

## Nervous System 3 Infections

Prof John Simpson

- this lecture is now on the intranet
- issue of lumbar puncture in raised ICP
- review your microbiology!

### Most organisms can target the brain

- bacteria
- viruses
- protozoa
- metazoa
- fungi
- *prions*

### Transmission of infection to NS

- blood borne
  - septicaemia, viraemia, infected blood cells, septic embolism (e.g. endocarditis, bronchiectasis, IV drug use)
- direct spread
  - adjacent infection, head injury etc
- trauma (including iatrogenic - LP, ventriculo-peritoneal shunts)
- vertical transmission in pregnancy
- (important role for immunosuppression)

### Bacterial infections

- problems arise because of inflammatory reaction or tissue destruction
- result in meningitis or abscess

### Meningitis

- inflammation in subarachnoid space (arachnoid and pia mater) strictly speaking = *leptomeningitis*
- *pachymeningitis* = predominantly dural disease
  - usually direct spread of infection from skull (otitis media, mastoiditis or fracture)
  - Gram-neg bacilli from middle ear, haemolytic strep from sinuses or mixed organisms, often with *Staph aureus*, from skull fractures.
  - can cause dural abscess]

## Pachymeningitis

- epidural infection
  - suppuration between dura and skull or vertebral column - abscess (SOL)
- subdural infection
  - abscess unusual
  - pus spreads in subdural space over hemispheres causing subdural empyema.
  - involvement of subdural vessels may cause thrombophlebitis and venous infarction of brain

## Meningitis (i.e. leptomeningitis)

- usually blood-borne infection, but can be direct spread from the skull bones
- most common bacteria –
  - neonates: coliforms, streptococci
  - 2-5 years: haemophilus
  - older children - adults: meningococcus, pneumococcus
  - old age: pneumococcus
- in immunocompromised
  - pneumococcus, meningococcus, listeria
- (TB and syphilis also important causes)

## Meningitis

- incubation period ~ 4 days
- once in SA space, bacteria multiply
- pathogenetic effects follow release of agents inducing fever and acute inflammation (hyperaemia, exudation etc)
- inflammatory exudate can raise ICP and can reduce cerebral blood flow

## Meningococcal meningitis

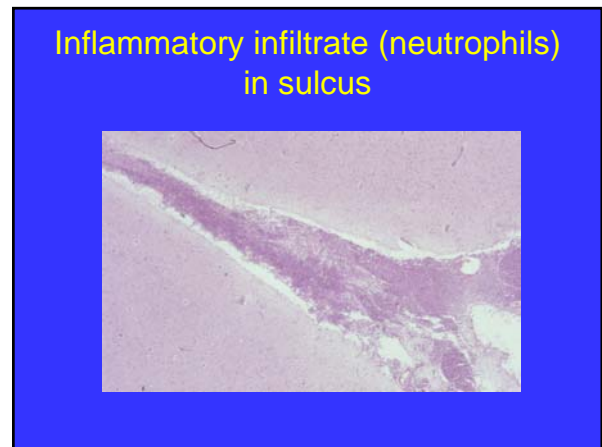
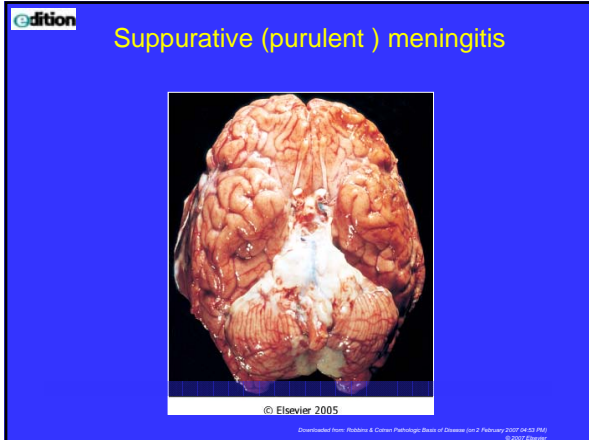
- commonest variety worldwide, but less so in Malawi
- sporadic (URT) or epidemics in small communities (droplet spread from asymptomatic nasal carriers)
- petechial rash can herald DIC accompanied by potentially lethal adrenal haemorrhage (Waterhouse-Friederichsen syndrome)
- (immunisation programmes in colleges etc)

## Pneumococcal meningitis

- commonest meningitis in Malawi
- usually sporadic cases
- at all ages
- not just in AIDS

## Pathology of bacterial meningitis

- meningeal and superficial cortical vessels congested, often haemorrhagic: cord can be involved too
- infiltrate of neutrophils, so often obvious suppuration – basal cisterns and sulci
- CSF often turbid - reduced glucose, increased cells (neutrophils) and increased protein
- complications (~ 25% die) include –
  - cerebral abscess, subdural empyema, cerebral infarction, obstructive hydrocephalus, epilepsy, cranial nerve palsies (VI & VIII)
  - and DIC if meningococcal



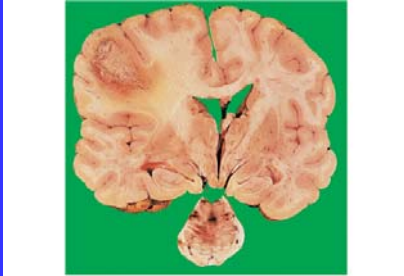
### Cerebral abscess

- usually from
  - direct spread - sinuses or middle ear
  - septic sinus thrombosis - spread of infection from mastoid or middle ear via sigmoid sinus
  - blood spread, e.g. infective endocarditis, bronchiectasis etc - often multiple abscesses in parietal lobes
- adjacent brain markedly oedematous
- abscesses frequently enlarge and become multiloculate

### Cerebral abscess

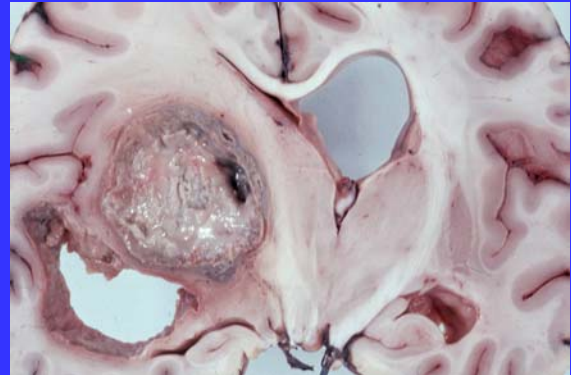
- presentation can be similar to meningitis, but often with focal signs, epilepsy and fever
- but also act/present as space-occupying lesions
- complications include –
  - meningitis
  - focal neurological deficit
  - epilepsy
  - herniation of the brain

## Cerebral abscess

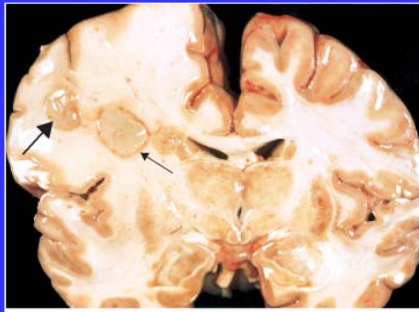


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## Cerebral Abscess



## Cerebral abscesses



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## NS tuberculosis

- secondary to infection (75% primary) elsewhere
- meningitis (espec. in young) and/or abscesses (tuberculomas)
- meningitis from rupture of subependymal tubercles
  - (rarely from direct spread from vertebral body)
  - thick gelatinous exudate in basal cisterns and sulci
  - causes subacute meningitis with occasional isolated cranial nerve palsies
  - but can be non-specific and diagnosed only after LP
- tuberculomas present like other cerebral abscesses

## NS syphilis

- blood spread
- effects include –
  - silent meningitis during 1ry and secondary stages
  - meningeal thickening in tertiary stage, causing cranial nerve palsies
  - gummas, causing cerebral or spinal compression
  - tabes dorsalis due to degeneration of dorsal columns
  - “general paralysis of the insane” due to cerebral atrophy in chronic infection

## Viral infections of NS

- usually haematogenous spread during viraemia
  - usually cause meningitis or encephalitis
- neural spread along peripheral sensory nerves by retrograde axonal transport, e.g. rabies
- some viruses are neurotropic - tend to spread specifically to CNS from initial site of infection, e.g. polio virus from the gut
- pathogenetic effects because of multiplication inside NS cells or immune response (with lymphoid infiltration) to virus

## Effects of viral infections

- usual effect is meningitis
- less commonly encephalitis
- also
  - reactivation of latent viral infection (e.g. zoster)
  - 'slow' virus infections responsible for subacute spongiform encephalopathy, rare cause of dementia
  - acute disseminated encephalomyelitis, demyelinating disorder, resulting from virus-induced immune reaction

## Viral meningitis

- common
- acute onset, but usually less severe than bacterial meningitis
- usually haematogenous spread
- common organisms –
  - mumps
  - echovirus
  - coxsackie
  - HSV

## Viral meningitis

- meninges infiltrated by mononuclear cells (lymphocytes, plasma cells and macrophages) with typical perivascular lymphocytic cuffing in meninges and superficial brain
- characteristic CSF – normal glucose, increased cells (lymphocytes) and slight increase protein

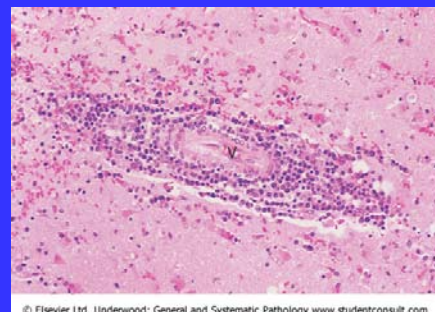
## Viral encephalitis

- most commonly HSV, EBV, zoster and arboviruses
  - mode of spread varies with virus
  - viral type may also determine part of brain affected
- pathology
  - mononuclear infiltration - as perivascular cuffing
  - +/- cell lysis and phagocytosis of cell debris by macrophages - when neurones involved, process is known as neuronophagia
  - reactive astrocytes and microglia, often in cell clusters
  - vasogenic oedema
  - viral inclusions may be diagnostic, e.g. 'owl-eyes' CMV and Negri bodies in rabies

## Viral encephalitis

- most cases mild, self-limiting conditions, but may result in death or severe
- most common effects – fever, personality change and seizures
- focal neurological signs very unusual
- (some viruses can also damage brain not by invasion, but secondary to an immune mediated demyelination)

## Perivascular cuffing in viral encephalitis

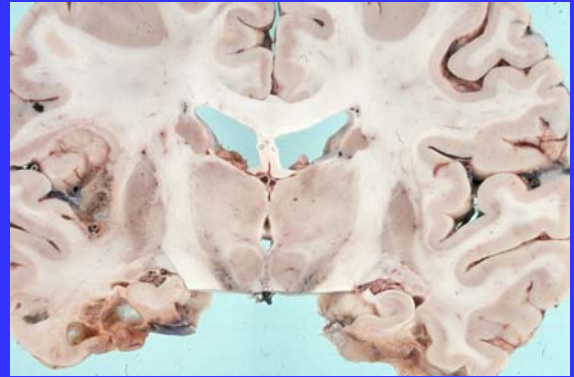


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## Congenital and childhood viral disease

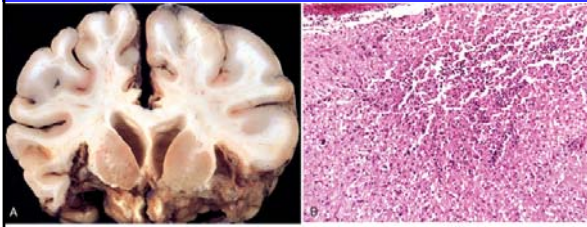
- CMV and rubella commonest NS viruses
  - cause necrotising encephalomyelitis resulting in developmental malformations and microcephaly, particularly if infected during first trimester
- persistent viral infections - rare diseases in which infection occurs in early life, with NS disease occurring years later
  - e.g. subacute sclerosing panencephalitis caused measles virus

## Herpes Simplex Encephalitis



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## Herpes simplex encephalitis



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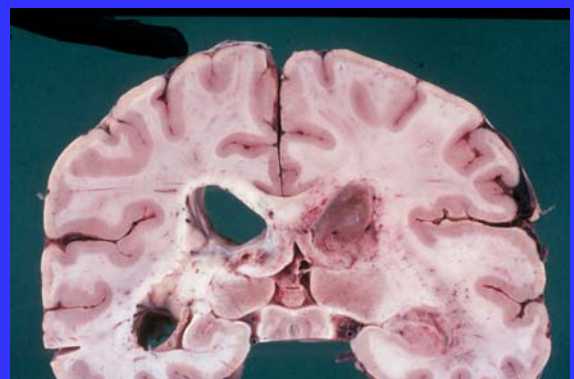
## Parasitic infections - neurocystocercosis

- (all parasitic infections uncommon unless human parasites endemic)
- most important here is taenia solium, causing neurocystocercosis
  - predilection for NS, causing cysts in brain parenchyma and/or subarachnoid space
  - either SOLs in brain (typically seizures) or cord - or meningitis, often more important in chronic repair phase (obstr. hydrocephalus, cranial nerve palsies)

## Parasitic infections - toxoplasmosis

- most frequent cause of focal NS disease in AIDS
- ~ 50% patients in Africa and Europe
- often constitutional symptoms/signs at first, but then more obviously neurological ones, sometimes with localising signs
- ICP may be raised with coma/death if untreated

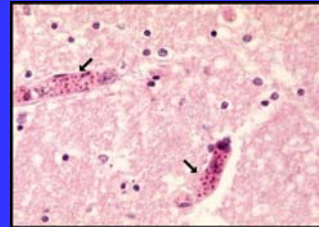
## Cerebral toxoplasmosis



## Cerebral malaria

- usually only seen in children under 10 or newcomers to falciparum malarial areas
- acute diffuse parenchymal disease accompanied by fever +/- meningitis
- rapidly fatal in ~ 25-50%
- histological hallmark is sequestration of microcirculation by parasitised/non-parasitised red cells
- causes ring-like lesions in brain

## Cerebral malaria – parasites in vessels



## Malaria

- decreased flexibility and increased sticking/rosetting of red cells occlude microcirculation
  - probably cause hypoxia, often with petechial haemorrhages and tiny granulomas
- curiously, raised ICP not due to oedema, but ?increased blood volume
- mechanism of coma is not clear
  - ? increased cerebral glycolysis producing lactate and/or interference with neurotransmission

## Other parasitic infections

- trypanosomiasis
  - chronic meningoencephalitis
- entamoeba histolytica
  - amoebic abscess
- echinococcus granulosus
  - hydatid cyst
- toxocara canis
  - eosinophilic meningitis with granulomas

## Fungal infections of NS

- more common in immunosuppression
- usually blood spread from lungs, but also direct
- cryptococcus
  - usually causes meningitis
- candida and aspergillus
  - usually cause abscesses
- mucormycosis
  - usually uncontrolled diabetics – granulomatous nasal infection spreading to brain

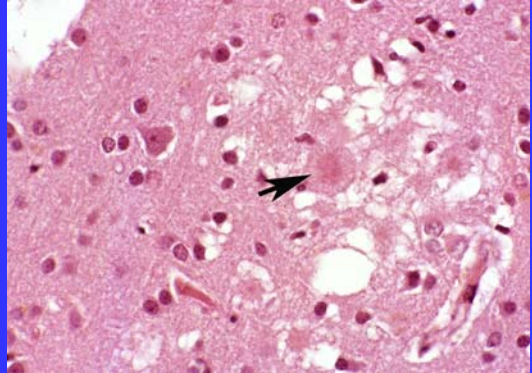
## Prion disease

- CJD (Creutzfeldt-Jakob disease)
- variant CJD

## CJD (Creutzfeldt-Jakob disease)

- presents in adults as rapidly progressive dementia often with focal signs – always fatal
- sporadic disorder in 1:1 000 000 per year worldwide
- transmissible to primates by modified host protein, prion protein
- human-human transmission recorded from electrode implantation, grafts and human growth hormone
- cortical atrophy, neuron loss and reactive proliferation of astrocytes, but no inflammation
- numerous small vacuoles present in neuron and glial processes, so known as spongiform encephalopathy
- akin to kuru in New Guinea

## Prion plaques in variant CJD



## Variant CJD

- new variant form of CJD identified in young patients in UK
- probably from transmission of BSE (bovine spongiform encephalopathy - 'mad cow' disease) to humans by contaminated beef
- several hundred cases of variant CJD so far - ? in future?

## Fetal NS infections

- rubella (deafness, blindness, microcephaly)
- CMV (microcephaly)
- toxoplasma (microcephaly)
- syphilis (tertiary forms include GPI, tabes dorsalis and meningovascular syphilis)
- (HIV)

We'll cover NS infections in immunosuppression and HIV in the next lecture, along with tumours of the NS