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TRANSIENT HYPERGLYCEMIA IN ACUTE CEREBROVASCULAR PATIENTS AND POST-STROKE FATIGUE

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Post-stroke fatigue (PSF) is a common symptom after acute cerebrovascular events (ACE).

***The objectives** of this study were to identify associations of transient hyperglycemia at hospital admission in acute ACE patients with risk of PSF and certain PSF domains during the first year after ACE occurrence.*

***Material and methods.** We enrolled in the study 252 non-diabetic patients with ACE. Acute transient hyperglycemia was defined as blood glucose level more than 6,0 mmol/l at hospital admission. Patients' characteristics had been evaluated at hospital stay, at 1, 3, 6, 9 and 12 months after ACE occurrence. PSF was measured by three self-report questionnaires: fatigue assessment scale, multidimensional fatigue inventory-20 and fatigue severity scale.*

***Results.** In multivariate logistic regression analysis acute transient hyperglycemia had significant direct associations with PSF (according to all used scales) as well as with each PSF domain at hospital stay, whereas at 1 month after ACE occurrence these associations were significant only for global, physical and mental PSF domains. In the later time points there were no any associations between acute transient hyperglycemia and PSF. Risk of PSF and PSF physical component during hospital stay directly depends on transient hyperglycemia degree, irrespective of other factors (there were statistical increased risks of PSF between fourth and first quartiles of plasma glucose concentration).*

***Conclusions.** 1. Acute transient hyperglycemia at hospital admission in ACE patients was associated with increased risk of global PSF and certain PSF domains only within the first month after ACE occurrence. 2. Risk of global PSF and its physical component at hospital stay directly depends on the level of acute transient hyperglycemia.*

***Key words:** post-stroke fatigue, transient hyperglycemia.*

Introduction. Nowadays stroke is one of the most serious health problems of our society that associated with enormous economic and social burden. Post-stroke fatigue (PSF) is a common but often overlooked symptom after acute cerebrovascular events (ACE) [5].

PSF represents a complex interaction of biological, psychosocial, and behavioral phenomena [13]. Throughout biological factors increased glucose level in acute stroke considered as potential risk factor of PSF in early post-stroke period [11] as well as in long-term perspectives [9, 12]. During acute stroke, stress stimulates the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system leading to release of stress hormones, which increase glucose levels [7].

On the other hand, PSF is understood as being multidimensional with mental, physical, motivational and other aspects [1, 4]. In our previous works we showed that each PSF component has some specific predictors [2,3]. However, up to now almost nothing is known about connections between acute transient hyperglycemia and risk of each PSF domain in different post-stroke periods.

The objectives of this study were to identify possible associations of transient hyperglycemia at hospital admission in acute ACE patients with risk of global PSF and certain PSF domains during the first year after ACE occurrence.

Material and methods. We enrolled in the study 252 patients with ACE: 168 with ischemic strokes, 37 with hemorrhagic strokes and 47 with transient ischemic attacks. Patients were included in the study if they agreed to participate and were able to provide informed consent. Exclusion criteria were diabetes mellitus (because increased glucose level may be a manifestation of disease itself but not of acute transient hyperglycemia) and major medical illness that could cause secondary fatigue (oncological, hematological diseases, cardiac, liver, kidney and respiratory insufficiency, progressive angina pectoris, acute myocardial infarction), alcohol abuse, consciousness impairments, insufficient cognitive ability (Mini-Mental State Examination scores less than 24), depressive and anxious disorders (Hospital Anxiety and Depression Scale scores more than 10 for both pathologies), impaired speech function to participate (severe dysphasia or dysarthria), impaired language or written ability to complete the study questionnaire, severe functional disabilities (modified Rankin scale scores ≥4).

Acute transient hyperglycemia was defined as blood glucose level more than 6,0 mmol/l at hospital admission.

Patients' characteristics had been evaluated consequently in certain time points: at hospital stay and then at 1, 3, 6, 9 and 12 months after ACE occurrence.

PSF was measured by three self-report questionnaires: fatigue assessment scale (FAS), multidimensional fatigue inventory-20 (MFI-20) and fatigue severity scale (FSS). PSF was identified, according to FAS, – at a score ≥22, according to FSS – at a mean score ≥4. For every MFI-20 subscale dimensions (global, physical, mental, motivational and activity-related fatigue) critical value was 12 or more [14].

Socio-demographic factors such as age, gender, marital status (married/single), formal education level (higher/non-higher), pre-stroke employment status (employed/unemployed) were recorded. Pre-stroke fatigue was diagnosed retrospectively if patients reported fatigue lasting longer than 3 months before the stroke [6]. Patients' tobacco smoking status was classified as “non-smoker” (who didn't smoke at least 1 year before the stroke) or “current smoker” (who smoked regularly for the last 1 year before stroke). Subjects were grouped by the level of alcohol consumption (number of drinks per week): none or moderate (≤7 for women and ≤14 for men) and heavy (>7 for women and >14 for men).

Signs of anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (anxiety and depression sub-scales using a cut-off of 4, which has been recommended for persons who have had a stroke) [10]. Apathy symptoms were assessed by the Starkstein apathy scale (a cut-off point 14 or more from the total score of the scale was used to dichotomize the patients into apathetic and non-apathetic). Cognitive impairments were evaluated by the Montreal cognitive assessment (cut-off scores less than 26) [8]. Sleepiness was measured using Epworth scale (scores 10 or more indicate excessive daytime sleepiness).

We diagnosed the presence of most spread acute post-stroke complications (pneumonia, urinary tract infections (UTI), pyrexia). Post-stroke pneumonia was diagnosed as inspiratory crackles and fever or radiographic evidence or purulent sputum. The presence of UTI was defined as clinical signs of dysuria in combinations with significant leukocyturia (≥20 cells per visual field). Temperature >37.5°C for more than 24 hours for which no cause has been identified was considered as pyrexia.

For anthropometric characteristics of abdominal obesity was used waist circumference (cut-off 102 cm for males and 88 cm for females). The co-morbidities included arterial hypertension, ischemic heart disease and atrial fibrillation.

Continuous variables were represented as mean (M) and standard deviation (SD), categorical data were represented by number (n) and percentage (%). Univariate logistic regression analysis was performed to analyze the odds ratio (OR) with 95% confidence intervals (CI) of factors associated with PSF. Variables having a p value less than 0,05 in the univariate analysis were selected and evaluated by multivariate logistic regression models. Patients with acute transient hyperglycemia were ranked into quartiles according to blood glucose level. Logistic regression was used to calculate the OR of PSF risk between quartiles of blood glucose values. P values less than 0,05 were considered significant. Statistical analyses were performed using SPSS 14.0 statistics software.

Results and discussion.

First of all, throughout all studied time points, acute transient hyperglycemia was statistically associated with increased risk of PSF only at hospital stay and 1 month after ACE occurrence.

Table 1.Characteristics of the baseline study sample

Characteristics		Value
age (years), M±SD		61,7±7,1
males, n (%)		127 (50,4%)
married, n (%)		178 (70,6%)
higher education, n (%)		80 (31,7%)
pre-stroke employment, n (%)		80 (31,7%)
pre-stroke fatigue, n (%)		51 (20,2%)
current smokers, n (%)		66 (26,2%)
heavy alcohol consumption, n (%)		32 (12,7%)
anxious signs, n (%)		65 (25,8%)
depressive signs, n (%)		67 (26,6%)
apathy symptoms, n (%)		61 (24,2%)
cognitive impairments, n (%)		107 (42,5%)
excessive daytime sleepiness, n (%)		92 (36,5%)
pneumonia, n (%)		25 (9,9%)
UTI, n (%)		34 (13,5%)
pyrexia, n (%)		35 (13,9%)
abdominal obesity, n (%)		86 (34,1%)
co-morbidities	arterial hypertension, n (%)	222 (88,1%)
	ischemic heart disease, n (%)	197 (78,2%)
	atrial fibrillation, n (%)	63 (25,0%)

Of all the characteristics that are presented in Table 1, in univariate logistic regression analysis only pre-stroke fatigue, anxious signs and pneumonia had significant associations with PSF at hospital stay and only pre-stroke fatigue, cognitive impairments had the same associations 1 month after ACE. So, only these above-mentioned variables were included in multivariate logistic regression analysis of associations between acute transient hyperglycemia and risk of PSF in corresponding time points after ACE occurrence.

Table 2. Associations between acute transient hyperglycemia and risk of PSF at hospital stay

PSF scale	Logistic regression model, OR	
	univariate	Multivariate
FAS	2,2 (CI, 1,2-4,1; p=0,01)	2,1 (CI, 1,1-4,0; p=0,02)

FSS		2,0 (CI,1,1-3,7; p=0,03)	2,0 (CI, 1,1-3,7; p=0,03)
MFI-20, fatigue dimensions	global	2,5 (CI, 1,3-4,6; p<0,01)	2,4 (CI, 1,2-4,6; p=0,01)
	physical	2,6 (CI, 1,4-4,9; p<0,01)	2,4 (CI, 1,3-4,6; p=0,01)
	mental	2,8 (CI, 1,5-5,2; p<0,01)	2,6 (CI, 1,4-5,0; p<0,01)
	motivational	2,4 (CI, 1,3-4,5; p<0,01)	2,3 (CI, 1,2-4,6; p=0,02)
	activity-related	2,3 (CI, 1,2-4,3; p=0,01)	2,2 (CI, 1,1-4,2; p=0,02)

Table 2 shows that acute transient hyperglycemia had significant direct associations with PSF (according to all used scales) as well as with each PSF domain at hospital stay that can indicate acute transient hyperglycemia as independent risk factor for PSF development. Importantly, these associations were retained in multivariate analysis. In other works it also had been shown that admission hyperglycemia was associated with PSF (according to FSS) in acute stroke patients [3, 4].

Table 3. Associations between acute transient hyperglycemia and risk of PSF at 1 month after ACE

PSF scale		Logistic regression model, OR	
		univariate	Multivariate
FAS		1,9 (CI, 1,0-3,6; p=0,04)	-
FSS		2,8 (CI, 1,5-5,5; p<0,01)	2,9 (CI, 1,5-5,7; p<0,01)
MFI-20, fatigue dimensions	global	2,3 (CI, 1,2-4,6; p=0,01)	-
	physical	3,0 (CI, 1,6-5,8; p<0,01)	-
	mental	3,0 (CI, 1,5-5,7; p<0,01)	3,0 (CI, 1,5-6,0; p<0,01)

As can be seen from Table 3, in univariate logistic regression analysis acute transient hyperglycemia had significant associations with global PSF and only with certain (not all) PSF domains after 1 month after ACE occurrence. It's interesting that unlike hospital stay, majority of these associations disappeared in multivariate analysis.

In the later time points (3, 6, 9, 12 months after ACE) there were no any significant associations between acute transient hyperglycemia and PSF.

From time-based PSF conception, acute transient hyperglycemia, as a biological factor, can be considered as predictor of the so-called «early» PSF (PSF that present only in early post-stroke period) [2], whereas most likely for PSF persistence are needed some more additional factors.

Up to now, only one work is devoted to connections between acute transient hyperglycemia and PSF during later post-stroke periods: acute serum glucose level was positively correlated with FSS score at 6 and 12 months after the stroke [5].

All cases of acute transient hyperglycemia were ranked on quartiles by blood glucose level: Q1 (6,1-7,5 mmol/l), Q2 (7,7-8,8 mmol/l), Q3 (8,9-10,5 mmol/l) and Q4 (>10,6 mmol/l). Among all calculations there were statistical increased risks of PSF only between fourth and first quartiles of plasma glucose concentration at hospital stay.

Table 4. Associations between acute transient hyperglycemia level (fourth quartile compared to first quartile) and risk of PSF at hospital stay

PSF scale		Logistic regression model, OR	
		univariate	Multivariate
FAS		6,3 (CI, 1,4-28,3; p=0,02)	9,4 (CI, 1,5-61,1; p=0,02)
FSS		5,5 (CI, 1,3-22,7; p=0,02)	8,0 (CI, 1,4-45,4; p=0,02)
MFI-20	global	5,5 (CI, 1,3-22,7; p=0,02)	9,4 (CI, 1,5-61,1; p=0,02)
	physical	5,5 (CI, 1,3-22,7; p=0,02)	9,4 (CI, 1,5-61,1; p=0,02)
	mental	4,1 (CI, 1,1-16,1; p=0,04)	-

Table 4 demonstrates that risk of PSF during hospital stay directly depends on transient hyperglycemia degree irrespective of other factors.

Up to now there are no explanations about associations between acute transient hyperglycemia and PSF. Maybe in these mechanisms are involved (directly or indirectly) multifaceted deleterious effects of hyperglycemia on brain tissue and cerebral vessels reactivity [25]. Anyway, this question requires further special research.

From clinical point of view it's important to take into account acute transient hyperglycemia for PSF clinical course prognostication.

Conclusions.

1. Acute transient hyperglycemia at hospital admission in ACE patients was associated with increased risk of global PSF and certain PSF domains only within the first month after ACE occurrence.

2. Risk of global PSF and its physical component at hospital stay directly depends on the level of acute transient hyperglycemia.

Future investigations should be directed toward interconnections between acute transient hyperglycemia and post-ischemic inflammatory response due to risk of PSF.

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ТРАНЗИТОРНА ГІПЕРГЛІКЕМІЯ ПРИ ГОСТРИХ ПОРУШЕННЯХ МОЗКОВОГО КРОВООБІГУ ТА ЇЇ ЗВ'ЯЗОК З ПОСТІНСУЛЬТНОЮ ВТОМОЮ

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Постінсультна втома (ПІВ) – розповсюджене ускладнення гострих порушень мозкового кровообігу (ГПМК).

Мета дослідження: *вивчити асоціації між наявністю транзиторної гіперглікемії під час госпіталізації у пацієнтів з ГПМК та ризиком наявності окремих компонентів ПІВ протягом першого року після розвитку ГПМК.*

Матеріал та методи. *В дослідження було включено 252 пацієнти без цукрового діабету. Гостра транзиторна гіперглікемія діагностувалась при рівні глюкози крові більше 6,0 ммоль/л під час госпіталізації. Обстеження пацієнтів проводилося під час перебування в стаціонарі, через 1, 3, 6, 9 та 12 місяців після розвитку ГПМК. Наявність ПІВ визначалась за трьома опитувальниками: шкалою оцінки втоми, шкалою важкості втоми та багатомірною шкалою оцінки втоми.*

Результати. *За результатами мультиваріантного логічного регресійного аналізу, гостра транзиторна гіперглікемія має прямі, статистично достовірні асоціації з ризиком наявності ПІВ (згідно усіх шкал), так і з усіма компонентами ПІВ (глобальним, фізичним психічним, мотиваційним, пов'язаним з активністю) протягом періоду перебування пацієнтів в стаціонарі, тоді як через 1 місяць після ГПМК ці асоціації залишалися достовірними тільки для глобального, фізичного та психічного компонентів ПІВ. В більш пізніх строках спостереження не було виявлено будь-яких достовірних зв'язків між гострою транзиторною гіперглікемією та ризиком наявності будь-якого компоненту ПІВ. Крім того, ризик ПІВ та її фізичного компоненту протягом пері-*

оду знаходження в стаціонарі, незалежно від соціо-демографічних та клініко-неврологічних факторів, прямо асоціюється зі ступенем вираженості транзиторної гіперглікемії (спостерігався статистично підвищений ризик ПІВ у пацієнтів з вищим, у порівнянні з нижчим квартилями показників глюкози крові).

Висновки. *1. Гостра транзиторна гіперглікемія під час госпіталізації з приводу ГПМК прямо асоціюється з підвищеним ризиком глобальної ПІВ та окремих її компонентів протягом першого місяця після розвитку ГПМК. 2. Під час перебування в стаціонарі з приводу ГПМК, ризик глобальної ПІВ та її фізичного компоненту прямо залежить від рівня транзиторної гіперглікемії.*

Ключові слова: *постінсультна втома, транзиторна гіперглікемія.*