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Original Article

Relationship between neutrophil count in cerebrospinal fluid and cerebral infarct appearance in head MRI on tuberculous meningitis patients

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ABSTRACT

Objectives: To determine the relationship between neutrophils count in cerebrospinal fluid and cerebral infarction in head magnetic resonance imaging (MRI) on patients with tuberculous meningitis

Methods: A diagnostic study was done on patients with tuberculous meningitis (TBM) who underwent head MRI examination and cerebrospinal fluid analysis at Dr. Hasan Sadikin General Hospital from January 2015 to September 2016. TBM was diagnosed by Mycobacterium tuberculosis isolation from cerebrospinal fluid. Cut-off value of neutrophil count was determined using receiver operating characteristics (ROC) curve. Conformity test was done using Kappa test.

Results: Thirty seven subjects were recruited in this study. Higher neutrophil count in CSF was observed on subjects with cerebral infarction ($p < 0.05$). Cut-off value of neutrophil count in CSF was determined as > 41 %. There was a moderate conformity between higher neutrophil count in CSF and cerebral infarction appearance in MRI ($p < 0.05$, Kappa score 0.529).

Conclusion: Higher neutrophil count was associated with the appearance of cerebral infarct in head MRI on adult patients with tuberculous meningitis.

1. Introduction

Tuberculosis (TB) is an important global health problem. The disease causes severe health burden in millions of people every year. In 2020, the World Health Organization (WHO) reported that there were 10 million new tuberculosis cases globally. During the same period, the death rate from tuberculosis reached 1.2 million people worldwide. It was also noted that there were 19,653 cases of extrapulmonary tuberculosis in Indonesia in 2014 [1–3].

One of the most common forms of extrapulmonary tuberculosis in the central nervous system is tuberculous meningitis (TBM). Acknowledged as a pathological entity for the first time in 1836, TBM is characterized by inflammation of brain lining (meninges) due to infection with *Mycobacterium tuberculosis* bacteria originating from hematogenous spread elsewhere [4–6]. Central nervous system involvement in extrapulmonary tuberculosis accounts for 2–5 % of all tuberculosis cases and 5–10 % of all extrapulmonary tuberculosis cases. Tuberculous meningitis has high mortality and morbidity rate. About 15–68 % of all TBM patients would die and more than half of those would suffer from neurological deficits [4–6].

The definitive diagnosis of tuberculous meningitis is traditionally made by finding tuberculosis bacteria in the cerebrospinal fluid either by direct staining, culture or by other methods such as polymerase chain reaction (PCR) [7]. Given the difficulty of establishing a definitive diagnosis of tuberculous meningitis, computed tomography (CT) scans and magnetic resonance imaging (MRI) are expected to play a role in determining an accurate and earlier diagnosis [8].

Previous research has shown that the most common radiology findings of TBM in descending order are meningeal enhancement, hydrocephalus, basal exudates, cerebral infarction, and tuberculomas [9]. Cerebral infarction in TBM occurs because of vasculitis affecting the vessels of the Circle of Willis, the vertebrobasilar circulation, and the perforating branches of the middle cerebral artery [9]. There are two places where infarction often occurs, namely: the anterior part which is better known as the "tuberculous zone" which includes the caudate nucleus head, anteriomedial thalamus, and the anterior part of the internal capsule. Meanwhile, the posterior portion is known as the “ischemic zone” which includes the posterior portion of the internal capsule, the lentiform nucleus, and the posterolateral thalamus [10].

Cerebral infarction on head MRI examination shows a hypointense

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image on T1-Weighted Imaging (T1WI) and hyperintense on T2-Weighted Imaging (T2WI). Moreover, Diffusion-Weighted Image (DWI) may also be used in order to determine the cerebral infarction in TBM. The MRI has a higher sensitivity than CT scan in detecting cerebral infarction [11,12]. However, the MRI features for cerebral infarction in TBM vary over different stage. It may also happen in other diseases as well such as vascular infarction [9]. There has been no study on the relationship between the number of neutrophils in the CSF and the appearance of cerebral infarction on MRI of the head in MTB patients in Indonesia.

This study aims to determine the relationship between neutrophils count in cerebrospinal fluid and cerebral infarction in head magnetic resonance imaging (MRI) on patients with tuberculous meningitis.

2. Methods

This is a diagnostic study determined to assess conformity between neutrophils count in cerebrospinal fluid and the appearance of cerebral infarction in head MRI. This study used 5 % error bound and 95 % confidence interval limit, with the power of test considered to be 90 %.

Subjects for the study were TBM patients aged > 18 years old who underwent cerebrospinal fluid analysis and head magnetic resonance imaging on January 2015 to September 2016. Patients with contraindications of MRI examination, uncooperative during the examinations, malignancy, history of head trauma, prior stroke, or other neurological diseases were excluded from the study. Subjects were divided into two groups based on the appearance of.

Tuberculous meningitis diagnosis was established by positive *Mycobacterium tuberculosis* on isolation or polymerase chain reaction (PCR) examination. Neutrophil count was assessed in the cerebrospinal fluid which was acquired by spinal tapping. Neutrophil count was expressed as percentage. Magnetic resonance imaging was done using Magnetom Essenza® 1.5 Tesla with Syngo Software (Siemens Healthcare GmBH®, Germany). The magnetic resonance imaging was done during the same week as the diagnosis establishment. Cerebral infarction was determined by hyperintense area on T2-weighted image (T2WI) or diffusion-weighted imaging (DWI) sequence and hypointense area on T1-weighted image (T1WI) without any mass effect. The MRI reading was blindly done by two neuroradiologists with > 10 years of experience on different occasions.

The infarcts obtained from head MRI examinations are acute – subacute, as evidenced by Diffusion-Weighted Image (DWI) examination which provides an area of diffusion restriction, indicating an acute – subacute infarction. The examples of cerebral infarction in this study can be found on Fig. 1.

The study was approved by the Ethical Research Committee, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia. All human studies had been done complied with the Declaration of Helsinki guidelines. Written informed consent was obtained from each subject before recruitment to the study. Collected data were then analyzed using SPSS for Macintosh ver. 20.

The clinical characteristics of subjects were analyzed descriptively. The relationship between neutrophil and cerebral infarction appearance was assessed using either unpaired T or Mann Whitney test. Cut-off value of neutrophil count was determined using receiver operating characteristics (ROC) curve. Conformity test was done using Kappa test. The p value and confidence interval of 95% are displayed whenever possible.

3. Results

A total of 37 subjects were recruited for the study, consisting of 20 male and 17 female TBM patients. General characteristics of subjects can be seen on Table 1.

After learning the general characteristics of subjects, comparison of neutrophil count between cerebral infarction and non-cerebral infarction group was done. The results can be found on Table 2.

Furthermore, cut-off value of neutrophil count in cerebrospinal fluid was determined using ROC curve. Based on the ROC curve analysis, the cut-off point was determined to be 41 %, with sensitivity of 55 % and specificity of 100 %. The ROC curve can be found in Fig. 2, while the conformity test between parameters can be found on Table 3.

Table 1
General characteristics of subjects.

Variables	N = 37
Age (years), mean ± standard deviation	32.59 ± 13.3
Age category (years)	
< 20	6 (16.2 %)
20–35	19 (51.4 %)
36–50	8 (21.6 %)
> 50	4 910.8 %)
Gender	
Male	20 (54.1 %)
Female	17 (45.9 %)
Neutrophil count (%), median (range)	25 (1–83)
Cerebral infarction appearance	
Yes	20 (54.1 %)
No	17 (45.9 %)

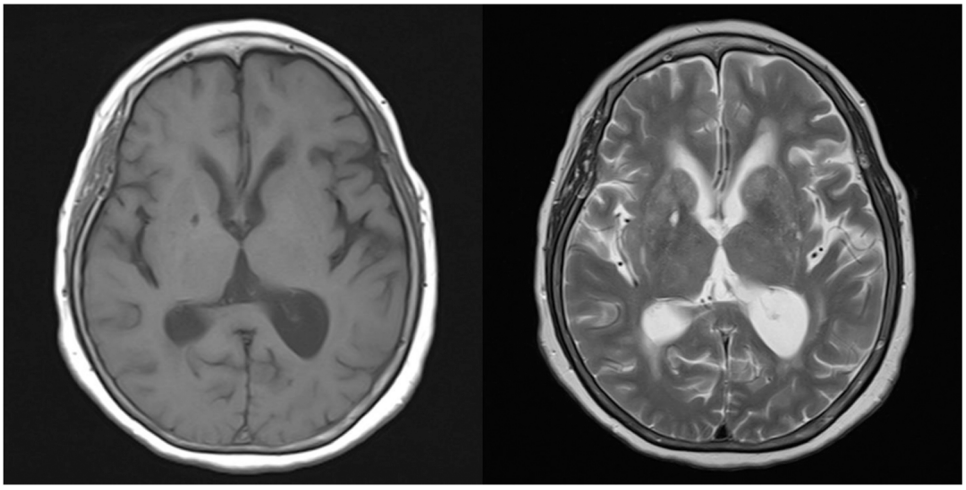

Fig. 1. Hypointense lesion in T1WI (left) and hyperintense lesion in T2WI (right) in the right putamen of a patient with tuberculous meningitis, suggesting a chronic cerebral infarction.

Table 2
Neutrophil count between groups.

Variables	Cerebral infarction		p
	(+)	(−)	
Neutrophil count (%), median (range)	43.5 (10–83)	25 (1–40)	**0,025**

* Mann Whitney U test.

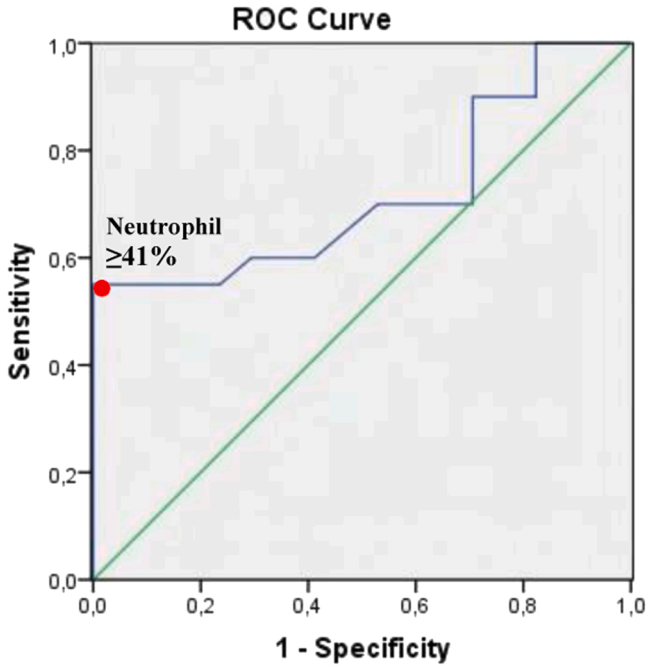

Fig. 2. ROC curve of neutrophil count in CSF.

Table 3
Conformity Test Between Parameters.

Variables		Cerebral infarction		p	Kappa score
		(+)	(−)		
Neutrophil count	> 41 %	11	0	**< 0.001**	**0.529**
	< 41 %	9	17		
Total		20	17		

Based on the conformity test done in this study, it can be concurred that there was a moderate conformity between neutrophil count in cerebrospinal fluid and cerebral infarction in head MRI (Kappa 0.529, $p < 0.001$).

4. Discussion

It was known form this study that higher neutrophil count was associated with the appearance of cerebral infarct in head MRI. Similar results in this study were obtained by Koh et al. [13]. In his research, Koh et al. studied 38 patients with tuberculous meningitis, 8 of whom had cerebral infarction. The median percentage of neutrophils in the cerebrospinal fluid in patients with tuberculous meningitis with cerebral infarction was higher than in patients with tuberculous meningitis without cerebral infarction (68 % vs. 31 %, $p < 0.05$) [13].

The concentration of neutrophil in the cerebrospinal fluid will increase in the early phases of infection. However, it has yet to be accepted as a parameter for the diagnosis of TBM. In a previous study, normal cerebrospinal fluid cytology results were seen in 21.4 % of TBM cases, whereas neutrophil predominance was seen in only 39 % of cases [14]. Another study by Puccioni-Sohler and Brandão found elevated neutrophil count in the cerebrospinal fluid from patients with positive cultures for *Mycobacterium tuberculosis* [15]. These conflicting results have made neutrophil count to be rather controversial in its use.

In contrast with neutrophil count, the appearance of cerebral infarction in head MRI on TBM patients is considered as a suggestive characteristic. Previous study has shown that the concept of cerebral infarction in head MRI is categorized into “tuberculous zone” and “ischemic zone”. It was also known that 67 % of all TBM patients had cerebral infarction, most of which were in either both or ischemic zones [16]. The predominant factor of cerebral infarction appearance in TBM patients was the involvement of perforators and terminal cortical branches rather than occlusion on major intracranial arteries (as seen in atherosclerosis) [16].

Cerebral infarction in TBM patients is an important clinical parameter, as it is a major risk factor of permanent disability following the infection. Patients with cerebral infarction had more prominent focal weakness on presentation and focal weakness or dementia as sequelae [17]. Moreover, it is also known as an independent predictor of mortality among TBM patients [18]. However, only a few treatments such as corticosteroids are known to have any effect on cerebral infarction prevention [18].

The limitation in this study was its single-center nature. Due to the data being acquired only in a healthcare center, sampling bias could not be excluded in the study. Furthermore, there was no categorization of cerebral infarction characteristics based on the time of occurrence (acute, subacute, chronic). Further study is needed to validate the results in more general population.

5. Conclusions

It is concluded in this study that higher neutrophil count was associated with the appearance of cerebral infarct in head MRI on adult patients with tuberculous meningitis.

CRediT authorship contribution statement

Muhammad Irvanie Rama Harahap: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Farhan Anwary:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation.

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Conflict of Interest

Authors declare that there is no conflict of interest in this study.

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Previous Presentation

Authors declare that the study has never been presented on scientific presentation before.

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