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IP Indian Journal of Neurosciences

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Review Article

CNS tuberculosis meningitis-Short review

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ARTICLE INFO

Article history:
Received 24-08-2024
Accepted 16-09-2024
Available online 03-10-2024

Keywords:
CNS tuberculosis meningitis
Mycobacterium tuberculosis
Antitubercular therapy
Cerebrospinal fluid analysis
HIV CoInfection

ABSTRACT

Central Nervous System (CNS) tuberculosis (TB) meningitis, a severe extrapulmonary manifestation of TB, poses significant diagnostic and therapeutic challenges due to its high morbidity and mortality rates, especially in immunocompromised individuals such as those with HIV. The pathogenesis involves hematogenous dissemination of Mycobacterium tuberculosis from a primary infection site, often the lungs, leading to invasion of the central nervous system. This process triggers a robust immune response characterized by neuroinflammation, cerebral edema, and vasculitis, ultimately causing neurological damage. Genetic factors, such as LTA4H polymorphisms, also influence the severity of inflammation and patient outcomes. CNS TB is disproportionately prevalent in regions where TB and HIV are endemic, notably in sub-Saharan Africa and Southeast Asia. Recent data from 2024 show that HIV-positive individuals are particularly vulnerable, with CNS TB accounting for up to 10% of all TB cases in this population. In India, where TB-HIV co-infections are common, diagnostic delays and limited access to advanced molecular diagnostics exacerbate the disease burden. In a clinical setting, patients may exhibit general symptoms like headache, fever, stiff neck, and altered mental status. Diagnostic evaluation includes cerebrospinal fluid (CSF) analysis and imaging studies, with nucleic acid amplification tests (e.g., GeneXpert MTB/RIF) providing rapid confirmation of the disease. Treatment follows World Health Organization (WHO) guidelines, including an intensive two-month phase of anti-TB therapy followed by a continuation phase. Adjunctive corticosteroid therapy, particularly with dexamethasone, helps reduce mortality by controlling neuroinflammation. On the other hand, careful observation for medication toxicity and side effects like immune reconstitution inflammatory syndrome (IRIS) is critical, particularly in HIV-TB co-infected patients. Early diagnosis, prompt treatment, and targeted public health interventions are crucial in reducing the impact of CNS TB, particularly in high-burden regions.

1. Introduction

Central Nervous System (CNS) tuberculosis (TB) meningitis, a severe extrapulmonary TB manifestation, poses significant diagnostic and therapeutic challenges due to high morbidity and mortality, especially in immunocompromised individuals like those with HIV. It occurs when Mycobacterium tuberculosis infects the meninges, leading to inflammation in the brain and spinal cord. Though less common than pulmonary TB, CNS TB is disproportionately prevalent in areas with endemic TB, such as sub-Saharan Africa and Southeast Asia.[1]

Recent 2024 data highlight that HIV-positive individuals are at particularly high risk, with CNS TB accounting for up to 10% of all TB cases in this group. Globally, the highest burden remains in regions with endemic TB and high HIV rates. In India, which continues to report significant TB-HIV co-infections, CNS TB remains a pressing concern.[2,3] Due to the lack of access to advanced molecular diagnostics, especially in low-resource settings,

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https://doi.org/10.18231/j.ijn.2024.028

diagnostic delays worsen mortality rates. This highlights the urgent need for improved diagnostics and focused public health interventions to lessen the impact of CNS TB, particularly in vulnerable populations.

2. Pathogenesis

A severe form of tuberculosis affecting the CNS, tuberculous meningitis (TBM) is caused by the hematogenous dissemination of Mycobacterium tuberculosis from a primary site of infection, usually the lungs. Numerous complex processes are involved in the pathogenesis:

2.1. Hematogenous dissemination and CNS invasion

The blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB) were both crossed by the bacilli during their initial bloodstream spread. This may occur through direct endothelial cell invasion or trafficking within infected immune cells, such as macrophages and neutrophils. Once in the CNS, M. tuberculosis can establish infection in the meninges or form tuberculomas.[4,5]

2.2. Neuroinflammatory response

Upon invasion, antigen presentation by microglia, astrocytes, and neurons triggers a robust immune response. Pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and chemokines are released, which further disrupt the blood-brain barrier and attract a large number of immune cells to the CNS. This influx of immune cells into the subarachnoid space contributes to inflammation in the basal cisterns, which can obstruct cerebrospinal fluid flow and increase intracranial pressure.[6]

2.3. Cerebral edema and vasculitis

Inflammatory exudates in TBM cause vasogenic and cytotoxic edema, contributing to raised intracranial pressure. Disruption of cerebral blood vessels can lead to infarctions, further exacerbating the neurological damage seen in TBM patients. Hydrocephalus is a common complication resulting from the obstruction of CSF pathways by inflammatory debris.[7]

2.4. Genetic and immunologic factors

Host genetic variables, including variations in the LTA4H gene, have a major impact on how severe the inflammatory response is in TBM. For example, the hyperinflammatory phenotype is associated with higher morbidity, while a hypo-inflammatory response can lead to inadequate pathogen clearance. This genetic variability also affects steroid responsiveness, with certain genotypes showing better outcomes when corticosteroids are used adjunctively.

2.5. Pathogen-host interaction

Mycobacterial factors, including the ability to evade immune clearance by modulating macrophage activity and preventing phagosome-lysosome fusion, are critical in establishing chronic infection. The bacilli may form granulomas, which help contain the infection but also contribute to persistent inflammation and tissue damage.[6,7]

Recent research utilizing transcriptomic, proteomic, and metabolomic technologies has provided novel insights into TBM pathogenesis, revealing biomarkers that may predict disease progression and therapeutic response. Furthermore, adjunctive therapies targeting specific inflammatory pathways, including the use of higher-dose rifampicin and adjunctive immunomodulatory treatments like aspirin, are under investigation to improve outcomes in this often-devastating disease.

3. Clinical Evaluation

Because the symptoms of CNS tuberculosis (TB) meningitis are non-specific, particularly in the early stages, a comprehensive clinical evaluation is necessary for the clinical diagnosis.

4. History and Symptoms

Patients usually arrive with a history of tuberculosis exposure, along with additional risk factors like immunocompromised status (e.g., HIV infection) or recent travel to an area where tuberculosis is endemic. Symptomatic evaluation includes Headache: Persistent, intense headaches are common in TB meningitis, often worsening over time. Fever: Low-grade initially, but may escalate with disease progression. Neck stiffness: A hallmark of meningeal irritation. Altered mental status: Ranging from confusion to coma in advanced cases. Other symptoms include Nausea, vomiting (often due to increased intracranial pressure), photophobia, and seizures in severe presentations.[8]

5. Cerebrospinal Fluid (CSF) Analysis

A lumbar puncture is central to diagnosing TB meningitis, allowing for detailed CSF analysis, including Pleocytosis: Typically lymphocyte-predominant with white cell counts greater than 100 cells/mm^3. Protein elevation: Markedly elevated (100–500 mg/dL). Hypoglycorrhachia: CSF glucose levels are often <40% of concurrent blood glucose levels, and a CSF/blood glucose ratio <0.4 is strongly indicative of TB meningitis. Imaging before lumbar puncture, particularly in cases where increased intracranial pressure or mass effect is suspected, is recommended to prevent complications such as herniation.[7,8]

6. Diagnostic Tests

To confirm the diagnosis, the following microbiological and molecular tests are crucial:

1. Acid-Fast Bacilli (AFB) Staining: Despite being highly specific, its sensitivity remains low (10–40%), limiting its diagnostic utility as a stand-alone test.[9]
2. CSF Culture: Culturing M. tuberculosis on solid media (e.g., Lowenstein-Jensen) is a cornerstone diagnostic tool but may take weeks to yield results.[9]
3. Nucleic Acid Amplification Tests (NAATs): Tests like GeneXpert MTB/RIF are essential for prompt diagnosis because they detect M. tuberculosis DNA in the CSF quickly—often within hours—and with a sensitivity of approximately 70 percent.[10]

7. Imaging Studies

While not diagnostic on their own, neuroimaging via CT or MRI is essential for identifying complications of TB meningitis, such as:

Hydrocephalus: Manifesting as dilated ventricles
Tuberculomas: Seen as ring-enhancing lesions
Cerebral edema: Indicating raised intracranial pressure[11]

8. Adjunct Diagnostic Tests

Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRAs): While useful for detecting latent TB, they are less reliable for diagnosing active CNS TB, though they may provide supportive evidence in the context of clinical suspicion.[12]

8.1. TB meningitis mimics

Key mimics include viral, bacterial, and fungal meningitis, neurosarcoidosis, and carcinomatous meningitis. Differentiating TBM from these conditions requires a thorough clinical evaluation, cerebrospinal fluid (CSF) analysis, and advanced neuroimaging, alongside microbiological tests like GeneXpert or cultures. In cases where TBM mimics remain unresolved, management should focus on empirical treatment tailored to the most likely diagnosis, while keeping TB therapy on board or if the clinical suspicion remains high. Multidisciplinary collaboration, is essential to avoid delays in diagnosis and treatment, as both TBM and its mimics can be life-threatening if not promptly addressed.[13]

8.2. Treatment

The World Health Organization (WHO) and National Tuberculosis Elimination Program (NTEP) guidelines for antitubercular therapy (ATT) for CNS TB (tuberculous meningitis) are followed in India; however, because the disease is complex, the ATT regimen has been modified for CNS involvement.[14]

1. Intensive Phase (2 months):
   (a) Rifampicin (RIF): 10mg/kg/day (maximum 600mg)
   (b) Isoniazid (INH): 5mg/kg/day (maximum 300mg)
   (c) Pyrazinamide (PZA): 25 mg/kg/day (maximum 2000mg)
   (d) Ethambutol (EMB): 15mg/kg/day (maximum 1600mg)
2. Continuation Phase (10 months):
   (a) Rifampicin (RIF): 10mg/kg/day
   (b) Isoniazid (INH): 5mg/kg/day

The total duration of treatment is 12 months for uncomplicated cases, but this may be extended to 18-24 months for complicated cases involving hydrocephalus, tuberculomas, or drug-resistant TB. Anti-TB treatment and the start of antiretroviral therapy (ART) must be carefully coordinated in patients who are also HIV positive in order to avoid complications such as immune reconstitution inflammatory syndrome (IRIS). Close monitoring for drug toxicity, especially hepatic and visual assessments due to hepatotoxicity and ethambutol-related optic neuritis, is essential. Pyridoxine supplementation is done to prevent INH-induced neuropathy.

The Thwaites regimen for dexamethasone in the management of CNS TB (tuberculous meningitis) is based on a tapering schedule to reduce inflammation in the central nervous system and mitigate complications like cerebral edema and hydrocephalus. This regimen typically involves the

1. Initial dose as follows -
   (a) Severe disease (grade II or III):
      i. 0.4mg/kg/day intravenously (IV) for the first week.
   (b) Milder disease (grade I):
      i. 0.3mg/kg/day IV for the first week.
2. Tapering regimen:
   (a) The dose is reduced gradually over 6-8 weeks:
      i. Week 2: 0.3mg/kg/day
      ii. Week 3: 0.2mg/kg/day
      iii. Week 4: 0.1mg/kg/day
      iv. Week 5: 3mg/day
      v. Week 6: 2mg/day
      vi. Week 7: 1mg/day
      vii. Week 8: Discontinued

Depending on how severe the illness is and how the patient responds, the regimen varies slightly. Dexamethasone is usually administered intravenously in the initial phases,

followed by oral administration as the dose is tapered. In patients with TB meningitis, corticosteroids such as dexamethasone have been demonstrated to lower mortality and neurological sequelae, particularly in more severe cases. However, its use must be monitored closely for potential side effects like hyperglycemia, gastrointestinal bleeding, and infections. [15]

9. Monitoring and Management

Regular monitoring for potential drug toxicities, especially hepatotoxicity from anti-TB medications and optic neuritis from ethambutol, is critical. Liver function tests and visual assessments should be routinely conducted. Neurological monitoring for signs of elevated intracranial pressure and seizures is also essential.

10. Conclusion

The diagnosis as well as treatment of CNS TB meningitis need careful consideration of clinical, laboratory, and imaging findings. Early diagnosis and appropriate treatment, including the use of first-line anti-tubercular drugs and supportive care, can lead to improved patient outcomes.

11. Conflict of Interest

None.

12. Source of Funding

None.

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Cite this article: Sharma J, Sharma A. CNS tuberculosis meningitis-Short review. *IP Indian J Neurosci* 2024;10(3):126-129.