Author(s): David Miller, M.D., Ph.D., 2009

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Central Nervous System (CNS) Viruses

M1 Infectious Diseases/Microbiology Sequence

David J. Miller, M.D., Ph.D.
Objectives

• Appreciate both common and unique features of CNS virus pathogenesis

• Recognize the importance of early diagnostic testing and empiric therapy for suspected herpes simplex virus encephalitis

• Know the arbovirus life cycle and those pathogens endemic in the U.S.

• Know the indications and procedures for rabies post-exposure prophylaxis

Reading assignment: Schaechter’s 4th edition, chapters 32, 33, 35, and 41
## CNS viruses

<table>
<thead>
<tr>
<th>Group</th>
<th>Examples</th>
<th>Onset</th>
<th>Non-Human Vector</th>
<th>Seasonal</th>
<th>Diagnosis</th>
<th>Antiviral Rx</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteroviruses</td>
<td>Coxsackie viruses Echovirus Poliovirus</td>
<td>Acute to subacute</td>
<td>None</td>
<td>Yes</td>
<td>• Clinical • CSF exam/PCR • Culture</td>
<td>No</td>
<td>No (except polio)</td>
</tr>
<tr>
<td>Herpes virus</td>
<td>Herpes simplex virus (HSV) Herpes B virus</td>
<td>Acute (Latency)</td>
<td>None</td>
<td>No</td>
<td>• Clinical • CSF exam/PCR • EEG/MRI</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Arboviruses</td>
<td>West Nile virus (WNV) Eastern equine encephalitis virus (EEEV) La Crosse virus (LACV)</td>
<td>Acute</td>
<td>Insects</td>
<td>Yes</td>
<td>• Clinical (exposure) • CSF exam/PCR or serologies</td>
<td>No</td>
<td>No for most</td>
</tr>
<tr>
<td>Rabies</td>
<td>-</td>
<td>Subacute to chronic</td>
<td>Animals</td>
<td>No</td>
<td>• Clinical syndrome including exposure • Skin biopsy • CSF/peripheral serologies • Postmortem exam</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Common characteristics of CNS virus infections

• **Clinical presentation**
  – Typically acute onset
  – Healthy hosts are often afflicted
  – Frequently occurs as meningoencephalitis
    • Meningitis – fever, headache, stiff neck
    • Encephalitis – meningitis with mental status changes (seizures, decreased consciousness, confusion)
    • Myelitis – focal neurological signs localized to spinal cord

Continuum of viral CNS infections

- Pure encephalitis (Rabies virus)
- **Meningoencephalitis** (Most infections)
- Pure meningitis (Coxsackie virus)
Common characteristics of CNS virus infections

Diagnosis

- Clinical presentation
- CSF exam essential
  - Lymphocytic pleocytosis (100-2,000)
  - Occasionally increased RBCs (esp. HSV)
  - Increased protein, normal glucose
  - Gram stain negative
  - Identification of virus (Cx, PCR) or intrathecal IgM response diagnostic
- Peripheral serologies
  - Often not helpful in acute setting (except IgM)
  - Convalescent titer helpful retrospectively
CNS virus pathogenesis

Exposure

Dissemination

CNS Entry

Inflammation

Clinical Disease

Pathogenic event
- Epithelial layer disruption
- Local replication

Viremia
- Secondary amplification

Blood-brain barrier disruption
- Axonal transport

Direct and indirect cell damage

Target cells
- (neurons, glial cells, endothelial cells)
29 year old male presents to the emergency room in July because of increasing headache and stiff neck for the past 2 days. He also complains of low grade fever and eye pain, but no mental status changes or focal neurological deficits. The patient works at a preschool, and one week ago he had a “cold” that went away without treatment. When you walk into the ER room and turn on the lights to evaluate him he gives you the “evil eye”, rapidly puts his hands over his face, and wants to know when he will get his pain medication. His physical exam is unremarkable except for temperature of 38.4°C, mild neck stiffness, and photophobia.
29 year old male presents to the emergency room in *July* because of increasing *headache and stiff neck* for the *past 2 days*. He also complains of low grade fever and eye pain, but *no mental status changes or focal neurological deficits*. The patient works at a *preschool*, and one week ago he had a “*cold*” that went away without treatment. When you walk into the ER room and turn on the lights to evaluate him he gives you the “evil eye”, rapidly puts his hands over his face, and wants to know when he will get his *pain medication*. His physical exam is unremarkable except for temperature of 38.4°C, mild *neck stiffness*, and *photophobia*.

*What do you do next?*
CSF profile

Tube #1 – 152 WBC, 95% mononuclear
  0 RBC
Tube #4 – 202 WBC, 90% mononuclear
  5 RBC

Protein - 85 mg/dL
Glucose – 72 mg/dL
Gram stain negative

Diagnosis?
Enteroviruses

- **Family**: *Picornaviridae*
  - Other members: rhinovirus, hepatitis A virus
- **Non-enveloped, single-stranded (+) RNA virus**
- **Multiple members responsible for CNS infections**
  - Poliovirus
  - Coxsackie viruses (A and B)
  - Enteroviruses (68, 70, 71 …etc.)

Coxsackie A virus
CNS Enterovirus Pathogenesis

• **Exposure route/dissemination**
  – Gastrointestinal or respiratory
  – Primary replication in Peyer’s patches

• **CNS entry**
  – Transfer across endothelial barrier vs. retrograde neuronal transport

• **Cell damage**
  – Direct cell lysis
    • motor neuron, medulla oblongata
  – Immune-mediated
**Enterovirus Clinical Manifestations**

- **Epidemiology**
  - Seasonal (summer-fall), outbreaks

- **Primary symptoms**
  - Encephalitis/myelitis with polio and EV71
    - Potentially severe and lethal
    - Location-dependent
  - Meningitis with others
    - Usually mild although it can be prolonged (>week)
  - Respiratory/GI prodrome seen

- **Associated syndromes**
  - Herpangina (coxsackie A virus)
  - Pleurodynia (coxsackie B virus)
  - Myocarditis (coxsackie A or B virus)
  - Hemorrhagic conjunctivitis (coxsackie A or EV70)
Enterovirus Susceptibility

- Normal healthy people at risk

- Neonates at risk for overwhelming disease
  - Sepsis after intrapartum or perinatal exposure

- Immunocompromised at risk for chronic meningoencephalitis
  - Immunoglobulin deficiency
  - Antibody response the primary mechanism for virus clearance
Enterovirus Diagnosis, Treatment, and Prevention

• **Diagnosis**
  – Clinical suspicion, epidemiology
  – CSF profile
  – CSF culture, PCR
  – Serologies of limited value

• **Treatment**
  – Symptomatic (pain control, hydration)
  – Pleconaril for neonatal disease
    • Compassionate use

• **Prevention**
  – Vaccine available for poliovirus only
    • Inactivated vaccine (Salk) recommended for use in U.S. since 2000
  – Prophylactic IVIG for chronic immunoglobulin deficiency patients
78 year old female was brought to the emergency room by her daughter because of confusion. Over the past week the patient has been progressively forgetful, but it was thought by the family just to be normal “Alzheimer’s”. However, the past 2 days she has had low grade fevers, mild headache, and has been hallucinating and complaining of strange smells. In the ER she has a generalized seizure. On exam she has a low grade temperature (38.1°C), her vital signs are stable, but she is postictal and minimally responsiveness. CSF exam shows 350 WBCs (90% mononuclear), 2,500 RBCs, normal glucose, and elevated protein (100 mg/dL). Non-contrast head CT is negative. MRI is obtained.
78 year old female was brought to the emergency room by her daughter because of **confusion**. Over the past **week** the patient has been progressively forgetful, but it was thought by the family just to be normal “Alzheimer’s”. However, the past 2 days she has had **low grade fevers**, **mild headache**, and has been **hallucinating** and complaining of **strange smells**. In the ER she has a **generalized seizure**. On exam she has a low grade temperature (38.1°C), her vital signs are stable, but she is postictal and minimally responsiveness. CSF exam shows **350 WBCs** (90% mononuclear), **2,500 RBCs**, normal glucose, and elevated protein (100 mg/dL). Non-contrast head CT is negative. MRI is obtained.

**Diagnosis?**
Herpes Simplex Virus (HSV) Encephalitis

- **Family:** *Herpesviridae*
  - Full lecture on this family later in course

- Both HSV-1 and HSV-2 can cause CNS disease

- Most common cause of sporadic (non-epidemic) viral encephalitis in the U.S.
HSV Encephalitis Pathogenesis

• **Exposure route/dissemination**
  – Primary exposure (cutaneous)
  – Reactivation from latency (sensory ganglion)

• **CNS entry**
  – Direct neuronal spread

• **Cell damage**
  – Direct cell lysis and inflammatory responses
HSV Encephalitis Clinical Manifestations

• Epidemiology
  – Approximately 1,500 cases per year in U.S.
  – Mortality rate without treatment >70%

• Primary symptoms
  – Fever, headache
  – Progressive neurological symptoms
  – Focal symptoms represent region of brain involvement (temporal lobe common)
  – Mental status changes frequent
  – Seizures

• Meningitis and myelitis also seen
  – Primary genital HSV
  – Recurrences possible (Mollaret’s meningitis)

• Long-term neurological sequelae possible
  – Especially without prompt therapy
HSV Encephalitis Diagnosis, Treatment, and Prevention

• **Diagnosis**
  – Clinical suspicion (ACT quickly!)
  – CSF profile
    • Lymphocytic pleocytosis, increased RBCs common, high protein
  – CSF PCR is gold-standard diagnostic test
  – Peripheral serologies useless
  – MRI helpful if positive but not specific for HSV
  – EEG also helpful but not specific
    • Localized spike and slow wave pattern

• **Treatment**
  – Acyclovir – start empirically with meningitis antibacterials if any clinic suspicion

• **Prevention**
  – No vaccine available
6 year old male was brought to the emergency room in August by his parents with new onset seizures. He has no past medical history and takes no medications. The seizure started earlier today and came on without any prodromal symptoms. No one else has been sick. The family raised horses and the father noted that several have been acting “funny” lately, but he hasn’t called the veterinarian. CSF profile shows a mild lymphocytic pleocytosis and elevated protein, bacterial gram stain is negative, and non-contrast head CT is unremarkable. Head MRI shows diffuse inflammatory changes. Patient is started on broad-spectrum antibiotics and anti-seizure medications, but despite aggressive supportive care never regains consciousness and dies one week later.
6 year old male was brought to the emergency room in August by his parents with new onset seizures. He has no past medical history and takes no medications. The seizure started earlier today and came on without any prodromal symptoms. No one else has been sick. The family raised horses and the father noted that several have been acting “funny” lately, but he hasn’t called the veterinarian. CSF profile shows a mild lymphocytic pleocytosis and elevated protein, bacterial gram stain is negative, and non-contrast head CT is unremarkable. Head MRI shows diffuse inflammatory changes. Patient is started on broad-spectrum antibiotics and anti-seizure medications, but despite aggressive supportive care never regains consciousness and dies one week later.

Diagnosis?
Arboviruses

- **Arthropod-borne viruses**

- 534 registered arboviruses
  - 134 documented human pathogens

- Major vectors

![Mosquito and Tick Images]
Arbovirus Families

- Flaviviruses (single-stranded positive-sense RNA viruses)
  - *West Nile virus*
  - *St. Louis encephalitis virus*
  - *Japanese encephalitis virus*
  - Yellow fever virus
  - Dengue virus

- Togaviruses (single-stranded positive sense RNA viruses)
  - *Eastern, western, and Venezuelan equine encephalitis viruses*

- Bunyaviruses (segmented single-stranded negative sense RNA viruses)
  - *La Crosse virus*
  - Rift Valley fever virus
Arbovirus Transmission Cycle

- **Endemic vector**
  - "Promiscuous" mosquito (bridge or epidemic vector)

- **Enzootic Cycle**
  - Reservoir host (eg. birds, rodents, primates)

- **Epizootic Transmission**
  - Incidental hosts (eg. horses, humans)

- **Clinical disease**

**Resources**
- (Horse) Thomas Springer ([wikimedia commons](https://commons.wikimedia.org/wiki/user:johnspringer))
- (Squirrel) Krötzsch ([wikimedia commons](https://commons.wikimedia.org/wiki/user:krotzsch))
- (Bird) US National Park Service, White Sands National Monument
- (Mosquito) Prof. Frank Hadley Collins, James Gathany CDC PHIL #9178
Arboviral Diseases in Humans

**Systemic febrile illness**
- West Nile virus
- Dengue virus
- Rift Valley fever virus
- Chikungunya virus

**Hemorrhagic fever**
- *Yellow fever virus*  
  *(Drs. Carlos Finlay and Walter Reed, 1900)*
- Dengue virus
- Rift Valley fever virus

**Encephalitis**
- West Nile virus
- Japanese encephalitis virus
- Eastern equine encephalitis virus
- La Crosse virus
Arbovirus Meningoencephalitis
Pathogenesis

- **Exposure route/dissemination**
  - Replication within insect vector required
  - Primary exposure is cutaneous
  - Respiratory transmission demonstrated experimentally
  - Local replication followed by viremia

- **CNS entry**
  - Hematogenous
    - Traverse BBB endothelium through unknown mechanism
  - Direct neuronal spread for respiratory exposure (olfactory bulb)

- **Cell damage**
  - Neurons are primary targets for many viruses
  - Direct cell death and inflammatory responses
Arbovirus Epidemiology

• Seasonal (summer/fall)

• Incidence varies with virus and time

• Extremes of age more susceptible to severe disease

• Mortality rate varied with virus
  – Eastern equine encephalitis virus (EEEV) ~50%
  – West Nile virus (WNV) ~10%
  – La Crosse virus (LACV) <1%
Arbovirus Meningoencephalitis Clinical Manifestations

• **Primary symptoms**
  – Most infections asymptomatic or produce non-specific “viral syndrome”
  – Fever, headache, seizures
  – Neuronal targets dictate clinical symptoms
    • Anterior motor neurons (WNV) – poliomyelitis
    • Basal ganglia neurons (JEV) – Parkinsonian Sx

• **Long-term neurological sequelae possible**
Arbovirus Meningoencephalitis
Diagnosis, Treatment, and Prevention

• Diagnosis
  – Clinical suspicion
  – Social history/exposure/travel provide important clues
  – CSF profile
    • Lymphocytic pleocytosis, high protein
  – CSF PCR, intrathecal IgM
  – Acute and convalescent serologies useful for epidemiology

• Treatment
  – Supportive

• Prevention
  – Inactivated vaccine available for JEV
  – Live attenuated YFV vaccine also available
  – Vector control efforts
Arboviruses as Potential Bioweapons

• High morbidity and mortality
• No effective treatments (limited prevention)
• Potential for aerosol transmission
• Public anxiety elicited by insect-borne infectious diseases (especially central nervous system infections)
• Genetics are easily manipulated
• Simplified large-scale production and purification
• CDC/NIAID category B agents
A patient of yours calls you at 3 AM in a panic. They just found a live bat in their 1 year old daughter’s room and they are terrified about rabies. The bat was quickly removed by opening the window and they don’t think their child was bitten (she was still sleeping). They want to know what to do.

What do you tell them?
Rabies Virus Encephalitis

- Family: *Rhabdoviridae*
- Large enveloped virus
- Single-stranded negative sense RNA genome
Rabies Virus Encephalitis
Pathogenesis

• Exposure route
  – Peripheral lesion with saliva exposure
  – Long incubation period (weeks to years)

• CNS entry
  - Retrograde axonal transport from peripheral nerves
  - Temporal pattern of presentation depends in part on length of inoculation site from CNS

• Dissemination
  – Anterograde transport often back through same axon
  – Highly innervated salivary gland frequently involved

• Neuronal damage
  – Direct virus-induced injury with MINIMAL inflammatory responses
  – Mild histopathological changes contrast to dramatic clinical symptoms
Rabies Virus Encephalitis Clinical Manifestations

• Epidemiology
  – Disease recognized for thousands of years (2300 B.C.)
  – Only handful of cases in U.S. per year
  – More common in underdeveloped countries
  – Only 10-20% of “true” exposures will result in disease

• Reservoir (U.S.)
  – Bats, skunks, raccoons, and foxes
    • 32/35 U.S. cases (1958-2000) from bats
    • 26/32 cases without known bat bite
  – Rodents, lagomorphs, and domestic dogs/cats almost never infected

• Primary symptoms
  – Fever, dysphagia, hydrophobia, increased muscle tone
  – Progression to coma and death
Negri body
Rabies Virus Encephalitis Diagnosis, Treatment, and Prevention

• **Diagnosis**
  – Clinical suspicion with exposure history
  – CSF profile (cell count, glucose, protein) often unhelpful
  – CSF/tissue PCR
  – DFA of neck skin biopsies
  – Serologies can be helpful

• **Treatment**
  – None (universally fatal once symptoms develop)

• **Prevention**
  – Louis Pasteur developed first vaccine in late 1800’s
  – Vaccination (inactivated virus) and post-exposure prophylaxis
Other CNS viruses

• Other herpes viruses
  – Epstein-Barr virus (EBV)
  – Cytomegalovirus (CMV)
  – Varicella zoster virus (VZV)
  – Human herpes virus 6 (HHV-6)
  – Herpes B virus (simian herpesvirus)

• Mumps virus

• Measles virus

• Lymphocytic choriomeningitis virus (LCMV)

• Human immunodeficiency virus (HIV)
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