RESEARCH LETTER

Assessment of neurocognitive functions in patients with vasovagal syndrome

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Introduction It is well known that global brain hypoperfusion which occurs during cardiac arrest firstly affects the areas with high oxygen demand, such as those involved in cognitive processes.[1,2] This raises the question whether short-term global brain hypoperfusion accompanying syncope may also adversely affect the intellectual capacity. An association has been found between the development of clinically symptomatic orthostatic hypotension and an increased risk of future mild cognitive impairment and dementia.[3]

So far, there have been few attempts to assess the impact of reflex syncope on the neurocognitive function.[4] This is especially important considering the high frequency of reflex syncope, which is the most common cause of loss of consciousness in all age groups, including young people.[5,6]

Over the last decade, neuropsychological tests assessing executive functions that control the course of complex cognitive processes requiring concentration and sustained attention have been dynamically developing.[7] In the present study, we used some of these tests (the memory span test [the Corsi test], the test of attention continuity [DAUF], and the Cognitron test [COG]) to examine the effect of recurrent loss of consciousness in patients with vasovagal syncope.

Patients and methods **Study population** The study group included patients with a history of recurrent syncope or presyncope of a probable reflex etiology who were referred for further diagnostics, including the head-up tilt test (HUTT). A total of 42 individuals were initially included in the study group. However, neuropsychological diagnostics and HUTT were performed in 40 patients.

The control group, consisting of individuals with no clinical history of syncope and/or presyncope, was matched in terms of sex, education, and age (+/– 5 years) to 30 randomly selected participants from the study group. The above criteria were used in the selection of the control group, as they are known to be significant confounding factors that influence the results of the neuropsychological tests used in our study (Vienna Test System).

Criteria for exclusion from the study comprised 1) diseases of the central nervous system (CNS) and other diseases potentially affecting the neurocognitive function, 2) an intellectual status that would make it impossible to complete a neuropsychological examination using computer software, and 3) the lack of consent to participate.

Head-up tilt test All patients in the study group underwent HUTT according to the Italian protocol.[8,9] The test was considered finished at the onset of syncope or upon completion of the full study protocol in the absence of syncope.

Neuropsychological tests Before HUTT the patients from the study group underwent a battery of neuropsychological tests: DAUF, COG, and Corsi. After completing the HUTT protocol, all study patients repeated the Corsi test. All control participants performed the same battery of neuropsychological tests as the study group, except for the second Corsi test. The tests were performed on a computer, using a licensed software Vienna Test System by Schuhfried (Mödling, Austria; Supplementary material, *Figures S1–S3*).[10]

The DAUF and COG tests examine the continuity and selectivity of attention at specific intervals. The Corsi test is a study of visual-spatial fresh memory and visual-spatial learning.[10,11]

We analyzed and compared the test results of the study and control groups, as well as the results

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TABLE 1 Comparison of the neuropsychological test results in the study patients and controls, as well as the results of the memory span test before and after the head-up tilt test in the study group

Parameter		Study group (n = 40)	Control group (n = 30)	*P* value
Age, median (IQR)		38 (23.25–53.5)	38 (22.75–60.25)	0.58[a]
Sex, n	Male	8	4	0.46[b]
	Female	32	26	
Education, n	Vocational education or secondary education without a high school diploma	16	7	0.34[b]
	Secondary education with a high school diploma	14	13	
	Higher education	10	10	
DAUF	The sum of correct responses, percentile, median (IQR)	15 (7–34)	34 (16–58)	0.009[a]
	Mean correct reaction time, s, mean (SD)	0.97 (0.14)	0.89 (0.15)	0.03[c]
COG: mean incorrect reaction time, s, median (IQR)		1.09 (1.0–1.19)	1.03 (0.95–1.15)	0.11[a]
		Corsi-1 (n = 40)	Corsi-2 (n = 40)	*P* value
Test execution time, s, mean (SD)		256.2 (130.2)	226.0 (101.8)	0.04[d]
Mean difference		–381.83		

a Wilcoxon rank sum test

b Pearson χ^2 test

c *t* test

d Paired *t* test

Abbreviations: COG, Cognitron; Corsi, memory span test; Corsi-1, results of the Corsi test before HUTT; Corsi-2, results of the Corsi test after HUTT; DAUF, test of attention continuity; HUTT, head-up tilt test, IQR, interquartile range

of the Corsi test before and after HUTT in the study group.

Statistical analysis Statistical analyses were performed using JMP software, version 15.0.0 (SAS Institute Inc., Cary, North Carolina, United States). Continuous variables were presented as mean and SD or median with interquartile range (IQR). For qualitative variables, numbers were given. Continuous variables were compared with the *t* test. The change in continuous values over time (eg, Corsi test results before and after HUTT) was analyzed with the paired *t* test. Ordinal variables were compared using the nonparametric Wilcoxon rank sum test. Categorical variables were compared using the Pearson χ^2 test. The observed differences were considered significant if the *P* value was below 0.05 in the 2-tailed test.

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

Results In the study group, the median number of syncope episodes per patient was 2 (range, 0–150; IQR, 1–5.25), while the median number of presyncope episodes was 30 (range, 0–1000; IQR, 10–100).

The results of HUTT are presented in Supplementary material, *Table S1*. The study group and the control group were comparable in terms of the age, education, and sex structure. When analyzing the results of the Corsi test performed in the study group before (Corsi-1) and after HUTT (Corsi-2), it was noted that the time needed to perform the test after the completion of HUTT was significantly shorter than the time needed to complete it before HUTT (226 vs 256 s; $P = 0.04$).

The mean reaction time for correct answers in the DAUF test was significantly longer in the study group than in the control group ($P = 0.03$; Supplementary material, *Figure S4*). Also, the control participants had a significantly greater number of correct answers in the DAUF test than those in the study group ($P = 0.009$; Supplementary material, *Figure S5*).

We did not find any significant differences in the Corsi and COG test results between the 2 groups (**TABLE 1**).

Discussion Previous studies assessing the potential influence of syncope on neurocognitive functions were focused mainly on middle-aged and elderly patients, in whom possible cognitive deficits are more easily noticeable. One of the novel findings of the present work stems from the characteristics of the study population, which was much younger than in other studies conducted so far. The median age in the study group was only 38 years.

The results of the Corsi test performed in the study patients before and after HUTT confirm that the possible damage to the CNS in the course of a single syncope episode is so small that it would not be noticed at the functional level. There was no deterioration in the Corsi test results after HUTT, and we even found some improvement, possibly due to the learning curve phenomenon. These results are contradictory to those obtained in the pilot study,[4] in which a deterioration of short-term memory was observed (the Corsi test). The discrepancy is probably due to the different selection criteria for the study and control groups, and the small size of these groups in the earlier study. Although a single syncope episode will not lead to sudden, evident neurological deficits, the aggregation of certain microinjuries within the CNS due to recurrent syncope may, in the long term, result in neurocognitive dysfunction.

In our study, we observed that the patients with a history of syncope and / or presyncope experienced a significant deterioration of neurocognitive functions expressed by worse results of the DAUF test in comparison with the controls.

The relationship between the occurrence of syncope and deterioration of neurocognitive functions was also observed by Frewen et al,[12] who found that individuals with a history of syncope or falling in the last 12 months achieved worse results in the Montreal cognitive assessment test. Deterioration of the neurocognitive function in elderly people with a history of syncope and unexplained falls was also demonstrated by de Ruiter et al.[13] In this study, worsening of the neurocognitive function was common and concerned as many as 58% of the patients with a history of syncope or unexplained falls.[13]

Recent studies conducted among patients with long COVID-19 symptoms point to the frequent occurrence of orthostatic intolerance with recurrent hypotonia accompanying prolonged standing.[14] In the same group of patients, neurocognitive disorders in the form of a so-called brain fog are very frequent.[15] The results of our study may indicate a possible causal relationship between these disorders.

Limitations Our study had an observational design and was not a formal, statistically powered trial. That is why the sample size was relatively small.

The number of syncope and presyncope episodes was self-declared by the participants by completing a pre-assessment questionnaire, and has not been verified otherwise. Therefore, it may not be accurate, especially in the patients with a large number of episodes.

For the study, it was decided to select 3 tests assessing short-term memory and concentration. Due to their substantial time consumption, we were unable to carry out more tests evaluating other neurocognitive functions.

Conclusions The results of our study highlight the fact that the problems associated with impaired executive and cognitive functions in individuals with vasovagal syncope may start at an early age, and then worsen with time. This observation is extremely important considering the fact that even a slight deterioration of neurocognitive functions in young people can affect their quality of life.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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