Viral Encephalitis

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

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

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.

Typical CSF findings in selected CNS infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Protein (mg/dL)</th>
<th>Cell Count (WBC/mm$^3$)</th>
<th>Cell Type</th>
<th>Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0-15</td>
<td>0-5</td>
<td>Lymph</td>
<td>60-75</td>
</tr>
<tr>
<td>Bacterial Meningitis</td>
<td>2D-5D</td>
<td>100-1000</td>
<td>PMN (may be normal early)</td>
<td>100-1000</td>
</tr>
<tr>
<td>Viral meningitis/encephalitis</td>
<td>0-2D</td>
<td>10-500</td>
<td>Lymph (early PMN)</td>
<td>Normal (low in LCM, HSV, encephalitis)</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>10-30</td>
<td>&lt;500</td>
<td>Lymph</td>
<td>50 (may be normal early)</td>
</tr>
<tr>
<td>Cerebrospinal meningitis</td>
<td>10-50</td>
<td>10-200</td>
<td>Lymph</td>
<td>&lt;40 (may be normal early)</td>
</tr>
</tbody>
</table>

Viral causes of acute encephalitis/encephalomyelitis

- Virus Family/Genus
- Specific viruses

- Adenoviridae
  - Adenovirus
- Arenaviridae
  - LCMV (lymphocytic choriomeningitis virus), Lassa
- Bunyaviridae
  - Ebola, Marburg
- Filoviridae
  - Ebola, Marburg
- Flaviviridae
  - Yellow fever virus, West Nile virus
- Herpesviridae
  - HSV-1, HSV-2, VZV, CMV
- Paramyxoviridae
  - (Paramyxovirus) Mumps
  - (Morbillivirus) Measles, Hendra, Nipah
- Paroviridae
  - Parovirus B19
- Rhabdoviridae
  - Rabies
- Reoviridae
  - California tick fever
- Togaviridae
  - Dengue virus
- Togaviridae
  - Japanese B virus
- Togaviridae
  - St. Louis encephalitis virus

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

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)

Olfactory spread

- Olfactory spread

Neural spread
**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
- **PRESENCE OF FOCAL NEUROLOGIC FINDINGS IN ADDITION TO FEVER AND HEADACHES – THINK ENCEPHALITIS**
- Prognosis

**Diagnosis and Treatment**
- **Diagnosis**
  - History and Physical
  - CSF profile
    - Mild-moderate 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**

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**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
  - 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 ***

**“ARBOVIRUSES”**

- *arthropod-borne viruses*

  West Nile virus -- a flavivirus, ssRNA, enveloped

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**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
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

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

<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*</td>
</tr>
<tr>
<td></td>
<td>(ssRNA+,env)</td>
<td>Eastern Equine*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venezuelan Equine</td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>Flavivirus</td>
<td>Japanese B antigenic complex</td>
</tr>
<tr>
<td></td>
<td>(ssRNA+,env)</td>
<td>St. Louis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>West Nile*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Murray Valley</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Tick-borne antigenic complex)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Central European encephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Russian spring-summer encephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Powassan</td>
</tr>
<tr>
<td>Bunyaviridae</td>
<td>Bafavirus</td>
<td>LaCrosse*</td>
</tr>
<tr>
<td></td>
<td>(ssRNA neg. segmented, env)</td>
<td>California encephalitis</td>
</tr>
</tbody>
</table>
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, paresthesias in hand (dog bite) x 2 days
- Later that day, agitation, hypersalivation, hydrophobia
- Coma and death five days later

Arboviral Encephalitis Prevention

Rabies

- 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

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)

Average Mortality in Patients with Symptomatic Encephalitis (according to viral etiology)

- Rabies
- HSV - untreated
- HSV - treated
- JBE - overall
- JBE - children
- TBE - RSSE
- TBE - CE
- SLE
- EEE
- WEE
- La Crosse
- Flaviviruses
- Alpha-viruses

Mortality
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