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Central Nervous System INFECTIONS (NOT MENINGITIS)

Cerebrospinal Fluid DISORDERS

Geetika Gupta, MD
May 18, 2011
CNS Infections

- Meningitis
  - Inflammation of the pia and arachnoid
- Encephalitis
  - Inflammation of the brain
- Brain Abscess
  - Usually encapsulated structure with inflammatory cells and pathogen
- Parameningeal Infections

CSF Disorders

- aqueductal stenosis
- tumoral hydrocephalus
- isolated ventricles
- arachnoid cysts
- multiloculated hydrocephalus
- fourth ventricular outlet obstructions
Differential diagnosis of infections of the CNS

Meningitis

**Bacterial**

*Aseptic*: infections with a negative Gram stain and culture or noninfectious causes

Infections

**Viral**

Bacteria with negative Gram stain and culture: bacteria with negative Gram stain with usual stain and technique and not culturable with usual media

Organisms not able to grow on routine culture media: Mycobacteria, Treponema(syphilis), Mycoplasma (tuberculosis), Chlamydia, Borrelia burgdorferi (Lyme disease)

**Nonviral**

Fungal

Meningeal inflammation secondary to adjacent pyogenic infections

Eosinophilic meningitis (parasitic CNS infections)

Noninfectious cause

Neoplasms (meningeal carcinomatosis or leptomeningeal carcinomatosis)

Systemic diseases that affect the CNS: systemic lupus erythematosus, sarcoidosis,

Drugs (intrathecal chemotherapy)

Encephalitis

**Infections**

**Viral** (WNV, EEE, H1N1, WEE, HSV, St Louis, EBV, HZV, CMV)

**Nonviral**

Bacteria: bacteria with negative Gram stain and culture

Rickettsia

Fungi

Protozoa

Helminthos

Borrelia

Brain abscess

**Bacterial**

**Nonbacterial**

Fungi

Protozoa

Parasites

Parameningeal infections

Brain abscess

Subdural empyema

Epidural abscess
Other considerations

- Acute disseminated encephalomyelitis (ADEM)
- CNS disease
- Hemorrhage
- Strokes
- Venous thrombosis
- Aneurysms
- Migraines/Other headaches
- Hematologic disorders
- Hyperviscosity syndromes
- Polycythemia
- Leukocytosis/leukostasis
- Platelet disorders
- Thrombocytosis
- Coagulopathy
- Encephalopathies
- Metabolic
- Hypoxia
- Ischemia
- Intoxications
- Organ dysfunction
- Systemic infection
- Delirium/dementia
- Seizures
- Nonconvulsive status epilepticus
- Legionnaire disease
- Posttransplant lymphoproliferative disorder
- Prion diseases
- Epstein-Barr virus
- Posterior fossa syndrome
Case

13 yo male arrives in ED with chief complaint of vomiting and fever for 2 days.
In ED patient has labs, CT and LP.
Diagnosis: Viral meningitis
Disposition: Home with supportive therapy
Outcome: Patient died 2 days later
Autopsy: meningoencephalitis
Etiology.........
Arboviral Encephalitis

Geetika Gupta, MD

University of Michigan Health System
St Joseph Mercy Health System
Objective

• Understand arborviral encephalitis as it pertains to EM

• Questions

  1. Are there specific clinical features to be considered for *arboviral* encephalitis

  2. Are there any laboratory/ radiology studies *from the ED that are crucial*

  3. Does *specific* management change outcome

  4. Upcoming considerations
Direct Spread

- Frontal sinusitis
- Ethmoid sinusitis
- Dental infections
- Otitis media, mastoiditis

Hematogenous Seeding

- Brain abscess
- Middle cerebral artery
- Chronic pulmonary infections
- Skin infections
- Endocarditis Congenital heart disease
- Intra-abdominal and pelvic infections

Patrick J. Lynch, Wikimedia Commons
Hematogenous via anthropod vector bite (ex. arboviruses) into the bloodstream

Inhalation (ex. LCMV, C. psittacosis) into the respiratory system

Neutral via animal vector bite (ex. rabies virus) into the skin

Gastrointestinal via infected dairy food into the gastrointestinal system (ex. brucellosis)

United States Department of Agriculture, Wikimedia Commons

National Institutes of Health, Wikimedia Commons

CDC/Barbara Andrews, Wikimedia Commons

Tompw, Wikimedia Commons

Alvesgaspar, Wikimedia Commons

Lee Ostrom, Wikimedia Commons

Tompw, Wikimedia Commons
Herpes simplex virus via olfactory tract or trigeminal n.

Rabies viruses transmission via peripheral wound to dorsal root ganglion to brain
intracerebral

subdural

epidural

Subdural empyema

Area of epidural abscess

Area of intracerebral abscess

Patrick J. Lynch, Wikimedia Commons

James Heilman, Wikimedia Commons
Pathophysiology

• **Cross the blood brain barrier**
  – Hematogenous, direct, neuronal
    • transport across the cell by endocytosis (transcellular passage) (eg, meningococci or Streptococcus pneumococci)
    • transport between the cells (paracellular passage) can occur after endothelial injury or following disruption of the intracellular endothelial connections
    • within WBCs during diapedesis.
      – During certain disease states, the endothelial cells become damaged and the blood-brain barrier becomes porous, allowing pathogens to transverse the blood-CSF barrier

• **Replicate**

• **Activate inflammatory cascade via brain cells**
  – Release of cytokines → breaks down the blood brain barrier
  – Activation of inflammatory mediators (eg, nitric oxide [NO], reactive oxygen species [ROS], matrix metalloproteinases [MMPs])
  – Chemokines → Recruitment of white blood cells (WBCs) to the site of infection
  – Cytotoxic events
• **Damage to CNS**
  – By direct invasion
  – By inflammatory cascade
• **Inflammatory mediators:**
  – Direct neurotoxicity
  – Increase vascular permeability
  – Increase cerebral blood flow
• **Physiologic events**
  – Cerebral edema
    • Vasogenic edema: loss of blood-brain barrier
    • Cytotoxic edema: from cellular swelling and destruction
    • Obstruction to CSF outflow at arachnoid villi
  – Cerebral hypoperfusion from local vascular inflammation and/or thrombosis
  – Loss of autoregulation
• **ENCEPHALITIS**
  – Involvement of the tissue itself
  – Ischemic lesions associated with vasculitides
The Good Ole’ Mosquito
Summer is Arriving

- Muggy weather
- Standstill water
- Birds, rodents
- Vacation

Source undetermined
Arbovirus

- Eastern Equine Virus
- Western Equine Virus
- St Louis Virus
- La Crosse Encephalitis
- West Nile Virus
- Dengue fever
- Powassan Encephalitis
- Chikungunya
- Yellow Fever
- Nipah Virus
EEEV by STATE
1964 – 2009
182 cases
Western Equine Encephalitis Virus Neuroinvasive Disease Cases
Reported by State, 1964-2009

640 cases
St. Louis Encephalitis Virus Neuroinvasive Disease Cases Reported by State, 1964-2009

4482 cases
California Serogroup Virus Neuroinvasive Disease Cases* Reported by State, 1964-2009

* Neuroinvasive disease includes cases reported as encephalitis, meningoencephalitis, or meningitis. Most reported cases of California serogroup virus neuroinvasive disease are due to La Crosse encephalitis virus. Cases are reported by state of residence.
West Nile virus (WNV) neuroinvasive disease incidence reported to ArboNET, by county, United States, 2010

as of December 28, 2010

Per 100,000 Population*

- 0.0
- 0.01 - 0.99
- 1.00 - 2.49
- 2.50 - 9.99
- >= 10.00

* Scales are different for state and county incidence maps

Centers for Disease Control
Dengue Encephalitis in Key West

Source undetermined
## Dengue Symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>28</td>
<td>(100)</td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
<td>(79)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>23</td>
<td>(82)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18</td>
<td>(64)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>14</td>
<td>(50)</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>(54)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>6</td>
<td>(21)</td>
</tr>
</tbody>
</table>

* Percentages might not add to 100% because of rounding.
Arboral Encephalitis

• Case per year: 150-3000
• Sequele
  – Greatest with EEE
• Annual Cost
  – $150 million including vector control and surveillance
• History
  • Geographic and seasonal factors.
  • Foreign travel or migration history.
  • Contact with animals (for example, farm house) or insect bites.
  • Immune status.
  • Occupation.
Are there specific clinical features to be considered for Encephalitis?

Signs and symptoms "at presentation"* for all hospitalised adult encephalitis cases in three Hunter New England hospitals, Australia, July 1998-December 2007

<table>
<thead>
<tr>
<th>Symptoms at presentation</th>
<th>Cases, n = 74 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>57 (77.0%)</td>
</tr>
<tr>
<td>Altered Consciousness State (ACS) including irritability and/or coma</td>
<td>51 (68.9%)</td>
</tr>
<tr>
<td>Headache</td>
<td>46 (62.1%)</td>
</tr>
<tr>
<td>Encephalitis &quot;triad&quot;(headache, fever, ACS)</td>
<td>26 (35.1%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>24 (32.4%)</td>
</tr>
<tr>
<td>Focal neurological signs</td>
<td>23 (31.1%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>19 (25.7%)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>13 (17.6%)</td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>11 (14.9%)</td>
</tr>
<tr>
<td>Abnormal behaviour</td>
<td>9 (12.1%)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (9.5%)</td>
</tr>
<tr>
<td>Myalgia and/or arthralgia</td>
<td>2 (2.7%)</td>
</tr>
</tbody>
</table>

*a sign/symptom was considered to be present "at presentation" if the patient/next of kin reported to have had the sign/symptom in the 24 hours prior to presentation or if it was documented in the patient record during the first 48 hours of their admission.
• CBC, Chemistry, LFT, ESR, CRP, U/A, CXR
• CT Brain
• LP
  – Specific serology ELISA, PCR
---------
• MRI
• EEG
• PET scan
• PCR studies
Serum

• In general
  – Relative lymphocytosis

• WNV: anemia, leukopenia, thrombocytopenia

• Rickettsial and hemorrhagic viral infections
  – Leukopenia and thrombocytopenia

• IgM Arbovirus testing
  – Results can take 2 weeks
Is CT required before LP?

– It is preferred
– CT scan of the head is used to identify patients at higher risk for herniation with intracranial pathology such as hydrocephalus, mass lesions, cerebral edema, and midline brain shift.
– Herniation from LP requires both increased ICP and obstruction to free CSF flow and equilibration

  – 234 patients....
    • Age greater than 60,
    • seizure in the past 1 week,
    • immunocompromise,
    • history of CNS disease,
    • altered mental status, gaze or facial palsy, abnormal language
    • inability to answer two questions or follow two commands,
    • visual field abnormalities, and
    • arm or leg drift
  – 96 patients (41 %) did not have these features and the CT was abnormal 3%- 9% of the time
    • 1 out of 11 patients can have an abnormal CT
LP and the needle

• Atraumatic needles significantly reduced the incidence of moderate to severe headache and the need for medical interventions after diagnostic lumbar punctures, but they were associated with a higher failure rate than standard needles
  – Randomised controlled trial of atraumatic versus standard needles for diagnostic lumbar puncture.

• A noncutting needle should be used for patients at high risk for PDPH, and the smallest gauge needle available should be used for all patients.
  – Postdural puncture headache and spinal needle design. Metaanalyses.
CSF results

• Bacterial vs Viral
  – > 1000 WBC
  – Low glucose
  – High protein
  – EEEV pleocytosis with predominant neutrophils
  – HSV has high RBC

  – 2093 children (serum WBC, CSF WBC, CSF protein, seizure, gram stain)
  – 4% of patients with bacterial meningitis had none of these criteria
EEG/MRI/ EMG

• MRI
  – WNV: anterior horn cells
  – HSV, LaCrosse virus: temporal horns

• EEG
  – HSV and LaCrosse similar
Questions from patients

• I found a dead bird what should I do?
• My friend has a mosquito virus?
• Can I nurse with my infection?
• Am I contagious?
• Should I buy the fancy mosquito catcher?
• What should I do when I go outside?
• What are my chances of getting encephalitis?
• I have flu like symptoms with fever and headache...
West Nile Virus

• First isolated in West Nile region of Uganda in 1937
• Arrived in the US in 1999
• Crows, ravens, blue jays
• Symptoms
  – Flu like mild
  – 1 out of 150 develop encephalitis
• 2000/2001
  – News media
  – Dead birds
• 2002
  – 4100 cases –largest epidemic
    • 3000 with meningoencephalitis
    • 246 deaths
  – 13 cases via blood transfusion
• Likely life long immunity
• Transmitted through placenta, breast milk, organ transplants
• Long-term
  – Fatigue
  – Memory impairment
  – Weakness
  – Headache
  – Balance problems
WNV 2010
29 patients
25 neuroinvasive

Source undetermined
US WNV 2010

981 patients
601 neuroinvasive, 45 deaths

Source undetermined
Clinical presentation

• 20-40% patients
• Incubation 2-14 days
• Typical 3-10 days......median 60 days
  – Patnaik et al, Emergency Infectious Disease
    • 531 patients....54 percent symptoms for 30 days
      79 percent missed work for 16 days

• Similar to dengue fever
• 3-6 days
  – Fever eye pain
  – Headache pharyngitis
  – Malaise N/V/D
  – Backpain abdominal pain
  – Myalgia rash (maculopapular)
West Nile Fever Rash
Neuroinvasive WNV

• Meningitis, Encephalitis, Flaccid Paralysis
• Most Susceptible
  – Elderly, alcoholics, diabetics
    • Bode, WNV disease, a descriptive study of 221 patients hospitalized in 4 county region in Colorado, Clinics of infectious Disease 2003, 2006
• Presentation
  – EPS, tremor, myoclonus, instability, bradykinesia, seizure, encephalopathy, confusion, coma, death
  – Flaccid paralysis (Guillian – Barre)
    • Need to confirm neuropathy before initiating symptoms
Diagnosis/Treatment

- Serologic testing with EIA for IgM Ab
  - Within first 8 days of symptoms
- LP if neuro or mental status changes
  - EIA of IgM Ab
- Nucleic Acid testing in immunocompromised
- Supportive
LaCrosse Virus/ California serovirus

- Similar to WNV...no flaccid paralysis
- 80-100 encephalitis cases
- Incubation 5-15 days
- Fever for 2-3 days
- Neuroinvasive cases usually under 16 yo
- Usually full recovery
  - Rare: seizure, hemiparesis, behavior or cognitive d/o
  - Mortality <1%
- CSF best way to dx with IgM Ab
LAC 2010
70 patients
St. Louis virus encephalitis

• Symptoms similar to all arboviral infections
  – <1% patients have symptoms
    • 40% have HA and fever
    • 90% elderly develop encephalitis
  • Incubation 5-15 days

• Fatality 5-10%

• 1975
  – 2000 cases in Ohio-Mississippi River Basin
SLE 2010

Source undetermined
SLE 2010
8 patients

Source undetermined
Eastern Equine Encephalitis

• Rarely symptomatic
• Incubation 4-10 days
• Systemic infection last 1-2 weeks
• In neuroinvasive forms (4-5% of infections)
  – 35% mortality, death at day 2-10 of symptoms
  – Sudden high fever, HA, seizure, disorientation, vomiting, restless, drowsy, anorexia
  – Survivors with SIGNIFICANT brain damage
    • Intelligence seizure CNS dysfunction
    • Personality disorder paralysis death
Transmission cycle of EEEV

Mosquito vector

Dead-end hosts

Bridge vector

Amplifying host
EEE 2010
10 patients

Source undetermined
Source undetermined
Henipah (Nipah) Virus Encephalitis

- 1998-1999
- Malaysian pig farmers and health care workers
- 200 cases
- Transmission
  - Secretions from pigs, fruit bats
  - Human to human?
  - CDC
- Bangladesh Bans Sale of Palm Sap After an Unusually Lethal Outbreak
  - New York Times

DONALD G. McNEIL Jr. Published: March 21, 2011
Clinical Features

Clinical Features of Nipah Virus in Humans

Characteristics:
- Fever
- Migraine
- Vomiting
- Emphysema
- Myalgia
- Encephalitis (may relapse after recovery)
- Meningitis
- Disorientation
- Neurologic deficits (may persist after recovery)
- Coma
- Death

Case-fatality rate: 40%*

*From APHIS Center for Emerging Issues 1999 (see References).
Bottom Line

• Altered mental status
  – Encephalopathy
  – Consider infection
  – Summer months in Michigan think arbovirus
  – Supportive treatment
  – CT and LP ....a MUST....admit abnormals

• CLOSE FOLLOW UP

• Case: Lawsuit filed in 2001, Verdict for defense 2003, Appeal closed 2009

• HSV : acyclovir
• Influenza: oseltamavir, raniditine
• Arbovirus: no medication