West Nile Virus

Amber Vasquez, MD
Assistant Professor of Internal Medicine,
Infectious Diseases
Associate Program Director,
Infectious Diseases Fellowship
The Ohio State University Wexner Medical Center

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.

Source: CDC/P.E. Rollin
Photo Credit: Cynthia Goldsmith
Epidemiology - Transmission

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

Source: CDC

Epidemiology - Transmission

- Mosquito-borne
  - Seasonality: May - October
  - Weather patterns may affect outbreaks
- Blood transfusion
- Organ/Tissue transplants
- Transplacental
- Breastfeeding

2014 Neuroinvasive Disease Cases

Reported to ArboNET
Source: CDC

2012 Neuroinvasive Disease Cases

Reported to ArboNET
Source: CDC
Incidence 2002-2013 (with 2014 cases)

Source: Ohio Department of Health
Data as of 02/02/2015

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

**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:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>Elevated</td>
</tr>
<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

Shandra Day, MD
Assistant Professor, Infectious Diseases
Associate Medical Director of Clinical Epidemiology
The Ohio State University Wexner Medical Center

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

Mosquito feeds \[\text{Viremia}\] Mosquito refeeds \[\text{Viremia}\]

Days | 1 | 5 | 12 | 16 | 20 | 24
--- | --- | --- | --- | --- | --- | ---
Human #1 | Human #2

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

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: CDC
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

<table>
<thead>
<tr>
<th>Aedes aegypti</th>
<th>Aedes albopictus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source: CDC</td>
<td>Source: CDC</td>
</tr>
<tr>
<td>Photo Credit: Paul I. Howell, MPH</td>
<td>Photo Credit: Paul I. Howell, MPH</td>
</tr>
</tbody>
</table>

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>75-100</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>48-72</td>
</tr>
<tr>
<td>Back Pain</td>
<td>34-50</td>
</tr>
<tr>
<td>Nausea</td>
<td>50-89</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: Preparedness and Response for Chikungunya Virus Introduction in the Americas, CDC/PAHO 2011

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

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

### Pathogenesis

**Acute Infection**
- Virus infects musculoskeletal tissues
  - Skeletal muscles, myotendinous insertions, joint capsules
  - Triggers inflammatory cell infiltration

**Chronic Disease**
- Disseminates to the CNS in animal models
  - Meningeal and ependymal cells
- Transmitted through maternal-fetal blood exchange during delivery

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

<table>
<thead>
<tr>
<th>Chronic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Persistent virus replication and/or lack of virus antigen clearance</td>
</tr>
<tr>
<td>- Pro-inflammatory immune response</td>
</tr>
</tbody>
</table>

### Management

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Supportive care and pain control</td>
</tr>
<tr>
<td>- NSAIDs helpful but avoid until Dengue ruled out</td>
</tr>
<tr>
<td>• Occasionally steroids and DMARDs in chronic disease</td>
</tr>
<tr>
<td>- Rebound effect when steroids stopped</td>
</tr>
<tr>
<td>• Current study evaluating the use of hyperimmune immunoglobulins</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Avoid mosquito bites</td>
</tr>
<tr>
<td>• Vector control</td>
</tr>
</tbody>
</table>

### 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