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Antibody detection tests for early diagnosis in tuberculous meningitis

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SUMMARY

Background: Tuberculous meningitis (TBM) is the most severe form of tuberculosis. Microbiological confirmation is rare and treatment is often delayed. Early diagnosis and immediate initiation of treatment are essential for effective TBM control. A systematic review was performed in this study to assess the diagnostic accuracy of detecting antibodies against *Mycobacterium tuberculosis* in the cerebrospinal fluid (CSF), according to standard methods. Test performance was summarized using a bivariate random-effects meta-analysis.

Methods: Studies were identified by a search of the literature, up to July 25, 2015, in the EMBASE and MEDLINE databases via Ovid SP and PubMed. The Cochrane Library was also searched for original, peer-reviewed molecular epidemiology studies that reported the diagnosis of TBM based on antibody detection in the CSF.

Results: Thirty-six articles (58 studies) were identified. The sensitivity of antibody detection was 0.75 (95% confidence interval (CI) 0.66–0.82), specificity was 0.98 (95% CI 0.96–0.99), and the area under the receiver operating characteristic curve (AUROC) was 0.97 (95% CI 0.95–0.98). By subgroup analysis, the detection of anti-M37Ra was the highest (AUROC 0.99, 95% CI 0.98–1.00), followed by anti-antigen 5 (AUROC 0.99, 95% CI 0.97–0.99) and anti-M37Rv (AUROC 0.97, 95% CI 0.95–0.98).

Conclusions: For the early diagnosis of TBM based on antibodies in the CSF, the detection of anti-M37Ra, anti-antigen 5, or anti-M37Rv provides the greatest sensitivity and specificity.

1. Introduction

Tuberculosis (TB) is a global public health priority, being the single leading cause of death due to bacterial infection and the second cause of death due to an infectious disease, accounting for 1.3 million deaths worldwide each year.[1] By 2012, the prevalence of active TB cases had fallen by 37% globally since 1990.[2] However, there are an estimated 8.6 million new cases of TB (range 8.3–9 million) globally per year, equivalent to an incidence of 122 cases per 100 000 population.

Tuberculous meningitis (TBM) is a severe complication of TB that predominantly affects young children. Early treatment is vital to prevent morbidity and mortality, emphasizing the importance of early diagnosis. Bacteriological methods, such as Ziehl–Neelsen staining and bacterial culture, remain the gold standard for the laboratory diagnosis of TBM, because they identify the causative agent of the disease, i.e. *Mycobacterium tuberculosis*, in cerebrospinal fluid (CSF). However, the acid-fast bacilli are seldom detected in CSF smears, and culture methods are not only time-consuming, but are also less sensitive. This lack of a sensitive method for early diagnosis is the most common cause of delay, and has led to the World Health Organization (WHO) recommending the Xpert MTB/RIF assay (Cepheid, Inc., Sunnyvale, CA, USA) as the preferred initial test for the diagnosis of TBM over conventional tests for the diagnosis of TB in lymph nodes and other tissues.[3] However, this new technology is expensive, preventing its use in many of the areas where the epidemic is most severe.[4]

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Considerable efforts have been made over the past three decades to devise a rapid test for *M. tuberculosis* based on antibody detection. As a result of recent efforts to develop new tools for the diagnosis of *M. tuberculosis*, several new diagnostics have been introduced and evaluated.[5–7] However, an accurate point-of-care test that could be used within the peripheral clinical setting with limited laboratory facilities has not yet been successfully developed.[8] Systematic reviews have previously assessed the diagnostic accuracy of adenosine deaminase (ADA) detection for *M. tuberculosis* in the CSF (10 studies).[9] Depending on the classification of culture-negative clinical *M. tuberculosis*, pooled sensitivity estimates range from 75% to 83%, and pooled specificity from 89% to 93%. However, focus has only been on the detection of ADA, and neither of the previously published reviews appraised studies involving antibody detection. The objective of the current systematic review was to estimate the diagnostic accuracy of antibody detection tests using CSF specimens for TBM in adults and children with and without TBM infection.

2. Methods

A standard protocol for systematic reviews and meta-analyses was followed,[10] and methods recommended by the Cochrane Diagnostic Test Accuracy Working Group were used.[11]

2.1. Data sources

Four databases were searched systematically for relevant citations: EMBASE (January 1974 to August 2015) and MEDLINE were searched via Ovid SP, PubMed (January 1946 to 25 July 2015), and the Cochrane Library via the Wiley Online Library (Issue 12 of 25, July 2015). Databases were searched for original, peer-reviewed molecular epidemiology studies that reported the diagnosis of TBM based on antibody detection in the CSF. Keywords were collected through expert opinion, literature review, controlled vocabulary (medical subject headings (MeSH) and Excerpta Medica tree (EMTREE)), and reviewing the results of test searches. No language restrictions were imposed on the search criteria. The search results were de-duplicated using EndNote X5.

2.2. Search strategy

The search strategy included a combination of the following terms: "tuberculosis", "meningeal", and "diagnosis". The search strategy is reported in full in the online **Supplementary Material**.

2.3. Eligibility criteria

Positivity by culture was used for TBM, as well as positivity in a smear or on histopathological examination; positivity by commercial NAA (1-naphthylacetic acid) tests was accepted because these tests provide high specificity.[12,13]

2.4. Study selection

Initially, two reviewers (TYH and QLW) independently screened the citations for relevance. Then, based upon pre-specified selection criteria, these two reviewers independently reviewed the full-text articles. Disagreements with regard to the study selection were resolved by discussion between the reviewers.

2.5. Data analysis

Data were analyzed using Stata/IC 13.0 (StataCorp LP, College Station, TX, USA). Forest plots were used to visually display sensitivity and specificity estimates, and the 95% confidence intervals (95% CI) (using exact methods for proportions) from each study were constructed using MetaDiSc 1.4 software (developed by the Unit of Clinical Biostatistics team of the Ramón y Cajal Hospital in Madrid Spain). Hierarchical summary receiver operating characteristic (HSROC) curves were analyzed to explore the influence of threshold effects and to produce a global summary of test accuracy. Heterogeneity of accuracy estimates was assessed using the I^2 test. Subgroup analyses were performed to study the effects of different antibody detection tests. The area under the receiver operating characteristic curve (AUROC) (with 95% CI) was analyzed by *Z*-test in the subgroups.

2.6. Assessment of study quality

The QUADAS (Quality Assessment of Diagnostic Accuracy Studies) criteria were used to assess the quality of diagnostic accuracy in the studies.[14] All studies were assessed against the following four quality items: flow and timing, reference standard, index test, and patient selection. All criteria were classified as 'high risk', 'low risk', or 'unclear risk' based on the information available in the publication (see **Supplementary Material** Figure S1). Studies were judged according to data used for the meta-analysis, which may not have been all the data available in the publication. This would apply if the study assessed the performance of the antibody assay in *M. tuberculosis* suspects, as well as in healthy controls. If possible, data from healthy controls were excluded for the main analysis.

3. Results

The selection of the studies included in this review is summarized in Figure 1. From the database search, 397 citations were identified. Two hundred thirteen unique articles were left after excluding duplicate articles. Following the screening of titles and abstracts, 98 potentially relevant articles were identified and these were then retrieved for full-text review. Of these, 36 papers (58 studies, 5247 participants) were considered eligible for this study.[15–50]

3.1. Characteristics of studies included

The studies included were performed in India ($n = 23$),[16–20,24–26,30–37,39–42,46,47,50] South Africa ($n = 1$),[15] China ($n = 4$),[22,38,44,45] Kuwait ($n = 1$),[27] Russia ($n = 1$),[49] Thailand ($n = 1$),[48] Colombia ($n = 1$),[23] Santiago ($n = 1$),[43] the Philippines ($n = 1$),[29] Korea ($n = 1$),[21] and the UK ($n = 1$).[28] CSF specimens were used for detection

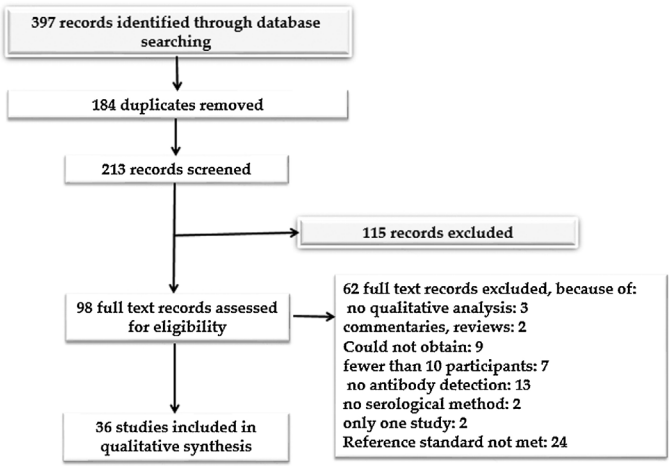

Figure 1. Flow chart of the selection of studies using antibody detection to diagnose tuberculous meningitis.