CNS infections are urgent and important

- Mortality is significant recovery is slow and post infection deficits occur in over 50% of cases
- Apart from aciclovir and ART treatment for most infective causes of encephalitis is non-existent.
- Starting aciclovir early is crucial
- Negligence settlements for missed HSV can run into millions of pounds
- LP can help in terms of HSV management but over 62% of patients remain undiagnosed.
Quiz

1. A CT scan should always be performed before a LP
2. You can remove safely 15ml of CSF during an LP
3. A white cell count of 6 in the CSF is considered normal
4. Low CSF glucose indicates bacterial meningitits
5. A negative HSV PCR in CSF excludes HSV encephalitis
6. CSF Neutrophilia excludes encephalitis
7. Parotitis is present in all cases of mumps encephalitis
Encephalitis versus Meningitis

• Delirium due to fever can be difficult to distinguish from AMS but in general meningitis patients do not have Altered mental status

• Motor and sensory deficits and ataxia are associated with encephalitis, however cranial nerve deficits occur with both

• Altered behaviour and personality changes

• Slow onset over days
Important aspects of history

- Where has the patient been?
- Animal contact
- Insect and arthropod bites
- Immunocompromised status
- Recent infections/vaccinations
- Recent respiratory infections
Infectious Causes

- HSV/Enterovirus/VZV/HIV/Mumps
- Influenza/Mycoplasma/LCM/Listeria
- EBV/HHV6/CMV/Adenovirus/JC-PMLE
- WNV/Dengue/JE/Lyme
- EE/WEE/St Louis/RMSF
- Rabies
- Nipah/Hendra
- Syphilis
A note on HSV Encephalitis

• Untreated mortality is 70% treated still 19% but 44-62 have significant CNS deficit
• Culture sensitivity is <10%
• IgG/IgM sensitivity up to 85%
• HSV PCR 98% but please note if CT features and EEG are suggestive of HSV and CSF is negative then continue treatment.
• HSV PCR remains positive for up to 1 week
• The early CT scan can be inconclusive in up to 50% of patients and should be repeated.
Sleepy head!
• 54 yr old taxi driver

• A&E;
  – “General slowness” for 1 week
  – 7/7 prior home from work with headache & slept for 24hrs
  – Then c/o of fever, lethargy & anorexia
  – Became unsteady on feet & talking “silly”
  – Day 4 GP diagnosed labyrinthitis
  – But headaches continued, more unsteady, slurred speech
Examination

- T 37.6°C, GCS 15/15, HR 58 bpm, BP 132/75 mmHg
- CVS/ RS/GI all normal
- Neuro
  - slow but normal gait
  - Slurred speech
  - Cranial nerves normal
  - Tone, power & reflexes normal all 4 limbs
  - Coordination deficient upper limbs
  - 8/10 mental test score
Differential diagnosis?

• Encephalopathy due to;
  – Severe sepsis
  – Toxic
  – Metabolic

• Ischaemic stroke

• Vasculitis

• Bacterial meningitis

• Encephalitis
Investigations

• Haem, biochem incl glucose normal, except mildly elevated CRP at 28mg/l

• CT head
  – Area of hypoattenuation in right frontal & temporal lobes reported as in keeping with acute ischaemia cerebral infarction

• A right fronto-parietotemporal stroke diagnosed and admitted to stroke rehab ward
Consultant ward round (Day 3 admission – Mon)
• Symptoms static; Intermittent pyrexia
• Encephalitis considered

<table>
<thead>
<tr>
<th>Clinical case</th>
<th>Normal range (Adult)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening pressure</td>
<td>17 cm H₂O</td>
</tr>
<tr>
<td>Protein</td>
<td>2.90 g/l</td>
</tr>
<tr>
<td>CSF glucose</td>
<td>Glucose 3.1 (serum 6.6 mmol/l) (47%)</td>
</tr>
<tr>
<td>Cell counts</td>
<td>WCC 5140/mm³ (99% lymphocytes)</td>
</tr>
</tbody>
</table>

• MRI:
Diffuse hyperintensities
Right frontal, parietal & Temporal lobes
Lymphocytic CSF

- Viral Meningitis
- Viral Encephalitis
- Mycobacterium tuberculosis
- Listeria monocytogenes
- Fungal – cryptococcal
- Partially treated bacterial meningitis/ early bacterial?
- Parameningeal bacterial infections (cerebral abscesses etc...)
- Mycoplasma
- HIV
- Syphilis

- Drugs e.g.
  - NSAIDs
  - Trimethoprim
- Autoimmune encephalitis
- ADEM
- MS
- Neoplastic/paraneoplastic
- Vasculitis
- Other autoimmune disorders e.g. SLE
- Sarcoid
Progress

• Treatment started on day 3
  – IV acyclovir 10mg/kg, amox 3g qds, gent 5mg/kg od

• 3 days into treatment
  – Less hesitant speech
  – HSV-1 DNA detected in CSF
  – Antibacterial drugs stopped
  – IV aciclovir 2 weeks (then 4 weeks valaciclovir)

WHAT DO YOU THINK OF TREATMENT?

• Despite treatment, patient remained off work and continues to have word-finding difficulties & cognitive slowing
Why encephalitis is missed

• Wrongly attributing a patient’s fever and confusion
• Failure to recognise a febrile illness and consider infection
• Ignoring a relative says patient behaviour, “not quite right” you say GCS is 15
• Patient is assumed to be drunk or drugged
• Failure to properly investigate a patient with a fever and seizure
• Failure to do a lumbar puncture or if delayed LP failure to start aciclovir.
What are the likely outcomes?

• Death
• Full recovery with no symptoms
• Some disability
  – Memory impairment
  – Speech impairment
  – Unable to walk
  – Bed ridden, full care needed
Epidemiology and Incidence

- Viral, bacterial and tick causes
- Total western incidence
  - 0.7-13.8 per 100,000
- *Herpes simplex* virus encephalitis most common
- Average DGH (300,000)
  - 15-30 cases per year
  - 1-2 viral encephalitis per month
Clinical presentation of encephalitis

• Classically
  – Headache
  – Altered or reduced consciousness
  – Personality or behaviour change in a patient with a fever or history of febrile illness

• Subtle presentations
  – Low grade fever,
  – Behavioural changes
  – Speech and language disturbances

• HSV-1 features where temporal or frontal lobes affected may include
  – Olfactory hallucinations
  – Simple or complex partial seizures
  – Bizarre behaviour
  – Neuropsychiatric features
### Signs and symptoms

- Severe headache
- Fever
- Cognitive/behavioural/personality change

### Symptoms more suggestive of SAH:
- Sudden onset

### Symptoms more suggestive of infection:
- Focal/febrile seizures

### If SAH AND CNS infection collect samples 1-8:
- If CNS Infection only collect purple (1, 2, 3, 5, 6, 7)
- If SAH only collect black cross hatch (1, 2, 3, 4, 7, 8)

Also consider additional pathogens if considering CNS infection in an immunocompromised person — discuss with your local microbiologist/ID physician & collect additional samples as requested.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Type</th>
<th>Volume</th>
<th>Pathology</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CSF</td>
<td>2.5ml</td>
<td>Universal</td>
<td>Protection from light</td>
</tr>
<tr>
<td>2</td>
<td>Fluoride EDTA/ Universal</td>
<td>0.5ml</td>
<td>Glucose + Protein</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CSF</td>
<td>2.5ml</td>
<td>Universal</td>
<td>Microbiology (Cell count)</td>
</tr>
<tr>
<td>4</td>
<td>CSF</td>
<td>1ml</td>
<td>Universal</td>
<td>Xanthochromia</td>
</tr>
<tr>
<td>5</td>
<td>CSF</td>
<td>2ml</td>
<td>Universal</td>
<td>Virology</td>
</tr>
<tr>
<td>6</td>
<td>Blood</td>
<td>4ml</td>
<td>Plain Serum</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Blood</td>
<td>3ml</td>
<td>Fluoride EDTA</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Blood</td>
<td>4ml</td>
<td>Serum Gel</td>
<td></td>
</tr>
</tbody>
</table>

### Microbiology (Cell count) | Glucose + Protein | Microbiology (Cell count) | Xanthochromia | Virology | Glucose | Liver profile
• Any delay > 6 hours start aciclovir

1st CSF WCC may be normal in approx 10%

If you are unsure - ask
<table>
<thead>
<tr>
<th><strong>Opening Pressure</strong></th>
<th>High/Very High</th>
<th>Normal/High</th>
<th>High</th>
<th>10-20cm</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colour</strong></td>
<td>Clear/Cloudy</td>
<td>“Gin” Clear</td>
<td>Cloudy</td>
<td>Clear</td>
<td>Cloudy/Yellow</td>
</tr>
<tr>
<td><strong>Cells/mm³</strong></td>
<td>Normal-High 0-1000</td>
<td>Slightly Increased 5-1000</td>
<td>High/Very High 100-50000</td>
<td>&lt;5</td>
<td>Slightly Increased 25-500</td>
</tr>
<tr>
<td><strong>Differential</strong></td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Neutrophils</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td><strong>CSF/Plasma Glucose</strong></td>
<td>Normal-Low</td>
<td>Normal</td>
<td>Low</td>
<td>66%</td>
<td>Low-Very Low (&lt;30%)</td>
</tr>
<tr>
<td><strong>Protein (g/L)</strong></td>
<td>Normal-High 0.2-5.0</td>
<td>Normal-High 0.5-1</td>
<td>High &gt;1</td>
<td>&lt;0.45</td>
<td>High-Very High 1.0-5.0</td>
</tr>
</tbody>
</table>

**Diagnosis**
- Fungal
- Aseptic meningitis or encephalitis
- Purulent Meningitis
- Normal
- Tuberculous meningitis

CSF Interpretation is vital
# Investigations – CSF PCR

<table>
<thead>
<tr>
<th>All patients</th>
<th>Immuno-compromised</th>
<th>Children</th>
<th>If clinically indicated</th>
<th>Travel history</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-1</td>
<td>EBV</td>
<td>EBV</td>
<td>Measles,</td>
<td>West Nile Virus</td>
</tr>
<tr>
<td>HSV-2</td>
<td>CMV</td>
<td>CMV</td>
<td>Mumps</td>
<td>Dengue</td>
</tr>
<tr>
<td>VZV</td>
<td>HHV 6 &amp; 7</td>
<td>HHV 6 &amp; 7</td>
<td>Chlamydia</td>
<td>Tick-borne encephalitis virus (if appropriate exposure)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
<td>Mycoplasma Influenza</td>
<td>Rabies</td>
</tr>
<tr>
<td>Parechovirus</td>
<td>Influenza A &amp; B</td>
<td>Influenza A &amp; B</td>
<td>JE, WEE,EE, St Louis, MVE,</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Parvovirus B19</td>
<td>Parvovirus B19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rotavirus</td>
<td></td>
</tr>
</tbody>
</table>
Investigations

- HIV testing in all cases of encephalitis (BHIVA guidelines)
- CSF PCR (usually tiered set of investigations with HSV/VZ/Enterovirus in first tier second tier suggested by evidence of Mumps/Measles recent vaccination, travel history or if Immunocompromised)
- CSF and serum IgG and IgM as appropriate
- T/S and NPA and faeces if enterovirus or respiratory viral illness considered
- Vesicle fluid culture and Molecular testing
- If associated with atypical pneumonia, test serum for Mycoplasma and chlamydia
- Autoantibodies: NMDAR antibodies, VGKC antibodies
- Brain biopsy, nucal skin testing
Start aciclovir within 6 hours

• HSV encephalitis
  – Aciclovir 10mg/kg IV
• +/- antiepileptic for seizures
• +/- steroids or other immunomodulatory agents
Imaging in encephalitis

• Early CT
  – Typically shows low density lesions, oedema, shift
  – May show infarction/haemorrhage later
  – **BUT CAN BE NEGATIVE IN EARLY HSV**

• Initial MRI usually positive
  – T2, T2 Flair

• Diffusion weighted MRI may be more sensitive

• Lesions
  – Typically **fronto-temporal** and **parietal** lobe in HSV
  – Basal ganglia in some arboviral encephalitides
  – Hippocampal in limbic encephalitis eg VGKC antibodies
  – Brain stem, rhomboencephalitis
Is the EEG useful?

• Typically shows generalised slowing
• May show focal seizures
• May show PLEDS (periodic lateralizing epileptiform discharges)
  – Once thought to be pathognomonic


<table>
<thead>
<tr>
<th></th>
<th>All encephalitis (n=203)</th>
<th>HSV (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>51/170 (30%, 23–37)</td>
<td>18/32 (56%, 38–74)</td>
</tr>
<tr>
<td>MRI</td>
<td>102/169 (60%, 53–68)</td>
<td>25/28 (89%, 71–98)</td>
</tr>
<tr>
<td>EEG</td>
<td>100/120 (83%, 75–89)</td>
<td>22/27 (81%, 62–94)</td>
</tr>
</tbody>
</table>
Complications

• Monitor renal function and keep adequately hydrated
  – Rare risk of renal failure from aciclovir
• If patient deteriorates despite treatment
  • Venous sinus thrombosis
  • Cerebral infarction
  • Subtle motor or non-convulsive status epilepticus
  • SIADH
  • Aspiration pneumonia
  • Other HAI
Patients and their family should be put in contact with patient-orientated support services

www.encephalitis.info
Questions?