CSF Evaluation in Neurological Infections

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Conflict of interest NONE
Learning Objectives

• CSF examination is the tool for diagnosis of neurological infections.
• Obtaining CSF through a lumbar puncture is safe and essential.
• CSF findings are the best guide for management.
• There are some contraindications for lumbar puncture in acute neurological infections.
How can a microbe affect CNS function?

• Direct
  – Invasion of parenchyma of brain
    • Viral encephalitis
    • Cerebral abscess
  – Invasion of supporting structures of brain
    • VZV large-vessel vasculopathy
How can a microbe affect CNS function?

• Indirect
  – Immune-mediated CNS damage
    • Acute disseminated encephalomyelitis
  – Infection-triggered metabolic catastrophes
    • Reye’s syndrome
  – Toxin-mediated diseases
    • Tetanus
  – Consequence of systemic sepsis
    • Septic encephalopathy
Burden of neurological infection

“rare complications of common infections”

- Cerebral malaria – estimated 445,000 deaths from all malaria / yr*
- Tuberculosis – 1/4 World’s pop infected (for which 5-10% lifetime risk of falling ill)*
- Japanese encephalitis – 68,000 cases / yr of which ~30% fatal*
- Measles – estimated 89,789 deaths globally yr*
- Rabies – estimated 55,000 deaths / yr worldwide & 15 million post-exposure treatments*
- Tetanus – 49,000 deaths in <5 years old worldwide*
- Leprosy – in 2012 173,358 new cases worldwide (reduced from 804,000 in 1998)*

*Source: WHO website – data for 2015; accessed Jan 2014
Classes of organisms causing CNS infections

• Viruses – multiple: DNA & RNA
• Bacteria – aerobic & anaerobic
• Fungi & yeasts – e.g. *Cryptococcus neoformans*
• Protozoa – e.g. *Toxoplasma gondii*, *Naegleria* spp, trypanosomes & malaria
• Helminths (worms) – e.g. *Taenia solium* & *Echinococcus granulosus*
How do CNS infections cause damage?

• Vicious cycle
  – Microbial invasion causes inflammatory response
    • Blood brain barrier breakdown
    • Cytokine release
    • Endarteritis & microvascular thrombosis
      (e.g. bacterial meningitis)
  – Raised ICP
    • Vasogenic, interstitial & cytotoxic cerebral oedema
  – Direct neuronal injury
    • Resulting in neuronal necrosis or apoptosis
Neuroinfection Syndromes

• **Acute:**
  - *Meningitis* (Enterovirus, mumps & HSV-2)
  - *Ventriculitis* (CMV in immunosuppressed)
  - *Encephalitis* (including arboviral)
  - *Myelitis* (e.g. poliomyelitis, JE, WNE, & Rabies)
  - *Radiculitis & ganglionitis* (e.g. shingles, Bell’s palsy)
Neuroinfection Syndromes

• Subacute & chronic
  – Subacute sclerosing panencephalitis (measles)
  – Progressive multifocal leucoencephalopathy
    • Human polyoma virus JC
  – HIV dementia (HIV Neurocognitive disorders – HAND)
  – Tropical spastic paraparesis (HTLV-1)
Diagnosis of Neurological Infection

• The neurological formulation:
  • Anatomy
  • Pathogenetic mechanism
  • Aetiology

• The ID mantra:
  • Why did this person?
  • From this place?
  • At this time, get this disease?

Acute Infectious Meningitis

- Viral causes
  - Incidence ~11 / 100,000 / year
  - Common aetiologies:
    - Enteroviruses (85-95% cases)
    - Herpes simplex virus type-2
    - Mumps (n.b. current epidemic amongst those born between 1982-1990)
  - Predominantly children & young adults
  - Usually benign & only requiring symptom relief
Acute Infectious Meningitis

• Bacterial causes
  – Incidence 3-5 / 100,000 / year
  – Aetiologies accounting for 85% cases:
    – *Neisseria meningitidis* (Meningococcus)
    – *Streptococcus pneumoniae* (Pneumococcus)
    – *Haemophilus influenzae*
    – Rarer causes include Listeria, *E. coli*, TB, *Strept suis*
  – Different organisms in different age groups
  – High morbidity & mortality
Investigation of suspected CNS infections

• Anatomy – *imaging techniques & EEG*

• Pathology & aetiology – *analysis of CSF*

• Contraindications to LP (without imaging):
  – Reduced level of consciousness
  – Focal neurological signs
  – Immunosuppression
  – Papilloedema
  – Anticoagulation / bleeding disorder
    • Nb not corrected by imaging!
Risk Factors for Cerebral Herniation Following Lumbar Puncture for Bacterial Meningitis

**Clinical Risk Factors**

- Stupor or coma
- Dilated or fixed pupils
- Fixed deviation of eyes or absent oculocephalic reflex
- Papilledema
- Recent seizures
- Decorticate or decerebrate posturing
- Hemiparesis
- Hypertension with bradycardia

**CT Factors for Increased Risk of Future Brain Herniation**

- Lateral shift of cerebral midline structures indicating unequal supratentorial intracranial pressure
- Loss of suprachiasmatic and basilar cisterns indicating the supratentorial pressure is greater than infratentorial; the lateral ventricles may be either large or small
- Obliteration or shift of the fourth ventricle indicating increased posterior fossa pressure
- Obliteration of the superior cerebellar and quadrigeminal plate cisterns with sparing of the ambient cisterns indicating upward cerebellar transtentorial herniation
- Masses in the cerebral hemisphere or cerebellum
- Infarction or occlusion of the superior sagittal sinus or draining veins
CSF Tests

• Cell count & cytology
  – Mononuclear vs polymorphs
• Gram stain (60-90% +ve)
• Antigen detection (e.g. Cryptococcus)
• Microbial culture
  – for pyogenic bacterial meningitis
    • Pre-antibiotics 70-85% +ve & post-antibiotics 50%
  – Low sensitivity for viruses
• CSF/plasma glucose or CSF lactate
  • CSF [lactate] >3.5 mmol/L
• Nucleic acid detection (PCR)
  • For meningococcus ≈91% sensitivity & specificity
  • Standard for many viruses
• CSF antibody tests
Fig 2 Electronmicrograph showing blebbing (b) of the outer membrane of Neisseria meningitides

Gram Stain available in 4hrs
60-90% Number of organisms

*N. meningitidis* may occur intracellularly or extracellularly in PMN leukocytes and will appear as gram-negative, coffee-bean shaped diplococci.

*S. pneumoniae* may occur intracellularly or extracellularly and will appear as gram-positive, lanceolate diplococci, sometimes occurring in short chains.

*H. influenzae* are small, pleomorphic gram-negative rods or coccobacilli with random arrangements.
Common causes of Community Acquired BM are *S pneumoniae and N meningitides*
Fig 2: Cerebrospinal Fluid appearances in bacterial meningitis
(A) Normal CSF. (B) Yellow trubid CSF. (C) CSF Gram-positive diplococci (Streptococcus pneumoniae) Brouwer et al Lancet 2012;380:1684-92.
A. Gram + diploccoci S pneumonie
B. Neutrophils G – rods E coli

C. CSF intracellular G+ cocci S suis
D. Skin G+ S pneumoniae

E. Optochin Disc differentiate S pneumoniae
F. Optochin Sensitive S pneumoniae

G. Spider web Pro>1.5 gm/L
H. ZN stain Single AFB

Scarborough & Thwaites Lancet Neurol 2008;7:637-648
<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Bacterial</th>
<th>Viral</th>
<th>Tuberculous</th>
<th>Fungal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening Pressure (cm CSF)</td>
<td>12–20</td>
<td>Raised</td>
<td>Normal/mildly raised</td>
<td>Raised</td>
<td>Raised</td>
</tr>
<tr>
<td>Appearance</td>
<td>Clear</td>
<td>Turbid, cloudy, purulent</td>
<td>Clear</td>
<td>Clear or cloudy</td>
<td>Clear or cloudy</td>
</tr>
<tr>
<td>CSF WCC (cells/uL)</td>
<td>&lt;5</td>
<td>Raised</td>
<td>Raised (typically 5–1000)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Raised (typically 5–500)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Raised (typically 5–500)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Predominant cell type</td>
<td>n/a</td>
<td>Neutrophils&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Lymphocytes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Lymphocytes&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>CSF protein (g/L)</td>
<td>&lt;0.4</td>
<td>Raised</td>
<td>Mildly raised</td>
<td>Markedly raised</td>
<td>Raised</td>
</tr>
<tr>
<td>CSF glucose (mmol)</td>
<td>2.6–4.5</td>
<td>Very low</td>
<td>Normal/slightly low</td>
<td>Very low</td>
<td>Low</td>
</tr>
<tr>
<td>CSF/plasma glucose ratio</td>
<td>&gt;0.66</td>
<td>Very low</td>
<td>Normal/slightly low</td>
<td>Very low</td>
<td>Low</td>
</tr>
</tbody>
</table>

CSF — cerebrospinal fluid; WCC — white cell count.

Local laboratory ranges for biochemical tests should be consulted and may vary from these quoted here.

A traumatic lumbar puncture will affect the results by falsely elevating the white cells due to excessive red cells. A common correction factor used is 1:1000.

<sup>a</sup> Occasionally the CSF WCC may be normal (especially in immunodeficiency or tuberculous meningitis).

<sup>b</sup> May be lymphocytic if antibiotics given before lumbar puncture (partially treated bacterial meningitis), or with certain bacteria e.g. *Listeria monocytogenes*.

<sup>c</sup> May be neutrophilic in enteroviral meningitis (especially early in disease).

<sup>d</sup> May be neutrophils early on in the course of disease.
<table>
<thead>
<tr>
<th><strong>TABLE 7-3</strong> Cerebrospinal Fluid Diagnostic Studies for Meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Cell Count With Differential</td>
</tr>
<tr>
<td>▶ Glucose and Protein Concentration</td>
</tr>
<tr>
<td>▶ Stain and Culture</td>
</tr>
<tr>
<td>Gram’s stain and bacterial culture</td>
</tr>
<tr>
<td>India ink and fungal culture</td>
</tr>
<tr>
<td>Viral culture</td>
</tr>
<tr>
<td>Acid fast smear and <em>Mycobacterium tuberculosis</em> culture</td>
</tr>
<tr>
<td>▶ Antigens/Antibodies if Fungal Meningitis Is in the Differential</td>
</tr>
<tr>
<td>Cryptococcal polysaccharide antigen</td>
</tr>
<tr>
<td>Histoplasma polysaccharide antigen</td>
</tr>
<tr>
<td><em>Coccidioides immitis</em> complement fixation antibody</td>
</tr>
</tbody>
</table>
Polymerase Chain Reaction (PCR)

- Broad range bacterial (16S ribosomal DNA) Takes 48hrs
- Specific meningeal pathogen
  - Reverse transcriptase for enteroviruses Takes 4hrs
  - Herpes simplex virus type 1 and type 2
- West Nile virus
- Epstein-Barr virus
- Varicella-zoster virus
- NAAT for *M. tuberculosis* Nuclide acid amplification test Modified ZN stain
- Human immunodeficiency virus (HIV) RNA

Antibodies

- Herpes simplex virus (serum and CSF IgG to calculate antibody ratio)
- Varicella-zoster virus IgM and IgG antibody index
- Arthropod-borne viruses (West Nile virus IgM)

*Borrelia burgdorferi* antibody index

CSF = cerebrospinal fluid; DNA = deoxyribonucleic acid; IgG = immunoglobulin G; IgM = immunoglobulin M; NAAT = nucleic acid amplification test; RNA = ribonucleic acid.

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Accuracy of CSF results to differentiate bacterial meningitis, in case of negative gram-stained smear

• **CRP**, **PCT**, CSF WCC, absolute Neutrophil count and CSF/blood glucose, CSF protein, levels were significantly higher in the BM group.

• However, as a diagnostic indicators of BM, none of these variables except PCT was more efficient than the emergency physician.

• CSF results have a modest role in distinguishing BM from NBM in a negative gram stain for bacteria.

• **PCT** serum levels seem to be an excellent predictor of BM.
Box 4. Risk factors for a fatal outcome in meningococcal disease.

- Rapidly progressing rash
- Coma
- Hypotension and shock
- Lactate > 4 mmol/L
- Low/normal peripheral white blood cell count
- Low acute phase reactants
- Low platelets
- Coagulopathy
- Absence of meningitis
<table>
<thead>
<tr>
<th>FOUR score</th>
<th>GCS score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye response</strong></td>
<td></td>
</tr>
<tr>
<td>4. Eyelids open or opened, tracking or blinking to command</td>
<td>4. Eyes open spontaneously</td>
</tr>
<tr>
<td>3. Eyelids open but not tracking</td>
<td>3. Eyes open to verbal command</td>
</tr>
<tr>
<td>2. Eyelids closed but open to loud voice</td>
<td>2. Eyes open to pain</td>
</tr>
<tr>
<td>1. Eyelids closed but open to pain</td>
<td>1. No eye opening</td>
</tr>
<tr>
<td>0. Eyelids remain closed with pain</td>
<td></td>
</tr>
<tr>
<td><strong>Motor response</strong></td>
<td></td>
</tr>
<tr>
<td>4. Thumbs-up, fist, or peace sign</td>
<td>6. Obeys commands</td>
</tr>
<tr>
<td>3. Localizing to pain</td>
<td>5. Localizing pain</td>
</tr>
<tr>
<td>2. Flexion response to pain</td>
<td>4. Withdrawal from pain</td>
</tr>
<tr>
<td>1. Extension response to pain</td>
<td>3. Flexion response to pain</td>
</tr>
<tr>
<td>0. No response to pain or generalized myoclonus status</td>
<td>2. Extension response to pain</td>
</tr>
<tr>
<td></td>
<td>1. No motor response</td>
</tr>
<tr>
<td><strong>Brainstem reflexes</strong></td>
<td></td>
</tr>
<tr>
<td>4. Pupil and corneal reflexes present</td>
<td></td>
</tr>
<tr>
<td>3. One pupil wide and fixed</td>
<td></td>
</tr>
<tr>
<td>2. Pupil or corneal reflexes absent</td>
<td></td>
</tr>
<tr>
<td>1. Pupil and corneal reflexes absent</td>
<td></td>
</tr>
<tr>
<td>0. Absent pupil, corneal, and cough reflex</td>
<td></td>
</tr>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
</tr>
<tr>
<td>4. Not intubated, regular breathing pattern</td>
<td>5. Oriented</td>
</tr>
<tr>
<td>3. Not intubated, Cheyne-Stokes breathing pattern</td>
<td>4. Confused</td>
</tr>
<tr>
<td>2. Not intubated, irregular breathing</td>
<td>3. Inappropriate words</td>
</tr>
<tr>
<td>1. Breaths above ventilator rate</td>
<td>2. Incomprehensible sounds</td>
</tr>
<tr>
<td>0. Breaths at ventilator rate or apnea</td>
<td>1. No verbal response</td>
</tr>
<tr>
<td><strong>Verbal response</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FOUR = Full Outline of Unresponsiveness; GCS = Glasgow Coma Scale.
UK adult meningitis guidelines

**Patient with Suspected Meningitis (and no signs of shock or severe sepsis)**

**Bloods**
- Blood Cultures
  - Full blood count, urea, creatinine, electrolytes, liver function tests and clotting screen
  - Procalcitonin (or CRP if unavailable)
  - Meningococcal and Pneumococcal PCR
  - Serology sample
  - Glucose

**Throat swab**
- Bacterial Culture

**CSF**
- Opening Pressure
- Microscopy, Culture and Sensitivity
- Meningococcal and Pneumococcal PCR
- Protein
- Glucose
- Lactate

**Further tests** (if no aetiology identified on first panel)
- If **bacterial meningitis** seems likely:
  - 16S rRNA PCR on CSF
- If **viral meningitis** seems likely:
  - CSF PCR for:
    - HSV 1, HSV 2, VZV and Enterovirus.
  - Stool for Enterovirus PCR
  - Throat swab for Enterovirus PCR

**Patient with Suspected Meningococcal sepsis**

**Blood Cultures**
- Full blood count, urea, creatinine, electrolytes, liver function tests and clotting screen
- Procalcitonin (or CRP if unavailable)
- Meningococcal and Pneumococcal PCR
- Serology sample
- Glucose

**Throat swab**
- Bacterial Culture

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If any of the following features are present LP should be delayed:

- Signs of severe sepsis or rapidly evolving rash
- Respiratory or cardiac compromise
- Anticoagulant therapy/known thrombocytopenia
- Infection at the site of LP
- Focal neurological signs
- Presence of papilloedema
- Continuous or uncontrolled seizures

* inability to see the fundus is not a contraindication to LP
** LP may be safe at lower levels of consciousness
† Neuroimaging should be performed before LP for these indications.

Once the patient is stable and if meningitis is likely (with or without sepsis) an LP may still be diagnostically useful, even after several days.

**Figure 1** Investigations algorithm.

**Notes:**
- PCR – Polymerase Chain Reaction; CSF – cerebrospinal fluid; HSV – herpes simplex virus; VZV – varicella zoster virus; LP – lumbar puncture; CRP – C-reactive protein; GCS – Glasgow Coma Scale; rRNA – ribosomal ribonucleic acid.
Bacterial Infections of the Central Nervous System

Karen L. Roos, MD, FAAN

“The evidence supports the use of dexamethasone at the initiation of therapy and for the first 4 days”.

The identification of and eradication of the pathogen with antimicrobial therapy is the easy part.
It is the recognition of the disorder, the understanding of which diagnostic studies to obtain and their limitations, and the management of the neurologic complications that require the expertise of a neurologist.

Continuum (Minneap Minn) 2015;21(6):1679–1691.
Accuracy of Cerebrospinal Fluid Biochemical Analysis in Patients With Suspected Bacterial Meningitis

<table>
<thead>
<tr>
<th>CSF Test</th>
<th>Positive Likelihood Ratio (95% CI)</th>
<th>Negative Likelihood Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count ≥500/µL</td>
<td>15 (10-22)</td>
<td>0.30 (0.20-0.40)</td>
</tr>
<tr>
<td>Glucose &gt;39.6 mg/dL (&gt;2.2 mmol/L)</td>
<td>23 (13-40)</td>
<td>0.50 (0.40-0.60)</td>
</tr>
<tr>
<td>Blood glucose ratio ≤0.4</td>
<td>18 (12-27)</td>
<td>0.31 (0.21-0.45)</td>
</tr>
<tr>
<td>Blood glucose ratio &lt;0.4</td>
<td>145 (20.4-1029)</td>
<td>0.25 (0.15-0.40)</td>
</tr>
<tr>
<td>Briem, 1983*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate &gt;27 mg/dL (&gt;3 mmol/L)</td>
<td>2.9 (2.4-3.5)</td>
<td>0.20 (0.06-0.50)</td>
</tr>
<tr>
<td>Komorowski et al, 1986</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate ≥31.5 mg/dL (≥3.5 mmol/L)</td>
<td>13 (8.6-20)</td>
<td>0.20 (0.06-0.50)</td>
</tr>
<tr>
<td>Lannigan et al, 1980</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindquist et al, 1988</td>
<td>25 (16-38)</td>
<td>0.12 (0.06-0.20)</td>
</tr>
<tr>
<td>Briem, 1983†</td>
<td>38 (15-94)</td>
<td>0.01 (0.001-0.20)</td>
</tr>
<tr>
<td>Summary</td>
<td>21 (14-32)</td>
<td>0.12 (0.07-0.23)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid.  
*n = 245.  
†n = 218.

Infection can cause CNS dysfunction in a variety of ways.

Neurological infections may not be common but have high morbidity & mortality. The economic burden of these diseases is considerable.

Examining the CSF is the crucial procedure.

Early treatment is essential for optimum outcome.
Resources

Further papers (to those referenced already):


Davies & Thwaites Infections of the nervous system. Pract Neurol (2011); 11:121-131.