Pediatric Infectious Diseases Case Based Learning

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Pediatric Infectious Diseases
March 1st, 2014
Case 1 - History

- 3-1/2 month old baby boy with history of hemophilia and GER.
- Acute onset of erythematous rash with generalized distribution.
- Fever, 101.4F.
- Twitching of the left arm with eyes deviated to the right side and staring, lasting for about 30 minutes, followed by fussiness.
- August 2012.
Case 1 - History

- Full term baby, delivered at 39 weeks, SVD.
- No perinatal complications.
- Pregnancy unremarkable except for preterm labor at 29 weeks.
- Unremarkable prenatal screening labs.
- The mother denies any STD’s.
- No maternal fever during delivery.
- Medications: bethanecol and ranitidine.
- Family history significant for hemophilia & MGM with epilepsy.
- Living with parents. No recent travel history.
Physical Examination

- Stable vital signs, fever 38.2 C, axillary.
- Erythematous, macular rash with generalized distribution.
- Seizure activity with eyes rolled up to the right side and staring. Twitching of left arm and leg. The episode lasted one minute and 30 seconds.
Labs

- CBC: WBC 12 (N25%, L65%, M44%), Hgb 11 and platelets 217,000.
- CRP: < 0.5
- Serum electrolytes normal.
- UA: Normal.
- LP: WBC 32 (N30%, L26%, M44%), no RBC, glucose 43, protein 43. Gram stain: Negative.
- CT scan brain: Normal.
Differential Diagnosis

- Bacterial meningitis
- Enterovirus meningitis
- HSV meningoencephalitis
- St. Louis Encephalitis
- Normal CSF for age
- Measles
- Unspecific aseptic meningitis
Additional Labs

- CSF culture
- Enterovirus PCR
- HSV PCR
- Blood culture
- Urine culture
- RSV
- Flu
Treatment

- Regular floor
- Close monitoring
- Cardiac monitor
- IVF
- Empiric intravenous Ceftriaxone
- Empiric Acyclovir
- Neurology consultation
- EEG
- Phenobarbital
MRI Brain
Hospital Course

- Clinical improvement but high persistent fever.
- Abnormal EEG.
- No more seizures after phenobarbital.
- Blood culture negative.
- Urine culture negative.
- CSF culture negative.
- Enterovirus PCR negative.
- HSV PCR negative.
Any recommendations at this time?

- Continue antibiotics and discontinue acyclovir.
- Continue antibiotics and acyclovir.
- Continue only acyclovir.
- Discontinue antimicrobials and observe.
- Send additional testing.
Diagnosis

- West Nile titers in CSF (8/5/12)
  - IGG: 0.22
  - IGM: 1.68 positive

- West Nile titers in serum (8/5/12)
  - IGG: 1.01
  - IGM: 4.56 positive

- West Nile titers in serum (9/7/12)
  - IGG: 4.19 positive
  - IGM: 33.09 positive
Probable Transmission?

- Mosquito bite
- Breastfeeding
- In utero
- False positive results
- Cross reactivity with other viral illness
West Nile virus (WNV) activity reported to ArboNET, by state, United States, 2012 (as of September 11, 2012)

Almost 40 percent of all cases have been reported from Texas.
### West Nile Virus Human Infections, 1999-2012, USA

<table>
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<th>Year</th>
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Approximate Global Distribution of West Nile Virus, by State/Province, 2007

West Nile Virus - The most widespread of the flaviviruses
West Nile Infection

- Asymptomatic - ≈ 80%
- Mild febrile illness - ≈ 20%
- Neuroinvasive disease - ≈ 1%
- Incubation period goes from 2 - 14 days (usually 2-6d).
- Diagnosis by serologic testing in serum and/or CSF.
- No specific therapy.
Ways of Transmission

- The vast majority of WNV infections are acquired through mosquito bite.
- In 2002 previously unrecognized mechanisms were described:
  - Through blood transfusion and transplantation.
  - Transplacentally.
  - Through breast milk.

O’Leary DR, Hayes EB. Pediatrics 2004. 113 (5): 1375-1381
West Nile in Newborns

- In August 2002, a 20 year old pregnant woman in her 27th week was hospitalized in NY due to a febrile illness and neurological symptoms. Reactive WN IgM in serum and CSF.
- The baby was delivered at 38 weeks of gestation. The baby had bilateral chorioretinitis, severe white matter loss, cystic lesion in left temporal lobe. WNV IgM was detected in mother’s serum, cord blood and infant serum.

[Link to CDC report](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5150a3.htm)
2003 WNV Pregnancy Registry

- Collaboration with clinicians / local and state health departments
- Pregnancies complicated by WNV illness reported to CDC
- Clinical status of mother and infant collected following informed consent
- Placenta, umbilical cord, cord blood, and breastmilk collected at time of delivery
2003 WNV Pregnancy Registry

- 77 women infected with WNV during pregnancy in 16 states
- 71 delivered 72 babies
- 4 women have miscarriages
- 2 had elective abortions
- One infant had WNV meningitis at 10 days. Mother with WNV within 6 days of delivery.
- One infant born with rash and CoA, WNV IgM positive at one month, maternal WNV at delivery.
- One baby had WNV encephalitis and underlying lissencephaly at 17 days and subsequently died.

3 possible congenital infections

Pediatrics. 2006 Mar;117(3):e537-45
One case report of possible breast milk transmission of WNV.

Since 2003 the CDC collected reports of maternal or infant WNV infection during the breastfeeding period.

Milk samples from infected mothers were evaluated for antibodies and WNV PCR.
<table>
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<tr>
<th>Case</th>
<th>Days After Onset of Maternal Illness</th>
<th>IgA</th>
<th>IgM</th>
<th>IgG</th>
<th>WNV Neutralizing Antibody Titer</th>
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<th>SLEV Neutralizing Antibody Titer</th>
<th>RNA</th>
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<th>IgG</th>
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</table>

P indicates positive; N, negative; —, testing not performed.

*To indicate specificity to WNV, only samples with neutralizing antibody titers ≥10 and 4 times higher than corresponding titers to SLEV were considered positive.*
Screening for asymptomatic mothers is not recommended.

Pregnant women with symptoms compatible with WNV infection should be tested.

Fetal evaluation should include detailed u/s examination no sooner than 2-4 weeks after onset of WNV symptoms.

Prevention of mosquito bites is key during pregnancy and breastfeeding.
Case 2 - History

- 6 month old LAM.
- Negative past medical history.
- One day history of fever and cold symptoms.
- Acute altered mental status, sleepy and difficult to arouse.
Case 2 – Physical Exam

- Stable vital signs.
- Sleepy but arousable. Reactive to touch and stimulation.
- Decreased tone.
- Right TM with redness and fluid in middle ear.
- Normal cardiovascular and pulmonary exam.
- Normal abdominal examination.
- No rashes.
Case 2 - Labs

- CBC: WBC 15.2 (N8%, L76%, M12%, many variant Ls), Hg 11 and Hct 35, platelets 197,000.
- CMP and UA: Normal.
- Toxicology screen positive for acetaminophen.
- LP: WBC 158 (7%N, 52%L, 41%M), RBC 16, glucose 49 and protein 440. Gram Stain negative.
- RSV negative.
- Rapid Flu was positive for Influenza A.
Case 2 – Imaging Studies

- CXR: C/W viral lower respiratory infection vs RAD.
- CT scan brain w/o contrast: Abnormal patchy hypodensity of the white matter bilaterally and both thalami. No cortical involvement.
Case 2 - Differential Diagnosis

- Bacterial meningitis
- Enterovirus meningoencephalitis
- HSV meningoencephalitis
- ADEM
- Vasculitis
- Acute necrotizing encephalitis
- Toxic metabolic encephalopathy
Additional Laboratories

- Blood culture
- Urine culture
- CSF culture
- HSV PCR CSF
- Enterovirus PCR CSF
Additional Labs

- Flu A PCR respiratory – positive
- Flu B PCR respiratory - negative
- H1N1 PCR respiratory - negative
- Flu PCR CSF - negative
- Viral CSF culture - negative
- Metabolic work up - normal
Case 2 - Treatment

- Oseltamivir
- Amantadine
- High dose methylprednisolone
- IVIG
- All of the above
Case 2-Treatment

- PICU admission for 3 days.
- Received IV Ceftriaxone and Vancomycin first 48 hours.
- Received Acyclovir until HSV PCR available.
- Oseltamivir 3 mg/kg BID for 10 days.
- Solumedrol 1 mg/kg every 6 hours for 5 days and then changed to oral prednisone.
CASE 2 – Clinical Progress

- Progressive neurological improvement.
- Normal visual evoked potentials.
- Normal EEG.
- Discharged home 11 days after admission on weaning schedule of prednisone for 6 weeks.
- Follow up ID Office 2 weeks later and he was back to normal.
Influenza and Neurological Manifestations

- Neurologic complications of influenza have been well described in the literature since the diagnosis of encephalitis lethargica during the 1918 influenza pandemic.
- Neurologic manifestations of influenza are now known to include:
  - Encephalitis
  - Acute Disseminated Encephalomyelitis
  - Guillain-Barre Syndrome
  - Transverse Myelitis
  - Acute Necrotizing Encephalopathy
  - Reye’s Syndrome

Acute Necrotizing Encephalopathy

- Reports of ANE began surfacing from Japan during the influenza epidemics of the mid- and late 1990s.
- Acute necrotizing encephalopathy, first described in 1995 has been linked to influenza, as well as other infectious illnesses such as with HHV6-6, measles, parainfluenza virus and *Mycoplasma*.
- Influenza-associated central nervous system (CNS) dysfunction has also been reported, although infrequently, in Europe and USA.
Acute Necrotizing Encephalopathy - Proposed Diagnostic Criteria

- Acute onset of encephalopathy with or without convulsions.
- Lack of CSF pleocytosis. Many showed elevated protein.
- Multifocal, symmetric brain lesions affecting the thalamus bilaterally, brainstem, tegumentum, cerebral periventricular white matter and cerebellar medulla.
- Exclusion of resembling diseases (HUS, hypoxia, heat trauma, neurodegenerative disorders, Reye’s syndrome).
The pathogenesis of ANE and Influenza remains unknown. Doubt direct viral insult and suspect more an immune reaction:

- In Japanese children with influenza associated encephalopathy, influenza RNA was rarely detected.
- US publications of cases in children and adults with influenza encephalopathy have not identified influenza by PCR and/or culture from CSF but from respiratory samples.
Cytokine induced neurotoxicity:
- Rapidity of onset.
- Lack of viral antigens in brain tissue.
- Hyperactivated cytokine response:
  - High plasma concentrations of IL6 and TNF α,
  - High serum and CSF concentrations of IL6, IL8, IP-10, MCP-1 in 3 adults with influenza encephalopathy.
Acute Necrotizing Encephalopathy: Prognosis and Mortality

- The mortality can reach about 30%.
- Abnormal LFT and thrombocytopenia were strongest predictors of mortality.
Acute Necrotizing Encephalopathy-Mortality

- Diffuse cerebral edema and perivascular hemorrhage in the bilateral thalami and putamina.
- Congestion of arteries, veins and capillaries.
- Acute swelling of oligodendrocytes.
- Progressive rarefaction of tissue.
- Necrosis of neurons and glial cells.
- No viral antigens in brain tissue samples.
ANE Association with H1N1-US

- Encephalopathy associated with the novel H1N1 influenza strain was reported in a case series of 4 pediatric patients in the United States in May 2009.
- All 4 patients had mild seizures and/or altered mental status, and all recovered fully without any neurological sequelae at discharge.
- There is one report of a 7-year-old that progressed to brain death.
Acute Necrotizing Encephalopathy-Therapy

- Supportive care.
- Antiviral therapy (Amantadine and Oseltamivir).
- Methylprednisolone pulse therapy.
- Large doses of IVIG.

✓ Reduced mortality from 30% to 15% in Japan.
Case 3 - History

- 12-year-old girl was admitted to CCMC for FUO, with fevers for 1 month.
- Intermittent fever for weeks. OM treated with amoxicillin 4 weeks ago. OM treated with azithromycin 7 days PTA. High fever and chills, headache, nausea, abdominal discomfort in the past week, and admitted to outside hospital.
Case 3

- **ROS:** c/o fevers, chills, ear pain, sore throat, headache, abdominal pain, vomiting, diarrhea. No cough, runny nose, jaundice, urinary symptoms, rash, extremity swelling or pain.

- **PMH:** negative except for recurrent OM. No medications. NKDA. Immunizations UTD. Development normal.

- Lives with mother, stepfather and 18 mo and 4 yo siblings. Sibling just recently had fever. Family hx is unremarkable.
Case 3

PE: Afebrile on admission, but febrile to 41.2°C in the first 24 hours of hospitalization. Normal HR, RR, BP. 37.5 kg. Alert, chills, distressed but nontoxic.

- HEENT with posterior OP erythema. TM’s normal. Possible mild frontal swelling.
- Chest/CV normal.
- Abd mildly distended, mildly tender, no HSM, no rebound.
- Extremities normal.
- Skin without rash.
- Neuro nonfocal.
Case 3

What diagnostic study would you like next?

1. Stool culture
2. ECHO
3. CT head with contrast
4. Sinus x-rays
5. Bone scan
Mastoids on the left are opacified. There is erosion of the inner skull table at the level of the mastoids. Loculated subdural fluid collections with thick meningeal enhancement is noted in the posterior fossa left greater than right. There is meningeal enhancement in the posterior fossa at the level of the pons. The left sigmoid sinus is smaller than the right but there does appear to be blood flow.
Case 3

- Neurosurgery took patient to the OR the morning of HD #3. Left suboccipital burr hole drilled and thick yellow-brownish pus coursed freely from the burr hole. Bilateral epidural suboccipital empyemas drained and irrigated. Cultures sent. PICC placed.

- Neurotology consulted and took patient to the OR on HD #4 for left mastoidectomy, drainage of a left posterior fossa epidural abscess, and placement of bilateral pressure equalization tubes. Cultures were again sent from the OR. Concern for probable sigmoid sinus thrombosis ➔ MRI and MRV of brain done on HD #4, and showed sigmoid sinus thrombosis.
After the CT on HD #2, IV ceftriaxone, vancomycin and metronidazole were begun.

Admission blood culture and epidural abscess cultures grew a streptococcus species, identified on HD #5 as *Streptococcus intermedius*. The organism was not viable for in-house susceptibility testing and was sent out. It was found to be susceptible to erythromycin, meropenem, linezolid, penicillin and vancomycin.

Difficulty tolerating ceftriaxone and metronidazole, so treatment changed to meropenem.

Heparin drip started HD #6 (24 hours post-op), and transitioned to Lovenox.

Patient is doing well; plan for 6 weeks IV antibiotics and 3 months Lovenox.
Mastoiditis

- Most common suppurative complication of acute otitis media; in half of cases, acute mastoiditis is the first evidence of acute otitis media.
- Acute mastoiditis—symptoms less than one month.
- Masked mastoiditis—low-grade persistent middle ear and mastoid infection, occurring in patients with persistent middle-ear effusion or recurrent episodes of AOM with sufficient antibiotic tx.
- Chronic mastoiditis—infection of mastoid air cells lasting months to years.
Mastoiditis-Microbiology

- *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus* most common.
- *Pseudomonas aeruginosa* if hx of recurrent AOM and recent antibiotic use, and perforation of TM.
Mastoiditis - Diagnosis

- Clinical dx with ear pain, postauricular tenderness, erythema, swelling, fluctuance or mass, and displacement of the auricle (down and out in < 2yo, up and out in > 2yo). Also, usually fever. Edema of the EAC, TM perforation, otorrhea may be present.
- CT temporal bone with contrast if lacking characteristic findings or to determine severity.
- CT brain with contrast if suspect intracranial complications.
- MRI with contrast best for evaluating extraaxial fluid collections and vascular complications.
Mastoiditis--Management

- Uncomplicated: IV antibiotics, myringotomy +/- tympanostomy tube placement. Simple mastoidectomy if no improvement in 48 hours. Change to oral antibiotics once definite clinical improvement, to continue for a total of about 3 weeks.
- Complicated, with extracranial or intracranial complications: IV antibiotics, myringotomy/tubes, mastoidectomy; drainage of subperiosteal abscess; drainage of intracranial suppurative collections; anticoagulation for venous sinus thrombosis.
- Antibiotic choice: We usually start with ceftriaxone and clindamycin. This patient with intracranial extension of infection was treated more broadly, as for a brain abscess.
Mastoiditis—Extracranial Complications

- Subperiosteal abscess
- Facial nerve palsy
- Hearing loss
- Labyrinthitis with tinnitus, hearing loss, nausea, vomiting, dizziness, vertigo, nystagmus
- Osteomyelitis of other parts of the skull; e.g. petrositis
- Bezold abscess—neck abscess located beneath sternocleidomastoid and digastric muscles.
Mastoiditis - Intracranial Complications

- Meningitis
- Temporal lobe or cerebellar abscess
- Epidural or subdural abscess
- Venous sinus thrombosis
Case 4

- 11-year-old girl with high fevers 104-106 degrees for eight days, and fatigue, with illness starting 12/3/12.
- Tested negative for influenza and group A Strep four days into the illness. EBV titers c/w past infection. CBC with leukopenia and mild thrombocytopenia.
- 6 days into the illness, developed rash starting on abdomen and spreading to legs, back and face. Some lesions palpable.
- Achy all over; c/o headache with fever.
- No vomiting, diarrhea, URI symptoms.
PMH: Unremarkable, with no hospitalizations, surgery, illnesses.

Medications: Ibuprofen and acetaminophen for fever.

NKDA.

Immunizations: UTD including flu vaccine.


Family Hx: Mother with hx of uterine cancer; paternal aunt with arthritis followed by a rheumatologist and treated with an injection Q 3 months.
Case 4

- **PE:** Temp in ED 40.2, current temp afebrile, P 99, RR 21, BP 106/55. Wt 39 kg.
- HEENT normal, except possible mild conjunctival injection.
- No adenopathy.
- Chest clear.
- CV RRR without murmur.
- ABD benign, no HSM.
- EXT normal, no swelling.
- Skin with faint nonblanching light purple 2-3 mm macular rash mainly on the trunk, with a few papules. No palmar or plantar rash.
Labs on admission:

- WBC 3.9 with 20 segs, 40 bands, 37 lymphs, 3 monos.
- Hgb 11.6, Hct 33.3, Plt 89,000, ESR 21, CRP 6.1.
- CMP normal except for AST 159, ALT 183, bilirubin normal.
- CXR normal.
- Monospot negative.
- Rapid influenza testing negative.
- Parvovirus serology sent.
- Blood and urine cultures sent.
Case 4

Summary: 11-year-old girl with high fevers for 8 days, fatigue, myalgias/arthralgias, vasculitic rash, mild leukopenia, mild anemia, thrombocytopenia, elevated transaminases, elevated CRP and mildly elevated ESR.
Case 4

What is the most likely diagnosis?
A. Viral infection
B. Rheumatologic disorder
C. Rickettsial infection
D. Kawasaki Disease
E. Neisseria meningitidis infection
Case 4

What further lab evaluation would you like to do?

A. Blood culture
B. Viral studies—respiratory viral PCR panel, EBV PCR, CMV PCR, adenovirus PCR
C. Rheumatologic workup—ANA, RF, complement levels
D. Serologic studies for RMSF, Ehrlichia, Leptospirosis
E. All of the above
Hospital course: Empirically treated with ceftriaxone and doxycycline.
She defervesced, rash faded, and she felt much improved by discharge on hospital day #4.
Followup labs with normal WBC, improving plt count and ALT, AST.
Home on doxycycline to complete a 7 day course.
Case 4

Labs from hospitalization:

- Adenovirus, EBV, CMV blood PCRs negative.
- Respiratory viral PCR panel negative.
- Parvovirus, Ehrlichia chaffeensis, Rickettsia rickettsii, Leptospirosis serology negative.
- ANA, RF negative; C3 and C4 normal.
- Blood and urine cultures negative.
Labs at follow-up, 16 days after onset of illness:

- CBC with WBC 7.4, Hgb 11.7, Plt 343k.
- AST 60, ALT 111.
- Parvovirus and Ehrlichia serology negative.
- *Rickettsia* IgG negative, and IgM 1:512.
- Hepatitis panel negative for Hep A,B,C infection.
Rickettsia rickettsii: Small tickborne coccobacillus, obligate intracellular bacterium.

Primary targets of infection are endothelial cells lining the small vessels of all major tissues and organ systems. Causes diffuse microvascular injury and fluid leakage into extravascular spaces.
Zoonosis: Occurs throughout North, Central and South America. Complex life cycle involves several species of ticks and mammals. Humans are incidental hosts.

- *Dermacentor variabilis*: Most important vector in North America, transmitting infection in southern, midwestern and coastal US and Canada.

- *Dermacentor andersoni*: Main vector in Rocky Mountain states.

- 90% of cases April to September.
Clinical manifestations: Abrupt onset high fever, frontal headache, nausea, vomiting, generalized myalgia esp. in lumbar region, thigh and calf.

In pediatric cases, may see irritability, severe abdominal pain, splenomegaly, conjunctivitis, periorbital edema.

Rash starts 2-4 days into illness; begins as pink blanching macules on distal extremities, spreading centrally. Classic rash is petechial with distribution including palms and soles; not observed until 5 days of illness; 10% of pts may have atypical or absent rash.

Severe manifestations: Interstitial pneumonitis, ARDS, myocarditis, DIC, meningoencephalitis, renal failure, gangrene.
RMSF

- Laboratory findings: Hyponatremia, hypoalbuminemia, anemia, thrombocytopenia; WBC usually nl to elevated.
- Diagnosis: Serology most commonly used, but in 50% of pts, antibodies not detectable until 2nd week of illness. Fourfold or more increase in titers between serum samples 3-4 weeks apart is diagnostic. Probable diagnosis with a single IFA serum titer of 1:64.
Treatment:

- Start tx empirically immediately when suspected.
- Doxycycline drug of choice for adults and children: 100 mg BID for >45 kg; 2.2 mg/kg BID for <45 kg. IV doxy for severe dz. Duration at least 3 days after clinical improvement, and a minimum of 5-7 days.
- With doxy tx, defervesce in 24-48 hrs; may be slower in severe illness.
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