Clinical Manifestations and Diagnosis

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CME Disclosure

• No financial conflicts of interest.
9yo girl presented in August with a 4-day history of frontal headache, nausea, and vomiting.

Initially diagnosed with a viral syndrome by PCP.

Over the next 24 hours, she had increased frontal headache, somnolence and emesis.

On day 8 of symptoms developed intermittent hallucinations, and increased agitation.

Pt became more lethargic at home, referred to the ED.

Upon ED arrival, noted to be febrile, meningeal signs were subtle, but she has having agitation and altered sensorium.
Past Med Hx: Asthma
Past Surg Hx: none
Family Hx: HTN, DM
Immunizations: UTD
Social Hx:
– 4th grade
– Lives with parents and 2 siblings
– No pets/travel/sick contacts

Meds:
• Vancomycin
• Ceftriaxone

Allergies: amoxil (rash)
Any other questions you may want to ask?

Exposure History

• Sick contact
• Recent illness
• Substance exposure or abuse
• Travel
• Animal, insect including tick bites
• Water exposure
Water exposure

• Fresh water
  – Lakes
  – Rivers
  – Ponds
  – Hot springs

• Unchlorinated sources
  – Pools
  – Wells
  – Sprinklers
Physical exam

Tmin 95.5, Tc 98.2   HR: 76   RR: 28   BP: 106/73

- General: NAD, in bed, agitated, but with episodes of cooperation with exam
- HEENT: PERRL, MMM, oropharynx clear
- NECK: no lymphadenopathy. Pain on flexion; but full range of motion
- RESP: CTA bil.
- CVS: RRR, no murmur, no peripheral edema.
- ABD: NT/ND, +BS, no HSM.
- NEURO: CN II-XII grossly intact. No apparent focal deficit. Intermittent agitation, and hallucinations
• Evaluation was done with LP for CSF analysis (including cultures, enterovirus and HSV PCR), CBC with Diff, Blood cx.

• Admitted to the floor with the clinical diagnosis of meningoencephalitis.
Labs

- **CSF (LP):** Opening pressure >55
  WBC 3180 (N80), RBC 70
  Glucose 25, Protein 345

- **18** × **278**
  N70 B5

- **Na 137**
- **Cr 0.9**
- **AST 50, ALT 30**
- **Alb 4**

She was started on Vancomycin, ceftriaxone and Acyclovir
Any suggestion for laboratory testing

- Wet prep
- Gram stain --- Pathology request to look for trophozoites
- Amoeba culture
- PCR
Summary of events

Day 0
- Fresh water exposure

Day 4
- Headache
- Nausea
- Emesis
- Fever
- Diagnosed with a Viral Syndrome

Day 8
- ED Evaluation
  - CSF
  - WBC 3180 (N 80%)
  - RBC 70
  - Glucose 25
  - Protein 345
- Vancomycin
- Ceftriaxone
- Acyclovir

Wet prep was done and was positive for Amoeba
Encephalitis Overview

• Differential Diagnosis
• PAM presentation
General Causes

• Infections
  – Bacteria (Bartonella, Lyme, Mycoplasma)
  – Viruses (EV, HSV, arboviruses, rabies)
  – Fungi (Cryptococcus, Coccidioides)
  – Parasites (Naegleria, cysticercosis, malaria)

• Immune-mediated
  – Systemic inflammatory diseases: eg. SLE
  – Parainfectious: e.g. Mycoplasma, ADEM
  – Paraneoplastic: e.g. NMDA receptor antibodies
Anti-NMDAR Encephalitis

- N-Methyl-D-Aspartate receptor antibodies
- Described in 2007
- Median age 19 years – 40% children
- May occur with ovarian teratomas
- Common psychiatric and behavioral symptoms
Primary Amoebic Encephalitis

- *Naegleria fowleri*
- 1962-2013, 132 U.S. cases, 34 Florida cases
  - 4 survivors
  - 84% children <18, >75% males
- Acquired from freshwater lakes, rivers, hot springs, pools or tap water
  - Found in ½ of Florida lakes surveyed
  - Exists in lake bottom sediment
- Thrives in freshwater at >86°F, prefers 115°F
- Killed by drying and chlorine 1 ppm

Naegleria fowleri

life cycle
Primary Amoebic Encephalitis

• Incubation period: 1-5 days
• Symptoms: headache, fever, nausea, vomiting
  – Later stiff neck, mental status changes, seizures
• Death in about 5 days (1-12 days)
CSF Indices in PAM

• WBC count: 300-26,000/mm$^3$
  – Mostly neutrophils
• RBC count: 0-24,600/mm$^3$
• Protein: 100-1000 mg/dL
• Glucose: <10 mg/dL

Number of Case-reports of Primary Amebic Meningoencephalitis Caused by *Naegleria fowleri* (N=132) by State of Exposure*— United States, 1962–2013

- State of exposure unknown for 4 cases.
- Does not include one case from USVI.
Factors to Highlight Specific Etiologies

- Age
- Animal contact
- Insect contact
- Underlying or recent disease (medical or family history)
- Travel
- Recreational activities
- Vaccination status

Animal Contacts

• Bats: rabies virus, Nipah virus
• Cats: rabies virus, *Bartonella henselae*, *Coxiella burnetti*, *Toxoplasma gondii*
• Dogs: rabies virus
• Old world primates: herpes B virus
• Raccoons: rabies virus, *Baylisascaris procyonis*
• Rodents: lymphocytic choriomeningitis virus
• Sheep and goats: *Coxiella burnetti*
• Skunks: rabies virus

Insect Contacts

- Mosquitos: WNV and other arboviruses, malaria, Japanese encephalitis virus
- Ticks: tickborne encephalitis virus, *Bartonella henselae*, ehrlichiosis, *Rickettsia rickettsiae*, *Borellia burgdorferi*

Underlying Disease

- Agammaglobulinemia: enteroviruses, *Mycoplasma pneumoniae*
- Other immunocompromised: HSV, CMV, EBV, VZV, WNV, Toxoplasma, M. tuberculosis, fungal infections
- Recent illness or vaccination: ADEM (acute disseminated encephalomyelitis)

International Travel

- Africa: rabies, WNV, malaria, trypanosomiasis
- Australia: Murray Valley encephalitis virus, Japanese encephalitis virus, Hendra virus
- Central and South America: rabies, arboviruses, malaria, RMSF, cysticercosis
- Europe: WNV, tickborne encephalitis virus, Anaplasma phagocytophila, Lyme disease
- India, Nepal: rabies, Japanese encephalitis virus, malaria
- Middle East: WNV, malaria
- Russia: tickborne encephalitis virus
- SE Asia, China, Pacific Rim: Japanese encephalitis virus, tickborne encephalitis virus, Nipah virus, malaria, cysticercosis

Domestic Travel

- Ohio & Mississippi river valleys: blastomycosis and histoplasmosis
Domestic Travel

• Northeastern, upper Midwest: Lyme disease

Incidence per 100,000
By county, 2012

CDC. MMWR 2014; 61(53)1-121.
Domestic Travel

• Central Atlantic: RMSF

Incidence per 100,000
By county, 2012

CDC. MMWR 2014; 61(53)1-121.
Domestic Travel

- Desert southwestern states: Coccidioidomycosis

73% in Arizona, 25% in California

Number in 2012
By state

CDC. MMWR 2014; 61(53)1-121.
Recreational Activities

- Camping/hunting: all mosquito or tick related infections
- Sexual contact: HIV, syphilis
- Spelunking: rabies, *Histoplasma capsulatum*
- Swimming in fresh water: enteroviruses, *Naegleria fowleri*

Unvaccinated Status

- *Bordetella pertussis*
- *Haemophilus influenzae b*
- Influenza virus
- Japanese encephalitis virus
- Measles
- Mumps
- *Neisseria meningitidis*
- Rubella
- *Streptococcus pneumoniae*
- Varicella zoster virus
Encephalitis Management

• Supportive care: manage seizures, cerebral edema, septic shock, SIADH
• Brain MRI with and without contrast preferred
• EEG as indicated
• Empiric therapy for specific pathogens: antibacterials, acyclovir, PAM therapy
• Steroids, IVIG for postinfectious forms
  – ADEM, NMDAR encephalitis
Specific Laboratory Diagnosis

Cerebrospinal Fluid

• Polymerase chain reaction (PCR) for HSV and enteroviruses
• PCR for parechovirus in infants
• As indicated:
  – PCR for VZV, HHV-6
  – India ink & cryptococcal antigen, measles antibody
  – Wet mount or Wright-Giemsa stain for amoebae
• Get extra CSF and save it!
Specific Laboratory Diagnosis

Nasopharyngeal wash or swab
• Enteroviruses
• *Mycoplasma pneumoniae*
• Adenovirus
• RSV
• Influenza A & B
Specific Laboratory Diagnosis

Acute phase serum
• *Mycoplasma pneumoniae*
• Arboviruses
• NMDA receptor antibodies
• EBV
• Parvovirus B19
• Measles
• Additional as indicated by history
Conclusions

• Ask the right questions to narrow the huge differential diagnosis.
  – Animal contacts
  – Insect contacts
  – Travel
  – Recreational activities
  – Immunization status
• Get enough CSF for extra testing.
• Order the correct tests.
• Start empiric therapies early.
Questions

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