Management of suspected viral encephalitis and meningitis in adults

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Acute bacterial meningitis: key facts

- 0.6-4 per 100 000/year adults in developed countries
- Immunization programmes have had a marked effect on the aetiological agents responsible in recent years. (HIB, meningitis A&C/ A,C,Y, W1135
- 80-90% of all cases in adults due to S.pneumoniae (pneumococcal meningitis) and N. meningitidis (meningococcal meningitis),
Meningitis-presentation

• Initial presentation can be very non-specific, with symptoms such as fever and cold limbs.

• The **classic triad** of:
  
  fever,
  
  neck stiffness and
  
  altered mental status (GCS ≤14)

only found in **44%** of patients with acute bacterial meningitis.
Culture proven bacterial meningitis

- **95%** of patients have **two** of the following signs or symptoms and
- **99%** have at least **one**.
  - Headache,
  - Fever,
  - Neck stiffness,
  - Altered mental status.
Examination...

Kernig’s sign: sensitivity 5% specificity 95%,
- Flexing the hip and extending the knee.
- Positive result causes pain in the back and the legs

Brudzinski’s sign: sensitivity 5% specificity 95%,
- Performed supine
- Head is passively flexed
- A positive result is when flexion at the hips occurs to lift the legs

Nuchal Rigidity: sensitivity 30% specificity 68%
- Clinical determination of next stiffness and inability to passively flex and extend the neck.
Tests:

Lumbar puncture
- Opening pressure
- **Paired** CSF and plasma glucose (+ lactate)
- Protein
- Cell count, microscopy & culture
- Meningococcal / pneumococcal PCR
- Enterovirus/ HSV/ VZV PCR
- M.tb if indicated (5mls CSF)

Blood
- Meningococcal / pneumococcal PCR (EDTA blood)
- Blood cultures
- Blood glucose (with LP)
- U&E LFT CRP
- FBC clotting
- +/-malaria film,
- HIV test
- Serology to store
When is it safe to LP WITHOUT CT?

• GCS 15/15
• No focal neurology
• No history of recent seizures
When to CT before LP…

- Mod-severe impaired consciousness/ fluctuating consciousness GCS <13
- Focal neurology (eg unequal pupils)
- Abnormal posturing
- Papilloedema
- After seizures – until stabilised
- Relative bradycardia with hypertension
- Systemic shock
- Coagulation abnormalities
- Local infection at LP site
- Suspected meningococcal septicaemia
## CSF results in meningitis

<table>
<thead>
<tr>
<th>Test</th>
<th>normal</th>
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<td>very high</td>
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</table>
Empiric Treatment

• IV 2g 6 Cefotaxime / ceftriaxone immediately after LP

• if LP will be delayed for more than 30 minutes give IV antibiotics first
Corticosteroids in adult meningitis

• Consider dexamethasone
  – 0.15mg/kg qds for 4 days
• started with or just before the first dose of antibiotics,
  – particularly where pneumococcal meningitis is suspected
  – Do not give unless you are confident you are using the correct antimicrobials
  – Stop the dexamethasone if a non-bacterial cause is identified
Differential diagnosis of acute bacterial meningitis

Infections
- Other bacterial meningitis, Fungal meningitis TB meningitis , amoebic meningitis, syphilis
- Atypical infections in the immunocompromised eg Toxoplasma gondii
- Viral meningitis/ encephalitis
- **Tonsillitis**

Drugs/ toxins

Inflammatory
- Systemic lupus erythemaotosus, sarcoidosis, Behcet’s disease, Sjorgen’s syndrome

Malignant
- Carcinomatous or lymphomatous meningitis

Vascular
- Subarachnoid haemorrhage
- Intracranial venous thrombosis
Case 1

- Jo a 19 year old student
  - Returned from gap year to start at University
    - Has a 1 week history of fever
    - 2 days of neck stiffness and
    - a new rash
This was his rash:
Meningococcal rash

Rash is only present in 11-26% of adults with acute bacterial meningitis.

Purpuric meningococcal rash = septicaemia
no Lumbar puncture is required
Start empiric IV antibiotics (2g ceftriaxone of cefotaxime) immediately

(Although ideally after blood cultures and plasma samples for PCR have been taken )
Outcomes: Meningococcal meningitis

- Mortality 4 - 8% for children and up to 7% for adults
- Most patients die of systemic complications, mostly sepsis
- Unfavourable outcomes predicated by:
  - Signs of sepsis,
  - advanced age,
  - infection due to meningococci of clonal complex 11
  - high bacterial load as determined by quantitative PCR
Survivors of meningococcal disease

• 10% suffer from hearing loss
• 10% have arthritis as a complication
  – either due to haematogenous bacterial seeding of joints (septic arthritis) or by
  – immune complex deposition in joints (immune-mediated arthritis).
• immune-mediated arthritis typically develops from day 5 of the illness or during recovery from the infection, generally involves large joints
Prevention of secondary cases of Meningococcal meningitis

- Up to 10% of people carry Neisseria meningitidis asymptomatically
- Household contacts or those with >4 hours contact with the index case are advised to have prophylactic treatment.
- Recommended regimens include:
  - Ciprofloxacin 500 mg as a single dose;
  - or rifampicin 600 mg every 12 hours for 2 days;
  - or i/m ceftriaxone [unlicensed indication] 250 mg as a single dose

No secondary prevention is required for Pneumococcal meningitis
Prevention of secondary cases of Haemophilus influenza meningitis:

- Rifampicin 600 mg once daily for 4 days;

- *or* (if rifampicin cannot be used) i/m or i/v ceftriaxone [unlicensed indication] 1 g once daily for 2 days;
HPA Data: Haemophilus influenzae type b laboratory reports: England and Wales, 1990-2010

- Hib vaccine introduced
- Hib catch-up campaign
- 12-month Hib booster introduced
Meningococcal disease by subtype
HPA UK
Changing epidemiology

- HiB vaccination – ↓ in nos of infants/neonates
- A&C vaccination ↓ in nos of meningitis C
- but ↑ Group B (85-90% of cases)
- Travel ↑ W135- and Y

Outcomes: Pneumococcal meningitis

• Mortality in adults,
  – ranges from 20-37% in developed countries to
  – 51% in resource-poor areas.
  – Most common causes of death cardiorespiratory failure, stroke, status epilepticus, and brain herniation.

• Unfavourable outcomes predicted by:
  – low admission Glasgow coma score,
  – cranial nerve palsies on admission,
  – raised erythrocyte sedimentation rate,
  – high CSF protein concentration,
  – CSF leukocyte count of <1,000 leukocytes/mm3.
Pneumococcal meningitis survivors…

• Up to 50% of survivors have some form of neurological sequelae,
  – including deafness,
  – focal neurological deficits,
  – epilepsy, and
  – cognitive impairment (up to 27%) mainly slowness.

  • Loss of cognitive speed does not change over time after bacterial meningitis;
  • there is a significant improvement in physical impairment in the years after bacterial meningitis
Listeria meningitis

- *Listeria monocytogenes* accounts for 2% of meningitis in the USA.
- More common in those with a degree of immunosuppression.
- 26 of 147 cases *Listeriosis* in UK 2011 reported to HPA were pregnancy associated.
Presentation of Listeria meningo-encephalitis

• Approximately 43% have fever,
• headache and
• altered mental status at presentation.

• 10% have a brainstem encephalitis, usually in middle-aged previously healthy individuals (71% of cases)
• 80% have hyponatremia
Treatment of *Listeria monocytogenes* meningitis

- Cephalosporins do NOT treat *Listeria* infections
- 21 day course of IV ampicillin or amoxicillin antibiotic recommended with at least one week of gentamicin.
- If penicillin allergic
  - Trimethoprim-sulfamethoxazole (co-trimoxazole/septrin)
Outcomes: *Listeria monocytogenes* meningitis/ meningo-encephalitis

- Mortality in
  - children varies from 15-17% and in
  - adults from 17-27%
  - Brainstem encephalitis 35%

- of the survivors 55% have neurological sequelae.
Encephalitis: the scale of problem:

- Western settings: 0.7-3.8/ 100,000 all ages
  - Approx 0.7-12.6 / 100,000 for adults
  - Approx 10.5-13.8/ 100,000 for children

- Aetiological agent identified in 15-72% of cases
  - Most commonly diagnosed in Europe & USA:
    - HSV encephalitis 1:250,000-500,000
      - 10% HSV-2
    - Varicella Zoster virus
    - Enterovirus
Encephalitis - what is it?

• Encephalopathy:
  – Clinical syndrome of altered mental status:
  – ↓Consciousness, altered cognition, personality or behaviour

• Encephalitis: inflammation of brain
  – pathological diagnosis
  – Surrogate clinical markers used: including CSF change or inflammation on imaging
Case 2: Bank Holiday Monday…

- 17 year old male born Democratic Republic of Congo
- In UK (Leeds 1 year)
- 2 week history of headaches seen by GP given ibuprofen
Examination

- Confused
- Obs stable T 36.7, BP 132/82 Pulse 80
- Neck stiff
- No focal neurol

CT verbal report head normal
CXR normal lung fields – thoracic scoliosis
Working diagnosis

1. Encephalitis - empiric acyclovir and cefotaxime given in A&E
2. Drugs/ substance abuse (not likely according to Dad)
LP results

- Opening Pressure 28cm
- WBC: 230 x 10^6/L, RBC: <1
  - WBC Differential - polys: 15% Lymphs: 85%
- CSF glucose 1.3mmol/l,
  - (no paired plasma sample)
- CSF lactate 8.0mmol/l (<2)
- CSF protein 2.21g/l (0.2-0.4)
- CSF gram stain negative
Lab results

- Na 128, CRP 7.5
- WCC slight lymphopenia 0.66(1.0-4.5)
- Blood cultures neg at 48 hrs
- CSF
  - Adenovirus PCR: Not detected
  - Enterovirus PCR: Not detected
  - HSV PCR: Not detected
  - VZV PCR: Not detected
  - Parechovirus PCR : Not detected
- CSF AAFB smear neg
LP results

- CSF lymphocytosis typical of viral infections
- Differential includes
  - TB
  - Listeria
  - Brucellosis
  - Partially treated acute bacterial meningitis
How to distinguish viral vs bacterial infection

• Clinical setting
• Low glucose ratio
• Higher CSF protein
• CSF lactate <2 mmol/l bacterial infection unlikely

• Traumatic tap correction:
• Subtract 1 WC for every 7000x10^6/L RBC in the CSF and 0.1g protein for every 100 RBC
MRI brain

Multiple nodules,

Presumed tuberculomas
Assessment of patient

- Current or recent febrile / influenza-like illness
- New onset seizures
- Focal neurological symptoms
- Rash (eg varicella zoster, enterovirus)
- Travel history
- Recent vaccinations (ADEM)
- Fresh water contact (leptospirosis)
- Exposure to mosquito or tick bites
- Known immunocompromise
- HIV risk factors
Patient 3: 50 year old female

Admitted Jan 2013: collapse at home, confused and disorientated.
- Whilst in A&E had two tonic clonic seizures. No previous history of seizures.
- Bloods: Na 133, Urea 5.0, creat 51. WCC 6.7, CRP <5.
- CXR: NAD, CT head: NAD.

LP performed under sedation due to agitation.
- Opening pressure: 28.5. Protein 0.24, glucose 4.8,
- CSF WCC 6, lymphocytes 6, viral screen negative

- Episode of reduced GCS requiring ventilation: started on IV acyclovir, cefuroxime and phenytoin. Transferred to ICU.

- MRI head: high signal within the left hippocampal structures, likely secondary to encephalitis.
- EEG: consistent with encephalitis.

- Continued with acyclovir
- Discharged to nursing home
MRI: diffuse symmetrical high T2 signal within hippocampi & Amygdala bilaterally
## CSF interpretation

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Normal</th>
<th>Bacterial</th>
<th>Viral</th>
<th>Tuberculous</th>
<th>Fungal</th>
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<tbody>
<tr>
<td>Opening pressure</td>
<td>10-20 cm</td>
<td>High</td>
<td>Normal/High</td>
<td>High</td>
<td>High/ Very high</td>
</tr>
<tr>
<td>Colour</td>
<td>Clear</td>
<td>Cloudy</td>
<td>“Gin” clear</td>
<td>Cloudy / yellow</td>
<td>Clear / cloudy</td>
</tr>
<tr>
<td>Cells</td>
<td>&lt;5</td>
<td>100-50,000</td>
<td>5-1000</td>
<td>&lt;500</td>
<td>0-1000</td>
</tr>
<tr>
<td>Differential</td>
<td>Lymphocytes</td>
<td>Neutrophils</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>CSF/plasma glucose</td>
<td>50-66%</td>
<td>&lt;40%</td>
<td>Normal</td>
<td>Low-very low (&lt;30%)</td>
<td>Normal-low</td>
</tr>
<tr>
<td>Protein (g/l)</td>
<td>&lt;0.45</td>
<td>&gt;1</td>
<td>0.5-1</td>
<td>1.0-5.0</td>
<td>0.2-5.0</td>
</tr>
</tbody>
</table>

Solomon et al Journal of Infection 64, 347-373, 2012
Encephalitis guidelines

• If LP delay > 6 hours start IV Aciclovir (10mg/kg)tds
• If CSF HSV+ 14 days IV Aciclovir
  – repeat LP at 14 days – if still positive for further 7 days Aciclovir
  – Repeat LP again and further 7 days aciclovir if HSV +ve and continue until PCR neg
  – If HSV neg initially consider HSV CSF IgG at 10-14 days
• Imaging – ideally MRI within 24-48hrs
CSF findings in HSV encephalitis

- Opening pressure mod ↑
- Mod CSF pleocytosis – 10s -100s x10^6/L
- Mildly ↑ protein
- Normal CSF: plasma glucose ratio
- HSV can be hemorrhagic with CSF red cell count elevated in 50% of cases
If its negative repeat it..HSV

- HSV PCR in CSF between day 2-10 of illness
  - overall sensitivity and specificity >95% in immunocompetent adults

- If initial HSV PCR negative, a second CSF taken 3-7 days later will often be HSV positive
MRI in encephalitis

• MRI more sensitive than CT
• MRI changes highly specific (87.5%) for PCR confirmed HSV encephalitis
• EEG helpful if uncertain if psychiatric or organic cause and if subtle motor or non-convulsive seizures suspected.
Early aciclovir: benefits

- Aciclovir improves outcome reducing mortality to <20-30% in HSV
- If no antiviral mortality > 70%
- Outcome often poor even with treatment, worse with:
  - ↑ age
  - ↓ GCS,
  - delays of > 48hrs between admission and starting treatment
- NB aciclovir S/E: crystalluria causing obstructive nephropathy can occur within 4 days and affects up to 20% of patients
Other causes of encephalitis

• Varicela Zoster Virus
  – Aciclovir 10-15 mg kg 8 hrly
  – Steroids if vasculitic component

• Enterovirus
  – supportive treatment
  – If severe disease consider pleconaril or
  – IV immunoglobulin
Key points

• To CT or not CT
• Glucose… paired plasma/CSF
• Lactate- CSF
• HIV testing (aseptic meningitis/ encephalitis)
• Empiric treatments
• +/- Steroids
Useful references


  - Epidemiology, Diagnosis, and Antimicrobial Treatment of Acute Bacterial Meningitis. Matthijs C. Brouwer, Allan R. Tunkel, and Diederik van de Beek CLINICAL MICROBIOLOGY REVIEWS, July 2010, p. 467–492 Vol. 23, No. 3

  - Corticosteroids for acute bacterial meningitis (Review) Brouwer MC, McIntyre P, de Gans J, Prasad K, van de Beek D. Cochrane collaboration 2010

Useful weblinks

British Infection Association Meningitis algorithm
• http://www.britishinfection.org/drupal/sites/default/files/MeningitisAlgorithm03.pdf

• www.meningitis-trust.org
• http://www.encephalitis.info/

UK encephalitis study
• http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947353425