

## Viral Encephalitis

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

## Typical CSF findings in selected CNS infections

Condition	Pressure (cmH <sub>2</sub> O)	Cell Count (WBC/mm <sup>3</sup> )	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 #1

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

## Viral causes of acute encephalitis/encephalomyelitis

Virus Family (genus)	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
Picomaviridae	Poliovirus, Coxsackie virus, Echovirus
Reoviridae	Colorado tick fever
Retroviridae (Lentivirus)	HIV
Rhabdoviridae	Lyssavirus, Rabies
Togaviridae (Alphavirus)	Eastern equine, Western equine, Venezuelan equine

## Definitions/Descriptions

- Encephalitis vs. Meningitis
- 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

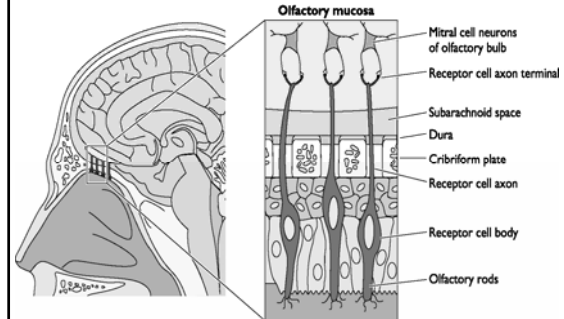
## Pathogenesis (I)

- 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)

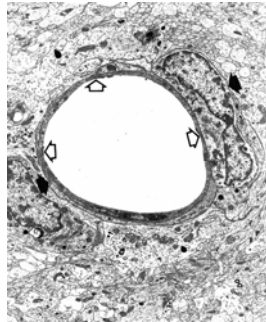
- Entry
  - Respiratory, GI, GU, skin, ocular conjunctiva, blood
- Invasion
- Entry into central nervous system
  - Hematogenous dissemination
  - Neural dissemination
- Neurovirulence and Immunopathology

## Olfactory spread



## Hematogenous Spread

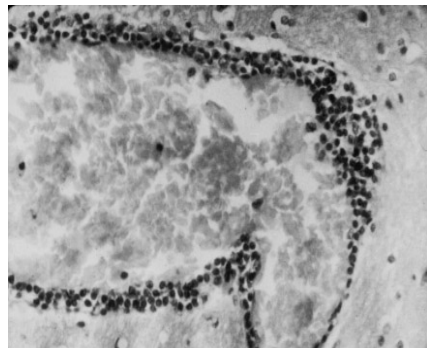
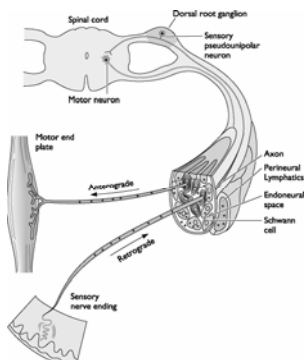
- Occurs despite blood brain barrier with tight junctions
- Via choroid plexus
- Via infection of cerebral capillary endothelial cells
- Via diapedesis

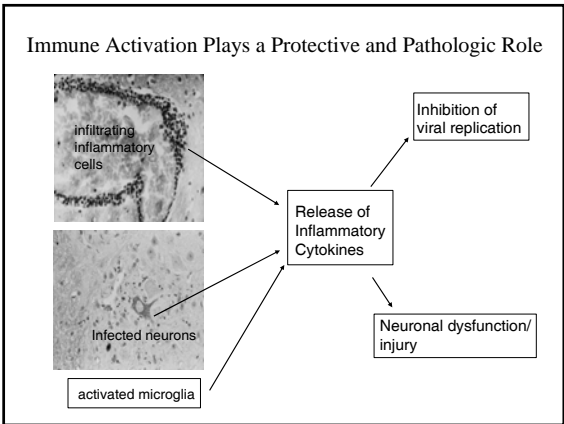


## Pathogenesis (III)

- 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)

## Neural spread





## 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

## 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 scenario #1

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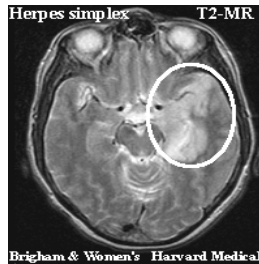
## Clinical Features

- Headache
- Fever
- Altered consciousness
- Confusion, cognitive impairment, personality changes
- Seizures
- Weakness and movement disorders
- **PRESENCE OF FOCAL NEUROLOGIC FINDINGS IN ADDITION TO FEVER AND HEADACHES – THINK ENCEPHALITIS**
- Prognosis

## HSV encephalitis

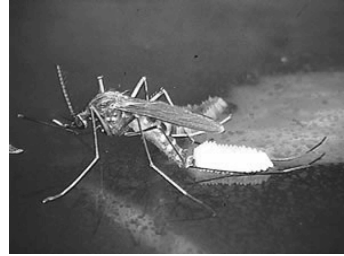
- The major treatable viral encephalitis
- Most common cause in U.S. of sporadic, fatal encephalitis
- Usually HSV1 (HSV 2: meningitis)
- Occurs year-round, kids and adults
- Reactivation > primary but can be either
- Retrograde transport into CNS via olfactory or trigeminal nerves
- Necrotizing encephalitis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

## HSV encephalitis -- MRI



## “ARBOVIRUSES”

(arthropod-borne viruses)



West Nile virus -- a flavivirus, ssRNA, enveloped

## HSV encephalitis

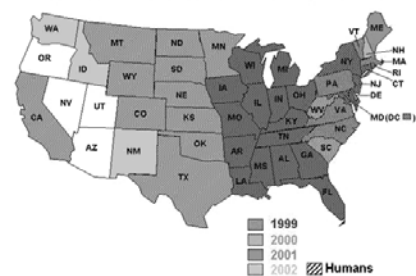
- Clinical
  - as above, particularly personality changes and bizarre behavior, amnesia, hypomania
  - Sudden onset, no prodrome
- Diagnosis
  - as above, plus sometimes RBCs in CSF
  - MRI and EEG with temporal lobe findings
  - PCR of CSF 98% sensitive, 94% specific
- Treatment
  - Acyclovir is well-tolerated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



## Clinical scenario #2

- 60 yo man from Queens is admitted in August with fever, weakness, nausea x 3 days
- On day 4 of hospitalization, confusion, proximal muscle weakness, decreased DTRs, respiratory difficulty requiring ventilatory support
- 7 other patients, similar, flaccid paralysis

West Nile Virus in the United States, 1999 - 2002



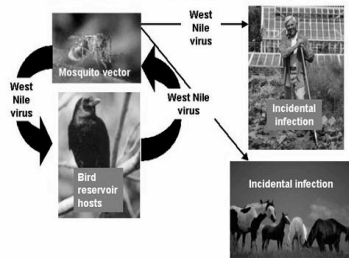
## U.S. WNV Activity 2004



## 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 Virus Transmission Cycle



## West Nile encephalitis

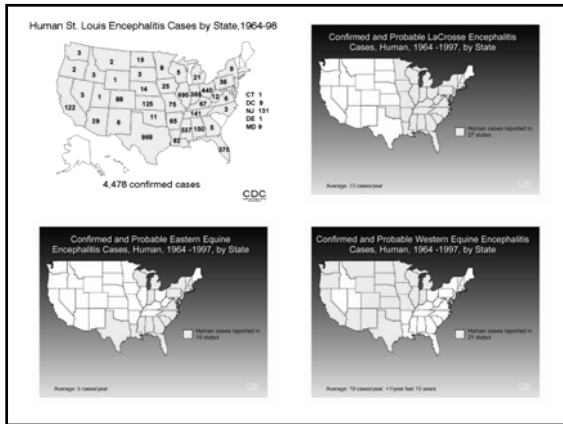
- Diagnosis
  - Most sensitive screening test is IgM ELISA in CSF and/or serum
  - NYSDOH PCR panel on CSF includes arboviruses, enteroviruses, HSV, CMV, VZV, EBV
- Treatment
  - Supportive; experimental interferon, ribavirin, immunoglobulin
- Reporting to DOH
- Prognosis

## Arboviral encephalitis: 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 target in CNS
- Neurovirulence due primarily to neuronal dysfunction and neuronal death induced directly by virus
- Age of host is of paramount importance in determining neuroinvasion/neurovirulence

## Arboviral encephalitis: classification

Family	Genus	Species
Togaviridae	Alphavirus (ssRNA+, env)	Western Equine*
		Eastern Equine*
		Venezuelan Equine
Flaviviridae	Flavivirus (ssRNA+, env)	(Japanese B antigenic complex)
		Japanese B****
		St. Louis*
		West Nile*
		Murray Valley
		(Tick-borne antigenic complex)
		Tick-borne encephalitis
		Central European encephalitis
		Russian spring-summer encephalitis
		Powassan
Bunyaviridae	Bunyavirus (ssRNA neg, segmented, env)	LaCrosse* California encephalitis


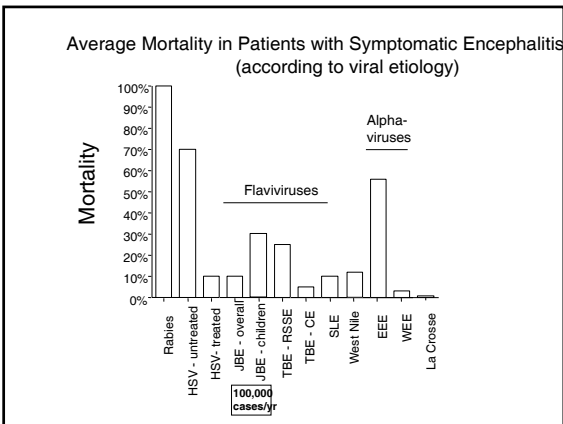


## Rabies Virus



- 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


## Arboviral Encephalitis Prevention

## Clinical scenario #3

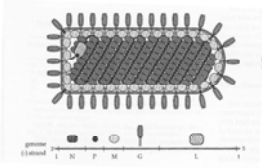
- 32 yo woman returns to NYC in June after traveling to India, Nepal, Thailand, Vietnam
- In July, brought to ER by boyfriend because intermittent periods of extreme agitation and aggressive behavior x 1 day
- She, lucid, complains of headache, malaise, paresthasias in hand (dog bite) x 2 days
- Later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

## Rabies epidemiology

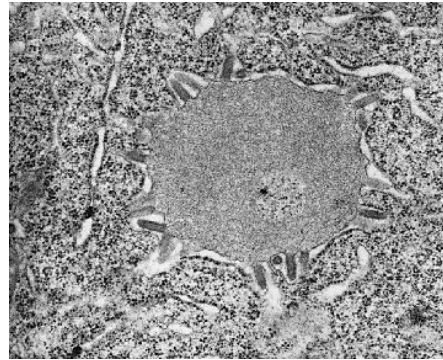


- 60,000 estimated human deaths annually worldwide
- 1-3 deaths per year in U.S.
- Dogs in developing countries
- Wild animals in developed countries (skunk, raccoon, fox, bat)
- Bites, inhalation, transplant
- U.S., major source is bat (often no history of a bite)

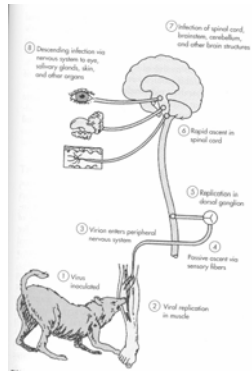
## Rhabdovirus structure/proteins



- 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

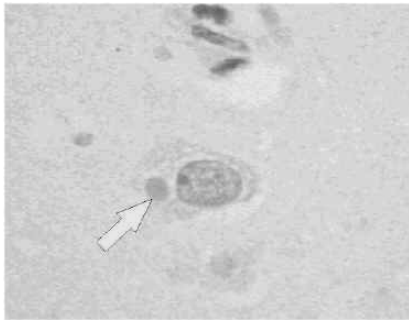


## Rabies pathogenesis



## Rabies - Clinical features

- Incubation period 1 week to 1 year+
- 100% fatality rate once symptoms occur in an unvaccinated individual (until now??)
- 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 – THERE IS NO EFFECTIVE TREATMENT ONCE SYMPTOMS ARISE
  - ?Recent 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