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Original Article

Diagnostic scoring system for tuberculous meningitis among adult patients with non-suppurative and non-bacterial meningitis☆

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ABSTRACT

Tuberculous meningitis (TBM) is the most severe form of extra-pulmonary tuberculosis. The definite diagnosis of this disease is difficult and can result in delayed treatment. Conventional culture yields low sensitivity while high-sensitivity diagnostic techniques are costly and unpractical. Adenosine deaminase (ADA) is used to diagnose several settings of extra-pulmonary tuberculosis but it is limited in TBM especially among HIV-infected patients. We retrospectively reviewed the data of patients with non-suppurative meningitis and compared the patient data with TBM and other causes including carcinomatous, lymphomatous, lymphocytic and fungal meningitis. We found that HIV infection, diabetes mellitus, duration of symptoms <14 days, radiologic findings of hydrocephalus, and CSF ADA level >10 IU were associated with TBM. The scoring system based on these parameters and their coefficients in the final model achieved an area under the receiver operating characteristic curve of 0.95,625. The indices were HIV infection = 5, diabetes mellitus = 3, duration of symptoms <14 days = 5, hydrocephalus = 4, and ADA in CSF >10 IU = 5. Based on the assumed costs of the patients with false negative and false positive, an appropriate cut off value of 10 was selected and the sensitivity was 92% and specificity was 89%.

1. Introduction

Tuberculous meningitis (TBM) caused by *Mycobacterium tuberculosis* is the most devastating form of extra-pulmonary tuberculosis with a high mortality and long-term neurological disability [1]. The global incidence of TBM is relatively low but tends to increase among patients with immunosuppressive agents, accessing transplantation, diabetes mellitus, and HIV infection [2]. Especially in the era of highly active antiretroviral therapy (HAART), patients with HIV infection who live relatively long will potentially develop both age-dependent and HIV-related risk factors [3]. Several studies have shown that unfavorable clinical outcomes of TBM were associated with delayed time to start anti-tuberculous agents. Thus early recognition of this disease is challenging [4–6]. Diagnosing TBM is difficult due to the wide-ranging clinical characteristics, non-specific radiologic findings, and various cerebrospinal fluid (CSF) results [7]. Furthermore, a definite diagnosis with identification of *M. tuberculosis* in the CSF with routine techniques, that include Ziehl–Neelsen staining (acid-fast staining) and mycobacterial culture, also have poor sensitivity due to the low number of tubercle bacilli in the CSF [8].

Worldwide, large numbers of patients with TBM go undetected or receive delayed appropriate management and many die without treatment [2]. Although empirical anti-tuberculous agents seemed to be an effective strategy, many patients with other chronic meningitides that mimic TBM, for example carcinomatous

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meningitis and chronic fungal meningitis, were harmed from adverse reactions to these drugs and from delayed diagnosis [9]. Recent advanced molecular techniques, such as Gene Xpert MTB/RIF assay, loop-mediated amplification test for tuberculosis and line probe assay for tuberculosis, seemed to be promising methods for a rapid diagnosis of tuberculosis. However, these techniques are unpractical due to the relatively high cost and the requirement for experienced technicians. In addition, these techniques have limited data on the diagnosis of TBM [10–12]. Adenosine deaminase (ADA) is an enzyme involved in purine metabolism. ADA is distributed in the body fluids and has been used in the diagnosis of several types of *M. tuberculosis* infection [13]. The measurement of ADA in clinical specimens is simple and affordable but data on the diagnosis of TBM are still inconclusive and depend on the characteristics of the targeted patients [14–16]. In addition, the elevation of CSF ADA is non-specific for TBM in HIV-infected patients owing to the unclear distinguishing level from other HIV-related diseases [17]. The level for differentiation of TBM from suppurative meningitis, which is caused mostly by bacterial infection, is poor because these conditions also result in relatively high ADA levels [17]. However, the initial clinical manifestations and available bacterial detection techniques are relatively sufficient to distinguish TBM from bacterial meningitis. Therefore, we focused on the limitation of differentiating between TBM and non-suppurative meningitis with the existing laboratories in our setting. A scoring system seemed to be the appropriate diagnostic tool based on gathering and weighting the sufficient data of the patients with non-suppurative meningitis. The objective of this current study was to conduct a diagnostic scoring system to predict TBM based on a retrospective review of the data of patients with non-suppurative meningitis focusing on clinical manifestations, radiologic findings, and routine laboratory tests.

2. Materials and methods

2.1. Setting

The study was conducted at Songklanagarind Hospital which is a tertiary-care hospital and referral center in southern Thailand. The hospital has 800 patient beds and approximately 29,000 patient admissions per year. The hospital has a fully computerized database which was established in 2002. This database includes clinical data and information on laboratory results, radiologic findings, and treatment of the patients.

2.2. Study design

The study was a retrospective review of adult (age ≥18 years) patients who visited the hospital between 1 January 2002 and 31 December 2016 and had clinical conditions compatible with non-suppurative meningitis with the following criteria: 1) at least 1 presenting symptom of fever, headache, seizure or depressed consciousness; 2) at least 1 physical examination sign of fever, cervical stiffness, alteration of consciousness, cranial nerve palsy or plegia/paresis; 3) CSF study showing at least 1 piece of evidence of white blood cells (WBCs) ≥5 cells/high power field (HP) which were <50% polymorphonuclear leukocytes of all WBCs, glucose ≤60 mg/dL or CSF plasma glucose ratio ≤0.4, or protein ≥50 mg/dL. The exclusion criteria were patients with brain abscess with or without parameningeal infection and bacterial meningitis and at least 1 of the following laboratory results: conventional bacterial cultures, *Streptococcus pneumoniae* DNA and antigen detection from CSF and clinical specimens, serologic test or clinical response with conventional antibiotic(s) without clinical subsequence of TBM. The study protocol was approved by the Institutional Review Board (IRB) of the Faculty of Medicine of Prince of Songkla University.

2.3. Data collection

The medical records of all enrolled patients were reviewed from the computerized database. The extracted demographic data included age, sex, comorbidities including documentation of diabetes mellitus, HIV infection, and other immune compromised status such as corticosteroid use at a dosage equivalent to or higher than 10 mg of prednisolone daily for more than 5 days within 4 weeks prior to the onset of infection. Clinical data included presenting symptoms, physical examination, initial laboratory results, CSF findings, and radiologic findings.

2.4. Adenosine deaminase activity (ADA) assay

ADA was determined using the conventional method described by Galanti and Giusti which is routine service in our institute [18]. The method quantifies the ammonia released by deamination of adenosine added to 50 μL of CSF by incubation in the standard solution of phenol and nitroprusside in an alkaline medium. The solution was composed of a phosphate buffer (4.73 $NaH_2PO_4H_2O$ and 5.62 $Na_2HPO_412H_2O$ in distilled water and diluted to 1000 mL with boiled distilled water) and 140 mLof adenosine, ammonium sulfate solution (1.982 g of anhydrous ammonium sulfate in distilled water). The phenol/nitroprusside solution was prepared with 10 mLof phenol and 50 mg of sodium nitroprusside in 500 mL of distilled water. The alkaline medium was prepared with 125 mL of 1 N NaOH and 16.4 mL of 5% w/v NaOCl mixed to 1000 mL in distilled water. The mixture of CSF and solution was incubated in a 37 °C water bath for 1 h. Ammonia released from the 7.05-mL incubated mixture was determined spectroscopically with absorbance at 628 nm wavelength compared against the incubated mixture of water with a standard solution.

2.5. Diagnosis of causes of non-suppurative meningitis

A definite TBM diagnosis was based on at least 2 of 3 laboratory results: 1) detection of acid-fast staining bacilli from CSF or brain tissue; 2) identification of *M. tuberculosis* from mycobacterial culture from CSF or brain tissue; or 3) demonstration of *M. tuberculosis* DNA in the CSF or brain tissue. A probable TBM diagnosis was based on the inclusion criteria of the study with these 3 criteria: 1) confirmation of extracranial tuberculosis with acid-fast staining, mycobacterial culture or detection of *M. tuberculosis* DNA; 2) clinical response with conventional anti-tuberculosis agents including isoniazid, rifampicin, pyrazinamide, ethambutol, and additional options of ofloxacin or levofloxacin and selected aminoglycosides (streptomycin and amikacin); and 3) detection of acid-fast staining bacilli from CSF or brain tissue without confirmation from mycobacterial culture or detection of *M. tuberculosis* DNA. All repositories of CSF and other specimens of the enrolled patients were tested with mycobacterial culture and polymerase chain reaction (PCR) for detection of *M. tuberculosis* DNA. In this current setting, we used real-time PCR with commercial kits of Anyplex™ Plus (MTB/NTM/MDR-TB Detection, version 1.1) (Seoul, Korea). The other selected diagnostic procedures were flow cytometry for lymphocytic, lymphomatous and carcinomatous meningitis, cytological study including specific staining for lymphomatous and carcinomatous meningitis, fungal culture and antigen detection of fungal meningitis, and multiplex-PCR for herpes virus and herpes viral meningitis. Multiplex-PCR for herpes virus and fungal culture were tested from the repositories of CSF of the enrolled patients.

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