Approach to fever with altered sensorium

Dr P Senthur Nambi
Overview

• Definition of terms
• Differential diagnosis
• Points from history/epidemiology
• Investigations
• Specific management
Definitions

ENCEPHALOPATHY
- Diffuse disturbance of brain function without inflammation

ENCEPHALITIS
- Dysfunction of brain associated with inflammation

FEBRILE ENCEPHALOPATHY
- a/c onset of fever (<1wk) + alteration of consciousness >12 hrs
Acute Encephalitis Syndrome

Defined as a person of age > 1 month, at any time of year with

➢ acute onset of fever

➢ change in mental status (confusion, disorientation, coma)

AND/OR

➢ new onset of seizures (excluding simple febrile seizures)

which lasts for >24 hours with no other identifiable cause
Encephalitis = inflammation of the brain

Encephalitis + meningitis: meningoencephalitis

Infectious causes:
- Viral
- Bacterial
- Fungal
- Parasitic

Non infectious cause:
- ADEM
- Auto-immune encephalitis
- Other e.g. multiple sclerosis
Post monsoon effect..
Fever with altered sensorium

Start ceftriaxone, acyclovir, doxy
Save CSF

Always R/O Malaria

CT/MRI CSF

Infectious

Meningitis
Encephalitis
CNS abscess

Tropical Infections
Sepsis ass. Encephalopathy

Non Infectious

ADEM
CVT
NMS, Heat stroke

Never ignore TBM
Consider Dengue, Chikungunya, Lepto, Typhus, Typhoid
Think of Rabies, JE when you are stuck
<table>
<thead>
<tr>
<th>History</th>
<th>Maculopapular</th>
<th>Petechiae/purpura</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever with rash</td>
<td>Vesicles</td>
<td>Eschar</td>
</tr>
<tr>
<td></td>
<td>Herpes labialis</td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea, vomiting</td>
<td>Enteroviruses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polio</td>
<td></td>
</tr>
<tr>
<td>Myalgia, arthralgia</td>
<td>Dengue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leptospirosis</td>
<td></td>
</tr>
<tr>
<td>Parotitis</td>
<td>Mumps</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EB virus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td></td>
</tr>
</tbody>
</table>
## History

<table>
<thead>
<tr>
<th>Season</th>
<th>Post monsoon - JE, Dengue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel</td>
<td>JE, Nipah</td>
</tr>
<tr>
<td>Family illness</td>
<td>Entero virus, TB</td>
</tr>
<tr>
<td>Exposure</td>
<td>Dog bite - Rabies Vaccine - ADEM Mosquito - JE, dengue</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>Cryptococcus, TB</td>
</tr>
<tr>
<td>Unpasteurised dairy product</td>
<td>Brucella</td>
</tr>
<tr>
<td>Clinical pointers</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Skin rash</strong></td>
<td>Dengue, Measles</td>
</tr>
<tr>
<td><strong>Herpangina</strong></td>
<td>Coxsackie</td>
</tr>
<tr>
<td><strong>Purpura</strong></td>
<td>Dengue, Chikungunya, Sepsis</td>
</tr>
<tr>
<td><strong>Jaundice</strong></td>
<td>Dengue, Malaria, Lepto, Sepsis</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>Dengue, Sepsis</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Neck stiffness, LN, Fundus</td>
</tr>
</tbody>
</table>
Non-infectious causes of fever

Over production of heat
- Neuroleptic malignant syndrome
- Malignant hyperthermia
- Drugs - cocaine, salicylate
- Thyrotoxic encephalopathy
- Convulsive status epilepticus
- Catatonic schizophrenia

Impaired heat dissipation
- Anticholinergic toxicity e.g. amitryptiline
- Heat stroke
Investigations

• BLOOD INVESTIGATIONS
  – Complete blood count and peripheral smear
    • Relative lymphocytosis in viral meningitis
    • Leucopenia & thrombocytopenia – in rickettsial inf & viral haemorrhagic fevers
    • Malaria
  – Blood culture
  – Blood biochemistry, sugar
Initial approach to fever with altered sensorium

- Strongly suspect meningitis
  - CT if focal signs or immune compromised
  - Single dose dexamethasone
  - Single dose antibiotic/acyclovir after drawing blood cultures
  - LP
**Recommended criteria for adult patients with suspected bacterial meningitis who should undergo CT prior to lumbar puncture**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompromised state</td>
<td>HIV infection or AIDS, receiving immunosuppressive therapy, or after transplantation</td>
</tr>
<tr>
<td>History of CNS disease</td>
<td>Mass lesion, stroke, or focal infection</td>
</tr>
<tr>
<td>New onset seizure</td>
<td>Within 1 week of presentation; some authorities would not perform a lumbar puncture on patients with prolonged seizures or would delay lumbar puncture for 30 min in patients with short, convulsive seizures</td>
</tr>
<tr>
<td>Papilledema</td>
<td>Presence of venous pulsations suggests absence of increased intracranial pressure</td>
</tr>
<tr>
<td>Abnormal level of consciousness</td>
<td>...</td>
</tr>
<tr>
<td>Focal neurologic deficit</td>
<td>Including dilated nonreactive pupil, abnormalities of ocular motility, abnormal visual fields, gaze palsy, arm or leg drift</td>
</tr>
</tbody>
</table>
Lumbar Puncture

- Gram stain & culture
- AFB stain & culture, Gene Xpert MTB-rif
- Special staining
- Viral PCR- HSV, VZV
- Save sample!

<table>
<thead>
<tr>
<th>Tube Number</th>
<th>Volume Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (biochemistry)</td>
<td>0.5ml (10 drops)</td>
</tr>
<tr>
<td>2 (cytology)</td>
<td>1 ml (20 drops) (6 ml for flow cytometry)</td>
</tr>
<tr>
<td>3 (microbiology)</td>
<td>10ml (full tube)</td>
</tr>
</tbody>
</table>
CSF analysis

- False positive elevations of CSF WBC: traumatic lumbar puncture, intracerebral or subarachnoid hemorrhage

- Seizures: CSF pleocytosis (neutrophilic), < 80/mm

- Traumatic lumbar puncture: CSF protein concentration determined by subtracting 1 mg/dL of protein for every 1000 RBC

- CSF may be stored at +4°C if delays in processing for virus culture or viral PCR will be less than 24 hrs

- If greater delays are likely, CSF should be frozen at -80°C
<table>
<thead>
<tr>
<th>Category</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial Meningitis</strong></td>
<td>• PMN</td>
</tr>
<tr>
<td></td>
<td>• High protein, low sugar, gram stain</td>
</tr>
<tr>
<td><strong>Aseptic Meningitis</strong></td>
<td>• Few lymphocytes</td>
</tr>
<tr>
<td></td>
<td>• Normal protein</td>
</tr>
<tr>
<td></td>
<td>• Normal sugar</td>
</tr>
<tr>
<td><strong>Viral Encephalitis</strong></td>
<td>• Lymphocytic</td>
</tr>
<tr>
<td></td>
<td>• Normal sugar, normal to slightly raised protein</td>
</tr>
<tr>
<td><strong>Tuberculous Meningitis</strong></td>
<td>• Lymphocytic</td>
</tr>
<tr>
<td></td>
<td>• High protein, low sugar</td>
</tr>
</tbody>
</table>
Encephalitis (Viral)

- Arbo viruses (50% in epidemics)
- HSV

- Entero virus
- VZV

- EBV
- CMV
- Rabies
Encephalitis mortality

![Graph showing the mortality rates of different encephalitis viruses.]

- Rabies: 100% mortality
- HSV untreated: 70% mortality
- HSV treated: 10% mortality
- JBE overall: 10% mortality
- JBE children: 10% mortality
- TBE RSSE: 10% mortality
- TBE CE: 10% mortality
- SLE: 10% mortality
- West Nile: 10% mortality
- EEE: 50% mortality
- WEE: 0% mortality
- La Crosse: 0% mortality

*100,000 cases/yr*
Arbovirus encephalitis in India

Flaviviridae
➢ Japanese Encephalitis virus
➢ West Nile virus
➢ Dengue

Togaviridae (Alphavirus)
➢ Chikungunya

Rhabdoviridae
➢ Chandhipura virus
Viral encephalitis

Directed therapy not available

Directed therapy available

All others

HSV
Neuroimaging

• CT is less sensitive than MRI & is normal in upto 33% of patients

• Characteristic neuroimaging changes:
  ✓ Fronto temporal changes in HSV
  ✓ Thalamic & midbrain changes in Japanese encephalitis
  ✓ Basal exudates after contrast in TB Meningitis
  ✓ Basal ganglia ring enhancing lesion in Toxoplasmosis
  ✓ Multiple ring enhancing lesions in tuberculoma
Lab diagnosis of viral encephalitis

- CSF cultures in encephalitis: disappointing
  Negative in >95% of cases of HSV-1 encephalitis

- Serum antibody determination is less useful for viruses with high seroprevalence rates (HSV, VZV, CMV, EBV)

- CSF serology is more useful than serum serology alone
• JE - CSF IgM ELISA

• WNV IgM antibodies is diagnostic of WNV encephalitis

• Dengue - Serum/CSF IgM ELISA
  Highest positivity in 2nd week

• HSV - CSF PCR initial stage (96% sensitivity & 99% specificity)
JE in India

Endemic / natural cycle

Amplification cycle

Culex tritaeniorhynchus (other Culex spp.)

„rice fields“

dead-end hosts

Culex tritaeniorhynchus (other Culex & Aedes spp.)

„farms“

rural infections

rural & peri-urban infections
WNV in India!!

• Antibodies against WNV - first detected in humans in Bombay in 1952

• Virus activity has been reported in southern, central, and western India

• WNV has been isolated from
  * Culex vishnui - Andhra Pradesh, Tamil Nadu
  * Culex quinquefasciatus - Maharashtra

• WNV isolated from humans in Karnataka State

West Nile Virus: Recent outbreaks

WNV in Kerala

- May - July 2011 in Kerala, India
- 208 AES cases
- 4 deaths
- 33% - children
- 67% - adults

WNV in Assam

<table>
<thead>
<tr>
<th>District</th>
<th>No. with acute encephalitis syndrome</th>
<th>JEV No. positive/no. tested</th>
<th>WNV No. positive/no. tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhemaji</td>
<td>1</td>
<td>0/1</td>
<td>0/0</td>
</tr>
<tr>
<td>Dibrugarh</td>
<td>29</td>
<td>9/29</td>
<td>6/29</td>
</tr>
<tr>
<td>Golaghat</td>
<td>81</td>
<td>47/81</td>
<td>2/18</td>
</tr>
<tr>
<td>Jorhat</td>
<td>15</td>
<td>8/15</td>
<td>0/15</td>
</tr>
<tr>
<td>Lakhimpur</td>
<td>6</td>
<td>5/6</td>
<td>0/6</td>
</tr>
<tr>
<td>Sivasagar</td>
<td>30</td>
<td>9/30</td>
<td>2/30</td>
</tr>
<tr>
<td>Tinsukia</td>
<td>5</td>
<td>2/5</td>
<td>2/5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>167</td>
<td><strong>80/167</strong></td>
<td><strong>12/103</strong>†</td>
</tr>
</tbody>
</table>

*JEV, Japanese encephalitis virus; WNV, West Nile virus.
†One person was not included because the address could not be verified.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 5, May 2011

Genome Announc. 2013 May-Jun; 1(3)
Therapy in acute bacterial meningitis

- S. pneumoniae
- Neisseriae meningitidis
- Haemophilus influenzae
- Listeria if age >65, pregnancy, immunocompromised

Initial empiric therapy
- Ceftriaxone
- Ampicillin if immune compromised or >65
- Acyclovir if HSV suspected

After cell count & Gram stain
- Stop acyclovir

After culture
- As per sensitivities
- Ask for MIC if pneumococcus grown
Other treatment

- Doxycycline 100mg BD

- Dexamethasone
  - 0.15 mg/kg q6h for 2–4 days with the first dose administered
  - 10–20 min before, or at least concomitant with the first dose of antibiotic
  - adults with suspected or proven pneumococcal meningitis
CSF Penetration of antibiotics

Excellent
• Metronidazole
• Rifampicin
• Chloramphenicol
• Fluoroquinolone
• Cotrimoxazole
• Linezolid

Poor
• Macrolides
• Aminoglycosides
• Clindamycin

Good with inflamed meninges
• Beta lactams
• Vancomycin
H/O fever with seizures, altered sensorium ..
# Predisposing Conditions & Microbiology of Brain Abscess

<table>
<thead>
<tr>
<th>Predisposing Condition</th>
<th>Usual Microbial Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otitis media or mastoiditis</td>
<td>Streptococci, <em>Bacteroides</em>, <em>Prevotella</em> * <em>Enterobacteriaceae</em></td>
</tr>
<tr>
<td>Sinusitis (frontoethmoid or sphenoid)</td>
<td>Streptococci, <em>Bacteroides</em> spp * <em>Enterobacteriaceae</em>, <em>Staph. aureus</em>, <em>Haemophilus</em> spp.</td>
</tr>
<tr>
<td>Dental sepsis</td>
<td><em>Fusobacterium</em>, <em>Prevotella</em> and <em>Bacteroides</em> spp., streptococci</td>
</tr>
<tr>
<td>Penetrating trauma or postneurosurgical</td>
<td><em>S. aureus</em>, streptococci, <em>Enterobacteriaceae</em>, <em>Clostridium</em> spp.</td>
</tr>
<tr>
<td>Predisposing Condition</td>
<td>Antimicrobial Regimen</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>Otitis media or mastoiditis</td>
<td>Metronidazole + third-generation cephalosporin*</td>
</tr>
<tr>
<td>Sinusitis (frontoethmoid or sphenoid)</td>
<td>Metronidazole + third-generation cephalosporin*†</td>
</tr>
<tr>
<td>Dental infection</td>
<td>Penicillin + metronidazole</td>
</tr>
<tr>
<td>Penetrating trauma or postneurosurgical</td>
<td>Vancomycin + third-generation cephalosporin*‡</td>
</tr>
<tr>
<td>Lung abscess, empyema, bronchiectasis</td>
<td>Penicillin + metronidazole + sulfonamide§</td>
</tr>
<tr>
<td>Bacterial endocarditis</td>
<td>Vancomycin + gentamicin</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Third-generation cephalosporin*</td>
</tr>
<tr>
<td>Unknown</td>
<td>Vancomycin + metronidazole + third-generation cephalosporin*‡</td>
</tr>
</tbody>
</table>
Sepsis associated encephalopathy

- Poorly understood CNS condition
- Manifests as lethargy, delirium
- Pathogenesis
  - bacterial invasion of brain
  - endotoxins
  - derangement of neurotransmitters
  - microvascular changes
Is Your Patient Encephalopathic Because of His or Her Antibiotic Therapy?
CID, Feb 2016

- Delusions/hallucinations - macrolides/quinolones/procaine penicillin
- Myoclonus & seizures (54% nonconvulsive) - penicillin or cephalosporins
- Cerebellar findings - metronidazole
- Language alteration (aphasia) - cefipime
Thanks..