KARDIOLOGIA POLSKA

Polish Heart Journal
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957

Online first
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ISSN 0022–9032 e-ISSN 1897–4279

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Article type: Short communication

Received: September 7, 2022

Accepted: January 5, 2023

Early publication date: February 11, 2023

Evaluation of microdamage to the central nervous system, expressed by an increase in plasma concentration of specific neuronal enolase in the course of vasovagal syncope

Short title: Evaluation of microdamage to the central nervous system due to vasovagal syncope

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INTRODUCTION

One of the most common forms of reflex syncope is vasovagal syncope. The long-term influence of recurrent reflex syncope on the central nervous system (CNS) is not yet fully understood.

In recent years, plasma measurments of neuron specific enolase (NSE) have been used in neurological diagnostics of nervous system damage. Neuronal damage leads to an increase in the concentration of this enzyme in the blood plasma and is used as an indicator of brain damage in conditions where neurons are destroyed relatively rapidly [1, 2].

Regarding studies evaluating the influence of syncope on the CNS based on the measurement of enzyme markers, only few reports can be found in the literature [3]. The goal of our study

was an evaluation whether a single episode of vasovagal syncope leads to central nervous system damage, expressed by an increase in the plasma concentration of NSE.

METHODS

Study population

The study included 42 consecutively enrolled patients with a history of recurring episodes of syncope, presyncope or both, in whom cardiogenic syncope was excluded in the course of prior diagnosis, and who were qualified for further examination using the head-up tilt test (HUTT).

Exclusion criteria:

- Central nervous system conditions such as post-stroke status, transient ischaemic attack, Alzheimer's disease, Parkinson's disease, epilepsy, post-CNS trauma;
- Neuroendocrine tumors;
- Haemodynamically significant stenosis of the carotid arteries (USG Doppler);
- Pregnancy;
- Absence of consent of the patient;
- Age <16 and >75 years old.

Head-up tilt test

The head-up tilt tests were performed according to the guidelines of the European Society of Cardiology. In all patients, the Italian Study Protocol of HUTT was applied [4, 5]. During the HUTT, the following parameters were continuously monitored: electrocardiogram and blood pressure in a non-invasive “beat to beat” manner using the BMEYE NEXFIN monitor. Mechanisms of vasovagal reaction were classified according to the Vasovagal Syncope International Study (VASIS) classification into the following types of vasovagal syncope (VVS): mixed, cardiodepressive and vasodepressive [6]. Additionally, the duration of hypotension (systolic blood pressure [SBP], <70 mm Hg) during HUTT was assessed and analysed regarding the type of vasovagal syndrome.

Laboratory tests

Before starting HUTT (NSE-1) and two hours after the completion of HUTT (NSE-2) the plasma NSE concentration was assessed by electrochemiluminescence (ECLIA) using the Elecsys NSE reagent. Values below 16.3 ng/ml were considered normal and any increase in NSE concentration was considered as an increase in NSE after HUTT. As the study

population was dominated by patients with a positive HUTT result, the analysis of NSE concentrations focused mainly on the haemodynamic mechanism of syncope, not only on its occurrence.

Statistical methods

Statistical analyses were performed using JMP software, version 15.0.0 (SAS Institute Inc.). Categorical variables are presented as numbers and percentages. Continuous variables were expressed as mean, standard deviation (SD) or median (interquartile range [IQR]). Differences between groups for continuous variables were compared using the Student's t-test, Mann-Whitney test or Kruskall-Wallis test, depending on the distribution of the variable and the number of compared groups. In order to compare the concentrations of NSE1 with NSE2, the Wilcoxon

signed-rank was used. Pearson's chi-squared test or Fisher Exact test (if 20% of cells have expected count less than 5) compared categorical variables. ROC curves for selected variables were plotted to identify cut-off points differentiating populations, depending on the presence or absence of an increase in NSE concentration after the test. The Pearson’s linear correlation between the duration of hypotension and NSE-2 concentration was presented [7]. The observed differences were considered statistically significant if the *P*-value was below 0.05.

Ethics

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Jagiellonian University Medical College (nos. 122.6120.150.2016 and 122.6120.95.2017). Each participant provided written informed consent before enrollment in the study.

RESULTS

A total of 42 people were enrolled. The complete, planned biochemical diagnostics were performed in 34 patients. The head-up tilt test was performed in all 42 patients.

In some patients (47.1%; 16 out of 34 patients) there was an increase in the plasma concentration of NSE after HUTT but, despite the observed dynamics, these values mostly remained within the accepted laboratory norm (<16.3 ng/ml). The NSE value exceeded the accepted norm in one person before the test (16.99 ng /ml) and in two people after HUTT (20.39 ng/ml and 21.66 ng/ml).

We found out that the plasma concentration of specific neuronal enolase before (NSE-1) and two hours after HUTT (NSE-2) did not differ significantly ($P = 0.98$) at these two time points

(Supplementary material, *Table S1*) and there were also no statistically significant differences in the plasma concentration of NSE after HUTT regarding its result (positive, negative, doubtful) (P = 0.51) (Supplementary material, *Table S2*) or syncope occurence during HUTT (Supplementary material, *Table S3*).

We discovered that there was a statistically significant correlation between the NSE-2 value and the duration of hypotension during HUTT, defined as SBP <70 mm Hg, regardless of the HUTT result. Moderate linear correlation between the duration of hypotension and NSE-2 concentration was observed (r = 0.53; P = 0.002). More frequently, a statistically significant increase in NSE –2 was observed in the mixed type than in the cardiodepressive type of vasovagal reaction. The hypotonia duration was also significantly longer in the mixed type of VVS (Table 1).

Further univariate analysis allowed the definition of prolonged hypotension (SBP <70 mm Hg, P = 0.010) as a risk factor for NSE increase after HUTT. Analysis of the ROC curve showed that in a patient with a duration of hypotension accompanying syncope > 60 seconds, it can be predicted with a sensitivity of over 93% and a specificity of over 71% that it will cause CNS microdamage, expressed as an increase in NSE after HUTT (area under the curve [AUC], 0.81; 95% confidence interval [CI], 0.65–0.97).

DISCUSSION

In the literature, some cases are described when syncope is accompanied by transient focal neurological symptoms [8, 9]. However, the potentially damaging influence of short-term, global hypoperfusion of the CNS during syncope may have a somewhat greater impact on higher cognitive functions, the evaluation of which is not straightforward [10–12].

In this study we observed that there was no statistically significant increase in plasma NSE concentration within two hours of the head-up tilt test. These observations are consistent with the results of the study by Lee et al. [13], who assessed the diagnostic possibilities of using plasma NSE assays for the clinical differentiation of seizures and syncope.

Further analysis of our data showed that the microdamage of CNS is occuring during syncope only when some haemodynamic features of a syncope episode, such as prolonged hypotension, are present. The hypotensive mechanism was also identified as the major causative factor in neurological complications of syncope in the study by Weihong Chu et al. [8] on post-HUTT aphasia. It has been also found an association between the development of clinically symptomatic orthostatic hypotension and an increased risk of future mild cognitive impairment and dementia [14]. This raises the question what can be the consequences of the

prolonged hypotension accompanying recurrent vasovagal syncope for the intellectual capacity of people experiencing it.

Limitations

Some of the limitations of our work are : relatively small study group, possibly higher values of NSE concentration in the following hours after HUTT and the possible effect of undiagnosed neurological diseases or neuroendocrine tumors on NSE values.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

Conflict of interest: None declared.

Funding: None.

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Table 1. The comparison of patients in relation to the type of vasovagal syndrome (VVS)

	VVS type		*P*-value
	Cardiodepressive	**Mixed**	
Age, years, mean (SD)	39.9 (17.8)	41.2 (18.8)	0.84
Sex, female, n (%)	14 (82.4)	14 (87.5)	0.99
Hypotonia duration, seconds, median (IQR)	57.4 (41–73.25)	80 (60–148.75)	0.03
NSE 1, ng/ml, median (IQR)	8.21 (4.43–8.86)	7.50 (5.74–9.02)	0.75
NSE 2, ng/ml, median (IQR)	7.58 (3.81–8.33)	7.64 (5.68–9.58)	0.16
NSE increased after HUTT (NSE2>NSE1), n (%)	3 (25.0)	10 (62.5)	0.049