West Nile Virus

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Case

- 51-year-old woman presents to clinic in August
- Recently returned from hiking with her family one week ago
- Fevers, abdominal pain, nausea/vomiting x 4d
- Myalgia, arthralgia, headache
- Recently resolved non-itchy rash
- Physical exam otherwise unremarkable
- Influenza and RSV PCR - negative, HIV PCR negative, EBV negative, etc.
- Blood and urine cultures negative
West Nile Virus (WNV)

- Flavivirus
  - Japanese Encephalitis serogroup
  - Closely related to St. Louis Encephalitis Virus

- Mosquito-borne (arbovirus)

- First case:
  - Febrile woman
  - West Nile district of Uganda
  - 1937

- Sporadic outbreaks

Emergence in the U.S.

- October 1999 - CDC MMWR reports outbreak of human arboviral encephalitis in NYC
- Similar to strain circulating in Israel and Tunisia
- New infectious disease emerged in the U.S.

Epidemiology - Transmission

- Mosquito vector: *Culex pipiens*
- Reservoir: Birds (esp. crows, ravens, jaybirds)

Epidemiology - Transmission

- Mosquito-borne
  - Seasonality: May - October
  - Weather patterns may affect outbreaks
- Blood transfusion
- Organ/Tissue transplants
- Transplacental
- Breastfeeding
West Nile virus neuroinvasive disease incidence reported to CDC by year, 1999-2013

Source: ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention

Incidence 2002-2013 (with 2014 cases)

Source: Ohio Department of Health
Data as of 02/02/2015
2001 - 2014 Ohio WNV

**WNV Infection**

- **Incubation period:** typically 2-6 days (range 2-14 days)
- **70-80%** subclinical or asymptomatic
- **~20%** experience flu-like illness
- **<1%** experience neuroinvasive disease

- Febrile and Meningitis cases
  - Fatigue, Headache, etc. may last weeks to months
- Encephalitis and poliomyelitis
  - Potential for long-term neurologic sequelae

**Human Case Statistics**

<table>
<thead>
<tr>
<th>Year</th>
<th>Human Cases</th>
<th>Deaths</th>
<th>Median Age</th>
<th>Age Range of Cases</th>
<th>Earliest Date of Symptom Onset</th>
<th>Asymptomatic Blood Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>0</td>
<td>0</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>2002</td>
<td>441</td>
<td>31</td>
<td>61</td>
<td>2 - 98 years</td>
<td>15-Jul</td>
<td>n/a</td>
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<tr>
<td>2003</td>
<td>108</td>
<td>8</td>
<td>49</td>
<td>11 - 90 years</td>
<td>12-Jul</td>
<td>6</td>
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<tr>
<td>2004</td>
<td>12</td>
<td>2</td>
<td>49.5</td>
<td>12 - 87 years</td>
<td>5-Jul</td>
<td>1</td>
</tr>
<tr>
<td>2005</td>
<td>61</td>
<td>2</td>
<td>53</td>
<td>22 - 96 years</td>
<td>14-Jun</td>
<td>14</td>
</tr>
<tr>
<td>2006</td>
<td>48</td>
<td>4</td>
<td>57.5</td>
<td>2 - 86 years</td>
<td>1-Aug</td>
<td>10</td>
</tr>
<tr>
<td>2007</td>
<td>23</td>
<td>3</td>
<td>52</td>
<td>11 - 86 years</td>
<td>12-Jul</td>
<td>9</td>
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<tr>
<td>2008</td>
<td>15</td>
<td>1</td>
<td>57</td>
<td>20 - 86 years</td>
<td>9-Jul</td>
<td>1</td>
</tr>
<tr>
<td>2009</td>
<td>2</td>
<td>0</td>
<td>36.5</td>
<td>11 - 62 years</td>
<td>27-Aug</td>
<td>0</td>
</tr>
<tr>
<td>2010</td>
<td>5</td>
<td>0</td>
<td>46</td>
<td>4 - 74 years</td>
<td>9-Jul</td>
<td>0</td>
</tr>
<tr>
<td>2011</td>
<td>21</td>
<td>1</td>
<td>55</td>
<td>14 - 83 years</td>
<td>1-Aug</td>
<td>6</td>
</tr>
<tr>
<td>2012</td>
<td>122</td>
<td>7</td>
<td>57.5</td>
<td>4 - 91 years</td>
<td>10-Jul</td>
<td>13</td>
</tr>
<tr>
<td>2013</td>
<td>24</td>
<td>4</td>
<td>71.5</td>
<td>38 - 82 years</td>
<td>29-Jul</td>
<td>4</td>
</tr>
<tr>
<td>2014</td>
<td>13</td>
<td>1</td>
<td>65</td>
<td>19 - 79 years</td>
<td>27-Jul</td>
<td>0</td>
</tr>
<tr>
<td>AVG</td>
<td>64</td>
<td>5</td>
<td>55</td>
<td></td>
<td>64</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>893</td>
<td>64</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>64</td>
</tr>
</tbody>
</table>

Source: Ohio Department of Health
Data as of 01/13/2015

Case

- 70-year-old man w/HTN, CAD
- Presents in July with mild-mod headache and subtle personality changes
- CSF pleocytosis (419 cells/μL), lymphocyte predominance (66%), increased protein (93 mg/dL), and normal glucose (69 mg/dL)
- Fever and worsening MS requiring intubation


Case

- MRI: chronic ischemic changes and nonspecific signals within the middle cerebellar peduncle bilaterally.
- Eleven days later, WNV IgM positive in the CSF (titers of 1:8) → WNV encephalitis.
- 40 day ICU stay with residual left-sided weakness and near-complete improvement in his mental status.

Non-Neuroinvasive Disease

- Acute systemic febrile illness
  - Headache
  - Weakness
  - Myalgias
  - Arthralgia
  - Lymphadenopathy
  - GI symptoms
  - Transient maculopapular rash

- Self-limiting
- Some symptoms may linger weeks-months

Neuroinvasive Disease

- Meningitis
  - Clinically indistinguishable from other viral meningitis etiologies
  - Fever
  - Headache
  - Nuchal Rigidity

CSF studies:

<table>
<thead>
<tr>
<th>WBC</th>
<th>Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Late</td>
<td>Lymphocytic</td>
</tr>
<tr>
<td>Glucose</td>
<td>Normal</td>
</tr>
<tr>
<td>Protein</td>
<td>Elevated</td>
</tr>
</tbody>
</table>
Neuroinvasive Disease

- Encephalitis
  - Fever
  - AMS
  - Seizures
  - Focal neuro deficits
  - Tremor
  - Parkinsonism

- Acute Flaccid Paralysis
  - Clinically identical to poliomyelitis
    - Absent DTRs
    - Intact sensation
  - May progress to respiratory failure
  - MRI: Anterior spinal cord signal abnormalities

- Mortality:
  - About 10% with neurologic disease

Case
- August 2012, man with NHL admitted for chemo & auto SCT
- Screened for subclinical infections – all negative
- 10 days after SCT: GI complaints, fever, hypotension
- 20 days after SCT: developed AMS, somnolence, resp failure
- CSF: elevated glucose (103 mg/dL) and normal protein (44 mg/dL) with two white blood cells/mm3.
- CSF culture, gram stain, AFB, HSV, Crypto, HHV6, VZV, BK virus, JC virus → all negative


Case
- WNV not done
- MRI: meningeal and cortical changes consistent with inflammation
- Pt expired
- Postmortem showed diffuse encephalitis, WNV IgM positive on serum, PCR positive on brain and spinal cord tissue

Diagnosis


Management

- Treatment is supportive
- Encephalitis: follow closely for elevated ICP and seizures
- Respiratory failure in poliomyelitis patients may develop rapidly
Prevention

- Vaccines available for prevention of equine WNV infection
- No vaccines licensed for human use.

- Mosquito control programs
- Reporting dead crows and bluejays
- Personal protection

The 5 D’s of Mosquito Control

- Drain or Dump mosquito
- Dress
- DEET
- Doors
- Dawn and Dusk
Chikungunya

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Chikungunya virus (CHIKV)

- RNA virus, Alphavirus genus
  - Two envelope glycoproteins (E1 and E2)
- First isolated in 1953 in Tanzania
  - Name means “that which bends up”
- Mosquito-borne
  - Enzootic
  - Mosquito-human-mosquito cycle

Source: Wikimedia Commons

Adapted from: Preparedness and Response for Chikungunya Virus
Introduction in the Americas. CDC/PAHO 2011
Epidemiology

- **Asian Lineage**
  - Primarily transmitted by *Aedes aegypti*
- **Indian Ocean Lineage**
  - Adapted to *Aedes albopictus*
  - Mutation in E1 and E2 envelope glycoprotein genes

**Source:** CDC

Arrival in the Americas

- Active CHIKV circulation in Saint Martin
  - October 2013
  - Asian Lineage strain
  - Not efficiently transmitted by *Ae. albopictus*
- Local transmission in 44 countries or territories
- 1.3 million suspected cases
  - Greatest number of cases in Dominican Republic, Colombia, and El Salvador

**Source:** Wikimedia Commons

**Data as of April 10, 2015**
Transmission in the US

- July 2014
  - First cases of transmission within the continental US
- 2,492 cases of reported in US in 2014
  - 11 locally transmitted cases

Prospects for Spread

**Aedes aegypti**

**Aedes albopictus**

Source: CDC

Photo Credit: Paul I. Howell, MPH

Source: CDC

Photo Credit: Paul I. Howell, MPH

Source: CDC
Acute Infection

- Acute onset of high fever (>39°C) with severe joint pain
  - Headache and rash also common
- Incubation period about 3 – 7 days
  - Fever onset associated with viremia
- Acute phase lasts approximately 1 week

<table>
<thead>
<tr>
<th>Symptom or Sign</th>
<th>Frequency Range (% of Symptomatic Pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>76-100</td>
</tr>
<tr>
<td>Polyarthralgias</td>
<td>71-100</td>
</tr>
<tr>
<td>Headache</td>
<td>17-74</td>
</tr>
<tr>
<td>Rash</td>
<td>28-77</td>
</tr>
<tr>
<td>Myalgias</td>
<td>46-72</td>
</tr>
<tr>
<td>Back Pain</td>
<td>34-50</td>
</tr>
<tr>
<td>Nausea</td>
<td>50-69</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4-59</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>12-32</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3-56</td>
</tr>
</tbody>
</table>

Source: Wikimedia Commons
Photo Credit: 2012-01-09 Chikungunya on the right feet at The Philippines” by Nsaa
Table adapted from: Preparedness and Response for Chikungunya Virus Introduction in the Americas. CDC/PAHO 2011

Acute Infection

- High morbidity, low mortality
  - ~ 80% develop significant symptoms
  - Significant economic effects
- Complications
  - Mortality rate 0.3 to 1%
  - Newborns, elderly, and comorbid medical conditions
  - Encephalopathy/encephalitis, myocarditis, hepatitis, multi-organ failure
  - Vertical transmission (~50% transmission rate)
Chikungunya vs Dengue

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Chikungunya</th>
<th>Dengue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Rash</td>
<td>Day 1–4</td>
<td>Day 5–7</td>
</tr>
<tr>
<td>Retroorbital Pain</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Consistent</td>
<td>Rare</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Common</td>
<td>Absent</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>Common</td>
<td>Absent</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Possible</td>
<td>Common</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Outcome</td>
<td>Arthralgia for months to years</td>
<td>Possible fatigue for weeks</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Early and mild</td>
<td>Delayed and possibly severe</td>
</tr>
</tbody>
</table>

Table adapted from: Curr Infect Dis Rep 2011;13:218-228

Chronic Disease

Subacute (2 to 3 months)
- Symptom relapse after initial improvement
- Polyarthritis, tenosynovitis, Raynaud’s
- Depression, fatigue, weakness

Chronic (> 3 months)
- 15 to 50% of patients
- Distal polyarthritis and tenosynovitis
  - Previously injured joints and bones
- Occasionally develop a destructive arthritis
  - Rheumatoid arthritis-like polyarthritis
- Fatigue, depression, and loss of quality of life
**Diagnosis**

### Acute Infection
- Frequently a clinical diagnosis
- Serum PCR
- Acute and convalescent serology
  - IgM positive after 5 days
  - 4-fold increase in convalescent IgG

### Chronic Disease
- Serology
  - IgM can persist for months
- IgG levels and persistence correlate with chronic disease activity

Adapted from: Preparedness and Response for Chikungunya Virus Introduction in the Americas. CDC/PAHO 2011

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**Pathogenesis**

### Acute Infection
- Virus infects musculoskeletal tissues
  - Skeletal muscles, myotendinous insertions, joint capsules
  - Triggers inflammatory cell infiltration
- Disseminates to the CNS in animal models
  - Meningeal and ependymal cells
- Transmitted through maternal-fetal blood exchange during delivery
Pathogenesis

Chronic Disease

• Persistent virus replication and/or lack of virus antigen clearance
  – Pro-inflammatory immune response

Management

Treatment

• Supportive care and pain control
  – NSAIDs helpful but avoid until Dengue ruled out
• Occasionally steroids and DMARDs in chronic disease
  – Rebound effect when steroids stopped
• Current study evaluating the use of hyperimmune immunoglobulins

Prevention

• Avoid mosquito bites
• Vector control
## Vaccine Development

- Life-long immunity following CHIKV infection
- Simpler vaccine target than dengue
- Virus-like particle vaccine in development
  - Completed phase 1 dose-escalation trial
  - Vaccine was safe, well tolerated, and immunogenic
- Several other vaccine candidates also being developed
- Multiple financial and logistical challenges

### References