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Original Article

대사성 뇌병증에서 삼상파의 중요성

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박강민 · 신경진 · 하삼열 · 박진세 · 김시은 · 김형찬 · 김성은

Significance of Triphasic Waves in Metabolic Encephalopathy

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Background: Triphasic waves are one of the electroencephalographic patterns that can be usually seen in metabolic encephalopathy. The aim of this study is to compare the clinical and electrophysiologic profiles between patients with and without triphasic waves in metabolic encephalopathy, and reassess the significance of triphasic waves in metabolic encephalopathy. **Methods:** We recruited 127 patients with metabolic encephalopathy, who were admitted to our hospital. We divided these admitted patients into two groups; those with and without triphasic waves. We analyzed the difference of duration of hospitalization, mortality rate during admission, Glasgow Coma Scale, severity of electroencephalographic alteration, and presence of acute symptomatic seizures between these two groups. **Results:** Of the 127 patients with metabolic encephalopathy, we excluded 67 patients who did not have EEG, and 60 patients finally met the inclusion criteria for this study. Patients with triphasic waves had more severe electroencephalographic alterations, lower Glasgow Coma Scale, and more acute symptomatic seizures than those without triphasic waves. After adjusting the clinical variables, Glasgow Coma Scale and acute symptomatic seizures were only significantly different between patients with and without triphasic waves. **Conclusions:** We demonstrated that patients with triphasic waves in metabolic encephalopathy had more significant impairment of the brain function. (Korean J Clin Neurophysiol 2014;16:15-20)

Key Words: Metabolism, Encephalopathy, Seizure, Electroencephaography, Triphasic waves

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Introduction

Metabolic encephalopathy encompasses a diverse array of systemic conditions that result in global cerebral dysfunction in the absence of structural brain injury.[1] The major causes of metabolic encephalopathy are organ failure, electrolyte abnormalities, endocrine abnormalities, nutrition deficiencies, sepsis, toxins, and withdrawal states.[1]

Triphasic waves are one of the electroencephalographic (EEG) patterns, which can be usually seen in metabolic encephalopathy.[2] The morphology of triphasic waves is medium to high amplitude (100-300 μV) with large positive sharp waves followed by small negative components.[2,3] The frequency of triphasic waves is usually 1.5 to 2.5 Hz, often occurring in clusters, and a fronto-occipital lag may be

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present.[2,4]Although triphasic waves are frequently predominant in the frontal regions, they are occasionally at its maximum in the posterior regions.[3,5] These waveforms were initially believed to be specific for hepatic encephalopathy.[3,4] However, they can also be seen in patients with other metabolic encephalopathies, including uremia, sepsis, hypoxia, or hypoglycemia.[2,4-6] Even in non-metabolic or structural disorders, such as craniopharyngioma, thalamic glioma, pontine infarction, meningeal carcinomatosis, Binswanger disease, multifocal lymphoma, and Alzheimer dementia, triphasic waves are rarely observed.[4,5,7] The mechanism underlying triphasic waves remains unknown, but abnormal oscillatory discharges between cortex and thalamus were suggested.[8,9] The previous studies have reported a poor prognosis of triphasic waves in metabolic encephalopathy.[5,10] However, the association between triphasic waves and other clinical, electrophysiologic profiles were not determined by the previous studies.

The aim of this study is to compare the clinical and electrophysiologic profiles between patients with and without triphasic waves in metabolic encephalopathy, and reassess the significance of triphasic waves in metabolic encephalopathy.

Methods

This study was conducted with an approval of the Institutional Review Board at our institution. This case-control observational study was performed retrospectively in a single tertiary hospital, serving a population of approximately 400,000 individuals. From our hospital database, we recruited 127 patients with a diagnosis of metabolic encephalopathy, who were admitted to Haeundae Paik Hospital over a period from March 2010 to October 2012. The inclusion criteria were patients with 1) typical clinical histories and laboratory findings of hepatic failure (hepatic encephalopathy), renal failure (uremic encephalopathy), hypoxia (hypoxic encephalopathy), hypoglycemia (hypoglycemic encephalopathy), hyponatremia (hyponatremic encephalopathy), sepsis (septic encephalopathy), or drug intoxication (drug induced encephalopathy), 2) deterioration of consciousness, 3) no structural lesions that could cause deterioration of consciousness in brain computed tomography (CT) or magnetic resonance images (MRI), 4) EEG during hospitalizationin our hospital, and 5) no previous seizure history. We excluded patients who were suspected of nonconvulsive status epilepticus such as mental deterioration abated minutes after administration of intravenous lorazepam.

We divided the patients into two groups; those with and without triphasic waves in the initial EEG. Triphasic waves were defined as 1) bilaterally synchronous bursts or run waveforms consisted of three phases (negative, positive, and negative phase sequentially), 2) having the amplitude of 100-300 μV and the frequency of 1.5 to 2.5 Hz, and 3) having no extra-spike component or polyspikes (Fig. 1). All patients took EEG within 24 hours after admission. EEG recordings were done with gold electrodes attached with electrode paste using the international 10-20 system. The EEG was recorded with 32 channels and lasted at least 30 minutes. We used the duration of hospitalization and mortality rate during the admission as a prognostic marker. To determine the degree of impairment of consciousness, we scored all patients according to the Glasgow Coma Scale (GCS) at the same day of the EEG recording. In addition, we classified the severity of EEG alterations as mild to moderate and severe according to the frequency of background activities under agreement with two investigators. The mild to moderate EEG alteration was defined as the background activities consisted of mainly alpha or theta rhythms, whereas the severe EEG alteration

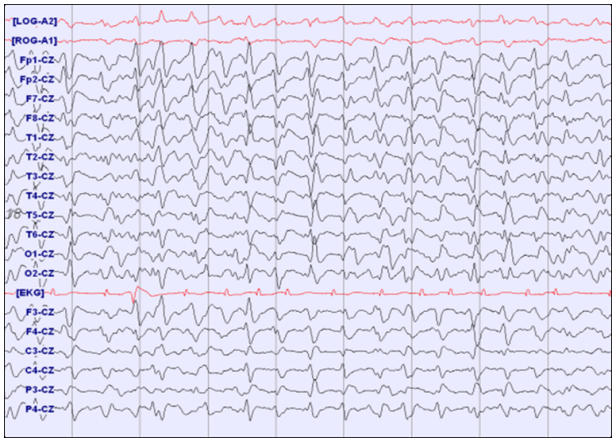

Figure 1. An electroencephalography of the 85-year-old woman with acute renal failure shows bilateral synchronous, frontally dominant runs with waveforms of phase: negative, positive, negative, and fronto-occipital lag.

was defined as those consisted of mainly delta rhythms or very low amplitude rhythms like flat. We defined acute symptomatic seizures as clinical seizures at the time of metabolic encephalopathy, occurring within 1 week.[11]

The primary endpoint for this study was a presence of triphasic waves in the EEG as a dependent variable. The differences were analyzed with the duration of hospitalization, mortality rate during the admission, the severity of EEG alterations, GCS, and the presence of acute symptomatic seizures as independent variables. We analyzed the variables using Fisher's exact test for categorical variables, and Student's t-test or the Mann-Whitney U-test for numerical variables. For multivariate analyses, we dichotomized GCS as >10 or ≤10, and the duration of hospitalization as >19 or ≤19 days. All of these cutoff values were calculated using areas under receiver operating characteristics curves. We performed multiple logistic regression analyses using the dependent variables. We excluded the patients who expired during admission from analyzing the duration of hospitalization with Mann-Whitney U-test, but included them into the array of the duration of hospitalization >19 days in a multivariable analysis. All statistical tests were performed, using MedCalc®. For all calculations, a *p*-value of less than 0.05 was considered statistically significant.

Results

Of the 127 patients with metabolic encephalopathy, we excluded 67 patients who did not have EEG, and 60 patients finally met the inclusion criteria for this study. Thirty four patients were men and 26 patients were women. The median age was 73 years (95% CI 68-76 years, range: 20-91 years). Amongst 60 patients with metabolic encephalopathy, 18 patients had uremic encephalopathy, 11 had hypoxic encephalopathy, eight had drug induced encephalopathy, seven had hyponatremic encephalopathy, six had hepatic encephalopathy, five had hypoglycemic encephalopathy, and five had septic encephalopathy. The median duration of hospitalization was 21 days (95% CI 16-32 days, range 3-153 days). Thirty percent (18/60) of the patients with metabolic encephalopathy expired during admission. Of the expired patients, nine patients had uremic encephalopathy, seven had hypoxic encephalopathy, one had hyponatremic encephalopathy, and one had septic encephalopathy. The median GCS was 11 (95% CI 10-12, range: 3-15). Fifty seven percent (34/60) of the patients with metabolic encephalopathy showed severe EEG alteration. Thirteen percent (8/60) of the patients with metabolic encephalopathy had acute symptomatic seizures.

Of the 60 patients with metabolic encephalopathy, 13 patients showed triphasic waves on initial EEG, whereas 47 patients did not have triphasic waves on initial EEG. Of the 13 patients with triphasic waves, five had uremic encephalopathy, three had hypoxic encephalopathy, three had hypoglycemic encephalopathy, and two had hepatic encephalopathy. Table 1 shows a comparison of the clinical and electrophysiological profiles between patients with and without triphasic waves. The patients with severe alterations on EEG (12/13 vs. 22/47, p=0.0038 by Fisher's exact test), GCS (9 score vs. 12 score, p=0.0157 by Mann-Whitney U-test), and the presence of acute symptomatic seizure (5/13 vs. 3/47, p=0.0326 by Fisher's exact test) were significantly different

Table 1. A comparison of the clinical and electrophysiologic profiles between patients with and without triphasic waves in metabolic encephalopathy

Parameter*	Metabolic encephalopathy with triphasic waves (n=13)	Metabolic encephalopathy without triphasic waves (n=47)	*p*-value
Median duration of the hospitalization (days)	24 (6-74)	20 (3-153)	0.8826
Mortality during the admission	4 (31)	14 (30)	0.1844
The severe EEG alteration	12 (92)	22 (47)	0.0038
Median GCS	9 (4-13)	12 (3-15)	0.0157
Acute symptomatic seizures	5 (39)	3 (6)	0.0326

CI; confidence interval, EEG; electroencephalography, GCS; Glasgow Coma Scale.
*Values are presented as number (range) or number (%).

Table 2. Results of multivariate analysis of variables in patients with and without triphasic waves

Independent variable	Adjusted odds ratio	95% confidence interval	*p*-value
Severe EEG alteration	5.9	0.64-55.07	0.1175
GCS (≤10)	6.6	1.03-41.81	0.0463
Acute symptomatic seizures	7.6	1.06-54.68	0.0431

EEG; electroencephalography, GCS; Glasgow Coma Scale.

between the two groups. Patients with triphasic waves had more severe EEG alterations, lower GCS, and had more acute symptomatic seizures than those without triphasic waves. After adjusting the clinical variables, multivariable analysis showed that GCS and acute symptomatic seizure were the only independently significant variables (Table 2). The risk of having GCS ≤ 10 was at least 6 times higher in the patients with triphasic waves than those without triphasic waves, and also the risk of having acute symptomatic seizures was at least 7 times higher in patients with triphasic waves than those without triphasic waves. However, patients with triphasic waves revealed more prolonged hospitalization than those without triphasic waves, but without statistical significance (duration of hospitalization: >19 vs. ≤19 days, OR 1.9, 95% CI 0.43-8.87).

Discussion

Although the morphological features of triphasic waves may resemble generalized periodic epileptiform discharges (GPEDs) which have three phases per complex, it can be differentiated from GPEDs by several features, such as lower frequency, more posterior frontal/central maximum, absence of extra-spike component, fronto-occipital lag, increase or diminish with stimulation, longer complex duration, more blunted upward first phase and downward second phase, and wider angle between the second and third phases of triphasic waves.[12-14] In addition, GPEDs can have phase reversals and polyspikes, whereas triphasic waves have fewer phase reversals and polyspikes.[12] Response of waveforms to stimulation is another useful way to discriminate triphsic waves and GPEDs. Triphasic waves increase with stimulation such as auditory, visual, and noxious method, whereas GPEDs are not influenced by external stimuli.[13]The differences can be also clarified on the clinical ground. In contrast to GPEDs, patients with triphasic waves usually do not recover mental deterioration after administration of benzodiazepine.[14] Triphasic waves are not epileptiform discharges, and seizures are not generally associated with triphasic waves.[15] However, one of the most interesting findings in our study was that acute symptomatic seizures were more common in patients with triphasic waves than those without triphasic waves. We don't know exactly why acute symptomatic seizures are more common in patients with triphasic waves, but we believe that patients with triphasic waves may have more impaired brain function than those without tripahsic waves. We scored all patients according to the GCS, and the GCS was significantly lower in patients with triphasic waves than those without tripahsic waves. Therefore, our study suggests that patients with triphasic waves have more deteriorated consciousness than those without triphasic waves, and we could suppose that patients with triphasic waves have more impaired brain function. In addition, existence of periodicity on the EEG also suggests severe brain impairment in patients with triphasic waves. The terminology of the periodicity may be applied to the waves occurring in sequence at an approximately regular rate or intermittently regular intervals.[16] The periodicity represents a profound disruption of electrophysiological rhythms and indicative of significant acute or subacute brain impairment.[16,17] The pathophysiologic mechanisms of acute symptomatic seizure caused by brain impairment are incompletely understood, but may include changes in the permeability of blood-brain barrier, which may allow drugs or toxins to pass across the blood-brain barrier, dysfunction of glial cells that regulate the extracellular environment of the neurons, presence of parenchymal hemorrhage, release of excitotoxins, such as glutamate, free radical damage, and alteration of energy metabolism.[18,19] Taken all together, it is a reasonable conclusion that patients with periodic EEG patterns, such as triphasic waves, may have more significant impairment of

the brain function, and this impairment of the brain function may result in acute symptomatic seizures.

It has been reported that triphasic waves indicate a poor prognosis.[5,10] However, our study showed that the mortality rate was not different between the patients with and without triphasic waves, but the etiology was the most important prognostic factor for the mortality rate. The mortality rate was higher in uremic and hypoxic encephalopathy, and lower in septic and hyponatremic encephalopathy, whereas none of the patients with hepatic, hypoglycemic, and drug induced encephalopathy died during admission in this study. It was a consistent finding that the patients with hypoxic encephalopathy had a particularly poor prognosis,[10] and our study also showed that not only hypoxic encephalopathy, but also uremic encephalopathy had a poor prognosis than other metabolic encephalopathy.The mortality rate of this study was about 30%, which is relatively high for the patients with metabolic encephalopathy. A plausible explanation for this finding may be selection biases. This study was conducted in a single tertiary referral hospital which was one of the largest hospitals in our city. Thus, our patients comprise a group with very severe metabolic encephalopathy. They had a poor general condition, and usually had several co-morbid diseases.

A previous study demonstrated that slowing of the brain activities was proportional to the severity of the brain dysfunction.[20] Consistent with the previous study, all of the patients with triphasic waves in our study revealed a tendency to more severe alterations of EEG, but multivariate logistic regression showed that the severity of EEG was not a significant variable associated with triphasic waves.

There are several limitations to these findings. First, this study was retrospectively conducted with a small sample size. Second, we initially studied 127 patients with metabolic encephalopathy, but only 60 patients were included and analyzed. The most common etiology of the patients excluded from this study was typical hepatic encephalopathy, in whom no further evaluation for diagnosis was needed using EEG. Third, we used the duration of hospitalization and mortality rate during admission as a prognostic marker, but these markers could be affected by other factors, such as patient's economic state, co-morbid diseases, or propensity of physician. More suitable markers for prognosis may be needed. Controlled clinical trials with larger sample sizes are recommended in the future to validate the findings of this study. With the limitation of our study, the authors suggest that the EEG is still a useful tool in metabolic encephalopathy, and the patients with triphasic waves have a greater tendency to have acute symptomatic seizures.

We demonstrated that patients with triphasic waves in metabolic encephalopathy had lower GCS, and more frequent acute symptomatic seizures, reflecting more significant impairment of the brain function than those without triphasic waves.

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