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Neuro-TB: The Battle between Tuberculosis and the Nervous System

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Review Article

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Abstract

Tubercular nervous system involvement, a serious manifestation of tuberculosis (TB), can occur through either direct or indirect mechanisms, leading to a wide range of neurological symptoms. Tuberculous meningitis (TBM) is the most common form, often presenting with progressive headaches, fever, altered mental status, and focal neurological deficits. Other forms of nervous system involvement include tuberculomas, which are localized granulomatous lesions that can cause focal deficits depending on their location in the brain or spinal cord. Diagnosis relies on clinical suspicion, cerebrospinal fluid analysis, neuroimaging, and microbiological culture, while management involves a combination of anti-tubercular therapy and sometimes surgical intervention. Early diagnosis and treatment are crucial to reduce morbidity and mortality associated with tubercular nervous system involvement. This review aims to explore the pathophysiology, clinical manifestations, diagnostic approaches, and treatment options for this serious complication of TB.

Keywords: Tubercular Nervous System Involvement; Tuberculous Meningitis; Tuberculomas; Pott's Spine; Tubercular Myelitis; Tubercular Neuritis; Neurological Manifestations; Tuberculosis; Cerebrospinal Fluid Analysis; Neuroimaging; Anti-Tubercular Therapy

Abbreviations

TB: Tuberculosis; CNS: Central Nervous System; PNS: Peripheral Nervous System; CSF: Cerebrospinal Fluid; ICP: Intracranial Pressure; PCR: Polymerase Chain Reaction; ETV: Endoscopic Third Ventriculostomy.

Introduction

Tuberculosis (TB) is a contagious disease primarily caused by the bacterium *Mycobacterium tuberculosis*. It most commonly affects the lungs, leading to pulmonary tuberculosis, but can also involve other parts of the body, including the brain, kidneys, and spine. TB spreads when an infected person coughs, sneezes, or talks, releasing airborne particles that can be inhaled by others. There are two main forms of the disease: latent TB and active TB. In latent TB, the bacteria are dormant and do not cause symptoms or spread, while active TB leads to symptoms such as persistent cough, chest pain, fatigue, weight loss, and night sweats. If untreated, active TB can be life-threatening. The disease remains a major global health concern despite being preventable and treatable, particularly in areas with high rates of poverty and limited access to healthcare resources [1,2].

Neurological manifestations of tuberculosis (TB) occur when *Mycobacterium tuberculosis* affects the central nervous system (CNS), leading to conditions such as tuberculous meningitis, intracranial tuberculomas, and spinal TB.

- **Tuberculous Meningitis:** This is the most common CNS complication of TB and typically presents with symptoms like headache, fever, neck stiffness, confusion, and neurological deficits. If untreated, it can result in severe complications such as coma or death [1].
- **Intracranial Tuberculomas:** These are localized masses of infected tissue in the brain, which can cause seizures, headaches, and focal neurological deficits, such as weakness or sensory loss [3].
- **Spinal Tuberculosis:** When TB affects the spine, it can lead to back pain, nerve compression, and even paralysis if the spinal cord is involved [3]. Early diagnosis and treatment are critical to managing these neurological manifestations and preventing long-term damage or death. Rare neurological manifestations of TB include conditions where the *Mycobacterium tuberculosis* infects parts of the nervous system outside the typical forms of tuberculous meningitis or intracranial tuberculomas. These include TB neuritis, and cranial nerve involvement.
- **TB Neuritis:** This involves inflammation of peripheral nerves, often causing symptoms like weakness, numbness, or paralysis. It may affect the optic nerve (optic neuritis) or other cranial and peripheral nerves, leading to vision problems or limb weakness [4].
- **Cranial Nerve Involvement:** TB can occasionally affect cranial nerves, leading to symptoms such as hearing loss, vision impairment, or facial muscle weakness due to nerve inflammation [5].

These rare manifestations require prompt diagnosis and treatment with anti-TB drugs and sometimes additional therapies to prevent long-term neurological damage [5].

Discussion

Mycobacterium tuberculosis is the causative agents of TB, a highly contagious bacterial infection that primarily affects the lungs but can involve other organs in the body. These bacteria are characterized by a number of distinctive features that allow them to survive and persist in the host for long periods, often leading to latent or active TB infection [1].

Mycobacterium tuberculosis is a slow-growing, aerobic, rod-shaped bacterium that is typically 0.2 to 0.5 micrometers in diameter and 1.0 to 4.0 micrometers in length. The bacterium has a thick, waxy cell wall, primarily composed of mycolic acids and lipoarabinomannan. This unique structure makes the bacteria highly resistant to many common disinfectants, and also protects them from being easily killed by the immune system, particularly by macrophages. It also contributes to the bacterium's ability to persist in a dormant (latent) state within the body for extended periods, a hallmark of TB infection [6].

Mycobacterium tuberculosis is transmitted primarily through airborne droplets when an infected person coughs, sneezes, or talks. These droplets can be inhaled by individuals in close proximity to the infected person, which is why TB is most commonly spread in crowded or poorly ventilated environments. Once inhaled, the bacilli reach the lungs, where they can infect the alveoli and be engulfed by alveolar macrophages. In the case of latent TB, the bacteria are contained within granulomas (clusters of immune cells), but in active TB, the bacteria multiply and cause tissue damage [1].

Mycobacterium tuberculosis is known for its ability to develop resistance to antibiotics, particularly when treatment is not completed as prescribed. The bacteria's slow growth rate, along with its ability to enter a dormant state, complicates treatment. Drug-resistant TB can occur due to mutations in the genes of the bacteria that affect their ability to metabolize or be killed by drugs. This includes multi-drug-resistant tuberculosis (MDR-TB), which is resistant to at least the two most potent TB drugs, isoniazid and rifampin, and extensively drug-resistant tuberculosis (XDR-TB), which is resistant to a wider range of drugs, making it much more difficult to treat [7].

When *M. tuberculosis* enters the lungs, it primarily infects the alveolar macrophages, which are part of the body's first line of defence. However, due to the mycolic acids and other components of the bacterial cell wall, the bacilli can survive within macrophages, evading the host's immune response.

The immune system reacts by surrounding the bacteria with a granuloma, a structure composed of immune cells, including macrophages, T lymphocytes, and fibroblasts. In latent TB, the bacteria remain contained in these granulomas without causing symptoms. However, if the immune system is weakened, such as in cases of HIV infection or malnutrition, the bacteria may become active, leading to tissue destruction and the characteristic symptoms of TB, such as chronic cough, weight loss, and fever [8].

Tuberculosis (TB) can spread to the central nervous system (CNS) and peripheral nervous system (PNS) through several mechanisms, resulting in a variety of neurological manifestations. The process generally involves hematogenous spread (via the bloodstream), direct extension from adjacent structures, or rarely, direct infection of nerves [8].

Spread to the Central Nervous System (CNS)

The Most Common Way TB Reaches the CNS is Through Hematogenous Dissemination. When *Mycobacterium Tuberculosis* Enters the Bloodstream, it can Spread Throughout the Body, Including to the Brain and Spinal Cord. This Can Occur in Several Ways:

- **Tuberculous Meningitis:** The most common form of CNS TB, tuberculous meningitis occurs when the bacteria infect the meninges, the protective membranes surrounding the brain and spinal cord. Once in the bloodstream, the bacteria invade the subarachnoid space, leading to inflammation of the meninges. This can result in symptoms such as fever, headache, neck stiffness, confusion, and in severe cases, coma or death if left untreated [4].
- **Cerebral Tuberculomas:** In some cases, TB bacteria can form localized granulomas in the brain, which are referred to as cerebral tuberculomas. These are masses of infected tissue that may cause focal neurological deficits, such as seizures, motor weakness, or sensory changes, depending on the area of the brain involved. The exact mechanism for the formation of tuberculomas is unclear, but it is thought to result from the body's immune response to the bacterial infection [9].
- **Spinal Tuberculosis (Pott's Disease):** TB can also spread to the spine, causing a condition known as Pott's disease. This occurs when M. tuberculosis infects the vertebrae and may extend to the spinal cord itself, leading to back pain, deformity, and potentially paralysis if the spinal cord becomes compressed. The bacteria reach the spine through the bloodstream, infecting the vertebrae and surrounding structures [10].

Spread to the Peripheral Nervous System (PNS)

TB can also affect the peripheral nervous system, although this is less common than CNS involvement. TB reaches the PNS through different mechanisms, such as direct infection of nerves or spread from adjacent tissues.

- **TB Neuritis:** TB can cause inflammation of peripheral nerves, referred to as TB neuritis. This can result from the direct spread of the infection to the nerves, leading to symptoms like pain, weakness, numbness, and even paralysis. One of the most commonly affected nerves is the optic nerve, leading to optic neuritis and, in severe cases, vision loss. Other cranial nerves or peripheral nerves may also be affected, depending on the site of infection [5].
- **Cranial Nerve Involvement:** TB can affect cranial nerves, especially the optic, facial, and vagus nerves. For example, in tuberculous optic neuritis, the infection affects the optic nerve, leading to vision impairment or blindness. Similarly, involvement of the facial nerve can cause facial paralysis. Although rare, these manifestations occur in cases of advanced or untreated TB, particularly in immunocompromised individuals [3].

Global Prevalence of Tuberculosis

World Health Organization (WHO) estimated that approximately 10.6 million people developed TB worldwide in 2022, and about 1.6 million people died from the disease that same year [11]. TB continues to be a leading cause of death globally, particularly in low- and middle-income countries [1].

The burden of TB is not evenly distributed across the world. The highest rates of TB are found in regions such as Southeast Asia, Sub-Saharan Africa, and the Western Pacific. India, China, Indonesia, the Philippines, Pakistan, and Nigeria together account for a substantial proportion of the global TB burden [8]. The continued high prevalence in these regions can be attributed to factors such as inadequate healthcare infrastructure, overcrowding, and socio-economic challenges like poverty and malnutrition [12].

In addition to the sheer number of TB cases, the emergence of drug-resistant forms of the disease, such as multi-drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), has compounded the problem. MDR-TB, which is resistant to at least two of the most powerful first-line drugs, poses a particularly serious challenge. In 2022, an estimated 450,000 people globally were diagnosed with rifa1mpicin-resistant TB, a key indicator of MDR-TB [12]. This is concerning because drug-resistant TB requires much longer and more complex treatment regimens, increasing both healthcare costs and the risk of poor patient outcomes [8].

The global TB response is guided by the WHO's End TB Strategy, which seeks to reduce TB deaths by 90% and cut TB incidence by 80% by 2030. This ambitious plan emphasizes universal access to care, improving the quality of diagnostics, increasing treatment regimens, and addressing the social determinants of health that contribute to TB transmission, such as poverty and malnutrition [11].

Prevalence of Tuberculosis in India

India has the highest TB burden in the world, accounting for approximately 27% of all global TB cases. According to the WHO Global TB Report 2023, an estimated 2.6 million people in India developed TB in 2022, making it the country with the largest number of cases [13]. India also faces a disproportionately high number of TB-related

deaths, contributing to about 23% of global TB mortality. This is primarily due to factors such as a large population, widespread poverty, and inconsistent access to quality healthcare services [1].

Several Factors Contribute to the High Prevalence of TB in India

- **Overcrowding and Poor Sanitation:** Overcrowding in urban slums and rural areas creates an environment conducive to the spread of TB. Poor sanitation and lack of access to clean water further exacerbate the situation, making it difficult to control the spread of the disease [14].
- **Malnutrition:** Malnutrition is a key factor that increases the risk of TB in India. Many individuals with compromised nutrition have weakened immune systems, which makes them more susceptible to TB infection. Additionally, malnutrition can slow recovery in individuals already infected with TB [15].
- **Co-infection with HIV:** India also faces a dual burden of TB and HIV. People living with HIV are more susceptible to TB due to their weakened immune systems. The coexistence of these two diseases makes diagnosis, treatment, and management even more complicated [16].
- **Drug Resistance:** India has a significant problem with drug-resistant TB, particularly MDR-TB. As of 2022, there were over 130,000 cases of MDR-TB in India [17]. Drug-resistant TB is harder and more expensive to treat, often requiring second-line drugs that are less effective and have more severe side effects [16,17].

Prevalence of CNS TB and PNS TB

The global burden of CNS TB is difficult to quantify precisely due to its relatively low incidence compared to pulmonary TB. CNS TB may represent approximately 5% of all TB cases globally. CNS TB primarily manifests as tuberculous meningitis, which accounts for about 70% of CNS TB cases, followed by tuberculomas and spinal TB. The incidence of CNS TB is particularly high in countries with a high burden of tuberculosis, such as India, sub-Saharan Africa, and Southeast Asia [18-20]. PNS tuberculosis is a rarer form of extrapulmonary TB. The prevalence of PNS TB is much lower than CNS TB. The prevalence of PNS TB is most commonly observed in countries with high TB burdens, particularly in sub-Saharan Africa, India, and Southeast Asia. However, PNS TB remains a rare complication, accounting for only a small percentage of all TB cases globally. Diagnostic challenges, such as the difficulty in distinguishing PNS TB from other causes of neuropathy, contribute to the relatively low detection rate. Also, due to the rarity of this form of TB, it is often underrecognized. The diagnosis may be delayed or missed and therefore exact prevalence is unkown [21].

Tuberculous Meningitis

Tuberculous meningitis (TBM) is a serious and often fatal form of TB that involves inflammation of the meninges due to infection with *Mycobacterium tuberculosis*. It is the most common form of CNS tuberculosis, accounting for about 70-80 % of CNS TB cases globally. TBM is a progressive life-threatening disease with high morbidity and mortality that can lead to irreversible neurological damage and complications. The disease is particularly common in regions with a high burden of tuberculosis, such as sub-Saharan Africa, Southeast Asia, and parts of India. Early diagnosis and prompt treatment are critical to improving outcomes, as delayed treatment can lead to significant neurological impairment and death [1].

Pathophysiology and Clinical Features

The pathogenesis of TBM begins when *M. tuberculosis* spreads from a primary pulmonary source or another extrapulmonary site (such as lymph nodes or bones) to the bloodstream, ultimately reaching the meninges. The inflammation caused by the bacteria leads to the accumulation of inflammatory cells, which further disrupt the blood-brain barrier and result in an altered environment within the CNS. This can increase intracranial pressure, impair cerebrospinal fluid (CSF) circulation, and cause a variety of neurological deficits and sequelae. TBM is most often seen in young children and young adults, immunocompromised individuals (especially those with HIV/AIDS), and individuals with poor access to healthcare or malnutrition [18]. The disease progresses in stages, with the initial stage being asymptomatic or presenting with mild nonspecific symptoms. The spread results in the formation of granulomas, which consist of infected macrophages, lymphocytes, and multinucleated giant cells. The granulomatous inflammation obstructs cerebrospinal fluid (CSF) flow and elevates intracranial pressure (ICP), leading to the clinical manifestations of the disease. The inflammation from TBM can also affect vascular structures, resulting in ischemic changes, including cerebral infarction. The disease process can lead to a cascade of secondary effects, such as brain edema, hydrocephalus, and damage to the cranial nerves, particularly the facial nerve (cranial nerve VII), which can result in facial paralysis [18].

The Clinical Presentation of TBM Can is Insidious and Often Mimics other Forms of Meningitis, Making Early Diagnosis Difficult. Symptoms Typically Develop Over 1 to 3 Weeks and Include:

- **Headache**: Often the first symptom that has a gradual onset, it is typically progressive and worsening as the

diseases progresses.

- **Fever**: Common in the early stages, often accompanied by chills, night sweats, malaise and weight loss.
- **Malaise**: Fatigue, weakness, and a general feeling of being unwell are common.
- **Neck Stiffness**: Albeit a classic sign of meningitis, it may not always be evident, particularly in the early stages.
- **Altered Mental Status**: Ranges from irritability and confusion to stupor and coma in severe cases.
- **Seizures**: Occur in about 10-30% of patients, particularly in children and those with more severe forms of the disease. They may be generalized or focal, often in patients with more severe forms of the disease.
- **Focal Neurological Deficits**: Such as cranial nerve palsies (especially cranial nerve VII, the facial nerve) and motor deficits present as disease progresses. Hydrocephalus and increased intracranial pressure (ICP) lead to further deterioration in mental status, and in the absence of treatment, these complications can result in death [18].

As the disease progresses, symptoms worsen, and neurological deficits may appear. If untreated, TBM can result in coma, persistent seizures, or death due to complications like increased intracranial pressure, cerebral edema, or infection spreading to other areas of the brain. The prognosis of TBM largely depends on the stage at diagnosis and the promptness of treatment initiation. In children and immunocompromised individuals, TBM tends to present more acutely and with more severe outcomes due to delayed diagnosis and treatment [18].

Diagnosis

Diagnosing TBM is challenging due to the nonspecific nature of the symptoms. The disease can be misdiagnosed as viral or bacterial meningitis. Besides, it is difficult to identify *M. tuberculosis* in the CSF. However, advances in diagnostic methods have significantly improved detection rates [21].

Cerebrospinal Fluid (CSF) Findings

CSF Analysis is Crucial for Diagnosing TBM. Typical Findings Include:

- **Pleocytosis**: An elevated white blood cell (WBC) count, typically with a predominance of lymphocytes. The total WBC count is usually in the range of 100 to 500 cells/µL but can sometimes be higher in more severe cases.
- **Hypoglycorrhachia**: Low glucose levels in the CSF are a hallmark of TBM. In TBM, the glucose concentration is often less than 40 mg/dL, which is significantly lower than the normal range of 50-80 mg/dL.
- **Elevated Protein Levels**: CSF protein levels are typically elevated in TBM, often greater than 100 mg/dL, but they can reach even higher levels in advanced disease. The normal range is 20-45 mg/dL. This elevation reflects the inflammatory response [21]. However, these findings are not entirely specific to TBM, and the definitive diagnosis usually requires **microbiological confirmation.**
- **Positive Ziehl-Neelsen Stain**: Acid-fast bacilli (AFB) may be seen in the CSF under microscopy using a Ziehl-Neelsen stain, though this test is positive in only a small percentage of cases (approximately 20-30%).
- **Positive PCR for *M. Tuberculosis*:** Polymerase chain reaction (PCR) testing has significantly improved the speed and sensitivity of diagnosing TBM, with sensitivity rates ranging from 60-90%. PCR detects M. tuberculosis DNA in the CSF and provides a much quicker result compared to traditional methods.
- **CSF Culture**: Culture of the CSF on solid media remains the gold standard for diagnosis but is time-consuming, often requiring up to 6 weeks for results. However, it is highly specific and can provide information on drug resistance [22].

Recent Advancements in Diagnostic Technology Have Significantly Improved the Ability to Detect TBM:

- **Gene Xpert MTB/RIF**: This PCR-based test can detect M. tuberculosis DNA and rifampicin resistance in CSF, providing results within hours. It has greatly enhanced the speed and sensitivity of TBM diagnosis, especially in low-resource settings.
- **Lateral Flow Urine Antigen Assays**: These are non-invasive tests that detect M. tuberculosis antigens in urine, which may be helpful in diagnosing TBM in certain contexts.
- **Multiplex PCR**: Multiplex PCR techniques that simultaneously detect various pathogens, including M. tuberculosis, are emerging as valuable tools for diagnosing TBM, particularly in cases where there is co-infection with other pathogens [23,24]. In some settings, Magnetic Resonance Imaging (MRI) of the brain is often performed in patients with suspected TBM. It can reveal characteristic signs such as:
- **Basal Meningeal Enhancement**: This is one of the most common findings in TBM, indicating inflammation of the meninges at the base of the brain.
- **Hydrocephalus**: Increased fluid accumulation in the brain can be seen, either communicating (increased CSF volume) or obstructive (blockage of CSF flow).
- **Tuberculomas**: Focal granulomatous masses, which may be seen as ring-enhancing lesions, can be present in the parenchyma of the brain [25].

Stages of Tuberculous Meningitis

The grading system for TBM is primarily used to assess the disease based on clinical, radiological, and cerebrospinal

fluid (CSF) findings, as well as the patient's neurological status. The most commonly used grading system is the Banjara or Prasad classification.

The clinical course of TBM is divided into four stages, which reflect the progression of the disease:

- **Stage 1 (Prodromal or Initial stage)**: It is the earliest stage. This stage lasts for about 1 to 2 weeks and is characterized by nonspecific symptoms such as headache, fever, and malaise. At this stage, patients generally do not exhibit significant neurological deficits. Early recognition is difficult due to the nonspecific nature of these symptoms. Early signs of meningitis, like neck stiffness, may begin to develop but are not always present. CSF findings: White blood cells (WBC): 100–500 cells/μL (mainly lymphocytes); Glucose: Low (typically < 40 mg/dL); Protein: Elevated (typically > 100 mg/dL). At this stage, the disease can easily be mistaken for other viral or bacterial infections. Grade I TBM is often responsive to treatment when identified early. With appropriate anti-tubercular therapy and corticosteroids, most patients can recover without significant long-term sequelae [26].
- **Stage 2 (Meningeal Stage)**: It is a more advanced stage of the disease. This stage typically lasts for 1 to 2 weeks and involves more severe symptoms (headache, fever, vomiting) and signs such as neck stiffness, photophobia, and altered mental status (confusion and irritability). CSF findings show elevated WBC: 500–1,000 cells/μL (lymphocytic pleocytosis); Glucose is very low (< 30 mg/dL) and protein is significantly elevated (> 100 mg/dL). At this stage, if untreated, patients may develop cranial nerve palsies, including facial nerve palsy. early initiation of therapy is crucial to prevent progression to more severe stages. Corticosteroid therapy is often included to manage inflammation, and patients may require interventions such as ventriculoperitoneal (VP) shunting or external ventricular drainage if hydrocephalus develops [26].
- **Stage 3 (Severe Stage)**: It is a more severe and advanced stage of the disease, often marked by life-threatening complications. Lasting up to 3 weeks, this stage is marked by severe complications such as increased intracranial pressure, coma, seizures, and hydrocephalus (with markedly elevated intracranial pressure). There may be significant neurological deficits (focal neurological deficits and cranial nerve palsies), and the patient's condition may deteriorate rapidly without intervention. CSF findings show elevated WBC: 1,000–5,000 cells/μL (predominantly lymphocytes), very low glucose (< 30 mg/dL) and markedly elevated protein (> 200 mg/dL). Patients in this stage are at high risk of death or severe disability if treatment is delayed. Imaging studies, particularly MRI, are crucial in this stage, revealing significant meningeal enhancement, widespread brain edema, and the development of hydrocephalus. Cerebral infarctions due to vascular compromise may also be noted, along with evidence of significant basal meningeal inflammation. In this stage, prompt treatment is crucial for improving survival. The combination of anti-tubercular therapy, corticosteroids, and management of complications such as hydrocephalus or seizures is critical to reducing mortality and preventing severe neurological sequelae [26].
- **Stage 4 (Chronic Stage)**: It the most severe stage of the disease. This stage occurs after several weeks or months and is associated with permanent neurological sequelae, such as persistent cognitive dysfunction, motor deficits, and cranial nerve damage. The long-term prognosis depends on the severity of the disease and the timeliness of intervention. It is associated with severe neurological damage and poor prognosis. Patients at this stage may present with profound coma or deep stupor, complete loss of consciousness, significant multiorgan failure, brain herniation (caused by raised intracranial pressure), severe cerebral edema, widespread infarctions in the brain. In some cases, death can occur due to complications such as raised intracranial pressure, brain herniation, or septic shock. CSF findings can show very high WBC (5,000–10,000 cells/μL, or more), very low glucose: Extremely low (< 10 mg/dL), and significantly elevated protein (> 500 mg/dL). Imaging studies may show widespread brain damage, including multiple cerebral infarctions, hydrocephalus, and severe meningeal enhancement. At this stage, the role of therapy is primarily supportive, and the prognosis is poor, with a high likelihood of death or irreversible neurological disability [26].

Several Factors Influence the Progression to Higher Grades of TBM, Including

- **Delayed Diagnosis:** The longer the delay in initiating treatment, the more likely the disease is to progress to severe stages.
- **Immune Status:** Immunocompromised individuals, such as those with HIV, are at a higher risk of severe disease and complications.
- **Age:** Children and the elderly are more susceptible to developing severe TBM and its complications.
- **Treatment Adherence:** Failure to adhere to the prescribed anti-tubercular regimen or corticosteroid therapy can lead to worse outcomes [26].

Treatment

The Treatment of TBM Requires a Combination of Anti-Tubercular Drugs and Supportive Care. The Standard Regimen Typically Involves:

First-Line Anti-Tubercular Drugs

- Isoniazid
- Rifampicin
- Pyrazinamide
- Ethambutol [27]

These drugs are given for an extended duration (9-12 months) to ensure complete eradication of the bacterium and to prevent relapse. In patients with MDR-TB, second-line drugs such as **levofloxacin**, **moxifloxacin**, and **capreomycin** may be used [27].

The role of **corticosteroids** is crucial in the management of TBM. Dexamethasone treatment significantly improves survival and neurological outcomes in TBM patients. Steroids, typically **dexamethasone**, are given to reduce inflammation and prevent damage caused by the immune response. They help mitigate complications like hydrocephalus, cerebral edema, and alleviate raised intracranial pressure which can lead to permanent brain damage [27].

The use of **corticosteroids**, particularly **dexamethasone**, plays a critical role in the treatment of TBM. Corticosteroids help reduce the inflammatory response within the brain and decrease the risk of complications such as

- **Cerebral Edema**: Steroids reduce swelling in the brain, which can lead to improved neurological outcomes.
- **Hydrocephalus**: By reducing inflammation and decreasing CSF production, corticosteroids can help prevent or alleviate hydrocephalus, a common complication in TBM.
- **Cranial Nerve Damage**: The inflammation in the meninges can lead to cranial nerve damage, and steroids can help minimize this risk [27].
- **Reduce Inflammation**: By modulating the immune response and reducing granulomatous inflammation, corticosteroids can prevent damage to the brain parenchyma and reduce the risk of ischemic injury [18,28,29]. Steroids are typically initiated at the start of anti-tubercular treatment and are gradually tapered over a period of 4 to 6 weeks. Several studies have shown that steroid treatment can significantly reduce mortality and improve neurological outcomes in TBM patients, especially when administered early in the disease process and in high-risk populations such as children and immunocompromised individuals [18,22]. TBM can lead to several severe complications, many of which can result in permanent neurological impairment.
- **Hydrocephalus**: This is one of the most common complications of TBM, resulting from the obstruction of CSF flow due to inflammation of the meninges. Hydrocephalus can lead to elevated intracranial pressure, brain herniation, and death. Increased CSF accumulation can cause significant brain damage and requires interventions like **ventriculoperitoneal shunt** placement or external ventricular drainage [29].
- **Cerebral Infarctions**: Inflammation of the blood vessels in the brain can lead to the formation of blood clots, resulting in ischemic strokes. These infarctions can cause focal neurological deficits, including hemiparesis and cognitive impairment and focal neurological deficits. Patients with ischemic strokes may require anticoagulant therapy, though this must be carefully managed to avoid hemorrhagic complications. In some cases, surgical intervention may be needed to relieve vascular obstruction [29].
- **Cranial Nerve Palsies**: Especially involving the facial nerve (cranial nerve VII), which may result in facial weakness or paralysis. Other cranial nerves, including the oculomotor and abducens nerves, can also be involved, causing diplopia and other visual disturbances. Physical therapy and rehabilitation can help improve outcomes in patients with facial nerve paralysis or other cranial nerve deficits [29].
- **Seizures**: Seizures occur in 10-30% of TBM patients, particularly in those with severe disease or associated brain infarctions. Seizure management may include the use of **antiepileptic drugs (AEDs)**. . Common AEDs include **levetiracetam**, **valproate**, and **phenytoin** [29].
- **Cognitive Deficits**: Persistent cognitive deficits, including impaired memory, concentration, learning difficulties, and intellectual disability, are common in patients who survive TBM. These deficits can significantly impact a patient's quality of life, particularly in children [29].

In addition to pharmacological treatment, patients may require intensive monitoring in a hospital setting, particularly in the initial stages of treatment [29].

Prognosis and Outcome

The prognosis for TBM is variable, depending on several factors, including the patient's age, immune status, comorbidities, and the promptness of diagnosis and treatment. When treated early, the survival rate can be high, and many patients make a full recovery. However, delayed treatment or diagnosis often results in severe complications such as neurological deficits, intellectual disability, and death. The case-fatality rate for TBM remains significant, particularly in low-resource settings where access to healthcare is limited. In these settings, delayed diagnosis and inadequate treatment contribute to poor outcomes, including a **high rate of neurological impairment** in survivors [30].

Challenges in Management

Despite the Availability of Effective Treatments, Managing TBM Remains Challenging Due to the Following Factors:

- **Diagnostic Delays**: TBM's nonspecific symptoms and

the difficulty in obtaining microbiological confirmation delay diagnosis in many cases. In resource-limited settings, diagnostic facilities may be insufficient, which further delays treatment.

- **Drug Resistance**: Multi-drug-resistant TB (MDR-TB) is an emerging problem in TBM, and when it occurs, treatment becomes more complex and the prognosis worse. MDR-TB in TBM requires the use of second-line anti-tubercular drugs, which are less effective and have more severe side effects [5].
- **Co-Infection with HIV**: In areas with a high prevalence of HIV, the incidence of TBM is higher, and patients with both TBM and HIV are at increased risk of treatment failure and death. HIV compromises the immune response, making it harder to control the TB infection [31].

Tuberculoma

Tuberculoma is a granulomatous lesion caused by *Mycobacterium tuberculosis* in the CNS, most commonly affecting the brain but occasionally involving the spinal cord. It typically occurs as a result of hematogenous spread from pulmonary tuberculosis or the reactivation of latent tuberculosis. Tuberculomas are part of the spectrum of CNS TB, which is an important and often devastating manifestation of extrapulmonary tuberculosis [1].

Pathophysiology of Tuberculoma

The development of tuberculomas follows the hematogenous spread of *M. tuberculosis* to the CNS. This is often due to the reactivation of latent TB, particularly in immunocompromised individuals. The bacteria enter the bloodstream, then localize to the brain parenchyma where they form granulomas.

These granulomas consist of macrophages, T lymphocytes, and multinucleated giant cells, which work to contain the infection. Over time, the central area of the granuloma undergoes caseous necrosis, creating a necrotic core surrounded by inflammatory tissue. Eventually, fibrotic changes occur, and calcium deposits may lead to the characteristic calcification of tuberculomas detectable via neuroimaging [32,33].

The immunologic process behind tuberculoma formation is complex, involving the body's innate and adaptive immune responses. *M. tuberculosis* can evade the immune system in the early stages, but as the infection persists, granulomas form as an attempt to contain and control the bacteria. This process leads to tissue damage and necrosis, contributing to neurological symptoms and complications if not properly managed [32].

Stages of Tuberculoma

The Progression of Tuberculoma can be Classified into Four Stages:

- **Primary Infection**: *M. tuberculosis* enters the bloodstream after the initial pulmonary infection and can disseminate to the CNS. At this stage, the infection might remain subclinical, with no immediate symptoms.
- **Granuloma Formation**: The immune system responds to the infection by forming granulomas. These collections of immune cells attempt to isolate the pathogen. The granuloma is a hallmark of tuberculosis and can be observed using advanced imaging techniques.
- **Necrosis and Caseation**: Central necrosis develops within the granuloma, leading to caseous necrosis, where the tissue takes on a cheese-like appearance. This stage is crucial as the necrotic tissue provides an environment for bacterial survival and potential proliferation.
- **Fibrosis and Calcification**: The final stage involves the formation of a fibrotic capsule around the tuberculoma. This fibrosis helps to control the spread of infection. Calcium deposition in the necrotic core may occur, leading to calcification that can be observed on CT or MRI scans [33]. Although tuberculomas can theoretically affect any part of the central nervous system, they are most commonly found in the brain parenchyma, especially in the cerebral hemispheres, basal ganglia, and cerebellum. The following locations are particularly noteworthy.
- **Cerebral Hemispheres:** This is the most common site for tuberculomas, particularly in the frontal and parietal lobes. Lesions in this region can cause focal neurological deficits, such as hemiparesis or aphasia, depending on their size and location.
- **Basal Ganglia:** Tuberculomas in the basal ganglia are often associated with movement disorders like tremors or rigidity and can cause significant cognitive impairments.
- **Cerebellum:** Lesions in the cerebellum can present with ataxia, dysmetria, and other coordination difficulties.
- **Spinal Cord:** Though rarer, tuberculomas can also involve the spinal cord, causing symptoms such as motor weakness, sensory deficits, and in severe cases, paralysis [34].

The locations of the lesions contribute to the clinical presentation of tuberculomas, which can range from nonspecific symptoms like headache to focal neurological deficits and seizures.

Clinical Presentation of Tuberculoma

The Clinical Presentation of Tuberculoma is Highly Variable, Depending on Factors Such as Lesion Size, Number, and Location. Common Symptoms Include:

- **Seizures**: These are among the most common manifestations, occurring due to the irritative effects of

the tuberculoma on the surrounding brain tissue. Focal seizures are especially common.

- **Headaches**: Due to increased intracranial pressure (ICP) from the growing lesion or surrounding edema, headaches are frequent in tuberculoma patients.
- **Focal Neurological Deficits**: Depending on the location of the lesion, patients may experience motor deficits (hemiparesis), speech difficulties (aphasia), or sensory changes.
- **Systemic Symptoms**: Fever, weight loss, night sweats, and malaise may also occur, particularly in the early stages of infection, resembling the systemic symptoms of active pulmonary tuberculosis.
- **Cognitive Decline**: In cases where the tuberculoma involves areas responsible for higher cognitive functions, patients may experience memory loss, confusion, and changes in personality.
- **Signs of Raised Intracranial Pressure:** Vomiting, papilledema, and altered consciousness can occur if the tuberculoma causes significant swelling or obstructs cerebrospinal fluid (CSF) flow [34].

Tuberculomas are Often Classified into Stages, Reflecting the Extent of Disease Progression and Clinical Severity:

- **Stage I (Early Stage):** At this stage, patients may present with mild symptoms such as headache and low-grade fever, without significant neurological deficits. Imaging findings may show small, well-defined lesions with little or no surrounding edema.
- **Stage II (Progressive Stage):** The disease progresses with worsening symptoms, including focal neurological signs, seizures, and more pronounced radiological findings such as increasing size of the tuberculoma and surrounding edema. CSF analysis typically shows moderate pleocytosis, low glucose, and elevated protein.
- **Stage III (Severe Stage):** By this stage, patients may develop significant mass effect, leading to increased intracranial pressure, coma, or focal neurological deficits. Severe complications such as hydrocephalus and cerebral herniation may occur.
- **Stage IV (Chronic Stage):** This stage is associated with the resolution of active infection but often leaves behind permanent neurological damage due to scarring or brain atrophy. The lesions may calcify, as observed on imaging [34].

Diagnosis of Tuberculoma

Neuroimaging

Neuroimaging is crucial in diagnosing tuberculomas. Both **MRI** and **CT** scans are valuable tools, though MRI is preferred due to its superior resolution and ability to detect early inflammatory changes.\

- **MRI**: Tuberculomas on MRI typically appear as well-defined, ring-enhancing lesions with surrounding edema. The central core of the lesion may be hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging. Contrast enhancement is used to identify the granulomatous tissue surrounding the necrotic core.
- **CT**: In chronic cases, calcification within the tuberculoma may be evident, often appearing as a well-defined hypodense mass with a ring of enhancement. Calcified tuberculomas are especially visible on non-contrast CT scans [35]. Advances in imaging technology, such as **functional MRI** and **stereotactic navigation systems**, have improved the precision of tuberculoma surgery, allowing for less invasive procedures with better outcomes [35].

Cerebrospinal Fluid (CSF) Findings

CSF Analysis Plays a Pivotal Role in Diagnosing Tuberculomas, Particularly in the Context of Suspected CNS TB. Typical Findings Include:

- **Pleocytosis**: CSF white blood cell (WBC) count is usually elevated, with a predominance of lymphocytes. Counts may range from 10 to 200 cells/μL, reflecting the inflammatory response in the CNS.
- **Elevated Protein**: CSF protein levels are often elevated (greater than 1 g/L), which reflects the disruption of the blood-brain barrier and the inflammatory response.
- **Low Glucose**: A classic finding in CNS tuberculosis, glucose levels in the CSF are often reduced, typically less than 40 mg/dL, as the bacteria and inflammatory cells consume glucose.
- **Positive AFB Smear or Culture**: The presence of acid-fast bacilli (AFB) in CSF is diagnostic, though cultures or PCR tests for *M. tuberculosis* are often necessary for confirmation due to the paucibacillary nature of CNS TB (3). In many cases, CSF cultures for *M. tuberculosis* may be negative due to the localized nature of the infection. However, PCR-based methods can sometimes provide more rapid and accurate diagnosis.
- **Polymerase Chain Reaction (PCR):** PCR testing for *M. tuberculosis* DNA has become increasingly valuable in diagnosing tuberculomas, especially when cultures are negative or unavailable. PCR can detect the bacteria more rapidly than traditional culture methods.
- **Biopsy and Histopathology:** In some cases, a biopsy of the lesion may be necessary to confirm the diagnosis, particularly when imaging findings are ambiguous. Histopathology typically reveals the characteristic granulomatous inflammation seen in tuberculosis [35].

CSF Can is Normal in Many Cases. The Treatment of Tuberculoma Involves a Combination of Anti-Tubercular

Therapy and, When Indicated, Surgical Intervention. The Cornerstone of Treatment is Anti-Tubercular Chemotherapy, Which Typically Includes:

- **Isoniazid (INH):** A first-line drug for treating TB.
- **Rifampin (RIF):** Another first-line anti-tubercular drug.
- **Pyrazinamide (PZA):** Often used in the initial phase of treatment.
- **Ethambutol (EMB):** Used to treat multidrug-resistant strains or in the initial phase [35]

Corticosteroids, especially **dexamethasone**, are used as adjunctive therapy in the management of tuberculomas, particularly to control the inflammatory response and prevent or reduce complications related to cerebral edema. Steroids help to decrease the surrounding inflammation and alleviate symptoms such as headaches and seizures. Corticosteroids also play a critical role in the surgical management of tuberculomas, particularly in controlling inflammation, minimizing the risk of brain edema before and after surgery, and enhancing recovery [18,29,35].

However, their use is carefully balanced because steroids can suppress the immune response and potentially worsen the underlying tuberculosis infection. The American Academy of Neurology (AAN) suggests steroids be introduced in patients with significant peri-lesional edema or in those with large lesions causing a mass effect. The typical regimen involves starting with a high dose of corticosteroids, followed by a tapering dose over several weeks [36].

Complications of Tuberculoma

Tuberculomas can lead to several serious complications, including:

- **Hydrocephalus**: The tuberculoma or the associated inflammatory response can obstruct the CSF pathways, leading to hydrocephalus. This can cause increased ICP, leading to further neurological deterioration necessitating surgical intervention such as ventriculoperitoneal shunting or external ventricular drainage.
- **Raised Intracranial Pressure:** As the tuberculoma enlarges, it can cause significant mass effect, leading to increased intracranial pressure. This can manifest as headache, vomiting, altered consciousness, and, in severe cases, cerebral herniation.
- **Seizures**: Seizures are a common complication of tuberculomas, particularly focal seizures. They are usually treated with antiepileptic drugs (AEDs), but in some cases, surgical intervention may be needed.
- **Neurological Deficits**: Direct compression of surrounding brain tissue by the tuberculoma can result in focal neurological deficits, such as hemiparesis, visual disturbances, and aphasia.
- **Cerebral Edema**: Inflammation surrounding the tuberculoma can lead to significant cerebral edema, increasing ICP and causing neurological deterioration, sometimes leading to herniation.
- **Cerebral Infarction:** Larger tuberculomas may cause vascular compromise, leading to cerebral infarction, which may worsen neurological deficits.
- **Persistent Cognitive Dysfunction:** Even after successful treatment of the infection, patients may experience long-term cognitive impairment, particularly if the tuberculoma was large or in an area of the brain responsible for higher functions.
- **Spinal Cord Tuberculomas**: Though less common, tuberculomas can also affect the spinal cord, leading to motor and sensory deficits. In severe cases, this may result in paraplegia or quadriplegia [37].

Surgical Management

In cases of large tuberculomas or those causing significant neurological deficits or mass effect, surgery may be required. Surgical intervention may be considered in the following situations:

- **Mass Effect or Raised Intracranial Pressure**: When a tuberculoma causes significant swelling or mass effect, leading to raised intracranial pressure (ICP), surgery may be necessary. This is particularly true in cases where the patient exhibits signs of life-threatening increased ICP, such as altered consciousness, vomiting, and papilledema, which are not adequately managed by medical therapy alone.
- **Intractable Seizures**: If seizures persist despite adequate anti-tubercular treatment and antiepileptic medications, surgical removal of the tuberculoma may be needed to control the seizures, especially in cases with large or accessible lesions that are deemed to be the focus of seizure activity.
- **Progressive Neurological Deficits**: In cases where the tuberculoma is causing significant neurological deficits (e.g., hemiparesis, aphasia, or cranial nerve palsies) that do not improve with medical treatment, surgery may be indicated.
- **Hydrocephalus**: If a tuberculoma leads to obstructive hydrocephalus, surgical interventions such as ventriculoperitoneal shunting may be necessary to alleviate the buildup of cerebrospinal fluid (CSF) and prevent further complications.
- **Failure of Medical Treatment**: In rare cases where the tuberculoma does not respond to medical therapy or where drug resistance is suspected, surgery may be required for tissue biopsy and definitive treatment.
- **Cerebral Infarction**: In cases where the tuberculoma leads to cerebral infarction due to compression of major blood vessels, surgical removal of the mass may be necessary to prevent further ischemic damage [38].

The type of surgical procedure chosen depends on the location and size of the tuberculoma, as well as the patient's general health. Common surgical approaches include:

Craniotomy and Lesion Removal

In cases where the tuberculoma is located in accessible areas of the brain, such as the cerebral hemispheres, a **craniotomy** may be performed to surgically remove the lesion. During this procedure, a portion of the skull is temporarily removed to allow access to the brain. The surgeon carefully excises the tuberculoma, making sure to minimize damage to surrounding brain tissue. **Microsurgical techniques** may be employed to ensure precise removal while preserving critical brain structures. Craniotomy is most commonly indicated for large, accessible, and symptomatic tuberculomas that are not amenable to medical treatment alone.

Endoscopic or Minimally Invasive Surgery

Endoscopic procedures have gained popularity for certain tuberculomas, particularly those located in deep or difficult-to-reach areas, such as the basal ganglia or brainstem. Endoscopy allows for less invasive approaches with smaller incisions, leading to quicker recovery and fewer complications compared to traditional craniotomy. **Endoscopic third ventriculostomy (ETV)** can also be performed if the tuberculoma is associated with hydrocephalus. This procedure creates an alternative pathway for CSF to flow, bypassing the obstructed ventricles, and may be combined with the excision of the tuberculoma.

Ventriculoperitoneal Shunt

If a tuberculoma causes obstructive hydrocephalus and surgery to remove the lesion is not immediately feasible, a **ventriculoperitoneal (VP) shunt** may be placed to divert excess CSF from the ventricles into the peritoneal cavity. This procedure can help relieve ICP and prevent brain damage while awaiting resolution of the tuberculoma with medical therapy.

Biopsy for Diagnosis

In cases where the diagnosis of tuberculoma is unclear and other possible diagnoses need to be ruled out, a **biopsy** may be performed. A biopsy can help confirm the presence of *Mycobacterium tuberculosis* and ensure appropriate treatment. This is usually done if the lesion's clinical or radiological features are ambiguous or if other causes of the mass, such as brain tumors or abscesses, are suspected.

Stereotactic Surgery

For deep-seated lesions, stereotactic surgery may be used to access and excise the tuberculoma. This technique allows for precise localization of the lesion and minimizes damage to surrounding tissue [39].

Postoperatively, patients who undergo surgery for tuberculoma require close monitoring to manage complications and optimize recovery. This may include:

- **Anti-tubercular Therapy**: After surgery, patients should continue with anti-tubercular drugs to ensure the complete resolution of the infection. This may include a combination of **isoniazid**, **rifampin**, **ethambutol**, and **pyrazinamide**, depending on drug sensitivity.
- **Seizure Management**: If the patient experiences postoperative seizures, antiepileptic drugs (AEDs) such as **levetiracetam** or **valproic acid** may be prescribed to prevent further episodes.
- **Monitoring for Hydrocephalus**: Patients who have undergone surgery for tuberculoma should be monitored for signs of hydrocephalus. In some cases, a VP shunt may need to be placed or adjusted to manage CSF flow.
- **Neurological Rehabilitation**: Following surgery, patients may benefit from neurological rehabilitation to improve cognitive function, speech, and motor abilities, especially if the tuberculoma has caused significant neurological deficits [38].

The outcomes of surgical treatment for tuberculomas can vary, depending on the location and size of the lesion, the patient's general health, and the presence of any comorbidities. Complications can arise from surgery, including:

- **Infection**: As with any surgical procedure, there is a risk of postoperative infection, which can be particularly concerning in the case of tuberculomas, as the surrounding tissue may still harbor M. tuberculosis.
- **Neurological Damage**: Surgical excision of a tuberculoma may lead to unintended damage to nearby brain structures, potentially resulting in new neurological deficits or worsening of preexisting ones.
- **Cerebral Edema**: After removal of a tuberculoma, there is a risk of cerebral edema (swelling of the brain) as part of the inflammatory response. This can exacerbate neurological symptoms and, in severe cases, may require additional medical interventions such as corticosteroids or osmotic diuretics.
- **Hydrocephalus**: Although shunting may help alleviate hydrocephalus, there is still a risk that the patient may develop persistent or recurrent hydrocephalus, requiring further surgical interventions.
- **Recurrence of Tuberculoma**: Although rare, there is a possibility that tuberculomas may recur after surgical removal if the underlying tuberculosis infection is not adequately treated or if the patient is immunocompromised [38].

Differential Diagnosis

Tuberculomas need to be differentiated from other conditions that present as space-occupying lesions in the brain. These include:

- **Brain Tumors**: Gliomas, meningiomas, and metastatic lesions can mimic the appearance of tuberculomas on neuroimaging. A detailed clinical history, biopsy, and histopathological examination are crucial for differentiating these lesions.
- **Abscesses**: Brain abscesses often present similarly to tuberculomas, with ring-enhancing lesions on imaging. However, abscesses usually have a more fluid-filled central core. They are typically associated with a history of infection elsewhere in the body and may present with a more acute course. Abscesses often have a more diffuse ring-enhancing appearance on MRI.
- **Neurocysticercosis**: This parasitic infection can cause granulomatous lesions that resemble tuberculomas, especially in endemic areas. Neurocysticerccosis can also cause seizures and focal neurological deficits. Imaging studies, such as CT scans, help in distinguishing between the two.
- **Multiple Sclerosis**: In some rare instances, lesions in MS may mimic the ring-enhancing appearance of tuberculomas, although they usually lack the associated inflammatory changes seen in tuberculosis [39].
- **Fungal Infections**: Fungal infections like cryptococcosis or histoplasmosis can also cause granulomatous lesions in the CNS, requiring differentiation based on culture and serological tests [40].

Spinal Tuberculosis

Spinal tuberculosis (TB), also known as Pott's disease, is a condition caused by *Mycobacterium tuberculosis* that affects the vertebrae and can lead to significant neurological impairment if left untreated. The disease typically affects the thoracic and lumbar spine and can lead to spinal deformities, pain, and neurological deficits [40].

Pathophysiology of Spinal Tuberculosis

The primary cause of spinal tuberculosis is *M. tuberculosis*. When the bacterium spreads to the spine, it often affects the intervertebral discs and adjacent vertebrae, leading to osteomyelitis and discitis. The progression of infection results in vertebral collapse, kyphosis, and potential involvement of the spinal cord and nerves.

The pathogenesis of spinal TB is primarily hematogenous, with the bacilli reaching the vertebral column through the bloodstream, usually after primary pulmonary infection [40].

The process starts with the formation of granulomatous lesions in the bone, and eventually, these may lead to the formation of abscesses and destruction of the vertebral bodies. The disease typically progresses through four stages: the initial infection stage, the vertebral collapse stage, the abscess stage, and the neurological impairment stage (if untreated or inadequately treated) [40].

Stages of Spinal TB

Spinal tuberculosis progresses in several stages, and its clinical manifestations vary depending on the stage of disease.

The stages include:

- **Initial Infection:** The bacteria initially infect the bone marrow or disc space, often without significant symptoms.
- **Vertebral Collapse:** As the infection destroys the vertebrae, spinal deformities, such as kyphosis, may occur. Pain and inflammation become more prominent at this stage.
- **Abscess Formation:** The infection spreads to surrounding tissues, forming paravertebral or epidural abscesses, which can compress nearby nerve roots or the spinal cord itself.
- **Neurological Impairment:** This stage, also known as "spinal cord involvement," results from direct pressure from abscesses or bone fragments, leading to potential paralysis or other neurological deficits [41].

Clinical Features

The clinical presentation of spinal tuberculosis can be highly variable, but common symptoms include:

- **Back Pain:** This is often the most prominent symptom, typically worsening at night. It may be localized or diffuse.
- **Neurological Deficits:** These can include weakness, sensory loss, or bladder/bowel dysfunction if the spinal cord or nerves are compressed.
- **Deformity:** As the vertebrae collapse, a characteristic "gibbus" deformity (a sharp, angular kyphosis) may develop.
- **Systemic Symptoms:** Fever, night sweats, weight loss, and fatigue, which are typical of tuberculosis infections in general [42].

TB Myelitis and Spinal Tuberculoma

TB myelitis is a form of spinal tuberculosis in which the spinal cord itself becomes infected. This can occur due to direct extension from the vertebral bodies or through hematogenous spread. The infection leads to inflammation of the spinal cord, which can result in motor and sensory deficits depending on the location of the involvement [43].

A spinal tuberculoma is a localized mass of tuberculous infection within the spinal canal, usually in the epidural or subdural spaces. These lesions can cause significant compression of the spinal cord and its nerve roots, leading to neurological symptoms. Tuberculomas are typically seen in advanced stages of the disease when abscess formation occurs [43].

Diagnostic Approaches

The diagnosis of spinal tuberculosis is based on a combination of clinical features, imaging, and microbiological testing.

- **Clinical Assessment:** A detailed history and physical examination are crucial, particularly in identifying systemic signs of tuberculosis.
- **Radiological Imaging:**

X-ray: Initial imaging typically shows vertebral collapse, disc space narrowing, and evidence of paravertebral abscesses.
MRI: MRI is the gold standard for imaging spinal tuberculosis, providing detailed information on the extent of vertebral destruction, abscess formation, and spinal cord involvement. It is highly sensitive in detecting spinal TB, particularly with contrast administration.
CT scan: In some cases, a CT scan may be used to assess bony changes and guide surgical planning [44].

- **Microbiological Diagnosis**

CSF analysis: In cases of TB myelitis or spinal tuberculoma, cerebrospinal fluid (CSF) analysis is crucial.

- **The CSF findings typically include:**

Pleocytosis: The white blood cell count is usually elevated, often with a predominance of lymphocytes.
Low Glucose Levels: The glucose concentration in the CSF is typically reduced due to bacterial consumption.
Elevated Protein: The protein concentration is often elevated in TB myelitis and spinal tuberculoma due to the inflammatory response.
Positive Acid-Fast Bacilli (AFB) Staining or Culture: The identification of M. tuberculosis in CSF by PCR or culture confirms the diagnosis.
PCR and Culture: Polymerase chain reaction (PCR) can detect the DNA of M. tuberculosis in CSF, and culture remains the gold standard for diagnosis, though it may take several weeks [45].

Recent developments in molecular diagnostics, particularly PCR-based techniques, have significantly improved the detection of spinal tuberculosis. These methods can identify *M. tuberculosis* DNA in CSF, biopsy, or tissue samples more quickly than traditional culture methods. Furthermore, the introduction of liquid culture systems has improved the yield and speed of culture-based diagnostics [46].

Treatment of Spinal Tuberculosis

The treatment of spinal tuberculosis typically involves a combination of medical therapy and, in some cases, surgical intervention.

Anti-tuberculosis therapy

Standard treatment includes a 6-month regimen of first-line anti-tuberculosis drugs: rifampin, isoniazid, pyrazinamide, and ethambutol. In some cases, treatment may need to be extended to 12 months, especially in the case of drug-resistant tuberculosis.

Drug resistance should be suspected if there is a poor response to treatment, and drug susceptibility testing is essential in such cases [47].

Steroid Therapy

Corticosteroids, such as prednisolone, are often used in conjunction with anti-tuberculosis drugs to reduce inflammation and prevent neurological complications. Steroids are particularly helpful in cases where spinal cord compression or significant inflammation is present, such as in TB myelitis or spinal tuberculomas.

The use of steroids, however, is controversial in some settings and should be carefully monitored due to potential side effects, including immunosuppression and risk of secondary infections [47].

Surgical Management

Surgery is indicated in cases where there is neurological deterioration due to spinal cord compression, severe deformity, or a large abscess. Procedures may include decompression of the spinal cord, abscess drainage, and spinal fusion to stabilize the spine after vertebral destruction.

The surgical approach depends on the location of the disease and the severity of neurological involvement. In some cases, minimally invasive techniques such as endoscopic or percutaneous procedures may be used [48].

Complications and Their Management

- **Neurological Complications:** These include paraplegia, quadriplegia, and sensory deficits, which occur due to direct compression of the spinal cord or nerve roots by infected tissues or abscesses. Immediate treatment with corticosteroids and surgical decompression is often required to prevent permanent neurological damage.
- **Spinal Deformity:** Kyphosis and scoliosis can result from vertebral destruction. Early diagnosis and treatment can prevent the progression of deformity, but in severe cases, corrective surgery may be necessary.

- **Abscess Formation:** Paravertebral and epidural abscesses can lead to pressure on the spinal cord or nerves. These abscesses may require surgical drainage if they cause significant compression or do not respond to medical treatment [49].

Differential Diagnosis

Several conditions must be considered in the differential diagnosis of spinal tuberculosis:

- **Pyogenic Spinal Infections:** These may present with similar clinical features but are typically associated with more acute onset and higher fever.
- **Vertebral Metastasis:** Tumors, such as those from lung, breast, or prostate cancer, can also affect the spine, but they usually present with a different pattern of symptoms and imaging findings.
- **Brucellosis:** This zoonotic infection can cause spinal osteomyelitis and discitis, with a similar clinical presentation to tuberculosis [50].

Peripheral Nervous System Tuberculosis (PNS TB) and Cranial Nerve Tuberculosis (CN TB)

Tuberculosis of the peripheral nervous system (PNS TB) and cranial nerve tuberculosis (CN TB) are rarer manifestations of the disease, but they present unique challenges for diagnosis and treatment. Both forms of TB are associated with high morbidity due to their often insidious onset and the complexity of their management. Peripheral nerve involvement is less frequent but is still an important manifestation, particularly in immunocompromised individuals or in regions with high TB endemicity [51,52].

PNS TB results from the hematogenous spread of MTB or direct extension from contiguous structures. Similarly, cranial nerve TB typically arises from direct extension of TB from the paranasal sinuses, middle ear, or other adjacent structures. *Mycobacterium tuberculosis* can invade the nerves either via the bloodstream or lymphatics, producing localized inflammation that may result in neurological deficits [53].

Pathology and Locations The pathology of PNS TB is characterized by the formation of granulomas, which are the hallmark of TB infection. The most common site of involvement in PNS TB is the brachial plexus, followed by the lumbar and cervical nerve roots. The involvement of the cranial nerves, especially the second, third, fifth, seventh, and eighth cranial nerves, is a well-documented feature of CN TB typically due to extension from adjacent structures like the paranasal sinuses or the temporal bone. Histopathological examination of affected tissues shows caseating granulomas, which are indicative of active tuberculosis infection. The TB bacilli may invade the nerve sheath or directly infect the nerve, leading to a range of symptoms depending on the nerve involved [54,55]

Clinical Features of PNS and CN TB PNS TB can present with a variety of neurological symptoms, depending on the specific nerve involvement. Symptoms may include motor weakness, sensory loss, and pain. The early manifestations are often nonspecific, which can delay diagnosis. If the brachial plexus is affected, patients may present with pain, weakness, and sensory deficits in the upper limb. Involvement of the lumbar or cervical roots can lead to radicular pain and motor deficits in the corresponding limbs [56].

In CN TB, the symptoms are more variable, depending on which cranial nerve is involved. Optic nerve involvement: This may lead to optic neuritis, resulting in visual disturbances and potentially blindness. Facial nerve involvement: Patients may present with facial weakness or paralysis, often resembling Bell's palsy but with the addition of systemic TB symptoms. Cochleovestibular nerve involvement: Patients may report hearing loss or vertigo due to TB infection of the eighth cranial nerve [56].

Stages and Complications the progression of both PNS TB and CN TB can be divided into various stages:

- **Initial Infection:** The Mycobacterium tuberculosis bacilli initially infect the nerve or adjacent structures.
- **Granulomatous Inflammation:** This stage is characterized by the formation of granulomas and tissue destruction. Symptoms begin to appear as the inflammation affects nerve function.
- **Chronic Inflammation and Fibrosis:** Over time, the inflammation can lead to chronic damage to the affected nerve, potentially resulting in permanent neurological deficits [57].

The Complications of PNS TB and CN TB Can be Severe, Including:

- **Chronic Pain:** Nerve involvement often leads to persistent pain, which can be difficult to manage.
- **Motor Deficits:** Weakness or paralysis in the affected muscles can significantly impair function.
- **Sensory Deficits:** Loss of sensation may be associated with nerve damage.
- **Permanent Blindness or Deafness:** If the optic or cochlear nerves are involved, permanent loss of vision or hearing may occur.
- **Infection Spread:** In rare cases, TB can spread to the CNS, leading to meningeal TB or tuberculomas, with associated neurological impairment [58].

CSF Findings The diagnosis of TB in the nervous system often involves the analysis of cerebrospinal fluid

(CSF). CSF findings in both PNS TB and CN TB are typically consistent with an infectious and inflammatory process. Common CSF abnormalities in TB include:

- **Pleocytosis:** Elevated white blood cell count, often with a predominance of lymphocytes.
- **Low Glucose Levels:** The glucose concentration is typically lower than 40 mg/dL, as the TB bacilli consume glucose.
- **Elevated Protein Levels:** Protein concentrations are often elevated in TB meningitis or tuberculomas, with levels typically ranging from 100 to 500 mg/dL.
- **Positive acid-fast bacillus (AFB) smear or PCR:** The detection of Mycobacterium tuberculosis through PCR or AFB smear is confirmatory in many cases [59].

Historically, the diagnosis of TB in the peripheral nervous system and cranial nerves relied on clinical suspicion and the identification of *Mycobacterium tuberculosis* in tissue samples, either through culture or AFB staining. However, newer diagnostic techniques, such as nucleic acid amplification tests (NAAT), including PCR-based methods, have improved the ability to detect TB more rapidly and accurately. PCR for *Mycobacterium tuberculosis* DNA can be performed on CSF, biopsy samples, or aspirates from affected nerves, providing a quicker and more reliable diagnosis than conventional culture methods [60].

Treatment of Complications the treatment of PNS and CN TB involves both antitubercular therapy and supportive care. The standard regimen for TB includes a combination of first-line antitubercular drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol. Treatment usually lasts for 6-9 months, with the first two months involving all four drugs, followed by isoniazid and rifampicin for the remainder of the treatment. In cases with severe complications, such as TB meningitis or extensive cranial nerve involvement, treatment may need to be extended. Steroids play a key role in the management of PNS and CN TB. They are primarily used to control inflammation and reduce the risk of nerve damage. In cases of TB meningitis or TB with significant cranial nerve involvement, corticosteroids such as dexamethasone are administered to reduce the inflammatory response, alleviate symptoms, and prevent complications [59,61].

Complications such as nerve damage or persistent neurological deficits are managed through physical therapy, pain management, and in some cases, surgery. In cases of vision or hearing loss, cochlear implants or prosthetic devices may be considered [62].

Differential Diagnosis The differential diagnosis of PNS and CN TB is broad and includes other causes of neurological deficits such as:

- **Leprosy:** Leprosy can cause similar sensory and motor deficits, but typically affects the distal nerves and is not associated with systemic tuberculosis.
- **Syphilitic Neuropathy:** Neurosyphilis can mimic TB with similar neurological involvement, including cranial nerve palsies.
- **Sarcoidosis:** This condition can also lead to granulomatous inflammation of the peripheral nerves and cranial nerves.
- **Neoplasms:** Malignant tumors affecting the brain, cranial nerves, or peripheral nerves may present similarly to TB, especially in the case of cranial nerve palsies [63,64].

Antitubercular Therapy

Antitubercular therapy consists of several regimens, classified into first-line, second-line, and extended ATT. The goal of treatment is to completely eradicate *Mycobacterium tuberculosis* while minimizing the risk of resistance development and limiting side effects, particularly those affecting the nervous system [65].

First-Line ATT

The World Health Organization (WHO) recommends a standard four-drug regimen for the treatment of drug-sensitive TB, which includes Rifampicin (RIF), Isoniazid (INH), Pyrazinamide (PZA), and Ethambutol (ETH). These drugs are effective in targeting various aspects of the M. tuberculosis life cycle [65,66].

- **Rifampicin (RIF)**: A potent bactericidal agent, Rifampicin inhibits bacterial RNA synthesis by binding to DNA-dependent RNA polymerase. It is used as a cornerstone in the treatment of TB due to its efficacy and bactericidal properties. Rifampicin is known to cross the blood-brain barrier, making it effective in treating TB meningitis and other CNS involvement [67].
- **Isoniazid (INH)**: Isoniazid acts by inhibiting the synthesis of mycolic acids in the bacterial cell wall, leading to bacterial cell death. It is another key component in the first-line regimen, often administered in combination with Rifampicin [68].
- **Pyrazinamide (PZA)**: PZA is particularly effective in acidic environments, such as those found within granulomas, and it contributes to the sterilization of latent infection [69].
- **Ethambutol (ETH)**: Ethambutol inhibits the synthesis of the bacterial cell wall by targeting arabinosyl transferase. It is used primarily to prevent the emergence of drug resistance [70].

These drugs are generally well-tolerated, although they are not without side effects, particularly in the context of long-term use [71].

Second-Line ATT

Second-line drugs are typically used when first-line therapy fails, either due to drug resistance or intolerable side effects. The second-line drugs are less potent, more expensive, and often come with more severe side effects. The second-line treatment regimen includes:

- **Fluoroquinolones**: Drugs such as Levofloxacin and Moxifloxacin are commonly used, acting as bactericidal agents by inhibiting DNA gyrase [72].
- **Injectables**: Kanamycin, Amikacin, and Capreomycin are examples of injectable agents that are reserved for multidrug-resistant (MDR) TB. These are used due to their potent bactericidal action but are associated with significant side effects, including nephrotoxicity and ototoxicity [73].
- **Other Oral Agents**: Ethionamide, Para-aminosalicylic acid (PAS), and Clofazimine are used for more resistant forms of TB, and they may cause significant gastrointestinal and neurological side effects [74].

Second-line ATT regimens are usually more toxic, and the duration of treatment is longer than first-line regimens, potentially increasing the risk of adverse outcomes, including neurological complications [75].

Extended ATT

In cases of extensively drug-resistant tuberculosis (XDR-TB), a more prolonged and intensive regimen is necessary. This includes the use of drugs not typically included in first-line or second-line therapies, such as Linezolid and Bedaquiline. The extended treatment regimens may last up to 24 months, depending on the severity and resistance profile of the infection. Extended ATT regimens carry even higher risks of side effects, especially neurotoxicity, due to the prolonged use of multiple potent agents [76].

Neurological Complications of ATT

Antitubercular therapy, particularly in its extended form, is associated with a variety of neurological complications. These may result from the toxicities of the medications themselves or from the direct impact of TB infection on the CNS [77].

Peripheral Neuropathy

Peripheral neuropathy is a well-known side effect of Isoniazid (INH), which inhibits vitamin B6 (pyridoxine) metabolism. Deficiency in pyridoxine leads to nerve damage, particularly affecting the sensory and motor nerves in the limbs. This neuropathy manifests as numbness, tingling, and pain, primarily in the hands and feet. Prophylactic administration of pyridoxine has been shown to reduce the incidence of INH-induced neuropathy [77].

Optic Neuritis and Retrobulbar Neuritis

Ethambutol (ETH) is particularly associated with optic neuritis, a condition that can lead to visual disturbances and even permanent vision loss if left untreated. The mechanism is thought to involve the inhibition of myelin synthesis in the optic nerve. The risk of optic neuritis increases with higher doses and prolonged use of Ethambutol. Regular monitoring of visual acuity is recommended during treatment with this drug [78].

Encephalopathy and Cognitive Dysfunction

Rifampicin and other antitubercular drugs, such as Pyrazinamide, can cross the blood-brain barrier and affect the CNS. Rarely, these drugs can cause encephalopathy, which presents as confusion, delirium, and cognitive dysfunction. The mechanism is not entirely understood but may involve drug-induced metabolic changes, direct neurotoxicity, or interactions with other medications [79].

Seizures

Seizures may occur as a result of Rifampicin's interaction with the central nervous system. Although rare, it has been reported that Rifampicin can lower the seizure threshold, particularly in individuals with a history of neurological disorders or when used in combination with other antiepileptic medications [80].

TB Meningitis and Related Complications

In TB meningitis, the central nervous system is directly affected by the mycobacterial infection, which leads to inflammation of the meninges. Neurological symptoms include headache, fever, nausea, and altered mental status. The treatment of TB meningitis requires an aggressive ATT regimen that can involve the use of first-line drugs like Rifampicin, INH, and Pyrazinamide, often combined with corticosteroids. While the medications are generally effective in reducing the bacterial load, the inflammatory process may cause permanent neurological damage if not treated early enough [81].

Drug-Induced Parkinsonism

Parkinsonism has been reported in patients receiving prolonged therapy with Ethionamide and other second-line agents. The exact cause is not fully understood but is thought to be related to dopaminergic dysfunction induced by the drugs. Symptoms include tremors, rigidity, and bradykinesia, which can mimic Parkinson's disease [82].

Management of Neurological Complications

The management of neurological complications requires a multidisciplinary approach involving neurologists,

infectious disease specialists, and pharmacologists. The primary strategies include:

- **Early detection and monitoring**: Regular monitoring of neurological function, including visual acuity and sensory and motor function, is essential to detect complications early and modify treatment regimens if necessary [83].
- **Adjunctive therapies**: For cases of peripheral neuropathy, vitamin B6 supplementation is effective. In cases of optic neuritis, dose reduction or discontinuation of Ethambutol may be necessary [84].
- **Corticosteroids**: In cases of TB meningitis or encephalopathy, corticosteroids may be used to reduce inflammation and improve outcomes. However, the potential for drug interactions and side effects must be carefully considered [85].
- **Modification of ATT regimens**: If a neurological complication is deemed related to a specific drug, substitution or discontinuation may be required, especially in the case of second-line or extended ATT [86,87].

Conclusion

Tubercular diseases of the nervous system (TDNS), though relatively rare in developed countries, remain a significant health concern in regions with high tuberculosis burden. These diseases, which include tuberculous meningitis, spinal TB, and tuberculomas, present unique diagnostic and therapeutic challenges. Early detection is critical to prevent irreversible neurological damage and improve patient outcomes. Despite advances in imagings and molecular diagnostics, the insidious onset of symptoms often leads to delays in diagnosis, contributing to high morbidity and mortality. The management of TDNS primarily involves a combination of anti-tubercular therapy and supportive measures, with corticosteroids playing a crucial role in preventing inflammation-related damage. However, drug-resistant TB and complications from prolonged treatment remain obstacles to effective management. Research into novel diagnostic tools, more effective treatment regimens, and the pathophysiology of TDNS is essential for improving patient care. Continued vigilance, particularly in high-risk populations, is necessary to reduce the burden of these devastating diseases.

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