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

Pathogenesis (II)

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

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

<table>
<thead>
<tr>
<th>Virus Family</th>
<th>Specific viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoviridae</td>
<td>Adenovirus</td>
</tr>
<tr>
<td>Arenaviridae</td>
<td>LCMV (lymphocytic choriomeningitis virus), Lassa</td>
</tr>
<tr>
<td>Bunyaviridae</td>
<td>La Crosse, Rift Valley</td>
</tr>
<tr>
<td>Filoviridae</td>
<td>Ebola, Marburg</td>
</tr>
<tr>
<td>Flavivirus Complex</td>
<td>ST. Louis, Murray Valley, West Nile, Japanese B, Tick-borne</td>
</tr>
<tr>
<td>Herpesviridae</td>
<td>HSV-1, HSV-2, VZV, HHV-6, EBV, CMV, Herpes B</td>
</tr>
<tr>
<td>Paramyxoviridae</td>
<td>Mumps</td>
</tr>
<tr>
<td>(Morbillivirus)</td>
<td>Measles, Hendra, Nipah</td>
</tr>
<tr>
<td>Picornaviridae</td>
<td>Poliovirus, Coxsackie virus, Echovirus</td>
</tr>
<tr>
<td>Retroviridae</td>
<td>Colorado tick fever</td>
</tr>
<tr>
<td>(Lentivirus)</td>
<td>HIV</td>
</tr>
<tr>
<td>Rhabdoviridae</td>
<td>Lyssavirus, Rabies</td>
</tr>
<tr>
<td>Togaviridae (Alpha)</td>
<td>Eastern equine, Western equine, Venezuelan equine</td>
</tr>
</tbody>
</table>
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)

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.

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.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pressure (cm H2O)</th>
<th>Cell Count (WBC/mm³)</th>
<th>Cell Type</th>
<th>Glucose (mg/dL)</th>
<th>Protein (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>9-18</td>
<td>0-5</td>
<td>Lymph</td>
<td>50-75</td>
<td>15-40</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>20-50</td>
<td>10-100,000</td>
<td>&gt;80% PMN</td>
<td>&lt;40 (may be normal-early)</td>
<td>100-1000</td>
</tr>
<tr>
<td>Viral meningitis/ encephalitis</td>
<td>9-20</td>
<td>10-500</td>
<td>Lymph (early PMN)</td>
<td>Normal (Low in LCM, HSV, mumps)</td>
<td>50-100</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>18-30</td>
<td>&lt;500</td>
<td>Lymph</td>
<td>&lt;100 (may be normal-early)</td>
<td>100-300</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>18-30</td>
<td>10-200</td>
<td>Lymph</td>
<td>&lt;40 (may be normal-early)</td>
<td>50-300</td>
</tr>
</tbody>
</table>

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

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

**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

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**U.S. WNV Activity 2007**

**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

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**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

<table>
<thead>
<tr>
<th>Family</th>
<th>Genus</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Togaviridae</td>
<td>Alphavirus</td>
<td>Western Equine, Eastern Equine, Venezuelan Equine</td>
</tr>
<tr>
<td></td>
<td>(ssRNA+, env)</td>
<td></td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>Flavivirus</td>
<td>Japanese B antigenic complex, Tick-borne antigenic complex, Dengue, Yellow Fever</td>
</tr>
<tr>
<td></td>
<td>(ssRNA+, env)</td>
<td></td>
</tr>
<tr>
<td>Bunyaviridae</td>
<td>Bunyavirus</td>
<td>LaCrosse, California encephalitis</td>
</tr>
<tr>
<td></td>
<td>(ssRNA-, segmented env)</td>
<td></td>
</tr>
</tbody>
</table>

Total: 254 cases

**Human Eastern Equine Encephalitis Cases by State, 1964-2007**

Total: 640 cases

**Human Saint Louis Encephalitis Cases by State, 1964-2006**

Total: 4658 cases

**Human California Sengroup Viral Encephalitis Cases by State, 1964-2007**

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
- LP 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)