Viruses causing CNS disease
Mechanisms of Human Disease

TM Gallagher

LECTURE OUTLINE – CNS VIRUSES

1. Virus entry into the CNS
2. Herpes viruses
3. Entero viruses
4. Arbo viruses
5. Measles
6. Rabies
7. Unconventional agents
Viruses from many different families can cause neurological diseases.

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**STEPS REQUIRED FOR NEURONAL VIRUS INFECTION**

1. **Enter** the neuron at the axon, sensory terminal or cell body, depending on the site of infection.

2. **Transport** the virus particle or subviral particle to the neuronal cell body where virus replication occurs.

3. **Replicate** the virus genome.

4. **Assemble** virus particles that **egress** from the infected neuron in a directional manner.

**HERPES SIMPLEX VIRUS INFECTIONS**
Olfactory neurons are unique CNS cells because their dendrites are exposed in the olfactory epithelia.

Retrograde transport brings herpes viruses from peripheral sites to CNS.
Anterograde transport brings herpes viruses back from CNS to peripheral sites.
Herpes viruses are set apart by their ability to transport in neurons bi-directionally in neurons.

HERPES SIMPLEX
- Often latent in neurons, but can be reactivated
- Reactivated virus transport to epithelia (as depicted here) --- epithelial lesions
- Reactivated virus transport into CNS --- lethal encephalitis
**HERPES SIMPLEX ENCEPHALITIS - BRAIN SECTIONS**

**Table 1. Usual Composition of the Cerebrospinal Fluid in Various Infections**

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Acute Bacterial</th>
<th>Fungal and Viral</th>
<th>Herpes Encephalitis</th>
<th>Brain Abscess</th>
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<tbody>
<tr>
<td>Leukocytes (no. / μl)</td>
<td>0-6</td>
<td>&gt;1000</td>
<td>100-500</td>
<td>10-1000</td>
<td>10-500</td>
</tr>
<tr>
<td>% Neutrophils</td>
<td>0</td>
<td>&gt;50</td>
<td>&lt;10</td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Red blood cells (no. / μl)</td>
<td>0-2</td>
<td>0-10</td>
<td>0-2</td>
<td>10-500</td>
<td>10-100</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>40-80</td>
<td>&gt;30</td>
<td>&lt;30</td>
<td>&gt;30</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Protein (mg/dl)</td>
<td>20-50</td>
<td>&gt;100</td>
<td>50-100</td>
<td>&gt;75</td>
<td>50-100</td>
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*Diagnostic values refer to the ratio of glucose levels in the blood to those in the CSF.*

Perform PCR to determine whether HSV DNA is in the CSF.

**During CNS infections, peripheral blood may not show signs of inflammation, but cerebrospinal fluid often does.**

**A tough USMLE 1 question: Best answer is HSV encephalitis**

A 24 year old man is brought to the physician by his wife after he had two days of progressive confusion. His temperature is 101°F but has no other abnormalities. When he speaks, he enunciates clearly and his phrasing is of average length. However he uses words and word-like utterances in a manner that makes little sense. He doesn’t follow any commands. What is the likeliest diagnosis?

1. cerebral toxoplasmosis
2. herpes simplex encephalitis
3. hiv encephalopathy
4. meningococcal meningitis
5. subdural empyema
Viruses from many different families can cause neurological diseases

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Enterovirus infection, 
Primarily meninigitis
Sometimes spinal cord involvement, 
and myelitis / paralysis

USMLE 3 Q-Bank Question:
An 18-year-old female had an episode of mild intestinal infection. Approximately 6 days later, she developed severe headaches, vomiting and fever. She was alert and oriented but had mild nuchal rigidity. A spinal tap revealed CSF high in cell count and protein level. Bacteriological culture of the CSF resulted in no growth. The physician’s report indicated aseptic meningitis. Electron microscopic analysis of CSF particles would MOST likely reveal which of the following?
A. Enveloped viruses with globular projections
B. Naked icosahedral viruses with projections at each vertex
C. Minute naked viruses
D. Bullet shaped viruses with surrounding envelopes
E. Double-shelled icosahedral viruses
Answer is “C”
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**FLAVIVIRUS INFECTIONS:** (West Nile; Dengue Fever)

**Meningitis vs Encephalitis**

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ARBOVIRUS INFECTIONS (equine encephalitis virus, St. Louis encephalitis virus, La Crosse encephalitis virus, West Nile virus…)

West Nile Virus (WNV) is the most common:

-- In 2008, 1379 reported WNV cases; 37 deaths.
-- Age risk groups are adults over age 50 and immunocompromised.
-- Estimated that < 1% of WNV infections cause recognizable disease.
-- Disease symptoms include fever, headache, stiff neck, disorientation, muscle weakness, paralysis.

WEST NILE ARBOVIRUS INFECTIONS
Endemic in insects and bird vectors, on entering humans, highly virulent, causing meningitis

West Nile Virus Transmission Cycle

www.cdc.gov

Zika Virus

ORIGINAL ARTICLE Zika Virus Associated with Microcephaly
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Table 3. Forms of involvement of the CNS in connection with measles

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<th>Type</th>
<th>Characteristic features</th>
<th>Etiology</th>
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<td>No detectable virus; appearance a short time after rash; perivascular inflammatory</td>
<td>Postulated autoimmune reaction against brain tissue</td>
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<td>encephalitis</td>
<td>changes and demyelination</td>
<td></td>
</tr>
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<td>Acute progressive</td>
<td>Presence of complete virus; cytolytic replication in brain tissue; inflammation</td>
<td>Nonrestricted virus replication due to the absence of normal cell-bound</td>
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<td>immunity</td>
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<td>SSPE</td>
<td>Develops many years after acute disease; presence of viral inclusion bodies in brain</td>
<td>Progressive dissemination of a defective virus infection in the presence</td>
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<td>cells; inflammation; general destruction of brain tissue</td>
<td>of a normal immune response; no production of infectious extracellular</td>
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<td></td>
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USMLE Q: Bank Question:

Several conventional viruses and unconventional agents cause slow degenerative diseases of the central nervous system. Which virus best matches the following clinical vignette or disease description? A 17-year-old girl is diagnosed with subacute sclerosing panencephalitis. Her CSF has a high titer against a paramyxovirus, which can be rescued by fusion with permissive cells. Viral particles are absent from a brain biopsy specimen.

A. Measles
B. Rubella
C. HIV
D. Polyoma
E. Prions

Answer is "A"

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Rabies virus particles
Uni-directional (retrograde) transport from peripheral sites to CNS

**PROGRESSION OF SYMPTOMS FROM RABIES INFECTION**

- Pneumothorax
- Intravascular thrombosis
- Secondary infections
- Pituitary dysfunction
- Hypovolemic shock
- Ventricular fibrillation or asystole
- Cardiac arrhythmia, cardiac arrest
- Coma
- Hyperventilation, hypoxia
- Aphasia, incoordination or other CNS signs
- Paresis, paralysis
- Hydrophobia, pharyngeal spasms
- Confusion, delirium, hallucinations
- Marked hyperactivity
- Anxiety, agitation, depression
- Fever
- Anorexia, nausea, vomiting
- Headache
- Malaise, lethargy
- Pain or paresthesias at site of bite

**Clinical State**

- Incubation Period: 20-90 days
- Prodrome: 2-10 days
- Acute Neurological Phase: 2-7 days
- Coma: 0-14 days
- Recovery: several months

**Exposure First Symptom**

- First neurological sign
- Onset of coma
- Death occurs or recovery begins

**VISS INJURY**

- Yes: Rabies vaccination
- No: Observation

**Make Sure to Wear Proper Personal Protective Equipment (PPE)**

- Yes: Appropriately don PPE
- No: Observation

**Has the Animal Died?**

- Yes: Observation
- No: Capture

**Capture the Animal**

- Yes: Appropriate restraint
- No: Observation

**Has the Animal Attacked You?**

- Yes: Observation
- No: Capture
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“INFECTIOUS” ENCEPHALOPATHIES

**Human**

Kuru

Creutzfeldt-Jakob disease (CJD)

Gerstmann-Sträussler-Scheinker (GSS disease)

Fatal familial insomnia (FFI)

**Animal**

Scrapie (sheep and goats)

Transmissible mink encephalopathy

Bovine spongiform encephalopathy (mad cow disease)

Chronic wasting disease (mule, deer, and elk)
Kuru Disease:

“Plaques” in Cerebellum

Forming “Prion” Plaques:

“Catalyst” is altered form of an endogenous protein

Altered proteins form aggregates

Aggregates accumulate in neurons
Fifteen unrelated men, all in their late twenties, developed progressive neurological disorders. Symptoms included presenile dementia and ataxia. Serum and CSF antibody were negative in ELISA tests against a battery of known neurotropic viruses. Each of the men had received, 10-15 years earlier, a series of growth-stimulating treatments with pituitary growth hormone. A preliminary diagnosis of Creutzfeldt-Jakob disease was made. The MOST likely cause of the illness is which of the following agents?

A. Slow virus
B. Unconventional agent
C. Classical virus
D. Latent virus
E. Virus

Answer is “B”