Meningitis mortality in Neurology Ward of Dr. Cipto Mangunkusumo hospital Jakarta

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Abstrak

Angka kematian meningitis tidak mengalami penurunan walaupun terdapat penurunan angka kejadian meningitis dan berkembangnya penemuan antibiotik baru. Tujuan penelitian ini adalah melaporkan pola kematian meningitis dan mengetahui faktor yang berhubungan dengan kematian akibat meningitis pada penderita yang dirawat. Penelitian potong lintang menggunakan data rekam medis penderita meningitis yang dirawat di bangsal Neurologi RS Cipto Mangunkusumo Jakarta dari Januari 1997 – Desember 2005. Data dilaporkan dalam bentuk tekstular dan table, dan kemudian dilakukan analisis menggunakan Chi-kuadrat untuk data kategorikal dan Student's "t" test untuk data numerical. Analisis menggunakan program SPSS v 13 for Windows. Penelitian ini mengikutsertakan 273 penderita, yang terdiri dari 81 wanita dan 192 pria, dengan usia antara 12 sampai 78 tahun. Seratus empat belas penderita meninggal dan 159 hidup. Penurunan kesadaran, terutama sopor (OR 10.44, p 0.000) dan koma (OR 53.333, p 0.000), dan adanya hemiparesis (OR 2.068, p 0.009) berhubungan dengan keluaran. Angka kematian meningitis masih tinggi (41.8%). Dari penelitian ini didapatkan tingkat kesadaran dan hemiparesis berhubungan dengan angka kematian. ***(Med J Indones 2006; 15:236-41)***

Abstract

Mortality rate of meningitis is not decreased even though there is decreasing meningitis rate and advanced development of antibiotics. The purpose of this study is to find out meningitis mortality pattern and to evaluate factors related to meningitis mortality in hospitalized patients. Study was done using retrospective data from medical records of the patients administered in the Neurology ward of Cipto Mangunkusumo hospital from January 1997 – December 2005. Data were reported descriptively in texts and tables, and analyzed with Chi-square for categorical data and Student's "t" test for numerical data, then for final model using multinomial logistic regression analysis. Two hundred and seventy three patients were included in this study, consisted of 81 female patients and 192 male patients age between 12 to 78 years old. A hundred and fourteen patients died during and 159 patients lived. Decreased level of consciousness, especially stupor (OR 10.44, p 0.000) and coma (OR 53.333, p 0.000), and presence of motor weakness (OR 2.068, p 0.009) had relationship with outcome. Mortality rate of meningitis is still high (41.8%) because there are some factors that affect its prognosis. From this study, onset, level of consciousness, and motor weakness are predictors for meningitis death. ***(Med J Indones 2006; 15:236-41)***

Keywords: *meningitis, acute meningitis, chronic meningitis, death*

Meningitis remains a major cause of death and long-term neurologic sequelae worldwide and it's management needs to be reviewed periodically. Mortality rate due to meningitis decreased impressively until mid-fifties. This striking reduction was clearly due to introduction of newer antimicrobial agents. However, between the sixties and the nineties, the prognosis did not substantially improve and the mortality rate remained roughly stable.[1-3] It is unclear why there was no further improvement of the prognosis during three decades, despite new and more potent antibiotics and despite broader availability of critical care medicine. In Indonesia, meningitis remains as a health problem with high mortality rate.

During the past two decades, important progress has been made in understanding the pathogenesis of meningitis. The mechanisms of inflammation have been elucidated. The pathogenesis of cortical necrosis on the one hand and hippocampal apoptosis on the other have been studied. It has been shown that oxidative radicals plat a crucial and noxious role for cerebral blood flow and consecutive cortical brain damage. In addition, the complex effects of nitric oxide have been analysed.[4]

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In Indonesia, there are few studies on the epidemiology of the infection in adults. In this study, we like to report the mortality rate due to meningitis in our Neurology Department Ward from 1997 through 2004. We aimed to determine factors that related to death.

METHODS

We reviewed data from medical records of patients treated as meningitis in Neurology Department Ward Cipto Mangunkusumo Hospital during the period of 1997 through 2005. All of the patients with the diagnosis of meningitis were included in this study.

Meningitis was defined as an inflammation of two of the membranes that surrounded the brain and spinal cord. These membranes (the pia and arachnoid mater) were called the meninges and formed the subarachnoid space, which was filled with spinal fluid. Meningitis was classified according to how it presented over time. "Acute meningitis" was defined as a one-time event that usually did not reoccur. "Chronic meningitis" was defined as persistence or progression of pertinent neurologic signs and symptoms for period of at least 4 weeks. Fever, headache, and stiff neck were the three classic signs of meningitis.[5]

Deaths during hospitalization were recorded and used as outcome. We found out the relationship between age, sex, vomiting, and level of consciousness, motor disturbance sign, cranial nerve palsy, blood leucocyte level, CSF cell counts, CSF glucose level, CSF protein level, and meningitis type, with the outcome.

Data were analysed and were presented in textual, tables, and graphics using SPSS for Windows v 13.00.

RESULTS

There were 273 meningitis patients treated in our wards during the periods of 9 years, consisted of 42 (15.4%) acute meningitis and 231 (84.61%) chronic meningitis patients. Most of the patients were male 192 (70.3%), while only 81 (29.7%) were female, with mean of age 28.01 (± 11.20) years old and range of 12 to 78 years old. Fever was found in 246 (90.1%) patients, headache in 235 (86.1%) patients, and neck stiffness found in 236 (86.4%) patients. The combination of the three signs were found in 211 (77.3%) patients, and one or more of the three signs were found in 271 (99.3%) patients. Only 2 patients presented without one of the classical signs of meningitis. (table 1)

Table 1. Characteristics of Meningitis Patients

Variables	N	%	Mean (±SD)
Sex			
Female	81	29.7	
Male	192	70.3	
Age			28.01 (11.20)
Fever			
No	27	9.9	
Yes	246	90.1	
Headache			
No	38	13.9	
Yes	235	86.1	
Neck Stiffness			
No	37	13.6	
Yes	236	86.4	
Level of Consciousness			
Alert	49	17.9	
Drowsy	112	41.0	
Delirium	32	11.7	
Stuporous	67	24.5	
Comatose	13	4.8	
Vomiting			
No	141	52.4	
Yes	128	47.6	
Seizure			
No	172	64.2	
Yes	96	35.8	
Hemiparesis			
No	178	73.3	
Yes	72	26.7	
Cranial Nerve Palsy			
No	197	74.6	
Yes	67	25.4	
Blood Leucocyte (mg/dL)			11·894.30 (6224.785)
≤ 10·000	114	43	
>10·000	151	57	
Erythrocyte Sedimentation Rate (mm/hr)			48.69 (24.70)
≤50	111	74	
>50	39	26	
Cerebrospinal Fluid Cell Count (cell/mm^2)			395.51 (922.52)
≤500	73	77.7	
>500	21	22.3	
CSF Glucose (mg/dL)			47.103 (25.704)
>45	54	38.6	
≤45	86	61.4	
CSF Protein (mg/dL)			330.387 (684.783)
≤300	100	78.1	
>300	28	21.9	
Meningitis			
Acute Meningitis	42	15.4	
Chronic Meningitis	231	84.6	
Outcome			
Alive	159	58.2	
Death	114	41.8	

Table 2. Relationship between demography, clinical, laboratory variables, and outcome

Variable	Alive N (%)	Death N (%)	p	OR	95% CI
Sex					
Female	55(67.9)	2632.1			
Male	104 (54.2)	88 (45.8)	**0.036**	**1.790**	**1.037;3.090**
Age (years)	27.48 (10.75)	28.45 (11.81)	0.357	0.056	
Fever					
No	17 (63.0)	10 (37.0)			
Yes	141 (57.6)	104 (42.4)	0.589	1.254	0.552;2.850
Headache					
No	22 (57.9)	16 (42.1)			
Yes	136 (58.1)	98 (41.9)	0.979	0.991	0.495;1.984
Neck Stiffness					
No	24 (64.9)	13 (35.1)			
Yes	134 (57.0)	101 (43.0)	0.369	1.392	0.676;2.866
Level of Consciousness*					
Alert	40 (81.6)	9 (18.4)			
Drowsy	77 (68.8)	35 (31.3)	0.124	2.020	0.884;4.615
Delirium	17 (65.4)	9 (34.6)	0.157	2.353	0.796;6.958
Stuporous	20 (29.9)	47 (70.1)	**0.000**	**10.444**	**4.278;25.499**
Comatose	1 (7.7)	12 (92.3)	**0.000**	**53.333**	**6.124;464.480**
Vomiting					
No	81 (57.4)	60 (42.6)			
Yes	76 (59.4)	52 (40.6)	0.749	0.924	0.568;1.501
Seizure					
No	100 (58.1)	72 (41.9)			
Yes	58 (60.4)	38 (39.6)	0.716	0.910	0.547;1.514
Hemiparesis					
No	126 (63.6)	72 (36.4)			
Yes	33 (45.8)	39 (54.2)	**0.009**	**2.068**	**1.197;3.572**
Cranial Nerve Palsy					
No	115 (58.4)	82 (41.6)			
Yes	41 (61.2)	26 (38.8)	0.685	0.889	0.504;1.568
Blood Leucocyte (mg/dL)	12,942.86	23,062.69	0.903		
≤ 10·000	64 (57.1)	48 (42.9)			
>10·000	90 (59.6)	61 (40.4)	0.689	0.904	0.550;1.484
ESR (mm/hr)	48.34	54.88			
≤50	61 (75.3)	20 (24.7)			
>50	24 (61.5)	15 (38.5)	0.120	1.906	0.840;4.325
CSF Cell Count (cell/mm^2)*	396.62	1,093.13	**0.031**		
≤500	54 (79.4)	14 (20.6)			
>500	14 (66.7)	7 (33.3)	0.249	1.929	0.654;5.685
CSF Glucose (mg/dL)	46.908	37.000	0.077		
>45	47 (87.0)	7 (13.0)			
≤45	58 (70.7)	24 (29.3)	0.027	2.778	1.101;7.011
CSF Protein (mg/dL)	368.333	290.933	0.649		
≤300	78 (79.6)	20 (20.4)			
>300	20 (71.4)	8 (28.6)	0.359	1.560	0.600;4.057
Meningitis					
Acute Meningitis	24 (57.1)	18 (42.9)			
Chronic Meningitis	135 (58.4)	114 (41.8)	0.875	0.948	0.488;1.843

Patients who admitted to our wards came with decreased level of consciousness, indicated the involvement of brain functions in the inflammatory process (meningo-encephalitis). Only 17.9% patients admitted without loss of consciousness, while 24.5% patients admitted were stuporous.

The presence of focal neurological deficit was common in our patients. Seizure was found in 35.8% patients, hemiparesis in 26.7%, cranial nerve palsy in 25.4% patients.

Laboratory tests were not recorded in all of the patients. The mean of blood leucocyte level was 11 894.30 mg/dl, the mean of erythrocyte sedimentation rate was 48.69 mm/hr, and mean of CSF cell count was 395.51 cell/mm^2, where 22.3% of it was more then 500 cell/mm^2. Mean of CSF glucose level was 47.10 mg/dl, while mean of CSF protein level was 330.39 mg/dL.

The death rate in this study was 41.8% during 1997 through 2005 periods. Data from this study showed that there was relationship between male sex and outcome (OR 1.790, p 0.036). Decreased level of consciousness, especially stuporous (OR 10.44, p 0.000) and coma (OR 53.333, p 0.000), and presence of motor weakness (OR 2.068, p 0.009) had relationship with outcome.

Laboratory examinations were not done in all of the patients in this study. Analyses of the laboratory test did not show any significant relationship with outcome in our study. However, there were tendency of worse outcome in the patients with higher erythrocyte sedimentation rate, higher CSF cell count, lower CSF glucose level, and higher CSF protein level. Fifteen (38.5%) patients with ESR >50 mm/hr had unfavourable outcome compare to 20 (24.7%) patients with ESR ≤ 50 mm/hr. Patients with CSF cell counts >500 cells tended to have worse outcome than ≤ 500 cells (33.3% vs. 20.6%). The result of CSF glucose level tests showed that patients with glucose level ≤ 45 mg/dL tended to have worse outcome (29.3% vs. 13.0%). CSF protein level tests did not show significant relationship with outcome, protein level >300 mg/dL had unfavourable outcome more than protein level ≤ 300 mg/dL (28.6% vs. 20.4%).

In this study, there was no difference between meningitis type and outcome. Almost forty three percents patients with acute meningitis died compare to 41.8 percents patients with chronic meningitis.

DISCUSSION

Meningitis was greatly feared infectious disease because it struck and killed rapidly and as many as 25 percent of survivors had sequale such as permanent brain damage, mental retardation, or hearing loss. Mortality due to meningitis was decreased significantly in the early period of introduction of potent anti-biotics; thereafter, the mortality were not altered although there is development in antibiotics potency. In this study, the mortality was 41.8%. This mortality rate was high compare to the mortality rate reported in other publications in the United States (5-40%)[1,16] and Asia (15-50%). The increased number of HIV-related CNS infection supported the high death rate in this study. The cases of HIV complication in CNS were increased since 2003 in our hospital and they contributed to the high death rate. As in many countries in South East Asia, the number of HIV-positive and AIDS patients is still increasing, leading to a rising number of opportunistic infections including CNS manifestation.[6-9]

In our study, most of the patients were young adults with the mean of age were 21 years old. This result was lower than mean of age of the patients reported in Thailand (29.6 years old).[5] There was male predominance (70.3%) in this study that was consistent with previous study.

The clinical presentations of patients admitted to our hospital showed that altered level of consciousness, seizure, hemiparesis, cranial nerve deficit were found in most of the patients. These clinical presentations were found also in previous studies.[10-13]

Presence of altered level of consciousness and hemiparesis were significantly related to mortality. As in previous studies, the degree of consciousness related to clinical severity of the patients and had sufficient impact on the prognostic for the mortality. Hemiparesiswas found in 26.7% of the patients and 54.2% of them were dead compare to only 26.4% who did not had hemiparesis. Hemiparesis, as altered level of consciousness, in these patients was considered as the involvement of the brain functions (meningo-encephalitis), thus as found in other studies result in worse outcome.[1,10,11,14,15]

The search for better understanding of pathophysiology and better treatment of meningitis was needed to improve the outcome. Multiple cytokines play an important regulatory role in the control of inflammation.

TNF-α, IL-1β, and IL-6 are major early response cytokines that trigger, often in synergy, a cascade of inflammatory mediators, including other cytokines, arachidonic acid metabolites, chemokines, and reactive nitrogen and oxygen intermediates. Increased concentrations of these cytokines have been detected in CSF samples of bacterial meningitis and concentrations of IL-1β are associated with significantly worse disease outcome or disease severity. Influx leukocytes to subarachnoid space due to increased expression of adhesion molecules and uncontrolled expression of proinflammatory mediators will release a complex variety of potentially cytotoxic agents including oxidants and proteolytic enzymes (e.g., matrix metalloproteinase [MMP]), which may contribute to tissue destruction. Inflammatory host reaction result in vasculitis, blood-brain barrier (BBB) disruption, hydrocephalus, and cellular swelling. This process cause further vicious circle of pathophysiologic alterations, leading to neuronal injury and high intracranial pressure. Further research on the biomolecular alterations of the disease process will be relevant the development of therapeutic interventions strategies in meningitis. [4]

This study has some limitations. Because of the retrospective nature, we might have missed the patients due to inaccurate information in medical status. Laboratory tests are not found in many cases, leading to insignificant relationship to outcome as found in other studies, however the laboratory tests result that tends to have worse outcome are similar to previous studies.[9]

Cerebrospinal fluid (CSF) examinations and analysis are still an important diagnostic tool, and they can predict the outcome of both acute bacterial and chronic meningitis. Because of that, the CSF examinations must be performed in all suspected meningitis patients.

Cerebrospinal fluid (CSF) examinations results in this studies do not give the significant number to predict death, however in other studies, CSF pressure ≥450 mmH_2O, cell counts >5000/μL, CSF glucose concentrations <40 mg/dL, or protein concentrations ≥300 mg/dL are the risk factors for death outcome. In this study, cell counts of the death are 1093 mg/dL, glucose concentrations 37mg/dL, and protein concentrations 291 mg/dL are similar to previous studies. This study does not give significant statistic results due to lack of data.[14-16]

Because there is still high death rate especially in acute bacterial meningitis, it is likely suggested to examine the gram stain of CSF, micro-organisms culture and resistance to find out the causative bacteria and to administer the right antibiotics. In this study there is no culture examination result because most of the patients arrived in late stage, poor economic status, so patients could not afford to pay for the examinations, and disapproval of patient's family.[17,18]

In summary, meningitis remains public health problem due to high mortality rate. The increased prevalence of HIV/AIDS disease provides increased number of meningitis cases and may contribute to increased mortality rate. Better understanding of pathophysiology is needed to improve adjunctive treatment other than mere better antibiotics.

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