# Neurotuberculosis: Different facets of a single disease

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## ABSTRACT

Tuberculosis (TB) can affect the meninges, brain or spinal cord, individually or in various combinations leading to neurotuberculosis. Tuberculous meningitis (TBM) is the most severe manifestation of central nervous system tuberculosis, with extremely high mortality (20-50%) and severe neurological morbidity among survivors. In spite of spectacular progress in diagnostic techniques and therapeutic approaches, TBM represents a serious global health burden, especially in tuberculosis-endemic areas and in immunocompromised groups. This review combines the existing evidence on TBM epidemiology, pathophysiology, clinical presentation, diagnostic strategies, and evidence-based management strategies. We have included developments in molecular diagnostics such as GeneXpert Ultra, new drug regimens including bedaquiline and linezolid, and adjuvant therapies such as corticosteroids and thalidomide. Drug-resistant TBM, pediatric age groups, and HIV coinfection situations are also emphasized with particular focus. The review includes case based illustrations and imaging to cover various categories of tubercular meningitis and spinal tuberculosis with its complications so that pragmatic approach can be utilized in the diagnosis and management of various aspects of neurotuberculosis.

**Keywords:** Tuberculous meningitis, neurotuberculosis, CNS tuberculosis, drug-resistant TB, molecular diagnostics, corticosteroids, hydrocephalus

## Introduction

Tuberculosis is still one of the world's largest health crises with about 10 million cases occurring worldwide annually as per WHO global reports.[1] Of this huge burden, about 2-5% are diagnosed as having tuberculous meningitis and this accounts for about 10% of all extrapulmonary tuberculosis. The actual incidence of tuberculous meningitis is still hard to determine due to the difficulty in diagnosis and poor surveillance systems worldwide. Nonetheless, WHO estimation statistics reveal that 300,000 to 490,000 people live with tuberculous meningitis annually, and it is the most common cause of bacterial infection of the brain in high tuberculosis burden environments.

Local epidemiological data reveal alarming trends, with countries like Nepal recording an estimated 68,000 tuberculosis patients and 16,000 deaths in the year 2023 alone according to the data from Nepal Tuberculosis Center.[2]The disease disproportionately affects vulnerable populations like young children and those infected with HIV, representing a true medical emergency with mortality rates of over 50% in advanced stages. Those who survive do so with disabling long-term neurological deficits that significantly compromise quality of life and functional status.

The extensive under-reporting of cases of tuberculous meningitis indicates the intrinsic challenges of microbiological diagnosis confirmation and the weakness of existing

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surveillance systems. In this review we have tried to synthesize the latest evidence on various spectrum of neurotuberculosis with illustrative real cases and practical approach to diagnose, image and treat them. In this review, a systematic search was conducted across major databases, including PubMed, CINAHL, Scoups, Cochrane Library, and Google Scholar, using the search terms "tubercular meningitis", "neurotuberculosis" and "TBM" and relevant literature included.

## Epidemiology and Risk Factors

### Global Disease Burden

The geographical distribution of the burden of tuberculous meningitis is heavily skewed, with an estimated incidence of 100,000 to 300,000 cases annually worldwide. Among some of the high-burden countries are India, China, Indonesia, and Nigeria, where poverty, malnourishment, and HIV co-infection converge to form ideal conditions for the transmission of tuberculosis and advancement to central nervous system disease.[1]

The epidemiology is also complicated by the interplay between latent and active tuberculosis infection. The majority of tuberculosis infections are latent for the individual's lifetime, and just 5-10% of infections will progress to active disease. Interestingly, approximately 90% of active infections are reactivation of latent infection rather than symptomatic presentations of primary infection, highlighting the absolute importance of intact immune system function in the progression of disease.[3]

### Risk Factors for Development

Multiple risk factors contribute to the development of active tuberculosis and subsequent central nervous system involvement. Various studies done shows HIV co-infection, other immunocompromised status, Diabetes Mellitus, Malnutrition, Chronic lung diseases and heavy intake of alcohol as the primary risk factors for development of tuberculosis and indoor air pollution, end stage renal disease, tobacco use, exposure to silica and other pneumoconiosis and chronic malabsorptive stage as the secondary risk factors.

HIV infection represents the most significant risk factor for both tuberculosis acquisition and central nervous system involvement. Individuals with HIV demonstrate a 3-fold increased mortality risk during tuberculosis treatment, with tuberculosis accounting for 35% of global mortality among HIV-positive individuals in 2015.[4] Central nervous system tuberculosis occurs 5 times more frequently in HIV-positive patients, contributing to the higher mortality rates observed in this population.

Children represent a particularly vulnerable demographic, with approximately 20% of pediatric tuberculosis cases involving central nervous system manifestations.[5] The immature immune system in children and especially those child not vaccinated with BCG, predisposes them to disseminated tuberculosis and increased risk of CNS involvement. Clinical presentations in pediatric populations often differ significantly from adults, with less prominent headache symptoms and more frequent manifestations of irritability, restlessness, anorexia, and protracted vomiting.

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculous meningitis represents the most challenging clinical scenario, with mortality rates approaching 70%.[6] The emergence of drug resistance significantly complicates treatment regimens and necessitates prolonged therapy with potentially more toxic agents.

### Pathogenesis and Immunological Mechanisms

The pathogenesis of tuberculous meningitis involves a complex sequence of events beginning with primary pulmonary infection (Figure 1). *Mycobacterium tuberculosis*, an obligate aerobic acid-fast bacillus, primarily gains entry through inhalation into alveolar spaces. From this initial site, secondary dissemination to extrapulmonary sites occurs through bacteremia and lymphatic drainage, with preferential seeding of highly oxygenated tissues including the brain.[7]

Central nervous system tuberculosis begins with the formation of small caseous tubercles, termed "Rich foci", which can develop throughout the brain, spinal cord, and meninges.[8] These lesions represent the initial pathological manifestation of CNS tuberculosis and serve as the source for subsequent meningeal involvement. Tuberculous meningitis manifests when tuberculous bacilli enter the subarachnoid space through rupture of a Rich focus located in the cerebral cortex or meninges as shown in Figure 1. Following mycobacterial release into the subarachnoid space, the pathological process predominantly affects the basilar area and basal meninges, creating characteristic clinical and radiological findings.

The presence of mycobacteria in the subarachnoid space triggers a robust inflammatory response characterized by predominantly Th1-mediated inflammatory cascade develops, involving the release of key cytokines including tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and matrix metalloproteinases (MMPs).[9] This inflammatory response, while intended to control infection, contributes significantly to tissue damage and clinical complications.

Basilar artery inflammation leads to vasculitis, a major pathological mechanism underlying stroke occurrence in approximately 40% of TBM cases. The inflammatory exudate characteristically envelops prominent subarachnoid anatomical structures, including cerebral arteries and cranial nerves, creating a pathological environment conducive to vascular compromise.[10]

The inflammatory exudate creates bottleneck situations in cerebrospinal fluid flow at the tentorial opening level and narrows the aqueduct, leading to non-communicating (obstructive) hydrocephalus.[11] The most frequent hydrocephalus type in TBM is communicating hydrocephalus, secondary to blockage of focal CSF resorption by inflammatory exudate in the basal cisterns.

There are certain polymorphisms which predispose a person to be susceptible for tubercular meningitis and subsequent complications due to inflammatory cascade activation. Important among these are polymorphism in Toll Interleukin 1 receptor domain which resulted in decreased production of IL-6 thus being susceptible for inflammation. Similarly, polymorphism in leukotriene A4 hydrolase gene (LTA4H) which encodes a protein affecting the production of leukotriene B4 (an inflammatory eicosanoid), affects the risk for inflammation in TBM.[12] The polymorphism rs17525495 with CT genotype in LTA4H gene determines inflammation, with patients who possess the homozygous TT genotype having the highest level of inflammation.

**Clinical Manifestations and Disease Staging**

Tuberculosis (TB) can affect the meninges, brain or spinal cord, individually or in various combinations leading to neurotuberculosis. Conceptually, clinical CNS infection is seen to comprise three categories of illness: subacute or chronic meningitis, intracranial tuberculoma, and spinal tuberculous arachnoiditis.

Clinically and radiologically Neurotuberculosis is broadly divided into Intracranial and spinal tuberculosis (Table 1).

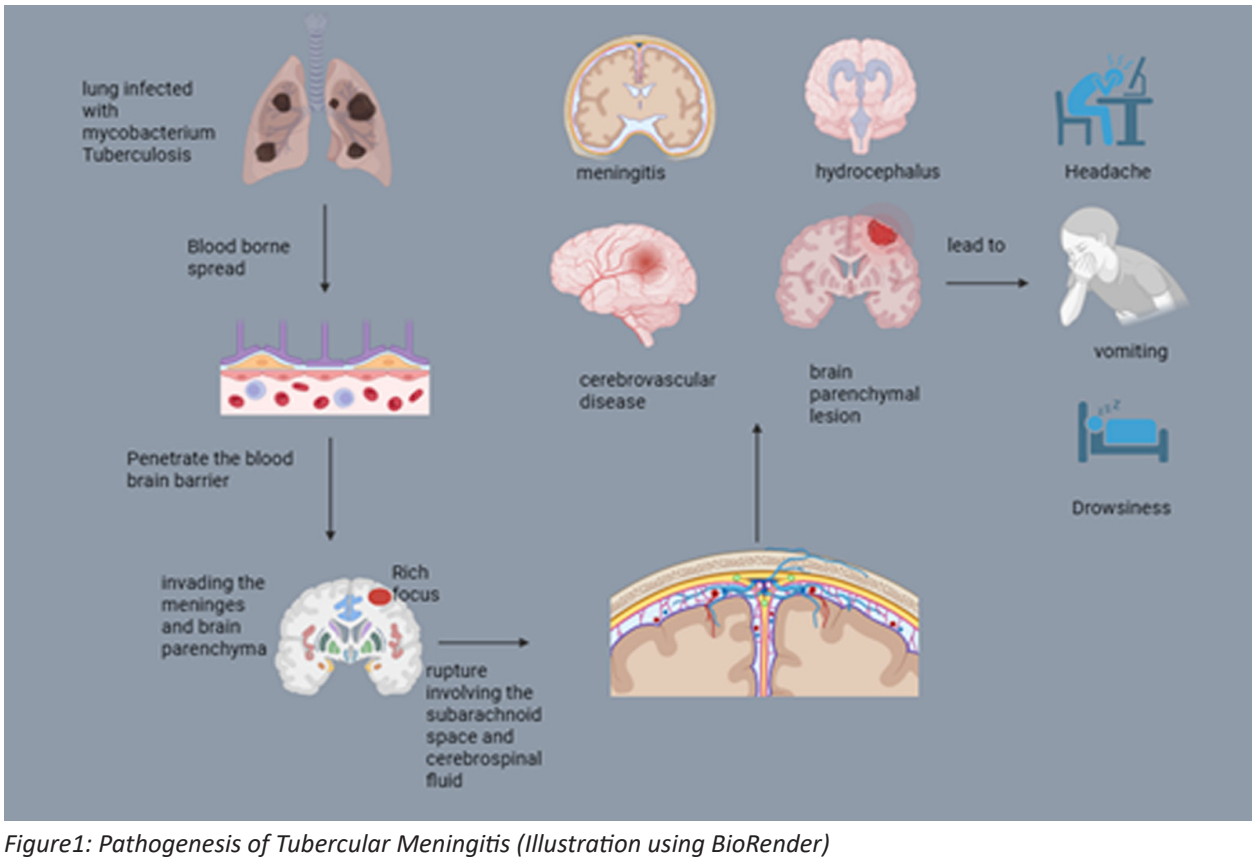



*Figure1: Pathogenesis of Tubercular Meningitis (Illustration using BioRender)*

**Table 1: Different forms of Intracranial and spinal Tuberculosis**

| Intracranial Tuberculosis | Spinal Tuberculosis |
|---|---|
| A) Meningeal Form:<br>1) Leptomeningitis –(**Figure 6)**<br>2) Pachymeningitis-(**Figure 3)**<br>B) Parenchymal Form:<br>1) Tuberculoma **(Figures 5, 10, 11, 12)**<br>2) Disseminated/Miliary Tuberculomas<br>3) Tuberculous abscess<br>4) Tuberculous cerebritis<br>5) Rhombencephalitis<br>6) Encephalopathy | 1) Extradural Form (**Figure 9)**<br>2) Intradural Extramedullary Form<br>3) Intramedullary Form **(Figure 8)**<br>4) Spinal arachnoditis **(Figure 10)** |

"Tuberculous meningitis'' typically presents as a subacute, progressive febrile illness that evolves through three distinct phases (Table 2). Initial phase of illness is known as prodromal stage characterized by non-specific constitutional symptoms comprising of malaise and lassitude, low-grade fever, intermittent headache, vague neck or back discomfort and subtle personality changes. After 2-3 weeks, a more defined meningitic phase emerges which presents with protracted severe headache with clinical features of meningismus, neck stiffness, persistent vomiting, mild confusion and altered mental status, various degrees of cranial nerve palsy and long-tract neurological signs. The final phase and devastating of all phases is the paralytic phase characterized by severe neurological deterioration in form of delirium progressing to stupor and coma. Other manifestations include generalized or focal seizures, multiple cranial nerve deficits, hemiparesis and hemiplegia. Overall clinical severity is most often graded by using the modified British Medical Research Council (MRC) criteria given in following table with higher grades associated with higher mortality.[13]

The clinical features of TBM are influenced by the immune response against M. tuberculosis. Very young children (<1 year of age) and those with advanced HIV-1 co-infection are highly susceptible to M. tuberculosis, which frequently leads to uncontrolled extrapulmonary dissemination and meningitis.[14] In these groups, the presentation of TBM can be abrupt, and can rapidly progress to severe coma and prostration with high mortality; furthermore, these individuals have an increased risk of active tuberculosis in other organs.

Clinical presentations in children demonstrate important differences from adult manifestations with headache less commonly reported, prominent irritability and restlessness, anorexia and feeding difficulties, protracted vomiting episodes and earlier seizures.

**Table 2: Modified British Medical Research Council Staging System for** Tuberculous **Meningitis[13]**

| Stage | Clinical Features | GCS Score | Mortality Rate |
|---|---|---|---|
| I | Non-specific symptoms: fever, headache, malaise, vomiting <2 weeks | 15 | <10% |
| II | Cranial nerve palsies, focal neurological deficits, confusion | 11-14 | 20-30% |
| III | Coma, seizures, severe focal deficits, hemiplegia | ≤10 | 50-70% |

Cranial neuropathy is seen in 29–38% of patients, most affected being abducent nerve. Cranial neuropathy is more common among patients older than 25 years, having altered sensorium, hemiparesis, papilledema, signs of meningeal irritation, severe functional disability, cerebrospinal fluid (CSF) protein > 2.5 g/L, CSF cell count more than100/mm3, optochiasmatic arachnoiditis (OCA), and hydrocephalus.[15]

Stroke represents one of the most common and devastating complications of tuberculous meningitis, occurring in approximately 30-60% of cases.[16,17] These strokes typically occur in the basal ganglia due to involvement of small penetrating arteries surrounded by exudates in the basal cisterns. However, abnormalities

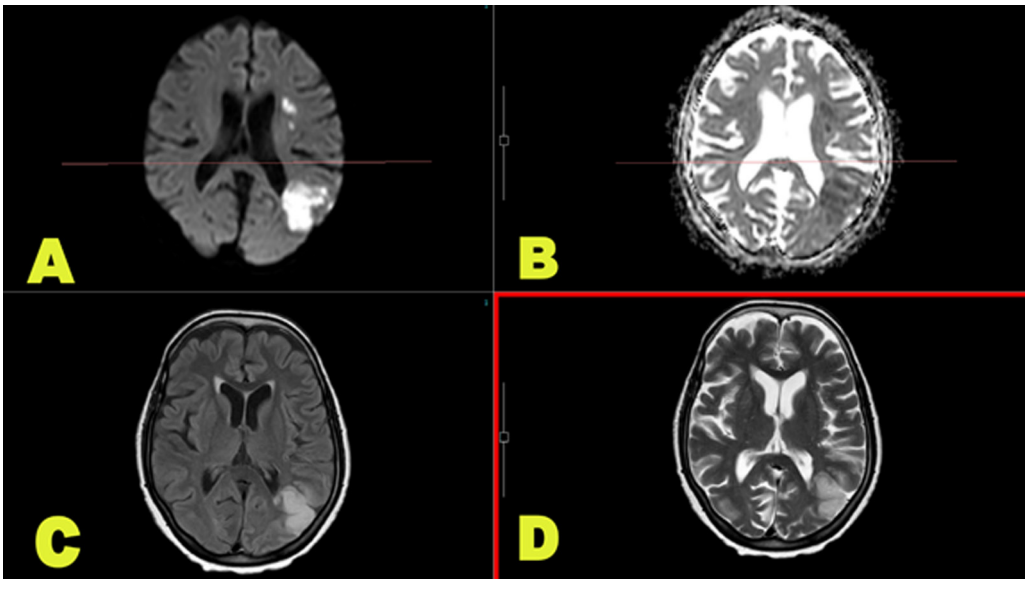



*Figure 2: Multifocal acute infarction in the left frontoparietal lobe involving the MCA territory and watershed areas evidenced by areas of diffusion restriction (A) with corresponding low ADC signal (B) and T2 & FLAIR hyperintensities(C&D) in the lady with diffuse arachnoditis involving brain and spinal cord after 3 months of ATT treatment, presenting with confusion and severe agitation with slurred speech.*

of large anterior circulation arteries are also common due to tuberculous vasculopathy and can present with watershed infarction as shown in Figure 2. The proposed mechanism for stroke includes endothelial reactions to inflammatory exudates, proliferative and necrotizing arteritis, hypercoagulable states and direct vascular invasion. Recent findings indicate that strokes related to tuberculous meningitis are linked to various abnormal platelet indices such as mean platelet volume, platelet distribution width, platelet-large cell ratio, and platelet aggregometry while other hematologic parameters remain unaffected. This suggests that primary platelet dysfunction may contribute to stroke development in these patients.[18]

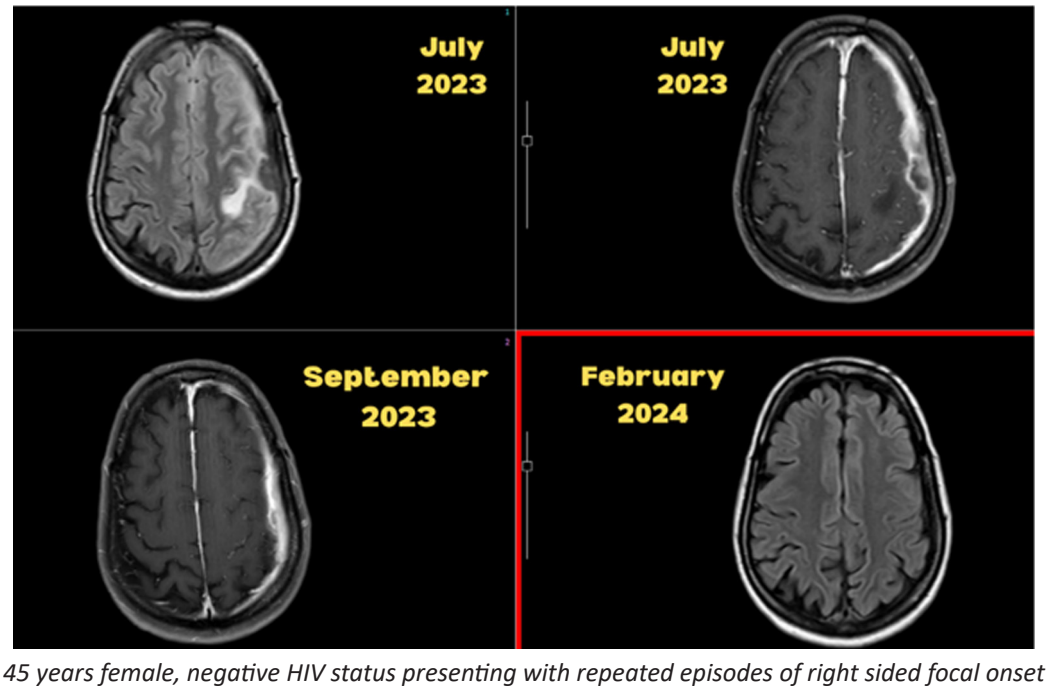



**Figure 3***: 45 years female, negative HIV status presenting with repeated episodes of right sided focal onset motor seizure with head adversion to right with secondary generalization. MRI head shows Vasogenic edema involving the left parietal lobe with overlying thickened T2 hypodense* **enhancing pachymeninges** *(July 2023). Progressive reduction in the pachymeningeal enhancement after 2 months of ATT (September 2023) and complete resolution of the thickened meninges and vasogenic edema (February 2024).*

Predictors of stroke among individuals with tuberculous meningitis include more advanced disease stage, HIV co-infection, presence of basal exudates, optochiasmatic arachnoiditis, focal neurologic deficits, cranial nerve palsy, hydrocephalus, meningeal enhancement, and vision impairment. Additionally, the occurrence of stroke in tuberculous meningitis is linked to significantly worse outcomes, including a 2.6-fold increase in the likelihood of any adverse outcome, a 4.5-fold higher chance of prolonged hospitalization, and an 8.8-fold greater likelihood of multiple hospital admissions.[19]

Seizures occur in approximately 34% of individuals with tuberculous meningitis in a case series from India, with distinct temporal patterns, 30% occur within the first month (early seizures),70% occur after one month (late seizures).[20] Majority of seizure demonstrate focal onset and nearly 25% present with status epilepticus. Study of associated factors for seizure include early seizures associated with meningeal irritation, pachymeningeal involvement with parenchymal oedema as in Figure 3 and late seizures more common with tuberculomas (as illustrated in cases in Figure 4 and Figure 5), infarcts, and hyponatremia. Status epilepticus was associated with 3-fold higher mortality in a cohort of tubercular meningitis from China.[21]

Hydrocephalus represents a frequent and serious complication requiring prompt recognition and management as illustrated in our case in Figure 6. Clinical manifestations include progressive headache, diplopia and visual disturbance, papilledema, altered consciousness and focal neurological deficit depending on area involved in various Central Nervous system axis. Rare presentations with acute onset dizziness with persistent vomiting and ataxia mimicking acute vestibular neuronitis can also occur as illustrated in our case Figure 7.

There can be atypical presentations in patients who are Immunocompromised and especially in HIV coinfected patients in form of, milder meningismus, higher CSF neutrophil counts, more frequent atypical radiological findings and increased risk of paradoxical reactions, The other commonly described atypical presentation is encephalitic syndrome particularly in children manifesting as stupor and coma, convulsions, absence of clear meningitis signs and minimal CSF abnormalities.

Several studies have described the clinical features that are most predictive of TBM, leading to the development of diagnostic scoring systems. The findings vary according to the population in which they were derived, with age and HIV status accounting for much of this variation. Nevertheless, these scoring systems serve to highlight the key distinguishing features of TBM: long-term symptoms (>5 days), lower numbers of CSF leukocytes (<1000 cells per mm3) than are typically observed in other forms of bacterial meningitis, CSF leukocytes comprised of <90% neutrophils, elevated CSF protein (>100 mg/dl), and a low CSF to blood glucose ratio (<0.5) compared with uninfected individuals. The most commonly used and tested scoring system was developed by Thwaites et al[22] in Vietnam (Table 3) and in different studies found to have sensitivity of 86% and specificity of 79%. Subsequent studies have shown various results and its use in patients with HIV population was skeptical as it was not predictive enough to differentiate tubercular meningitis from cryptococcal meningitis as shown in a study from Malawi.

**Table 3: The Vietnam diagnostic rule[22]**

| Entry criteria |
|---|
| • Adult (age >15 years) with meningitis and ratio of CSF to plasma glucose <0·5 |
| **Clinical features and scores** |
| • Age ≥36 years (score +2) |
| • Age <36 years (score 0) |
| • Blood white cell count ≥15×10$^9$/L (score +4) |
| • Blood white cell count <15×10$^9$/L(score 0) |
| • History of illness ≥6 days (score –5) |
| • History of illness <6 days (score 0) |
| • CSF white cell count ≥0 • 75×10$^9$/L (score +3) |
| • CSF white cell count <0 • 75×10$^9$/L (score 0) |
| • CSF neutrophils ≥90% of total white cells (score +4) |
| • CSF neutrophils <90% of total white cells (score 0) |
| **Interpretation** |
| • Total score ≤4 = tuberculous meningitis |
| • Total score >4 = alternative diagnosis |

"Tuberculomas" are space-occupying lesions consisting of granulomatous reactions to M. tuberculosis infection that are believed to arise from the hematogenous spread of mycobacteria to the

brain parenchyma.[23] Microscopic granulomatous foci, called Rich foci, develop over time, organizing into encapsulated granulomatous mass lesions. Tuberculomas are similar to tuberculous abscesses, but abscesses are often larger and have a pus-filled cavitary center. Tuberculomas and tuberculous abscesses are usually discussed together because their clinical presentation, radiologic findings, diagnosis, and treatment are similar, and they are ultimately only definitively differentiated based on pathologic features.

Approximately 10% of individuals with tuberculous meningitis have concomitant tuberculomas, but tuberculomas can also occur in the absence of meningitis and without evidence of TB infection outside the CNS and can develop anywhere within the CNS including the brain parenchyma, spinal cord, or subdural, epidural, subependymal, or subarachnoid spaces. Overall, tuberculomas are more common in children, in whom they tend to be infratentorial, but are more commonly supratentorial in adults. Lesions are solitary in one-third of cases and multiple in the remainder.[24] Clinical presentation typically consists of focal neurologic deficits corresponding to the site of the lesion, accompanied by headaches, fever, and often, seizures.

Atypical presentation with acute onset dizziness with protracted vomiting often mistaken for demyelinating lesion, resembling acute vestibular syndrome initially in young females can be missed if detail evaluation and imaging is not done as illustrated in Figure 7.

Paradoxical expansion of tuberculomas, defined as the development of a new tuberculoma or enlargement of an existing tuberculoma while on appropriate TB treatment, is not uncommon and usually occurs within 3 months of initiating TB treatment. The case illustrated in Figure 4 is a case of paradoxical reaction in an immunocompetent young girl who presented with increasing headache more than 1 year after start of antitubercular medicine .[25] This is more common in people with HIV, especially in those initiating antiretroviral therapy for the first time, in which case it is a manifestation of Immune reconstitution inflammatory syndrome (IRIS).

"Spinal Tuberculosis" as with the varied manifestations of intracranial TB, TB can involve every compartment of the spine including bony

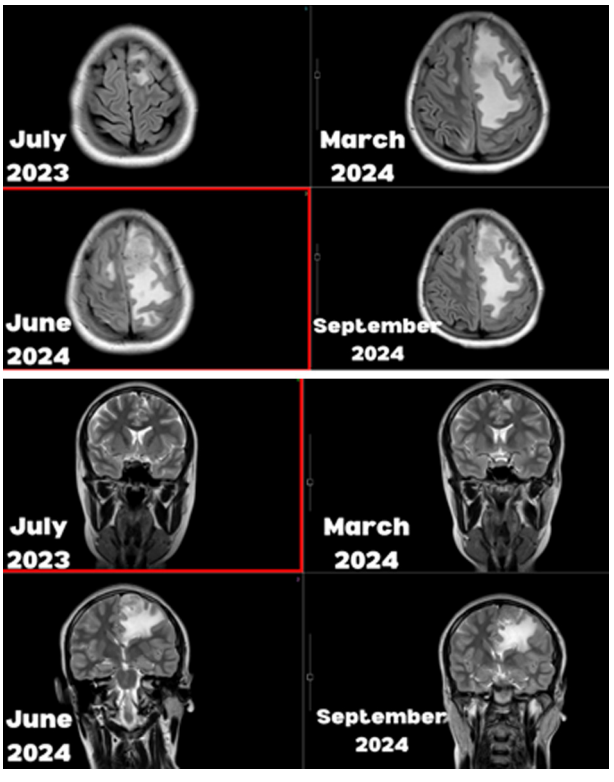



*Figure 4: 13 yrs girl with disseminated tuberculosis including multiple tuberculoma in brain presenting with status epilepticus. Post ATT, there is increase in perilesional edema which gradually becomes progressive and results in mass effect evidenced by midline shift and subfalcine hernaition when imaged after a year representing Paradoxical reaction (PR) treated with steroid and thalidomide.*

structures, intradural and extradural spaces, the spinal cord, and nerve roots. The thoracic and lumbar regions are most commonly involved, but cervical involvement occurs in more than one quarter of affected individuals and is associated with more frequent neurologic sequelae than other locations.[26] The most common manifestations of spinal TB are spondylitis and intradural tuberculous spinal infections including radiculomyelitis, spinal arachnoiditis, intramedullary tuberculomas, and myelitis. Atypical presentation with cauda conus feature is illustrated in Figure 8, who presented with bilateral lower limb weakness with bowel and bladder involvement of more than 3 months duration and biopsy from the conus lesion shows caseating granuloma and patient improved with ATT and steroid with partial recovery of paraparesis.

"Spondylitis", also known as Pott's disease, is the most common form of spinal TB and accounts for 50% of cases of skeletal TB and presents with evolving nonspecific back pain that is then followed by kyphosis (which can often be detected clinically

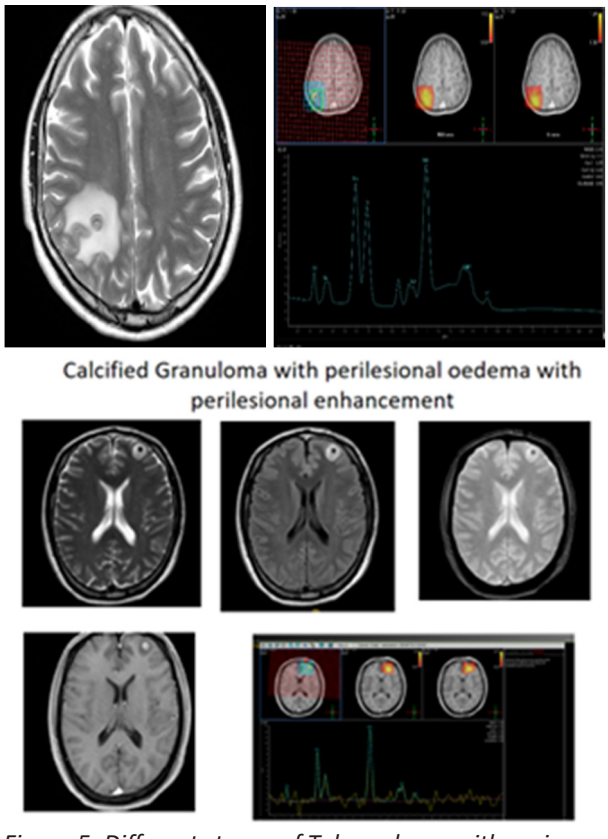



*Figure 5: Different stages of Tuberculoma with various stages and sequences in MRI along with MRS*

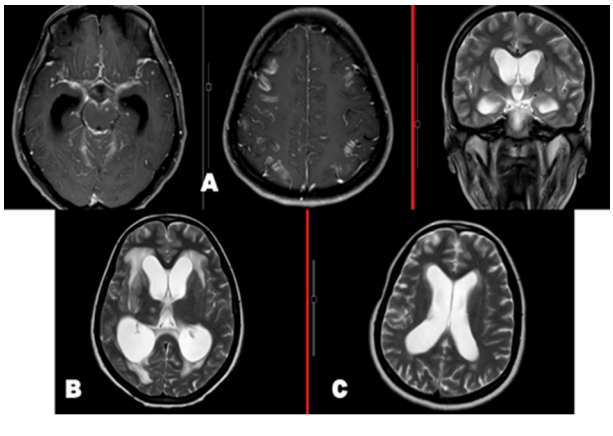



*Figure 6: 30 years immunocompetent lady presenting with fever, headache of 3 weeks duration with increasing drowsiness of 1 week duration along weight loss and other constitutional features. MRI head showing A and B: Tiny nodular enhancing lesions in bilateral basal ganglia- thalamic location, brainstem and cerebellum along with diffuse leptomeningeal enhancement overlying bilateral cerebral hemispheres & basal cisterns and resultant ooze decompensated extraventricular obstructive hydrocephalus- suggesting Tubercular meningitis. Imaging done 2 months after initiation of ATT(B) still revealed basal exudates along with hydrocephalus & periventricular ooze which improved on subsequent follow up (C)*

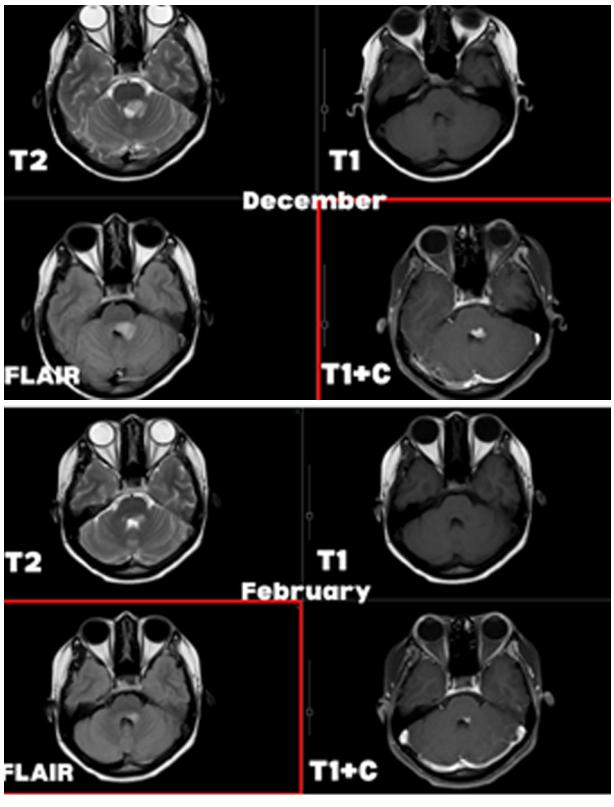



*Figure 7: Ill-defined T2 hyper and T1 isointense lesion with perilesional edema in the pontine tegmentum which on post contrast study shows homogeneous enhancement. Subtle meningeal enhancement noted in the basal cistern. Compared to initial images (December) the lesion shows significant decrease in size, in the images post 2 months ATT (February).*

as a gibbus formation on the back), sensory symptoms, bowel and bladder symptoms, and, finally, paraparesis.[27] Progression through these stages occurs over the course of months to more than 1 year. Acute presentations of neurologic deficits are not uncommon because of vertebral fracture or abscess formation with subsequent spinal cord compression as in Figure 9. Imaging classically shows edema and bony destruction of the vertebral body with paravertebral granulomatous exudates or abscess. The thoracic cord is the most common location, and spondylitis often involves three or more consecutive vertebral bodies while sparing the intervertebral disks. More severe vertebral body destruction and kyphosis have been reported in HIV-uninfected adults with spondylitis whereas people with HIV are more likely to develop epidural abscesses anterior to the vertebral body.

Spinal meningitis (arachnoiditis) can either occur de novo or as part of cranial TBM. De novo spinal meningitis (arachnoiditis) is a rapid or slow,

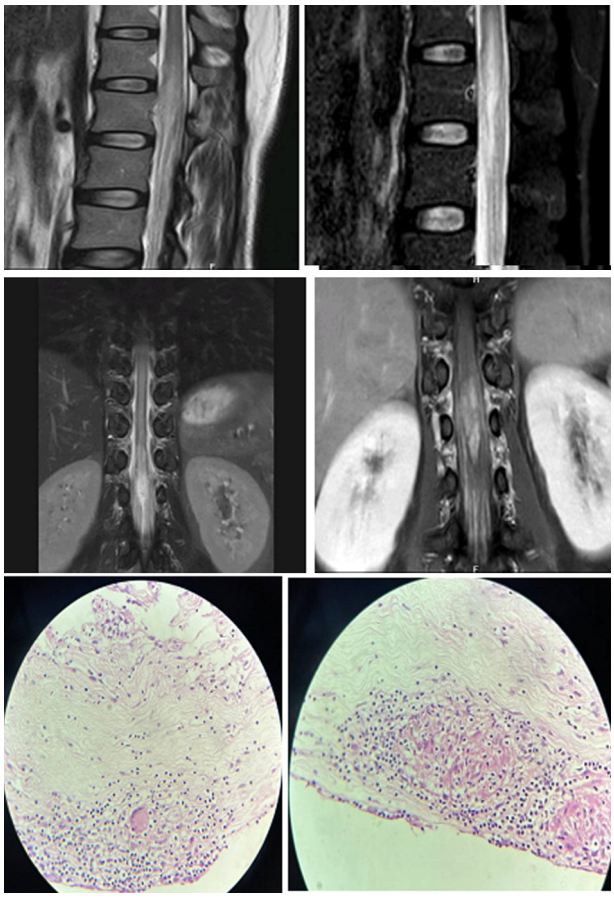


*Figure 8: 41 years female with progressive paraparesis with bowel and bladder involvement of 5 months duration with fever and constitutional features*

*MRI of spine T2 and T1 contrast revealed an ill-marginated heterogeneously enhancing lesion measuring approximately 9.5x8.0x48 mm (APxTRxCC) in the region of conus medullaris with associated thickening and enhancement of cauda equina nerve roots.*

*Histopathological examination of arachnoid sample revealed thickened arachnoid and glial tissue with infiltration of lymphocytes with few epithelioid cell granulomas along with Langhans type giant cell. Ziehl-Neelsen stain did not reveal acid-fast bacilli.*

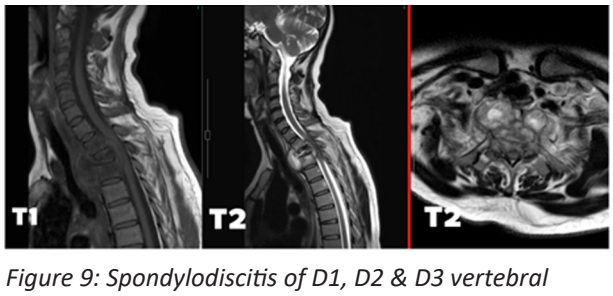



*Figure 9: Spondylodiscitis of D1, D2 & D3 vertebral bodies and intervertebral discs with compression fracture of D2 vertebral body and associated paravertebral and epidural collection resulting in cord compression.*

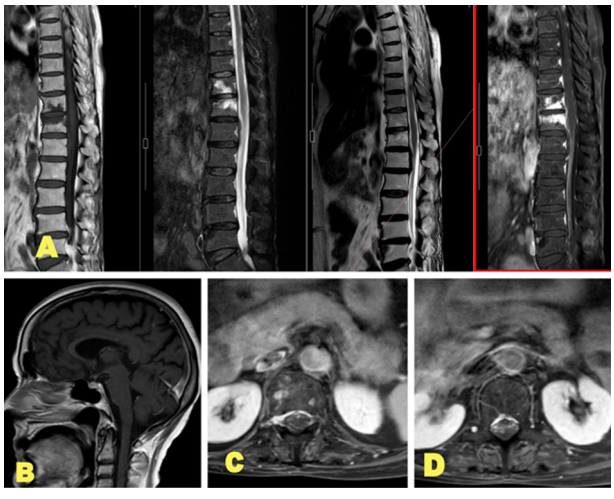



*Figure 10: 65 years, immunocompetent lady presented with gradually progressive weakness of extremities and gradually deteriorating sensorium with bowel and bladder incontinence.*

*A:T1/T2/STIR/T1+C Sagittal image of dorsolumbar spine showing marrow signal changes with enhancement at D11 & D12 vertebral bodies with small anterior subligamentous soft tissue suggesting Spondylodiscitis. Features of Arachnoiditis as evidenced in the post contrast sequences as B: minimal premedullary and prepontine meningeal enhancement, C&D: Diffuse meningeal enhancement with clumping of cauda equina nerve roots.*

single or multiple level, ascending or transverse radiculomyelopathy.[28] In the subacute form of the disease, although maximum severity is reached within 2–5 days, the condition then remains stationery and patients may present weeks after onset. Paralysis of the limbs tends to be severe and takes the form of upper or lower motor neuron or combined pattern weakness. Our case which has been illustrated in Figure 10 presented with gradually progressive weakness of more than a month duration with altered sensorium along with bowel and bladder involvement. It is not uncommon to find absent deep reflexes in the lower limbs with flaccidity, in the presence of extensor plantar responses and sensory loss for all modalities with a level on the trunk. Acute urinary retention can be a presenting feature, mimicking transverse myelitis when there is a certain sensory level over the trunk. Flaccid areflexic paralysis may imitate Guillain–Barre syndrome (GBS). Retention of urine, severe root pain and sensory loss are useful clinical clues to distinguish spinal TB meningitis from GBS.

## Diagnostic Approaches and Challenges

A clue to the diagnosis of neuro tuberculosis may be obtained from other extra-neural sites.

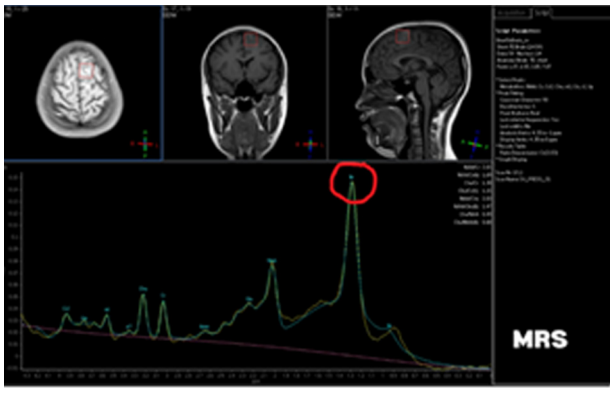



*Figure 11: 13 years girl, HIV negative status, presented with status epilepticus and found to have disseminated tuberculosis involving brain , lungs, abdomen and eye. Imaging of Brain showing T1/T2 hypointense nodules with adjacent vasogenic edema showing enhancement in post contrast imaging in the left high frontal lobe in the parasagittal location.*

*Corresponding* **MRS** *shows elevated lipid/lactate peak***.**

Evidence of lung involvement is seen in 40–52% patients and otomastoiditis is reported to be a frequent accompaniment of TBM. The presence of tuberculous spondylodiscitis, abdominal tuberculosis or pelvic tuberculosis also point to a diagnosis of CNS TB. The finding of choroid tubercles on fundoscopy indicates the presence of TB.

## Cerebrospinal Fluid Analysis

CSF analysis remains the cornerstone of tuberculous meningitis diagnosis, despite inherent limitations in sensitivity and specificity. Classical findings in CSF are Lymphocytic pleocytosis (100-500 cells/µL) with elevated protein (100-500 mg/dL) with low glucose (<45 mg/dL) with CSF to serum glucose ratio <0.5. However, polymorphonuclear leucocytes may predominate in the first ten days, and this is seen in 10–32% of cases which tends to be replaced subsequently by a lymphocytic predominance. There are rare cases of persistent neutrophilic meningitis. TBM patients with HIV co-infection are likely to have no CSF pleocytosis and lower CSF protein than HIV negative patients.

ADA levels in CSF though nonspecific as it is also elevated in other inflammatory conditions, represent a valuable diagnostic marker with threshold >10 U/L and sensitivity 95%, specificity 90%. Traditional microbiological methods demonstrate significant limitations as Acid-fast bacilli in CSF smear has very low yield with only 10-20% sensitivity and Mycobacterial culture in

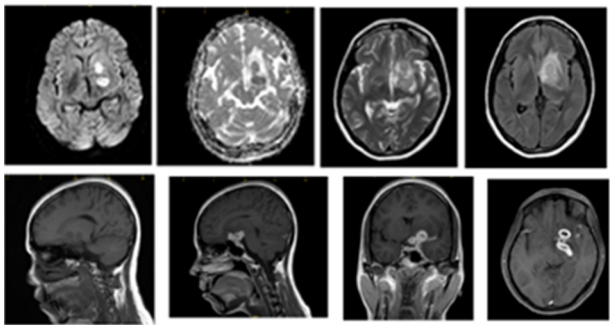


*Figure 12: Heterogeneously T2 Hypointense area with central T2 high signal showing perilesional edema and diffusion restriction in left basal ganglia. On Post contrast imaging this nodule shows ring enhancenment and the adjacent suprasellar cistern shows nodular meningeal enhancement .*

Lownstein Jensen (LJ) media has 25-70% sensitivity but requires 2-8 weeks with additional time for drug susceptibility testing. Newer systems, such as radiometric BACTEC and biphasic (Roche Septi–Chek) culture, improve the speed of mycobacterial recovery by 7–10 days.

The targets used in TB polymerase chain reaction (TB–PCR) technique are IS 6110 DNA sequence, 65 kDa gene and MPB64 gene. False-negative PCR results are not uncommon and are attributed to several factors, such as treatment effect on CSF, extremely low bacterial counts, the presence of inhibitory factors to PCR, small volume of tested CSF and the method of extraction of DNA, and therefore, its clinical utility is questionable.

Cartridge-based nucleic acid amplification test (CBNAAT), commercially available as GeneXpert test is a PCR-based method for detection of TB. It also detects rifampicin resistance as it targets the rpoB gene of mycobacteria.[29] It uses 1 ml CSF and can give a result in less than 2 hr. In 2010, WHO endorsed the GeneXpert technology and incorporated it into their programs, but a negative test does not rule out a diagnosis of TBM.A second generation GeneXpert test (Ultra) is also available that is relied on detection and amplification of a multicopy gene target with sensitivity of 95% in TBM cases. Ultra contains a larger reaction chamber than Xpert, with two additional different multicopy amplification targets.[30] Line probe assays (LPA) are based on PCR and reverse hybridization methods. LPA identify mutations associated with drug resistance within a week. Emerging metagenomic NGS platforms offer comprehensive pathogen detection with rapid identification of *M.*

*tuberculosis* with detection of resistance mutant and differentiate from other pathogens. CSF LAM (lipoarabinomannan) ELISA demonstrates particular utility in HIV-positive patients as it has enhanced sensitivity in immunocompromised hosts with rapid turnaround time and also has point-of-care potential.[31]

## Neuroimaging Findings

### Magnetic Resonance Imaging

MRI represents the optimal neuroimaging modality for TBM evaluation, the characteristic findings in MRI include basal meningeal enhancement, tuberculomas (ring-enhancing lesions), basal ganglia infarcts, hydrocephalus and brainstem involvement. The characteristic findings in MRI of various stages of tuberculoma has been tabulated in Table 4 and has been illustrated in the MRI head imaging Figures 5, 11 and 12. CT also is valuable in the evaluation especially when patient is very sick, in emergency situation and in situations where MRI is not available or is contraindicated as it helps to detect hydrocephalus, identify calcification pattern and identification of tuberculoma. MRI plays a crucial role in prognosticating patients with CNS tuberculosis. Presence of large, multiple lesions in eloquent locations, marked perilesional edema, hydrocephalus and infarcts are predictors of bad prognosis.

Magnetic resonance spectroscopy (MRS) shows elevated lipid peaks which resonate at 0.9 and 1.3 ppm due to fatty acids contained in the caseous material within the tuberculous lesions and helps to discriminate between tuberculous and non-tuberculous granulomas.

On diffusion-weighted imaging, TB abscesses appear hyperintense due to restricted diffusion. On MR perfusion imaging, the core of tuberculoma show low regional cerebral blood volume (rCBV) and the wall showed increased rCBV due to upregulated expression of vascular endothelial growth factor (VEGF), a measure of angiogenesis.[24,32]

At our hospital basic brain sequences are typically acquired, including post-contrast 3D FLAIR, postcontrast 3 D T1, and Proton MTI spectroscopy (PMRS) [Short TE (20–35 ms), 2D single voxel acquisition] for practical purposes. Additional sequences are obtained as necessary, with the entire process usually lasting 20–25 min. For spine imaging, sagittal images of the entire spine are obtained initially. If abnormalities are detected, a dedicated scan of the affected area is performed, taking approximately 45 min. A dedicated scan of

**Table 4: Different stages of Tuberculoma and their characteristic MRI finding**

| Tuberculoma Stage | T1 | T2 | FLAIR (Fluid-attenuated inversion recovery) | Diffusion-weighted imaging | SWI/GRE | T1 + Gadolinium |
|---|---|---|---|---|---|---|
| Noncaseous granuloma | Iso/hypointense | Hyperintense | No suppression | No restriction | No blooming | Homogenous enhancement |
| Caseous granuloma | Iso/hypointense with hyperintense peripheral ring | Hypointense | No suppression | No restriction | No blooming | Homogenous or ring like enhancement |
| Noncaseous granuloma with liquefied center | Iso/hypointense with hyperintense peripheral ring | Hyperintense peripheral ring with hyperintense center | Partial suppression of signal | Heterogenous hyperintensity | Subtle but complete peripheral blooming | Ring like enhancement |
| Calcified granuloma | Iso/hypointense | Hypointense | No suppression | No restriction | Blooming present | No enhancement |
| Tubercular brain abscess | Hypointense | Hyperintense with perilesional oedema and mass effect | No suppression | Diffusion restriction in center | No blooming | Well defined wall with ring enhancement |

the entire spine is conducted if there is suspicion of conditions such as tuberculous arachnoiditis, transverse myelitis, or spinal cord abscess, which typically takes about 1 h and 15 min. In suspected spine tuberculosis, the different sequences of whole spine include T1, T2- in axial, and sagittal planes, Short tau Inversion Recovery (STIR) sequence - in sagittal, and coronal planes and T1 fat-saturated pre- and post-contrast -in axial, sagittal, and coronal planes.

**Treatment Strategies and Management**

The antitubercular treatment currently administered for Tuberculous Meningitis (TBM) is largely adapted from pulmonary tuberculosis protocols and fails to address the unique clinical characteristics of TBM, which necessitate specialized therapeutic approaches.[33] Present regimens for TBM are not founded on TBM-specific clinical trials but rather on developments from pulmonary tuberculosis "short course" treatments. Unlike pulmonary tuberculosis where the primary objective is long-term cure with low mortality, TBM management must focus on reducing early mortality and mitigating long-term neurological damage. Crucial to TBM treatment is the use of antitubercular agents that can quickly reach therapeutic levels in the brain. While cerebrospinal fluid (CSF) drug concentrations are often measured, they do not accurately reflect drug penetration into brain tissue, which is vital for efficacy. Furthermore, there is limited pharmacometric data validating the current treatment regimens regarding drug choice, dosing, or duration specifically for TBM (Algorithm 1).

The evidence base supporting recommended antituberculosis chemotherapy regimens (i. e, drugs, doses, and durations) for patients with tuberculous meningitis is weak due to paucity of targeted studies addressing TBM. Recommendations for the treatment of patients with drug-susceptible tuberculous meningitis generally include four drugs (i.e. rifampicin, isoniazid, pyrazinamide, and ethambutol) at standard doses for at least 2 months, followed by rifampicin and isoniazid for a further 10 months as outlined in the Algorithm 2 of treatment of Tubercular management in both HIV positive and negative patients with TBM and also dose and duration mentioned in Table 5 .[34]

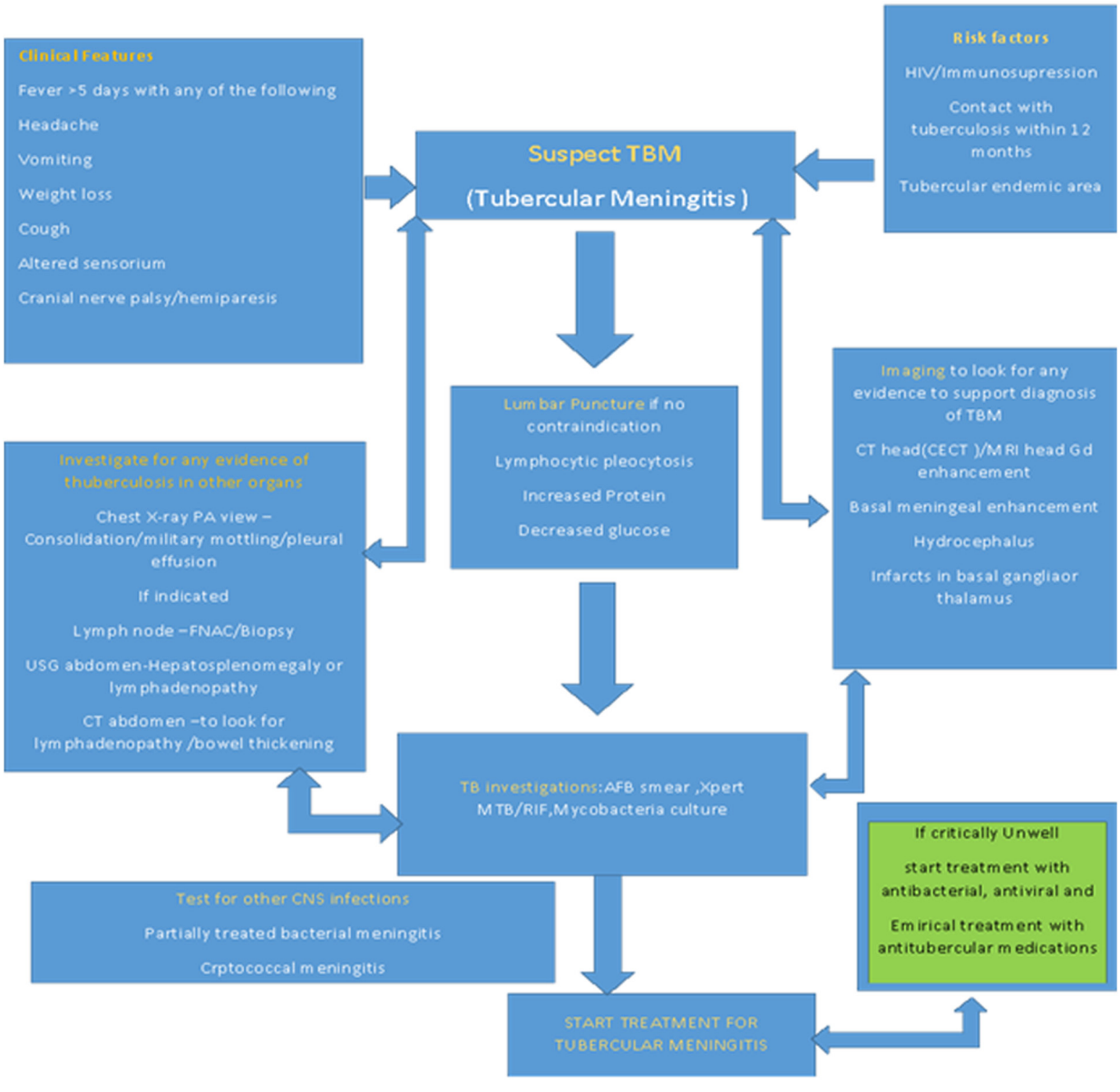
In August 2021, the WHO released a rapid communication proposing a 6-month intensified treatment regimen as a possible alternative to the traditional 12-month course for children and adolescents with tuberculous meningitis, despite limited supporting evidence from randomized controlled trials.[35]

Drug-resistant tuberculous meningitis remains challenging to diagnose, and the most effective treatment strategy has yet to be established. Isoniazid resistance is common (i.e. 20–30% of cases in some settings) and impairs treatment responses in patients with tuberculous meningitis, especially in individuals with HIV.[36] There is high mortality rate in patients suffering from Multidrug resistant-tuberculous meningitis owing to the absence of a standardised treatment approach and few drugs among the recommended that adequately penetrate the blood–brain barrier. CNS pharmacokinetic data on the new antituberculosis drugs delamanid, bedaquiline, and pretomanid are still not sufficient to draw a conclusion.[37]

A systematic review of nine randomised controlled trials, including 1337 participants, reported that adjunctive corticosteroids reduced deaths from tuberculous meningitis by almost a quarter (risk ratio 0·75, 95% CI 0·65–0·87) but had no effect on disabling neurological deficits.[38] The mechanism by which corticosteroids confer benefit, and their optimum starting dose or tapering regimen, are still unknown. It remains uncertain whether their therapeutic benefits are influenced by the LTA4H genotype and HIV status key questions currently being explored in two ongoing clinical trials.

Aspirin acts by irreversibly inhibiting the cyclo-oxygenase pathways of arachidonic acid metabolism and the production of prostanoids involved in inflammation and thrombosis.[12] Anti-inflammatory effects occur at high doses by inhibition of proinflammatory prostaglandins and by triggering the production of specialised proresolving mediators. A phase 2, placebo-controlled trial involving 120 HIV-negative adults with tuberculous meningitis indicated that high-dose aspirin (1000 mg/day) may help reduce the risk of brain infarctions and mortality.[39,40]

Immunomodulatory treatment with thalidomide (a TNF inhibitor) has been studied in animals and humans with tuberculous meningitis, with contrasting results.[41] Thalidomide has been prescribed safely at much lower doses (i.e. 3–5mg/kg/day) in 38 South African children with CNS tuberculosis-related complications. Thalidomide



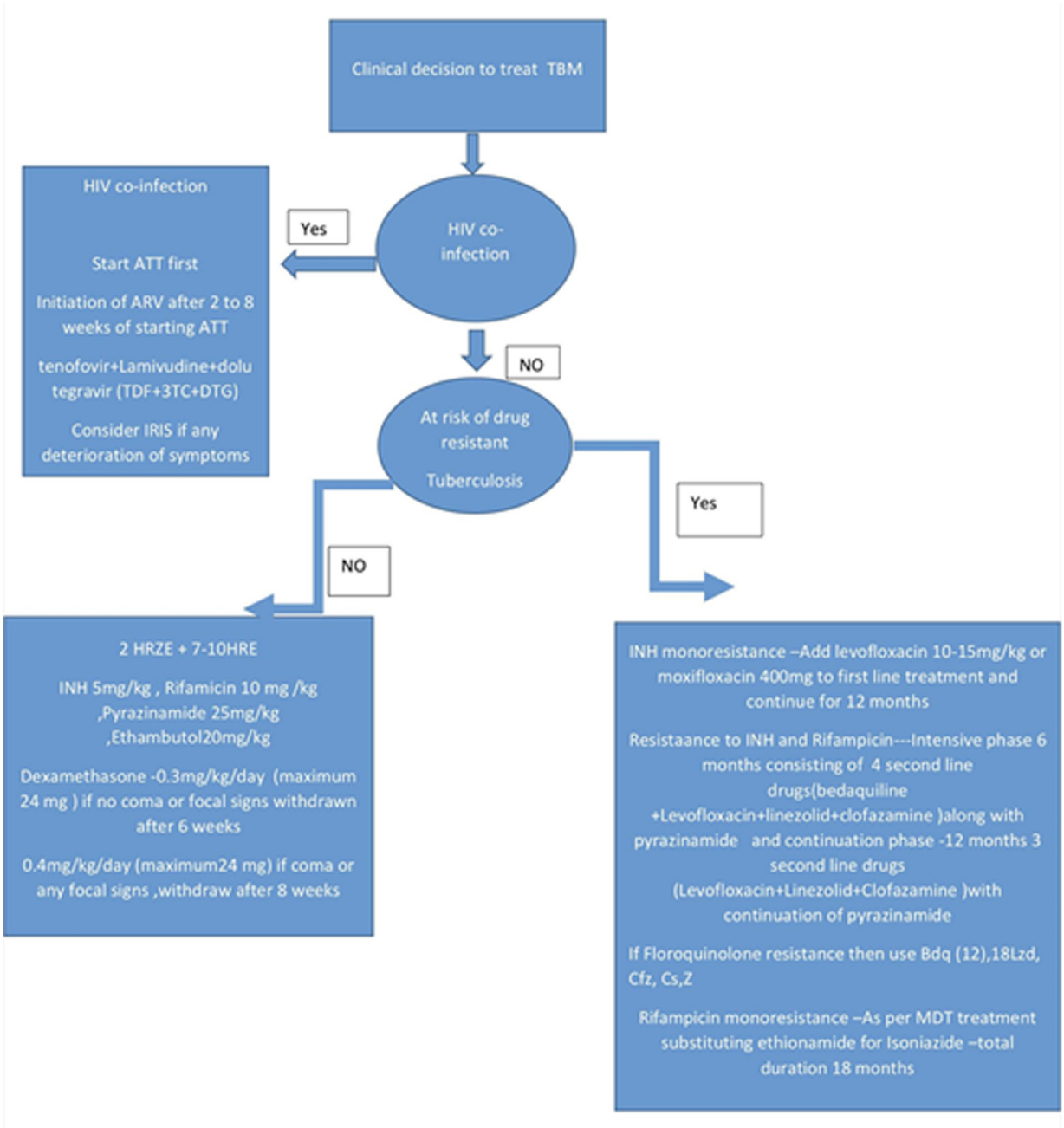

*Algorithm 1: Basic diagnostic workflow in a case of Tubercular Meningitis*

appeared to cause clinical and radiological improvement in 16 South African children with progressive tuberculosis cerebral pseudoabscesses and five English adults who had favourable outcomes.[42]

Infliximab, a potent tumour necrosis factor alpha (TNFα) inhibitor, was given to a patient of TBM with paradoxical reaction, with resolution of brain inflammation.[43]

Medical management is advocated in most cases of brain tuberculomas, and surgery is indicated only in patients who do not respond to drugs or have a rise of intracranial pressure. With 9 months treatment of tuberculomas, there was clinical subsidence in approximately 90% of patients and radiological clearance in 80%. The time taken for complete resolution of brain tuberculomas depends on the initial size, those smaller than 2.5 cm resolving entirely in 5–8 months and 50% of > 2.5 cm size resolving over 12 months.[24]

Patients undergoing antitubercular therapy (ATT) may experience a paradoxical reaction (PR), characterized by the emergence of new lesions or a worsening of existing symptoms despite initial clinical improvement as illustrated in Figure 4. This reaction is driven by a delayed-type immune response to Mycobacterium tuberculosis, leading to granuloma formation and elevated levels of TNF-α, a




*Algorithm 2: Treatment of Tubercular Meningitis in HIV positive and Naive patient with different resistance pattern*

key mediator in PR pathogenesis, often necessitating an increase in steroid dosage.[44] MTB isolated from the granuloma in case of PR is often drug sensitive. In TBM patients, paradoxical reactions (PR) may present with elevated CSF lymphocyte counts, neutrophil-predominant pleocytosis, or increased CSF protein levels, sometimes accompanied by a resurgence of basal exudates. PR can also manifest as the growth of existing tuberculomas or the emergence of new ones, typically occurring around four months into treatment. Hydrocephalus is a frequent complication of TBM, often necessitating interventions such as ventriculoperitoneal shunt placement or endoscopic third ventriculostomy. A systematic review and meta-analysis of ventriculoperitoneal shunt insertion in adults with HIV (including three studies and 75 patients) reported 12 months survival of only 33·3%.[45]

A systematic review and meta-analysis of endoscopic third ventriculostomy in patients with tuberculous meningitis (including eight studies and 174 patients) estimated that endoscopic third ventriculostomy had a 59% pooled success rate and a 15% complication rate.[46] How patients should be

**Table 5 (a, b & c): Antitubercular medications used in Tubercular meningitis**

**Table 5a: First-line Drugs for the Treatment of Drug-Sensitive TBM**

| Drug | WHO Recommended Daily Dose | WHO Recommended Duration | CSF Penetration (CSF/plasma concentration | Important Adverse Effects |
|---|---|---|---|---|
| Rifampicin | 10 mg/kg (8–12); max. 600 mg | 12 months | 10–20% | Hepatotoxicity, orange urine, many drug interactions |
| Isoniazid | 5 mg/kg (4–6); max. 300 mg | 12 months | 80–90% | Hepatotoxicity, peripheral neuropathy, lupus-like syndrome, confusion, seizures |
| Pyrazinamide(Z) | 25 mg/kg (20–30) | First 2 months | 90–100% | Hepatotoxicity, arthralgia, gout |
| Ethambutol | 15 mg/kg (15–20) | First 2 months | 20–30% | Dose-related retrobulbar neuritis, more common in renal impairment |
| Streptomycin | 15 mg/kg (12–18); max. 1 g | First 2 months | 10–20% | Monitor plasma concentrations when possible; causes nephrotoxicity and ototoxicity |

**Table 5b: Second-line Drugs for the Treatment of TBM**

| Drug | WHO Recommended Daily Dose | WHO Recommended Duration | CSF Penetration (CSF/plasma concentration | Important Adverse Effects |
|---|---|---|---|---|
| Levofloxacin | 10–15 mg/kg | Throughout treatment | 70–80% | Nausea, headache, tremor, confusion, tendon rupture (rare) |
| Moxifloxacin | 400 mg | Throughout treatment | 70–80% | Nausea, headache, tremor, confusion, tendon rupture (rare) |
| Amikacin | 15–30 mg/kg; max. 1 g IV or IM | Intensive phase only | 10–20% | Monitor plasma concentrations when possible; causes nephrotoxicity and ototoxicity |
| Kanamycin | 15–30 mg/kg; max. 1 g IV or IM | Intensive phase only | 10–20% | Monitor plasma concentrations when possible; causes nephrotoxicity and ototoxicity |
| Capreomycin | 15 mg/kg IV or IM | Intensive phase only | No data (probably very low) | Monitor plasma concentrations when possible; causes nephrotoxicity and ototoxicity |
| Ethionamide or prothionamide | 15–20 mg/kg; max. 1 g | Throughout treatment | 80–90% | Anorexia, nausea, vomiting, gynaecomastia, hypothyroidism, confusion, seizures |
| Cycloserine(Cs) | 10–15 mg/kg; max. 1 g | Throughout treatment | 80–90% | CNS toxicity: depression, seizures, neuropathy; co-administration with pyridoxine recommended |
| Linezolid(Lzd) | 600 mg | Throughout treatment | 30–70% | Myelosuppression, optic neuropathy; co-administration with pyridoxine recommended |

**Table 5c: Other Drugs Used to Treat MDR Tuberculosis (Uncertain Benefit in TBM)**

| Drug | WHO Recommended Daily Dose | WHO Recommended Duration | CSF Penetration (CSF/plasma concentration) | Important Adverse Effects |
|---|---|---|---|---|
| Clofazimine(Cfz) | 1 mg/kg<br>100 to 200 mg (Adult) | No recommended duration | Limited data (probably low) | Can discolour skin orange/red; photosensitivity |
| Para-aminosalicylic acid | 200–300 mg/kg<br>8-12 gm (Adult) | No recommended duration | No data (probably very low) | Vomiting, diarrhoea, reversible hypothyroidism (increased risk with ethionamide) |
| Bedaquiline (Bdq) | 400 mg for 2 weeks, then 200 mg thrice weekly | New drug | Probably very low (but data from one patient only) | Nausea, vomiting, arthralgia, QT prolongation; metabolized through CYP3A4; rifampicin halves concentrations |
| Delamanid | 200 mg | New drug | No data | Nausea, vomiting, dizziness rarely; QT prolongation |

selected for either procedure, the precise timing, and the benefit of surgical shunting are uncertain.

## Prognosis and Long-term Outcome

Meta-analyses on treatment outcomes in adults and pediatric tuberculous meningitis, which found that neurological disability was present in 32% of adult survivors but 54% of pediatric survivors. In these studies, the mortality rates were similar, 23% in adults and 19% in children, but adult deaths were influenced by HIV coinfection (57% in patients with coinfection vs 16% in patients without HIV infection). Outcomes appear to be worse in children aged <2 years and adults >60 years, and factors that commonly contribute to poor outcome across the lifespan include brain infarcts and proxy markers of severe disease (like hydrocephalus, focal neurology, Glasgow Coma Scale, and perturbations in CSF parameters). Cognitive impairment and epilepsy were seen in 12% and 11% of patients, respectively, on long-term follow-up.[47,48]

Various studies have shown a mortality range between 9.8 and 57% for TBM and Mortality at 6-month follow up was 17–20.7%. Predictors of mortality in adults were the stage of disease, age, duration of symptoms prior to admission, culture or PCR positive status, lower CSF lymphocyte count, elevated CSF protein, altered sensorium, leucocytosis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), hydrocephalus, delayed or interrupted treatment and resistance was associated with increased mortality, but the presence of tuberculoma in patients does not seem to affect the prognosis.[50]

## Conclusion

Tuberculous meningitis (TBM) remains a severe manifestation of tuberculosis, particularly affecting vulnerable groups such as children, individuals with HIV, and those in resource-limited settings. Despite advances in diagnostics, therapeutics, and understanding of disease mechanisms, TBM continues to cause significant mortality and long-term disability. Promising developments like GeneXpert Ultra, metagenomic sequencing, and newer antitubercular drugs such as bedaquiline and linezolid are steps forward, while the demonstrated benefit of adjunctive corticosteroids underscores the importance of evidence-based care.

Key challenges persist—most notably, the need for rapid, point-of-care diagnostics and shorter, more effective treatment regimens. Timely detection of drug-resistant TBM, along with emerging research in host-directed therapies and neuroprotection, may offer future breakthroughs. Translating scientific progress into practical solutions suitable for high-burden, low-resource settings must be a global priority.

Ultimately, addressing TBM requires sustained collaboration across research, clinical care, and policy. Early diagnosis, prompt and aggressive management, and equitable access to care remain central to reducing the burden of this devastating disease.

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