CNS Infections Viruses in July

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Outline

- 1. Meningitis
- 2. Encephalitis
- 3. CSF viral testing in HIV infection
- 4. Prion disorders

CSF PCR testing

CNS infection history

- Travel
- Work
- Sex
- Contact
- Epidemics
- Animal contact
- Vaccination history
- Immunodeficiency
- Non-CNS symptoms

1. Meningitis

- Rapid diagnosis and treatment of bacterial causes
- Empirical antibacterial therapy after blood culture and before CT and LP if:
 - reduced LOC or
 - of focal signs or
 - papilloedema

Meningitis - viral

- Symptoms:
 - O Prodrome
 - O Fever
 - O Headache
 - O Photophobia
 - O Alert
 - No focal neurological signs
- CSF analysis:
 - Opening pressure normal
 - O Appearance clear
 - Cell count 5 -100
 - Cell type mononuclear
 - Protein normal or raised
 - Glucose normal

"Aseptic" meningitis – viral causes

- Mostly viral meningitis
- Enteroviruses
- HSV-2 (and HSV-1)
- Other herpes viruses e.g. VZV, EBV, CMV, HHV-6-7-8
- Mumps
- Adenoviruses
- HIV

Aseptic meningitis - non-viral infections

- Fungi e.g. Cryptococcus neoformans
- TB
- Syphilis and other spirochaetes
- Brucella
- Mycoplasma
- Parameningeal infection abscess, venous sinus, paranasal sinus
- Protozoa e.g. Naegleria fowleri
- Helminths e.g. Angiostrongylus cantonensis

Aseptic meningitis - non-infective causes

- Malignancy Ca, NHL, leukaemia
- Sarcoid, SLE, Behcet's disease, Vogt-Koyangi-Harada syndrome
- Drugs
 - intrathecal Rx
 - **O** NSAIDs
 - antibiotics (TMP, amoxycillin, cephalosporins)
- SAH

- Enterovirus look for other manifestations in patient and contacts
 - Contact history, epidemics
 - Summer and autumn
- HSV-2 associated with primary acquisition
 - Urinary retention
 - O Genital symptoms
 - O May be recurrent ("Mollaret's meningitis")
- VZV meningitis
 - Often without cutaneous disease

HSV - 2 meningitis and genital lesions

- 5/69 (7%) patients with HSV 2 DNA present had genital lesions
- 0/23 with recurrent meningitis had genital lesions
- 19% had history of genital herpes
- 82% had neither history nor lesions at presentation
- Is it real?
 - OQuestionnaire, retrospective, neurologists
 - O'Sullivan CE et. al. Mayo Clin Proc 2003;78:1347

CSF additional tests

- Enterovirus PCR
- HSV-2 PCR
- VZV PCR

- If risk factors for HIV or clinical signs of HIV or low glucose then:
 - Cryptococcal antigen
 - OIndian ink stain
 - OHIV testing

Other tests

Throat and stool culture for enteroviruses

If no diagnosis made with initial lx

- and syndrome resolves
 - **O**Test HIV
 - OTest syphilis
- and syndrome doesn't resolve
 - OTest for other pathogens/conditions
 - OEnsure that you have stored some serum at baseline for acute/convalescent testing
 - Often need to repeat LP

Viral meningitis - treatment

- Usually supportive as self-limiting
- Insufficient evidence for pleconaril
- Anti-HSV Rx not proven
 - Olf genital herpes then treat as usual

ED presentations

- All CSF samples
- Bacterial, fungal, proven SAH excluded
- > 5 WBC/mm³ defined meningitis
- 194 total
- 149 without meningitis
 - 3/147 PCR + enterovirus (2%)
 - Oi.e. enteroviral infections may not cause CSF pleocytosis
 - Hausfater P et. al. J Med Virol 2004; 73:137

- 45 with meningitis
 - O14 PCR positive (31%)
 - 8 enterovirus
 - 5 VZV
 - 1 HSV
 - 3 EBV (1 also enterovirus +)
 - •1 HHV-6
 - 010 alternate diagnoses made
 - Atypical pneumonia, migraine, TB/HIV, SLE/vasculitis, encephalitis, tumours, bacterial sepsis.

CSF PCR if no WBC?

- 974 consecutive specimens referred for PCR
- 2.5% + for 1 pathogen, 0.2% + for 2 pathogens (458 submitted for testing of more than one pathogen)
- Yield for herpes virus PCR (HSV, VZV, CMV, EBV)
 - ONormal WBC and glu 0/209 0%
 - OAbnormal WBC or glu 24/523 4.6%
 - O Abnormal WBC and glu 18/173 10.4%

Tang Y-W et. al. Clin Infect Dis 1999; 29: 803

Clinical utility of PCR in CNS infections

143/2162 patients positive (6.6%) (3.3% HIV+)

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C Enterovirus
                   54%
             77
OHSV – 1
           20
                   14%
             16
O VZV
                   11%
OEBV
             11
                   8%
OHSV (untyped) 7
                   5%
OHSV - 2
                   4%
             3
OCMV
                   2%
OJCV
                   1.5%
OHHV-6
                   0.7%
```

Jeffery KJM et. al. Lancet 1997; 349: 313

- Clinical classification
 - ODefinite 10/12 83%
 - OProbable 10/51 20%
 - OPossible 0/7 0%
 - OExcluded 2/340 0.6%
- Factors associated with PCR +
 - **OFever >37.5**
 - OWCC in CSF >5/uL
 - OVirus-specific rash

Clinical utility

- Positive PCR
 - ODefinite vs. Probable, possible, excluded
 - OLikelihood ratio 88.2
- Negative PCR result
 - OExcluded vs. others
 - OLikelihood ratio 0.1

Multiplex PCR

- Enterovirus
- HSV 1
- HSV 2
- VZV

- Many reports of similar technique
 - OMainly herpes viruses

2. Encephalitis - viral

- HSV -1 (and HSV 2)
- Arboviruses region specific
 - O Murray Valley, Kunjin Australian
 - O West Nile virus US
- Hendra virus and Nipah virus
- Japanese B
- Rabies and Australian Bat Lyssavirus
- Enterovirus esp. 71
- Influenza
- VZV
- Dengue fever

Encephalitis – non-viral

- Neisseria meningitidis
- Listeria monocytogenes
- Scrub typhus
- Leptospirosis
- Melioidosis (Burkholderia pseudomallei)
- Q fever (Coxiella Burnetii)
- Malaria
- TB
- Borrelia spp.
- Brucella spp.

Encephalitis – non-infective

- Ensure encephalopathy excluded
 OGlu, Na, thiamine, drugs
- Status epilepticus
- Inflammatory conditions
- Malignancy
- Acute disseminated encephalomyelitis

Encephalitis approach

- Aciclovir (and antibiotics) as soon as (meningo)encephalitis considered in DD
- Imaging
- CSF
- EEG
- Support as good outcome possible with some types of encephalitis
- Store serum and CSF for second round testing

Herpes Simplex Encephalitis

- Most common cause of encephalitis
- 1-4/1,000,000 per annum
- 50% have long term sequelae
- 80% untreated mortality
- Associated with reactivation or primary infection

HSE – clinical features

- Headache
- Fever
- Alteration in cognitive state
 - Confusion
 - OBehaviour change
 - ODysphasia
- Alteration in level of consciousness

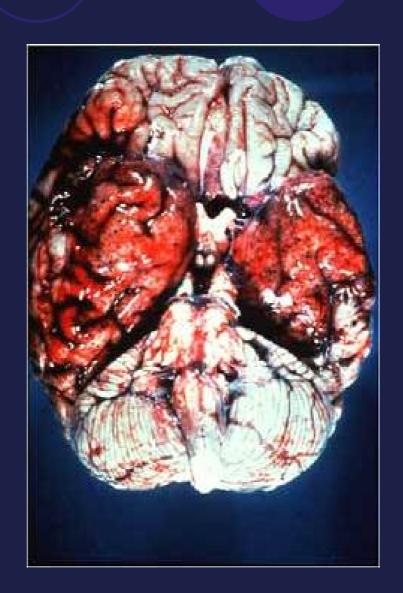
HSE - prognosis

- Worse if:
 - OOld
 - OGCS<7 poor outcome no matter age
 - OPresent >4 days before Rx 65 vs. 100% survival with Rx

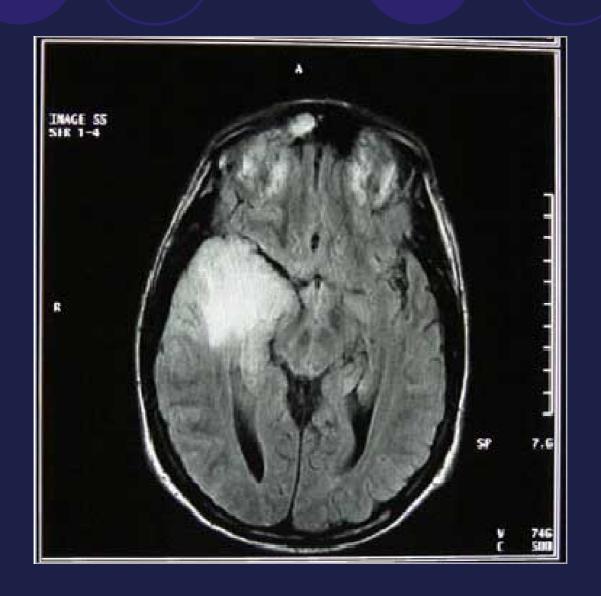
HSE - Investigations

- Imaging
- CSF analysis
- EEG
- Biopsy

HSE



HSE - MRI



HSE - CSF PCR vs. brain biopsy

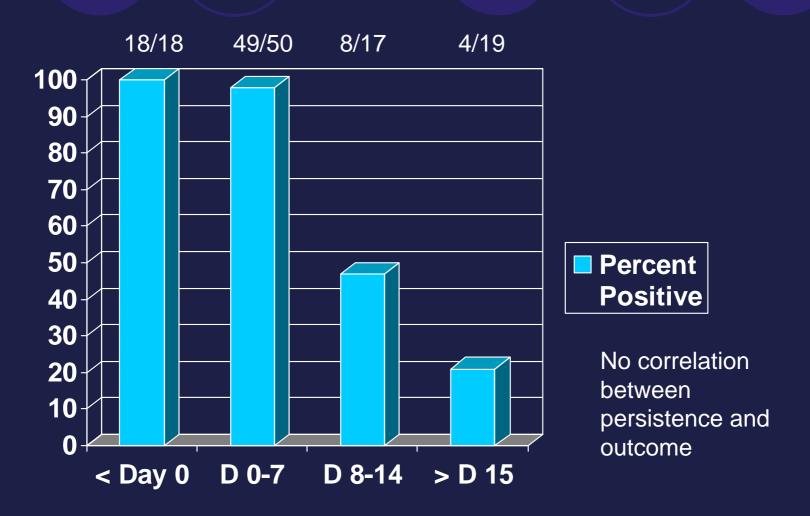
- Original gold standard
 - OHSV cultured from brain biopsy
 - OFrom treatment studies in 1970s-1980s

Lakeman FD et. al. J Infect Dis 1995; 171: 857

- Sensitivity 98%
- Specificity 94%
- PPV 95%
- NPV98%

- 3 Biopsy culture negative cases had CSF
 PCR +
- CSF HSV PCR as the new gold standard

HSV PCR detection after treatment



• Lakeman FD et. al. J Infect Dis 1995; 171: 857

HSE – HSV PCR negative

- Can be PCR negative early in course (<3 days)
- Repeat CSF analysis after 3 days of treatment
 - e.g. Tiege XD et. al. Clin Infect Dis 2003; 36: 1335

HSE - EEG

- Less sensitive than MRI
- Typically non-specific in first 5 days
- Lateralising periodic sharp and slow wave pattern

HSE

- Viral culture of CSF
 - O< 5% positive</p>
- Intrathecal antibody production
 - Control for BBB
 - OTakes 2-3 weeks to develop

HSE - treatment

- Aciclovir 10mg/kg q8h IVI for 14-21 days
 - ORelapses reported with short courses
 - **O**Exact duration unclear

Encephalitis other tests

- Japanese encephalitis
 - OCSF IgM
 - ONearly all positive by day 3 of illness
- Rabies
 - **ORT-PCR** on saliva and CSF
 - Wacharapluesadee S, Lancet 2001; 358:892-893.
- Brain biopsy
 - Only if non-invasive tests negative
- Talk to laboratory

Prevention

- Viral meningitis
 - ONot proven with Mollaret's meningitis, but could provide prophylaxis if genital herpes
- Viral encephalitis
 - OPregnant and genital HSV C section, antivirals
 - Childhood immunisations (polio, MMR)
 - ORabies pre and post exposure (and ABLV)
 - OJapanese B Encephalitis virus vaccine

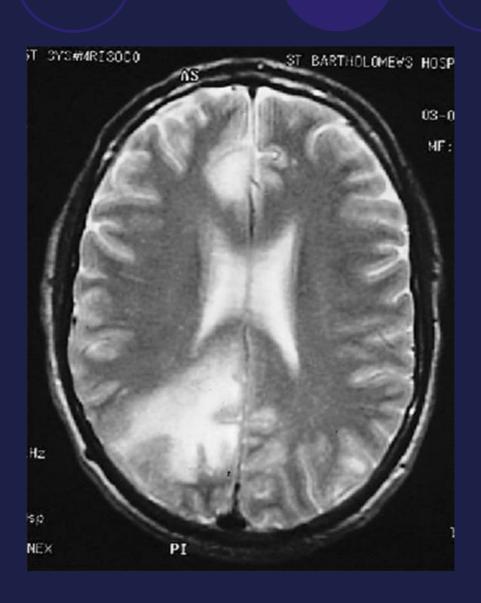
3. Viral PCR in HIV infection

- Progressive multifocal leukoencephalopathy (PML)
- Cytomegalovirus
- Primary CNS lymphoma (PCNSL)
- AIDS dementia complex (ADC)
 - OHIV encephalopathy

PML

- Typical clinical features
- Moderate-severe immunodeficiency
- Onset over weeks-months
- Cognitive, headache, sensory or motor, gait, vision, speech, swallowing
- Absence of fever
- Seizures infrequent

PML



PML

- JC virus (polyomavirus)
- JC virus PCR on CSF
 - 065% sensitive
 - **O**92-100% specific

 Therefore repeat CSF assessment if initially negative, before progressing to brain biopsy

PML - treatment

- HAART
- Steroids if inflammatory reaction
 - Olmmune restoration disease

Assessment of focal brain lesion

- Multiple focal brain lesions CD4<100/uL</p>
 - Empirically treat for toxoplasmosis
- Single focal brain lesion
 - OCSF EBV PCR reportedly highly sensitive and specific for diagnosis of PCNSL

BUT:

- O79 % specificity toxoplasmic encephalitis, cryptococcoma, HIV encephalopathy
- **OPPV** 29%
 - Ivers LC et. al. Clin Infect Dis 2004; 38: 1629

CMV

- CMV related neurological disease in AIDS
- Ventriculoencephalitis, radiculitis, myelitis
- CSF PCR more reliable than clinical assessment
 - Gozlan J et. al. AIDS 1995; 9: 253
- Treatment of CMV encephalitis
 - Oganciclovir
 - O+/- foscarnet

AIDS dementia complex

- HIV viral load in CSF correlates with degree of severity
- Presence of HIV in CSF is not diagnostic of ADC
- Therapeutic aim is for undetectable HIV viral load in CSF
- Use antiretrovirals with CSF penetration
 - ? Reducing plasma HIV viral load adequate

4. Prion diseases

- Transmissible spongiform encephalopathies
- Human and animal forms
- Rare
- Aberrant protein folding
- No treatment
- Invariably fatal
- Cause neurodegeneration
- latrogenic transmission concerns

- Sporadic CJD
 - ODementia, ataxia, myoclonus, others
 - ODetect 14-3-3 protein in CSF
- Familial TSE autosomal dominant
 - Familial CJD
 - Gerstmann-Straussler-Scheinker syndrome
 - Fatal familial insomnia
- Kuru
 - OPapua New Guinea

Variant CJD

- Bovine Spongiform Encephalopathy
- Younger
- 60% have psychiatric symptoms initially anxiety, insomnia, withdrawal
- 50% have 14-3-3 protein in CSF
- Tau protein in CSF
- MRI high T2 signal in posterior thalamus
- EEG not useful

Conclusions

- Staged investigations
 - common, treatable conditions first then uncommon, untreatable causes
- Store some serum and CSF
- Tests may need repeating
- Talk to your laboratory (especially when investigating uncommon causes)

Further reading

- Meningitis and Encephalitis
 - O Beaman MH and Wesselingh SL .Acute community-acquired meningitis and encephalitis. Med J Aust 2002; 176:389-396
- Prion diseases
 - Collins SJ et. al. Transmissible Spongiform Encephalopathies. Lancet 2004; 363: 51-61
- HIV
 - OHIV Management in Australia: a guide for clinical care. Australasian Society for HIV Medicine. 2003. Available on line at www.ashm.org.au