Abnormal electroencephalographyas predictor of mortality in meningoencephalitis

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ABSTRACT

Although the incidence of meningoencephalitis has decreased,howeverits mortality remainshigh. Electroencephalography (EEG) has an important role in the management of meningoencephalitis although the imaging modalities have replaced its position. Abnormality in EEG may appear earlier than in imaging so it is expected to predict mortality.The study aimed to investigate the prognostic role of EEG results in predicting mortality of meningoencephalitis.This was an observational prospective cohort study involvingmeningoencephalitis patients in Dr. Sardjito General Hospital,Yogyakartafrom July 2016 to January 2017 who underwent EEG examination.The patients who met the inclusion and exclusion criteria were divided into abnormal and normal EEG groups. The outcomewas the mortality during hospitalization. Furthermore, the type of EEG abnormalities associated with mortality were evaluated.Thirty-eight patients with the mean age was 33.61±20.37 yearwere involved in this study. Twenty-eight patients (73.7%) had abnormal EEG result and 10 patients (26.3%) death.Bivariate analysis showed that abnormal EEG result (p =0.028) and Glasgow Coma Scale (GCS) score (p =0.005) were significantly associated with mortality. Analysis for the type of EEG abnormalities found that only diffuse slowing (p =0.001) was significantly associated with mortality. Multivariate analysis showed either abnormal EEG result or GCS score were independently predictor of mortality. Abnormal EEG and GCS score were interrelated in affecting mortality.In conclusion, abnormal EEG resultin meningoencephalitis, diffuse slowing in particular, is predictor of mortality during hospitalization

ABSTRAK

Meskipuninsidensi meningoensefalitis menurun, namun mortalitas tetap tinggi. Elektroensefalografi (EEG) berperan penting dalam tatalaksana meningoensefalitis,meskipun modalitaspencitraan telah mengganti perannya. Abnormalitas pada EEGnampak lebih awal dibandingkan pencitraan sehingga diharapkan dapat memprediksi mortalitas.Penelitian ini bertujuan untuk mengkaji peran prognostik dari hasil pemeriksaan EEG dalam memprediksi mortalitas meningoensefalitis. Penelitian ini merupakan studi kohort prospektif observasional melibatkanpasien meningoensefalitis di RSUP Dr. Sardjito, Yogyakartadari bulan Juli 2016 sampai Januari 2017 yang menjalani pemeriksaan EEG.Pasien dibagi menjadi kelompok EEG abnormal dan normal. Luaran adalah kematian selama dirawat di rumah sakit.Tipe abnormalitas EEG terkait kematian dievaluasi.Sebanyak 38 pasien rata-rata berusia 33,61±20,37 tahun terlibat dalam penelitian.Sebanyak 28 pasien (73,7%) mempunyai hasil EEG abnormal dan pasien meninggal 10 (26,3%) orang. Analisis bivariat menunjukkan bahwa hasil EEG abnormal (p =0,028) dan skor *Glasgow Coma Scale* (GCS) berhubungan bermakna dengan kematian(p =0,005). Analisis terhadap tipe abnormalitas EEGmenunjukkan hanya perlambatan difus yang berhubungan bermakna dengan kematian(p =0,001). Analisis multivariat menunjukkan baik hasil EEG abnormal maupun skor GCS secara independen merupakan prediktorkematian. Elektroensefalografi abnormal dan skor GCS berhubungan dengankematian. Elektroensefalografi abnormal pada meningoensefalitis, utamanya perlambatan difus, merupakan prediktor kematian selama perawatan di rumah sakit.

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INTRODUCTION

Meningitis is one of the most common central nervous system infection.[1] In some cases, the inflammatory process occurs in both brain parenchyma and meninges, known as meningoencephalitis.[2] The incidence of meningitis has decreased since the widespread use of vaccinations, however, the mortality remains high. A study in the United States reported that mortality due to meningitis in 2006-2007 was 14.3%, not significantly differ with mortality rate from 1998 to 1999 which was 15.7%.[3] Previous study conducted at Dr. Sardjito General Hospital, Yogyakarta reported that more than a half of meningoencephalitis patients in the neurological wards died.[4]

The electroencephalography (EEG) examination may be useful to evaluate the extent of functional impairment and the presence of encephalopathy in meningoencephalitis.[5] Intracranial infections may cause various EEG abnormalities in both background and epileptiform activity. A previous study reported that diffuse slowing of background activity accounted for 66% of all EEG abnormalities. Other abnormalities, include focal slowing and epileptiform activity, also present in smaller percentage.[6]

The presence of various abnormalities in EEG is expected to help clinicians in determining the prognosis since they may appear earlier than imaging abnormalities. However, several previous studies showed conflicting results. A study in tuberculous meningitis suggests that the EEG abnormalities were not a significant prognostic factor for poor outcomes including death.[6] Two other studies in encephalitis showed contradictory results. The study by Sutter *et al*[7] reported that normal EEG images can predict survival independently, whereas other study by Singh *et al*,[8] showed that abnormalities in EEG does not predict functional outcomes either at the time of discharge or one year later. The aim of this study was to investigate the prognostic role of EEG results in predicting mortality of meningoencephalitis.

MATERIALS AND METHODS

This was an observational prospective cohort study. Mortality during hospitalization in meningoencephalitis patients who had normal EEG result was compared with those who had abnormal result. Furthermore, the type of abnormalities associated with mortality were evaluated. This study has been approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta. Every patient or relative involved was asked for approval by signing informed consent.

Patients selections

The diagnostic criteria in this study consisted of history of fever and one of these following clinical presentations: headache, neck stiffness as the sign of meningismus, altered consciousness, focal neurological signs; or a supportive analysis of the cerebrospinal fluid.[9] If there were any contraindications to lumbar puncture, then clinical criteria consisting of headache, fever, neck stiffness, with or without decreased consciousness.[10]

The inclusion criteria were all patients diagnosed with meningitis, encephalitis, or meningoencephalitis, those who underwent EEG examination during hospitalization, and willing to participate in the study by giving the consent. Patients who were unconscious or non-cooperative were represented by relatives for giving the consent. Exclusion criteria were subjects who have other intracranial lesions such as stroke or brain tumor.

Electroencephalography examination procedures

All patients underwent EEG examination once during hospitalization. EEG examination was performed in a supine position. The electrodeplacement was based on the 10-20 International System.To patients who were cooperative, the examination was initiatedwith the eyes opened, followed with the eyes closed. The activation procedure was performed when the patient closed his/her eyes. The activation procedure performed were photic stimulation and hyperventilation. Photic stimulation was a flash of light with a frequency of 1-30 Hz with a light placed 20-30 cm in front of the patient's face. Hyperventilation procedure was done by asking the patient to breathe deeply and fast for two minutes. EEG examination to patients who were unconscious or unable to follow commands were performed with eyes closed and used only photic stimulation. EEG results were assessed by a neurologist who certified in EEG readings.Subjects were classified based on the EEG result into normal and abnormal EEGgroup. The abnormalities were further divided into three broad categories: diffuse slowing, focal slowing, and epileptiform.

Statistical analysis

The independent variable was EEG result, whereas the dependent variable was the mortality during hospitalization. Confounding variables in this study were sex, age, the consciousnesslevel on admission presented in Glasgow Coma Scale (GCS) score, duration of symptoms prior to hospital admission, seizure, and Human Immunodeficiency Virus (HIV) infection status. Numerical data was presented as mean ± standard deviation (SD) when normally distributed, otherwise the median (minimum – maximum) was used. Independent samplest test or Mann-Whitney test was used to determine the association between numerical variables with mortality, where as Chi-square test was used for categorical variables. Multivariate analysis was performed, using logistic regression test. Association of each type of EEG abnormality with dependent variable was analyzed, using Chi-square test. The significance level wasdefined by p value of <0.05.

RESULTS

The study was conducted in Dr.Sardjito General Hospital, Yogyakartafrom July 2016 toJanuary 2017. There were 48 meningoencephalitis patients during study period. Among those patients, ninepatients did not undergo EEG examination and one patient had a coincidenceof brain tumor. The total subjects involved in this study were 38 patients.

Demography, clinical, and EEG characteristics of patients

Demographically, the mean age of the patients was 33.61±20.37 years (TABLE 1). Twentysix (68.4%) subjects were male. The duration of symptom prior to admission was nine (1 - 90) days. The GCS score on admission was 14 (6-15). Eighteen (47.4%) patients experienced seizure during illness. Human Immunodeficiency Virus (HIV) infection was found in 13 (34.2%) patients, however, the examination of HIV infection was not performed in seven patients. Patients who died were 10 (26.3%) patients. Electroencephalography results were abnormal in 28 (73.7%) patients with the most common abnormality found was diffuse slowing of background activity (75%). Some patients have more than one types of abnormalities.

TABLE 1. Demographic, clinical, and EEG characteristics

Characteristics	n (%)	Mean±SD/ Median(min–max)
Gender		
• Men	26 (68.4%)	
• Women	2 (31.6%)	
Age (year)		33.61±20.37
Onset before admission		9 (1 – 90)
GCS at admission		14 (6 – 15)
EEG at admission		7 (2 – 32)
Length of stay (days)		14 (5 – 51)
Seizure		
• Yes	18 (47.4%)	
• No	20 (52.6%)	
HIV infection		
• Positive	13 (34.2%)	
• Negative	18 (47.4%)	
• Unknown	7 (18.4%)	
Outcome		
• Died	10 (26.3%)	
• Survive	28 (73.7%)	
EEG results		
• Normal	10 (26.3%)	
• Abnormal	28 (73.7%)	
EEG abnormalities		
• Diffuse slowing	21 (75%)	
• Focal slowing	7 (25%)	
• Epileptiform	16 (57.1%)	
Background activity		
• Delta	5 (13.2%)	
• Delta – tetha	9(23.7%)	
• Tetha	6(15.8%)	
• Tetha – alfa	2(5.3%)	
• Alfa	16 (42.1%)	

Factors associated with mortality

Bivariate analysis (TABLE2) showed a significant difference in mortality proportion between patients with abnormal EEG compared with normal EEG (p=0.028). Assessment of demographic characteristics such as sex and age showed no significant association with mortality. Analysis of the GCS score found a significant difference (p = 0.005) between patients who died compared to those who survive. Other clinical variables such as seizure, HIV infection, or comatose conditions on admission were not significantly associated with outcome.

TABLE 2. Analysis of factors associated with mortality

Factors	Outcome		p
	Died	Survive	
EEG [n(%)]			
• Abnormal	10 (35.7)	18 (54.3)	0.028
• Normal	0 (0)	10 (100)	
Gender[n(%)]			
• Men	6 (23.1)	20 (76.9)	0.694
• Women	4 (33.3)	8 (66.7)	
Seizure[n(%)]			
• Yes	3 (16.7)	15 (83.3)	0.181
• No	7 (35)	13 (65)	
HIV[n(%)]			
• Positive	5 (38.5)	8 (61.5)	0.403
• Negative	5 (27.8)	13 (72.2)	
Coma[n(%)]			
• Yes	2 (50)	2 (50)	0.279
• No	8 (23.5)	26 (76.5)	
Age (mean±SD years)	39.50±14.89	31.50 ± 21.8	0.292
GCS median(min – max)	9.5 (6–15)	15 (6–15)	0.005
Onset median(min – max day)	10.5 (3–30)	9 (1–90)	0.294

Association of EEG abnormalities with mortality

Association of each type of EEG abnormality with outcome were analyzed (TABLE 3). Ten subject (47.6%) with diffuse slowing died while all subject without diffuse slowing survived. Diffuse slowing (FIGURE 1) was the only abnormality associated with mortality (p = 0.001).

TABLE 3. Association of EEG abnormality with mortality

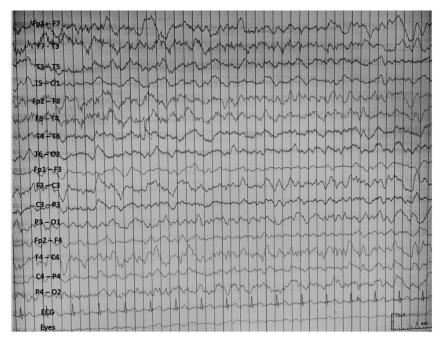| Abnormalities [n(%)]	Outcome		p
	Died	Survive	
Diffuse slowing			
• Yes	10 (47.6)	11 (52.4)	0.001
• No	0 (0)	17 (100)	
Focal slowing			
• Yes	3 (42.9)	4 (57.1)	0.257
• No	7 (22.6)	24 (77.4)	
Epileptiform			
• Yes	4 (25)	12 (75)	0.589
• No	6 (27.3)	16 (72.7)	

FIGURE 1. Electroencephalogram ofone patientshowed diffuse slowing with delta-tetha activity of 3 – 5 Hz.

Multivariate analysis on independent association with mortality

The multivariate analysis using logistic regression test showed that neither abnormal EEG results nor the GCS score on admission was independently associated with mortality (TABLE4). The relative risk (RR) of mortality in abnormal EEG group were not obtainedsincethere were no subject died on normal EEG group.

TABLE 4. Multivariate analysis on independent association with mortality

Variables	p	RR	95% CI
Step 1			
• Abnormal EEG	0.999	-	-
• Seizure	0.148	0.272	0.046 – 1.591
• GCS	0.105	0.785	0.586 – 1.052
Step 2			
• Abnormal EEG	0.999	-	-
• GCS	0.055	0.760	0.575 – 1.005

DISCUSSION

This study showed that abnormal EEG were significantly associated with mortality of meningoencephalitis in bivariate analysis. However, multivariate analysis did not show independent association. The result of multivariate analysis indicated that abnormal EEG and GCS score were interrelated in influencing mortality. Further analysis of each type of EEG abnormality showed that the diffuse slowing (FIGURE 1) was significantly associated with mortality of meningoencephalitis.

Significant association between abnormal EEG and mortality was also confirmed in some previous studies. In

a study involving adult patients with encephalitis, there was a significant difference in mortality where 25.9% of patients with abnormal EEG died during hospitalization, but no subjects died in the normal EEG group (p = 0.01).[7] Another study involving patients aged ≤16 yearsalso showed that abnormal EEG were significantly associated with poor outcomes including death. The study found that the diffuse slowing especially continuous or frequent delta activity was significantly associated with poor outcomes and mortality.[11]

Several previous studies have shown the opposite results. A study by Misra *et al*[6] involving patients with tuberculous meningitis indicated that the EEG result failed to predict poor outcomes including death within six months. Another study with retrospective design in HSV encephalitis found that various EEG abnormalities, such as Periodic Lateralized Epileptiform Discharges (PLEDs), focal slowing, and epileptiform activity,were not associated with poor outcomes including death either at the time of discharge or after 6-12 months. However, the authors did not analyze the association of diffuse slowing and mortalitiy.[8]

Our study also found that subjects in died group had lower admission GCS score than the survive group (p =0.005). Further analysis by classifying GCS scores into ≤8 (coma) and>8 did not show association between coma and mortality (p = 0.279). The small number of comatose subjects on admission was presumed to affect this result. Several previous studies have found a significant association between GCS score and outcome. A long-term prospective study from 1997 to 2006 has been conducted to assess the predictors of outcome in bacterial meningitis. The results showed that low GCS score was one of the significant predictors for poor outcomes (p<0.001).[12] Other study by Wall *et al*[13] showed a similar result in which the mean GCS score of died group

was 10.2+3.6, whereas in the survival group was 12.2+2.8 (p < 0.001). Further analysis showed that GCS scores <8 and 8 - 11 were significantly associated with poor outcomes compared to GCS>11 with an Odds Ratio (OR) score 5.99 (95% CI: 3.31 - 10.86) and 1.67 (95% CI: 1.09 - 2.56), respectively.

In meningoencephalitis there may be increased production of pro-inflammatory cytokines by CSF leukocytes, microvascular endothelial cells, monocytes, astrocytes, and microglia.[2] This condition lead to vasogenic and cytotoxic brain edema, resulting in increased intracranial pressure. Hydrocephalus as result of inflammatory process in subarachnoid space may worsen the situation.[14,15] In encephalitis there may be a direct inflammatory process in the cerebral parenchyma which sometimes involve the meninges as well. The widespread process of parenchymal inflammation may cause brain edema that may also increase the intracranial pressure.[16,17] This condition may result in decrease of consciousness and death.[18] The aforementioned pathophysiological process will result in global cerebral dysfunction and encephalopathy. One study assessing the various etiologies of encephalopathy in pediatric patients showed that most encephalopathies were caused by bacterial meningitis (41%) and viral encephalitis (37%).[19] The encephalopathy may cause abnormalities in EEG result in which diffuse slowing is mostly seen. At a mild stage, there may be a slowing alpha rhythm but in worse conditions a slower frequency even delta activity can be found.[20] Study by Gandelman-Marton *et al.*[21] in West Nile Virus meningitis found that most subjects had a continuous slowing, in frontal and temporal regions predominantly. The presence of diffuse slowing seemed to be related to the severity of the disease. This is thought to be the reason for the significant association between the

diffuse slowing on EEG and the mortality found in the present study.

Diffuse slowing in central nervous system infection such as encephalitis generally has no specific diagnostic significance, but its role in determining the patient's prognosis is worth noting. Serial evaluation of diffuse slowing in encephalitis patients may determine the prognosis of the patient.[5] Focal slowing and epileptiform were not associated with outcome in our study. Both of these abnormalities failed to show the severity of cerebral dysfunction caused by encephalopathy.[22,23]

The low GCS score and the diffuse slowing of the EEG in meningoencephalitis are conditions that result from increased intracranial pressure. The abnormal EEG result and GCS score in this study were interrelated in influencing the mortality of the study subjects, so the multivariate analysis did not demonstrate them as an independent predictor of mortality.[18,20]

This study has several limitations. First, this study was a single center study with relatively small number of subjects that it may not represent the general population. The second is some other variables which potentially affect the outcome, such as the etiologic agents as well as the imaging results were not analyzed.

CONCLUSION

Abnormal EEG result in meningoencephalitis, diffuse slowing in particular, is predictor of mortality during hospitalization. EEG should be considered as one of the routine examination in the management of meningoencephalitis patients, considering its role in providing functional information of the brain as well as the patient's prognostic value. Further research, in larger scale as well, will be necessary to assess the role of etiologic agents and the imaging results as confounding factors in affecting

patients' outcome.

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