Tuberculosis of Central Nervous System

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ABSTRACT
Meningitis is the most serious manifestation of extrapulmonary tuberculosis. Being a paucibacillary disease, no single diagnostic test is sensitive and specific. Despite recent advances in diagnostic methods and ready availability of effective chemotherapy, more than 50% of the patients either die or are left with major neurological deficits due to delay in the diagnosis. HIV coinfection is associated with higher complications and case fatality rates. The only way to reduce the mortality and morbidity is early diagnosis and initiation of chemotherapy and steroids.

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INTRODUCTION
Tuberculosis (TB) in all its forms remains a challenging clinical problem and a public health issue of considerable importance and magnitude worldwide. Tuberculosis meningitis is the most devastating manifestation of TB. The World Health Organization (WHO) has estimated an annual incidence of 9.27 million new cases of TB worldwide, and the number of prevalent cases of about 13.7 million. Most of the disease burden is in Africa and South East Asia, where annual incidence rate is 356 and 182 cases per 10,000 population respectively.\(^1\) Tuberculosis has reemerged in industrialized countries, largely because of increase in travel from endemic countries to developed nations.\(^2\) This emergence is due in part to infection with human immunodeficiency virus (HIV), development of multidrug resistant \(M.\) \textit{tuberculosis}, and reduced resources for treatment and surveillance of patients.\(^2,3\) The occurrence of extrapulmonary TB is directly proportional to the prevalence of TB infection. Tuberculosis of the central nervous system (CNS) accounts for approximately 10% of extrapulmonary cases of or about 0.7% of all cases of TB.\(^4\)

CLASSIFICATION OF TB OF CNS
The response to tuberculous infection inside the nervous system varies from person to person, depending upon the immune status, concurrent illness, predisposing risk factor, disease burden and many other comorbid factors.\(^5\) Because of the varied manifestations of CNS TB in different permutations and combinations, no concrete classification is available. CNS TB can be classified on the basis of clinical features, cerebrospinal fluid (CSF) findings, radiological investigations and pathological changes into following groups:
- Tuberculous meningitis (TBM)
- Intracranial tuberculomas
- Tubercular abscess.

ETIOPATHOGENESIS OF CNS TB
Virtually, all tuberculous infection of CNS is caused by the human tubercle bacillus, \textit{M. tuberculosis}, an obligate aerobic bacteria, whose only natural reservoir is human. This organism is nonmotile, nonspore forming and slow growing, with a generation time of 15 to 20 hours. The complex antigenic structure of the cell wall includes polysaccharides, proteins, peptides, lipids and glycolipids with specific immunologic properties. These molecules determine the characteristic immune response to tuberculous infection and its resultant pathology.\(^5,6\) Less commonly, other mycobacteria may be involved.

It is agreed that CNS TB is almost never a primary infection of this organ. The organism in large majority of the cases is conveyed from the primary site in lungs, gastrointestinal tract, bone and lymph nodes by the bloodstream. As such, the patient is already in an allergic state or has developed a certain state of immunity before brain is infected. The initial tuberculous lesions (Rich focus) may be present in the meninges, the subpial and subependymal surface of the brain or the spinal cord.\(^1,6,7\) This focus may remain dormant for years after initial infection. Later, rupture or growth of one or more of these small lesions produces development of various types of CNS TB. The fate of these tubercles and the subsequent course of infection are a function of both the immunological capacity of the host and other incompletely understood genetic factors. Certain ethnic groups seem to be more susceptible to \textit{M. tuberculosis} than others. Studies using tuberculin conversion as a surrogate marker suggests that black skinned people are more susceptible to infection than white people.\(^8\) Recently, it has been proposed that certain polymorphisms in human NRAMP1 gene may affect susceptibility to pulmonary TB in West Africans.\(^9\)

Experimental evidence suggests that the virulence of individual strains of \textit{M. tuberculosis} is also significant and selected gene mutations have been shown to affect virulence.\(^10\) Recently, the complete genome sequence of \textit{M. tuberculosis} strain H37Rv has been determined.\(^11\) However, the specific mechanisms of neurovirulence are
as yet unknown. It is conceivable that certain isolates of \textit{M. tuberculosis} may target specific receptors facilitating meningeal involvement resulting in a neurotropism analogous to that of \textit{M. leprae} for peripheral nerves.\textsuperscript{7} 

Current theories of immunopathogenesis focus on the role and interaction between macrophages, the helper T cells and the organism. Cell mediated immunity is central to both the control of infection and the production of tissue damage.\textsuperscript{12} The CD4 T cells specific for mycobacterial peptides cause production of $\gamma$-interferons, which further activate macrophages. Activated macrophages produce interleukin 1-$\beta$ and tumor necrosis factor (TNF-\textit{\alpha}) which promotes granuloma formation.\textsuperscript{13} In TB sensitized animals, small concentrations of TNF-\textit{\alpha} resulted in substantial tissue necrosis.\textsuperscript{14} Rabbit models of TBM showed that CSF concentrations of TNF-\textit{\alpha} correlated with clinical progression.\textsuperscript{15} When thalidomide treatment (an immunomodulator) was combined with antitubercular drugs, 100\% of infected animals survived. There was a marked reduction in TNF-\textit{\alpha} levels, leukocytosis and brain pathology.\textsuperscript{15} These observations implicate TNF-\textit{\alpha} at least partly in the extent and severity of mycobacterial CNS pathology.\textsuperscript{16} 

Studies in humans have also shown elevated levels of TNF-\textit{\alpha}, interferon-$\gamma$ and IL-10 in patients of tubercular meningitis.\textsuperscript{17,18} Researches have also demonstrated over production of nitric oxide (NO) in patients of TBM, which was positively related to levels of TNF-\textit{\alpha}, indicating a possible role of nitric oxide in tissue inflammation and CNS damage.\textsuperscript{19} Matrix metalloproteinases (MMPs), a family of zinc dependent endopeptidases induce blood brain barrier breakdown and facilitate leukocyte extravasations in bacterial meningitis.\textsuperscript{20} Monocytes, the cells which are pivotal in immune responses to \textit{M. tuberculosis}, secrete a metalloproteinase MMP-9, which facilitate leukocyte migration across the blood brain barrier, but may cause cerebral injury.\textsuperscript{21} All these models provide evidence for important role of cytokines, in particular TNF-\textit{\alpha}, in the pathogenesis of CNS TB. Understanding the relative contribution of these cytokines will help us in formulating alternative therapeutic approaches and may contribute in early diagnosis of the disease.

**TUBERCULAR MENINGITIS**

Tubercular meningitis affects not only the meninges but also the parenchyma and the vasculature of the brain. Our understanding of the pathogenesis of TBM dates from meticulous studies that Arnold Rich and HA McCordock conducted at John Hopkin’s hospital in the 1920s and 1930s.\textsuperscript{22} In a brilliant series of postmortem examinations, they demonstrated that in nearly every case, there was a subcortical or meningeal focus from which bacilli gained access to subarachnoid space. After the release of bacilli into the subarachnoid space, dense gelatinous exudates form at the base of brain, which is most florid in the interpeduncular fossa and suprasellar region enveloping optic chiasma anteriorly and may extend throughout the preoptic cistern and surround the spinal cord.

Three general processes produce the subsequent neurological pathology, i.e. obliterative vasculitis, adhesion formation and an encephalitis or myelitis.\textsuperscript{23} A characteristic inflammation affects the blood vessels traversing the exudates. Small and medium-sized arteries are most often involved. The adventitial layer of vessels develops caseation necrosis and tubercles resulting in subendothelial cellular proliferation which may occlude the lumen of blood vessel, resulting in infraction.

These are most commonly seen in the distribution of middle cerebral and lateral striate arteries.\textsuperscript{24} Infarction through vasculitis accounts for an appreciable part of irreversible neurological sequelae. The adhesion formation of the basal subarachnoid cistern can result in obstruction of CSF and hydrocephalus, which can be communicating type or obstructive, depending on the site of blockage. Chronic untreated hydrocephalus can lead to atrophy of gray and white mater. Adhesions around the interpeduncular fossa can compromise cranial nerves, particularly II, III, IV and VI.\textsuperscript{23} Borderzone encephalitis describes a tissue reaction in the brain tissue adjacent to zones of thick exudates (Fig. 1). The brain tissue softens and astrocytic microglial and diffuse inflammatory reactions can be seen.\textsuperscript{23} Thus exudates, vasculitis, hydrocephalus, adhesion formation and encephalitis together exert their own effect on brain parenchyma in tubercular meningitis and hence on the clinical picture.

![Fig. 1: MRI brain coronal T2W image showing borderzone encephalitis in the region of left sylvian fissure](image)
CLINICAL FEATURES

The usual clinical picture consists of a prodrome of insidious onset of fever, malaise and headache, followed by prominent neurologic findings, including cranial nerve palsies and long tract signs. Continuous low grade fever is typically present in about 80% of patients. Cranial nerve palsies occur in 20 to 30% of patients. The sixth cranial nerve is most commonly affected. Vision loss can be due to optic atrophy or arachnoiditis, third ventricular dilation causing compression of optic chiasma (in hydrocephalus), optic nerve granuloma or ethambutol toxicity. Hemiplegia or Quadriplegia can occur secondary to infarction or tuberculosis. At times, abnormal movements may dominate the clinical picture in the form of choreiform or hemiballistic movements, athetosis, myoclonic jerks or ataxia. Seizures, focal or generalized, may occur during acute illness or months after treatment in 10 to 15% of patients. Examination reveals evidence of meningismus in 70 to 100% of patients in addition to cranial nerve palsies and other focal deficits. Fundoscopy may reveal papilledema and, at times, choroid tubercles in about 10% of patients with TBM. A staging system was introduced in 1947, which has since been widely adopted in the initial assessments of these patients and can be used to estimate prognosis (Table 1).27

Diagnosis

The rapid diagnosis of TBM is fundamental to clinical outcome. Clues to diagnosis of TBM include TB elsewhere in the body, a positive family history of TB, recent exposure to cases with active TB, a history of head trauma, alcoholism, immunocompromised state, including diabetes, chronic renal disease, HIV infection, etc. On general physical examination, careful attention should be given to presence of lymphadenopathy, spinal or other joint lesion, scrotal mass, draining sinuses, nonhealing vaginal ulcers, etc. Abnormalities of chest X-ray include miliary infiltration, hilar lymphadenopathy and upper lobe infiltrates. Mantoux positively may also help, if the suspicion is strong. The key to diagnosis lies in CSF analysis and radiological investigations.

Table 1: Clinical staging of patients with TBM27

<table>
<thead>
<tr>
<th>Stage (early)</th>
<th>Non-specific symptoms and signs</th>
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<td>Stage II (intermediate)</td>
<td>Lethargy or behavioral changes</td>
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<tr>
<td>Stage III (late)</td>
<td>Stupor or coma, abnormal movements</td>
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CSF

Typically the CSF is straw colored with cobweb-like appearance of the pellicle on the surface of CSF when allowed to stand for a short time is a characteristic feature, but not pathognomonic of TBM. Characteristically, the CSF shows lymphocytic pleocytosis, elevated proteins and decreased glucose. Cells between 100 and 500/μm³ are seen in up to 65% of cases. Lymphocyte predominant response is seen in up to 75% of cases, but the remainder may demonstrate polymorphonuclear leukocytosis. The CSF proteins range between 100 and 500 mg% in 65% of cases; under 100 mg% in 25% cases and greater than 500 mg in 10% cases. Cases with subarachnoid block develop extremely high protein content with xanthochromia. CSF sugar content, said to be characteristically low, was less than 45 mg% in only 17% of cases. Low chloride levels in CSF, considered earlier as a specific marker for TBM, is actually a reflection of coexistent serum hypochloremia and is not helpful in distinguishing TB infection from other bacterial or viral infection. In a study of 232 cases of TBM, characteristic tubercular pattern of CSF was seen in 143 cases, serous pattern in eight cases, pseudopyogenic response in 31 cases, encephalitic pattern in nine cases and a pattern of block in 12 cases. In 11 cases, CSF was normal.

Microscopy

Demonstration of acid-fast bacilli (AFB) in CSF by microscopy in smear and by culture on LJ solid medium is the ‘gold standard’ for diagnosis of TB of the CNS. AFB were visible on stained CSF sediments in 37% of patients on initial examination, but the yield rose to 87%, when the fluid from four serial spinal taps was examined. It is advisable to use the centrifuged sediment of more than 10 ml of CSF for acid fast staining and to spend at least 30 minutes examining each specimen. Sensitivity of microscopy is 106 AFB per ml of CSF by Ziehl-Neelsen stain. The isolation rate of M. tuberculosis has been reported to be higher from cisternal and ventricular than from lumbar CSF. Laboratories employing only solid media, such as Lowenstein-Jensen, may take up to 8 weeks to culture. M. tuberculosis semi-automated radiometric culture systems, such as Bactec 460 and automated continuously monitored systems have reduced culture times. Although such systems do reduce the time taken for culture, the decision to treat patient should not wait for culture results.

Alternative diagnostic approaches are as follows:

- Tuberculostearic acid, a structural component of mycobacteria, was first detected in CSF of TBM patient in 1983. Frequency pulsed electron capture gas liquid chromatography has been used to detect femtomole...
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Adenosine deaminase, produced by lymphocytes and monocytes, is elevated in CSF (with a value of more than 10 units) in patients of TBM with reported sensitivity and specificity of 99%. Adenosine deaminase is elevated with a reported sensitivity and specificity of 99%.

Serological techniques that detect intrathecal synthesis of antimycobacterial antibodies have been studied. A good test requires an antigen with high species specificity, like using a 35 kDa antigen from *M. tuberculosis* 100% sensitivity and 100% specificity were reported.

DNA/RNA amplification techniques: The conventional diagnostic modalities like microscopy and culture lack sensitivity and are time consuming and most often culture is negative in paucibacillary conditions. The nucleic acid amplification technique (NAA), notably the polymerase chain reaction (PCR) has revolutionized the investigative microbiology by facilitating direct detection and identification of infectious agent in the clinical samples in a very short time. The sensitivity varies from 33 to 90% and specificity from 88 to 100%. The sensitivity of PCR on CSF samples seem to be only a moderate improvement on that of culture.

For diagnosis of *M. tuberculosis*, large number of different sequences of Mycobacterium genome have been targeted. Most of the studies have targeted IS6110 sequence of *M. tuberculosis*; however, absence or presence of only a few copies of this sequence has been reported in some isolates. Studies from India have also reported that IS6110 is missing in 40% of North Indian population. There is need to use more than one target specific for *M. tuberculosis* complex to increased the sensitivity and specificity of the test. To overcome this limitation, multiplex PCR for diagnosis of MTB complex using IS6110, MPB64 and protein b was developed by Sharma et al. It had a sensitivity of 94.4% in culture/smear positive cases of tubercular meningitis and 85% in clinically diagnosed but culture negative cases of tubercular meningitis.

Another point of care test is novel NAAT test that has been developed to address the issues of feasibility and sensitivity. The Cepheid GeneXpert MTB/RIF assay uses hemi-nested RT PCR to amplify *Mycobacterium tuberculosis* (MTB) specific sequence of rpoB gene. To determine rifampicin (RIF) resistance, the rpoB gene is probed with molecular beacons within the RRDR region. This is a nearly fully automated assay, including bacterial lysis, nucleic acid extraction, amplification and amplicon detection. The test is run on the Genexpert platform using a disposable plastic cartridge with all required reagents. This assay had a 97% sensitivity of diagnosing pulmonary TB including 90% of smear negative patients; however, sensitivity and specificity of this assay in TBM needs to be established. Despite all these advancements, there is a need for novel diagnostic approaches if sensitive and specific methods are to become a reality.

Neuroimaging

The advent of computed tomography (CT) and magnetic resonance imaging (MRI) has provided insight into the disease progression, and gives prognostic and diagnostic information. They have greatly enhanced the diagnostic accuracy of CNS TB. Commonly identified neuroradiological features of TBM include basal meningeal enhancement (Fig. 2), hydrocephalus (Fig. 3) and infarctions in the supratentorial compartment and brainstem.

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**Fig. 2:** Contrast-enhanced MRI T1W axial image showing thick exudates at the perimesencephalic cistern, suprasellar cistern and left sylvian fissure

**Fig. 3:** MRI brain axial flair T2W image showing enlarged third and lateral ventricles in a patient of TBM
enhanced MRI is generally considered to be superior to CT in the evaluation of CNS TB.

In an attempt to establish CT criteria for the diagnosis of CNS TB, Kumar et al identified basal meningeal enhancement, ventriculomegaly, tuberculoma and infarcts as characteristics to distinguish CNS TB from pyogenic meningitis. They also suggested that basal meningeal enhancement, tuberculoma or both were 89% sensitive and 100% specific for TBM. Both CT and MRI are sensitive tool to detect the changes of TBM but they lack specificity. The radiological differential diagnosis includes cryptococcal meningitis, cytomegalovirus encephalitis, sarcoidosis, meningeal metastasis and lymphoma. Cranial nerve impairment is also common in TBM. Second, third, fourth, sixth and seventh cranial nerves are frequently involved. CEMRI may show thickening and enhancement of proximal portions of these cranial nerves.

Pachymeningeal

TB: Both focal and diffuse pattern of tubercular pachymeningitis exist (Fig. 4). Focal involvement of pachymeninges is also termed as en plaque tuberculoma which appear hypodense on plain CT head, isointense on T1-weighted (T1W) MR images, iso- to hypointense on T2-weighted (T2W) MR images and uniformly enhancing after contrast administration.

Intracranial Tuberculomas

These are circumscribed focal granulomatosus masses of tubercular origin affecting the brain parenchyma. They may present either with meningitis or as intracranial space occupying lesion. Intracranial tuberculomas develop in approximately 1% of all patients with active TB and 4.5 to 28% of patients with TBM. The lesions are firm, avascular and vary in size from 0.5 to 10 cm (usually >2 cm). Dastur et al demonstrated a tuberculoma incidence of 21.5% of all surgically removed intracranial space occupying lesions during 1953 to 66 with very high incidence of 45% in children less than 15 years of age. Cerebellum was the most common site of involvement in children. Presently, there is a declining trend in the incidence of tuberculomas to 4 to 10% of all space occupying lesions.

Pathology

A firm and creamy material occupies the center of the lesion. The rim is tough and gelatinous and appears hyperemic in unfixed tissues, surrounded by gliotic brain. Microscopy reveals a central area of caseous necrosis, surrounded by several discrete or confluent granulomas composed typically of epitheloid and Langhans type of giant cells. The surrounding brain shows edema and marked reactive hypertrophic astrocytosis associated with gliosis and edema.

CLINICAL FEATURES

The sign and symptoms depend on the size, location, stage of evolution of tuberculoma and the extent of surrounding reaction. Patient with intracranial tuberculomas usually seek medical attention for seizures, symptoms of raised intracranial tension (like headaches, vomiting, etc.) or the focal neurologic deficit. Constitutional symptoms commonly associated with tuberculous infection are seen in less than one-third of all patients. Pyrexia and weight loss is reported is 20 to 25% cases only. A positive Mantoux test should raise suspicion of tubercular nature of lesion. Evidence of active TB elsewhere in body is noted in 25 to 30% of cases.

Diagnosis

Brain imaging, either CT or MRI, are helpful in making the diagnosis of tuberculomas. On CT scan, tuberculomas are characterized as low or high density, rounded or lobulated masses and show intense homogenous or ring enhancement after contrast administration. They have an irregular wall of varying thickness, with marked perifocal edema and mass effect. ‘Target sign,’ a central calcification or nidus surrounded by a ring that enhance after contrast administration considered pathognomonic of tuberculoma, is rarely seen.

MRI features of tuberculoma depend on whether the granuloma is noncaseating or caseating with a solid or liquid center. The noncaseating granuloma typically is hypointense relative to brain on T1-weighted and hyperintense on T2-weighted sequences and, after contrast administration, shows homogenous enhancement. The granuloma with solid caseation appears relative hypointense to isointense on T1WI.
and iso to hypointense on T2WI (Fig. 5). The granuloma with central liquefaction of caseous material appears centrally hypointense on T1 and hyperintense with hypointense rim on T2W images. Rim enhancement is seen after contrast administration. The surrounding edema is hypointense on T1WI and hyperintense on T2WI. Usually, the characteristic picture is of multiple conglomerate ring and disk enhancing lesions involving different areas of cerebral hemisphere. Rarely, tuberculomas may have dural adhesions and closely resemble an en plaque meningioma.

At times, tuberculomas may be difficult to differentiate from other infections like fungal infections, noninfectious inflammatory lesions like sarcoidosis, neoplastic lesions like metastasis or gliomas. In vivo proton MR spectroscopy at times may be helpful in differentiation by demonstrating lipid peak seen in few of these cases. The magnetization transfer MR imaging technique (MTR) has recently received attention as an additional sequence to improve image contrast and tissue specificity in various brain diseases. The T1-weighted MR imaging in cases of tuberculomas showed hypointense core surrounded by hyperintense rim that was not clearly visible on T2-weighted images. The Magnetization transfer (MT) ratio from the MT hyperintense rim measured 21.5 ± 3.1, while from the core, it measured 25.3 ± 3.7. The hypointense core represents the solid caseation while the hyperintense rim represents the cellular component of tuberculoma on histopathology. Post-contrast T1-weighted MT images showed rim enhancement in all these cases. In developing countries, tuberculomas are frequently confused with cysticercus granuloma. The common imaging features which differentiate the two conditions are size more than 20 mm, irregular outline and marked perilesional edema. In doubtful cases, stereotactic diagnostic biopsy can help in establishing an accurate diagnosis. When to do a biopsy, however, is still a subject of debate.

**Paradoxical Increase and Appearance of New Lesions**

Rarely, symptomatic intracranial tuberculomas may develop while on antitubercular therapy (ATT) for CNS TB/TB else where in the body. The latent period, i.e. time between start of therapy and development of neurological manifestation ranged from 10 days to 27 months. In most cases, however, tuberculomas developed with 3 months after starting therapy. Paradoxical increase in size and number of tuberculomas has also been reported as an important cause of morbidity. These atypical responses constitute up to 8% of the total tuberculomas in few large series.

The mechanism behind the paradoxical progression or development of intracranial tuberculomas remains a subject of speculation. The initial belief that poor drug penetration into the CSF led to the selection of resistant organisms has fallen out of favor. It is now generally believed that the paradoxical response has an immunological basis. This hyper-reaction is based on similar phenomenon observed in other areas like the worsening of tuberculous lymphadenitis after starting ATT. Active TB can result in depression of delayed type of hypersensitivity (DTH) responses. The protein derivates of mycobacteria lead to increased interleukin-1 production which acts to suppress immune responses as well as production of immunosuppressive concentration of prostaglandin E2. Once active TB is under control and immunosuppression is resolved, enhanced DTH can lead to activation and accumulation of lymphocytes and macrophages at the site of bacillary deposition. If this activation occurs at the site of microscopic foci in the CNS, new tuberculomas appear. If it occurs at site of macroscopic foci they may enlarge. But, why this phenomenon occurs in only few cases need to be explored. Possibly, a combination of host immune response, virulence of bacilli, antigenic load, genetic factors and the effects of chemotherapy and steroids play a role.

There is no evidence that a change in therapy is warranted. Immunomodulatory drugs like corticosteroid therapy can be started or reintroduced in case of appearance of new lesions. Alternatively, if no response is seen then thalidomide, a potent inhibitor of tumor necrosis factor, has been shown to be a beneficial adjunctive therapy for severe disease in a dose of 50 mg twice a day. Few authors have even used cyclosporin in life-threatening situations. However, there is no consensus on the use of these therapeutic modalities and further studies needs to be done before using there potentially harmful drugs.
TUBERCULAR ABSCESS

Abscess formation is an uncommon feature of CNS TB. Tuberculous abscesses may by single or multiple. They are usually seen in immunocompromised or old individuals and resemble pyogenic abscess. They progress much more rapidly than tuberculomas. They lack the typical giant cell and epitheloid cell granulomatous reaction of tuberculomas but instead contain tubercle bacilli rich pus surrounded by a capsule.

Imaging reveals a lesion with liquid center, which has marked surrounding edema. Clinically features include rapidly progressive focal neurological deficit, raised intracranial pressure and focal seizures. Surgical exploration and drainage of pus produce excellent long-term results.

MANAGEMENT OF CNS TB

Within a professional lifetime, the outlook for patients of CNS TB has changed from certain death through survival with severe disability to a prospect of full recovery, due to advancements in understanding of its pathogenesis and drug therapy. However, the most elaborate regimens will be of little value if the patient has already developed adhesions, vascular occlusions and irreversible cerebral damage. Therefore, TBM should be regarded as a medical emergency and full treatment must be started if necessary on suspicion.

Antitubercular Therapy

The primary goal of anti TB chemotherapy is to kill tubercle bacilli rapidly, prevent the emergence of drug resistance and eliminate persistent bacilli from the host’s tissues to prevent relapse. It is theorized that there are three separate subpopulation of M. tuberculosis within the host. These population are defined by their growth characteristics and the milieu in which they are located. The largest of the subpopulation consists of rapidly growing extracellular bacilli. This population, because of its size, is most likely to harbor organisms with random mutations that confer drug resistance. Early experience in clinical trials demonstrated that multiple agents are necessary to prevent the emergence of a drug resistant population as a consequence of the selection pressure from administration of a single agent.

The frequency of these mutations that confer resistance is about $10^{-6}$ for INH and SM, $10^{-8}$ for Rif and $10^{-5}$ for EMB. In modern regimes, both INH and Rif have considerable ability to prevent the emergence of drug resistance when given with another drug.

The rapidly dividing population of bacilli is eliminated early in effective therapy within 2 months. The remaining subpopulation of M. tuberculosis account for treatment failures and relapses, especially when the duration of therapy is inadequate. These residual population include organism that are growing more slowly, often in the acidic environments provided by areas of necrosis and by the other group that is characterized by having spurts of growth interspersed with periods of dormancy. The sterilizing activity of a drug is defined by its ability to kill bacilli, mainly in these two subpopulation, that persist beyond the early months of therapy, thus decreasing the risk of relapse. RIF and PZA have the greatest sterilizing activity followed by INH and SM.

Isoniazid is the most powerful drug used in the treatment of TB, being responsible for killing the great majority of rapidly dividing bacilli. Because of its very good CSF penetration irrespective of meningeal inflammation, the efficacy of this drug is readily understandable. With a much smaller population of tubercle bacilli in TB meningitis, the role of companion drugs in preventing the growth of naturally resistant isoniazid mutants is much less important. However, there is now an increasing possibility of patients being infected in many third world countries with acquired isoniazid or streptomycin resistant strains. Whether significant numbers of semi-dormant tubercle bacilli occur in the brain, that are inherently susceptible to the sterilizing activities of rifampicin and pyrazinamide is not known.

Rifampicin’s contribution to the treatment of TBM is relatively modest and significantly less than that in pulmonary disease. The failure to demonstrate a beneficial contribution of PZA to the treatment of TBM despite excellent CSF penetration could be due to long treatment duration, which essentially precluded chances of demonstrating its sterilizing capability. There is no conclusive evidence to demonstrate the improvement in the outcome with the use of pyrazinamide. The good oral absorption, excellent CSF penetration and sterilizing effect on tubercle bacilli have resulted in mandatory inclusion of this drug in the intensive phase for the initial 2 to 3 months. It has been suggested that given the uncertain benefit and penetration of rifampicin, pyrazinamide should be given for the full duration of antitubercular therapy. The poor penetration of streptomycin in CSF despite concurrent meningeal inflammation suggests that its potential contribution to treatment of TBM is only marginal. The renal toxicity, ototoxicity and parenteral route of administration has limited the use of streptomycin.

Although the standard daily doses of rifampicin and streptomycin probably make only relatively modest contribution to the treatment of TBM, nevertheless they are given for many reasons like seriousness of disease, rapid therapeutic response, risk of single drug resistance and possibility of TB focus elsewhere in the body. Prothionamide is strongly favored by some as first line therapy as good
CSF concentrations are achieved at a dose of 20 mg/kg. The main drawback is a foul metallic taste, commonly occurring with nausea and vomiting. Drugs like isoniazid, pyrazinamide and cycloserine cross the blood brain barrier (BBB) freely, but the behavior of rifampicin, ethambutol and streptomycin is less predictable in the presence of inflamed meninges. The CSF concentration of these drugs is at least equal to or higher than those in the noninflamed meninges.

Those who treat TBM look enviously at the well-established protocols for management of other forms of the disease. There is no data from randomized controlled trial to serve as the basis of recommendations. Some authors have advocated longer course of therapy up to 2 years or even more, whereas other authors have suggested that short-term RIF based regimens for 6 to 9 months may be adequate.

The current United Kingdom guidelines suggest treatment for the first 2 months with rifampicin, isoniazid, pyrazinamide and a fourth agent (streptomycin, ethambutal, or prothionamide) followed by rifampicin and isoniazid for 10 months. Current UK guidelines recommend 12 months of ATT in uncomplicated cases of TBM, (including cerebral tuberculomas without meningitis) extending to 18 months should PZA be omitted. The study on long-term status of children treated for TBM in South India using three different regimens for 1 year also did not report any relapse on follow-up for 4 to 8 years in 100 cases indicating the adequacy of this regimen.

The American Thoracic Society/Centre for disease control recommends initiation of chemotherapy with isoniazid (INH 10 mg/kg/day up to 300 mg/day), rifampicin (RIF 10-20 mg/kg/day up to 600 mg/day), pyrazinamide (PZA 15 mg/kg/day up to 2 gm/day) and ethambutol (EMB 20 mg/kg/day up to 1.2 gm/day). After 2 months, PZA and EMB may be discontinued and INH and RIF continued for an additional 7 to 10 months, although optimal duration of chemotherapy is not defined.

Some studies using 9 months chemotherapy (2 months of INH, PZA, RIF, STM followed by 7 months of RIF, INH) at lower doses produced comparable outcomes. The experience of few authors after 9 years of prospective observation shows that short course chemotherapy is as effective as conventional long-term therapy in the treatment of extrapulmonary TB. Success with short course chemotherapy could be predicted due to presence of small bacterial population in extrapulmonary lesions as compared to cavitary pulmonary lesions. The lesions may be numerous, but individual lesions contain small population of organisms, easily reached by drugs.

Conventional therapy for 18 to 24 months is definitely effective but often not completed. Poverty, inability to collect drugs, inability to understand the rationale of long-term therapy and at times sheer carelessness lead to uninterrupted therapy or early discontinuation. The theoretical risk of recurrence of tuberculous, with more severity, greater possibility and mortality in form of infarcts of brain, optic nerve, etc. compelled few authors to continue ATT for longer duration. With tubercular meningitis, the penalties of failure are so grave that many authors propose to retain a policy of overkill with longer duration of ATT.

In an open-label, phase-two trial in a hospital in Indonesia, patients (aged >14 years) with TBM were randomly assigned to receive intensified treatment with high dose rifampicin (600 mg/day intravenously) with high dose of moxifloxacin along with other first line drugs for the initial 2 weeks followed by conventional treatment. Six months mortality was substantially lower in patients given high-dose rifampicin intravenously [10 (35%) vs 20 (65%)], which could not be explained by HIV status or severity of disease at the time of presentation.

**DOTS: DIRECTLY OBSERVED TREATMENT, SHORT COURSE**

Since the global resurgence of TB and associated rampant drug resistance in the 1990s directly observed therapy, short course (DOTS) has now become the WHO strategy for effective TB control. DOT regime consists of two phases: initial intensive phase (IIP) and a continuation phase (CP). WHO advocates directly observed, high dose intermittent therapy given thrice weekly. The CNS TB is put in category I of treatment for patients with seriously ill extrapulmonary CNS TB. The regimens used in this category include high dose short-term chemotherapy. For the IIP, isoniazid (H 600), rifampicin (R 450 mg), pyrazinamide (Z 1500 mg), ethambutol (E 1200 mg), are given thrice a week for initial 2 months (24 doses). For the continuation phase, H 600 mg and R 450 mg (600 mg in patients >60 kg) are given thrice a week for the remaining 4 months (54 doses), the first dose every week being directly observed. No large comparative studies have been done to show the efficacy and long-term safety of this regimen. However, a recent prospective study on 42 patients of TBM found DOTS to be effective, though large majority of neurologists are reluctant to use this regimen.

**ROLE OF CORTICOSTEROIDS**

The first controlled trial to suggest benefit in using corticosteroids in TBM was published in 1955. The white cell count in CSF fell faster in steroid group, recovery from acute phase was quicker, and none of the patients had long-term sequelae. In another major randomized, control trial,
the groups that benefited the most were those with disease of intermediate severity. Those presenting either in coma or mild disease received minimal benefit.

There is a rationale for steroid therapy in the management of patients with CNS TB. Corticosteroids restore damaged areas of vascular permeability, decrease CSF production, decrease free radical production, inhibit host mediators like cytokines and chemokines, leukotrienes, prostaglandins, MMPs at various steps.72 Recent studies have shown that corticosteroids improve both survival rate and neurological outcome in patients with TBM. A recent trial73 by Thwaites et al using dexamethasone in patients of TBM concluded improved survival in patients over 14 years of age, but does not prevent severe disability.74 A Cochrane meta-analysis of seven randomized controlled trials comprised a total of 1140 participants concluded that corticosteroids improved outcome in HIV-negative children and adults with TBM.75

Steroids are most beneficial in patients with raised intracranial pressure, cerebral edema, stupor, focal neurological deficits and spinal block. Patients with hydrocephalus, optochiasmatic or spinal arachnoiditis have also shown good response to steroids.73,74 The theoretical concern of reduced penetration of antitubercular drugs by use of steroids could not be substantiated in a study on CSF concentration of drugs with or without steroids.76

The recommended regimen of dexamethasone is 0.4 mg/kg/d in 1st week, 0.3 mg/kg/d in 2nd week, 0.2 mg/kg/d in 3rd week, 0.1 mg/kg/d in 4th week, then oral treatment with 4 mg/d to be reduced by every week. Usually, steroids are given for 8 to 12 weeks in tapering doses, depending on severity of disease.74

**Immunomodulating Drugs**

Immunomodulating drugs have been tried in the management of severe TB, often when disease is refractory to maximum medical therapy including systemic corticosteroids:

1. **Thalidomide**: A potent inhibitor of tumor necrosis factor α—has been shown to be a beneficial adjunctive therapy for severe TB meningitis in animal models and for refractory intracranial tuberculous abscesses in children and adults, refractory to medical management. Although thalidomide has shown promise in management of severe TB, its teratogenicity is likely to limit its use to refractory disease only.77,78

2. **Pentoxifylline**: This drug also blocks tumor necrosis factor α production. Pentoxifylline has been associated reductions in circulating HIV viral load in patients with TB.

3. **Cyclosporine**: The fulminant CNS TB in the form of increasing focal deficit or increasing lesions may respond to immunosuppressive drugs cyclosporine, in addition to steroids.78

4. Administration of ‘protective’ cytokines, like aerosolized interferon-γ and subcutaneous interleukin-2, have shown activity as adjuncts to chemotherapy.

5. Another method of immunomodulation, the use of heat killed preparation of M. vaccae as a therapeutic vaccine and other vaccines have been shown to lead to expression of protective cytokines in experimental studies.

6. Administration of nutritional supplements, vitamin A and zinc as immunomodulators need further assessment in TB treatment.

**HIV and TB**

HIV-infected persons are at markedly increased risk for primary or reactivation TB. This susceptibility is related to patterns of cytokines produced by T-lymphocytes. T1 lymphocytes which produce interferon-α are central to antimycobacterial immune defenses. In contrast, T2 lymphocytes, which produce interleukin-4 and interleukin-10, do not contribute to antimycobacterial immunity. When peripheral blood lymphocytes from HIV-infected patients with TB are exposed to M. tuberculosis, they produce less interferon-α, but similar interleukin-4 and interleukin-10, as compared with lymphocytes from HIV-negative patients with TB. These findings suggest reduced T1 response in HIV-infected patients, which contribute to their susceptibility to TB.79,80

Clinical studies have shown the detrimental effects of TB on the course of HIV infection. M. tuberculosis probably increases HIV replication by inducing macrophages to produce tumor necrosis factor-α, interleukin-1 and interleukin-6. The risk of death in HIV-infected patients with TB was reported to be twice that in HIV-infected patients without TB.

Involvement of CNS in TB is five times more common in HIV-positive patients. CNS involvement occurs in 10 to 20% patients with AIDS related TB, and in these patients, mortality is high. Clinical features, including imaging characteristics, are similar to those seen in patients without HIV infection. Intracerebral tuberculomas were more common in HIV coinfection.79,80

**MANAGEMENT OF CNS TB IN HIV COINFECTION**

Few studies have shown that the relapse rate is high in HIV-infected patients, who received 6 as compared to 9 to 12 months of ATT. Recent guidelines from CDC state that the minimal duration of therapy in 6 months, but if the clinical or bacteriologic response is slow, treatment should
be given for a total period of 9 months, or 4 months after cultures become negative.

Rifampicin induces the activity of cytochrome P450 CYP3A which lowers the concentration of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors to subtherapeutic levels. Therefore, concomitant administration of rifampicin with these drugs is not recommended. Rifabutin, a less potent inducer of CYP3A than rifampicin, can be administered in combination with protease inhibitor indinavir or nelfinavir, in a dose of 150 to 300 mg daily. The dose of indinavir should be increased to 1000 mg every 8 hours in patients receiving rifabutin and that of nelfinavir to 1250 mg every 12 hours.

ROLE OF SURGERY

Hydrocephalus is a common complication that may lead to permanent neurological damage or death if left untreated. Surgical therapy in the management of tubercular meningitis is required for relief of progressive hydrocephalus. Ventriculoperitoneal shunt is the treatment of choice in large number of series. Under cover of ATT, there is no risk of dissemination.

Surgical intervention is also required in some subgroups of intracranial tuberculomas, when vision or life is threatened due to severely elevated intracranial pressure; lack of desired clinical/radiological response to adequate medical therapy or when the diagnosis is in doubt.

Simple puncture, continuous drainage, fractional drainage, repeated aspirations through burr holes, stereotactic aspirations and total excision of the abscess are the treatment options for tubercular abscess.

CONCLUSION

CNS TB is a broad term meant to include wide varieties of clinical picture with varied pathology, CSF changes and radiological spectrum. Many factors play a role in pathogenesis of CNS TB like number and virulence of tubercle bacilli, liberation of caseous material without bacilli or of tuberculoprotein in the CSF, the effect of chemotherapeutic drugs and steroid, immune status and allergic background of the patient and the response of brain and meninges in particular. There have been great gains in our understanding of basic biology of TB, in the form of fully sequenced genome, efficient methods for genetic manipulation and a variety of in vitro and in vivo models in providing insight into issues of virulence, latency, and drug resistance. Many more milestones are yet to be achieved and newer research has to be focused on developing newer effective diagnostic tests, medications and vaccines. Larger trials are needed to demonstrate the efficacy of short-term therapy and DOTs. A multicenter collaborative study to establish clinical, bacteriological, biochemical and immunological factor is the need of the hour to improve the outcome in this treatable and curable disease of the CNS.

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