open.michigan

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

Citation Key

for more information see: http://open.umich.edu/wiki/CitationPolicy

Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

Public Domain – Government: Works that are produced by the U.S. Government. (17 USC § 105)

Public Domain – Expired: Works that are no longer protected due to an expired copyright term.

Public Domain – Self Dedicated: Works that a copyright holder has dedicated to the public domain.

Creative Commons – Zero Waiver

Creative Commons – Attribution License

Creative Commons – Attribution Share Alike License

Creative Commons – Attribution Noncommercial License

Creative Commons – Attribution Noncommercial Share Alike License

GNU – Free Documentation License

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

Public Domain – Ineligible: Works that are ineligible for copyright protection in the U.S. (17 USC § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

Fair Use: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (17 USC § 107) *laws in your jurisdiction may differ

Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.

To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.

Central Nervous System (CNS) Viruses

M1 Infectious Diseases/Microbiology Sequence

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

Spring 2010

University of Michigan
Medical School

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**

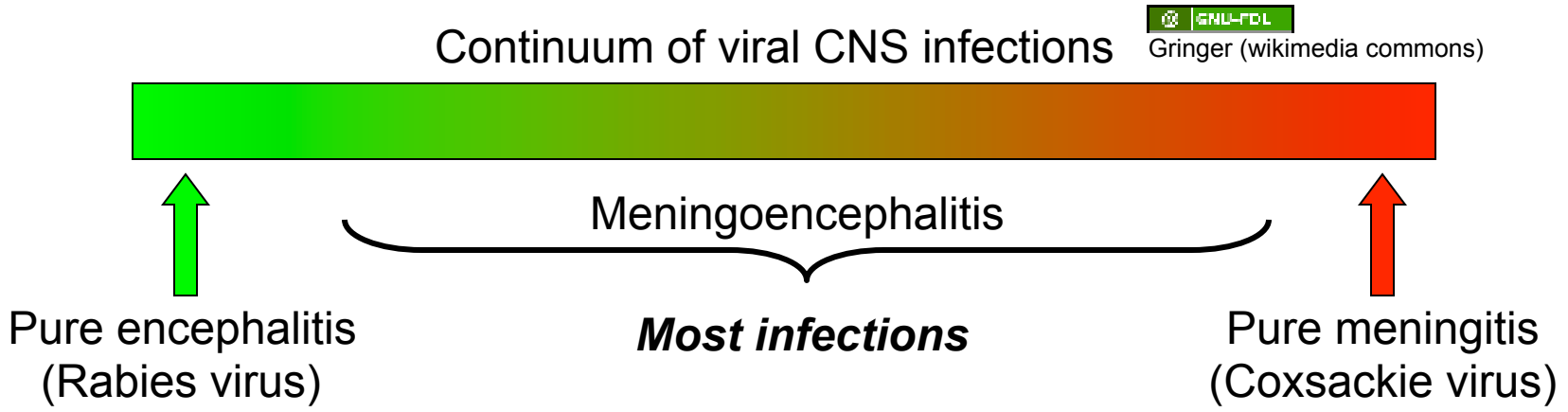
Reading assignment: Schaechter's 4th edition, chapters 32, 33, 35, and 41

CNS viruses

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

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



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

Pathogenic event

Exposure

Epithelial layer disruption
Local replication

↓

Dissemination

Viremia
Secondary amplification

↓

CNS Entry

Blood-brain barrier disruption
Axonal transport

↓

Inflammation

Direct and indirect
cell damage

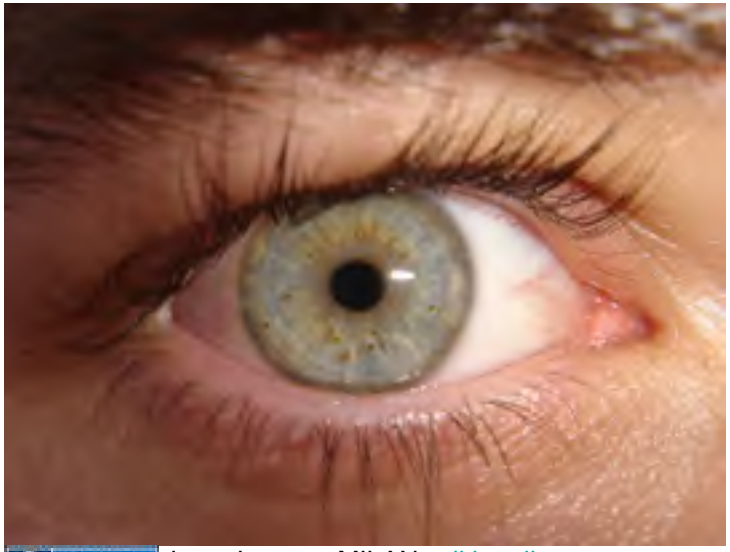
↓

Clinical Disease

↓

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.



PD-SELF Jean-Jacques MILAN, wikimedia commons

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?

PD-INCL

Source Undetermined

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.)

PD-GOV CDC PHIL #5630

Coxsackie A virus

CNS Enterovirus Pathogenesis

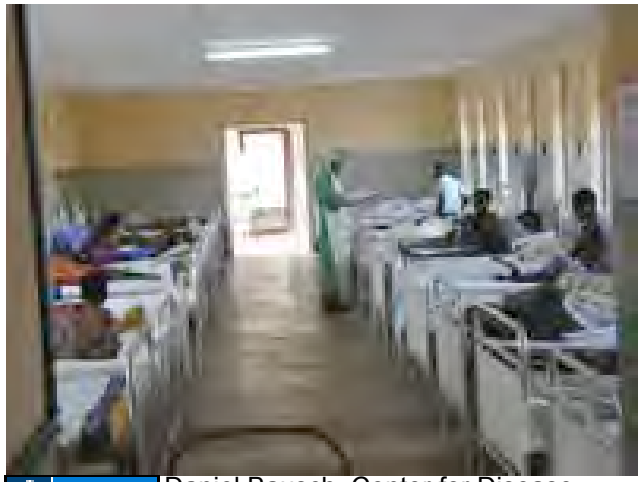
- **Exposure route/dissemination**
  - Gastrointestinal or respiratory
  - Primary replication in Peyer's patches
- **CNS entry**
  - Transfer across endothelial barrier vs. retrograde neuronal transport
- **Cell damage**
  - Direct cell lysis
    - motor neuron, medulla oblongata
  - Immune-mediated

PO-INEL Source Undetermined

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)

Patrick J. Lynch ,Carl Jaffe
wikimedia commons



Daniel Bausch, Center for Disease Control and Prevention

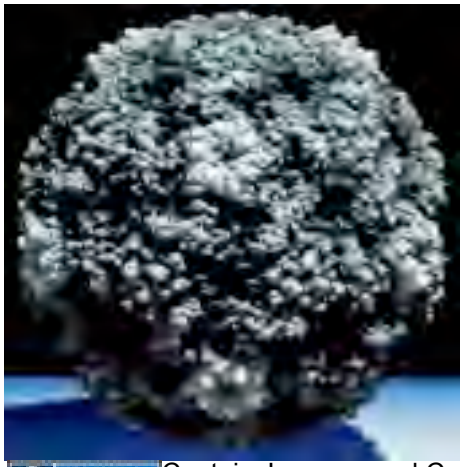
Enterovirus Susceptibility

- 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

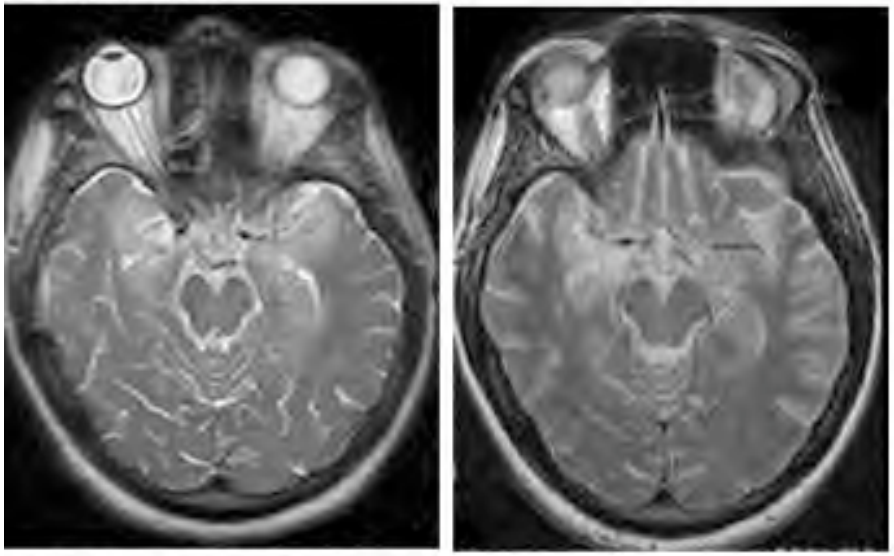


Captain Janeway and Captain Kirk, wikimedia commons

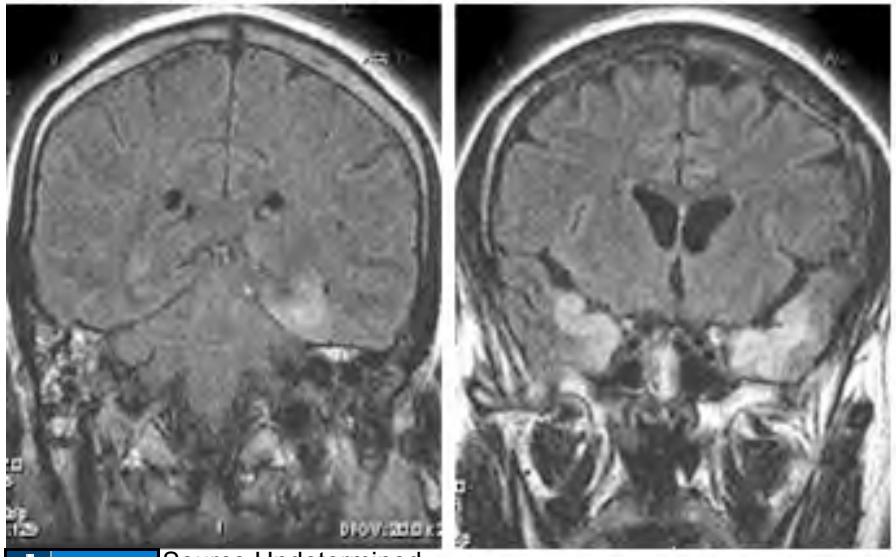
- **Prevention**
  - Vaccine available for poliovirus only
    - Inactivated vaccine (Salk) recommended for use in U.S. since 2000
  - Prophylactic IVIG for chronic immunoglobulin deficiency patients

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.

Axial T2



Coronal FLAIR



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

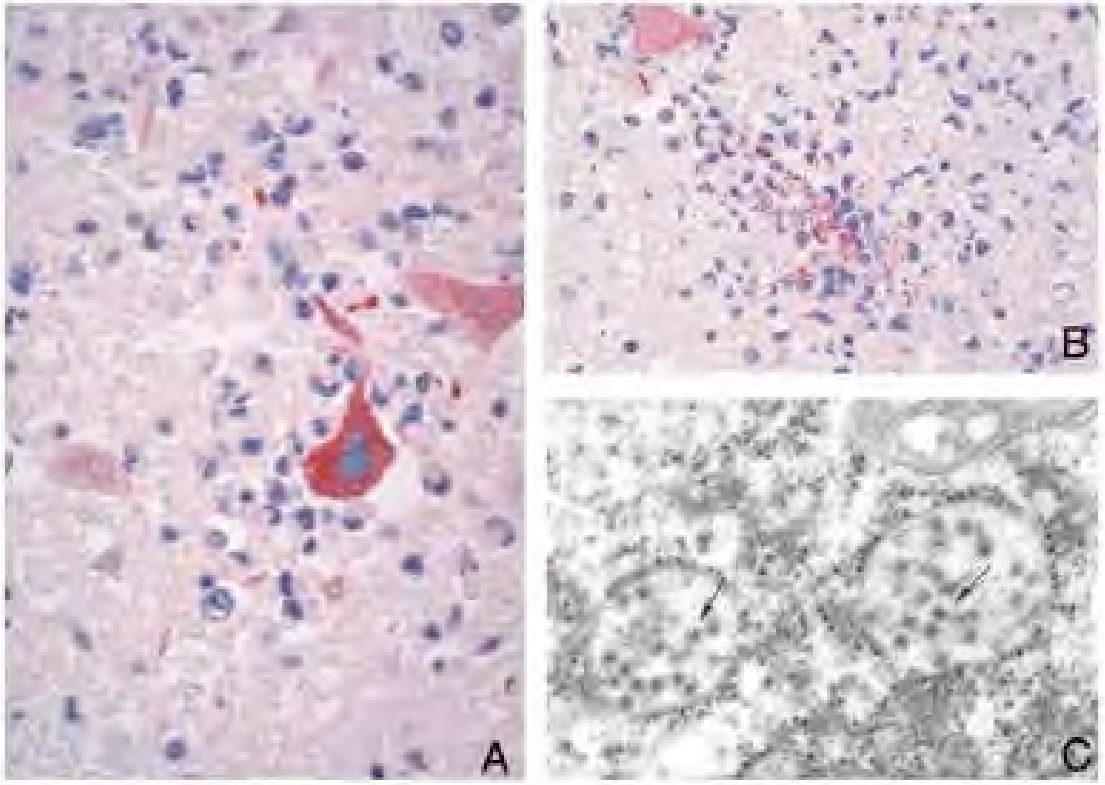
HSV Encephalitis Diagnosis, Treatment, and Prevention

- **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.

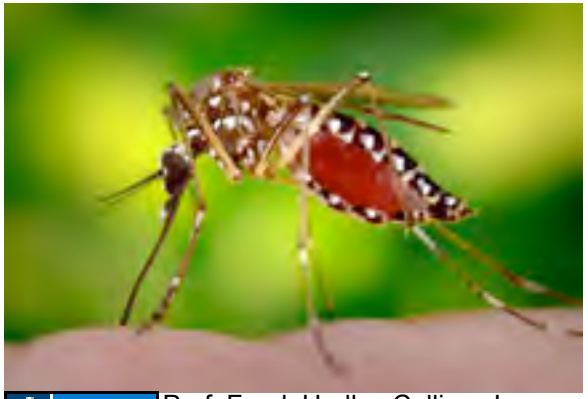


6 year old male was brought to the emergency room in *August* by his parents with *new onset seizures*. He has *no past medical history* and takes no medications. The seizure started earlier today and came on *without any prodromal symptoms*. No one else has been sick. The family raised *horses* and 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

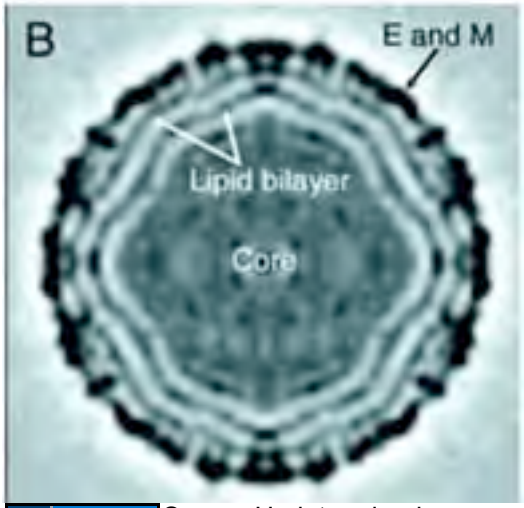


PD-GOV Prof. Frank Hadley Collins, James Gathany, CDC PHIL # 9178

PD-GOV Dr. Christopher Paddock, CDC PHIL #10877, James Gathany

Arbovirus Families

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



PD-TNCL Source Undetermined

- 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)

Epizootic
Transmission

Incidental
hosts
(eg. horses,
humans)

Enzootic
Cycle

Reservoir
host
(eg. birds,
rodents,
primates)

Clinical
disease

Arboviral Diseases in Humans

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

Lyle Conrad, Joel G. Breman, CDC PHIL # 7201

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

Source Undetermined

Encephalitis
West Nile virus
Japanese encephalitis virus
Eastern equine encephalitis virus
La Crosse virus

Source Undetermined

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 symtpoms
    - 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

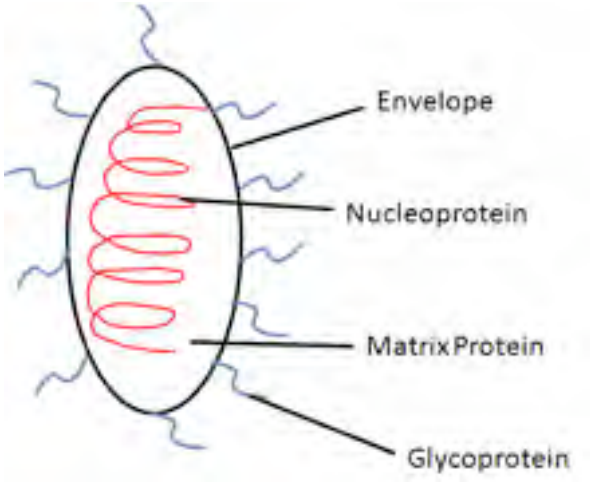
PD-GOV Henry Mathews, CDC PHIL #1402

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

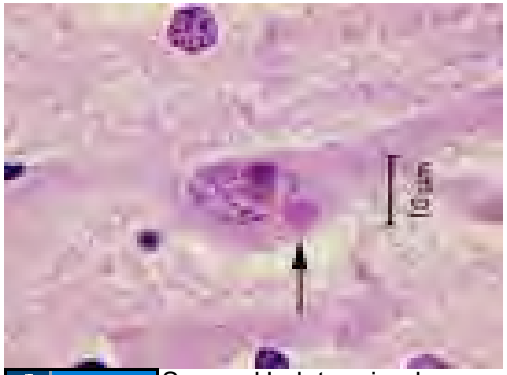
- **Neuronal damage**
  - Direct virus-induced injury with *MINIMAL* inflammatory responses
  - Mild histopathological changes contrast to dramatic clinical symptoms

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 bit
  - Rodents, lagomorphs, and domestic dogs/cats almost never infected
- **Primary symptoms**
  - Fever, dysphagia, hydrophobia, increased muscle tone
  - Progression to coma and death

PD-GOV CDC PHIL #6113

PD-GOV CDC PHIL #2539



PD-INCL Source Undetermined

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)**

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 5: David Miller
Slide 6: Gringer, Wikimedia Commons, http://en.wikipedia.org/wiki/GNU_Free_Documentation_License
Slide 8: Source Undetermined
Slide 10: Jean-Jacques MILAN, Wikimedia Commons, http://commons.wikimedia.org/wiki/File:My_eye.jpg
Slide 12: Source Undetermined
Slide 13: CDC PHIL #5630
Slide 14: Source Undetermined
Slide 15: Patrick J. Lynch ,Carl Jaffe, Wikimedia Commons, http://commons.wikimedia.org/wiki/File:Brain_bulbar_region.svg, CC:BY, http://creativecommons.org/licenses/by/2.5/deed.en Daniel Bausch, Center for Disease Control and Prevention
Slide 17: Captain Janeway and Captain Kirk, Wikimedia Commons, http://commons.wikimedia.org/wiki/File:BEV_Structure.jpg
Slide 19: Source Undetermined
Slide 26: Source Undetermined
Slide 28: Prof. Frank Hadley Collins, James Gathany, CDC PHIL # 9178; Dr. Christopher Paddock, CDC PHIL #10877, James Gathany
Slide 29: Source Undetermined
Slide 30: (Mosquito) Prof. Frank Hadley Collins, James Gathany CDC PHIL #9178; (Bird) US National Park Service, White Sands National Monument; (Squirrel) Krötzsch, Wikimedia Commons, http://commons.wikimedia.org/wiki/File:Sciurus_niger_(on_fence).jpg, http://commons.wikimedia.org/wiki/Commons:GNU_Free_Documentation_License; (Horse) Thomas Springer, Wikimedia Commons, http://commons.wikimedia.org/wiki/File:Fellpony2.jpg, http://commons.wikimedia.org/wiki/Commons:GNU_Free_Documentation_License
Slide 31: Lyle Conrad, Joel G. Breman, CDC PHIL # 7201; Source Undetermined; Source Undetermined
Slide 36: Henry Mathews, CDC PHIL #1402
Slide 38: Source Undetermined; Regents of the University of Michigan, CC:BY, http://creativecommons.org/licenses/by/3.0/
Slide 41: CDC PHIL #6113; CDC PHIL #2539; Source Undetermined