Advances in the diagnosis of tuberculous meningitis: an integrative review

Avanços no diagnóstico da meningite tuberculosa: uma revisão integrativa

Avances en el diagnóstico de la meningitis tuberculosa: una revisión integradora

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RESUMO

Objetivo: Analisar modalidades diagnósticas emergentes para a detecção da meningite tuberculose (TBM). **Metodologia:** Foi realizada uma revisão integrativa, guiada pela pergunta norteadora formulada a partir do modelo PICo: "Quais as técnicas recentes utilizadas no diagnóstico na meningite tuberculosa?" O estudo foi conduzido nas bases de dados PubMed, Scopus e Biblioteca Virtual em Saúde (BVS), utilizando descritores DeCS/MeSH "Neurotuberculosis", "Tuberculous meningitis", "Diagnosis", "Molecular diagnostics", "PCR" e "Advances". Foram incluídos artigos completos, publicados entre os anos de 2015 e 2025. **Resultados:** Foram identificados pela chave de busca 65 artigos, dos quais 6 foram utilizados a partir dos critérios de inclusão e exclusão. Assim, foram citados avanços moleculares, como o GeneXpert Ultra MTB/RIF, o uso de biomarcadores metabolômicos e o MBFT, os quais demonstraram progressos significativos no diagnóstico da TBM. **Conclusões:** A TBM é um desafio por sua alta mortalidade e diagnóstico complexo. Métodos tradicionais têm baixa sensibilidade e são lentos. Avanços moleculares, como GeneXpert Ultra MTB/RIF e biomarcadores, oferecem diagnóstico mais rápido e específico.

Descritores: tuberculose meningoencefálica; neurotuberculose; métodos laboratoriais.

ABSTRACT

Objective: To analyze emerging diagnostic modalities for the detection of tuberculous meningitis (TBM). **Metodology:** An integrative review was conducted, guided by the research question formulated using the PICo model: "What are the recent techniques used in the diagnosis of tuberculous meningitis?" The study was performed using the PubMed, Scopus, and Virtual Health Library (BVS) databases, employing DeCS/MeSH descriptors: "Neurotuberculosis," "Tuberculous meningitis," "Diagnosis," "Molecular diagnostics," "PCR," and "Advances." Full articles published between 2015 and 2025 were included. **Results:** The search retrieved 65 articles, of which 6 met the inclusion and exclusion criteria. Molecular advances such as GeneXpert Ultra MTB/RIF, metabolomic biomarkers, and MBFT were highlighted, showing significant progress in TBM diagnosis. **Conclusions:** TBM poses a challenge due to its high mortality and complex diagnosis. Traditional methods have low sensitivity and are time-consuming. Molecular advances, like GeneXpert Ultra MTB/RIF and biomarkers, provide faster and more specific diagnosis.

Descriptors: meningoencephalic tuberculosis; neurotuberculosis; laboratory methods.

RESUMEN

Objetivo: Analizar modalidades diagnósticas emergentes para la detección de la meningitis tuberculosa (TBM). **Metodología:** Se realizó una revisión integrativa, guiada por la pregunta formulada a partir del modelo PICo: "¿Cuáles son las técnicas recientes utilizadas en el diagnóstico de la meningitis tuberculosa?" El estudio se llevó a cabo en las bases de datos PubMed, Scopus y Biblioteca Virtual en Salud (BVS), utilizando descriptores DeCS/MeSH: "Neurotuberculosis", "Meningitis tuberculosa", "Diagnóstico", "Diagnósticos moleculares", "PCR" y "Avances". Se incluyeron artículos completos publicados entre 2015 y 2025. **Resultados:** Se identificaron 65 artículos mediante la búsqueda, de los cuales 6 cumplieron con los criterios de inclusión y exclusión. Se destacaron avances moleculares como GeneXpert Ultra MTB/RIF, biomarcadores metabolómicos y MBFT, que mostraron progresos significativos en el diagnóstico de la TBM. **Conclusiones:** La TBM es un desafío debido a su alta mortalidad y diagnóstico complejo. Los métodos tradicionales tienen baja sensibilidad y son lentos. Los avances moleculares, como GeneXpert Ultra MTB/RIF y los biomarcadores, ofrecen un diagnóstico más rápido y específico.

Descriptores: tuberculosis meningoencefálica; neurotuberculosis; métodos de laboratorio.

Introduction

According to the World Health Organization (WHO), tuberculosis (TB) is currently the leading cause of death from infectious disease globally, with an estimated 1.25 million deaths reported, which is almost double the number of deaths attributed to HIV/AIDS. Tuberculous meningoencephalitis (TBM) is one of the severe forms of extrapulmonary TB and accounts for about 1% of all TB cases worldwide. TBM is characterized by a subacute or chronic inflammation of the meninges caused by the invasion of the subarachnoid space by *Mycobacterium tuberculosis (Mtb)*. The mortality rate for TBM is 10% in the first week, rising to 80% by the fifth week. Furthermore, half of the survivors experience subsequent neurological deficit. [1,2]

The clinical diagnosis of TBM is challenging due to its insidious onset and non-specific clinical manifestations, which are similar to those observed in cryptococcal meningitis and partially treated bacterial meningitis. Although microbiological investigations aimed at isolating *M. tuberculosis* remain the gold standard, their low sensitivity and prolonged culture time limit their immediate clinical utility. Molecular diagnostic methods, in turn, have limitations, such as the need for high technical competence and high cost. Delayed diagnosis results in early death or permanent neurological morbidity, especially in vulnerable populations, such as children and people living with untreated HIV. Therefore, there is an urgent need to analyze rapid and accurate diagnostic tools. [2-6]

In the last decade, the field of TB diagnostics has been marked by significant advances, mainly with the development of new molecular tests and the improvement of pre-existing tests. Among these, nucleic acid amplification tests stand out, such as polymerase chain reaction (PCR) and its variations, which provide rapid and sensitive results. Moreover, the use of nanotechnology has helped improve the effectiveness of pre-existing techniques, such as the ELISA method, which helped direct gene amplification for its detection. [7,3,8]

Methodology

The present study consists of an integrative literature review, structured based on the following steps: construction of a guiding question, database search, data collection, critical analysis of the included studies, interpretation, and presentation of the results. In the first step, the guiding question was formulated based on the PICo strategy (P = population; I = interest; Co = context), defined as "What are the recent techniques used in the diagnosis of tuberculous meningitis?".

The search for articles was conducted in the PubMED, VHL (BVS), and Scopus databases, using the English search key composed of the health descriptors (DeCS/MeSH): ("Neurotuberculosis" OR "Tuberculous meningitis") AND ("Diagnosis" OR "Molecular diagnostics" OR "PCR") AND (“Advances”). Inclusion criteria were then defined: full articles, free access, published between 2015 and 2025, and written in Portuguese, Spanish, or English. Exclusion criteria included review articles, opinion articles, case reports, and articles outside the thematic focus.

Results

The application of the search key resulted in the identification of 65 articles. After analysis and application of the inclusion and exclusion criteria, a total of 59 articles were excluded (Figure 1). After excluding duplicate articles, 44 remained, which were then subjected to title and abstract reading upon application of the inclusion criteria. After analysis and application of the exclusion criteria, 21 articles were excluded for not covering the work's theme, 20 articles for being integrative reviews, 1 opinion article, 3 articles for not having free access, and 3 articles for being case reports. Finally, after a full reading, 1 article was excluded for being an opinion article, leaving six articles, all observational-experimental, to compose the integrative review. The selected articles that make up this review, as well as the main results, are presented in Table I.

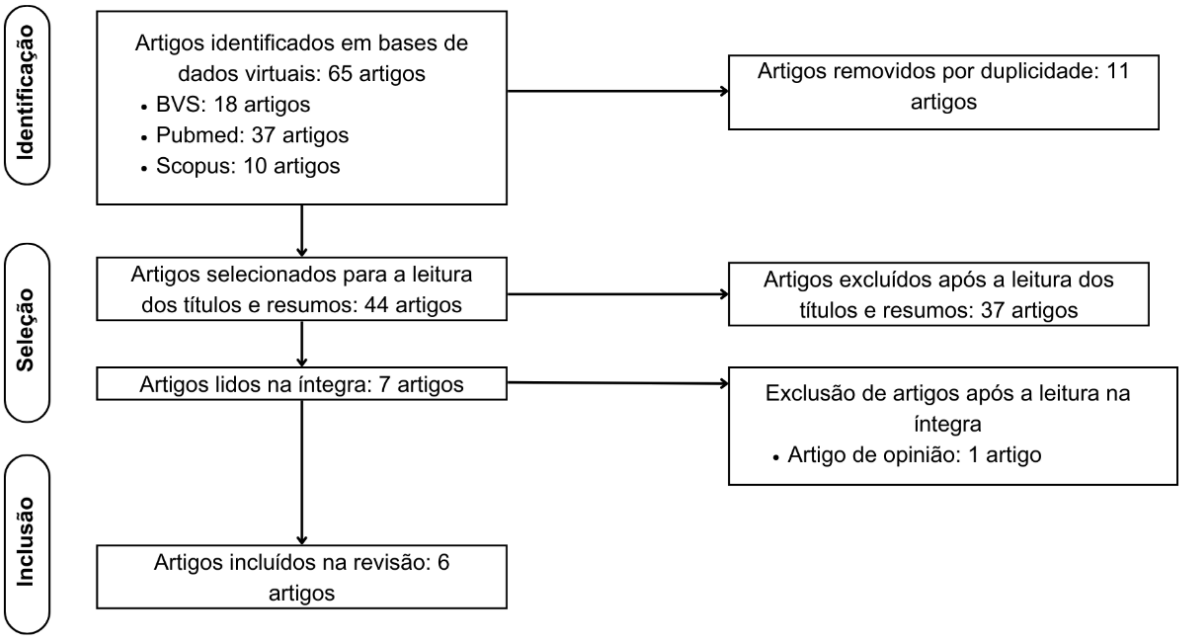

Figure 1 – PRISMA Flowchart(*Source: Prepared by the author*)

Table I – Articles included in the study for the construction of the integrative review on the molecular diagnosis of tuberculous meningitis.

Authorship and Year	Location	Study Type	Main Results
Song et al., 2022.	South Korea	Retrospective longitudinal observational study	The article addresses the analysis of medical records over 10 years to correlate the presence of the ADA enzyme in the CSF of TBM patients.
Maheswari et al., 2019.	India	Experimental longitudinal study (clinical trial)	Addresses the treatment outcomes in patients with various forms of neurological TB, whose treatment followed the standardized Revised National TB Control Program (RNTCP). Makes mention of diagnostic findings in TBM patients.

Yang et al., 2020.	China	Prospective longitudinal observational study	The article addresses the development of diagnostic methods for tuberculous meningitis based on clinical and laboratory characteristics.
Mason et al., 2017.	South Africa	Retrospective cohort longitudinal observational study	The study addresses the topic of the amino acid profile in the cerebrospinal fluid (CSF), highlighting the changes observed in children with tuberculous meningitis.
Patel et al., 2024.	India	Descriptive cross-sectional observational study	Different pathogens responsible for central nervous system infections, with TBM as one of the main conditions. The work emphasizes increased proteins in the CSF and imaging findings as the most commonly used diagnostic resources.
Sharma et al., 2020.	India	Experimental diagnostic evaluation study	Innovative diagnostic alternative for TBM, based on the MLAMP-MBF association, which combines high sensitivity and specificity with low cost and operational simplicity. Applicable in low-resource settings, where methods like Xpert Ultra still face logistical limitations. It also demonstrates the utility of multi-target approaches (IS6110 and IS1081) to expand case detection.

***Source**: Prepared by the author.*

Discussion

TBM remains one of the most severe and complex forms of extrapulmonary TB, marked by high mortality and frequent neurological sequelae among survivors. The disease begins with the hematogenous dissemination of *Mtb* from a primary pulmonary focus, with the formation and rupture of granulomas into the subarachnoid space, triggering intense inflammation and a basal exudate that compromises cranial nerves, cerebral vessels, and CSF flow. Clinically, TBM has an insidious and non-specific onset, with mild symptoms that evolve into severe neurological manifestations, favoring confusion with partially treated bacterial or cryptococcal meningitis, which delays diagnosis and treatment. [9,10]

As with clinical recognition, laboratory and imaging methods also have limitations. Currently, computed tomography (CT), magnetic resonance imaging (MRI), CSF (or LCR) analysis, and microbiological examinations are the main resources. Acid-fast bacilli smear microscopy, despite being simple and low-cost, has reduced sensitivity due to the low bacillary load characteristic of extrapulmonary TB forms. Culture, the traditional gold standard, takes weeks to months for *Mtb* growth, reducing its clinical utility given the urgency of early treatment. [9,11]

The integration of clinical, laboratory, and imaging findings is fundamental for the early diagnosis of TBM. Patel et al. (2024) demonstrated that diagnosis relies on classic CSF changes, such as lymphocytic pleocytosis and increased proteins, combined with imaging tests. Yang et al. (2020) reinforce that, although molecular techniques such as GeneXpert MTB/RIF (or TRM-TB) have high specificity, sensitivity remains limited in paucibacillary samples. Furthermore, Maheswari et al. (2019) show that definitive TBM confirmation still requires isolation of the bacillus from the CSF, which demands large volumes of CSF and adequate laboratory infrastructure. Other

methods, such as adenosine deaminase (ADA) dosage in CSF observed by Song et al. (2020), show high specificity and negative predictive value, in addition to reasonable sensitivity (89%), but are still undergoing validation and implementation studies. [12,13,10,14]

Recent advances in molecular biology offer faster and more sensitive alternatives. Mason et al. (2017) analyzed the metabolomic profile of CSF from children with suspected TBM and identified a significant elevation of amino acids, reflecting neuroinflammation and reinforcing the potential of biomarkers in early diagnosis. The technique of gas chromatography coupled with mass spectrometry (GC-MS) showed the capacity to differentiate TBM from other neurological conditions, highlighting its clinical applicability. [15]

Other innovations, such as the Line Probe Assay (LPA) and Whole Genome Sequencing (WGS), have transformed TB diagnostic techniques. LPA allows the detection of multi-drug resistance, while WGS enables a comprehensive and precise analysis of *Mtb* DNA, useful for identifying mutations, lineages, and supporting epidemiological surveillance. Despite the great potential, the high cost of these technologies still limits their large-scale adoption, especially in endemic countries like Brazil. [16,17,18]

The Magnetic Bead Flocculation Test (MBFT) also emerges as a promising alternative, with superior performance to conventional methods, speed (less than an hour), and low cost, characteristics that make it particularly useful in limited-resource settings. [19]

In Brazil, conventional microbiological examinations, such as smear microscopy and culture, are available through the Unified Health System (SUS), mainly in reference hospitals and central laboratories (LACEN). However, structural and logistical barriers hinder their effectiveness, as many samples need to be sent to specialized centers, delaying results. Although TRM-TB has been incorporated into SUS since 2013 and represents an important advance, its routine use in CSF is not yet universal, being restricted to higher complexity services. Challenges persist related to delayed results, regional inequality in infrastructure, and restricted access to molecular technologies for extrapulmonary diagnosis. This scenario highlights the need for strategies that expand access to rapid, sensitive, and standardized methods, especially in endemic regions and vulnerable populations. [9,11]

Final Considerations

TBM remains one of the greatest challenges of extrapulmonary TB, due to high mortality and diagnostic difficulties. Conventional methods, although widely used, have low sensitivity and delayed results, while more recent techniques, such as TRM-TB, still have limitations in paucibacillary samples. In this scenario, advances such as metabolomic CSF biomarkers, Line Probe Assays, genomic sequencing (complete and targeted), and MBFT emerge as promising alternatives, either due to their precision, speed, low cost, or applicability in low-resource settings. However, even with these advances, the full implementation of these methods in SUS still faces structural and logistical barriers, which maintains the effective diagnosis of TBM as a challenge in the Brazilian context.

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