Central nervous system tuberculosis

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Abstract

Central nervous system (CNS) involvement, one of the most devastating clinical manifestations of tuberculosis (TB) is noted in 5 to 10% of extrapulmonary TB cases, and accounts for approximately 1% of all TB cases. Definitive diagnosis of tuberculous meningitis (TBM) depends upon the detection of the tubercle bacilli in the CSF. Every patient with TBM should preferably be evaluated by imaging with contrast enhanced CT either before or within the first 48 hours of treatment. An extra-neural focus of tuberculosis should be sought clinically and radiologically in all patients with CNS TB as it may indicate safer and more accessible sites for diagnostic samplings. A minimum of 10 months treatment is warranted, prompted by the uncertain influences of disease severity, CNS drug penetration, undetected drug resistance and patient compliance. All patients with TB meningitis may receive adjunctive corticosteroids at presentation regardless of disease severity even for those with HIV infection. Drug resistance is strongly associated with previous treatment. The key principle of managing drug-resistant TB is never to add a single drug to a failing regimen. Early ventriculo-peritoneal shunting should be considered in those with hydrocephalus failing medical management. The single most important determinant of outcome is the stage of tuberculous meningitis at which treatment has been started.

Keywords: – meningitis, human immunodeficiency virus, mycobacterium, drug resistant, steroids.

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Introduction

Central nervous system (CNS) disease caused by *Mycobacterium tuberculosis* is highly devastating, and accounts for approximately 1% of all cases of tuberculosis (TB). It carries a high mortality and a distressing level of neurological morbidity, and disproportionately afflicts children and human immunodeficiency virus (HIV) infected individuals. The purpose of this review is to highlight the current epidemiological, clinical, diagnostic, and therapeutic aspects of CNS tuberculosis.

The global epidemiologic burden of TB

World Health Organisation estimates that 9.27 million new cases of TB occurred in 2007 (139/100,000 population), compared with 9.24 million new cases (140/100,000 population) in 2006 world over[1]. India, China, Indonesia, Nigeria, and South Africa rank first to fifth in the total number of incident cases. Among the 15 countries with the highest estimated TB incidence rates, 13 are in Africa, a phenomenon linked to the effect of high rates of HIV coinfection on the natural history of TB[2]. Incidence rates are falling world over except in Eastern Europe, where it is stable and increasing only in African countries with a low prevalence of HIV[1, 3].

Among the 9.27 million incident cases of TB in 2007, an estimated 1.37 million (14.8%) are HIV-positive[1]. The global number of incident HIV-positive TB cases is estimated to have peaked in 2005 at 1.39 million. The relative risk of developing TB in HIV-positive people compared to HIV-negative people (the incidence rate ratio) is 20.6 in countries with a HIV prevalence greater than 1% in the general population, about 26.7 where HIV prevalence range from 0.1% and 1%, and 36.7 in countries with a prevalence less than 0.1%.[4]

Prevalence

About 13.7 million prevalent cases were estimated in 2007 (206/100,000 population), a slight decrease from 13.9 million in 2006. The global prevalence of TB is estimated to have been declining since 1990. This decline is in marked contrast to the increase in TB incidence in the 1990s, which can be explained by a decrease in the average duration of disease as the fraction of cases treated in the DOTS programs

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increased and a comparatively short duration of disease among HIV-positive cases specifically with limited access to antiretroviral therapy (ART). The duration of TB among HIV-positive patients is relatively short for in people with advanced HIV infection, the progression to severe tuberculosis is rapid, with a marked reduction in life expectancy[5].

Infection of the CNS is one of the most devastating clinical manifestations of tuberculosis. In an American epidemiological study of extrapulmonary tuberculosis, up to 10% of cases showed CNS involvement[6], while CDC data indicated that 6.3% of extrapulmonary cases (1.3% of total tuberculosis cases) had CNS TB.[7] In a Taiwan study, 1.5% of TB deaths between 1997 and 2001 were attributable to CNS disease, a percentage that had increased from previous years[8].

Risk factors

Risk factors for CNS tuberculosis include age (children> adults) HIV-coinfection[9], malnutrition, recent measles in children[10], alcoholism, malignancies, the use of immunosuppressive agents in adults and disease prevalence in the community[11,12].

Clinical features

In most patients with tuberculous meningitis there is a history of vague ill health lasting 2–8 weeks prior to the development of meningeal irritation. These nonspecific symptoms include malaise, anorexia, fatigue, fever, myalgias, and headache. Adults with tuberculous meningitis (TBM) can often present with the classic meningitis symptoms of fever, headache and stiff neck along with focal neurological deficits, behavioral changes, and alterations in consciousness[14]. A history of tuberculosis is elicited in only approximately 10% of patients[14]. The presence of active pulmonary tuberculosis on chest X- ray ranges from 30 to 50%. Patients coinfected with HIV do not seem to have an altered presentation of TBM[15]. About 10% of cases with TBM have some form of spinal tuberculosis. (Table. 1)

Table 1: Classification of CNS tuberculosis[13]

Intracranial
Tuberculous meningitis (TBM)
Tuberculous encephalopathy
Tuberculous vasculopathy
CNS tuberculoma (single or multiple)
Tuberculous Brain Abscess
Spinal
Pott's spine and Pott's paraplegia
Non-osseous spinal tuberculoma
Spinal meningitis

Cerebrovascular complications of tuberculous meningitis that occur typically as multiple or bilateral lesions in the territories of the middle cerebral artery perforating vessels are termed as tuberculous vasculopathy. Vessel pathology appears to be a consequence of its immersion in the local inflammatory exudate. Infiltrative, proliferative and necrotising vessel pathologies have been described, leading to luminal thrombosis. There is some evidence that vasospasm may mediate strokes early in the course of the disease and proliferative intimal disease later strokes[16].

Children with TBM often present with fever, stiff neck, seizures, and abdominal symptoms such as nausea and vomiting. Headache occurs less often than in adults. Depending on the stage of presentation, neurological symptoms range from lethargy and agitation to coma. TBM in children develops most often within 3 months of primary tuberculosis infection[17]. A family history of tuberculosis can be identified in approximately 50 to 60% of children, and a positive tuberculin skin test is found in approximately 30 to 50%. [16] In children particularly, there appears to be a close association with disseminated (miliary) tuberculosis[17]. Clinical signs of patients presenting with TBM can be easily assessed for severity based on modifications of the Medical Research Council staging system, which has been shown to have considerable prognostic value. A more contemporary modification of the staging system is given in table 2[18].

Table 2: Contemporary criterion for staging TBM[18]

I	Alert and oriented without focal neurological deficits
II	Glasgow coma score of 14-11 or 15 with focal neurological deficits
III	Glasgow coma score of 10 or less, with or without focal neurological deficits

Cranial nerve palsies occur in 20–30% of patients and may be the presenting manifestation of TBM. The sixth cranial nerve is most commonly affected[19]. Vision loss due to optic nerve involvement may occasionally be a dominant presenting illness. Optochiasmatic arachnoiditis, third ventricular compression of optic chiasma (if hydrocephalus develops), optic nerve granuloma are possible factors for vision loss in these patients. Ophthalmoscopic examination may reveal papilloedema. Funduscopy may reveal choroid tubercles, yellow lesions with indistinct borders present either singly or in clusters. These choroid

tubercles are more frequent with tuberculous meningitis associated with miliary tuberculosis and are virtually pathognomonic (table 3), although they are present in only 10% of patients in whom the meningitis is not associated with miliary involvement[20].

Table 3: Diagnostic features of tuberculous meningitis

Clinical
fever and headache (for more than 14 days)
vomiting
altered sensorium or focal neurological deficit
CSF
pleocytosis (more than 20 cells, more than 60% lymphocytes)
increased proteins (more than 100 mg/dl)
low sugar (less than 60% of corresponding blood sugar)
India ink studies and microscopy for malignant cells should be negative
Imaging
exudates in basal cisterns or in sylvian fissure hydrocephalus
infarcts (basal ganglionic)
gyral enhancement
tuberculoma formation
Evidence of tuberculosis elsewhere

Adapted from[22]

Clinical manifestations of tuberculoma or tuberculous brain abscess depend largely on their location, and patients often present with headache, seizures, papilledema, or other signs of increased intracranial pressure. The presentation of brain abscess is more sub acute (1 week to 3 months) than tuberculoma but slower in onset than pyogenic brain abscesses[21]. See Table 4 for comparison of the presenting clinical variables independently predictive of tuberculous meningitis in various published studies.

Table 4: Comparison of the presenting clinical variables independently predictive of tuberculous meningitis in four published studies

Study	Kumar et al, 1999[23]	Youssef et al, 2006[24]	Thwaites et al, 2002[25]	Moghtaderi et al, 2009[26]
Setting	India	Egypt	Vietnam	Iran
Age group	Children (1month – 12years)	Children and adults (5months –56years)	Adults (16–70 years)	Older childrenand adults(9–80 years)
Variables predictive of tuberculous meningitis	History of illness >6 days CSF lymphocytes> 5 days>50% total whitecells Optic atrophy Abnormal movements Focal neurologicaldeficit	History of illness CSF lymphocytes> 30% total white cells CSF white cell count <1000x 10^3/ml Clear CSFCSF protein >100mg/dL	History of illness ≥ 6 daysCSF lymphocytes> 10%CSF white cell count<750 x 10^3/mlAge < 36 years Blood white cellcount <15,000 /ml	History of illness >5daysCSF lymphocytes >70% total white cells CSF white cellcount %1000x 10^3/ml Age >30 years

Tuberculous Encephalopathy (TBE)

TBE is a rare outcome usually more common in younger population and is characterized by diffuse brain edema and demyelination, which usually is extensive[27]. Microscopically it is characterized by microvascular necrosis with perivascular macrophage reaction and demyelination along with focal glial nodules in the white matter and occasional hemorrhagic lesions. Impaired consciousness, seizures, disseminated intravascular coagulation, signs and symptoms of meningitis with or without spinal fluid changes characterize this syndrome. This syndrome may be one of the leading causes of neurologic devastation and death in CNS TB patients with high alcohol intake.

Spinal tuberculosis

Involvement of the spine occurs in less than 1% of TB patients and it can be secondary to Pott's spine or as non-osseous spinal cord tuberculosis or spinal tuberculous meningitis. It is a leading cause of paraplegia in developing nations. In Pott's spine infection in the vertebral bodies usually starts in cancellous bone adjacent to an intervertebral disc or anteriorly under the periosteum of the vertebral body; the neural arch is rarely affected. Vertebral destruction leads to collapse of the body of the vertebra along with anterior wedging. Spinal cord compression in Pott's spine is mainly caused by pressure from a paraspinal abscess. Neurological deficits may also result from dural invasion by granulation tissue and compression from the debris of sequestrated bone, a destroyed intervertebral disc, or a dislocated vertebra. Rarely, vascular insufficiency in the territory of the anterior spinal artery has also been suggested. Neurological involvement can occur at any stage of Pott's spine and even years later, when there has been apparent healing, because of stretching of the cord in the deformed spinal canal. The thoracic spine is involved in about 65% of cases, and the lumbar, cervical and thoracolumbar spine in about 20%, 10% and 5%, respectively. The atlanto-axial region may also be involved in less than 1% of cases. Males are affected more often than females in most series, and the disease generally affects young persons.

Typically, there is a history of local pain, tenderness over the affected spine or even overlying bony deformity in the form of gibbus. Paravertebral abscess may be palpated on the back of a number of patients. These patients usually have acute or subacute, progressive, spastic type of sensorimotor paraparesis. The incidence of paraparesis in patients with Pott's spine varies from 27% to 47%.[28]

Non-osseous spinal cord tuberculosis can occur in the form of tuberculomas. Dastur [29] reviewed 74 cases of tuberculous paraplegia without evidence of Pott's disease and observed that extradural tuberculomas occurred in 64% while arachnoid lesions without dural involvement, and subdural/extramedullary lesions occured in 8% of patients in each group. Intramedullary tuberculomas are extremely rarely reported and are frequently located in the thoracic region. More than one site in the spinal cord may also be affected. The clinical features are indistinguishable from those of any extramedullary or intramedullary tumour, although acute worsening may occur. Non-osseous spinal cord tuberculomas may increase in size while the patient is on antituberculous therapy.

A predominantly spinal form of tuberculous meningitis may result from rupture of Rich's focus into the spinal arachnoid space rather than the basal meninges. The acute form presents with fever, headache, and radiating root pains, accompanied by myelopathy. The chronic form, usually localised to a few segments, presents with progressive spinal cord compression and may suggest a spinal cord tumour. The characteristic MRI features include CSF loculation and obliteration of the spinal subarachnoid space with loss of outline of spinal cord in the cervico-thoracic region and matting of nerve roots in the lumbar region. Spinal forms of tuberculous meningitis may be associated with syrinx formation[29].

Immune Reconstitution Inflammatory Syndrome and TB

Two forms of Immune Reconstitution Inflammatory Syndrome (IRIS) are recognized in the case of TB. (a) Paradoxical TB-IRIS occurs in patients diagnosed with TB and established on TB treatment before ART, who then manifest with recurrent or new TB symptoms and clinical manifestations after ART initiation.(b) Unmasking TB-IRIS occurs in patients who are not on TB treatment when they start ART, and who then have an unusually inflammatory presentation of TB in the first 3 months of ART [30].

Paradoxical TB-IRIS reactions during TB treatment (new or recurrent TB symptoms, or signs occurring after initial response to treatment) occur in patients not infected with HIV-1 and patients infected with HIV-1 and not on ART. Manifestations include recurrent fevers, worsening pulmonary infiltrates, enlarging pleural effusions, the development of TBM, new or enlarging tuberculomas, or tuberculous lesions developing at other anatomic sites. The pathogenesis has variably been attributed to a combination of the following factors: release of new antigen targets during mycobacterial killing, hypersensitivity to such antigens, and exaggerated immune restoration (following TB-induced immunosuppression) occurring on TB treatment. The development of paradoxical reactions in patients not infected with HIV-1 is associated with greater increases in total lymphocyte count on TB treatment. Paradoxical reactions are also far more frequent in the period after ART initiation than in patients not infected with HIV-1 and patients infected with HIV-1 and not on

ART (36% vs 2% vs 7%, respectively, in one study[31]. The risk factors for paradoxical IRIS are disseminated TB, low CD4 count before ART, and shorter interval from TB treatment to ART.It is important to investigate for other opportunistic infections and malignancies, TB treatment failure (due to nonadherence, TB drug resistance, or malabsorption of TB drugs), or drug reaction. In addition, TB-IRIS may develop in patients with undiagnosed rifampicin resistance, clinically indistinguishable from TB-IRIS which occurs in patients with drug-susceptible disease. If possible, drug susceptibility testing, preferably a rapid diagnostic assay, should be performed in all patients presenting with paradoxical TB-IRIS. Corticosteroids have been used for management of TB-IRIS when alternative diagnoses have been excluded. Unmasking TB-IRIS is less well characterized than paradoxical TB-IRIS, with fewer cases reported. A subset of these cases presenting with heightened intensity of clinical manifestations, particularly when there is evidence of a marked inflammatory component, during the first 3 months of ART are termed as "unmasking TB-IRIS."

Diagnosis

Investigations

Definitive diagnosis of tuberculous meningitis depends upon the detection of the tubercle bacilli in the CSF, either by smear examination or by bacterial culture. Standard staining techniques using such stains as Ziehl-Neelsen, Kinyoun, or auramine-rhodamine applied to CSF samples have been estimated to detect approximately 100 AFB/ml of CSF. It has been claimed that if large volumes of CSF are carefully examined the organism can be found in over 90% of centrifuged CSF specimens (Table 5), the highest detection rates being achieved in ventricular fluid.

Table 5: Methods to increase mycobacterial yield of CSF smear examination[29]

Examine the deposit on centrifugation of a 10 ml CSF sample exclusively for the staining and culture of *M.tuberculosis*.
Examine CSF before or shortly after starting anti-tuberculosis drugs
Centrifuge at high relative centrifugal force (3000g) for 20 minutes
Remove all but 200il of supernatant (which can be used for biochemical tests) and vigorously re-suspend deposit.
Dry two drops of deposit onto a microscope slide (the second directly on top of the first) covering a diameter of less than 1cm
Ziehl-Neelsen stain the dried deposit (auromine staining alone is not recommended).
Careful examination of the slide for at least 10 minutes starting from the areas of highest cellularity and extend the examination to at least 20 minutes if TBM is strongly suspected.
Examine several CSF samples over a few days

Rates of CSF culture positivity for clinically diagnosed cases range from 25% to 70%. The importance of obtaining a culture is that growth of MTB in culture allows drug sensitivity testing, which can have a large impact on appropriate drug selection and prognosis.

At any age, approximately 10% of total CSF volume can be taken for examination.

MTB has been isolated from significantly smaller CSF volumes from HIV infected than in uninfected individuals[29]. Once anti-tuberculosis medication is commenced, the sensitivity of smear and culture falls rapidly. The deposit should be stained and cultured on solid or in liquid media .An aliquot of deposit may be taken for nucleic acid amplification if required. Liquid culture media may recover more bacteria from CSF than solid media[32]. A tissue biopsy has much higher diagnostic yield than CSF for the diagnosis of tuberculoma and spinal tuberculosis. A careful search should be made for extra-neural disease that may be biopsied safely. Gastric aspirates and bone marrow aspirates may assist in detecting extra-neural tuberculosis in children. Stereotactic brain biopsy confirms the diagnosis of abscesses and atypical tuberculomas when others diagnostic tools fail.

Molecular and Biochemical Analysis

Currently available molecularly based techniques, include commercially available nucleic acid amplification (NAA) methods and other polymerase chain reaction (PCR) based methods, antibody detection, antigen detection, or chemical assays such as adenosine deaminase (ADA) and tuberculostearic acid measurements.

PCR technique

Commercial nucleic acid amplification (NAA) assays for the diagnosis of TBM are 56 percent sensitive

and 98 percent specific and the diagnostic yield of NAA increases when large volumes of CSF are processed[33]. The sensitivity of microscopy is similar to NAA for the diagnosis of TBM[34]. The sensitivity of CSF microscopy and culture falls rapidly after the start of treatment, whereas mycobacterial DNA may remain detectable within the CSF until one month after the start of treatment. NAA (e.g. PCR) may be performed on CSF for all forms of CNS tuberculosis[35, 36]. NAA assays that detect the rifampicin resistance genotype should be requested when the risk of drug resistant tuberculosis is high.

Tuberculin skin test (TST)

The diagnostic utility of skin testing being positive for CNS tuberculosis varies from 10-20%[37] to 50%.[38] The performance of the tuberculin skin test for the diagnosis of tuberculosis varies according to age, vaccination with BCG, nutritional status, HIV infection, and technique of administration[39]. TST like interferon-gamma release assays may provide indication of previous tuberculosis infection; neither is sufficiently sensitive nor specific to diagnose active disease[40].

Interferon- γ release assays (IGRAs): A major advance in recent times has been the development of T-cell-based interferon- γ release assays (IGRAs). IGRAs are in vitro tests that are based on interferon-γ(IFN- γ) release after T-cell stimulation by antigens (such as early secreted antigenic target 6 [ESAT6] and culture filtrate protein 10 [CFP10]) that are more specific to MTB than the purified protein derivative (PPD). Two IGRAs are currently available as commercial kits. Systematic reviews have reported strong evidence that IGRAs have high specificity that is unaffected by bacille Calmette- Guérin (BCG) vaccination[41, 42]. TST, in contrast, has high specificity in populations who have not been vaccinated with BCG but specificity is modest and inconsistent in populations vaccinated with BCG. The high specificity of IGRAs is proving to be useful in individuals vaccinated with BCG[43]. IGRAs may be excellent options in these populations and it seems to be at least as sensitive as TST[42]. Both these immune-based tests merely indicate a cellular immune response to recent or remote sensitization with MTB. IFN-γ can be easily induced in peripheral blood monocytes or whole blood through antigenic stimulation in sufficient quantities that it can be detected using simple technologies, such as ELISA. IGRA tests rely on detecting elevated IFN-γ production after stimulation with antigens (ESAT-6, CFP10). Because these antigens are largely restricted to members of the MTB complex, the tests are not confounded by BCG or environmental mycobacteria. Because IGRAs cannot distinguish between latent and active TB, a positive IGRA result may not necessarily indicate active TB. A negative IGRA result would not conclusively rule out active disease in an individual suspected to have TB (similar to the results of a TST). About 50% of patients with culture-confirmed TBM had no detectable MTB -specific interferon-gamma producing lymphocytes in peripheral blood at presentation[40].

The use of IGRAs is steadily increasing in countries with low or intermediate incidence. Despite the large number of publications on IGRAs, evidence is still limited on the prognostic value of these tests, and their added value in TB diagnosis[44]. There is growing evidence that the performance of IGRAs varies between countries with high and low incidence of TB[45]. Their role, if any, seems to be limited in low income countries with a high TB burden.

ADA

ADA is associated largely with lymphocytic proliferation and differentiation and is considered to be a marker of cell-mediated immunity[46]. The measured sensitivities and specificities of ADA in the CSF range from 44 to 100% and 71 to 100%, respectively[47]. In one study, ADA was not valuable in distinguishing TBM in patients with HIV infection.[48] Standardized cutoffs of ADA values for the diagnosis of TBM have not been established, and the values used in various studies ranged from >5.0 to >15 IU/liter. CSF ADA measurements have been found to be useful in predicting poor neurological outcomes among pediatric TBM cases[49]. Raised ADA activity in the CSF of patients with CNS TB lacks specificity. High CSF ADA activity has been reported from patients with lymphomas, malaria, brucellosis, pyogenic meningitis, cryptococcal meningitis, and cerebral lymphomas[50, 51]. CSF ADA activity is not recommended as a routine diagnostic test for CNS tuberculosis[35].

Tuberculostearic acid

Tuberculostearic acid is a fatty acid component of the M. tuberculosis cell wall[52]. Although its estimation has good sensitivity and specificity in limited studies, the requirement for expensive equipment has limited its clinical use.

Radiological Evaluation

Every patient with TBM should preferably be evaluated with contrast enhanced CT imaging before the start or within the first 48 hours of treatment[35]. Early brain CT can help diagnose TBM, and will provide important baseline information regarding surgical interventions for hydrocephalus. Choroid plexus enhancement with ventricular enlargement on imaging is highly suggestive of TBM. In TBM, MRI shows diffuse, thick, meningeal enhancement. Cerebral infarcts can be seen in nearly 30% of cases[53]. A study from South Africa reported that the combination of hydrocephalus, basal enhancement and infarction was 100% specific and 41% sensitive for the diagnosis of childhood TBM, although the authors suggested pre-contrast hyperdensity in the basal cisterns as the best predictor of TBM[54].

Contrast enhanced MRI is generally considered as the modality of choice. It is useful for assessment of the location of lesions and their margins, as well as ventriculitis, meningitis and spinal involvement (sensitivity 86%, specificity 90%)[55]. A large lipid, lactate peak has been used to specifically identify tuberculomas by magnetic resonance spectroscopy[56]. All patients should have a chest-X-ray as part of the diagnostic assessment[35]. Serial transcranial doppler ultrasonography (TCD) with blood flow velocity (Vm) and pulsatility index (PI) measurments, can be efficiently utilized to prognosticate outcome in tuberculous meningitis-related vasculopathy. In early phase I vasculopathy TCD reveals increased Vm and normal to moderately decreased PI and these patients have reversible ischemic deficits while late phase III is characterized by almost absent blood flow in one or more basal arteries and, accordingly, by associated brain tissue infarction and permanent severe neurological deficit or fatal outcome[57].

Treatment of CNS TB

The first combination therapy for TB consisted of para-aminosalicylic acid (PAS) and isoniazid (H) in addition to streptomycin, given for 24 months, and it became the basis for treatment of TB in the developed world for about a decade. In the mid 1960s, PAS was replaced by ethambutol (E), a better-tolerated drug, and the treatment duration was reduced from 24 to 18 months. In the late 1960s rifampicin-containing regimen including isoniazid, ethambutol, and streptomycin offered a predictable cure in more than 95% of patients with 9- to 12-month duration of therapy. In the early 1980s addition of pyrazinamide (Z) in the intensive phase of treatment, decreased the duration of a fully orally administered treatment to 6 to 8 months. Studies conducted in East Africa showed that the relapse rate after a 6-month regimen was reduced from 22% to 8% by the addition of pyrazinamide, and to 3% by the addition of rifampicin[58].

Since the 1980s the 6- to 8-month regimen, using a 4-drug combination (HRZE) in the initial phase followed by a 2-drug combination (HR or HE) in the continuation phase, has been widely accepted[59]. In 2004 the results of a multicenter randomized clinical trial, showed higher efficacy for the 6-month regimen (2 months of HRZE plus 4 months of HR: 2HRZE/4HR) compared with the 8-month therapy (2HRZE/6HE)[60]. The recommended first-line treatment agents for all forms of CNS tuberculosis are Isoniazid, Rifampicin, Pyrazinamide and Ethambutol taken daily either individually or in combination form (table 6).

Table 6: Recommended treatment regimen for CNS tuberculosis caused by fully susceptible *M. tuberculosis*

Drug	Daily Dose Children	Daily Dose Adults	Duration
Isoniazid	10-20 mg/kg	300 mg	10 to 12 months
Rifampicin	10-20 mg/kg	450 mg (<50 kg) 600 mg (>50 kg)	10 to 12 months
Pyrazinamide	15-30 mg/kg	1.5 g (<50 kg) 2.0 g (>50 kg)	2 months
Ethambutol	15-20 mg/kg	15 mg/kg	2 months

Adapted from [35]

Patients should be treated for a minimum of 10 months[35]. Therapy should be extended to at least 12 months in those who fail to respond, or if treatment interruptions have occurred for any reason. Isoniazid penetrates the CSF freely[61] and has potent early bactericidal activity. At standard doses isoniazid achieves CSF levels 10-15 times the minimum inhibitory concentration of *M. tuberculosis*[62]. The main disadvantage of INH is that resistance develops quite quickly when used as monotherapy though this does not seem to happen when it is used to eradicate the organism in a patient who has become infected but has not yet developed overt signs or symptoms of infection (chemoprophylaxis). Pyridoxine is extremely

effective in stopping the seizures, reversing the coma, and correcting the metabolic acidosis triggered by any acute overdose of isoniazid. Treatment is best given as a relatively rapid intravenous (IV) infusion, the standard dose being one mg of pyridoxine for every mg of isoniazid the patient is thought to have taken[63]. Crushed tablets can be given down a nasogastric tube if no IV preparation is readily available. Prompt treatment is called for because INH dose in excess of 90 mg/kg is extremely likely to trigger recurrent seizure activity, which can be fatal[64]. Rifampicin penetrates the CSF less well (maximum concentrations around 30% of plasma), but the high mortality from rifampicin resistant TBM has confirmed its key role in the treatment of CNS disease[65]. The incidence of ethambutol induced optic neuritis is less than 3% at the standard dose of 15-20 mg/kg though it is a concern, especially when treating comatose patients[66]. Fluoroquinolones are an effective fourth agent (if ethambutol is contraindicated), but should be avoided in women who are pregnant or breastfeeding and prolonged fluoroquinolone therapy is not advised for children[67]. Interruptions in treatment are an independent risk factor for death from TBM[68].

Rationale use of steroids in CNS TB

All patients with TBM may receive adjunctive corticosteroids regardless of disease severity at presentation. Adults (>14 years) should start treatment with dexamethasone 0.4 mg/kg/24 hours with a tapering course over 6 to 8 weeks. Children (d"14 years) should be given prednisolone 4mg/kg/24 hrs (or equivalent dose dexamethasone: 0.6 mg/kg/24 hrs) for 4 weeks, followed by a tapering course over 4 weeks[69]. The role of routine adjunctive corticosteroids for all patients with tuberculomas without meningitis, or with spinal cord tuberculosis is arguable albeit corticosteroids may be helpful in those patients whose symptoms are not controlled, or are worsening, on anti-tuberculosis therapy. Doses similar to those used for TBM should be given. Thalidomide may be helpful in patients with tuberculomas that are not responding to anti-tuberculosis drugs and high dose corticosteroids[70].

Management of CNS TB in HIV infected

CNS tuberculosis in HIV infected patients should be managed with the same anti-tuberculosis drug regimen as that recommended for HIV uninfected individuals; whenever possible the regimen should include rifampicin. Adjunctive corticosteroids are recommended for those with TBM and HIV infection. Starting anti-retroviral therapy depends upon balancing the risks of drug interactions and Immune Reconstitution Inflammatory Syndrome (IRIS) when started early and opportunistic diseases if delayed. If CD4 > 200 cells/ìl it is better to defer HIV treatment as long as possible, ideally until end of tuberculosis treatment[35]. Start anti-retroviral treatment (ART) if the CD4 count falls below 200 cells/ìl during tuberculosis treatment. If CD4 is 100-200 cells/ìL start ART after approximately 2 months of anti-tuberculosis treatment so that risk of IRIS is minimised. If CD4 is < 100 cells/ìL start ART within the first 2 weeks of anti-tuberculosis treatment. Rifampicin will induce the metabolism of protease inhibitors, delavirdine and nevirapine reducing the level of these drugs. When possible, treat with rifampicin and a non-nucleoside reverse transcriptase inhibitor (NNRTI), preferably efavirenz but the dose of efavirenz should be increased to 800mg. Rifabutin should be used if treatment with a protease inhibitor (PI) is required, but at a reduced dose (usually 150mg 3 times per week). If efavirenz and rifabutin are co-administered, a 450 mg daily dosage of rifabutin is recommended.

Management of common treatment complications, including drug-induced hepatitis

New or worsening neurological signs in patients on treatment for CNS tuberculosis should prompt immediate imaging. Hyponatraemia should be considered as a cause of coma and seizures. Slow correction of sodium either by sodium and water replacement if the patient is hypovolaemic, or by fluid restriction if they are euvoleamic is advised to prevent risk of myelinolysis.

If drug-induced hepatitis occurs, and if serum transaminases rise above five times normal stopping pyrazinamide, continuing isoniazid, rifampicin, ethambutol, and performing daily liver function tests is recommended[35]. If serum albumin falls, the prothrombin time rises, or the transaminases continue to rise, isoniazid and rifampicin should be withdrawn. Streptomycin and ethambutol should be given, along with moxifloxacin or levofloxacin. Rifampicin and isoniazid should be restarted once the liver function tests are normal (table 7).

Table 7: Suggested regimen for the reintroduction of anti-tuberculosis drugs following drug-induced hepatitis [35]

	Isoniazid		Rifampicin		Pyrazinamide
	Adult	Child	Adult	Child	
Day 1	150mg	5mg/kg	Omit	Omit	Omit
Day 2	150mg	5mg/kg	Omit	Omit	Omit
Day 3	300mg	10mg/kg	Omit	Omit	Omit
Day 4	300mg	10mg/kg	150mg	5mg/kg	Omit
Day 5	300mg	10-20mg/kg	300mg	5mg/kg	Omit
Day 6	300mg	10-20mg/kg	450mg	10mg/kg	Omit
Day 7	300mg	10-20mg/kg	450mg (<50kg)600mg (≥50kg)	10-20mg/kg	Consider reintroduction if normal liver function after 14 days of full doserifampicin and isoniazid. If pyrazinamide not used, treat for 18months

In a recent study 175 patients with a diagnosis of antituberculosis drug-induced hepatotoxicity (DIH) were randomized to receive 1 of 3 different predefined reintroduction regimens in which one group were given isoniazid, rifampicin, and pyrazinamide simultaneously at full dosage from day 1 while the other received antituberculosis drugs in a manner similar to that recommended in the American Thoracic Society guidelines for reintroduction and the third were administered drugs accordance with British Thoracic Society guidelines[71]. 19 patients (10.9%) had recurrence of DIH during follow-up and the recurrence rate was not significantly different between the 3 groups. Pretreatment serum albumin level was the only statistically significant predictor of future recurrence of DIH on reintroduction of antituberculosis drugs. Patients with life-threatening tuberculosis can be reintroduced simultaneously at full dosage safely from day 1 with all 3 of the potentially hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide).

Role of neurosurgery

Hydrocephalus, tuberculous brain abscess (TBA), and vertebral tuberculosis with cord compression are all indications for urgent neurosurgical referral though early hydrocephalus and tuberculous brain abscess can be successfully treated by drugs alone . So early recognition and timely treatment is critical in avoiding the surgery. TBA occurs in only 4% to 8% of patients with CNS TB who do not have HIV infection but in 20% of patients who do have HIV infection. The aim of surgical management of TBA is to reduce the size of the space-occupying lesion and thereby diminish intracranial pressure and to eradicate the pathogen. Early surgical drainage and chemotherapy are considered the most appropriate treatment for TBA and can be therapeutic as well as diagnostic. It should be carefully planned and individualized according to the patient's clinical condition, anatomic localization, and the number of lesions. Early anti tuberculous therapy (ATT) must be considered in all cases of suspected TBA even before surgery, in order to reduce the risk of postoperative meningitis. An open surgical excision is an appropriate treatment option for large, multiloculated cerebellar lesions that cause brain herniation and also in those that do not respond to aspiration while stereotactic-guided aspiration is preferred in eloquent or deep-seated areas such as the hypothalamus, thalamus, or deep temporal regions in order to prevent severe neurological sequelae. The main disadvantage of the latter option is the need for repeated procedures in as many as 70% of patients, and the high risk of rupture into ventricles or the subarachnoid space, which could lead to ventricular ependymitis or meningitis and worsening of neurological deficits. An early surgical procedure can improve the efficacy of ATT, promote a better clinical response after reduction of bacillary load and reduce mortality[72]. Hydrocephalus, either communicating(more common) or obstructive, is one of the commonest complications of TBM occurring in up to 85% of children with the disease in whom it is more severe than in adults. Patients with TBM and hydrocephalus who have a Glascow coma scale (GCS) of 15 (with or without focal neurological deficit) could be tried for a few days or a week on diuretics and steroids with close monitoring to detect any worsening or lack of improvement and a shunt should promptly be offered in case of failure of medical management. Ventriculoperitoneal shunt is the procedure of choice if the duration of illness is <4 weeks while endoscopic third ventriculostomy or ventriculoperitoneal shunt can be offered if duration

>4weeks. Patients with GCS >8 and <14 are better off with an early shunt procedure and so are those with GCS >3 and <8 who improve within 48 hours after an external ventricular drainage (EDV) while those with GCS >3 and <8 who fail the EDV trial are unlikely to benefit with shunt and are managed conservatively[73]. Urgent surgical decompression should be considered in all those with extradural lesions causing paraparesis[74].

Prognosis and sequelae

The single most important determinant of outcome, for both survival and sequelae, is the stage of tuberculous meningitis at which treatment has been started others being extremes of age, malnutrition, hydrocephalus, focal neurological deficit ,presence of miliary disease , underlying debilitating disease and alcoholism**.** If treatment is started in stage I, mortality and morbidity is very low, while in stage III almost 50% of patients die, and those who recover may have some form of neurological deficit[75]. Survivors manifest a variety of neurological sequelae. Intracranial calcification develops in 20% to 48% of patients with tuberculous meningitis, usually becoming detectable 2 to 3 years after the onset of the disease[76].

Conclusion

Early recognition and timely treatment of CNS TB is critical if the considerable mortality and morbidity associated with the condition is to be prevented. A minimum of 10 month-treatment is warranted, and the single most important determinant of outcome is the stage of tuberculous meningitis at which treatment has been started.

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