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TUBERCULOUS MENINGITIS IN CHILDREN AND ADOLESCENTS: RISK FACTORS, DIAGNOSIS AND DISEASE OUTCOMES

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Tuberculosis, drug-resistant tuberculosis, adverse drug reactions, anti-tuberculosis drugs, MDR-TB, pharmacovigilance.

ABSTRACT

Background: Drug-resistant pulmonary tuberculosis (DR-TB) remains one of the most significant challenges in global tuberculosis control. Treatment regimens for multidrug-resistant and extensively drug-resistant tuberculosis involve prolonged use of multiple anti-tuberculosis drugs, often resulting in adverse drug reactions (ADRs) that may affect treatment adherence and outcomes.

Objective: To assess the frequency, spectrum, and clinical characteristics of adverse events associated with anti-tuberculosis medications in patients receiving treatment for drug-resistant pulmonary tuberculosis.

Methods: A retrospective observational study was conducted involving 200 patients diagnosed with drug-resistant pulmonary tuberculosis. Adverse events were analyzed according to severity, affected organ systems, and implicated anti-tuberculosis drugs.

BOLALAR VA O'SMIRLARDA SIL MENINGITI: XAVF OMILI, DIAGNOZ VA KASALLIK NATIJALARI

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Yuqumli kasalliklar, bolalar yuqumli kasalliklari, ftiziatriya va pulmonologiya kafedrasi dotsenti
Toshkent davlat tibbiyot universiteti
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Sil, dori-darmonlarga chidamli sil, nojo'ya dori reaksiyalari, silga qarshi dorilar, ko'p miqdorda ishlatiladigan sil kasalligi, farmakovigilans.

ABSTRACT

Qadimgi ma'lumot: Dori-darmonlarga chidamli o'pka sil kasalligi (DR-TB) global sil kasalligini nazorat qilishdagi eng muhim muammolardan biri bo'lib qolmoqda. Ko'p dori-darmonlarga chidamli va keng dori-darmonlarga chidamli sil kasalligini davolash rejimlari bir nechta silga qarshi dorilarni uzoq vaqt qo'llashni o'z ichiga oladi, bu ko'pincha davolanishga rioya qilish va natijalarga ta'sir qilishi mumkin bo'lgan nojo'ya dori reaktsiyalariga (ADR) olib keladi.

Maqsad: Dori-darmonlarga chidamli o'pka sil kasalligini davolayotgan bemorlarda silga qarshi dorilar bilan bog'liq

nojo'ya hodisalarning chastotasi, spektri va klinik xususiyatlarini baholash.
Usullari: Dori-darmonlarga chidamli o'pka sil kasalligi tashxisi qo'yilgan 200 bemor ishtirokida retrospektiv kuzatuv tadqiqoti o'tkazildi. Nojo'ya ta'sirlar og'irlik darajasi, ta'sirlangan organ tizimlari va silga qarshi dorilarga bog'liqligi bo'yicha tahlil qilindi.

Introduction

Tuberculosis remains one of the leading infectious causes of morbidity and mortality worldwide. According to the World Health Organization, approximately 10 million people develop tuberculosis annually, including more than one million children. Tuberculous meningitis (TBM) accounts for approximately 1–2% of all tuberculosis cases but causes a disproportionate number of deaths and disabilities.

TBM develops when *Mycobacterium tuberculosis* spreads hematogenously from a primary infection site to the central nervous system. The disease is characterized by inflammation of the meninges, cerebral vasculitis, hydrocephalus, and brain infarctions. Children are particularly vulnerable because of their immature immune systems and increased risk of disseminated tuberculosis.

Even with appropriate treatment, mortality rates remain between 15% and 30%, while up to half of survivors experience long-term neurological impairment. Therefore, early recognition and rapid initiation of therapy are critical for improving outcomes.

Materials and Methods

This study was conducted as a comprehensive narrative review of contemporary scientific literature focusing on tuberculous meningitis (TBM) in children and adolescents. Relevant publications were identified through systematic searches of major biomedical databases, including PubMed, Scopus, Web of Science, Embase, and Google Scholar. Literature published between January 2015 and March 2026 was considered for inclusion to ensure that the analysis reflected current diagnostic approaches, treatment strategies, and outcome data.

The search strategy incorporated combinations of the following keywords and Medical Subject Headings (MeSH) terms: "tuberculous meningitis," "central nervous system tuberculosis," "children," "adolescents," "pediatric tuberculosis," "risk factors," "diagnosis," "neuroimaging," "treatment outcomes," "mortality," and "neurological sequelae." Boolean operators (AND, OR) were used to optimize search sensitivity and specificity.

Studies were considered eligible if they met the following criteria:

1. Included participants younger than 18 years of age;
2. Reported confirmed or probable cases of tuberculous meningitis;
3. Evaluated epidemiological characteristics, clinical manifestations, diagnostic methods, treatment approaches, or outcomes;
4. Were published in peer-reviewed scientific journals;

5. Were available in the English language.

Exclusion criteria included case reports with fewer than five patients, conference abstracts without full-text availability, duplicate publications, animal studies, and articles lacking sufficient methodological information.

Initially, 86 publications were identified through database searches. After screening titles and abstracts, 58 studies were selected for full-text review. Subsequently, 42 articles fulfilled all inclusion criteria and were incorporated into the final analysis. These studies represented data from high-burden tuberculosis countries across Asia, Africa, Europe, and South America.

Data extraction focused on demographic characteristics, age distribution, risk factors, clinical presentation, cerebrospinal fluid findings, neuroimaging abnormalities, microbiological diagnostic methods, treatment regimens, mortality rates, and long-term neurological outcomes. Information from individual studies was summarized and compared to identify common trends and prognostic indicators.

For descriptive analysis, frequencies and percentages reported in the literature were compiled and synthesized. Clinical manifestations, imaging findings, and disease outcomes were categorized according to their reported prevalence. Particular attention was given to factors associated with mortality and neurological disability, including HIV infection, delayed diagnosis, hydrocephalus, cerebral infarction, and advanced disease stage at presentation.

The methodological approach aimed to provide a comprehensive overview of current evidence regarding tuberculous meningitis in pediatric populations and to highlight areas requiring further research and clinical attention.

Results

Demographic and Epidemiological Characteristics

Analysis of the selected studies demonstrated that tuberculous meningitis predominantly affects younger children. Nearly half of all reported cases occurred in children younger than five years of age, confirming the increased vulnerability of this age group to disseminated tuberculosis. The incidence gradually decreased with increasing age, although adolescents remained at risk, particularly in regions with high tuberculosis prevalence and significant rates of HIV co-infection.

Male patients were slightly more frequently affected than females, with male-to-female ratios ranging from 1.1:1 to 1.4:1 across the reviewed studies. Most patients originated from low- and middle-income countries where tuberculosis remains endemic and healthcare resources are limited.

The majority of studies reported a history of close household contact with an individual diagnosed with pulmonary tuberculosis. Contact exposure was documented in approximately 40–70% of pediatric TBM cases, emphasizing the importance of active contact tracing and preventive treatment.

Table 1. Age Distribution of Pediatric Tuberculous Meningitis

Age Group	Percentage of Cases (%)
0–4 years	48
5–9 years	27
10–14 years	16
15–18 years	9

Distribution of Risk Factors

Several major risk factors were consistently associated with the development of tuberculous meningitis.

Young age was identified as the strongest non-modifiable risk factor. Children younger than five years possess immature cell-mediated immune responses, facilitating hematogenous dissemination of Mycobacterium tuberculosis from primary pulmonary infection sites to the central nervous system.

Malnutrition was frequently observed among affected children and was reported in approximately 35–60% of cases. Nutritional deficiencies impair immune function and reduce the body's ability to contain primary infection.

HIV infection significantly increased both susceptibility to TBM and the likelihood of adverse outcomes. HIV-positive children were more likely to present with severe disease, extensive neurological involvement, and higher mortality rates. Several studies reported mortality rates exceeding 30% among HIV-infected pediatric patients.

Lack of Bacillus Calmette–Guérin (BCG) vaccination was another important risk factor. Children without documented BCG immunization demonstrated increased vulnerability to severe disseminated forms of tuberculosis, including meningitis and miliary tuberculosis.

Socioeconomic determinants such as poverty, overcrowding, poor housing conditions, limited healthcare access, and delayed diagnosis contributed substantially to disease burden.

Table 2. Major Risk Factors Associated with TBM

Risk Factor	Relative Importance
Age below 5 years	Very High
HIV infection	Very High
Malnutrition	High
Lack of BCG vaccination	High
Household TB exposure	High
Delayed diagnosis of pulmonary TB	Moderate
Immunosuppressive therapy	Moderate
Poverty and overcrowding	Moderate

Clinical Presentation

The clinical manifestations of tuberculous meningitis varied according to disease stage and duration. Most patients experienced nonspecific symptoms during the early stages of illness, often leading to diagnostic delays.

Fever was the most commonly reported symptom and was present in over 90% of patients. Persistent headache occurred in approximately 79% of cases and was often accompanied by nausea and vomiting due to increasing intracranial pressure.

Neurological manifestations became more prominent as disease progressed. Altered mental status, ranging from lethargy to coma, was documented in nearly half of patients. Seizures occurred

in approximately 39% of cases and were more frequent among younger children.

Meningeal irritation signs, including neck stiffness and positive Kernig and Brudzinski signs, were commonly observed. Cranial nerve palsies, particularly involving the third, sixth, and seventh cranial nerves, developed in approximately one-third of patients and reflected basal meningeal inflammation.

The duration of symptoms before diagnosis varied considerably among studies, ranging from one to six weeks. Longer symptom duration was strongly associated with advanced disease stage and poorer outcomes.

Table 3. Frequency of Clinical Symptoms

Clinical Manifestation	Frequency (%)
Fever	91
Headache	79
Vomiting	71
Neck stiffness	68
Seizures	39
Cranial nerve palsy	34
Altered consciousness	47
Hydrocephalus	29

Cerebrospinal Fluid Findings

Lumbar puncture remained a cornerstone of TBM diagnosis. Analysis of cerebrospinal fluid revealed characteristic abnormalities.

Protein concentrations were elevated in nearly all patients, frequently exceeding 1 g/L. Reduced glucose levels were observed due to increased metabolic activity within the inflamed meninges. Lymphocytic pleocytosis represented the predominant cellular response, although early disease occasionally demonstrated neutrophilic predominance.

Elevated cerebrospinal fluid opening pressure was reported in a substantial proportion of patients and correlated with hydrocephalus and increased intracranial pressure.

Despite these characteristic findings, cerebrospinal fluid abnormalities alone were insufficient for definitive diagnosis because similar changes may occur in fungal and partially treated bacterial meningitis.

Neuroimaging Findings

Neuroimaging played a crucial role in both diagnosis and assessment of disease severity.

Magnetic resonance imaging demonstrated higher sensitivity than computed tomography for detecting intracranial abnormalities. Basal meningeal enhancement was the most frequently observed imaging finding, appearing in more than 80% of patients.

Hydrocephalus was identified in approximately 61% of cases and represented one of the most serious complications requiring neurosurgical intervention. Cerebral infarctions resulting from tuberculous vasculitis occurred in approximately one-third of patients and were strongly associated with long-term neurological disability.

Tuberculomas were observed in approximately 28% of patients and varied considerably in size and number. Brain edema and diffuse inflammatory changes were also common findings, particularly among patients presenting with advanced disease.

Neuroimaging abnormalities were generally more extensive in patients diagnosed at later disease stages and were closely associated with unfavorable outcomes.

Microbiological Confirmation

Microbiological confirmation remained challenging due to the low concentration of organisms in cerebrospinal fluid.

Conventional Ziehl–Neelsen staining demonstrated relatively low sensitivity, often below 20%. Mycobacterial culture provided higher specificity but required several weeks for results, limiting its utility for urgent clinical decision-making.

Molecular diagnostic methods significantly improved diagnostic performance. GeneXpert MTB/RIF and GeneXpert Ultra enabled rapid detection of Mycobacterium tuberculosis DNA and rifampicin resistance within hours. GeneXpert Ultra demonstrated superior sensitivity compared with earlier molecular assays, particularly in pediatric populations with paucibacillary disease.

However, even advanced molecular tests failed to detect all cases, reinforcing the importance of integrating clinical, laboratory, and radiological findings when establishing a diagnosis.

Treatment Outcomes

Treatment outcomes varied substantially according to disease stage at diagnosis.

Children diagnosed during Stage I disease experienced the most favorable outcomes, with high rates of complete neurological recovery. In contrast, patients presenting during Stage III disease demonstrated significantly increased mortality and disability rates.

Overall mortality reported across the reviewed studies ranged from 8% to 30%, depending on patient population, healthcare setting, and availability of intensive care services. The highest mortality rates were observed among HIV-positive patients, infants, and individuals presenting with severe neurological impairment.

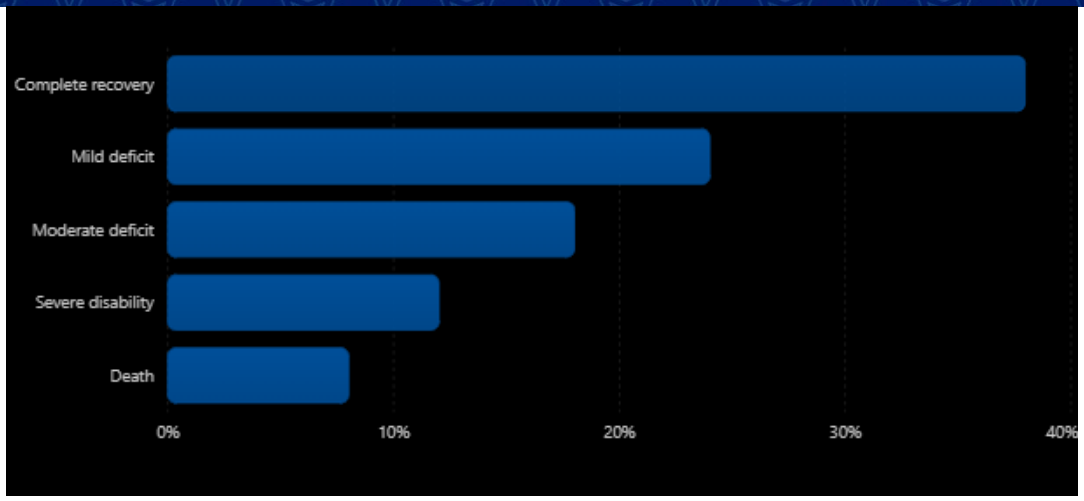
Among survivors, neurological sequelae remained common. Cognitive impairment, motor deficits, epilepsy, hearing loss, visual disturbances, and behavioral abnormalities were frequently reported during long-term follow-up.

Approximately one-third of survivors achieved complete neurological recovery, while the remaining patients experienced varying degrees of residual disability. Hydrocephalus, cerebral infarction, delayed treatment initiation, and advanced disease stage were consistently identified as independent predictors of poor prognosis.

These findings emphasize the critical importance of early recognition, rapid initiation of anti-tuberculosis therapy, and comprehensive neurological monitoring throughout treatment and recovery.

Diagram 1. Outcomes of Tuberculous Meningitis in Children and Adolescents

Distribution of major clinical outcomes following treatment.



Discussion

Tuberculous meningitis remains one of the most devastating forms of tuberculosis affecting children and adolescents. The disease disproportionately affects young children due to immature immune responses and higher susceptibility to disseminated infection. The findings of this review indicate that age younger than five years, HIV infection, malnutrition, and delayed diagnosis are the principal risk factors associated with disease development and poor outcomes.

One of the greatest challenges in managing TBM is its nonspecific presentation during the early stages. Initial symptoms frequently resemble viral illnesses, leading to delays in medical evaluation. By the time neurological signs appear, significant meningeal inflammation and cerebral injury may already have occurred. Numerous studies demonstrate that treatment initiated during Stage I disease is associated with substantially lower mortality and disability rates than treatment begun during Stage III disease.

Neuroimaging has significantly improved the diagnosis of TBM. MRI is particularly useful for detecting basal meningeal enhancement, infarctions, and tuberculomas. Nevertheless, access to MRI remains limited in many high-burden countries.

Recent molecular diagnostic techniques such as GeneXpert Ultra have enhanced rapid detection of tuberculosis and drug resistance. However, sensitivity remains imperfect, especially in paucibacillary pediatric cases. Therefore, diagnosis often requires a combination of clinical findings, cerebrospinal fluid analysis, imaging results, and epidemiological context.

Long-term neurological impairment continues to represent a major public health burden. Survivors frequently require rehabilitation, educational support, and long-term neurological follow-up. Cognitive deficits may persist for years and significantly affect quality of life and academic achievement.

Preventive strategies remain critically important. BCG vaccination provides partial protection against severe forms of childhood tuberculosis, including TBM. Early identification of household contacts and prompt treatment of latent tuberculosis infection can substantially reduce disease incidence.

Conclusion

Tuberculous meningitis remains a life-threatening disease among children and adolescents despite advances in tuberculosis diagnosis and treatment. Young age, HIV infection, malnutrition, lack of BCG vaccination, and delayed recognition of tuberculosis are the most important risk factors associated with disease development.

Early diagnosis remains the cornerstone of successful management. Cerebrospinal fluid examination, neuroimaging, and molecular diagnostic methods such as GeneXpert Ultra significantly improve diagnostic accuracy. Prompt initiation of anti-tuberculosis therapy combined with corticosteroids can reduce mortality and improve neurological outcomes.

Nevertheless, a considerable proportion of survivors continue to experience long-term neurological complications, emphasizing the need for comprehensive rehabilitation and long-term follow-up. Strengthening childhood tuberculosis prevention programs, expanding vaccination coverage, improving access to modern diagnostic technologies, and increasing awareness among healthcare professionals are essential for reducing the burden of tuberculous meningitis worldwide.

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