Clinical and Cerebrospinal Fluid Abnormalities as Diagnostic Tools of Tuberculous Meningitis

Fiona Lestari,[1] Sofiati Dian,[2] Ida Parwati[3]
[1]Faculty of Medicine Universitas Padjadjaran, [2]Department of Neurology Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital,Bandung, [3]Department of Clinical Pathology Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital,Bandung

Abstract

Background: Tuberculous meningitis (TBM) is the most severe form of extrapulmonary tuberculous (TB) disease and remains difficult to diagnose. The aim of the study was to determine the diagnostic value of clinical and laboratory findings of cerebrospinal fluid (CSF) examinations for diagnosing TBM using bacterial culture result as the gold standard.
Methods: A prospective cross sectional study was carried out to 121 medical records of hospitalized TBM patients in neurological ward at Dr. Hasan Sadikin General Hospital Bandung, from 1 January 2009–31 May 2013. The inclusion criteria were medical records consisted of clinical manisfestations and laboratory findings. The clinical manisfestations were headache and nuchal rigidity, whereas the laboratory findings were CSF chemical analysis (protein, glucose, and cells) and CSF microbiological culture. Validity such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) for clinical and laboratory findings were calculated, using bacterial culture result as the gold standard.
Results: The most clinical findings of TBM was nuchal rigidity and it had the highest sensitivity value, but the lowest spesificity value. Decreased of CSF glucose had the highest sensitivity value compared to other laboratory findings, but the value was low.
Conclusions: The clinical manisfestations and the laboratory findings are not sensitive and specific enough for diagnosing TBM. **[AMJ.2016;3(1):132–6]**

Keywords: Cerebrospinal fluid, clinical manisfestations, diagnostic tools, laboratory findings, tuberculous meningitis

Introduction

Tuberculous (TB) is one of the major health problems in the world, especially in developing countries.[1,2] Manifestations of TB can be pulmonary and or extrapulmonary, which 20.4% cases are extra-pulmonary TB.[3,4] Based on data from Centers for Disease Control and Prevention (CDC) in 2011, it was indicated that 5.7% extrapulmonary TB involved the Central Nervous System (CNS).[4,5] The most severe manifestation of CNS TB is Tuberculous Meningitis (TBM) which causes high mortality in children and adult.[5-8] The mortality rate of TBM in Bandung, the capital city of West Java, Indonesia, is 50% in the first week of admission to the hospital and increases to 67% after one month treatment in the hospital.[9] Early diagnosis and accurate treatment are promptly needed in order to improve the outcomes.[8,10,11]

Standardized diagnostic criteria for TBM have not been established, because the clinical manifestations of TBM are not specific, especially in the early stages of disease.[12] Patients usually come to the hospital after having headache, fever, nuchal rigidity, irritability, vomiting or even after having many neurologic symptoms and signs within a few days.[9,12] Many patients come with history of typical systemic symptoms of TB infection, such as cough, lethargy, weight loss, and night sweating that might be suggestive of TB, but also non-specific.[12] Lumbar puncture is the first procedure to be conducted for patients who are suspected with CNS infections. Routine analysis of cerebrospinal fluid (CSF)

Correspondence: Fiona Lestari, Faculty of Medicine, Universitas Padjadjaran, Jalan Raya Bandung-Sumedang Km.21, Jatinangor, Sumedang, Indonesia, Phone: +62 81931207624 Email: fiona.lestari@hotmail.com

in most patients with TBM shows clear appearance, increased protein, decreased glucose concentration (a CSF glucose to plasma ratio or absolute value) and pleocytosis with lymphocyte predominance.[12]

The aim of the study was to analyze the sensitivity and specificity of TBM clinical manifestations and cerebrospinal fluid abnormalities compared to bacterial culture result.

Methods

A restrospective cross sectional study was carried out to medical records of TBM patients in neurological ward at Dr. Hasan Sadikin General Hospital Bandung, top referral hospital for West Java Province, Indonesia from 1 January 2009 to 31 May 2013.

The inclusion criteria in this study were medical records of hospitalized TBM patients, consisted of clinical manisfestations and laboratory findings. The clinical manisfestations were headache and nuchal rigidity, whereas the laboratory findings were CSF chemical analysis (protein, glucose, and cells), CSF microbiological culture. From 509 available medical records, only 121 medical records which met the inclusion criteria (Figure 1). The operational variables in this study were defined as nuchal rigidity defined by a resistance to flexion of the neck due to muscle spasm of the extensor muscles; increased CSF protein defined by positive in concentration >100 mg/dL; decreased CSF glucose defined by positive in CSF to plasma glucose ratio of <50%; CSF pleocytosis with lymphocytic predominance defined by positive in CSF cells count 10 ? 500 /µL and lymphocyte >50%; CSF abnormalities defined by positive for all three CSF findings in increased CSF protein, decreased CSF glucose and CSF pleocytosis with lymphocytic predominance.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each variable using bacterial culture result as the gold standard. All of the clinical data were entered and calculated using computer. Prior to this study, ethical approval was obtained from the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital/Faculty of Medicine,

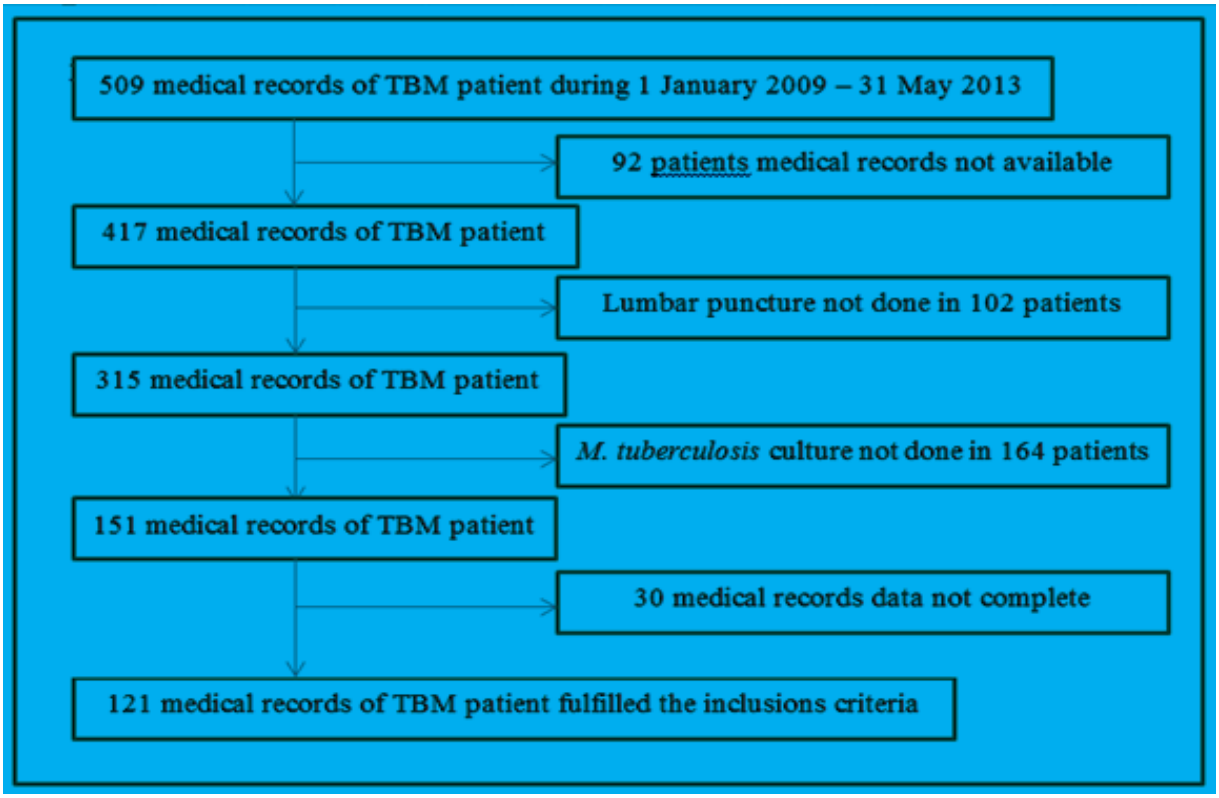

Figure 1 The Inclusion Criteria among 509 TBM Patients

Universitas Padjadjaran, Bandung, Indonesia (No.LB.02.01/C02/9324/VIII/2013).

Results

This study discovered that from 121 TBM cases, most of the patients had nuchal rigidity and headache. From the laboratory findings, the highest percentage of laboratory abnormalitiy was the decrease of the glucose level in CSF (Table 1). Moreover, only 28.93% had positive bacterial culture.

Among 6 variables identified and measured, the symptom of nuchal rigidity had the highest positive culture result, compared to other variables.

This study discovered that nuchal rigidity was the highest sensitivity among 6 variables, but the lowest specificity value. This study revealed that CSF abnormalities was the best variable which incorrectly identified the negative cultural result. All variables in this study showed low percentages for PPV, on the other hand the NPV showed higher percentages (Table 3).

Discussion

In this study, nuchal rigidity had the highest sensitivity and CSF abnormalities had the highest specificity among 6 analyzed variables. Among 121 patients, 93.39% patients had positive sign of nuchal rigidity and 88.43% patients complained of headache. In previous TBM study, it was reported on 77.2% patients with nuchal rigidity and 67% patients with headache.[8] There was an increase number of nuchal rigidity sign and headache in TBM patients. According to Rock et al.[7], adult TBM patients normally come with classic signs of meningitis such as fever, headache, and meningismus/nuchal rigidity.[7]

This study revealed that sensitivity for all of the variables was quite high but less specificity. Diagnosing TBM persistence is still difficult.[13] Sensitivity of nuchal rigidity in this study was 97% positive when cultural result was positive either. Nevertheless, specificity for nuchal rigidity was very low as 8%. It described that nuchal rigidity was not specific to identify the positive culture of TBM. Ideally, the greater sensitivity and specificity

Table 1 Clinical Manisfestations and Laboratory Findings

	Total n (%)
Clinical Manifestation	
Nuchal rigidity	113 (93.39)
Headache	107 (88.43)
Laboratory Findings	
Decreased of CSF* glucose	100 (82.64)
Increased of CSF protein	79 (65.29)
CSF pleocytosis lymphocytic predominance	60 (49.59)
CSF abnormalities	37 (30.58)
Positive bacteria in CSF culture	35 (28.93)

Note: *CSF= cerebrospinal fluid

Table 2 Clinical Manifestations and Laboratory Findings according to Bacterial Culture

	Positive Culture	Negative Culture	Total
Nuchal rigidity	34	79	113
Headache	30	77	107
Decreased CSF glucose	30	70	100
Increased CSF protein	22	57	79
CSF pleocytosis lymphocytic predominance	16	44	60
CSF abnormalities	9	28	37

Table 3 Sensitivity, Specificity, PPV and NPV of Clinical Manifestations and Laboratory Findings.

	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV** (%)
Nuchal rigidity	97	8	30	88
Headache	86	10	28	64
Decreased CSF glucose	86	19	30	76
Increased CSF protein	63	34	28	69
CSF pleocytosis lymphocytic predominance	46	49	27	69
CSF abnormalities	26	67	24	69

Note: *PPV= positive predictive value; **NPV= negative predictive value

of test will make a better diagnostic tool from identifying a disease. A prospective cross sectional study which comparing signs of meningeal inflammation (nuchal rigidity, head jolt accentuation of headache, Kernig's sign and Brudzinski's sign) to the reference CSF white cell count >5 cells as the gold standard concluded that physical signs of meningeal inflammation do not accurately discriminate between patients with meningitis from those without it accurately regarding the poor accuracy.[11] Moreover, headache and nuchal rigidity in meningitis caused by M. tuberculosis and in meningitis caused by other etiological factors cannot be differentiated.

Laboratory findings of CSF examinations revealed that CSF glucose have the highest sensitivity value but the lowest specificity value. A prospective cross-sectional study in the Philipines[5], using culture or acid fast staining or basal meningeal enhancement on computerized axial tomography (CT) head contrast as gold standard for analyzing the laboratory findings showed similar results.[5] This study revealed that 35 patients have positive result for M. tuberculosis. The culture results explained that 28.93% patients have definite diagnosis of TBM, and the remaining patients are categorized as probable or possible diagnosis TBM based on the scoring systems. However, the absence of mycobacterial findings in culture result does not exclude the patients from diagnosis of TBM.[12] One study in Philipine[5] reported that among 68 patients who were diagnosed with TBM, 5.9% culture positive or acid fast staining were found. Another study by Chaidir et al.[8] discovered that 36% TBM patients have positive culture. Study in Shanghai[13] reported that 12% of 25 patients TBM have positive culture. The CDC informed that culture was used as the gold standard for laboratory confirmation of TB disease.[14] Culture result positive established that patients have positive TBM infections. Ideally, sensitivity of a good culture media is 100% which it will grow the etiologic factor in whole TBM infections cases. Nonetheless, culture is an imperfect gold standard. Literature studies informed that M. tuberculosis culture has low sensitivity. It is limited because of the low concentration of bacilli in CSF, characteristic of mycobacterial itself with the need of high enrichment media, or because the patients have already taken the anti tuberculosis drugs before the lumbar puncture done.[5,13,15,16] The chances of positive diagnosis can be increased by doing more lumbar punctures.[12]

There are some limitations of this study. First, acid fast staining and Polymerase Chain Reaction (PCR) method were not used to identify bacteria in CSF. Polymerase Chain Reaction was not routinely done because it is expensive. Second, some medical records were not written completely enough and available to be analyzed in this study. Third, there is no separation calculation for the Human Immunodeficiency Virus (HIV)-co infection patient, which it possibly affects the clinical presentation and laboratory findings in TBM patients.

The ideal diagnostic tests which are validated, rapid, sensitive, and specific are absolutely needed so that appropriate and accurate therapy can be started early, toxicities of unnecessary treatment can be avoided, morbidity and mortality prevalences can be lowered. In conclusion, from clinical findings and laboratory examinations, we found that the sensitivity was quite high but lack for specificity. Combination of all CSF examinations abnormalities showed higher specificity, but less sensitivity. Culture result has low sensitivity.

References

1. WHO. Global tuberculosis report 2012. Geneva: World Health Organization, 2012.
2. Tai MLS. Tuberculous meningitis: diagnostic and radiological features, pathogenesis and biomarkers. Neuroscience & Medicine. 2013;4(2):101–7.
3. Pedoman Nasional Pengendalian Tuberkulosis. In: Indonesia KKR, editor. 2nd ed. Jakarta: Kementrian Kesehatan Republik Indonesia Direktorat Jenderal Pengendalian Penyakit dan Penyehatan Lingkungan; 2011. p. 1–99.
4. CDC. Reported tuberculosis in United States 2011. Atlanta: Central for Disease Control and Prevention; 2012. p. 1–154.
5. Pasco PM. Diagnostic features of tuberculous meningitis: a cross-sectional study. BMC Res Notes. 2012;5:49.
6. Galimi R. Extrapulmonary tuberculosis: tuberculosis meningitis new developments. Eur Rev Med Pharmacol Sci. 2011;15(4):365–86.
7. Rock RB, Olin M, Baker CA, Molitor TW, Peterson PK. Central nervous system tuberculosis: pathogenesis and clinical aspects. Clin Microbiol Rev. 2008;21(2):243–61.
8. Chaidir L, Ganiem AR, Van der Zanden A, Muhsinin S, Kusumaningrum T, Kusumadewi I, et al. Comparison of real time IS6110-PCR, microscopy, and culture for diagnosis of tuberculous meningitis in a cohort of adult patients in Indonesia. PloS One. 2012;7(12):e52001.
9. Basuki A, Dian S, editors. Neurology in daily practise. 2nd ed. Bandung: Bagian/UPF Ilmu Penyakit Saraf Fakultas Kedokteran UNPAD/ RS. Hasan Sadikin; 2011.
10. Christie LJ, Loeffler AM, Honarmand S, Flood JM, Baxter R, Jacobson S, et al. Diagnostic challenges of central nervous system tuberculosis. Emerg Infect Dis. 2008;14(9):1473–5.
11. Waghdhare S, Kalantri A, Joshi R, Kalantri S. Accuracy of physical signs for detecting meningitis: a hospital-based diagnostic accuracy study. Clin Neurol Neurosurg. 2010;112(9):752–7.
12. Marais S, Thwaites G, Schoeman JF, Torok ME, Misra UK, Prasad K, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis. 2010;10(11):803–12.
13. Quan C, Lu C-Z, Qiao J, Xiao B-G, Li X. Comparative evaluation of early diagnosis of tuberculous meningitis by different assays. J Clin Microbiol. 2006;44(9):3160–6.
14. CDC. Diagnosis of tuberculosis. Atlanta: Central for Disease Control and Prevention; 2005. p. 75–107.
15. Velenzuela PB, Mendoza MT, Ang C, Guzman JD. Validation of the Thwaites' diagnostic rule in the diagnosis of tuberculous meningitis in adults at the Philippine General Hospital. Philippine J Microbiol Infect Dis. 2008;37(1):11–9.
16. Thwaites GE, Tran TH. Tuberculous meningitis: many questions, too few answers. Lancet Neurol. 2005;4(3):160–70.