Emerging Infectious Diseases and Related Neurological Complications

May 19, 2017
Today’s Presentation

• Zika virus and associated neurological complications
• *Naegleria fowleri*
• Acute flaccid myelitis and EV-D68
Zika Virus History

• First isolated in a forest near Kampala, Uganda
  • 1947: first identified in rhesus monkeys
  • 1952: found in humans in Uganda and Tanzania
Current Numbers (*as of April 19, 2017)

- **United States**
  Locally acquired mosquito-borne cases reported: 223 (217 Florida and 6 in Texas)
  Travel-associated cases reported: 4,939
  Ohio: 85 cases

- **US Territories**
  Locally acquired cases reported: 36,426
  Travel-associated cases reported: 143
  Total: 36,426

[www.cdc.gov](http://www.cdc.gov)
Transmission

Mosquito bites—*Aedes aegypti* or *Aedes albopictus*

Sexual transmission
- Male → Male MMWR 4/16/16
- Female → Male MMWR 7/22/16
- Asymptomatic male MMWR 9/2/2016

Maternal→ fetal transmission in utero

Likely through blood transfusion (no cases documented in US)
- Platelet transfusion in Brazil (Motta IJ et al NEJM 2016)
Mosquito Ranges in the U.S.

Petersen NEJM 2016
Spread by Contact- 1 case report

- 73 yo man in Salt Lake, recently returned from trip to SW Mexico. Very high ZIKV viremia.
- Another patient (healthy 38 yo) developed conjunctivitis, fever, myalgia, rash 7-10 days later → urine positive PCR.
- Had assisted nurse in repositioning without gloves, had also wiped eyes.

Swaminathan S, NEJM 2016
Systemic Symptoms

80% asymptomatic

20% Zika Fever-fever, maculopapular rash, arthralgia, non-purulent conjunctivitis, myalgia, headache, retro-orbital pain, vomiting.

Symptoms usually last several days to 1 week
Neurological Symptoms

- Congenital infection and microcephaly - current estimates are that the risk of ZCS after infection during the first trimester of pregnancy ranges from 0.88 to 13.2%.
- Congenital ocular abnormalities (pigment mottling of the retina and chorioretinal atrophy).
- Meningoencephalitis.
- Myelitis.
- GBS (Guillan-Barre Syndrome) - current estimates are 0.24 GBS cases per 1000 ZIKV infections.

Thomas NEJM 2016
Zika Associated Microcephaly
Congenital Zika

• Mouse studies to understand effects of ZIKV on placenta crosses placental barrier

Mlaker NEJM 2016
Mysorekar, NEJM 2016
What is the Extent of the Problem?

- Pregnant Women in Rio De Janeiro
- Women who had developed rash in previous 5 days
- 117 live infants born to 116 ZIKV positive women
- 42% with grossly abnormal clinical exam or imaging or both

Brasil NEJM 2016
CT Findings

Hazin et al NEJM
2016
Ocular Findings

- Chorioretinal atrophy, pigment mottling, optic nerve atrophy
### Table 1. Expected and Observed Numbers of Cases of the Guillain–Barré Syndrome.

<table>
<thead>
<tr>
<th>Region</th>
<th>Population</th>
<th>Pro-ZIKV Period</th>
<th>ZIKV Transmission Period</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Annual Cumulative Incidence of GBS (95% CI)</td>
<td>Expected Cases of GBS per Week (95% CI)</td>
</tr>
<tr>
<td></td>
<td>no.</td>
<td>no. cases/100,000</td>
<td>no. wk.</td>
</tr>
<tr>
<td>Bahia, Brazil</td>
<td>15,203,934</td>
<td>97 (37 to 77)</td>
<td>0.37 (0.30 to 0.46)</td>
</tr>
<tr>
<td>Colombia</td>
<td>49,629,208</td>
<td>242 (43 to 436)</td>
<td>0.49 (0.44 to 0.54)</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>10,652,135</td>
<td>73 (47 to 114)</td>
<td>0.69 (0.55 to 0.83)</td>
</tr>
<tr>
<td>El Salvador</td>
<td>6,426,002</td>
<td>170 (99 to 241)</td>
<td>2.65 (2.27 to 3.06)</td>
</tr>
<tr>
<td>Honduras</td>
<td>8,423,917</td>
<td>110 (83 to 137)</td>
<td>1.31 (1.08 to 1.57)</td>
</tr>
<tr>
<td>Suriname</td>
<td>548,456</td>
<td>4 (-1 to 10)</td>
<td>0.73 (0.24 to 1.73)</td>
</tr>
<tr>
<td>Venezuela</td>
<td>31,292,702</td>
<td>214 (139 to 336)</td>
<td>0.69 (0.60 to 0.78)</td>
</tr>
</tbody>
</table>

Dos Santos T, NEJM 2016
Correlation in Timing

B Case Series of ZIKV Disease and GBS Aligned to the Week of Peak Incidence of ZIKV Disease

Dos Santos T, NEJM 2016
Colombia ZIKV GBS Experience

- 68 patients with median time of 7 days between onset of symptoms and GBS
- 50% had bilateral facial paralysis, 22% bulbar cranial nerves, 10% with CN’s 3/4/6, 31% required mechanical ventilation
- Tended to have persistence of virus in urine
- 78% had typical AIDP- only 2% AMAN
- 48% had parainfectious presentation
- 87% had antibodies against Dengue

Parra et al NEJM 2016
Meningoencephalitis Case Report

- 81 y/o man
- CSF- 41 cells (98% neutrophils)
Testing

• RT-PCR for nucleic acids - very specific but insensitive as testing can be negative after the viremia has ended (1 week)

• IgM antibody testing - problems with cross reactivity with other flaviviruses (Dengue)

• Call your hospital lab → samples forwarded to Ohio State Health Department → CDC in Atlanta and Division of Vector Borne Diseases in Ft. Collins
How long Does it Persist?

• Infant born with congenital ZIKV→ viremia persisted 67 days *(Almeida et al NEJM 2016)*

• Pregnant woman with viremia 107 days after onset of symptoms (higher viral load in placenta than serum-question if there was concurrent fetal infection to propagate this) *(Suy et al NEJM 2016)*

• In urine 48 days later *(Parra et al NEJM 2016)*
How long Does it Persist?

• 150 participants
• Median and 95\textsuperscript{th} percentiles until virus not detectable
• Serum: 14 and 54 days
• Urine: 8 and 39 days
• Semen: 34 and 81 days → current guidelines recommend condoms or abstaining from sex 6 months

Paz-Bailey NEJM 2017
News

Florida fights Zika virus by releasing thousands of bacteria-infected mosquitoes

Wolbachia stops the eggs of disease-carrying female Aedes aegypti mosquitoes from hatching
Vaccine Development

- Questions-
  1) aimed at preventing mosquito borne disease or at transmission by other routes?
  2) what strain will be used for candidate vaccine (Asian and African lineages)
  3) will the virus be prevalent each year, or sporadic?
  4) who will it be aimed at?
  5) used routinely or for outbreak control?
  6) where to use?

- Other flavivirus licensed vaccines: Yellow Fever (live-attenuated), Japanese encephalitis (inactivated), tick borne encephalitis, Dengue (live chimeric)
- 2 DNA vaccines in Phase 1 trials currently

Thomas NEJM 2016
Naegleria fowleri
Naegleria fowleri

• Free-living parasitic amebae
• Occurs in previously healthy children and young adults following exposure to warm freshwater
• 37 cases reported in US from 2006-2015 (in comparison to 34,000 drowning deaths during this time)
• Total US reported cases= 138 (135 fatalities)- last 2 in 2013
• One in a woman from Columbus who contracted it while in NC 2016
• Often direct invasion from olfactory nerve
• Trophozoites can be seen on wet-prep of CSF but often mistaken for monocytes
Naegleria fowleri

Average incubation 2-5 days
First symptom often change in smell/taste
Produces a diffuse meningoencephalitis and purulent meningitis
Often extensive cortical and herniation
Some cases of neurotrophilic myocarditis
If identified, treated with amphotericin B, but universally fatal in 95% of cases

Trophozoites can be seen on wet-prep of CSF but often mistaken for monocytes
Acute Flaccid Myelitis and Enterovirus D-68

Morbidity and Mortality Weekly Report

Acute Neurologic Illness of Unknown Etiology in Children — Colorado, August–September 2014

Daniel M. Pastula, MD1, Negar Aliabadi, MD1, Amber K. Haynes, MPH2, Kevin Messacar, MD3, Teri Schreiner, MD3, John Maloney, MD3, Samuel R. Dominguez, MD3, Emily Spence Davison, MPH4, Eyal Leshem, MD2, Marc Fischer, MD5, W. Allan Nix2, M. Steven Oberste, PhD2, Jane Seward, MBBS2, Daniel Feikin, MD2, Lisa Miller, MD4 (Author affiliations at end of text)
Acute Flaccid Myelitis (AFM) and Enterovirus- D68 (EV-68)

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• First case reported Aug 9, 2014 to CHCO
• Case definition: patients < 21 years of age, acute onset of limb focal weakness on or after August 1, 2014 and MRI showing spinal cord lesion largely restricted to the gray matter
**2014-**
**120 cases**

**2015-**
**21 cases**

**2016-**
**136 cases**

Association with increase in EVD68 respiratory illness
Clinical Symptoms in Colorado Cohort

- 12 children (9 M/3 F)
- PMhx: none (8), asthma (3), cardiac transplant (1)
- Prodromal illness pre-CNS symptoms 12/12
- Fever, cough, rhinorrhea
Neurological Features

- Stiff neck 83%, HA 58%, limb/back/neck pain in 67%
- Flaccid limb weakness: arm only (5/12), leg only (1/12), both arm and leg (4/12)
- Proximal weakness 10/12, asymmetric 7/12, preserved sensation 10/12
- CN’s: 50% with hypophonia/dysarthria
Testing

- **CSF:**
Pleocytosis 10/10, (CDC 72%)
Median 55 cells (IQR 14-62), protein >40 in 50% (max 92), glucose WNL 100%

- **PCR’s:**
CO- nasopharynx 5/11 + EVD68 (CDC 48%)
CSF- None in CO, 1/55 at CDC (blood contamination?)

- **EMG data:**
n=5: 18-27 days after CNS injury

- **How to test:**
Send myelitis patients for CSF for enterovirus RT-PCR testing
If positive samples can be sent to CDC for serotyping of the specific virus-contact hospital lab
Abnormal MRI spine in 11/12- T2 positive, non-enhancing, central-gray/anterior horns, confluent and longitudinally extensive (median 17 segs, range 4-20)

Brainstem in 9/12, dorsal pons/medulla 5/12, dentate 3/12
Treatment and Outcome (Colorado Cohort)

- IVIG 9/12 (1 g/kg x 2 days)
- Methylprednisolone (30 mg/kg x 3-5 days) 5/12
- PLEX 2/12
- Hospitalized mean 10.5 days
- 4/12 ICU- median 18 days (IQR 12.3-20.5)
- No/mild improvement in 10/12, 1 worse, 1 near resolution (milder symptoms at onset)
Martin JA et al, Outcomes of CO Children with AFM at 1 year. Neurology, in press
Virus isolated from spinal cords of infected mice transmitted disease when injected into naïve mice with loss of spinal cord motor neurons innervating paralyzed limbs.

Also found the ability to prevent AFM by pre-administering serum containing EV-D68 antibodies from previously infected mice.

Hixon et al 2017
IVIG Benefit in Mouse Model

IVIG Rx Reduces Motor Impairment:
EV-D68 IL/14-18952 IM (200 xTCID₅₀)

SEVERE

NONE

9-10 mice per group

Error bars are ± s.e.m.

Courtesy of Dr. Ken Tyler AAN 2017
Conclusions

• Neurologists should be aware of ZIKV given its neurological consequences. Is relevant to Ohio also because of possibility of sexual transmission.
• Though congenital ZIKV leading to microcephaly is the most prevalent neurological manifestation, there is also an association with GBS, and more rarely, case reports of meningioencephalitis and myelitis.
• *Naegleria fowleri* rarely results in human disease, but when does is nearly universally fatal.
• EV-D68 appears to be associated with an acute flaccid myelitis mainly in the pediatric population.
References