Neurotropic Flaviviruses

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Definition of Terms

- "Meningitis": Inflammation of the covering of the brain
- "Encephalitis": Inflammation of the brain itself
- "Meningoencephalitis"
- "Myelitis": Inflammation of the spinal cord
Neurotropic Flaviviruses

- Japanese encephalitis virus
- West Nile virus / Kunjin
- Dengue virus(es)
- Zika virus
- Saint Louis encephalitis virus
- Murray Valley encephalitis virus
- Tick Borne encephalitis virus
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## Japanese Encephalitis Serocomplex

<table>
<thead>
<tr>
<th>Virus</th>
<th>Geographic Distribution</th>
<th># cases / year</th>
<th>Human disease</th>
<th>Population at greatest risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese encephalitis virus</td>
<td>South and southeast Asia, China, Indonesia, northern Australia</td>
<td>Est. 70,000</td>
<td>Encephalitis, meningitis, anterior myelitis</td>
<td>Children</td>
</tr>
<tr>
<td>West Nile virus (including Kunjin)</td>
<td>Africa, Middle East, Europe, Americas, South / Southeast Asia, Australia</td>
<td>Approx. 1,000*</td>
<td>Encephalitis, Meningitis, anterior myelitis, fever, rash</td>
<td>Elderly, immunosuppressed</td>
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<td>* (&gt;3,000 during 2003 epidemic in US)</td>
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<tr>
<td>Saint Louis encephalitis virus</td>
<td>Americas</td>
<td>Occasional large outbreaks with hundreds of cases, but usually few sporadic cases</td>
<td>Encephalitis, Meningitis</td>
<td>Elderly, Immunosuppressed</td>
</tr>
<tr>
<td>Murray Valley encephalitis virus</td>
<td>Australia, Papua New Guinea</td>
<td>Few sporadic cases, occasional small outbreaks</td>
<td>Encephalitis</td>
<td>All ages</td>
</tr>
<tr>
<td>Feature</td>
<td>Japanese Encephalitis Virus</td>
<td>West Nile Virus</td>
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<tr>
<td><strong>Geographic area</strong></td>
<td>South / Southeast Asia, Pacific Rim, Northern Australia</td>
<td>Africa, Middle East, South Asia, Eastern Europe, Australia, North / Central / South America</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Main vectors</strong></td>
<td><em>Culex triaeniorhyncus, C. vishnui, C. pipiens</em></td>
<td><em>C. pipiens, C. tarsalis, C. quinquefasciatus</em></td>
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</tr>
<tr>
<td><strong>Main Vertebrate hosts</strong></td>
<td>Migrating birds, domestic fowl, pigs</td>
<td>Birds of family Corvidae and other passerine birds</td>
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</tr>
<tr>
<td><strong>Groups at risk</strong></td>
<td>Children in endemic areas, nonimmune adults</td>
<td>Elderly, immunocompromised</td>
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<tr>
<td><strong>Approximate Incidence</strong></td>
<td>50,000 – 70,000 cases annually in Asia</td>
<td>Sporadic cases in Africa, Europe; larger outbreaks (30 – 3000) in Middle East and North America</td>
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</tr>
<tr>
<td><strong>Ratio of symptomatic / asymptomatic infections</strong></td>
<td>1 in 25 (nonimmune adults); 1 in 250 – 1000 (children)</td>
<td>1 in 150</td>
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</tr>
<tr>
<td><strong>Patients presenting with encephalitis (%)</strong></td>
<td>60 - 75</td>
<td>58 - 62</td>
<td></td>
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<tr>
<td><strong>Case fatality rate (%)</strong></td>
<td>20 - 30</td>
<td>5 - 15</td>
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</tbody>
</table>

Adapted from Solomon, NEJM 2004;351(4):372
Japanese encephalitis (JE) Epidemiology

- Leading cause of viral encephalitis in Asia
- 50,000 – 70,000 cases reported annually to WHO
- Primarily in children
- Case fatality 20-30%
- 10,000-15,000 deaths estimated per year
- 30-50% of survivors have significant neurologic sequelae
Geographic range of Japanese encephalitis
West Nile Virus Epidemiology

• Isolation in 1937, West Nile district of Uganda

• **HISTORICALLY** (e.g., prior to 1996):
  • Infrequent outbreaks
  • Mild, dengue fever-like illness
  • CNS involvement rare
  • Wide distribution throughout Asia, Eastern Europe, Africa, Middle East
Asymptomatic Infection (likely)

~80% of infections

Generation of life-long immunity (presumed)
West Nile Fever
10-30% of infections
Fever, headache, rash, fatigue

Asymptomatic
~80%

“West Nile / JE Fever”
~20%

CNS disease
<1%

JEV / WNV Human Infection “Iceberg”
Asymptomatic ~80%  

~20% “West Nile / JE Fever”

<1% CNS disease

<1% of all infections

Meningitis, encephalitis, anterior myelitis

Neuroinvasive Disease (ND)
Clinical features of Japanese encephalitis / West Nile Virus

- Fever, headache, vomiting
  - Milder febrile illness, uncomplicated meningitis likely underestimated
- Altered mental status
- Movement disorders (25%)
- Cranial nerve palsy (10%)
- Generalized weakness
  - Anterior myelitis somewhat more common with WNV
- Seizures (more common with JEV)

JEV / WNV and Movement Disorders

- **Tremor**
  - Sometimes associated with other viral infections
  - Coarse; postural / kinetic
  - Occasionally functionally impairing

- **Myoclonus**
  - Quick, uncontrolled muscle twitching
  - Upper extremities, face
  - Bothersome to patients

- **Parkinsonism**
  - “Cogwheel” rigidity, bradykinesia, postural instability
  - Functionally impairing

- **OUTCOMES:** JE with poorer prognosis
  - Ongoing disability: JEV = 50%, WNV = 15-20%
JEV / WNV Anterior Myelitis

- Involvement of anterior horn cells -- acute, asymmetric paralysis (generally no sensory loss)

- Relatively infrequent - ~12% of cases of WNND; less frequent in JE

- May be younger in age, previously healthy

Sejvar et al. EID 2006
Dengue ‘Encephalitis’: the Case For and Against

- Dengue: flavivirus closely related to several other neurotropic viruses (WNV, JEV)
  - WNV, JEV – associated with hundreds of thousands of cases of neurotropic disease worldwide
  - Dengue – relatively few reports, despite its tremendous worldwide illness burden

- Many reports of ‘encephalitis’ unaccompanied by signs of CNS inflammation, or evidence of CNS viral invasion

- “Neurologic” signs associated with dengue may simply be temporally related; ‘causality’ difficult to substantiate
Challenges to Diagnosis of ‘Dengue Encephalitis’

- Lumbar puncture (LP) contraindicated in persons with hemorrhagic illness
- Vascular changes associated with dengue – difficult to differentiate true viral invasion or intrathecal IgM antibody detection from passive transfer across compromised blood-brain barrier
- Advanced neurodiagnostics (LP, neuroimaging, electroencephalography) often unavailable in dengue-endemic areas
Zika Virus

• Human illness identified in 1950’s, but associated with sporadic cases of mild rash illness
• 2007 – first sizeable outbreak in Yap
  • 100 cases, no neurologic manifestations
• 2013 – large ZIKV outbreak in French Polynesia
  • 42 Guillain-Barré syndrome (GBS) cases reported, population ~280,000
  • Magnitudes higher than expected incidence of GBS (1.2 cases / 100,000 / year
  • Many cases testing positive for ZIKV by PCR, MAC-ELISA
• 2015 – Emergence of ZIKV in Brazil
  • Again, increase in GBS in epidemic ZIKV areas
GBS outbreak followed peak in Zika cases in Salvador, Brazil.
Zika Virus and GBS in Americas

- Extremely and unusually high incidence of GBS in areas with Zika virus outbreaks
  - Salvador, Brazil: 7.6 cases / 100,000
  - Barranquilla, Colombia: 5.8 cases / 100,000
  - Puerto Rico: 6.8 / 100,000

- As of November 2018, at least 12 Central/South American and Caribbean countries reporting possible increases of GBS following introduction of Zika virus
  - Some with laboratory evidence of ZIKV infection
  - Strong evidence suggesting ZIKV associated with GBS
    - ‘Cause’ of GBS
Zika Virus and Other Neurologic Manifestations

- Anecdotal reports of other neurologic manifestations of ZIKV illness
  - Meningitis, encephalitis, myelitis, optic neuritis
  
  Generally isolated case reports or small case clusters; difficult to discern from background

  
  Nothing of magnitude seen with GBS

  
  Possible association may become clear with time

- ZIKV as ‘neurotropic’ virus??
  
  GBS: immune-mediated syndrome, not due to direct viral neuroinvasion

  
  ZIKV Congenital Malformations: Fetal brain is ‘different’; no evidence of inflammation in ZIKV – associated congenital anomalies

  
  ZIKV does not ‘appear’ to have same neurotropism as some other flaviviruses
Tick-Borne Encephalitis Virus

• Vectored by *Ixodes* ticks
  • Rarely, transmission from consumption of unpasteurized dairy products
• Geographic distribution temperate areas of Europe and Asia
• Two important genotypes – European and Far Eastern
• 2 / 3 of infections asymptomatic
• Clinical illness
  • European – biphasic course in 20 – 30%; initial mild illness with fever, myalgias, headache, then ~1 week asymptomatic period, followed by neurologic illness – encephalitis, meningitis, myelitis
    • Mortality 0.5 – 2%; neurologic sequelae in 10%
  • Far Eastern – more severe illness, monophasic
    • Mortality 20%; higher rates of neurologic sequelae
• Vaccine - adult and pediatric formulations; licensed in Europe, Canada
Thank You