Joint Session with ACOFP and Mayo Clinic: Zika and Other Neurological Infections

Marie F. Grill, M.D.
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Please check where applicable and sign below. Provide additional pages as necessary.

Name of CME Activity: 2016 AOA/ACOFP Osteopathic Medical Conference & Exposition (OMED)

Dates and Location of CME Activity: September 17-20, 2016 – Anaheim Convention Center, Anaheim, California

Topic: Joint Session with ACOFP and Mayo: Zika and Other Neurological Infections

Name of Speaker/Moderator: Marie Grill

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<table>
<thead>
<tr>
<th>Organization With Which Relationship Exists</th>
<th>Clinical Area Involved</th>
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Deadline: Friday, August 5, 2016
Zika Virus Infection and Associated Neurological Complications (and a few other neuro-ID highlights)

Marie Francisca Grill, MD ©2016
Department of Neurology
Mayo Clinic AZ

September 18, 2016
Outline

• Zika virus
  – Overview of symptoms, transmission, incidence
  – Associations with microcephaly and other birth defects
  – Other neurological complications, i.e. Guillain-Barre syndrome

• Other Neuro-ID Highlights
  – Encephalitis
    • West Nile Virus
    • St. Louis Encephalitis Virus
    • Herpes Simplex Virus Encephalitis
  – Acute Bacterial Meningitis
  – Coccidioidomycosis
Zika virus

• First identified in Zika forest in Uganda in 1947; sporadic cases in Africa and SE Asia; outbreak in Yap State Micronesia in 2007, and French Polynesia in 2013
• Intro to Americas in northeastern Brazil in 2015
• Asian and American strains closely related per genetic studies (Faria NR et al. Zika virus in the Americas: early epidemiological and genetic findings. Science 2016;352:345-9)

• Flavivirus (*Flaviviridae* family)
• Arbovirus ➔ mosquito-borne disease
  – Aedes aegypti
  – Aedes albopictus
    • Also carry Chikungunya, dengue
    • Bites day>>>night; bite multiple persons
    • Lay eggs in standing water
Countries and Territories with active Zika transmission (from CDC)
Zika Spread and Response

• NE Brazil → Central and South America and Caribbean (Puerto Rico, US Virgin Islands, now FL in continental US)
• Reports of increased cases of Guillain-Barre syndrome and microcephaly in 2015
• Jan 2016: CDC activated Emergency Operations Centre
• Feb 1, 2016: WHO declared public health emergency of international concern
• Feb 8, 2016: CDC elevated EOC to Level 1 (highest level) → authorities advised against travel to pregnant women; advocated condom use to prevent sexual transmission
Zika cases in US

CDC.gov as of 9/7/2016
Zika in the US

- All states with travel-related cases with exception of FL (N=2,921)
  - Includes 1 Utah case w/ unknown person-person transmission
- In Puerto Rico, 59 travel associated cases; 15,541 locally-acquired cases
  - 0 cases in American Samoa; 1 case in Virgin Islands
- Active outbreak in Florida: 2 areas in Miami-Dade county (N=43)

As of 9/7/2016
CDC’s Estimate of Potential Range of Aedes sp. Mosquitoes, 2016

- **Aedes aegypti**
- **Aedes albopictus**
Zika Virus Transmission

• Transmitted by mosquitoes
• Cases of sexually transmitted disease
  – Even if asymptomatic; before/during/after sx
• Maternal-fetal transmission
  – Throughout pregnancy
  – No cases of infection via breastmilk; breastfeeding still recommended
• Blood transfusion
  – No cases in US
  – Multiple reports in Brazil under investigation
• Lab exposure
Zika virus related symptoms

• 80% of those infected are asymptomatic
• Classic symptoms
  – Fever
  – Arthralgias (small joints, hands + feet)
  – Conjunctivitis
  – Rash (pruritic, maculopapular)
• Other sx may include myalgias, headaches/retro-orbital pain
• Typically mild self-limited illness, 3-7 day duration
Zika Virus: Diagnostics

- **Zika Virus Testing**
  - Contact local/state public health department
  - rRT-PCR
  - Check in both serum and urine w/in 14 days of sx
  - Positive test in either confirms; if negative, proceed with serological testing (IgM)
  - IgM typically positive 4 days to 12 weeks post-infection; use if negative rRT-PCR test or if >14 days of sx
  - Zika MAC-ELISA: in serum or CSF; cross-reactivity with other flaviviruses; any positive or indeterminate results then sent for PRNT testing
  - Pregnant women: even if asymptomatic, rRT-PCR test w/in 14 days if travel to area of active transmission or sex w/ partner who has traveled to affected area; check IgM in 1st and 2nd trimesters, reflex rRT-PCR test
  - Zika virus RNA can persist in serum of some pregnant women longer than had been previously reported; the longest documented duration of Zika virus RNA detection in serum is 10 weeks after symptom onset (Meaney-Delman D, Oduyebo T, Polen KND, et al. Prolonged detection of Zika virus RNA in pregnant women. Obstet Gynecol In press 2016; Driggers et al. Zika virus infection with prolonged maternal viremia and fetal brain abnormalities. N Eng J Med, 2016;374:2142-51.)
  - Trioplex rRT-PCR: tests for Zika, dengue, and Chikungunya; not FDA-approved but authorized under Emergency Use Authorization
  - Lab testing for infants; placental tissue
Zika virus associated neurological disease

- July 2015: increase in cases of GBS in NE Brazil (state of Bahia) reported to Ministry of Health → WHO
- October 2015: increase in cases of children born with microcephaly in NE Brazil (state of Pernambuco) reported
- Zika virus more prevalent in these areas at the time

- Remarkable persistence of Zika virus +RT-PCR in blood of pregnant women for weeks after initial infection
- Evidence of Zika virus in placental tissue (Martines RB et al. Notes from the field: evidence of Zika virus infection in brain and placental tissues from two congenitally infected newborns and two fetal losses – Brazil, 2015. MMWR 2016;65:159-60).
Congenital Zika virus disease

• WHO case definitions for microcephaly
  – small head circumference (<32cm but recently changed to <31.7cm for boys and <31.5cm for girls)
  – other causes of microcephaly excluded
  – laboratory evidence of Zika virus infection

• From 11/2015-4/2016 in Brazil
  – 7728 microcephaly cases reported
    • 194 confirmed Zika associated cases based on +test
    • 1004 confirmed based on brain imaging findings
Zika in Pregnancy: in utero risks


- Birth defects
  - Microcephaly
  - Intracranial calcifications (cortical-subcortical white matter junction)
  - Ventriculomegaly and extra-axial fluid, enlarged cisterna magna
  - Abnormal gyral patterns, i.e. polymicrogyria; cortical atrophy and malformation
  - Hypoplasia of cerebellum and brainstem
  - Delayed myelination
  - Thinning/hypoplasia of corpus callosum
  - Abnormal eye development: chorioretinal atrophy or scarring, focal pigment mottling, optic nerve abnormalities (hypoplasia, optic disc pallor, increased optic disc cupping), hemorrhagic retinopathy, abnormal retinal vasculature, lens subluxation, coloboma [predilection for macular area involvement]
Infants with Zika

- Exam findings:
  - Hypotonia
  - Hypertonia
  - Spasticity
  - Hyperreflexia
  - Severe irritability
  - Seizures
  - Clubfoot
  - Arthrogryposis (joint contractures)

- Severe microcephaly
- Skull collapse
- Overlapping cranial sutures
- Prominent occipital bone
- Redundant scalp skin
- Severe neurological impairment
Pregnancy Outcomes in US

- >1,000 pregnant women with laboratory evidence of possible Zika virus infection in the United States and U.S. territories
- 17 liveborn infants with birth defects
- 5 pregnancy losses with birth defects (includes miscarriages, stillborns and terminations)
- Reported to US Zika Pregnancy Registry and Zika Active Pregnancy Surveillance System
- Laboratory evidence of Zika though may be other contributing factors
<table>
<thead>
<tr>
<th>Reporting country/territory</th>
<th>Number of microcephaly and/or CNS malformation cases suggestive of congenital Zika infections or potentially associated with a Zika virus infection</th>
<th>Probable location of infection</th>
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<td>Brazil</td>
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<tr>
<td>Spain</td>
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<td>Suriname</td>
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Guillain-Barre syndrome (GBS)

- Autoimmune-mediated acute inflammatory polyradiculoneuropathy
- A peripheral nervous system disorder in which Immune system attacks myelin sheath surrounding axons of peripheral nerves, or may attack axons themselves
- Clinically, symmetric ascending weakness, sensory disturbances and diminished or absent reflexes
- CSF characteristic = albuminocytologic dissociation
- Usually triggered by prior infection (e.g. URI (influenza) or GI (Campylobacter jejuni)); also post-vaccination
- Brighton diagnostic criteria (w/ varying levels of diagnostic certainty)
  - Bilateral flaccid weakness, decreased/absent DTRs in affected limbs, CSF WBC <50, increased CSF protein, NCS c/w GBS subtype, absence of alternative dx (Fokke et al. Diagnosis of Guillain-Barre syndrome and validation of Brighton criteria. BRAIN 2014 Jan 137(Pt 1))33-43.)

- Has also been described in dengue virus and chikungunya virus
- Increased incidence of GBS cases reported in countries with active Zika infections
  - 1st reported in 2013 outbreak in French Polynesia
  - Reports in Brazil in 2015 (19% average increase compared to prior year)
Zika-related GBS

- **French Polynesia**
  - 3/2014: 1st Zika-related GBS case published, then 42 cases between 2013-2014 reported to WHO
  - Recently first case-control study (Cao-Lormeau VM et al. Guillain-Barre Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet 2016;387:1531-39.)
- Cases matched w/ pts p/w non-febrile illness and pts w/ acute Zika-virus without neurological sx
- 42 reported cases of GBS (estimated risk of 0.24 per 1000 Zika infections using 66% attack rate of Zika)
- Time between reported viral syndrome and neuro sx onset = median 6 days (IQR 4-10)
- Median age=42; 74% men
- Clinical presentation: generalized muscle weakness (74%; 64% symmetric), facial palsy (64%), incapacity to walk (44%), paresethesias (83%), dysphagia (24%)
- 62% w/ decreased/absent DTRs at presentation; 48% at nadir
- CSF: median WBCs= 4 (IQR 1-7); 93% increased protein concentration
- EMG/NCS (n=37) in 1st week w/ prolonged distal latencies and reduction in distal compound muscle action potential (CMAP) amplitudes, suggesting conduction abnormalities in distal nerve segments
- Repeat EMG/NCS at 4 months (n=19) w/ improvement: decrease in prolongation of distal latencies and near normalization of CMAP amplitudes → interpreted as c/w acute motor axonal neuropathy (AMAN) type
French Polynesia Cases

- Absence of fever and negative RT-PCR results for all pts in GBS group (urine not tested); 93% +IgM; 100% neutralizing Ab
- No significant difference in h/o dengue infection compared to control groups (dengue co-circulation)
- Anti-glycolipid Ab in 31%
  - Hypothesized other autoantibodies or unknown neurotoxic factors
- 33% developed trouble breathing at nadir; 29% required respiratory assistance
- 38% were admitted to ICU
- 100% were treated with IVIG
- 1 was treated with plasmapheresis
- Hospital stay: median 11 days for all; 51 days for ICU
- 0 deaths
- 57% able to walk without assistance post-discharge
Zika related GBS?

• Features atypical for GBS/AMAN type
  – Rapid progression to nadir (6 day median between sx onset and nadir)
  – Short plateau (4 day median)
  – Diagnostic criteria, including retained DTRs
  – High frequency of facial palsy (79%) (atypical for AMAN type)
  – Much less severe w/ faster recovery (atypical for AMAN type)
    • No deaths
    • 57% w/ full recovery after 3 months
  – Typical AMAN-associated anti-ganglioside antibodies rarely present
    • High overlap in peptides btwn Zika virus polyprotein and human proteins related to myelin/demyelination and axonal neuropathy supporting possible cross-reactivity – further research warranted (Lucchese et al. Zika virus and autoimmunity: from microcephaly to Guillain-Barre syndrome, and beyond. Autoimmun Rev 2016.)
  – Note also close proximity to viral illness

• To be distinguished from an acute flaccid paralysis due to poliomyelitis virus illness (anterior horn cell of spinal cord, rather than peripheral nerve disorder)
Other reported Zika-related GBS

- Brazil, Jan-Nov 2015, 1708 cases reported (19% increase from prior year) but not mandatory reporting, majority not tested for Zika (co-circulating viruses), diagnostic criteria unclear
- Other countries/territories reporting increased incidence of GBS cases with at least 1 w/ confirmed Zika virus infection: Dominican Republic, El Salvador, Suriname, Venezuela, French Guiana, Honduras, Jamaica, Martinique
  - No increase reported in Costa Rica, Grenada, Guadeloupe, Guatemala, Haiti, Panama, Puerto Rico
  (WHO, as of 9/15/2016)
Other Zika-associated Neurological Syndromes

• Acute myelitis
  – 15yo girl from Guadeloupe, 1/2016, L arm pain, HA, conjunctival hyperemia; 7 days later p/w L hemiparesis; L paresthesias, urinary retention; sensory level on exam; MRI spine showed lesions w/ edema in cervical and thoracic cord; +Zika RT-PCR in serum, urine, and CSF; tx w/ IV steroids x 5 days w/ improvement; 1 month f/u - mod leg weakness but walking unassisted, decreased cord edema in repeat imaging
    (Mecharles et al. Acute myelitis due to Zika virus infection. Lancet 2016;387:1481.)

  – Also described in other flaviviruses: dengue, JEV, WNV, SLEV
  – Establishing pattern of neurotropism
Other Zika-associated Neurological Syndromes

• Meningoencephalitis
  – Case#1: 81 yo man p/w fever, comatose 10 days after return from New Caledonia, L HP, RUE paresis, preserved DTRs, transient rash; MRI brain w/ asymmetric subcortical white matter hyperintensities on FLAIR, CSF w/ 41 WBCs (98% PMN), prot 76, +Zika in CSF by viral cx and RT-PCR; supportive care; extubated day 2, +hallucinations, LUE paresis; d/c’d from ICU day 17, full cog resolution day 38, mild residual LUE paresis (Carteaux et al. Zika virus associated with meningoencephalitis. N Eng J Med 2016.374;1595-6.)
Zika-associated meningoencephalitis

- Case#2: 47 yo nonpregnant woman in Brazil, arthralgias and pruritic rash 1/2016, 4 days later dvlpd leg weakness, dysarthria, and confusion; same day rapid decline, intubated; Zika RT-PCR neg in serum, positive in urine; CSF w/ 10 WBCs (80% lymphs), prot 111, -Zika PCR in CSF; +IgM in serum and CSF; CT head w/ massive cerebral edema → brain death (Soares et al. Fatal encephalitis associated with Zika virus infection in an adult. J Clin Virol 2016; Aug 30;83:63-65.)
“Based on a systematic review of the literature up to 30 May 2016, WHO has concluded that Zika virus infection during pregnancy is a cause of congenital brain abnormalities, including microcephaly, and that Zika virus is a trigger of GBS. The findings, which emerge from a causality framework that WHO developed in February 2016 to appraise the strengths and weaknesses of available evidence about the causal relationships, also identify gaps in research and provide direction for further work.”

?Host factors
?Mechanisms and spectrum of neurological disease
CDC Activity

Hotline and special recommendations for pregnant women re: avoiding travel; contraception use

Education/Prevention:
Protection from mosquito bites
- long-sleeved shirts, pants, hats
- insect repellant (DEET, icaridin, lemon eucalyptus extract)
- permethrin for clothing
- sleep w/ mosquito nets, air conditioned rooms w/ windows closed

Mosquito control: traps/testing, aerial spraying
<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Bacterial</th>
<th>Viral</th>
<th>Fungal</th>
<th>Tuberculosis</th>
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<td>Opening pressure (mm H2O)</td>
<td>180</td>
<td>Elevated 200-500</td>
<td>Normal</td>
<td>Normal-slightly elevated</td>
<td>Elevated</td>
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<tr>
<td>WBC (cells/mm³)</td>
<td>&lt;5 (lymphocytes and monocytes)</td>
<td>1,000-5,000 (range 100-10,000); PMNs</td>
<td>Lymphs</td>
<td>20-500; lymphs</td>
<td>10-500; lymphs</td>
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<tr>
<td>Protein (mg/dl)</td>
<td>45-50</td>
<td>Elevated &gt;45 (90%)</td>
<td>Normal-slightly elevated</td>
<td>Elevated</td>
<td>Elevated (100-500)</td>
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<tr>
<td>Glucose (mg/dl)</td>
<td>45-80 (65% of serum glucose)</td>
<td>Decreased &lt;40 (50-60%)</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased (35-40)</td>
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<td>Gram stain/culture</td>
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<td>Positive (60-90% + pathogen ID); Bacterial culture</td>
<td>Viral culture</td>
<td>Fungal culture</td>
<td><em>M. Tuberculosis</em> culture</td>
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<tr>
<td>Other</td>
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<td>PCRs: broad based and specific common pathogens</td>
<td>[RT]-PCR; Ab testing</td>
<td>India ink stain and cx; LA test for cryptococcal antigen</td>
<td>Acid fast smear</td>
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</table>
Viral Meningitis

- Clinical: p/w fever, HA, photophobia, nuchal rigidity, chills +/- constitutional sx (GI, URI); minimal ALOC
- CSF: mild lymphocytic pleocytosis (may be PMN predominance <24hrs), nml-mildly increased protein, nml-mildly decreased glucose; virus-specific PCRs
- Enteroviruses (coxsackieviruses, echoviruses, enteroviruses 68-71)=most common pathogen
  - Primarily fecal-oral contamination, also via respiratory droplets
- Also common: arboviruses (West Nile, St. Louis encephalitis, La Crosse, western equine encephalitis, Colorado tick fever, and tick-borne encephalitis viruses)
- HSV-2, HSV-1, EBV, VZV; HIV-1
Viral Encephalitis: Pathogens

- HSV-1, HSV-2
- Varicella-zoster (VZV) virus
- Adenovirus
- Epstein-Barr virus (EBV)
- Cytomegalovirus (CMV)
- Enterovirus
- Measles virus
- HHV-6
- HIV

- Tick-borne:
  - Tick-borne encephalitis virus
  - Powassan virus
  - Colorado tick fever virus
  - Lyme

- Mosquito-borne:
  - La Crosse virus
  - Snowshoe hare virus
  - St. Louis encephalitis virus
  - West Nile virus
  - Japanese encephalitis virus
  - Eastern equine encephalitis virus
  - Western equine encephalitis virus
  - Venezuelan encephalitis virus
  - Dengue virus
## Viral Encephalitis by region

<table>
<thead>
<tr>
<th>Virus</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Louis encephalitis</td>
<td>Central and Southeastern US (esp. Florida), western and central Canada, Mexico...and Maricopa County</td>
</tr>
<tr>
<td>La Crosse (California serogroup)</td>
<td>Midwest US in woodland areas (Wisconsin, Minnesota, Illinois, Indiana, Iowa, Ohio)</td>
</tr>
<tr>
<td>- snowshoe hare</td>
<td>-Canada, Rocky Mountains, Montana</td>
</tr>
<tr>
<td>Eastern equine encephalitis</td>
<td>East Coast from Massachusetts to Florida</td>
</tr>
<tr>
<td>Western equine encephalitis</td>
<td>Western North America (peak July-August)</td>
</tr>
<tr>
<td>Venezuelan equine encephalitis</td>
<td>Central and South America, cases in Texas</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Epidemic in China, northern Southeast Asia, northeast India, Nepal, Sri Lanka</td>
</tr>
<tr>
<td>Dengue</td>
<td>Hawaii, Asia, Africa, the Caribbean, Central and South America</td>
</tr>
<tr>
<td>Nipah virus</td>
<td>Malaysia, Bangladesh, India</td>
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</tbody>
</table>
Nonviral infectious encephalitis pathogens

- **Bacteria**
  - Borrelia burgdorferi (Lyme)
  - Anaplasma
  - Bartonella
  - Coxiella burnetii (Q fever)
  - Ehrlichia chaffeensis
  - Listeria
  - MTB
  - Mycoplasma pneumoniae
  - Rickettsia rickettsii (RMSF)
  - T. pallidum (syphilis)
  - T. whipplei

- **Fungi**
  - Cocci, Histo
  - Crypto

- **Parasites**
  - Amoebic: N. fowleri, Acanthamoeba
  - Baylisascaris
  - Balamuthia
  - Gnathostomiasis
  - Plasmodium falciparum
  - T. solium (NCC)
  - T. gondii
  - Trypanosomiasis
Neuroimaging Findings in Encephalitis
(adapted from Venkatesan et al CID 2013)

- Frontal lobe: N. fowleri
- Temporal lobe: Limbic encephalitis
- Basal ganglia or thalamus: Arbovirus (i.e. WNV), MTB
- Brainstem: Arbovirus, Listeria, Brucella, MTB
- Cerebellum: EBV
- Diffuse cerebral edema: respiratory viruses
- Space-occupying or ring-enhancing lesions: MTB and fungal, B. mandrillaris and Acanthamoeba, toxoplasma
- Hydrocephalus, basilar meningeal enhancement: MTB, fungal, i.e. Cocci
- Infarction/hemorrhage: MTB, fungal, respiratory virus
- Incomplete ring-enhancing lesions: ADEM (acute disseminated encephalomyelitis)
West Nile Virus: Clinical Syndromes

- Aseptic meningitis
- Meningoencephalitis: tremors prominent
- Acute flaccid paralysis: poliomyelitis-like syndrome (d/t direct infection of anterior horn cells); asymmetric
  - Also seen in SLEV, Chikungunya virus, enteroviruses
- Rhombencephalitis, movement disorders (parkinsonism), cerebellar dysfunction
West Nile Virus
Activity as of 9/13/2016

Per 100/000; www.cdc.gov
West Nile Virus: Neuroinvasive Disease
Activity as of 9/13/2016

Meningitis, encephalitis, acute flaccid paralysis
West Nile Virus

- ~20% symptomatic; CNS involvement in 1/150 infected patients
- Most at risk: older, immunosuppressed, chronic illness
- Clinical: p/w fever, flu-like illness, possibly rash, nausea, diarrhea
  - CNS sx often overlapping: encephalitis, aseptic meningitis, [radiculo]myelitis → AMS, paresis (e.g. acute bulbar/limb flaccid paralysis), tremor, seizures, Parkinsonian sx, HA, meningismus
- PMN predominance in CSF may last up to 48 hours-1 week
- Best for diagnosis=WNV IgM (may not be positive for up to 7 days after sx onset; may need repeat LP)
  - As with other antibody tests, look for 4-fold increase in IgG between acute and convalescent sera
  - WNV IgM may remains positive for months
- CSF PCR test (lower sensitivity)
- NAT (studied for use in screening for transfusion/transplant; may enhance diagnostic yield in symptomatic patients, esp w/in 8 days)
- Treatment: supportive care
  - No approved treatments
  - Experimental: IVIG, IFN, ribavirin

St. Louis Encephalitis Virus: Neuroinvasive Disease Reported Cases 2004-2013
SLEV

- May-October 2015: 23 cases in AZ
- 2016: 2 cases in SE NV so far
- (reported to CDC Arbonet)

- SLEV: another flavivirus
- Clinical presentation similar to West Nile Virus
HSV Encephalitis

- Clinical: subacute progressive fever, HA, behavioral changes, focal seizure activity, and focal neuro deficits
- MRI brain: high signal on T2 and FLAIR in medial and inferior temporal lobe extending up into insula
- EEG: Periodic lateralizing epileptiform discharges (PLEDs) maximal over temporal lobes
HSV Encephalitis

- CSF: increased OP, lymphocytic pleocytosis (5-500 WBCs), mild-mod increased protein, normal-mildly decreased glucose; +/- RBCs
- CSF viral cultures almost always negative
- PCR=gold standard for diagnosis
- BUT repeat LP if negative HSV PCR initially and strongly suspect as may be negative if:
  - LP within first 72 hours of sx
  - If acyclovir tx initiated
  - If inhibitors of PCR assay in CSF, i.e. porphyrin compounds from heme degradation in erythrocytes
- Keep autoimmune/paraneoplastic limbic encephalitis w/in differential
- Tx: Acyclovir 10mg/kg IV q8h x 14-21 days (may need to be renally adjusted)
A case in San Francisco

• 18 year old young woman admitted with status epilepticus
• Parents describe some atypical behavior over preceding several days
• MRI brain w/ abnml signal L temp lobe
• EEG w/ temporal PLEDs
• CSF w/ mild lymphocytic pleocytosis, +RBCs
• Empiric acyclovir initiated with subsequent improvement...HSV PCR neg...and then more hallucinations
• Repeat LP
Autoimmune/Paraneoplastic Limbic Encephalitis

- Repeat HSV PCR testing again negative; +NMDA-R antibodies
- Initiated on immunosuppressant tx w/ improvement; U/S for ovarian teratoma

- Autoimmune [non-infectious] limbic encephalitis
  - Paraneoplastic or non-paraneoplastic
    - Including lung, breast, testicular, thymus malignancies
    - NMDA-R Ab
    - AMPA-R and GABAB-R Ab
    - Voltage-gated potassium channel complex Ab (VGKC/LGi1 Ab)
    - Tx: Identify and treat underlying malignancy if present; immunosuppressants: steroids, IVIG, plasmapheresis, etc.
• HSV encephalitis vs mimics (Chow et al CID 2015)
  – HSV: mesial temporal lobe, insular cortex, cingulate gyrus
  – Temporal lobe encephalitis (251 cases): 43% infectious, 16% non-infectious
  – HSV (n=60), TB (n=8), VZV (n=7)
  – Autoimmune (n=21)
  – HSV clinical features: more likely older, white, acute presentation, fever; less likely rash, bilateral TL involvement, lesions outside TL, insula, cingulate

• DWI more sensitive than T2 axial/FLAIR
• FDG-PET: to track disease activity (e.g. anti-NMDA-R Ab)

Encephalitis Imaging
• Encephalitis cases in CA: 40-50% = unknown etiology (Glaser et al. CID Aug 2013)
• In young pts (<=18 yo): anti-NMDA-R encephalitis >4x more frequent than HSV-1, WNV, or VZV infection (include in ddx)
• ~20% of 100 w/ HSV encephalitis w/ initially negative HSV PCR (likely less, but should repeat CSF at 3 days if suspected)
• Dalmau: HSV-1 can trigger anti-NMDA-R encephalitis
• Consider rabies and amoebal infxns: Ballamuthia mandrillaris; Acanthamoeba (granulomatous, more indolent vs Naegleria fowleri)

California Encephalitis Project
Bacterial Meningitis

• Incidence: ~5-10/100,000 persons/year (0.6% of all deaths, WHO)
• A neurological emergency
• Early recognition is critical: meningitic syndrome → rapid evaluation → blood cx STAT → +/- CT head → lumbar puncture
• CT head recommended before LP if:
  – Patient immunocompromised
  – History of CNS disease
  – New onset seizure
  – Papilledema
  – Focal neurological deficit
  – Altered level of consciousness
Management of Bacterial Meningitis

• If delay to LP (i.e. waiting for neuroimaging), draw blood cx then start empiric abx

• Abx duration 7-21 days, depending on organism (gram neg bacilli and Listeria 21 days)

• Repeat LP in all patients w/ pneumococcal meningitis 24-36 hours after initiation of abx given increased incidence of PCN and cephalosporin-resistant strains
  – Gram stain should be negative and cx no growth
  – WBC may be elevated (increased w/in 18-36 hrs)

• Steroids: in suspected Pneumococcal meningitis in cases of community-acquired meningitis
  – Benefit only seen in high income countries, Strep pneumo in adults (decreased hearing loss, decreased neurological sequelae, decreased mortality in Strep pneumo; increased rate of recurrent fever but no other AEs)
  – Reserved for severely ill, meningitis complications
  – Continue if gram stain w/ gram + diplococci or + cx (?other ABM etiologies)
  – Give 15-20 min before or with 1st dose of abx (?timing not so important)
  – Dexamethasone 0.15mg/kg x 2-4 days

• Other studies: induced hypothermia, adjunctive glycerol → did worse
## Empiric Treatment in Bacterial Meningitis

<table>
<thead>
<tr>
<th>Age</th>
<th>Organisms</th>
<th>Empiric Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 month</td>
<td><em>S. Agalactiae</em> (group B strep), <em>E. coli</em>, <em>L. monocytogenes</em>, <em>Klebsiella</em> species</td>
<td>Ampicillin + Cefotaxime or Aminoglycoside</td>
</tr>
<tr>
<td>1 month – 2 years</td>
<td><em>S. pneumoniae</em>, <em>N. meningitidis</em>, <em>S. agalactiae</em>, <em>H. influenzae</em>, <em>E. coli</em></td>
<td>Vancomycin + 3\textsuperscript{rd} generation cephalosporin (e.g. Ceftriaxone) or 4\textsuperscript{th} generation (e.g. Cefepime)</td>
</tr>
<tr>
<td>2 years – 50 years</td>
<td><em>N. meningitidis</em>, <em>S. pneumoniae</em></td>
<td>Vancomycin + 3\textsuperscript{rd} generation cephalosporin</td>
</tr>
<tr>
<td>&gt; 50 years</td>
<td><em>S. pneumoniae</em>, <em>N. meningitidis</em>, <em>L. monocytogenes</em>, aerobic gram negative bacilli; <em>H. influenzae</em></td>
<td>Vancomycin + 3\textsuperscript{rd} generation cephalosporin + Ampicillin</td>
</tr>
</tbody>
</table>
A Case

• 73 yo man, hx HTN and CAD, from NM
• 12/2014: URI sx, myalgias, fatigue
• 1/2015: HA, 6 months progressive gait disturbance, now using cane; hypophonia; bradykinesia; progressive cognitive changes (confusion, forgetting apptmts)
• 7/2015: Mental status test: missed points for orientation, calculation, attention, construction, recall; breakdown of smooth pursuits; bradykinetic; simian posture, shortened steps, shuffling
The Workup

- CSF: 99 WBCs (93%L, 3%M, 3%N), prot 266, gluc 19 (serum glucose 100)

- CSF Cocci studies: Cocci IgM and IgG+ by EIA, Cocci IgG by ID, CF 1:16; serum Cocci studies also positive
Other Cocci Cases
Coccidioides immitis

- Endemic in the SW desert: AZ, CA, NM, TX
- Valley fever
  - pulmonary infxn (usually asymptomatic or self-limited)
  - Dissemination uncommon, but when occurs 1/3rd have CNS disease
- Clinically presents as chronic basilar meningitis (HA +/- CN palsies, ALOC)
- Complications: Hydrocephalus, vasculitis/stroke, myelitis/spinal block, coccidioidomas
- CSF pleocytosis: may be neutrophilic (early) or eosinophilic (70%)
- Complement fixation Ab test: 75% sensitivity, 100% specificity; cx only + 25% of cases; check IgM and IgG also; PCR test available in CSF
Coccidioidomycosis

- Without treatment, often fatal
- **Induction therapy:**
  - Fluconazole 400-1200mg daily (variable duration)
- More severe CNS disease/treatment failure:
  - Liposomal amphotericin B
- Consider intrathecal amphotericin
  - IT ampho 0.1-1.5mg per dose
- Consider short-term high dose steroids in setting of vasculitis
- **Lifelong suppression** required to prevent recrudescent disease
  - Fluconazole 400mg daily (often higher doses may be needed) (preferred d/t exceptional CSF penetration)
  - 78% w/ relapsing disease in those who discontinued tx (observational studies)
- Voriconazole and posaconazole: excellent activity vs C. immitis but limited studies (cost and side effects are common issues)
- VPS for hydrocephalus

Local to Global Perspectives and Challenges

• Increased use of immunosuppressants:
  – Post-transplant: mycophenolate mofetil
  – Biological drugs: monoclonal antibodies
    • E.g. PML (Natalizumab)
  – Release of latently infected immune cells and decreased immune surveillance

• Globalization: breakdown of geographical barriers
  – Expansion of geographic range
  – Re-emergence/resurgence

• Climate Change
  – E.g. Zika virus: unusually wet winter followed by warm summer in Southern Brazil and Uruguay (Aedes sp most active in warm weather, more people outside, more water storage containers)

• Ethical/social implication
  – Limited access to contraceptives, postponement of pregnancy

• Resource poor settings
  – Surveillance
  – Strain on medical system

Selected References/Further Reading

1. www.cdc.gov/mmwr/ (Centers for Disease Control and Prevention/Morbidity and Mortality Weekly Report)