

## Characteristics of Cerebrospinal Fluid in Tuberculous Meningitis Patients with Hydrocephalus

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### Abstract

**Objective:** To describe cerebrospinal fluid (CSF) characteristics in tuberculous meningitis (TBM) with hydrocephalus patients as diagnostic criteria of TBM.

**Methods:** A cross-sectional using retrospective method was applied in this study by obtaining medical records of TBM with hydrocephalus patients that were treated at Department of Neurosurgery Dr. Hasan Sadikin General Hospital, Bandung from January 2014–September 2016.

**Results:** Sixty one records were included in the study. Patient characteristics such as age, gender, and CSF laboratory features such as color and clarity, cells and differential count, protein, and glucose were recorded and descriptively analyzed. The majority of CSF macroscopic appearance was seen to be clear (88%) and colorless (88%). Median for CSF cell count was 25 cells/mm<sup>3</sup> with lymphocyte predominance (median: 76%). Increased protein from normal value range was seen in CSF (median: 50 mg/dL) while the mean for CSF glucose in this study remained in its normal value range (mean: 58.9±26.68 mg/dL) with lower CSF to blood glucose ratio (mean: 0.41±0.27).

**Conclusions:** Clear CSF with colorless appearance, lymphocyte pleocytosis, high protein level, and low CSF glucose as well as blood glucose ratio remain typical CSF characteristics of TBM patients found at the Department of Neurosurgery, Dr. Hasan Sadikin General Hospital, Bandung.

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### Introduction

Tuberculosis (TB) currently remains a major global health issue. Indonesia is currently in the top three in terms of TB cases where 10% of the total TB population in the world is found in this country.<sup>1</sup> One of extrapulmonary TB with high mortality and morbidity, especially in children, is tuberculosis meningitis (TBM).<sup>2</sup> Hydrocephalus is the most frequently found complication of TB and one of the predictors of mortality and morbidity.<sup>2</sup>

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Early diagnosis and proper management of TBM is an important factor that influences mortality and morbidity. Cerebrospinal fluid (CSF) examination is an important parameter in the diagnosis of TBM. This CSF examinations includes macroscopic, microscopic, chemical, and microbiological examinations. Bacterial culture or acid-fast bacilli (AFB) observation in CSF are used to establish TBM definitive diagnosis.<sup>2,3</sup> A previous study has reported that the ratio of positive culture results were 13% among TBM patients.<sup>4</sup> In several cases, low results of bacterial culture and AFB on CSF may be seen. Hence it is important to observe the macroscopic, microscopic, and chemical characteristic as a reference for the laboratory-based diagnosis of TBM.<sup>4</sup>

## Characteristics of Cerebrospinal Fluid in Tuberculous Meningitis with Hydrocephalus Patients

This study aimed to observe the chemical, macroscopic, and microscopic characteristics of CSF in TBM patients with hydrocephalus at the Department of Neurosurgery Dr. Hasan Sadikin General Hospital, Bandung.

### Methods

This design used in this study was retrospective cross-sectional descriptive study. TBM patients with hydrocephalus treated at the Department of Neurosurgery, Dr. Hasan Sadikin General Hospital, Bandung who met the inclusion and exclusion criteria were included. The inclusion criteria in this study were inpatients during the period of January 2014–September 2016, with a computerized tomography (CT) scan results that suggested hydrocephalus who had undergo CSF examination with specimens derived from ventricular drainage at the Clinical Pathology Laboratory of Dr. Hasan Sadikin General Hospital, Bandung, with macroscopic, microscopic, and chemical characteristic result, including protein and glucose levels. Exclusion criteria included congenital hydrocephalus, meningitis caused by organisms other than *Mycobacterium tuberculosis*, positive Human Immunodeficiency Virus (HIV) status, and incomplete medical record. Samples were selected using the total sampling method.

Approval from the Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran under the ethical clearance No. 102/UN6.C1.3.2/KEPK/PN/2016 was gained. This study was conducted from August to December 2016 by collecting data from the medical records of TBM inpatients with hydrocephalus who were treated at the Department of Neurosurgery, Dr. Hasan Sadikin General Hospital, Bandung. CSF of these patients were examined at the Laboratory of Clinical Pathology of the same hospital.

Variables used in this study were age, CSF color, clarity, leukocyte cell numbers, cell count percentage, protein level, and glucose level. Data were then analyzed descriptively by counting the number and percentage for the results of macroscopic examination while for microscopic and chemical examination results, mean and standard deviations or median and range were used based on the distribution of the data.

### Results

There were 477 patients with TBM in Dr. Hasan Sadikin General Hospital Bandung from 2014 to 2016. A total of 170 (35.6%) patients were treated at the Department of Neurosurgery Dr. Hasan Sadikin General Hospital, Bandung with 149 cases (31.2%) were diagnosed as TBM with hydrocephalus. Sixty six cases (44.3) met the inclusion criteria but five of them must be excluded, resulting a total of 61 (40.9%) cases. All were included in the study. All CSF samples collected from these 61 patients were taken from ventricular drainage such as extra ventricular drainage (EVD) or ventriculoperitoneal (VP) shunt.

The number of male patients was higher than the number of female patients (Table 1). Age categorization of children and adults in this study referred to the existing consensus in Dr. Hasan Sadikin General Hospital, Bandung with 0–14 years categorized as children, and >14 years classified as adults. The number of pediatric patients was higher when compared to adults patients. Median age was 6 years old with a range of 6 months–58 years.

Examination of CSF was performed on TBM patients with hydrocephalus and the results were compared to normal values and criteria from Marais *et al.*<sup>3</sup> (Table 2). Cerebrospinal fluid color in TBM patients with hydrocephalus

**Table 1 Distribution of Tuberculous Meningitis with Hydrocephalus Patients Based on Age and Gender**

Gender	Children	Adults	Total (%)
Male	20	15	34 (56)
Female	19	7	27 (44)
Total	39	22	61 (100)

in this study was generally colorless. Similarly, the clarity level of CSF in this study generally showed a clear result.

The median of the CSF leukocyte cells was 25 cells/mm<sup>3</sup> (range was 1-613 cells/mm<sup>3</sup>). The differential cell count of the cerebrospinal fluid was presented in the form of percentage of mononuclear (MN) and polymorphonuclear cells (PMN). Mononuclear cells were shown to be the dominant cell in the CSF. The scope of percentage for both PMN and MN was 0% to 100%. There were two cases which showed the percentage of PMN of 100%, with a CSF leukocyte cell count of 1 cell/mm<sup>3</sup> in both.

The median CSF protein was higher than the normal value but not as high as the one in Marais *et al.*<sup>3</sup> criteria. The mean CSF glucose was 58.9±26.68 mg/dL which was still in the normal limit. The CSF to blood glucose ratio

could only be calculated in 11 patients (mean: 0.41±0.27).

## Discussion

This study reveals that the prevalence of TBM with hydrocephalus is predominated by males. This finding is in agreement with the results of previous studies.<sup>4-6</sup> A study found that the prevalence of pediatric patient with TBM with hydrocephalus as complication is 71% while the same prevalence for adults is 12%.<sup>7</sup> This study also shows that more children has TBM with hydrocephalus compared to adult.

Macroscopic examination on the color and clarity of CSF was performed. The macroscopic appearance of CSF in this study was generally clear and colorless. This is in line with the

**Table 2 Cerebrospinal Fluid Examination in Tuberculous Meningitis Patients with Hydrocephalus**

Variable	Normal value	Marais <i>et al.</i> <sup>3</sup> Criteria for TBM	Result
<b>Macroscopic appearance</b>			
CSF color*	Colorless		
Colorless, n(%)			54 (88)
Yellowish, n(%)			4 (7)
Yellow, n(%)			3 (5)
Clarity	Clear	Clear	
Clear, n(%)			54 (88)
Cloudy, n(%)			6 (10)
Turbid, n(%)			1 (2)
<b>Microscopic examination</b>			25 (1-613)
CSF cells, median (range)	<5 cells/mm <sup>3</sup>	10-500 cells/mm <sup>3</sup>	cells/mm <sup>3</sup>
Differential count, median (range)			
PMN (%)**	<50%		24 (0-100)
MN (%)#	>50%	>50%	76 (0-100)
<b>Chemistry</b>			
Protein, median (range)	10-40 mg/dL	>100 mg/dL	50 (5-977) mg/dL
Absolute CSF glucose, mean±std deviation	50-80 mg/dL	<40 mg/dL	58.9±26.68 mg/dL
CSF to blood glucose ratio###, mean±std deviation	0.6	<0.5	0.41±0.27

Note: \*CSF = Cerebrospinal fluid; \*\*PMN = polymorphonuclear; #MN = mononuclear; ###Could only be done in 11 patients

diagnosis criteria of TBM according to Marais *et al.*<sup>3</sup> Tuberculous meningitis is a chronic disease characterized by clear CSF with not really high leukocyte count and is dominated by lymphocytes.<sup>3,8,9</sup> The inflammation response of T cell as TBM pathogenesis is demonstrated through the predominance of lymphocytes in microscopic examination of CSF, as seen in previous studies and this study.<sup>5,10-13</sup>

Marais *et al.*<sup>3</sup> stated that a diagnosis criteria of chemical examination of CSF includes an increase in CSF protein (>100 mg/dL). This study shows the amount of CSF protein was not greater than 100 mg/dL as stated in the criteria diagnosis by Marais *et al.*<sup>3</sup> However, the median CSF protein was in accordance with previous studies stating that the mean CSF protein was not more than 100 mg/dL despite the increase of the CSF protein value when compared to the normal value.<sup>6</sup> As the top referral hospital in West Java, Dr. Hasan Sadikin General Hospital, Bandung, in particular the hospital's Clinical Pathology Laboratory, has their own normal CSF protein range standard of 10–40 mg/dL. The CSF protein in TBM which is supposed to be increased according to the pathogenesis of TBM is considered as the result from the increased permeability of blood brain barrier or decreased reabsorption in the arachnoidalis villi.<sup>8,13</sup>

The normal value of glucose in CSF is 2/3 of the plasma glucose, or approximately 50 to 80 mg/dL.<sup>8,13</sup> As already explained in the criteria for TBM diagnosis, the CSF glucose should be less than 40 mg/dL (2.2 mmol/L) or the ratio between CSF glucose and plasma glucose is lower than 50%.<sup>3</sup> This decrease in glucose is resulted from anaerobic glycolysis caused by bacteria or disturbance in glucose transport mechanism.<sup>8,13</sup> The mean glucose level in this study was >40 mg/dL and was still in the normal range of CSF glucose. This is in contrast with the diagnostic criteria by Marais *et al.*<sup>3</sup> and some previous studies.<sup>6,9</sup> A previous study presented that the number of patients with glucose level <40 mg/dL was 48% or less than a half of all patients and that the glucose level had a wide range between 12.1–156.7 mg/dL as also shown in this study (2–135 mg/dL).<sup>11</sup> There are only 11 patients whose CSF glucose to blood glucose ratio can be measured (median: 0.41±0.27). This result is in line with the diagnostic criteria by Marais *et al.*<sup>3</sup> which stated that CSF glucose to blood glucose ratio is <50%.

Most previous studies that have discussed the CSF characteristics in TBM use CSF to blood glucose ratio <0.5 as one of diagnostic criteria

for TBM.<sup>4,14</sup> The previous studies showed that the sensitivity of the low absolute CSF glucose was low, that is 68% and 69.5%.<sup>12,15</sup> On the other hand, previous studies also showed that the sensitivity of low CSF to blood glucose ratio was 90%.<sup>15</sup> This explains why the normal absolute CSF glucose level cannot rule out the possibility of infection and it had also been suggested that considerations should be given to use CSF to blood glucose ratio as additional information for diagnosis of TBM.<sup>15</sup>

The difference of CSF content in this study compared to Marais *et al.*<sup>3</sup> criteria might be caused by the CSF source itself.<sup>16</sup> Previous study had shown difference CSF composition between ventricular and spinal CSF that may be caused by the disease's pathophysiology.<sup>16</sup> The impaired blood-brain barrier leads to a higher protein composition which may slow down the circulation of CSF and may impair CSF absorption or obstruct the CSF pathway that causes hydrocephalus after aggregation of CSF protein and leukocytes caudally.<sup>16</sup>

The median of age in this study (median: 6 years) reflects a higher distribution among children below 6 years old. Several previous studies have shown age-related variations in CSF protein content.<sup>8,17</sup> It is shown here that there is a lower protein CSF value in children when compared to adults and this might result in lower protein CSF in this study compared to the Marais *et al.*<sup>3</sup> criteria.<sup>8,17</sup>

Furthermore, the use of antimicrobial agent before ventricular drainage may also affect CSF protein and glucose content.<sup>18</sup> Time of interval median between the occurrence of tuberculosis to hydrocephalus development was 21 days (range: 3–180 days). In between, patients consumed antituberculous drugs. A previous study has shown that CSF glucose will increase and CSF protein will decrease significantly after the use of antibiotic, especially in the period of >12 hours postantibiotics.<sup>18</sup>

There are several limitations in the study including the small sample size, i.e. 61 samples. This is due to the limited time and rejection from some TBM patients with hydrocephalus to undergo ventricular drainage that includes both EVD and VP shunts. In addition, incomplete patient records and archives creates another limitation, especially when the result of CSF in patient who underwent ventricular drainage is missing. Another reason is that blood glucose measurement done 15–30 minutes prior to the ventricular drainage was not done in almost all samples. This makes the calculation of CSF to glucose ratio cannot be performed in almost all patients. Specimen was also taken from

ventricular drainage that may also affect the results compared to those of previous studies that mostly used lumbar fluid as specimens.

In conclusion, the diagnosis of tuberculous meningitis is still problematic, especially with the high number of the hydrocephalus seen. CSF presentations such as clear and colorless CSF, lymphocyte pleocytosis, increased protein level, and lower CSF to blood glucose ratio

are still the typical characteristics found in TBM with hydrocephalus in Dr. Hasan Sadikin General Hospital, Bandung. Examination of CSF in TBM may be done in every level of health facilities as it is the easiest way to diagnose this disease. This study suggests the use of CSF to blood glucose ratio as a routine examination to in TBM diagnosis.

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