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A Phenotypic Comparison between HIV Positive and HIV Negative Tuberculous Meningitis Patients

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Abstract

Background: Tuberculous meningitis (TBM) is the most common type of meningitis found in humans and the Human Immunodeficiency Virus (HIV) is a major risk factor of TBM. This study aimed to identify phenotype differences, such as clinical manifestations, cerebrospinal fluid (CSF) findings, and chest x-ray results between HIV positive and HIV negative TBM patients. **Methods:** This was a comparative analytical study of 123 TBM patients. The patients were divided into two groups based on their HIV status, and their phenotypes were compared. A retrospective cross sectional designed study was carried out in case report form using a TBM cohort and Rifampicin dose finding study in the neurological ward at the Dr. Hasan Sadikin General Hospital Bandung, between January 2015 and August 2016. Categorical data was analysed using Chi square tests and the alternative Fisher's Exact test and Mann-Whitney test was used for numerical data. P-values were significant if $p < 0.05$. **Results:** Of the phenotypic parameters, only the CSF results had statistical difference. HIV positive subjects had higher CSF to blood glucose ratios (0.42 vs. 0.18; $p = 0.001$) and fewer leukocyte cells (41 vs. 199; $p < 0.001$). **Conclusions:** CSF findings of TBM patients' revealed differences between HIV positive and negative patients, whilst clinical manifestations and chest x-ray results showed no differences.

Keywords: cerebrospinal fluid, chest x-ray, clinical manifestations, HIV, tuberculous meningitis

Introduction

Meningitis is an inflammation of the meninges; the membranes that protect the brain and spinal cord.[1] Based on the duration of the inflammatory process, meningitis can be categorised as acute, subacute, or chronic. Subacute or chronic meningitis is mostly as a result of a Mycobacterium tuberculosis infection.[1,2] Indonesia has very high prevalence rates of tuberculosis (TB) when compared to other countries in Asia, sitting at around 10%.[3] The Human Immunodeficiency Virus (HIV) is a large risk factor in tuberculous meningitis (TBM) patients.[2-4] Findings from a study on meningitis patients at the Dr. Hasan Sadikin General Hospital between 2006 and 2008, showed there were a total of 185 patients diagnosed with meningitis and 25% of those were HIV positive.[2]

The decrease in inflammatory reactions due to lower production of cytokines and inflammatory cells in patients with HIV play an important role in the pathogenesis of HIV related TB.[5-7] Based on the differences in the inflammatory response that occurs in HIV positive and negative TBM patients, it is hypothesised that there may be a difference in phenotype profiles such as clinical manifestations, cerebrospinal fluid findings, and chest X-ray results. A 2009 study undertaken in Texas, USA found that there were significant differences between HIV positive and negative TBM patients, particularly in relation to higher rates of loss of consciousness amongst HIV positive patients. However, similar studies undertaken in Vietnam and Spain found that there was no difference in the level of consciousness amongst HIV positive and negative TBM patients.8 Furthermore, an Indian based study reported that the clinical manifestations and cerebrospinal fluid (CSF) findings in TBM patients were not significant different between HIV positive and HIV negative patients.[9]

This study aimed to determine whether there were any differences in the phenotypic profiles amongst HIV positive and negative TBM patients in Indonesia. The phenotypic profiles that were focussed on were clinical manifestations (fever, headache, neck stiffness, paresis,

seizure, loss of consciousness, and other extrapulmonary tuberculosis), CSF findings (ratios between CSF and blood glucose, leukocyte cell counts, polymorphonuclear cell counts, and mononuclear cell counts), and chest X-ray results (normal, infiltration, cavitation, and miliary). It is hoped that this research will help improve early detection of TB meningitis amongst HIV positive and negative patients so that time specific treatment may be carried out.

Methods

This was a comparative analytical study that utilised data from a previous cross-sectional retrospective study of TBM patients who participated in the Rifampicin Dose Finding Study at the Neurology Department of the Dr. Hasan Sadikin General Hospital between January 2015 and August 2016. All participants of the study were TBM patients who had completed their TB treatment at the Neurology Department of the Dr. Hasan Sadikin General Hospital and total sampling methods were performed. The selection criteria of this study included all adult inpatients (aged ≥ 18 years old) from the Neurology Department of the Dr. Hasan Sadikin General Hospital. Participants had been diagnosed with TBM by definite diagnosis, probable diagnosis, or possible diagnosis (Table 1)[10], had HIV test results, a record of the clinical manifestations of meningitis, CSF findings, and chest X-ray results in their case report form (CRF). The exclusion criterion was incomplete CRF data.The variables noted in this study were the TBM patient's HIV status, age, gender, previous TB treatments, history of pulmonary TB, duration of illness, the clinical manifestations (temperature of ≥ 38.3 °C, headache, stiffness of the neck, paresis, cranial nerve palsy, seizures, loss of consciousness, extrapulmonary TB in addition to TBM), diagnosis of TBM (Table 1)[10], stage of TBM according to the Medical Research Council of Great Britain (Table 2)[11], CSF profiles (CSF and blood glucose ratio, the number of leukocytes, polymorphonuclear cells, and mononuclear cells), and chest X-ray results (normal, infiltration, cavitation, or miliary).

Data was presented in the form of proportion (%), median, and interquartile ranges. Chi squared tests were used for categorical data analysis with the alternative of Fisher's exact test. Mann-Whitney tests were used for numerical data analysis because the data distribution was not considered normal. P-values were significant if $p < 0.05$. This study received ethical approval from the Research Ethics Committee of the Dr. Hasan Sadikin General Hospital, Bandung, Number: 66/UN6.C1.3.2/KEPK/PN/2016.

Table 1 TBM Diagnosis[10]

Diagnosis	Criteria
Definite TBM	Clinical meningitis (nuchal rigidity and abnormal CSF parameters) and acid-fast bacilli in CSF
Probable TBM	Clinical meningitis and ≥ 1 of the following: Acid fast bacilli found in any sample other than from the CSF Suspect active pulmonary TB on the basis of chest X-ray Clinical evidence of the other extrapulmonary TB
Possible TBM	Clinical meningitis an at least 4 of the following: history of TB, duration of illness > 5 days, focal neurological signs, altered consciousness, yellow CSF, predominance of lymphocytes in the CSF, CSF: blood glucose ratio < 0.5

Notes: TBM, Tuberculous meningitis

Table 2. British Medical Research Council Clinical Criteria for Severity of TBM[11]

Stage/grade	Classic criteria
I	Fully conscious and no focal deficits
II	Conscious but with inattention, confusion, lethargy, and focal neurological signs
III	Stupor or coma, multiple cranial nerve palsies, or complete hemiparesis or paralysis

Notes: TBM, Tuberculous meningitis

Results

During the selected study period there were 176 adult patients diagnosed with meningitis (Figure 1). A total of 26 patients were excluded from the study as a result of cryptococcal meningitis (n = 10), bacterial meningitis (n = 8), or viral meningitis diagnoses (n = 8) leaving 150 patients with a TBM diagnosis. A further 27 patients were excluded from the study due to incomplete records, including no CSF findings (n = 3), no HIV test results (n = 10), chest X-ray results (n = 3), or incomplete date regarding their clinical manifestations on their CRF (n = 11). The remaining 123 patients, comprising of 20 (16.26%) HIV positive patients and 103 (83.74%) HIV negative patients were analysed.

The general characteristics of TBM (Table 3) showed significant differences between HIV positive and HIV negative patients, except for age (p = 0.488) and a history of pulmonary TB (p = 0.443). The majority of subjects were male, with a median age of 33 years in the HIV positive group and 31 years in the HIV negative group. Previous TB treatment in the TBM patients was more common in the HIV positive group compared to the HIV negative group (p = 0.026). The duration of illness in TBM patients who were HIV positive was longer than the HIV negative group (p = 0.006).

The clinical manifestations and stages of TBM in patients did not have significant differences between the HIV positive and negative groups (Table 3). Clinical manifestations such as fever (20.39%), headache (91.26%), neck stiffness (90.29%), and paresis (56.31%) were more common in the HIV negative group. Conversely, clinical manifestations such as cranial nerve palsy (85%) and extrapulmonary TB (20%) were more common in the HIV positive group. There were 18 TBM patients with extrapulmonary TB (11.38%), such as miliary TB (n = 3), spondylitis TB (n = 3), abdominal TB (n = 2), and lymphadenitis TB (n = 10). The percentage of TBM patients with a definitive diagnosis was higher in the HIV negative group (34.95%), whereas a possible diagnosis of TBM was more common in the HIV positive group (25%). Most TBM patients only had a probable diagnosis (61.79%) and had stage II TBM (76.42%).

Based on the Mann-Whitney tests, there were significant differences in the CSF to blood glucose ratio and CSF leukocyte cell counts amongst the HIV positive and negative groups. The results of the CSF findings (Table 4) showed the ratio of glucose in the CSF and blood was higher in the HIV positive group (p = 0.001), however the number of leukocytes in the HIV positive group was lower (p < 0.001). Chest X-ray results (Table 4) did not show any significant differences between the

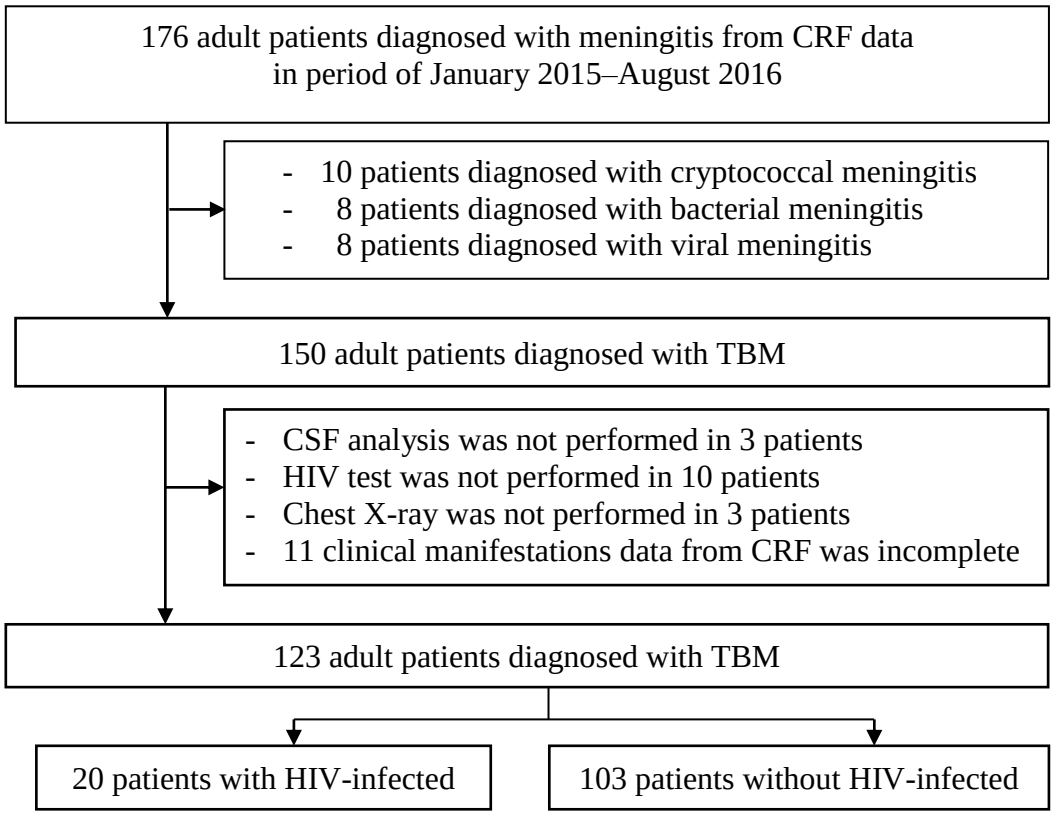

Figure 1. Flow of Patients Who Included in the Study

Table 3. General Characteristics, Clinical Manifestations, Diagnosis, and Stage of TBM Patients amongst HIV Positive and HIV Negative Patients

Characteristics	HIV positive (n = 20)	HIV negative (n = 103)	*p*
General Characteristics			
Age (years), median (IQR)	33 (26-41)	31 (24-39)	0.488
Gender, n (%)*			
Men	16 (80)	55 (53.4)	0.028
Women	4 (20)	48 (46.6)	
Previous TB treatment, n (%)*	9 (45)	22 (21.36)	0.026
History of pulmonary TB, n (%)	9 (45)	37 (35.92)	0.443
Duration of illness (days), median (IQR)*	90 (28-120)	30 (14-45)	0.006
Clinical Manifestations			
Fever (temperature ≥ 38.3°C), n (%)	4 (20)	21 (20.39)	0.968
Headache, n (%)	18 (90)	94 (91.26)	0.856
Neck stiffness, n (%)	18 (90)	93 (90.29)	0.968
Hemiparesis, n (%)	8 (40)	42 (40.78)	0.948
Paraparesis, n (%)	2 (10)	16 (15.53)	0.735
Seizures, n (%)	3 (15)	11 (10.68)	0.699
Cranial nerve palsy, n (%)	17 (85)	71 (68.93)	0.145
Loss of consciousness, n (%)			
GCS 12–14	10 (50)	57 (55.34)	0.661
GCS ≤11	6 (30)	24 (23.3)	0.572
Extrapulmonary TB in addition to TBM, n (%)	4 (20)	14 (13.59)	0.491
TBM Diagnosis*			
Definitive diagnosis, n (%)	2 (10)	36 (34.95)	0.001
Probable diagnosis, n (%)	13 (65)	63 (61.17)	
Possible diagnosis, n (%)	5 (25)	4 (3.88)	
TBM Stage			
Stage I, n (%)	0 (0)	5 (4.85)	0.51
Stage II, n (%)	15 (75)	79 (76.7)	
Stage III, n (%)	5 (25)	19 (18.45)	

Notes: n, number of patients; proportions (%), number of patients/number of available data;
IQR, interquartile range; GCS, Glasgow Coma Scale; TB, tuberculosis;
HIV, human immunodeficiency virus; TBM stadium based on Medical Research Council of Great Britain.
*$p < 0.05$
**Age and duration of illness were analysed by Mann-Whitney test
Gender, previous TB treatment, hemiparesis, and cranial nerve palsy were analysed by Chi squared test

Table 4. CSF Findings and Chest X-ray Results between HIV Positive and HIV Negative TBM Patients

Characteristics	HIV positive (n = 20)	HIV negative (n = 103)	*p*
CSF findings			
Ratio of CSF:blood glucose, median (IQR)*	0.42 (0.33-0.47)	0.18 (0.11-0.34)	0.001
Leukocytes (cells counts/mL), median (IQR)*	41 (3-99)	199 (57.5-404)	<0.001
% PMN, median (IQR)	22.5 (0.75-76.75)	39 (20-63)	0.325
% MN, median (IQR)	77.5 (23.25-99.25)	61 (36-80)	0.327
Chest X-Ray results			
Normal, n (%)	6 (30)	26 (25.24)	0.657
Abnormal, n (%)	14 (70)	77 (74.76)	
Infiltration, n (%)	11 (55)	49 (47.57)	0.543
Cavitation, n (%)	0 (0)	9 (8.74)	0.353
Miliary, n (%)	3 (15)	23 (22.22)	0.563
Others, n (%)	1 (5)	20 (19.42)	0.192

Notes: n, number of patients; proportions (%), number of patients/number of available data;
IQR, interquartile range; CSF, cerebrospinal fluid; MN, mononuclear;
PMN, polymorphonuclear; HIV, human immunodeficiency virus
*p-value <0.05
**CSF findings were analysed by Mann-Whitney test
Chest X-Ray results were analysed by Fisher's exact test

HIV positive and negative groups (p = 0.657). Infiltrates (48.78%) were the most common abnormality found in the chest X-rays of the subjects.

Discussion

In the present study, TBM (86.39%) was the most common type of meningitis followed by cryptococcal meningitis (5.68%), viral meningitis (4.55%), and bacterial meningitis (4.55%). These results were in accordance with a study conducted in South Africa in 2009, which found that meningitis was mostly caused by M. tuberculosis infections (56.87%).[12-14] Furthermore, males made up a larger proportion of the present study's population (57.72%), findings that are similar to studies carried out in Vietnam, which reported higher TBM rates in male patients (60.79%), with 88.5% of them being HIV positive. Additionally, studies carried out in South Africa, Europe, and Argentina have all reported higher percentages of male patients with TBM.[10,12,15]

Results from the present study suggest that HIV positive patients with TBM experienced a longer duration of illness. The duration of illness is defined as the time from the first clinical manifestations of meningitis until the patient presents at the hospital. In patients with HIV, activation of the inflammatory response occurs for a longer period however the inflammatory reaction is decreased, this results in many patients seeking treatment later than HIV negative patients.[5-7] In the present study, leukocyte cell counts of the CSF in HIV positive TBM patients were less than the HIV negative group. As such, patients who are HIV positive are more likely to present to hospital when their TBM had entered the advance stages because the initial clinical symptoms may not have been obvious.[1,16]

There were 11 HIV positive TBM patients (55%) who had never had TB treatment, whilst the others had a history of previous TB treatment. Previous treatment for TB was more common in the HIV positive group compared to the HIV negative group, as such patients who are HIV positive have a higher risk of relapse.[4] Furthermore, a higher percentage of TBM patients had a history of pulmonary TB in the HIV positive group (45%) compared to the HIV negative group (35.92%). These findings are in contrast with a Vietnamese study, which suggests there were no significant differences in previous TB treatments in HIV positive and negative TBM patients.[10]

HIV infections did not appear to affect the patient's clinical manifestations of TBM. These findings are in line with similar studies conducted in Vietnam, India, and Brazil. The clinical manifestations of TBM patients in Vietnam, such as fever, cranial nerve palsy, and stage of TBM in HIV positive patients were not significantly different to the HIV negative group.[10] Additionally in India, clinical manifestations such as headache, cranial nerve involvement, and endocrine dysfunction in TBM patients did not show any significant differences between the HIV positive and HIV negative groups.[12] Furthermore, a Brazilian study reported that the clinical presentation of HIV positive TBM patients were not specific.[17] In the present study, results from chest X-rays of the TBM patients were not significantly different between the two groups. These results are similar to a 2003 Vietnamese study, in which chest X-ray results of HIV positive and negative TBM patients showed no differences.[10]

There was a total of 16.26% of TBM patients who were HIV positive in the current study. A definite diagnosis of TBM was more common in the HIV negative group (34.95%), whilst a diagnosis of possible TBM was more common in the HIV positive group (25%). The majority of participants had a probable diagnosis of TBM (61.79%). These findings differ to those from the Vietnamese study, that found there was no significant difference between the diagnoses (definitive, probable, or possible) of HIV positive and negative TBM patients .10 Furthermore, a study in South Africa showed a high prevalence of HIV positive TBM patients (88.3%) and reported different results. Most HIV positive TBM patients were diagnosed with a definitive diagnosis (44.34%) compared to a probable diagnosis (20.01%) and a possible diagnosis (35.65%).[12] It could be concluded that HIV prevalence may affect the type of diagnosis used for TBM patients. Other factors that may influence the diagnosis is clinical settings with limited resources.[13,18] TBM can be difficult to diagnose and might be based only on clinical presentations and preliminary CSF findings, without definitive microbiologic confirmation.[19-21] Diagnostic imaging such as computed tomography or magnetic resonance imaging may also be used to diagnose TBM patients, however it is not widely available in some countries.[2,13] In the present study, computed tomography scanning was rarely available and decisions to perform lumbar punctures were based on clinical signs only. As such, only 31% of TBM patients were given a definitive diagnosis.

The majority of patients in the study were categorised as second stage TBM, however the stage of TBM between HIV positive and HIV negative patients did not show any statistical differences. These findings were again similar to those of a Vietnamese study that also showed there was no significant differences between the stages of TBM in HIV positive and negative patients.[10] Results from an Indian study showed that there were no differences in the CSF findings of TBM HIV positive and negative patients, whereas results of the present showed a significant difference.[22]

Additionally, results from the present study showed that leukocyte cell counts of HIV positive TBM patients were lower, and the ratio between the glucose in the CSF and the glucose in the blood was higher. Furthermore, CSF

analysis in TBM patients revealed there was an increase in lymphocytes with other inflammatory cells.[23,24] This is in contrast to the Vietnamese study, which found that TBM patients had a high CSF cell count, with neutrophil predominance. A low percentage of CSF lymphocytes were an abnormality that was found to be associated with death. Patients with advanced HIV usually had a low number of lymphocytes in the peripheral blood, which may be reflected in the low CSF lymphocyte count. Furthermore, TBM may stimulate increased HIV replication in the CNS compartment, thus resulting in the destruction of CSF lymphocytes.[25-27]

M. tuberculosis infections can lead to an increase of glucose consumption by inflammatory cells and changes in glucose transport from blood to the CSF, resulting in a decrease of the CSF to blood glucose ratio, which was <0.5.[2,28] In HIV positive patients, the inflammatory reaction was decreased due to a lower production of certain cytokines, such as Interferon-gamma, Tumour Necrosis Factor-alpha, and Interleukin. Cytokines play an important role in the pathogenesis of HIV related TBM. Inflammatory reactions, which are decreased in HIV positive individuals, could cause a decrease in inflammatory cells, thus there is less glucose consumption by inflammatory cells. Therefore, the ratio between CSF and blood glucose was higher in HIV positive patients.[5-7,28]

The present study has several limitations. Firstly, this was a cross-sectional retrospective study and as such there was some incomplete data on the CRFs, such as clinical manifestations (7.3%), HIV test results (6.7%), chest X-ray results (2%), and CSF findings (2%). Incomplete data regarding clinical manifestations may have influenced the results in this study as there were no significant differences between HIV positive and HIV negative patients, whereas similar studies did show significant differences. Secondly, a definitive diagnosis of TBM is difficult to establish, with only 31% of TBM patients having a definitive diagnosis in the present study. Lastly, we were only able to include patients in a single (large) hospital.

Conclusions

There were, significant differences in the CSF findings of HIV positive and negative TBM patients, whilst there were no significant differences in the clinical manifestations and chest X-ray results. HIV positive subjects had a higher CSF to blood glucose ratio and fewer leukocyte cells. As such, it is our recommendation that TBM patients, who have a higher CSF to blood glucose ratio and fewer leukocytes on CSF analysis, should be investigated for a possible HIV infection.

Conflict of Interest Statement

There were no conflicts of interest.

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