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Recent Advances in the Management of Tubercular Neuro-Infections

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Abstract

The CNS manifestations of tuberculosis cause significant morbidity and mortality. This review examines the magnitude, clinical presentation, investigations, differential diagnosis, complications and sequalae of such tubercular neuro-infections. Tuberculosis of spine with cord compression, and relationship between CNS tuberculosis and HIV-AIDS are also described. Treatment of CNS tuberculosis, with emphasis on multi-drug resistant tuberculosis has also been reviewed.

Key words -
Tuberculosis,
Tubercular meningitis,
Multi-drug resistant tuberculosis,
AIDS

Tuberculosis of the central nervous system (CNS) has been recognized since ancient days. A Vedic hymn dated approximately two millenia B.C. invokes a treatment ritual for "consumption seated in thy head ....." [1]. The first description of tubercular meningitis (TBM) is credited to Robert Whytt [2]. The final proof of tuberculosis as the cause of meningitis followed the discovery of Mycobacterium tuberculosis by Koch in 1882.

The CNS manifestations of tuberculosis cause significant morbidity and mortality. The introduction of streptomycin in 1946 and other drugs such as isoniazid, pyrazinamide and more recently, rifampicin revolutionised the treatment of tuberculosis. It was thought that with the indroduction of this regimen, the menace of tuberculosis could be contained. However, the past decade has seen a dramatic increase in the magnitude of the problem of tuberculosis. This is due to the epidemic of the acquired immuno deficiency syndrome (AIDS) and the emergence of multi-drug resistant (MDR-TB) tuberculosis. This has prompted with World Organisation (WHO) to declare tuberculosis a global emergency [3].

Epidemiology

The incidence of CNS tuberculosis is directly related to the prevalence of tuberculosis in a community. It has been estimated that approximately 10% of the patients with tuberculosis develop neurotuberculosis [4]. Autopsy studies indicate that TBM is three times more common in children than in adults.

AIDS has changed the epidemiological pattern of tubercular infection. Extrapulmonary tuberculosis and atypical mycobacteria such as the mycobacterium avium intracellulare complex (MAC) are more frequently seen in patients with AIDS. In an autopsy study of 900 subjects with AIDS the incidence of neuro tuberculosis was 0.3% [6].

The prevalence of MDR-TB have also been shown to occur in health care workers and immunocompetent persons [7].

Clinical disease

Tuberculosis of the CNS may manifest as tubercular meningitis, tuberculoma, or tuberculosis of the spine (Pott's disease) with neurological complications.

Tubercular meningitis

The illness begins insidiously. The initial symptoms are non specific and include malaise, bodyache, anorexia, fatigue and low-grade pyrexia. These symptoms last for one to three weeks and are followed by more pronounced headache, vomiting, and appearance of signs of meningeal irritation - neck stiffness, Kernig's and Brudzinski's signs. The patient may have seizures, confusion and drowsiness. Cranial nerve palsies may develop (the sixth nerve is most commonly involved, followed by the third, fourth, seventh, second, eighth and lower cranial nerves). Papilloedema may be present in some patients, due to hydrocephalus or adhesions around the optic nerve. Patients with miliary tuberculosis may have choroid tubercles on the retina. The patient may become unconscious and show decorticate or decerebrate posturing.

Infants may present with poor feeding, irritability, neck retraction and fullness of fontanelles. Older children may have unexplained fever, persistent headache and raised intracranial pressure. Elderly and immunocompromised patients may present with confusion or other neurological disturbances without fever. At the extremes of age TBM may have a fulminant course.

The severity of meningitis may be graded according to the British Medical Research Council grading system (1948) which has proved useful in predicting the prognosis. Stage I is the presence of nonspecific symptoms. Stage II is disturbed sensorium and minor focal neurological deficits like cranial nerve palsies. Stage III (advanced) is the presence of severe neurological deficits and coma.

Two unusual and rare forms of TBM have been described-tuberculous serous meningitis where a mild meningitis occurs followed by spontaneous recovery, and tuberculous encephalography where altered sensorium, seizures and focal neurological deficits are seen without meningitis.

Investigations

Routine laboratory studies may provide some clues to the diagnosis of TBM. Erythrocyte sedimentation rate may be elevated. White cell count may show leukocytosis or leukopenia, anaemia, leukopenia, and monocytosis are commonly associated with disseminated or miliary disease [9]. X-ray

changes like miliary disease, apical scarring, hilar adenopathy, and primary complex are common and noted in 50 - 90 % of children with TBM. Twenty five to fifty per cent of adults show evidence of pulmonary tuberculosis. The Mantoux test may be positive in 40-65% of the adult patients with TBM [8].

Cerebrospinal fluid (CSF) examination is essential for the diagnosis of TBM. CSF is usually clear and forms a 'cob-web' on standing. CSF protein is usually elevated upto 100-200 mg% and occasionally as much as 1-2 gm%. CSF glucose is low, usually between 18-45 mg%/dl. Cell counts are in the range of 50-300 cu mm [3]. and predominantly lymphocytic in nature. Rarely, polymorphonuclear leukocytes may predominate.

The hallmark of TB meningitis is the demonstration of organisms in CSF, by smear and culture. The yield of AFB in CSF varies from 15-80% in various studies. This can be increased by examination of more than 10 ml of CSF, repeated examination (at least three samples) and examination of the stained slide for more than 30 minutes.

CSF culture for Mycobacterium tuberculosis may be positive in 25-70% of patients and takes several weeks. Introduction of newer culture methods such as the BACTEC system may help in shortening culture time [9].

Elevated CSF adenosine deaminase levels seen in 73-99% of TBM patients are however, non-specific, being elevated in other types of meningitis as well. The sensitivity and specificity of enzyme-linked immunosorbent assays (ELISA) for detection of tubercular antigen or antibodies remains to be established. Estimation of tuberculo-stearic acid in CSF, although specific, is technically complicated. The most recent test is the ploymerase chain reaction (PCR) for detection of M. tuberculosis in CSF. This test, if standardised and validated, might become the most reliable and useful test for the diagnosis of tubercular infection [8], [10].

Imaging studies

Computerized tomography (CT) scan and magnetic resonance imaging (MRI) are extremely useful in demonstrating the pathology in TBM. Plain CT scans show iso- or hyperdense exudates in the subarachnoid spaces mainly in the basal cisterns. These exudates show intense enhancement with contrast. CT or MRI may reveal hyprocephalus, infarct, tuberculoma, abscesses and small contrast enhancing intraparenchymal miliary lesion [11], [12] MRI with contrast is helpful in detection of spinal cord pathology and arachnoiditis.

Differential diagnosis

TBM needs to be different from other forms of acute or subacute meningitis, virus infections, and cerebral abscess. Acute pyogenic meningitis is usually characterised by turbid CSF, a high cell count with polymorphunuclear leukocytosis, low glucose, and presence of causative organisms in culture. Viral meningitis may simulate TBM, but CSF glucose is usually normal. Involvement of meninges by malignant deposits in indicated by the presence of a typical cells in the CSF. Cryptococcal meningitis requires special methods of CSF examination eg. India ink staining of smears, culture on Sabouraud's

medium and testing for cryptococcal antigen.

Complication and sequelae of TBM

The risk of neurological disability depends on the stage of presentation. A poor prognosis is correlated with delayed diagnosis and when the patient presents in stages II and III of the British Medical Research Council grading. The sequelae include hemiparesis or paraparesis, seizures, cranial nerve palsies, hypothalamic-pituitary axis disturbances and cognitive impairment.

Tuberculomas

The exact incidence of tuberculomas is not known but before the advent of CT, tuberculomas were roughly four times less common than TBM [13]. Dastur et al in their article reported that 46% of intracranial space occupying lesions below the age of 15 years were tuberculomas [14].

Supratentorial tuberculomas are more common in adults and infratentorail lesions (mainly cerebellar) common in children [14]. They can be either solitary or multiple. Signs and symptoms depend on the location of the granuloma. They may present with manifestations of raised intracranial pressure, seizures or focal neurological deficits. Diagnosis is based on imaging, clinical suspicion and therapeutic response. A definite diagnosis can be made only by excision or stereotaxic biopsy and histopathological examination. Smears of tissue specimen for AFB are positive in 60% of the cases. Rarely the caseous center of a tuberculoma may get liquified to form an abscess which is treated surgically [15].

Radiological diagnosis of a tuberculoma is mostly presumptive. A history of fever, close contact with a person having tuberculosis and indirect evidence of tuberculosis elsewhere supports the diagnosis of tuberculoma. Tuberculomas appear is to hypodense on CT scan and show ring enhancement with contrast media [16]. Oedema is commonly seen in the surrounding parenchyma. The appearance on T2-weighted MR images is variable. Tuberculomas may appear either hypointense, or hyperintense with a peripheral hypointense rim [17].

Tuberculosis of the spine with cord compression

Tuberculosis of the spine is common in young adults but may occur at any age. It in one of the commonest cause of spinal cord compression. The lower thoracic vertebrae are most commonly effected. Infection first occurs in the superior or inferior vertebral margin, spreads to adjacent vertebrae and involves intervening disc. Formation of granulation tissue and a cold abscess may result in compression of the spinal cord and nerve roots.

Clinical features include backache, root pains, and symptoms and signs of cord compression. There is localized tenderness and kyphotic deformity (gibbus) [18].

X-rays of the spine show irregularity and loss of definition of the vertebral end plates of the contiguous vertebrae which are involved. Often paravertebral soft tissue shadows may be seen. MRI has enabled

early detection of vertebral lesions. Epidural abscess, spinal deformity and cord compression may also be seen [19].

CNS tuberculosis and AIDS

Approximately 5% of patients with AIDS have active tubercular infection [20]. Disseminated disease is more common with pulmonary as well as extrapulmonary involvement, including the CNS. The clinical spectrum of CNS tuberculosis with HIV infection includes meningitis, cerebral and spinal cord abscess and tuberculoma. The frequency of TBM in HIV infected subjects is five times higher than the normal population [21]. Infection with HIV does not appear to alter the clinical manifestations, therapy and outcome of TBM. However, adverse reactions to anti-tuberculous therapy are more common in these patients. There are reports of BCG vaccine administration in children with AIDS leading to M.bovis meningitis [8].

Opportunistic infections is AIDS due to atypical mycobacteria are not uncommon. In patients with MAC infection, single or multiple mass lesions appear to be more common than meningitis [20]. Meningitis due to MAC has been reported but is rare, and occurs as a part of advanced, widely disseminated infection in the AIDS patients.

Treatment of CNS tuberculosis

The most important factor in the treatment of CNS tuberculosis is early diagnosis and initiation of anti-tubercular treatment. The antimicrobial drugs commonly employed in the treatment of tuberculosis can be divided into first-line drugs include rifampicin (RMP), isoniazid (INH), pyrazinamide (PZA), ethambutol (ETB) and streptomycin (SM). The second-line-ethionamide, cycloserine and para-amino salicylic acid are rarely used. INH, RMP and PZA are bactericidal. INH, PZA and EMB penetrate the blood-brain-barrier easily. RMP and SM achieve optimal CSF levels only when the meninges are inflamed.

Multi-drug therapy is necessary to prevent the development of resistance and to kill dormant bacilli. The usual does of INH is 5-10 mg/kg/day, upto 300mg/day; RMP 10-20 mg/kg/day upto 600mg/day; PZA 15-30 mg/kg/day upto 1500mg/day and ETB 15-25 mg/kg/day upto 1200mg/day; SM 20mg/kg/day upto 1gm/day.

The optimal duration of treatment for TBM is unknown. Several studies suggests that 6 to 12 month of therapy is adequate for the treatment of CNS tuberculosis. Generally, treatment is recommended for a period of 18-24 months [15]. Clinical symptoms and CSF examination may worsen initially, after start of treatment, especially when patients are seen in stage II or III of the disease. Weight gain and a sense of well-being are the initial signs of response to treatment. Fever and cerebrospinal fluid abnormalities may persist for weeks to months after initiation of therapy in some patients [15].

Patients should be monitored for drug toxicity. Hepatic dysfunction is common with INH, especially in high doses. INH toxicity is probably due to toxic acetyl metabolites. RMP also causes hepatotoxicity, especially in patients with chronic liver disease, in alcoholics and the elderly, and may have to be withdrawn. INH also causes a peripheral neuropathy which may be prevented by administration of

pyridoxine. ETB may produce visual impairment due to optic neuritis which is reversible on discontinuation of the drug. SM causes vestibulocerebellar dysfunction resulting in imbalance of gait, especially in the elderly patients.

Corticosteroids are being frequently used as a therpeutic adjunct. A recent, large, controlled trial has demonstrated that dexamethasone increases survival and decreases sequelae in children with severe TBM [22]. Corticosteroids should be given to patients with hydrocephalus, threatened or established spinal block, visual failure, those who develop focal neurological deficits and the severely ill. The usual regimen is i.m.dexamethasone (16 mg/day in adults and 0.5 mg/kg/day in children) in divided doses, or oral prednisolone 60 mg/day for adults, 2 mg/kg/day for children, given in a tapering course over 3 to 6 weeks. There is no evidence that corticosteroids interfere with the penetration of anti-tuberculous drugs into the CSF. Intrathecal injection of corticosteroids is unnecessary.

Treatment of CNS disease due to atypical mycobacteria such as M.avium intracellulare should include at least two agents. Azithromycin (500 mg/day) or clarithromycin (500 to 1000 mg/day) should be given. The second drug may be ETB (15 mg/kg/day) and for those with severe illness, a third drug should be selected from among rifampicin (600 mg/day), rifabutin (450-600 mg/day), clofazimine (100-200 mg/day) or amikacin (7,5-15.0 mg/kg/day).

Surgical intervention is required in the management of obstructive hyprocephalus, although hyprocephalus without obstruction may be managed medically. A ventriculoperitoneal or ventriculo-atrial shunt is effective and should not be delayed until infection is eradicated. Surgery may also be necessary in the presence of tuberculomas or tuberculous abscesses developing along with TBM. However, tuberculomas often resolve with adequate medical therapy, and unless there is impending cerebral herniation or affection of the visual pathways, surgery may not be necessary. Surgery is indicated for spinal tuberculomas causing cord compression. Intrathecal hyaluronidase has been tried for tuberculous spinal arachnoiditis with good results in some instances [23]. However, no controlled studies are available.

Nursing care is very important during the acute illness when there are usual problems presented by unconscious patients, and during the prolonged phase of convalescence and rehabilitation. Fluid, electrolyte and acid-base disturbances are common, due to vomiting, inadequate fluid intake or SIAHD, and should be corrected. Anticonvulsants are often needed, especially in children.

Multi-drug resistant tuberculosis

The term denotes infection with strains of M. tuberculosis resistant to two or more first-line antituberculous drugs. The resistance may be due to infection by resistant organisms or may have been acquired during the course of treatment. In the last decade, the incidence of MDR-TB, especially among HIV-positive individuals has risen from 10% to 23% [24]. For U.S.A., as a whole nearly 90% of MDR-TB is found among HIV-seropositive patients with tuberculosis and with case-fatality of 25% among non-HIV patients with MDR-TB [25]. In third world countries drug resistance is estimated to be around 30%. Identification of drug-resistant M. tuberculosis is important. Treatment of MRD-TB should be aggressive and should include alternative drugs such as the fluoroquinolones (ciprofloxacin). Treatment is recommended for a minimum period of two years [24].

Newer anti-tuberculous drugs include derivatives of rifampicin such as rifabutin (for MDR-TB and

MAC disease), and rifapentene (for intermittent therapy regimens) [26]. M. tuberculosis produces betalactamase enzymes. A combination of clavulanic acid and amoxycillin is found to be effective against beta-lactamase.

Other experimental therapeutic strategies include the use of thalidomide which inhibits tumour necrosis factor (TNF) and use of cytokines like interleukin-2 and gamma interferon in AIDS patients with tuberculosis [26].

Conclusion

After many years in decline, there has been a resurgence of tuberculosis in both developed and developing countries, primarily due to the AIDS epidemic, and the emergence of multi-drug resistant organisms. AIDS has changed the epidemiological pattern of tuberculous infection, with a higher incidence of extrapulmonary tuberculosis, including CNS tuberculosis, and atypical mycobacterial infections. There is an urgent need for recognition of these changes, and for newer drugs and therapeutic strategies to combat the challenge that tuberculosis now poses.

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