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Original Article

Outcomes of tuberculous meningitis in children: a case review study

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Abstract

Background Tuberculous meningitis is a severe extrapulmonary complication of tuberculosis, with high morbidity and mortality rates.

Objective To assess the relationship between presenting clinical characteristics and outcomes of pediatric tuberculous meningitis.

Methods We present a case review study of all children diagnosed with tuberculous meningitis in Cipto Mangunkusumo Hospital, Jakarta between January 1998 and December 2004. We compared demographic, clinical, and diagnostic characteristics to clinical outcomes.

Results We included 43 patients. Common characteristics on admission were young age (mean 3.2 years), stage II and III tuberculous meningitis (91%), and neurological symptoms existing for more than 1 week, including convulsions (52%), unconsciousness (23%), meningeal irritation (56%), and cranial nerve palsy (67%). A common feature of tuberculous meningitis on computed tomography scan of the brain was hydrocephalus in 19/24 cases. Clinical outcomes were neurological sequelae (88%) and death (12%). Factors associated with poor outcome in univariate analyses were young age, as well as stage II and III tuberculous meningitis.

Conclusions Tuberculous meningitis starts with nonspecific symptoms and is often only diagnosed when brain damage has already occurred. Outcome is directly associated with age and the stage of tuberculous meningitis. Earlier diagnosis may significantly improve outcomes. **[Paediatr Indones. 2011;51:288-93]**.

Keywords: *tuberculous meningitis, outcomes, children*

There is high prevalence of tuberculous meningitis (TBM) in developing countries, including Indonesia, and the disease has a high mortality rate among infants and children.[1] Neurological complications are common,[2-7] and early diagnosis and specific treatment for tuberculosis (TB) are essential for prevention of sequelae or fatal outcomes.[8-10]

TBM is the most severe complication of TB and frequently occurs in childhood. Lympho-hematogenous spread from a primary pulmonary focus leads to the development of a Rich focus in the brain. Rupturing of this caseous granuloma into the subarachnoid space causes 3 features responsible for the clinical manifestations of TBM: development of further tuberculomata; basal inflammatory exudates that cause cranial nerve palsies and obstruct cerebrospinal fluid (CSF) passages, resulting in hydrocephalus; and obliterative vasculitis leading

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to infarctions. Once the Rich focus has ruptured, a prodromal period of nonspecific symptoms, such as fever, vomiting, and behavioral changes, develops. As the disease progresses, neck stiffness, loss of consciousness, motor deficits, and convulsions will follow. TBM diagnosis is often only considered once irreversible neurologic damage has already occurred.[11]

The outcome of TBM is known to be affected by age, stage of the disease at admission, and whether raised intracranial pressure (ICP) caused by obstructive hydrocephalus is actively treated.[2,6,12] The objective of this study was to assess the relationship between presenting clinical characteristics and outcomes of pediatric TBM.

Methods

All children diagnosed with TBM at Cipto Mangunkusumo Hospital, Jakarta, between January 1998 and December 2004 were included in this retrospective study. We compared demographic, clinical, and diagnostic data on admission and clinical outcomes after treatment. Demographic data included gender, age, Bacille Calmette-Guerin (BCG) immunization history, and possible tuberculosis contact.

A clinical diagnosis of TBM was made in all patients based on history and typical cerebrospinal fluid (CSF) changes, together with two or more of the following: positive (≥ 10 mm) Mantoux test; chest radiograph findings suggesting TB, ie., a miliary picture or hilar lymphadenopathy, often accompanied by a segmental lesion; acute hydrocephalus with basal enhancement on computed tomography (CT) scan,[2] and positive results of a second CSF analysis. **(Table 1)**

We scored stage of disease, duration of symptoms before admission, and type of presenting symptoms. TBM was staged using the British Medical Research Council recommendations to determine TBM severity. Stage definitions were as follows: stage I - prodromal phase with no definite neurological symptoms; stage II -signs of meningeal irritation with slight or no clouding of sensorium and minor (cranial nerve) palsies; stage III - severe clouding of sensorium, convulsions, focal neurological deficits and involuntary movements.[2]

Clinical outcome was defined as "good" in the case of mild neurologic sequelae or normal neurologic outcome, and defined as "poor" in the case of severe neurologic sequelae or death.

SPSS 13.0 (SPSS Inc, Chicago, IL) was used for statistical analyses. Statistical significance was determined at the 5% level. Categorical measurements were analyzed by means of the chi-square tests and Fisher's exact test in the case of 2 x 2 contingency tables with an expected cell frequency of less than 5. When cell frequencies were small, categories in certain variables had to be combined to get large enough frequencies for proper categorical analyses. Continuous variables were compared by Student's *t* test if normally distributed or by Mann-Whitney *U* test if not normally distributed. All P values were two-sided. The Ethics Committee of the University of Indonesia Medical School, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, approved this study.

Table 1. Mean differences between components of the first and second CSF testing

Mean differences	Paired Differences				
	SE		95% CI		
			Lower	Upper	
Cell1 – Cell2, (count/3)	402.5	247.35	-111.9	916.9	0.119
PMN1 – PMN2, (%)	8.1	2.97	1.7	14.6	0.017
MN1 – MN2 (%)	-8.1	2.97	-14.6	-1.7	0.017
Protein1 – Protein2, (mg/dl)	51.0	29.11	-11.1	113.0	0.100
Glucose1 – Glucose2, (mg/dl)	-2.4	6.26	-15.7	11.0	0.710
Sodium1 – Sodium2, (mg/dl)	-36.8	41.08	-127.2	53.7	0.390
Chloride1 – Chloride2, (mg/dl)	0.8	10.91	-23.3	24.8	0.946

PMN= Polymorphonuclear cells, MN = Mononuclear cells

Results

From January 1998 to December 2004, 72 patients were diagnosed with TBM. Twenty-nine patients were excluded due to lack of data. Of the 43 subjects included in our study, 20 (47%) were boys. The children ranged in age from 4 months to 14 years, with a mean age of 3.2 years. A history of adult TB contact was found in 25 (58%) patients and only 26 (60%) patients had received a single BCG vaccination. A small number of patients (9%) were admitted in the first stage of disease. The remaining 39 had neurologic manifestations (37 in the second stage and 2 in the third stage). (**Table 2**) The most common complaint was convulsions in 22 (51%) subjects and decreased consciousness in 10 (23%) subjects. Cranial CT was performed on 24 (56%) patients, showing hydrocephalus in 19 patients. Abnormal chest radiography was noted in 39 (91%) patients, with a variety of abnormalities including hilar adenopathy in 25 (58%), and miliary pattern in 8 (19%). All patients underwent Mantoux tuberculin (5 TU) skin testing, with 19 (44%) patients having a positive result (≥ 10 mm diameter induration). Lumbar puncture was performed on all patients and CSF was analyzed for protein and glucose concentrations, cell count and differential. All CSF results were compatible with TBM (i.e., predominance of lymphocytes with elevated protein and reduced glucose concentrations) as shown in **Table 3**. All patients were hospitalized for initial diagnosis and treatment, with a mean hospital stay of 6.2 (SE 2.2) days for patients who died and 20 (SE 2.2) days for disabled patients.

Table 2. Clinical and laboratory characteristics

Characteristics	< 2 year n = 28	> 2 year n = 15
BCG immunization, n	16	10
Mean duration of chief complaint, days (SE)	8.2 (2.77)	8.9 (2.34)
History of adult TB contact, n	18	7
Chief complaint, n		
Convulsions	20	2
Unconsciousness	5	5
Positive meningeal signs, n	13	11
Cranial nerve paresis, n		
CN III	12	4
CN VI	5	1
CN VII	6	1
Positive tuberculin test, n	9	10
Chest X-ray finding, n		
Specific	15	10
Miliary	6	2
Neuroimaging (N=24)		
hydrocephalus, n	13	6
Staging, n		
I	2	2
II	24	13
III	2	0

CN = cranial nerve

Table 3. Characteristics of cerebrospinal fluid

Cerebrospinal fluid findings	First, n = 43	Second, n = 20
Qualitative, n		
Color		
Clear	33	17
Xantochrome	10	3
Nonne's test		
Negative	34	17
+	9	3
Pandy's test, n		
Negative	1	5
+	7	7
++	24	4
+++	10	3
++++	1	1
Mean quantitative findings, (SE)		
Number of cells, count/mm3	481.9 (133.9)	219.1 (78.77)
PMN, %	16.9 (2.86)	9.1 (2.46)
MN, %	83.1 (2.86)	90.9 (2.46)
Protein, mg/dl	177.4 (2.86)	162.6 (19.17)
Glucose, mg/dl	29.2 (3.62)	33.5 (4.23)
Mean interval of second CSF result, days (SD)	11.9 (7.30)	

Table 4. Outcome of TBM by clinical characteristics, staging and first CSF results

	Death	Neurological sequelae	P
Mean age, months (SE)	13.4 (3.23)	41.4 (7.61)	0.017
< 2 year, n	5	23	< 0.001
> 2 year, n	0	15	
Chief complaint, n			0.302
Convulsion	4	18	
Unconsciousness	1	9	
Other	0	11	
Mean duration of chief complaint, days	3.0 (2.19)	9.2 (2.19)	0.014
Staging, n			0.181
I	0	4	
II	4	33	
III	1	1	
Mean duration of hospitalization, days	6.2 (2.56)	20.0 (2.21)	0.002
Mean CSF findings, (SE)			
Number of cells (count/mm3)	197.8 (129.80)	512.6 (147.15)	0.131
PMN, %	6.5 (3.50)	17.6 (3.00)	0.097
MN, %	93.5 (3.50)	82.4 (3.01)	0.097
Protein, mg/dl	164.0 (85.80)	178.8 (14.47)	0.880
Glucose, mg/dl	24.3 (7.06)	29.6 (3.93)	0.553

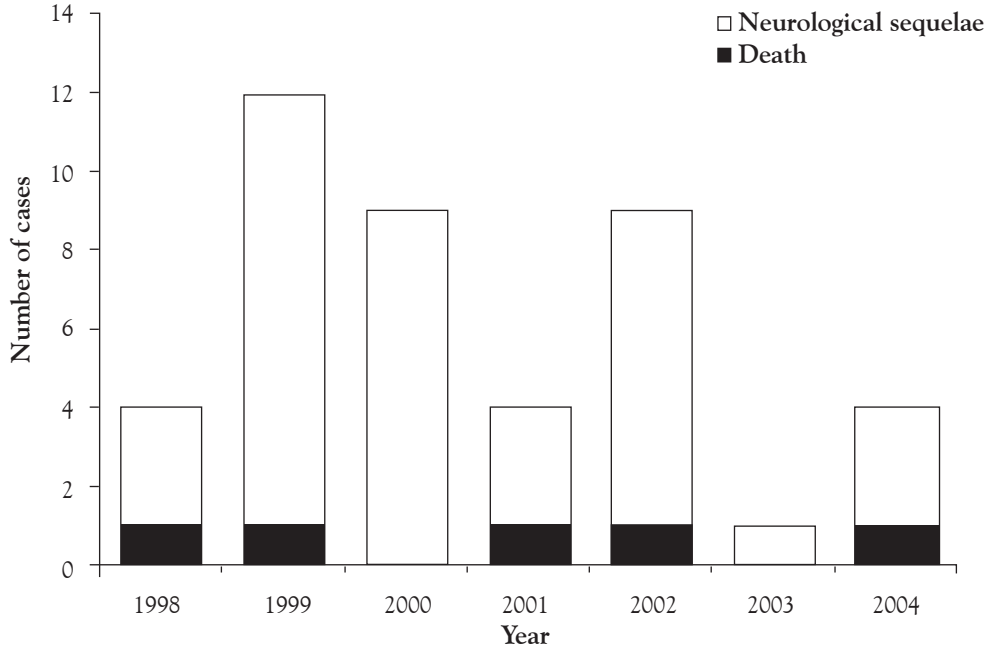

Figure 1. TBM patient outcomes by year of admission.

Discussion

We found that TBM mainly affected young children, as 28 (65%) of our subjects were below 2 years of age. Subjects' mean age was 38.2 months, comparable to that of other studies with mean ages ranging from 23 to 49 months.[2] Young age at presentation and the nonspecific nature of presenting symptoms partly explain the difficulty of early diagnosis. Presentation is often sub-acute, and the early symptoms of stage I TBM, such as low-grade fever, cough, vomiting, and general apathy, are often wrongly interpreted. We also

observed delayed diagnosis and commencement of TB treatment, as 57% of our patients were unwell for > 7 days before admission. Previous studies have reported the duration of symptoms before TBM diagnosis to range from 13 and 42 days,[2,6] while the mean duration of our study was 8.5 days.

The Mantoux test result was positive in 19 (44%) of our subjects. These results are higher compared to those previously reported, 16% in TBM.[2] Approximately 26 (60%) of our patients were vaccinated with BCG. The protective efficacy of BCG vaccination is not well-defined, ranging from 0 to 80%. However, it is thought that in childhood, the vaccination protects against serious complications such as TBM.[13-16]

CSF results in our subjects revealed that the majority of patients with TBM had low, predominantly lymphocytic CSF pleocytosis in the presence of raised protein levels and reduced CSF glucose concentrations. These CSF findings, especially if culture negative, are highly suggestive of TBM in areas with a high TB prevalence rate. Cerebrospinal fluid changes in TBM take longer times to normalize, therefore, serial CSF findings may retrospectively differentiate TBM from other types of meningitis in which CSF normalizes more quickly.[2,8]

Cranial nerve palsies were found in 29 (67%) subjects in our study, it is higher compare to other studies (20%-30%),[2,5] with the third, seventh and sixth cranial nerves most commonly affected at 37%, 16% and 14% of patients, respectively. We observed cranial nerve paralysis primarily in children aged < 2 years, usually associated with other neurological findings.

Hydrocephalus was observed by cranial CT in 19/24 patients. Common features of TBM on brain CT scan are reported to be hydrocephalus (82%), periventricular lucency (57%), infarctions (32%), and basal meningeal enhancement (75%).[2] Communicating hydrocephalus in TBM is usually caused by blockage of the basilar cistern with thick tuberculous exudates in the acute stage, and adhesive leptomeningitis in the chronic stage of disease. In some cases, blockage and dilatation of the fourth ventricle can produce structural hydrocephalus. It is important to note that communicating hydrocephalus is not specific for TBM, but can be associated with fungal meningitis, bacterial meningitis, cytomegalovirus infection, toxoplasmosis, and subarachnoid hemorrhage.[11]

The 12% mortality rate of our subjects was exceptionally low. All patients with stage I disease had minor neurological outcomes, and deaths did not occur in this group. Outcomes of TBM patients are influenced by many factors, such as severity of disease[2], effectiveness of antituberculous medication,[17] management of neurological complications (particularly hydrocephalus),[12] and appropriate use of general supportive measures.[18,19] Enhanced resolution of the basal exudate and improved survival rate were shown to be associated with the use of corticosteroids in TBM.[19] Most factors found to correlate with poor TBM outcomes can be directly traced to the degree of disease progression at the time of diagnosis. This applies to both the clinical and radiological characteristics of the disease. Dismal TBM outcomes will only improve when the diagnosis and initiation of treatment are made earlier.[2]

In conclusion, TBM affects mainly children below 5 years of age. Presentation is often sub-acute, and early symptoms are nonspecific. Outcome is directly associated with the stage of TBM at presentation. Delayed treatment due to misdiagnosis may result in progression to stage II and III of the disease, leading to high morbidity and mortality rates.

References

1. World Health Organization. Global tuberculosis control. c2010 [cited on 2010 Jan 15]. Available from: http://whqlibdoc.who.int/publications/2010/9789241564069_eng.pdf
2. Van Well GT, Paes BF, Terwee CB, Springer P, Roord JJ, Donald PR, et al. Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the western cape of South Africa. Pediatrics. 2009;123:e1-8.
3. Ozek E, Iplkcioglu AC, Erdal M. Intradural extramedullary tuberculoma mimicking enplaque meningioma. Neurol India. 2009;57:211-2.
4. Arulprakash S, Verma SP, Bhardwaj VK, Mishra SS, Chansoria M. Brain stem auditory evoked responses and visual evoked responses in children with tubercular meningitis. Indian Pediatr. 2006;43:631-4.
5. Moon S, Son J, Chang W. A case of oculomotor nerve palsy and choroidal tuberculous granuloma associated with tuberculous meningoencephalitis. Korean J Ophthalmol. 2008;22:201-4.

6. Roca B, Tornador N, Tornador E. Presentation and outcome of tuberculous meningitis in adults in the province of Castellon, Spain: a retrospective study. Epidemiol Infect. 2008;136:1455-62.
7. Chapp-Jumbo EN. Neurologic infections in a Nigerian university teaching hospital. Afr Health Sci. 2006;6:55-8.
8. Haldar S, Sharma N, Gupta VK, Tyagi JS. Efficient diagnosis of tuberculous meningitis by detection of *Mycobacterium tuberculosis* DNA in cerebrospinal fluid filtrates using PCR. J Med Microbiol. 2009;58:616-24.
9. Thomas MM, Hinks TS, Raghuraman S, Ramalingam N, Ernst M, Nau R, et al. Rapid diagnosis of *Mycobacterium tuberculosis* meningitis by enumeration of cerebrospinal fluid antigen-specific T-cells. Int J Tuberc Lung Dis. 2008;12:651-7.
10. Quan C, Lu CZ, Qiao J, Xiao BG, Li X. Comparative evaluation of early diagnosis of tuberculous meningitis by different assays. J Clin Microbiol. 2006;44:3160-6.
11. Täuber MG, Schaad UB. Bacterial infections of the nervous system. In: Swaiman KF, Ashwal S, Ferriero DM, editors. Pediatric neurology principles & practice. 4th ed. Philadelphia: Mosby Inc; 2006. p. 1571-95.
12. Rajshekhar V. Management of hydrocephalus in patients with tuberculous meningitis. Neurol India. 2009;57:368-74.
13. Clark M, Cameron DW. The benefits and risks of bacille Calmette-Guérin vaccination among infants at high risk for both tuberculosis and severe combined immunodeficiency: assessment by Markov model. BMC Pediatr. 2006;6:5.
14. Walker V, Selby G, Wacogne I. Does neonatal BCG vaccination protect against tuberculous meningitis? Arch Dis Child. 2006;91:789-91.
15. Sterling TR, Martire T, de Almeida AS, Ding L, Greenberg DE, Moreira LA, et al. Immune function in young children with previous pulmonary or milliary/meningeal tuberculosis and impact of BCG vaccination. Pediatrics. 2007;120:e912-21.
16. Anjay MA, Anoop P. Tuberculous meningitis: more evidence for protective effect of BCG. Arch Dis Child. 2007;92:277.
17. Vinnard C, Winston CA, Wileyto EP, MacGregor RR, Bisson GP. Isoniazid resistance and death in patients with tuberculous meningitis: retrospective cohort study. BMJ. 2010;341:c4451.
18. Nguyen TH, Tran TH, Thwaites G, Ly VC, Dinh XS, Ho Dang TN, et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med. 2007;357:2431-40.
19. Iliyasu Z, Babashani M. Prevalence and predictors of tuberculosis coinfection among HIV-seropositive patients attending the Aminu Kano Teaching Hospital, northern Nigeria. J Epidemiol. 2009;19:81-7.