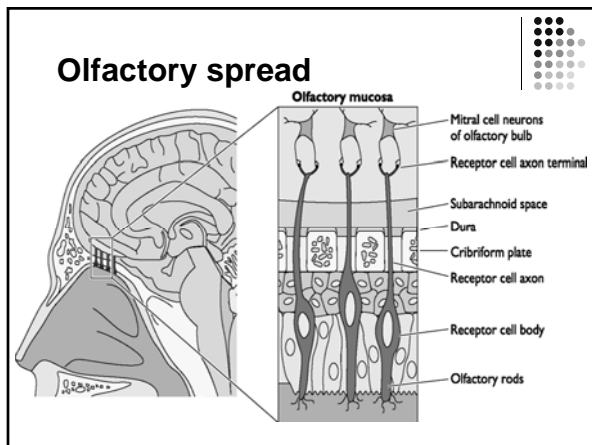
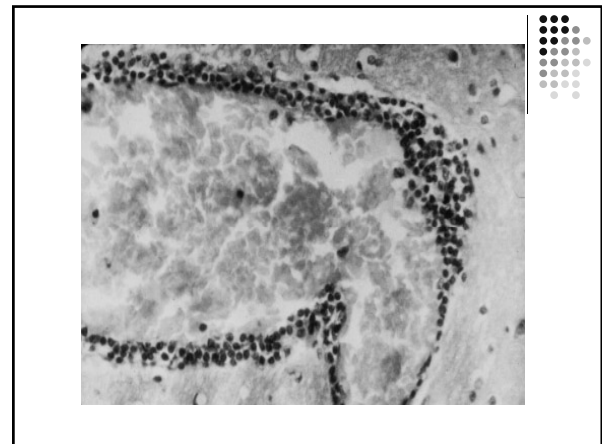
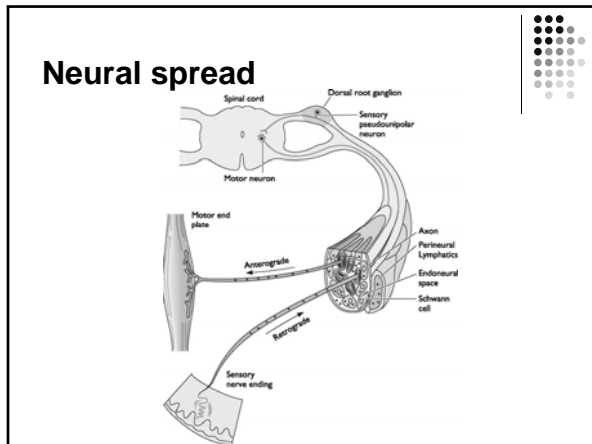
Viral causes of acute encephalitis/encephalomyelitis

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

Hematogenous Spread

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





- ### 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)

- ### 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

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.

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**

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.

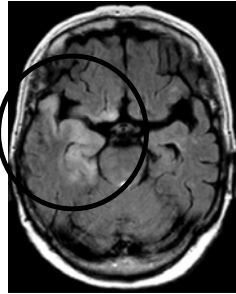
Typical CSF findings in CNS infections

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

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, v5211(2006)

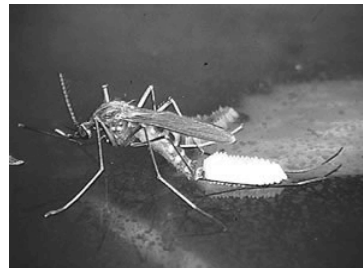
Clinical scenario B

- 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

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

“ARBOVIRUSES” (arthropod-borne viruses)



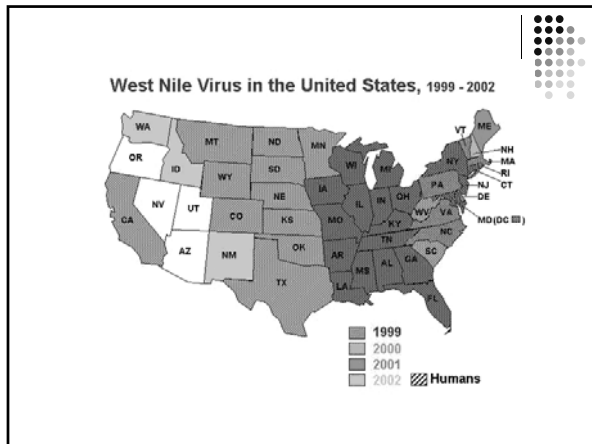
West Nile virus -- a flavivirus, ssRNA, enveloped

HSV Encephalitis - Prognosis

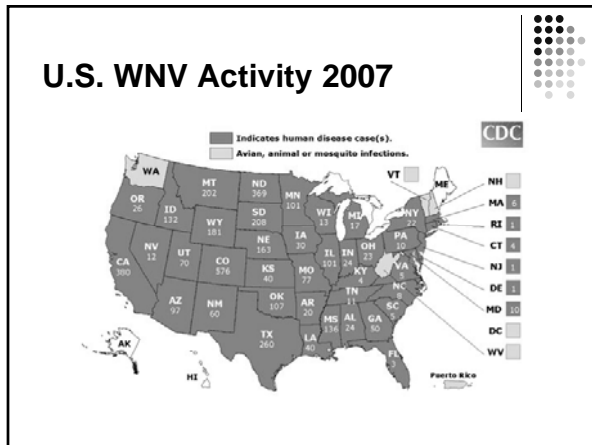
- 236 Patients diagnosed with HIV-1 Encephalitis in Sweden
- 14% mortality
- Among survivors:
 - 24% with epilepsy
 - 22% neuropsychiatric sequelae

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

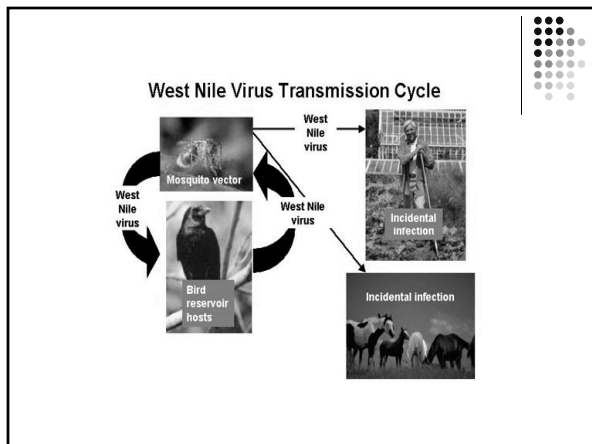




- ### Arboviral encephalitis: Pathogenesis
- Non-cytopathic in mosquito vectors
 - Cytopathic in most mammalian cells
 - Hematogenous entry into CNS
 - Arthropod bite -> replication in peripheral sites -> viremia -> CNS invasion
 - Neuron is primary CNS target
 - Neurovirulence from neuronal dysfunction 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

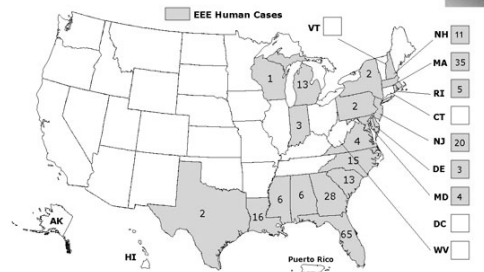


- ### West Nile encephalitis
- Diagnosis
 - Most sensitive screening test is IgM ELISA in CSF and/or serum
 - NYSDOH PCR panel on CSF includes arboviruses, enteroviruses, HSV, CMV, VZV, EBV
 - Treatment
 - Supportive; experimental interferon, ribavirin, immunoglobulin
 - Reporting to DOH
 - Prognosis

Arboviral encephalitis: classification

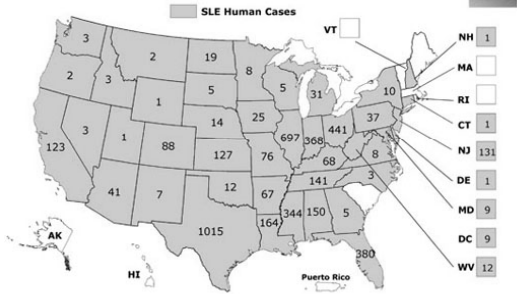
Family	Genus	Species
Togaviridae	Alphavirus (ssRNA+, env)	Western Equine Eastern Equine Venezuelan Equine
Flaviviridae	Flavivirus (ssRNA+, env)	Japanese B antigenic complex Tick-borne antigenic complex Dengue, Yellow Fever
Bunyaviridae	Bunyavirus (ssRNA-, segmented env)	LaCrosse California encephalitis

Human Eastern Equine Encephalitis Cases by State, 1964-2007



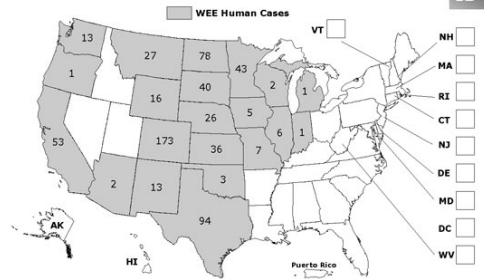
Total: 254 cases

Human Saint Louis Encephalitis Cases by State, 1964-2006



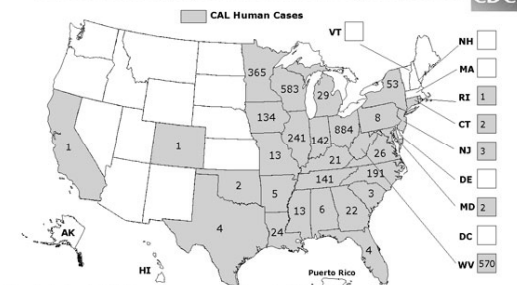
Total: 4658 cases

Human Western Equine Encephalitis Cases by State, 1964-2007



Total: 640 cases

Human California Serogroup¹ Viral Encephalitis Cases by State, 1964-2007



¹The majority of reported California serogroup cases are La Crosse virus (LAC).

Total: 3494 cases

Arboviral Encephalitis Prevention



Clinical scenario C:

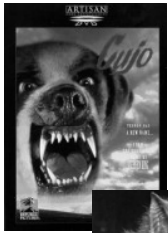
- 32 yo woman returns to NYC in June after traveling to India, Nepal, Thailand, Vietnam
- In July, brought to ER by boyfriend because intermittent periods of extreme agitation and aggressive behavior x 1 day
- She is lucid, complains of headache, malaise, paresthesias in hand at site of old dog bite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

Rabies epidemiology



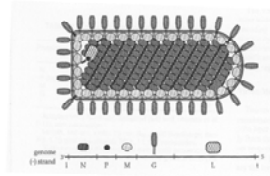
- 60,000 estimated human deaths annually worldwide
- 1-3 deaths per year in U.S.
- Dogs in developing countries
- Wild animals in developed countries (bat, skunk, raccoon, fox)
- Bites, inhalation, transplant
- U.S., major source is bat (often no history of a bite)

Rabies Virus



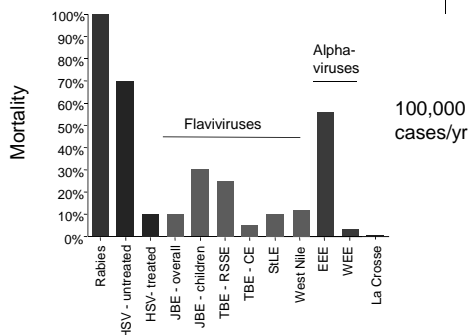
- Rabies
 - Sanskrit "to rage"
 - Latin "to rave"
- Rhabdoviridae family, Lyssavirus genus
 - Greek "frenzy"
- Isolated by Pasteur in 1880s
- Nonsegmented negative sense, single-stranded RNA, enveloped
 - Bullet-shaped

Rhabdovirus structure/proteins

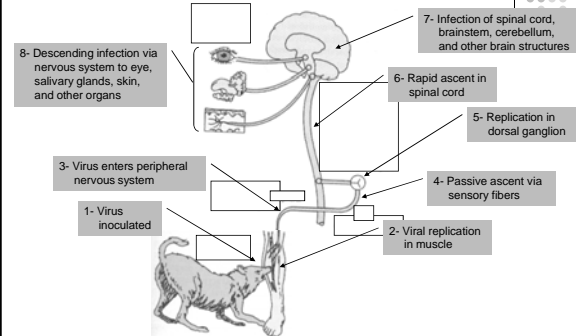


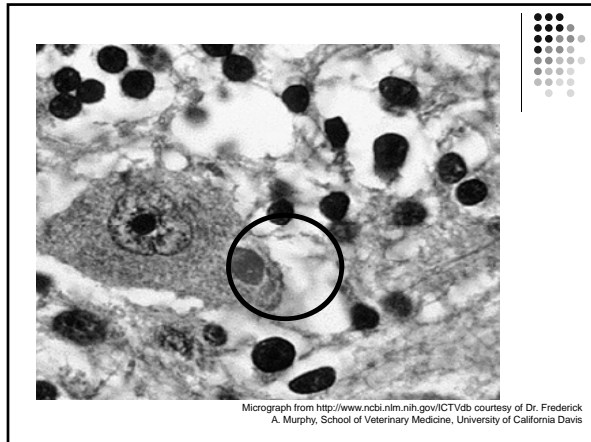
- L,P serve as RNA-dependent RNA polymerase
- N wraps the template (naked RNA not used) – Ribonucleoprotein core
- M – viral assembly and budding; host species
- G – glycoprotein; target for neutralizing antibodies

Mortality in Patients with Symptomatic Encephalitis



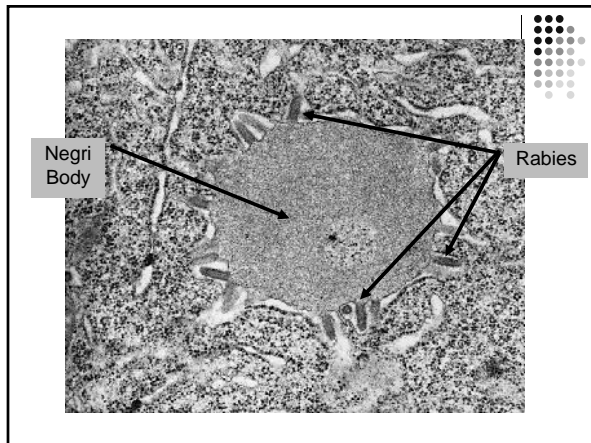
Rabies pathogenesis





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

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)