Althea Medical Journal. 2022;9(4):198–205

Outcomes of Tuberculous Meningitis Patients with or without Hydrocephalus from a Tertiary Hospital in West Java, Indonesia

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Abstract

Background: Tuberculous meningitis (TBM) is a severe form of extrapulmonary tuberculosis. One of the most common complications of TBM is hydrocephalus, with a higher risk of mortality. This study aimed to evaluate the outcome among TBM patients with or without hydrocephalus.

Methods: This study was a retrospective cross-sectional comparative analytical study. A total sampling was employed based on the number of traceable resumes of TBM patients treated at the Department of Neurology Dr. Hasan Sadikin General Hospital, Bandung, Indonesia in 2018.

Results: Of the 127 data of TBM patients, 55 (43.3%) had hydrocephalus, and 72 (56.7%) did not. The median age of TBM patients with and without hydrocephalus was 34 years (IQR 26–45) and 35 years (IQR 24–44), respectively. Decreased consciousness dominated the clinical symptoms for 94.5% in the hydrocephalus group and 84.7% in the non-hydrocephalus group. Hospital-acquired pneumonia occurred mainly in the hydrocephalus group (29.1%), whereas urinary tract infections mainly occurred in without hydrocephalus group (18%). There was a significant difference between the outcome of hydrocephalus and non-hydrocephalus (p=0.005). Mortality was higher in patients with hydrocephalus compared to those without hydrocephalus.

Conclusions: The outcome of TBM patients with hydrocephalus is worse than those without hydrocephalus, as reflected by a higher grade of TBM, higher mortality rate, and lower good recovery upon treatment administration. Therefore, prompt diagnosis and treatment are needed to improve the outcome and survival among TBM patients with hydrocephalus.

Keywords: Hydrocephalus, outcome, TB meningitis

Introduction

Tuberculosis (TB) is one of the oldest known diseases to affect humans, caused by infection with *Mycobacterium tuberculosis*. Indonesia is the third most infected country with TB globally after India and China. The World Health Organization (WHO) estimated that the incidence of TB in Indonesia in 2018 was around 316 per 100,000.[1] TB usually infects the lungs. However, it can also infect other organ systems, known as extrapulmonary TB. One severe form of extrapulmonary TB is tuberculous meningitis (TBM), which has high mortality.[2] The mortality rate for TBM is high, around 20–41%. Therefore, the most essential factors in lowering the complications and mortality rate are early diagnosis and treatment of the disease.[3]

The most common and significant factor that is closely correlated with the incidence of TBM is human immunodeficiency virus (HIV) co-infection.[4] Other factors contributing to the incidence of TBM include diabetes mellitus,[5] alcoholism, and chronic use of corticosteroids.[6] Progressivity of TB infection, whether pulmonal or extrapulmonal is several folds higher and more aggressive among immunocompromised individuals; hence, these patients are at higher risk of developing tuberculous meningitis and accounts higher rate of mortality.[7]

In TBM, *Mycobacterium tuberculosis* initially seeds the meninges and forms a highly

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https://doi.org/10.15850/amj.v9n4.2304

infectious foci termed Rich foci, specifically located beneath the pia mater, or attach to the adjacent ventricle and/or cortical tissue. Rupture of these bacteria-filled foci will induce excessively and life-threatening inflammatory reactions. Exudative lesion and debris produced from this process could potentially disrupt nearby tissues; if the exudate encloses the nervous system particularly cranial nerves, it will cause cranial nerve palsies. Vasculitis of the cerebrovascular system arises due to endothelial and basal membrane involvement. Another aspect that must be taken into account is that the exudate and inflamed meninges can also obstruct the cerebrospinal fluid (CSF) flow within the cerebral ventricle system, causing hydrocephalus.[8,9]

The prognosis of TBM is influenced by many factors. Previous findings suggest that clinical, laboratory, and radiological findings could predict the outcome of TBM.[10,11] Clinical parameters consisted of headache, seizure episode(s), positive neck stiffness, febrile, hydrocephalus, and neurological deficits upon examination (including comatose episode); laboratory parameters consisted of HIV serology test and/or other comorbidities, high CSF protein concentration, and meningeal enhancement on radiographical imaging are all associated with poorer prognosis of TBM.[10,11]

The incidence of hydrocephalus among adult patients with TBM is approximately 65%. Hydrocephalus is the cause of death and severe neurogenic deficits among TBM cases.[3] Several current studies have reported that TBM patients with hydrocephalus, particularly those who left untreated had poorer prognosis and significantly lower survival rate if compared with the TBM patients without hydrocephalus or TBM hydrocephalus patients that received treatment.[10–14] This study aimed to identify the difference between the outcome of TBM patients with or without hydrocephalus treated in a tertiary hospital.

Methods

This research was a retrospective cross-sectional comparative analytical study using the medical records of patients obtained from the Department of Neurology Dr. Hasan Sadikin General Hospital Bandung. Data collection and processing were carried out in August 2020.

The inclusion criteria were patients with a final diagnosis of TBM, admitted to the hospital in 2018, and aged >18 years. The exclusion criteria of this study were patients with a history of incomplete treatment and incomplete head imaging data. This research received ethical approval from the Research Ethics Committee of Universitas Padjajaran, with the number 650/UN6.KEP/EC/2020 and the Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung, with LB.02.01/X.2.2.1/19544/2020.

The data collected from the medical record included demographic data, length of stay, symptoms, physical examination, and supporting examinations among others sodium and blood sugar levels, cerebrospinal fluid analysis, head imaging, HIV status, nosocomial infections, medications, surgery performed, and the outcomes, that was assessed using the Glasglow Outcome Scale (GOS).

Determination of GOS interpretation was carried out when the patient was discharged from the hospital by determining the presence of language disorders, motoric strength, and consciousness. The data were then interpreted to be GOS 1 in patient who died; GOS 2 patient was coma; GOS 3 patient was in a sopor or somnolent state or had a degree of motor strength of 0 to 3 or had language disorders; GOS 4 patients was in compos mentis with a degree of motor strength 4; GOS 5 patient was in a state of compos mentis with a degree of motor strength of 5 or had mild neurological sequelae.

Data processing was carried out by calculating the mean, number, percentage, and interquartile range of characteristics of patients with or without hydrocephalus, including age, sex, symptoms, laboratory findings, radiology, TBM degree, HIV status, surgery performed, and nosocomial infection during treatment. The GOS interpretation was then analyzed using Mann-Whitney test.

Results

This study found 146 data of patients who were treated with a diagnosis of TBM, of whom 127 were included. In general, this study was dominated by males (51.9%). Interestingly, more females were in the group without hydrocephalus (54%). The mean age of TBM patients with and without hydrocephalus was not significantly different, which was 34 (IQR 26–45) and 35 (IQR 24–44), respectively. The most common length of stay was >7 days in most patients with hydrocephalus (54.4%) or without hydrocephalus (79%), as shown in Table 1. Furthermore, decreased consciousness was the most common clinical symptom in this study. Other symptoms, such as fever, nausea, headache, neck stiffness, and

Table 1 Characteristics of Adult Tuberculosis Meningitis Patients with or without Hydrocephalus Admitted to Dr. Hasan Sadikin General Hospital Year 2018

Characteristic	Tuberculous Meningitis (n=127)	
	With Hydrocephalus (n=55) n (%)	Without Hydrocephalus (=76) n (%)
Sex		
Male	33 (60)	33 (46)
Female	22 (40)	39 (54)
Age, in years–median (IQR)*	34 (26–45)	35 (24–44)
Length of stay		
>7 days	31 (56.4)	57 (79)
<7 days	24 (43.6)	15 (21)
Clinical symptoms		
Decreased consciousness	52 (94.5)	61 (84.7)
Fever	44 (80)	49 (68)
Nausea	16 (29.1)	13 (18)
Neck stiffness	47 (85.4)	56 (77.7)
Headache	48 (87.3)	52 (72.2)
Nerve disorder	5 (9.1)	7 (9.7)
Increased intracranial pressure	3 (5.4)	1 (1.3)
Seizure	3 (5.4)	7 (9.7)

Note: All data are presented in n (%) unless specifically stated, *There were some data not available

other signs of increased intracranial pressure (ICP), were higher in TBM with hydrocephalus.

There was various supporting examinations, as shown in Table 2. The mean blood sodium levels were lower in patients without hydrocephalus (130 mEq/L; IQR 126–137). Blood sugar levels were lower in TBM without hydrocephalus (107 mg/dL; IQR 94–126.7). The mean CSF protein content was higher in TBM with hydrocephalus (932 mg/dL; IQR 194.5–2228.5). The mean CSF cell count was higher in TBM with hydrocephalus (95 cells/mL; IQR 27.5–264.5). The percentage of CSF lymphocytes was higher in TBM without hydrocephalus (71%; IQR 40.5–91.2). The percentage ratio of CSF sugar to blood sugar was lower in TBM with hydrocephalus (21; IQR 10.75–31.25). The most common finding of head imaging in TBM with hydrocephalus was communicant hydrocephalus (78.2%). Interestingly, HIV positive in TBM without hydrocephalus (29.2%) was found to be higher than those with hydrocephalus (9.1%).

The diagnosis of TBM in this study was most commonly probable in both groups, with hydrocephalus (70.4%) and without hydrocephalus (78.6%). Grade 2 TBM was frequently found in both groups with hydrocephalus (78.2%) and without hydrocephalus (82.1%). The most common nosocomial infections in patients with hydrocephalus was hospital-acquired pneumonia (29.1%) and in patients without hydrocephalus was urinary tract infections (18%). The mortality number during treatment was almost twice higher in patients with hydrocephalus (51.6%) compared to those without hydrocephalus (26.6%). The mean length of stay to death in subjects with and without hydrocephalus was 4 days (IQR 2–13).

Anti-tuberculosis drugs (ATD) were given to all TBM patients. Surgery management for hydrocephalus was performed only in 25.4% of patients, and the others did not undergo surgery (74.6%), of whom 25.3% refused surgery, and the rest had no indication of surgery, as depicted in Table 3.

The outcome of TBM patients had shown that a higher mortality rate was found in hydrocephalus patients (56.4%), as shown in Table 4. In contrast, patients without hydrocephalus had moderate disability outcomes such as mild motor impairment (41.6%). There was a significant difference between the outcome of hydrocephalus and non-hydrocephalus (p=0.005) (data not shown).

Based on the GOS, the mean of the TBM with hydrocephalus was 1.49 (IQR 2–4) and without hydrocephalus was 2.53 (IQR 0–4) (data not shown).

Table 2 Supporting Examination of Adult Tuberculosis Meningitis Patients with or without Hydrocephalus Admitted to Dr. Hasan Sadikin General Hospital year 2018

Supporting Examination	Tuberculous Meningitis (n=127)	
	With Hydrocephalus (n=55) n (%)	Without Hydrocephalus (=76) n (%)
Laboratory examination		
Blood		
Blood natrium (mEq/L) – median (IQR)*	130 (126–137)	133 (126–133)
Blood glucose (mg/dL) – median (IQR)*	112 (95–123)	107 (94–126.7)
CSF		
Protein (mg/dL) – median (IQR)*	932 (194.5–2228.5)	233 (114–918)
Cell (sel/mL) – median (IQR)*	95 (27.5–264.5)	75.50 (7.5–206.5)
% lymphocyte – median (IQR)*	67 (38–91)	71 (40.5–91.2)
% CSF glucose:blood glucose ratio–median (IQR)*	21 (10.75–31.25)	32 (19–46.7)
Radiology		
Head CT scan		
Communicating hydrocephalus	43 (78.2)	0
Non-communicating hydrocephalus	12 (21.8)	0
HIV positive status*	5 (9.1)	14 (29.2)
Diagnosis of TBM*		
Definite	3 (11.1)	1 (3.6)
Probable	19 (70.4)	22 (78.6)
Possible	5 (18.5)	5 (17.8)
TBM grade		
1	0	3 (4.5)
2	43 (78.2)	55 (82.1)
3	12 (21.8)	9 (13.4)
Infection during treatment:		
HAP	16 (29.1)	7 (9.7)
Non-HAP	3 (5.4)	3 (4.2)
Bloodstreaminfection	6 (10.9)	5 (6.9)
Urinary tract infection	3 (5.4)	13 (18)
Surgicalsiteinfection	-	-
No infection	33 (60)	49 (68)
Number of patients died during the treatment	31 (56.4)	16 (26.6)
Length of stay until death - median (IQR)	4 (2 - 13)	4 (2–13)

Note: All data are presented in n (%) unless specifically stated, *There were some data not available

Table 3 Management of Adult Tuberculous Meningitis Patients

Management	Tuberculous Meningitis (n=127)	
	With Hydrocephalus (n=55) n (%)	Without Hydrocephalus (=76) n (%)
Drugs		
ATD	55 (100)	72 (100)
Mannitol	1 (1.8)	1 (1.4)
Acetazolamide	17 (30.9)	1 (1.4)
Anticonvulsant	2 (3.6)	7 (9.7)
Operation		
Operated	14 (25.4)	-
Not operated	41 (74.6)	72 (100)

Note: All data are presented in n (%) unless specifically stated, ATD= Anti-tuberculosis drugs

Table 4 Outcome in Adult Tuberculous Meningitis Patients

Outcome	Tuberculous Meningitis (n=127)	
	With Hydrocephalus (n=55) n (%)	Without Hydrocephalus (=76) n (%)
Death	31 (56.4)*	17 (23.6)
Neurovegetative state	1 (1.8)	0 (0)
Severe disability (patient dependent on daily support)	2 (3.6)	4 (5.6)
Moderate disability (patients independent in daily life)	7 (12.7)	30 (41.6)*
Good recovery	14 (25.5)	21 (29.2)

Note: All data are presented in n (%) unless specifically stated, * The most prevalent outcome.

Discussion

In this study, the most frequent clinical manifestation among TBM patients without hydrocephalus are decreased consciousness (94.5%), headache (87.3%), neck stiffness (85.4%), and fever (80%); while nausea, nerve disorder, seizure and increased intracranial pressure are in lesser percentage. Patients with hydrocephalus also had neck stiffness and headache. As for the TBM patients without hydrocephalus, different results were reported from case series gathered in China, where the headache was the most common reported symptom (89.2%), followed by fever, neck stiffness, nausea and or vomiting, weakness and anorexia, and other constitutional symptoms.[15] A systematic review has resulted the neck stiffness as the most commonly reported manifestation, followed by decreased alertness.[16]

Interestingly other study in Malaysia shows different order of manifestation among 143 adult TBM-hydrocephalus patients, the most common clinical presentations were fever (86.7%), followed by lesser percentage of neck stiffness, impaired consciousness, symptoms of raised intracranial pressure, hemiplegia, cranial nerve palsy, and seizure episode.[12]

Decreased consciousness is defined as a reduced or the absence of response towards external stimuli. In general, it can be caused either by a structural or localized abnormality within the central nervous system, systemic anomalies, or both. Structural abnormalities that could lead to decreased consciousness include acute stroke, traumatic cerebral injury, meningitis, intracranial hemorrhage, and cerebral distention as seen in hydrocephalus patients.[17] Mechanical assault from hydrocephalus, acute intracranial hemorrhage or direct trauma and tissue injury as the direct consequence of meningitis could damage the reticular activating system within the brainstem that projects into various neurological sites such as the thalamus, cortical layer and dorsal compartment of pons and midbrain, resulting in altered consciousness/sensorium.[18]

Pathophysiology of the origin of headaches in infectious diseases is not well understood. Intracranial hypertension syndrome, meningeal irritation, and activation of pain structures via the trigeminovascular system are some pathogenic mechanisms of headaches.[19] In this case, TBM patients with and without hydrocephalus also experienced symptoms that refer to increased intracranial pressures other than decreased sensorium and headache, such as nausea, nerve deficits, and seizure.

Commonly, the intracranial pressure is measured no higher than 20 mmHg. Since the cerebral compartment sits within the enclosed, complex cranial cavity, the other intracranial compartment will either deviates or compress as compensation for increased intracranial pressure; this phenomenon is also called as Monro-Kellie doctrine.[20] Hence, significant ventricular dilatation as occurs in hydrocephalus will produce mass effect towards the post-rema area and vertibulocochlear nerve, where nausea and vomiting is controlled.[21] Neck stiffness has long been known as a typical characteristic of meningeal irritation (i.e., meningitis). The mechanism underlying this process is not clearly explained. However, meningeal irritation is suggested to cause nociceptor activation within the spinal cord that passes on to the cervical region and triggers

muscle rigidity.[22] Seizure is considered a familiar entity in tuberculous meningitis, with the incidence ranging from 17–93%. Meningeal and ventricular inflammation are correlated with the prominent production of inflammatory cytokines (IL-1, IL-6, COX-2, and PGE-2); hence, activating microglia, astrocytes, and cerebral endothelial cells, resulting in epileptogenic activity within the brain. Meningitis also increases the permeability of blood-brain barrier, causing extravasation of interstitial fluid and edema, leading to seizure episodes.[23] The TBM accompanied by hydrocephalus is highly associated with the seizure.[12] Recurrent, uncontrolled seizures can progress to status epilepticus leading to a poor prognosis. Patients with central nervous system infection and recurrent seizures can be given anti-seizure prophylaxis to prevent recurrent seizures, at least during the acute period of illness.[23]

Cerebrospinal fluid analysis has a crucial role in the definitive diagnosis of meningitis. TBM is a chronic disease characterized by clear cerebrospinal fluid (CSF), increased protein concentration, lymphocyte-dominated pleocytosis, and a low glucose concentration.[13] In this study, an increase in protein concentration was four times higher in CSF groups with and without hydrocephalus. Disruption in the blood-brain barrier refers to an increase in CSF protein, which can inhibit CSF circulation, interfere with absorption, and even cause obstruction leading to hydrocephalus after the presence of CSF protein leukocyte aggregation.[12] This causes the increase in CSF protein to be higher in patients with hydrocephalus. This study showed an increase in white blood cells in the presence of lymphocyte dominance. A decreased ratio of CSF to blood glucose occurred in both groups. Decreased glucose is due to impaired glucose transport to the choroid plexus as decreased blood flow, blood-brain barrier transport, increased metabolism in the brain, and transport to the venous system.[24] Ventriculomegaly in hydrocephalus causes compression to the brain, leading to decreased blood flow and perfusion.[25]

The severity of TBM at the baseline of treatment was assessed according to the British Medical Research Council staging system and is divided into three grades.[26] Hydrocephalus might be significantly associated with advanced TBM grade.[3] Increased severity was significantly associated with delayed treatment, leading to increased mortality and morbidity.[27] In this study, grade 2 TBM is the most frequent in groups with hydrocephalus and without.

TBM can cause metabolic complications, among others, hyponatremia, which is occurred in more than 50% of patients. The most common cause of hyponatremia is cerebral wasting syndrome. In addition, it can also be caused by using diuretics to treat hydrocephalus.[15] This study found hyponatremia in hydrocephalus. The use of diuretics in hydrocephalus might contribute to the occurrence of hyponatremia.

Length of stay increases the risk of nosocomial infections and is associated with a poor prognosis.[16] The most frequent hospital infections were pneumonia and surgical site infection, followed by urinary tract infections and bloodstream infections.[17] This study shows that hospital-acquired pneumonia (HAP) occurs mostly in the group with hydrocephalus, whereas urinary tract infections (UTI) occur in the group without hydrocephalus. UTIs are primarily associated with catheter placement during treatment.[17] The high incidence of HAP in brain injury is associated with decreased consciousness resulting in microaspiration.18 This explains the higher incidence of HAP in subjects with hydrocephalus.

Patients without hydrocephalus were treated >7 days more than those with hydrocephalus. This is because the number of patients who died during the treatment was more prominent in patients with hydrocephalus. Thus, hydrocephalus is associated with higher mortality than those without hydrocephalus.

Anti-tuberculosis drugs (ATD) were administered to all subjects. Inflammation in the choroid plexus can increase excess CSF production, thereby increasing intracranial pressure and hydrocephalus in TBM.[28] High intracranial pressure occurred in 5.4% of patients with hydrocephalus and only 1.3% in subjects without hydrocephalus. Acetazolamide was administered to 30.9% of patients with hydrocephalus.

Acetazolamide administration in hydrocephalus is symptomatic in purpose and works by suppressing CSF production through carbonic anhydrase inhibition. Carbonic anhydrase is an enzyme necessary for CSF production and it dissociates carbonic acid into a positive hydrogen ion and a negative bicarbonate ion, the production of these products drives the activity of sodium/hydrogen exchanger (NHE) and anion exchanger (AE2) at the choroidal plexus epithelium, which promotes the CSF

release into the ventricle. Thus, carbonic anhydrase inhibition is a considerable non–surgical modality to symptomatically manage hydrocephalus.[29] Although the guideline and consensus regarding the use of acetazolamide for hydrocephalus in TBM cases are not clearly postulated, nearly half of the patients in a prospective cohort study from India had significant improvement and reduction of disability index after receiving both acetazolamide and mannitol.[3] Mannitol, frequently available in 20%, is an osmotic agent that increases extracellular osmolality, shifting water molecules from the intracellular into the extracellular compartment; this decreases the high intracranial tension resulting from the accumulation of cerebrospinal fluid.[29]

The outcome was assessed using GOS; which was died. Died under treatment occurred mostly in TBM with hydrocephalus. Our result shows a significant difference between the GOS of the TBM with and without hydrocephalus. Furthermore, the result showed that the GOS mean of TBM without hydrocephalus was higher than TBM with hydrocephalus, indicating that the outcome of TBM without hydrocephalus was better than those with the hydrocephalus. The outcome in patients with hydrocephalus had a worse outcome compared to those without hydrocephalus. Hydrocephalus was one of the predictors of mortality and morbidity in TB. Moderate disability occurs in many subjects without hydrocephalus. In accordance with previous research, prolonged treatment does not provide higher mortality but has a higher chance of developing neurological disability.[24] TBM patients with hydrocephalus tend to have poorer prognosis and survival than patients without hydrocephalus. Mortality rate is reported to be higher among TBM patients with hydrocephalus, along with disability index and survival.[10–14] Hydrocephalus is also considered a prognostic factor that could predict the poor outcome among TBM patients in a retrospective study from China.[30]

The limitation of this study is the use of retrospective data. Further research can be carried out using analytical methods to calculate the significance of the characteristics of TBM with and without hydrocephalus to the outcome.

In conclusion, TBM patients with hydrocephalus have a worse outcome than those without hydrocephalus, as reflected by the higher TBM grade, higher mortality rate, and lower good recovery upon treatment administration.

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