Diagnostic Methods for Tuberculous Meningitis: A Systematic Review

Métodos Diagnósticos para Meningite Tuberculosa: Uma Revisão Sistemática

Tamires Calaes Oliveira[1] ,Patrícia Guedes Garcia[2]

[1] Faculdade de Ciências Médicas e da Saúde de Juiz de Fora - Suprema (FCMS/JF).

[2] Doutora, Professora da Faculdade de Ciências Médicas e da Saúde de Juiz de Fora – SUPREMA.

*Tamires Calaes Oliveira. E-mail: tamirescalaes@hotmail.com

ABSTRACT

Introduction: Tuberculous meningitis (TBM) is associated with a high mortality and morbidity rate. The diagnosis of TBM remains a late clinical challenge, especially when resources are limited. Thus, new tests that can be used at the point of care are of utmost importance, especially for drug-resistant TBM, which has a dismal result. **Objective:** The objective of this systematic review was to verify, through a systematic review, diagnostic methods for tuberculous meningitis, demonstrating beyond the gold standard which should be observed in the exams and in the patient's clinic. **Method:** Studies published between 2014 and 2019 were analyzed, with reference to the Medline database via Pubmed, being used in the construction of the search phrase MeSH. The following inclusion criteria were established: original human articles in English. As exclusion criteria: unclear, poorly described or inadequate interventions and in the form of summaries. The following variables were used for study selection: Patient symptoms and analysis of clinical examinations. Result: This review included 5 articles that met the inclusion criteria and were relevant to the theme. **Conclusion:** This review highlights the main early signs and symptoms for the diagnosis of TBM, with a strong emphasis on neurological stage, along with rapid and clear diagnosis. In addition to the already established gold standard for Mycobacterium Tuberculosis isolation, it is necessary to use indicators such as lactate, glucose and cerebrospinal fluid (CSF) dosage, together with new techniques.

Keywords: Mycobacterium tuberculosis; Meningeal Tuberculosis; Diagnosis.

RESUMO

Introdução: Meningite tuberculosa (TBM) está associada com elevada taxa de mortalidade e morbidade. O diagnóstico de TBM continua um desafio clínico e tardio, especialmente quando os recursos são limitados. Assim, novos testes que podem ser usados no ponto de atendimento são de extrema importância, principalmente para TBM resistente a medicamentos, que apresenta um resultado sombrio. **Objetivo:** O objetivo desta revisão sistemática foi verificar, por meio de uma revisão sistematizada, métodos diagnósticos para meningite tuberculosa, demonstrando além do padrão ouro o que deve ser observado nos exames e na clinica do paciente. **Método:** Foram analisados estudos publicados entre 2014 e 2019, tendo como referência a base de dados Medline via Pubmed, sendo utilizado na construção da frase de pesquisa o MeSH. Foram estabelecidos os seguintes critérios de inclusão: artigos originais realizados em humanos, na língua inglesa. Como critério de exclusão: intervenções pouco claras, mal descritas ou inadequadas e na forma de resumos. Utilizou-se as seguintes variáveis para a seleção dos estudos: Sintomas dos pacientes e análise dos exames clínicos. Resultado: Fizeram parte desta revisão 5 artigos que se enquadraram nos critérios de inclusão e eram pertinentes ao tema. **Conclusão:** Esta revisão destaca os principais sinais e sintomas iniciais para o diagnostico de TBM, com grande ênfase no estagio neurológico, juntamente com o diagnóstico rápido e claro. Além do padrão ouro já estabelecido do isolamento do Mycobacterium Tuberculosis é necessário à utilização de indicadores como a dosagem do lactato, glicemia e proteínas no liquido cefalorraquidiano (LCR), juntamente com novas técnicas.

Palavras-chave: Mycobacterium tuberculosis;' Tuberculose Meníngea; Diagnóstico.

INTRODUCTION

Tuberculosis (TB) is a common and deadly infectious disease despite the existence of an effective treatment. Today it represents a major public health problem on a global scale[1].

In 2017, approximately 10 million people developed TB worldwide, of which about 1.6 million deaths were caused by such disease.[2] Tuberculous meningitis (TBM) is the most serious form of TB. More than half of patients treated with TBM die or suffer severe neurological sequelae, largely due to late diagnosis. TBM represents approximately 1% of all TB cases and approximately 5% of extrapulmonary TB cases.[3] In many parts of the world, tuberculosis is the most common cause of bacterial meningitis[4].

The absolute incidence of TBM varies greatly according to location, and it is influenced by the overall incidence of tuberculosis, age structure and HIV-1 seroprevalence within a population.[5] For patients co-infected with HIV, TBM mortality is about 60%[6,7].

In adults, the best-documented risk factor for TBM is HIV-1 co-infection. Among HIV-infected individuals living in areas where tuberculosis is highly endemic, the proportion of HIV-1-associated meningitis attributable to Mycobacterium tuberculosis can exceed 50%[7,8].

In developing countries, the diagnosis of pulmonary tuberculosis depends mainly on the isolation of acid-fast bacilli (AFB) in the direct examination of sputum. The diagnosis of extrapulmonary tuberculosis is less easy depending on the difficulty of obtaining material by invasive gesture (bone biopsy, cerebrospinal fluid, liver biopsy, etc.) and sometimes difficult bacteriological documentation (less bacterial inoculum)[9].

The diagnosis of these forms is often difficult and late, especially when resources are limited, which causes high mortality[10].

Late diagnosis and treatment are associated with a poor prognosis in TBM. Thus, new tests that can be used at the point of care are extremely important, especially for drug-resistant TBM, which has a dismal result[5].

The use of an absolute gold standard for microbiological confirmation is likely to lead to overestimations of diagnostic sensitivity, and the additional use of compound gold standards and latent class analyzes, as well as rational decision trees combining diagnostic information with data from clinical results, should also be part of the evaluation reaching a faster and more accurate diagnosis[5].

The aim of this study was to determine, by means of a systematic review, diagnostic methods for tuberculous meningitis, demonstrating beyond the gold standard what should be observed in the exams and in the patient's clinic.

METHODS

The most relevant studies originally published in the English language over the past 5 years were analyzed, using the Medline database as a reference, aiming at studies with greater clinical relevance, where original articles were chosen.

The present study used the following keywords to formulate the search phrase: ("Meningeal Tuberculosis" OR "Meningeal Tuberculosis" OR "TB Meningitis" OR "TB Meningitides" OR "Tubercular Meningitis" OR "Tubercular Meningitides" OR "Meningitis, Tuberculous" OR "Tuberculous Meningitides" OR "Tuberculous Meningitis" OR "Tuberculosis Meningitides" OR "Tuberculosis Meningitides" OR "Tuberculous Hypertrophic Pachymeningitides") AND ("Diagnoses" OR "Diagnoses and Examinations" OR "Postmortem Diagnosis" OR "Postmortem Diagnoses" OR "Antemortem Diagnosis" OR "Antemortem Diagnoses") AND ("Viral Meningitides" OR "Viral Meningitis"). The inclusion and exclusion criteria were applied based on the types of studies, language, the disease surveyed, along with its diagnosis and publication date from the points raised in each exposed item (Chart 1). For the selection of studies, the inclusion and exclusion criteria presented in Table 1 were applied.

RESULTS

4041 studies involving tuberculous meningitis and the diagnosis related to it were identified. However, from the application of the previously defined criteria, only 326 were part of the scope of this review. Of these, only 5 were eligible to be part of the scope of this study. Figure 1 shows the flowchart used to select the articles that were analyzed.

The articles that met the criteria have shown studies performed in various regions of the world, demonstrating pertinent points of the diagnosis of tuberculous meningitis concerning other meningitis or its severity, which from then on can lead to its lethality.

Table 1 shows the studies showing the studied samples, followed by the analyzes performed on medical records for the patient's clinic and laboratory analysis.

DISCUSSION

From the analysis performed through medical records and laboratory analysis, the articles demonstrated that it is possible to make a faster preliminary diagnosis with overestimation of sensitivity and greater reliability, thus being able to avoid late diagnosis and treatment that are associated with a poor prognosis[11,12,13,14,15].

In the article by Siddiqi et al. (2018)[14], the author reports that the main diagnostic component that showed increased values according to the disease severity stage is the lactate dosed from the cerebrospinal fluid.

In another study[13], the main factors that should be used for decision tree analysis were assembled in cases where quick decisions should be made where the result of the isolation of the bacteria cannot be expected. Among them are listed some determining points, such as sodium in the serum (hyponatremia), lactate and protein in the cerebrospinal fluid (CSF), difficulty in urination, and symptoms of cranial nerve paralysis.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	
Design:	• original articles
Intervention:	• diagnosis for tuberculosis meningitis
	Only in humans
	Individuals with symptoms of tuberculous meningitis
Language:	• English language
	Articles published less than 5 years ago
Exclusion criteria	
Intervention:	unclear, poorly described or inadequate
Type of Publication:	abstracts only
Main variables analyzed	
Patients' symptoms	
Analysis of clinical examinations	

Tabela 1. Sumário dos estudos e seus principais resultados referentes ao diagnostico.

ESTUDOS	AMOSTRA	INTERVENÇÃO	RESULTADOS
Jipa et al., 2017.[11]	31 patients with TBM 14 HIV-infected patients 62 HIV-uninfected patients with MV 18 HIV-infected patients with CM	Analysis of medical records: Duration of symptoms before admission, Neurological Stage, Dosage of cerebrospinal fluid: glycemia and protein.	RCS to distinguish TBM from VM: 96.7% sensitivity and specificity of 81.1%. RCS to distinguish TBM from VM: 96.7% sensitivity and specificity of 81.1%. When the 4 RCS criteria were present, the specificity increased by 100%.
BANKAR et al., 2018.[12]	738 patient samples	Laboratory analysis: Smears and stained using the Ziehl-Neelsen method. Samples inoculated in Lowenstein-Jensen medium. Xpert essay.	Xpert MTB/RIF test for diagnosing EPTB: Sensitivity = 84.91% Specificity = 86.72% RIF resistance: Sensitivity = 60.00% Specificity = 94.74%.
Lee et al., 2018.[13]	98 patients Age:> 18 years	Analysis of medical records: Clinical manifestations Underlying diseases Laboratory findings, including CSF and radiological findings.	The LDH level in the TBM group was 230.5 U/L and in the VM group it was 66.0 U/L; The protein level in the TBM group was 205.5 mg/dL, and in the VM group 91.0 mg/dL.
Siddiqi et al., 2018.[14]	55 patients Age: > 15 years	Laboratory analysis: CSF: lactate, protein, glucose, cell count, Gram stain, Ziehl-Neelsen technique and culture Haematological routine Biochemical routine	The average lactate levels in the phases inherent to gravity: Phase 1=1.93 mg/dl Phase 2=42.34 mg/dl Phase 3=78.77 mg/dl
Liu et al., 2019.[15]	50 patients	Analysis of medical records: Demographic information Clinics Radiological Laboratory data	Univariate analysis: age, CSF protein level, hydrocephalus and AARB were correlated with Paradoxical Reaction (PR) development. Multivariate analyzes: age, documented AARB and vertebral involvement were associated with the development Paradoxical Reaction (PR).

Regarding factors that worsen the condition or paradoxical reaction, which is the return of the initial symptoms after the beginning of treatment, the study by Liu et al. (2019)[15] presents the main parameters that can be predictive of this worsening, namely age, visualization of the bacteria by the documented method Alcohol-Acid Resistant Bacilli (AARB) staining, the cerebrospinal fluid protein level and vertebral involvement.

Jipa et al. (2017)[11] demonstrates in their study the use of rapid clinical score (RCS) as a parameter to separate tuberculous meningitis from other meningitis such as viral meningitis where the duration of symptoms before admission (DSBA), neurological stage according to the Medical Research Council (MRC), the ratio between CSF and blood glucose and CSF protein to assess the likelihood of TBM in patients with CSF clear meningitis.

In the article by Bankar et al. (2018)[12], they analyze the use of the diagnosis made through the Xpert Mycobacterium tuberculosis/rifampicin (MTB/RIF) assay, where a sensitivity of 84.91% and specificity of 86.72% can be verified. If the cases are positive for culture, the sensitivity reaches 94.12% and 80.56% in cases with negative sputum smear microscopy.

New metabolites are being studied to be used as TBM markers where in the future they can be used in order to increase the

reliability of the initial diagnosis. Li et al. (1017)[16] studied a total of 25 metabolites significantly different in CSF from TBM compared to VM.

Méchaï et al· (2019)[4] states that GeneXpert represents the most significant advance in TBM diagnoses in the last decade, but it lacks sensitivity and it cannot be used to rule out the diagnosis. A greater volume of CSF appears to be of interest in improving diagnostic performance.

Most of the studies presented prove that the lactate dosage in CSF is one of the main parameters to be analyzed, in addition, the symptoms of cranial nerve involvement are well documented.

The studies have some limitations whose interpretations and comparisons may be impaired, such as: 1) the articles present different aspects of the diagnosis of TBM; 2) use of different methods in the evaluation of the investigated factors, such as the use of medical records or the direct intervention in the patient.

CONCLUSION

In conclusion, TBM remains the most lethal form of TB. The best way to improve survival is through early diagnosis and treatment, which becomes necessary to highlight the main initial signs and symptoms, with great emphasis on the neurological stage, together with a quick and clear diagnosis. In addition to the already established gold standard for the isolation of M. Tuberculosis, it is necessary to use indicators such as the measurement of lactate, glycemia, and proteins in the CSF, together with new techniques that are being studied, such as the Xpert MTB/RIF assay, which should be used for both diagnosis, as well as to know the stage of the disease.

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