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Plasma Brain-Type Natriuretic Peptide Level Following Seizure and Syncope: Pilot Study

Kyung-Il Park

Department of Neurology, Seoul Paik Hospital, Inje University, Seoul, Korea

Background and Purpose: To explore the clinical feasibility of plasma brain-type natriuretic peptide (proBNP) level to differentiate the two major causes of transient unconsciousness, seizure and vasovagal syncope (VVS) in adult patients.

Methods: ProBNP levels were evaluated within 24 hours following attack in patients who had experienced a transient episode of unconsciousness. For confirmatory diagnosis, clinical history was reviewed thoroughly and several work-ups including electroencephalography and cerebral imaging and tilt-table test, were performed in cases of putative VVS, as a part of routine clinical approaches.

Results: According to various relevant evaluations, 15 patients were diagnosed as seizure (age, 40.3± 13.8 years) and 12 patients were VVS (age, 38.1±17.1 years). Plasma concentrations of pro-BNP were not different between two groups (p=0.714). Median level was 34.3 pg/mL (interquartile range: 12.9-91.1) in post-seizure group and 32.3 pg/mL (interquartile range 8.9-77.4) in post-VVS group. Additionally, it was not correlated with the sampling times within 24 hours after the episodes.

Conclusions: The plasma level of pro-BNP has a limited clinical value in differentiating seizure and vasovagal syncope in adults. However, the more validated results with a large population should be sought in the future studies to confirm its value. **(2014;4:14-17)**

Key words: Brain-type natriuretic peptide, Seizure, Syncope

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Corresponding author: Kyung-Il Park
Department of Neurology, Seoul Paik Hospital, Mareunnae-ro 9, Jung-gu, Seoul 100-032, Korea
Tel. +82-2-2270-0045
Fax. +82-2-2267-0916
E-mail; ideopki@gmail.com

Introduction

Although the differential diagnosis of syncope and seizure is critical in a patient experiencing transient loss of consciousness, it is still challengeable without clear clinical features or without a witness. A few key points are helpful. Syncope, especially vasovagal syncope (VVS), usually has longer preceding symptoms, while seizure accompanies tonic contraction of four extremities more frequently than syncope. In addition, patients with seizure regain their consciousness more slowly than patients with syncope because of postictal drowsiness or sleep. However, myoclonic jerks during syncope which characterizes 'convulsive syncope', may confuse them with motor seizures. Dizziness or visual symptoms prior to syncopal attacks also seem to be similar with visual aura of seizure. The duration of preceding symptom is usually short in cases of cardiogenic syncope like as seizure attack.[1] To differentiate the two diseases clearly, some biomarkers favoring a seizure attack in blood or cerebrospinal fluid (CSF), have been proposed,[2-6] but its clinical application has not made yet.

Therefore, this study aimed to explore the clinical feasibility of plasma N-terminal brain-type natriuretic peptide (proBNP) level to differentiate the two major causes of transient unconsciousness, seizure and vasovagal syncope (VVS) in adult patients.

Methods

The patients who presented in our emergency center or outpatient clinic of neurology department having a recent (<24 hours) history of transient unconsciousness between May and December 2011, were enrolled. The data of adults aged between 18 and 60 were prospectively collected. The blood samples were collected and the levels of proBNP were analyzed immediately after sampling. For confirmatory diagnosis, I took the clinical history thoroughly and performed electroencephalography (EEG) and brain imaging as indicated. When the clinical setting suggested VVS, head-up tilt table test was undergone. The head-up tilt table test was considered positive when hypotension and bradycardia accompanied a faint or near-faint symptom which is similar with a patient's previous experience.[7] Final decisions were made after discussing with a cardiologist. The inclusion criteria for seizure and

Table 1. Inclusion criteria of each group

Seizure group	Fulfill at least one of the following:
	1) Alleged epilepsy with history of previous recurrent stereotypic seizure-like movements
	2) First attack fulfilling at least one of the following
	a) Epileptogenic lesion on MRI
	b) Interictal or ictal epileptiform discharges on EEG
	c) Observed and monitored seizures by medical personnel
Syncope group	Fulfill all the following criteria
	1) No epileptiform discharge on EEG
	2) Prolonged prodromes (such as visual dimness, narrowing, and general weakness) or triggers compatible with VVS (emotional tension, prolonged standing and frightening)
	3) Positive isoproterenol head-up tilt table test

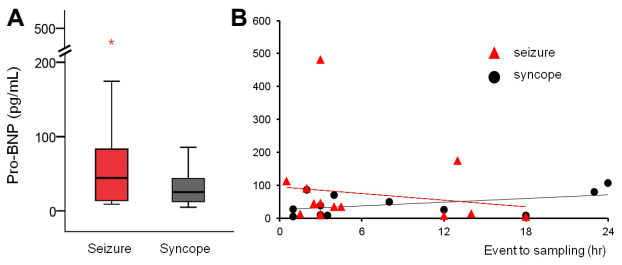

Figure 1. Plasma level of pro-brain type natriuretic peptide(proBNP). (A) Box plot shows no significant difference between seizure and syncope group (p=0.714). (B) Scatterplot shows that proBNP level is not correlated with a sampling time within 24 hours after ictus (p=0.592 in seizure group; p=0.135 in vasovagal syncope group).

syncope group are demonstrated in Table 1. Since that proBNP may be increased in cases of heart diseases or cardiogenic syncope comparing with other causes of syncope,[8] this study excluded the patients with heart diseases or any significant abnormalities in echocardiography and holter monitoring. Statistic analysis includes Mann-Whitney U test and Pearson correlation coefficient through SPSS21.0. p value < 0.05 is considered to be significantly different.

Results

Twenty seven patients including 12 with syncope and 15 with seizure(s), were eligible for analysis. Syncope group showed same sex ratio (male: female: 6:6) but, seizure group showed male preponderance (male: female=11:4). Mean age was 40.3 years (standard deviation: 13.8 years) in seizure group and 38.1 years (standard deviation: 17.1 years) in syncope, which is not statistically different. The detailed information in seizure group obtained from history and tests is summarized in Table 2. The Plasma levels of proBNP were not different between groups (p=0.714). Median value was 34.3 pg/mL (interquartile ranges, 12.9-91.1 pg/mL) in seizure group, and 32.3 pg/mL (interquartile ranges, 8.9-77.4 pg/mL) in syncope group (Fig. 1A). Also, significant correlation between sampling time and concentration of proBNP was not found (p=0.886 in the entire population; p=0.592 in seizure group; p=0.135 in syncope group) (Fig.1B).

Discussion

Brain-type natriuretic peptide plays a physiological role in natriuresis and blood pressure-lowing action mediated by rennin-angiotensin system. Although it is also synthesized and produced in hypothalamus, which is the reason we call it 'brain-type', it is mainly released from cardiac muscles to the circulation.[9,10] Once mechanical tension of cardiac myocytes increases, for example, hypertrophied or dilated cardiac muscles in heart failure, production of proBNP is induced. Thus, this peptide is widely used in diagnosing acute heart failure and determining a prognosis in chronic heart failure.[11] However, because its level is also high following acute brain insults such as traumatic brain injury, subarachnoid hemorrhage and stroke, its clinical usefulness in brain diseases is limited.[12]

In the current study, the plasma level of proBNP shortly after an attack was not different in both groups of patients. This result is not compatible with the previous study investigating proBNP within two hours following seizure in the pediatric population, where proBNP of epilepsy patients was higher than that of syncope or healthy control.[13] Because adults are more likely to have heart diseases than adolescence, indolent possibility in syncope group might dilute the difference of proBNP between two groups. I am not able to resolve completely whether the patient in VVS group do not have heart disease because cardiac work-ups such as, echocardiography, coronary angiography, holter monitoring, were not performed in all patients, despite of the

Table 2. Information of patients in seizure group

Sex/Age (years)	EEG	Image (location)	ProBNP (pg/mL)	Current AED (s)	First seizure
M/46	GE	Arachnoid cyst (Rt. T)	113.5	-	Yes
F/58	Rt. TLE	HS (Rt.)	481.6	+	No
M/60	Not done	Atrophy (Lt. T)	44.9	-	Yes
F/58	Lt. TLE	Normal	13.3	-	Yes
M/25	GE	Normal	9.0	+	No
M/42	Lt. TLE	HA (Rt.)	14.1	-	No
M/44	Diffuse slowing	EM (Rt. F)	5.0	-	Yes
M/48	Normal	EM (Rt. F)	8.3	-	Yes
M/55	Lt. FTLE	Normal	34.2	-	No
F/24	Rt. FLE	Normal	43.3	+	No
M/27	Normal	Normal	45.3	-	No
M/31	Normal	N.A	174.5	+	No
M/38	Not done	N.A	12.9	+	No
F/30	Normal	Normal	91.1	-	No
M/19	Not done	N.A	34.3	-	No

M, male; F, female; EEG, electroencephalography; GE, generalized epilepsy; TLE, temporal lobe epilepsy; FTLE, frontotemporal lobe epilepsy; T, temporal; HS, hippocampal sclerosis; HA, hippocampal atrophy; EM, encephalomalcia; F, frontal; N.A, not available; ProBNP, pro brain-type natriuretic peptide; AED, antiepileptic drug.

efforts to search for cardiac disease through simple chest radiography, electrocardiography, and symptoms as well. The different sampling timing also might be one of the causes of different results. Nevertheless, the current study deserves to be considered because this is the first attempt to utilize proBNP in differentiating VVS and seizure.

According to type of seizures, the level of proBNP can be different.[13] Current study, unfortunately, did not analyze separately based on type of seizure because seven patient of seizure group did not have a witness during an episode and the remaining nine patients experienced only generalized seizures.

Of interest, all three patients exceeding 110 pg/mL belonged to seizure groups. This small finding should be interpreted, but with caution. It is still controversial whether circulating proBNP after seizures is originated from hypothalamus or cardiomyocytes.[14] Seizure provokes an increase of sympathetic tone, which, in turn, may stimulate the release of proBNP from cardiomyocytes. The latter possibility was indirectly supported by the findings that both CK-MB and proBNP increase simultaneously following seizure.[2] However, this explanation is further complicated because vasovagal syncope also activates sympathetic tone temporarily,[15] which may increase proBNP according to the same assumption.[11] In other sense, this assumption is helpful to understand the similarities of proBNP between two group in this study.

Biomarkers implicated in seizure have been sought. Among these, S-100B was studies in blood and CSF in recent papers.[3,6] Recent attack of seizure as well as epilepsy itself appears to increase its release from glial cells into the blood and CSF. Tau protein in CSF, which is considered to be a biomarker of Alzheimer disease, was also suggested as another candidate.[4] Another study aimed to distinguishing seizure from parasomia and showed that neuron-specific anolase was higher following epileptic seizure.[5] It will be important to develop biomarkers in blood and CSF, because those biomarkers can be an prognostic factor of epileptogenesis, beyond its role of distinguishing other diseases from epilepsy. The molecules implicated in the temporal changes of brain pathology during epileptogenesis including neuroal loss, astrogliosis, reorganization of synaptic network, axonal sproutung, the change of blood-brain-barrier, and neuroinflammation should be pursued in the future studies.

There was no correlation between the level of proBNP and sampling times. Considering that proBNP reached the peak value a few days after traumatic brain injury[14] or subarachnoid hemorrhage[16] , extending the range of time-window or follow-up tests might alter the correlation results.

The limitation of this study is a small size of population. Because of that, I could not analyze the level of proBNP based on the frequency of seizures or syncope, duration of epilepsy, and presence or absence of antiepileptic drugs. More importantly, it is possible that VVS and epilepsy coexist. Recent study indicated that 21 percent of epilepsy patients demonstrated the positive head-up tilt table test.[17] Thus, even patients compatible to the criteria of syncope used in this study, still

have a possibility that their unconsciousness resulted from seizure.

So far, brain-type proBNP in blood is not feasible to be utilized in distinguishing seizure and vasovagal syncope in adult patients. The more validated results with a large population should be sought in the future to confirm it value.

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