Viral Encephalitis

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

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.

Definitions/Descriptions

- Encephalitis vs. Meningitis
- Viral meningitis
  - Fever, headache, n/v, malaise, stiff neck, photophobia
  - Enteroviruses, herpesviruses, “arboviruses,” acute HIV
- Viral encephalitis
  - Fever, headache, altered mental status, decreased consciousness, focal neurologic findings
  - Herpesviruses, “arboviruses,” enteroviruses (U.S.)
- Aseptic meningitis
- Meningoencephalitis
- Myelitis

Typical CSF findings in selected CNS infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pressure (cmH2O)</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>5-8</td>
<td>5-10</td>
<td>Lymph</td>
<td>70-110</td>
<td>15-40</td>
</tr>
<tr>
<td>Bacterial Meningitis</td>
<td>20-50</td>
<td>&gt;100,000</td>
<td>&gt;80% PMN</td>
<td>&lt;50 (may be normal early)</td>
<td>100-1000</td>
</tr>
<tr>
<td>Viral meningitis/encephalitis</td>
<td>1-20</td>
<td>10-500</td>
<td>Lymph (early PMN)</td>
<td>Normal</td>
<td>50-100</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>15-30</td>
<td>&lt;500</td>
<td>Lymph</td>
<td>&lt;50 (may be normal early)</td>
<td>50-300</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>15-30</td>
<td>10-200</td>
<td>Lymph</td>
<td>&lt;40 (may be normal early)</td>
<td>80-300</td>
</tr>
</tbody>
</table>

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

Viral causes of acute encephalitis/encephalomyelitis

- Virus Family               | Specific viruses
- (Adenoviridae)             | Adenovirus
- (Anelloviridae)            | LCMV (lymphohytic choriomeningitis virus), Lassa
- (Bunyaviridae)             | LaCrosse, Rift Valley
- (Filoviridae)              | Ebola, Marburg
- (Filoviridae complex)      | St. Louis, Marburg, West Nile, Japanese B, Tick-borne
- (Herpesviridae)            | HSV-1, HSV-2, ZEV, HIV-6, EBV, CMV, Herpes B
- (Paramyxoviridae)          | Measles, Hendra, Nipah
- (Picornaviridae)           | Poliovirus, Coxsackie virus, Echovirus
- (Rhabdoviridae)            | Rabies, Lyssavirus
- (Reoviridae)               | Eastern equine, Western equine, Venezuelan equine
- (Retroviridae)             | HIV
- (Togaviridae)              | Echovirus, Negri virus
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

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

Olfactory spread

- LF virus

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

Inhibition of viral replication
Release of inflammatory cytokines
Neuronal dysfunction/injury

activated microglia

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

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.

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

- 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)

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></td>
<td>Eastern Equine*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venezuelan Equine*</td>
</tr>
<tr>
<td>Flaviridae</td>
<td>Flavivirus</td>
<td>Japanese B antigenic complex</td>
</tr>
<tr>
<td></td>
<td></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>Tick-borne encephalitis</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>Bunyavirus</td>
<td>LaCrosse*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>racRNA reg. segmented, env</td>
</tr>
<tr>
<td></td>
<td></td>
<td>California encephalitis</td>
</tr>
</tbody>
</table>

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

- Clinical
  - Short incubation period (4-10 days)
  - Occurs late spring through early fall
  - Wide clinical spectrum: asymptomatic (most), to mild flu-like illness, to aseptic meningitis, to encephalitis (subtle mental status changes to severe confusion, coma)
- Diagnosis – isolate viral antigen or nucleic acid in CSF, serology
- Treatment -- supportive

Clinical scenario #2

- 66 yo man from Staten Island experiences onset in June of fever, chills, headache, nausea, vomiting, muscle aches, fatigue, muscle weakness, dizziness
- Two weeks later, abrupt onset of double vision and mental status changes

West Nile Virus

A flavivirus, ssRNA, enveloped

U.S. WNV Activity 2004

West Nile Virus in the United States, 1999 - 2002

Science Times

Clues to an Alien Virus

Securities Exchange to Crack the Mysteries of West Nile

Isolation Human disease cases (x)
African animal or monkey cases (x)
Cone Island, New York
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 prevention

- Personal protective measures
- Vector control
- Vaccination

Clinical scenario #4

- 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

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

- Rabies
- HSV - untreated
- HSV - treated
- JBE - overall
- JBE - children
- TBE - RSSE
- TBE - CE
- WestNile
- EEE
- WEE
- LaCrosse

Mortality

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 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