

Neurotuberculosis is a common neurological disorder in developing country with high morbidity and mortality. Diagnosis is based on clinical features, C.S.F. changes, & imaging. Polymerase chain reaction shows promise for the future. Appropriate antitubercular agents should be given as early as possible. Role of corticosteroids is controversial but should be administered to all patients presenting in stage III. Surgical procedures are directed when, hydrocephalus, focal lesions like intracranial tuberculomas, and tubercular abscesses when located in cerebral or cerebellar hemispheres, uncommonly in brainstem and very rarely in spinal cord. Almost all patients respond well to medical management.

CNS tuberculosis has different manifestations. The burden of CNS TB is directly proportional to the prevalence of TB infection. Tubercular meningitis is the most devastating form of extra-pulmonary TB with 30% mortality and disabling neurological sequelae in >25% survivors.

Increasing prevalence of HIV infection, in today's scenario, in under developed countries contributes to prevalence of neurotuberculosis. Other important risk factors includes over-crowding of urban population, poor nutritional status, appearance of drug-resistant strains of tuberculosis, ineffective tuberculosis control programmes, and Increase in migration from countries where tuberculosis is prevalent to the developed world.

May be the result of nonspecific sensitization while negative reactions occur in undernourished children. Serodiagnostic tests suffer from problems of specificity, even when very specific antigens are used, and are often least helpful in diagnostically difficult cases. Detection of antigen has proved to be of more value, especially with clean specimens such as cerebrospinal and pleural fluids. Detection of specific components of Mycobacterium tuberculosis by linked gas chromatography and mass spectroscopy is very sensitive and specific. Detection of specific DNA sequences of M. tuberculosis in specimens by use of labelled 'DNA sensitivity may be increased greatly by use of the polymerase chain reaction to amplify small amounts of the specific DNA. Non specific indicators of tuberculosis are generally unhelpful although the bromide partition test and assay of the enzyme adenosine deaminase in cerebrospinal fluid appear to be of value in the diagnosis of tubercular meningitis.

CLASSIFICATION OF NEUROTUBERCULOSIS

Intracranial

- Tubercular Meningitis (TBM).
- Tubercular Encephalopathy.
- Tubercular vasculopathy.
- CNS Tuberculoma (Figure 3).
- Tubercular brain abscess.

Spinal

- Pott's spine and Pott's paraplegia (Figure 6).
- Non-osseous spinal tuberculoma.
- Spinal meningitis.

PATHOPHYSIOLOGY

CNS tuberculosis is secondary to disease elsewhere in the body. Mycobacteria reach the brain by hematogenous route. The disease begins with the development of small tubercular foci (Rich foci) in the brain, spinal cord or meninges. The location of these foci and capacity to control them ultimately determine which form of CNS TB occurs.

TNF alpha play a important role in pathogenesis and leads to altered blood brain barrier permeability and CSF leukocytosis.

Tuberculoma: are firm, avascular, spherical granulomatous mass. These arise when tubercles in brain parenchyma enlarge without rupturing into subarachnoid space. Target sign is characteristic.

Clinical Features

- usually 2-8 cm in diameter.
- Symptoms are related to their size and location.
- Low grade fever, headache, vomiting, seizures, focal neurological deficit and papilloedema are usually present.

TUBERCULAR BRAIN ABSCESS

It is characterized by an encapsulated collection of pus containing viable bacilli without evidence of classic tubercular granuloma. Usually solitary, uniloculated or multiloculated of various size (Figures 1 and 4).

Clinical Feature

- Partial seizures, focal neurological deficit and raised ICT.

- 106 • CT and MRI shows a large size lesion with marked surrounding edema.

TUBERCULAR ENCEPHALOPATHY

Rare entity, still more common in younger population. Encephalopathy is characterized by convulsions, stupor and coma with signs of meningeal irritation or focal neurological deficit. CSF is largely normal. It is responsive to corticosteroids.

SPINAL TUBERCULOSIS

Seen in <1% of patients. Infection starts in cancellous bone usually adjacent to an inter vertebral disc or anteriorly under periosteum. Thoracic (65%), lumbar (20%), cervical (10%), atlanto axial (<1%). Para spinal abscess 55- 90%.

Clinical Features

- Local pain, tenderness over the affected spine or a gibbous associated with paravertebral muscle spasm or a palpable paravertebral abscess.
- Patient usually have acute or sub acute, progressive spastic type of sensorimotor paraparesis.

Non Osseous Spinal Cord TB

It can occur in form of tuberculoma. Extradural tuberculoma are most common while intramedullary tuberculoma are rare. Features are indistinguishable from those of any extramedullary or intramedullary tumours. These tuberculoma may increase in size while patient is on ATT.

Tubercular Arachnoiditis

Here mixed features of spinal cord or nerve involvement Presented with Subacute paraparesis with radicular pain and bladder dysfunction. The hallmark of diagnosis is the characteristic myelographic picture showing poor flow of contrast material multiple irregular filling defects, cyst formation and sometimes spinal block (Figure 5).

Spinal Form of Tubercular Meningitis

It may result from rupture of rich foci in spinal arachnoid space. The acute form present with fever, headache and root pains accompanied by myelopathy. The chronic form presents with spinal cord compression. It may be associated with syrinx formation.

Tubercular Meningitis

It is the commonest form of neurotuberculosis (70-80%), encountered in clinical practice. Clinical features include H/O vague ill health for 2-8 weeks prior to development of meningeal irritation. 3Non specific symptoms include malaise, anorexia, fatigue, low grade fever, myalgia and headache. Prodromal symptoms in children include irritability, drowsiness, poor feeding and abdominal pain.

PATHOLOGY

The tubercle bacilli form dense gelatinous exudate into subarachnoid space. This exudate envelops arteries and cranial nerves, creating a bottle neck in flow of CSF which leads to hydrocephalus. Most of neurological deficit is caused by hydrocephalus, adhesive arachnoiditis, and obliterative vasculitis.

EXAMINATION

Signs of meningeal irritation: neck stiffness, positive Kernig's and Brudzinski's sign.

Cranial nerve palsies- 20-30% Focal neurological deficit secondary to infarction.

Visual loss d/t optic nerve involvement, optochiasmatic arachnoiditis, 3rd ventricular compression of optic chiasma, occipital lobe infarction. Increasing lethargy, confusion, stupor, deep coma, decerebrate or decorticate rigidity.

TBM CLASSIFICATION- MODIFIED MRC CRITERIA

GRADE 1 :- alert and oriented (GCS 15) without focal neurological deficit.

GRADE 2 :- GCS 14-10 with or without focal neurological deficit.

GRADE 3 :- GCS less than 10 with or without focal neurological deficit.

DIAGNOSTIC FEATURES OF TBM

CSF

- Pleocytosis (>20 cells, >60% lymphocytes).
- Increased protein (> 100 mg/dl).
- Low sugar (< 60% of corresponding blood sugar).
- India ink studies and microscopy for malignant cells should be negative.

Imaging

- Exudates in basal cistern
- Hydrocephalus
- Infarcts
- Gyral enhancement

INVESTIGATIONS

Cerebrospinal fluid examination

- Definitive diagnosis is by detection of tubercle bacilli in the CSF either by smear examination or by culture.
- TLC count may be normal in presence of depressed cell mediated immunity (elderly and HIV +ve individual).

MOLECULAR AND BIOCHEMICAL ANALYSIS

- PCR based methods.
- Antibody detection.
- Antigen detection.
- Adenosine deaminase.
- Tuberculostearic acid measurement.

Adenosine Deaminase (ADA): ADA is an important enzyme in purine metabolism; irreversibly deaminates adenosine to inosine. It is associated with lymphocytic proliferation and differentiation and is a marker of cell mediated immunity. Two isoforms ADA1 and ADA2 are

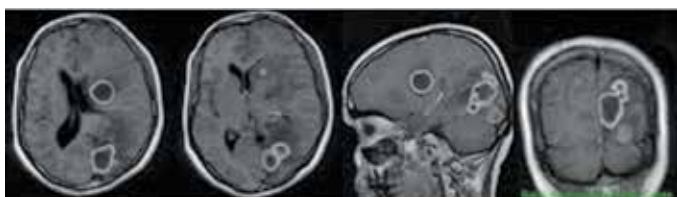


Fig. 1: Multi Tubercular Abscess

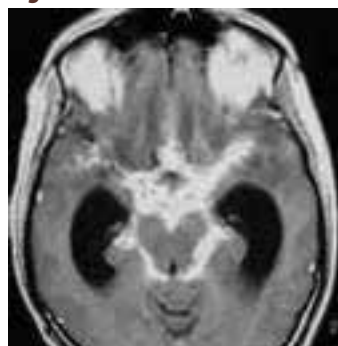


Fig. 2: TBM with Hydrocephalus



Fig. 3: Solitary Tuberculoma

known. ADA2 is the major contributor to the total ADA seen in TBM. Sensitivities and specificities range from 73-100% and 71-99% respectively.

While some studies showed statistically significant differentiation from aseptic meningitis and bacterial meningitis several other studies could not demonstrate a distinction between TBM and bacterial meningitis by ADA study alone.

High CSF ADA activity has been reported in patient with lymphoma, malaria, brucellosis, pyogenic meningitis and cerebral lymphoma.

Tuberculostearic Acid: It is a fatty acid component of *M. tuberculosis* cell wall, and has good sensitivity and specificity. It requires expensive equipments hence has limited clinical use.

Antibody detection

- Has poor sensitivity and specificity
- Cannot differentiate acute infection from previous infection.
- Cross-reactivity.

Antigen detection

- Theoretical advantage over antibody detection is that they would be released only as a result of host's immune response or treatment.

Molecular Methods: The challenges of applying NAA technique for rapid diagnosis of *M.tb* in CSF is b/s of low number of bacilli typically present in TBM and presence of amplification inhibitors in CSF. It has sensitivity of 56% and specificity of 98%; not ideal for ruling out TBM. They are useful as a supplement to conventional approaches.

Treatment: CNS tuberculosis is categorized under category 1 by WHO. According to BTS and ATS duration of treatment is 9-12 months. Ethambutol should be replaced by Streptomycin. Intensive phase (2 months) – Isoniazid, Rifampicin, Pyrazinamide and Streptomycin.

Continuation phase (7-9 months) – Isoniazid and Rifampicin.

FIRST LINE ATT Drug Daily Dose Children Adults
 Isoniazid 10-20 mg/kg= 300 mg, Rifampicin 10-20 mg/kg =450mg (<50 kg) =600mg (>50 kg), Pyrazinamide 30-35 mg/kg =1500 mg (<50 kg) =2000 mg (>50 kg), Streptomycin 20-40 mg/kg 15 mg/kg Isoniazid penetrates the CSF freely and has potent early bactericidal activity. Resistance to Isoniazid develop quickly if used as a monotherapy. Rifampicin penetrates the CSF less well, but high mortality from Rifampicin resistant TBM has confirmed its key role in t/t of CNS tuberculosis.

ADJUNCTIVE STEROID THERAPY

It was proposed that steroids causes' reduction of inflammation within subarachnoid space and modulation of the local production of proinflammatory cytokines and chemokines by microglia cells but the exact mechanism is not clear.

The Infectious Disease Society of America, CDC and ATC recommend the use of steroid therapy as an adjunctive therapy with standard anti tuberculosis therapy in CNS Tuberculosis. Adults (>14 years) should start treatment with dexamethasone 0.4 mg/kg/24 hr with a tapering course over 6-8 weeks.

Management of CNS TB in HIV Patient: These are managed with same ATT drug regime as that recommended for HIV uninfected individual. Adjunctive corticosteroids are recommended for those with TBM and HIV. Decision for starting ATT in newly diagnosed HIV patient depends on CD4 counts. Start ART if CD4 count falls below 200 during TB treatment. 100-200 Start ART after approximately 2 months of ATT treatment.

<100 Start ART within first 2 weeks of ATT treatment. If not available start between 2-8 weeks.

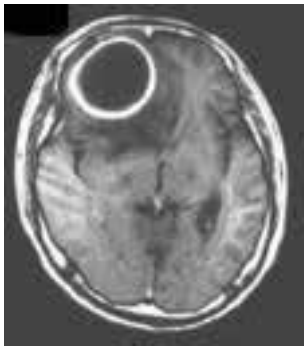


Fig. 4: Solitary Tubercular Abscess



Fig. 5: Tubercular Arachnoiditis



Fig. 6: Pott's Spine

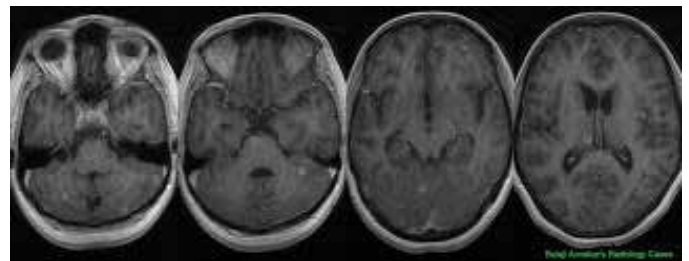


Fig. 7: Miliary Tuberculosis

ATT in patient who are already on ART

- When possible treat with Rifampicin and a non nucleoside reverse transcriptase inhibitor (NNRTI), preferably Efavirenz but the dose should be increased to 800mg.
- Rifabutin should be used if treatment with a protease inhibitor is required but at a reduced dose (150 mg 3 times per week).

Role of Surgery in CNS Tuberculosis: The aim of surgical management of TBA is to reduce the size of space occupying lesion and thereby diminish intracranial pressure and to eradicate the pathogen.

Indications

- Hydrocephalus (non-communicating) (Figure 2).
- Tubercular Brain Abscess-vertebral tuberculosis with cord compression. Early surgical drainage and chemotherapy are considered the most appropriate treatment for TBA. The aim of surgical management of TBM is to reduce the size of space occupying lesion and thereby diminish intracranial pressure and to eradicate the pathogen.

In patient with communicating hydrocephalus with GCS 15 could be tried on diuretics and acetazolamide. Early surgical intervention is considered in all patients with

non-communicating hydrocephalus and those who failed on medical management.

If duration of illness is <4 weeks – Ventriculoperitoneal shunt is procedure of choice.

If duration of illness is > 4 weeks– Endoscopic 3rd ventriculostomy can be offered.

In case of extradural lesions causing paraparesis, urgent surgical decompression is required.

Prognosis: The poor prognostic factors are:-

- Late stage of disease.
- Presence of miliary disease.
- Delay in initiation of treatment.
- Hydrocephalus.
- Focal neurological deficit.
- Extreme of age.
- Pre-existence of debilitating condition.
- Very abnormal CSF (very low glucose or elevated protein).

Comatose patients have a mortality of 50% and a high incidence of residual disability. The incidence of residual neurological deficits after recovery from TBM varies from 10-30%. Late sequelae include cranial nerve palsy, gait disturbance, hemiplegic, blindness, deafness, learning disability and dementia.

CONCLUSION

Early recognition and timely treatment of CNS TB is important in order to prevent the mortality and morbidity associated with it. The single most important determinant of outcome is the stage of the disease at which treatment has been started.

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