TUBERCULOUS MENINGITIS

Mycobacterium tuberculosis is an aerobic non-spore forming bacillus which may be cultured and stained by Ziehl–Neelsen stain. Infection occurs by person-to-person droplet spread. The organism is inhaled into the lower portion of the lungs and there multiplies locally before disseminating through lymphatic and haematological spread into other organs.

Tuberculous meningitis develops secondary to a caseating tuberculous focus adjacent to the CSF (Rich Focus). These usually develop following prior haematogenous dissemination of mycobacteria and in the absence of pulmonary tuberculosis.

Tuberculous meningitis is characterized by inflammatory meningeal adhesive exudates leading to a florid small and medium vessel vasculitis which culminates in occlusion of cerebral arteries and infarction. There is also a disturbance of CSF flow because of impairment of absorption at the arachnoid villi and blockage at the aqueduct and fourth ventricular outlet.

In tuberculous meningitis, vasculitis particularly affects the vessels at the base of the brain including the internal carotid, proximal middle cerebral and perforating vessels to the basal ganglia and internal capsule.

Clinical manifestations

Tuberculous meningitis is often preceded by a prolonged prodrome of non-specific malaise, anorexia, low-grade fever, myalgia, photophobia and headache. The development of meningitis may be insidious, associated with worsening headache, nausea, vomiting, focal or generalized seizures and progressive impairment of consciousness.

Cranial nerve palsies are common and often initially involve eye movements resulting from III, IV or VI nerve palsy. There may be facial weakness (VII), optic neuropathy (II), progressive hearing loss (VIII) and eventual bulbar involvement(X–XII). Fundal examination may show papilloedema, optic atrophy or the presence of choroid tubercles.

Other neurological signs include hemiparesis and hemiplegia as a consequence of vasculitic infarction or space-occupying tuberculomas. Movement disorders may be manifest as tremor, myoclonus, chorea, hemibellismus or dystonia and cerebellar ataxia may occur from direct involvement or vasculitic infarction. Cerebrovascular disease usually occurs in the distribution of the anterior circulation but may be posterior in distribution.

Diagnosis

Tuberculin skin test is variable in its response and unreliable. CSF examination is characterized by the presence of lymphocytic pleocytosis with a high protein and low glucose.

Direct examination of the CSF for acid–alcohol fast bacilli (AFB) requires the provision of large volumes of CSF and is experience dependent. AFB are only seen in up to 25% of cases with appropriate staining.

CSF culture is the diagnostic investigation but requires up to 6 weeks and is therefore of only limited value in clinical practice. Culture is positive in up to 70% of cases. CSF PCR for tuberculosis is a sensitive technique but is limited in its specificity and is difficult to undertake.
Radiology

Approximately 50% of patients with tuberculous meningitis may show evidence of previous tuberculosis on chest X-ray with up to 10% having miliary tuberculosis. CT brain is commonly abnormal with marked enhancing exudate in the basal cisterns.

There may also be hydrocephalus, parenchymal enhancement, evidence of cerebral infarction or cerebral oedema or focal tuberculosis. MRI is sensitive in showing meningeal enhancement, focal parenchymal abnormalities or the development of communicating or obstructive hydrocephalus.

Management of tuberculous meningitis

Treatment should commence with isoniazid, rifampicin, pyrazinamide and ethambutol for 3 months and this should be followed by a 6-month continuation phase of treatment with isoniazid and rifampicin. All antituberculous treatment carries significant toxicity.

Steroids are indicated in the acute phase particularly if there is cerebral oedema, spinal block, severe tuberculous meningitis, spinal arachnoiditis or cerebral vasculitis. Surgical intervention may be required in the presence of obstructive hydrocephalus that has not responded to medical treatment.

The outcome of tuberculous meningitis has remained poor and the mortality is still >20%, with severe neurological sequelae occurring in up to 30% of survivors.

CEREBRAL ABSCESS

This is a focal suppurative (pus forming) infection occurring within the cerebral parenchyma. It develops as a result of contiguous spread of infection from paranasal sinuses, mastoiditis, otitis media, osteomyelitis or following postoperative and posttraumatic infections.

Less commonly, it may arise as a result of haematogenous spread from distant sites including teeth and lungs. The causative agents depend on the underlying abnormality, and the age and immunological status of the patient.

Cerebral abscesses that arise from dental, frontal or ethmoid sinuses tend to involve the frontal lobe while those arising from the sphenoid sinuses or otitic infection particularly involve the temporal lobes.

Cerebral abscesses resulting from haematogenous spread tend to occur as multiple rather than single abscesses, often in the region of greatest blood flow, within the basal ganglia. The onset is with subacute or indolent fever, headache, nausea, vomiting, seizures or focal neurological signs.

Fever is variable and may be absent in up to 50% of patients usually those who are older; it tends to resolve rapidly with steroids. Rupture of an abscess into the ventricles may manifest as a severe headache and developing signs of meningism.

Investigation and Treatment

Routine hematology and biochemistry usually shows an elevation of the erythrocyte sedimentation rate (ESR), white cell count and blood cultures are only positive in about 10%.

CT scan may show a thin enhancing ring of uniform thickness. MRI with enhancement is more sensitive and will document the extent of surrounding edema more accurately. Lumbar puncture is contraindicated in patients with mass lesions.
Treatment is urgent, necessitating administration of appropriate antibiotic (flucloxacillin or Vancomycin + metronidazole + Ceftrioxone or ceftaxime) with surgical drainage or removal and control of cerebral edema.

**VIRAL DISEASE OF THE NERVOUS SYSTEM**

**VIRAL MENINGITIS**

Viruses cause an isolated aseptic meningitis characterized by symptoms and signs of meningeal irritation with a CSF pleocytosis. Non-polio enteroviruses are the most common cause of viral meningitis, these include coxsackie and echovirus strains.

The main causes include:

1. Echovirus
2. Coxsackie A, B
3. Enterovirus 70, 71
4. Mumps
5. Measles
6. Herpes simple virus 2 (HSV-2)
7. Varicella zoster virus (VZV)
8. Epstein–Barr virus (EBV)
9. Cytomegalovirus (CMV)

Viral meningitis is a relatively uncommon complication of systemic viral infection. Most viruses gain access to the body from the oropharynx. They are amplified (multiply) in lymphatic tissue, spread to the bloodstream (viraemia) and cross the choroid plexus or capillary endothelial cells to reach the CNS.

In viral meningitis there may be a flu-like prodrome followed by the sudden onset of intense frontal headache, fever and neck stiffness associated with photophobia, malaise, myalgia and severe nausea and vomiting. Although there is pyrexia, neck stiffness and meningeal signs, patients are generally less unwell than those with bacterial meningitis.

**Diagnosis**

The peripheral white cell count is usually normal but may be increased or decreased and liver function may be abnormal. The CSF is clear and colorless with a normal to moderately elevated pressure. The cell count may be up to 1000 cells/mm³, the majority are lymphocytes.

Viral isolation is undertaken from the throat, urine or stool and antibody studies are possible in serum or CSF. The detection of viral RNA or DNA is now undertaken using PCR in the serum or CSF.

**Management**

The treatment is supportive care but it is necessary to admit the patient if there is a possibility of bacterial meningitis. Herpes virus meningitis can be treated with a variety of antiviral agents including aciclovir, famciclovir, valaciclovir, ganciclovir and foscarnet.

The only therapy of clinical use for enterovirus meningitis is immune serum globulin, but the new antipicorna viral agent pleconaril may have an important role. The prognosis in viral meningitis is good with spontaneous recovery usually occurring within 1–2 weeks.
ENCEPHALITIS

Encephalitis is acute infection of the parenchyma of the brain caused by a virus, which results in a diffuse inflammatory process, often also involving the meninges. Encephalitis causes focal or multi-focal neurological deficits or seizure activity.

The most common severe forms of infectious encephalitis are those caused by:

1. HSV-1
2. VZV
3. EBV
4. CMV
5. HHV 6 and 7
6. Enteroviruses
7. Adenoviruses
8. Influenza virus A and B

Clinical features

The clinical manifestations of encephalitis are often most severe in infants and those over the age of 65. It is characterized by fever in 90% of patients. Seizures and impaired level of consciousness are common and help to distinguish acute infective encephalitis from viral meningitis.

The presence of headache, pyrexia and meningism suggest leptomeningeal irritation while parenchymatous involvement leads to focal neurological signs including seizures and alteration of consciousness progressing to stupor and coma.

More commonly, behavioral and speech disturbances develop and abnormal movements are associated with lesions in the basal ganglia.

HERPES SIMPLEX ENCEPHALITIS

The majority of cases of herpes simplex encephalitis (HSE) in adults are caused by HSV-1. Primary infection usually develops in the oropharyngeal mucosa before the virus is transported by retrograde transneuronal spread via the trigeminal nerve to establish latency in the olfactory bulb or trigeminal ganglion.

The presence of labial herpes has no diagnostic specificity to HSE. The herpes virus leads to inflammation, infection and necrotizing lesions particularly in the inferior and mesial temporal lobes which may also involve the orbital frontal cortex and limbic structures.

The onset of HSE is with fever, headache and alteration of consciousness which may develop gradually or rapidly over a matter of hours. The most common manifestations are personality change, dysphasia with progressive behavioral disturbance and occasional psychotic features.

Less typical features include the development of hemiparesis or a visual field defect (particularly superior quadrantic). Focal or generalized seizures are often associated with olfactory or gustatory hallucinations.

Investigation

The MRI characteristically shows high signal areas of unilateral or bilateral focal edema on T2 images in the medial and inferior temporal lobes. The electroencephalogram (EEG) is characterized by periodic stereotyped, lateralized sharp and slow wave complexes occurring at regular intervals between 2 and 3 seconds.
CSF is generally under an increased opening pressure and may show a mild to moderate lymphocytic pleocytosis of 5–500/mm³; there may be a mild to moderate elevation in the protein (0.6–6 g/L) and a normal or mildly decreased glucose.

PCR examination of the CSF is sensitive and specific for the detection of HSV DNA. Brain biopsy is now rarely undertaken but may be considered if diagnostic uncertainty remains.

**Management**

High-dose intravenous aciclovir (10–15 mg/kg body weight 8 hourly) reduces the mortality of HSE from 70% to 20%. It is also appropriate treatment for VZV-related CNS disease. Treatment should be continued for 14–21 days or at least until the PCR has become negative.

Occasionally, HSV may be resistant to aciclovir and foscarnet is indicated in this situation. Patients with HSE can develop seizures, which require specific treatment. Corticosteroids may be of value if cerebral edema develops and, occasionally, intracranial pressure monitoring and even surgical decompression may be necessary.

Although high-dose aciclovir has reduced mortality from HSE, there is still a significant morbidity that may occur including severe memory impairment (up to 69%), personality behavioral changes (up to 45%), epilepsy (up to 25%) and aphasia (up to 4%).

Early treatment is essential for the reduction of morbidity, particularly before the development of impairment of consciousness.