NEUROIMAGING CHARACTERISTICS AND POST-STROKE FATIGUE WITHIN THE FIRST 6 MONTHS AFTER ISCHEMIC STROKES

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Post-stroke fatigue (PSF) is a common and distressing syndrome for stroke survivors, associated with poor functional outcomes and higher mortality [1,2]. As known, PSF is multidomain entity which consist of physical, mental, emotional and other aspects [1]. The cause of PSF is likely multifactorial, with biological and psychological components, and may vary depending on timing after event [3]. At last time there is assumption that neuroanatomical changes may play a role in the development and persistence of PSF. But, up to now the impact of neuroimaging characteristics on PSF at the different stages of stroke remains controversial. It is therefore necessary to identify neuroimaging variables associated with certain PSF domains after ischemic strokes.

The objectives of this study were to identify neuroimaging characteristics associated with different PSF domains within first 6 months after ischemic strokes.

Material and methods. We enrolled in the study 107 patients with acute ischemic strokes. Patients were included in the study if they underwent head magnetic resonance imaging (MRI) during their hospital stay, agreed to participate and were able to provide informed consent. Exclusion criteria were 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) [4], depressive and anxious disorders (Hospital Anxiety and Depression Scale scores more than 10 for both pathologies) [5], 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).

PSF was measured by self-report multidimensional fatigue inventory-20 (MFI-20) questionnaire in definite time points: at hospital stay, in 1 month, in 3 months and in 6 month after stroke occurrence. MFI-20 covers global, physical, mental, activity-related and motivational fatigue dimensions. A cut-off of 12 out of 20 for every sub-scale has been suggested for use with people with stroke [6].

MRI studies were performed with a 1,5-T system (Siemens MAGNETOM Avanto 1.5T) and 0,2-T system (Signa Profile HD GE 0.2T). Brain MRI included T1-, T2-, fluid-attenuated inversion recovery (FLAIR) sequences and diffusion-weighted images (DWI).

The characteristics of acute lesions were examined in DWI. Acute infarcts locations were categorized as supratentorial (cortical-subcortical or subcortical) and infratentorial. MRI lesions for acute volumes were measured on DWI by ellipsoid model (ABC/2) in three perpendicular axes. The slice with the largest lesion was first selected by eye. The longest lesion axis on this slice was measured with the ruler tool «K-PACS V.1.6.0.» software. A second line was drawn perpendicular to the first at the widest dimension. These two measurements were called the A and B axes. A third axis, the C axis, was computed by multiplying the number of slices by MRI slice thickness (5 mm) [7].

White matter lesions derived from FLAIR imaging was graded from 0 to 3 on Fazekas scale on the basis of visual assessment both periventricular (0=absent, 1=caps or pencil lining, 2=smooth halo, and 3=irregular periventricular hyperintensities extending into deep white matter) and subcortical areas (0=absent, 1=punctuate foci, 2=beginning confluence of foci, and 3=large confluent areas) [8]. The total Fazekas scale score was calculated by adding the periventricular and subcortical scores [9]. Leukoaraiosis severity was graded according to the Fazekas scale as mild (1–2), moderate (3–4), and severe (5–6).

For measurement of brain atrophy we used planimetrical indexes: bifrontal index (BFI), bicaudate index (BCI), maximum diameter of the third ventricle and cortical atrophy index (CAI) [10]. BFI – maximum width of the anterior horns of the lateral ventricles in relation to the inner skull width at the same level. BCI – minimum width of the lateral ventricles in relation to the inner skull at the same level. CAI – sum of the width of the four widest sulci at the two highest scanning levels divided into maximum inner scull diameter.

Continuous variables with parametric distribution (according to Shapiro-Wilk test) were represented as mean±standard deviation. 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 neuroimaging variables associated with PSF domains. P-value less 0,05 was taken to indicate statistical significance. Statistical analysis were performed using SPSS 14.0 statistics software.

Results and their discussion. Patients' age ranged from 46 to 79 years (64,6±8,0 years). There were 51 (47,7%) males and 56 (52,3%) females.

Table 1 shows a relatively high prevalence of PSF within first 6 months post-stroke period. Also, this table demonstrates that PSF is a rather heterogeneous phenomenon with different dynamics of its domains during observation period.

Table 1. Frequencies of certain PSF domains during first 6 months after acute ischemic strokes

PSF domain	Time point after stroke onset			
	stay in hospital	1 month	3 month	6 months
global, n (%)	25 (23,4%)	24 (22,4%)	32 (29,9%)	31 (29,0%)
physical, n (%)	29 (27,1%)	29 (27,1%)	37 (34,6%)	36 (33,6%)
mental, n (%)	27 (25,2%)	25 (23,4%)	34 (31,8%)	33 (30,8%)
motivational, n (%)	26 (24,3%)	22 (20,6%)	26 (24,3%)	27 (25,2%)
activity-related, n (%)	28 (26,2%)	27 (25,2%)	33 (30,8%)	34 (31,8%)

Table 2. MRI characteristics of the study sample

Acute lesion location, n (%)	
cortical-subcortical	33 (30,8%)
subcortical	38 (35,5%)
infratentorial	36 (33,7%)
Infarct volume, cm3	16,4±10,4
Brain atrophy indexes	
BFI	0,34±0,04
BCI	0,23±0,06
third ventricle diameter, mm	8,1±2,1
CAI	0,04±0,02
Fazekas scale score, n (%)	
1	12 (11,2%)
2	29 (27,1%)
3	31 (29,0%)
4	27 (25,2%)
5	8 (7,5%)

First of all, univariate logistic regression analysis did not reveal any significant associations between rates of any PSF domain (global, physical, mental, motivational, activity-related) and infarct volumes at any time points within first 6 months after ischemic strokes. In the same manner, it has not been found any reliable statistical regularities between frequencies of any PSF domain and any brain atrophy indexes (BFI, BCI, third ventricle diameter, CAI) during the whole 6 months observation period.

On the other hand, it has been found some associations between cerebral infarct locations and the rates of definite PSF domains, but not earlier than 1 month after stroke onset. Univariate logistic regession analysis showed that presence of pure subcortical infarcts was significantly associated with increased risk of physical PSF in 1 month (OR, 3,15; CI, 1,26-7,86; p=0,01) and in 3 months (OR, 2,56; CI, 1,07-6,15; p=0,04) after stroke onset. In a similar way, it has been demonstrated significant associations between subcortical strokes and increased risk of activity-related PSF in 1 month (OR, 2,96; CI, 1,17-7,51; p=0,02) and in 6 months (OR, 2,71; CI, 1,12-6,58; p=0,03) after stroke. Moreover, cerebral infarcts of infratentorial locations were significantly associated with increased risk of global PSF in 3 months (OR, 2,91; CI, 1,24-6,83; p=0,01) as well as in 6 months (OR, 3,19; CI, 1,34-7,58; p=0,01) after disease onset. There were no any significant statistical regularities between cortical-subcortical stroke localization and rates of any PSF domain within the whole 6 months observation period.

Also, it has been identified some associations between extents of white matter lesions and risk of mental PSF. Univariate logistic regression analysis showed that the Fazekas scale score increment of 1 point was significantly associated with higher risk of mental PSF in 3 months (OR, 1,54; CI, 1,05-2,21; p=0,03) and in 6 months (OR, 1,79; CI, 1,20-2,65; p=0,04) after stroke onset. At the same time, frequencies of global, physical, activity-related and motivational PSF domains didn't have any significant associations with Fazekas scale score at any time point during 6 months post-stroke observation period.

According to a systematic review of biological correlates of PSF, there is no conclusive evidence on the association between PSF and lesion site [11]. However, the uncertainty regarding any association between PSF and lesion site might be attributed to 2 factors: the time of PSF assessment and how lesion site was classified [3]. In studies where a significant association between PSF and lesion site was reported, PSF was usually assessed within the first few months after stroke, and the associations were found with specific brain structures. In contrast, in studies which reported no association, PSF was often assessed during a later stage after stroke, and lesion site was classified more broadly [2,3].

Our study is one of the first studies devoted to neuroimaging characteristics and rates of different PSF domains in patients after ischemic strokes. Up to now only in one other study it has been shown that the cerebral lesion site might have a different impact depending on the type of

PSF, with a trend towards more physical PSF component in patients with subcortical lesions and more cognitive PSF component in patients with cortical lesions [12].

In general, we have found some regularities between stroke location, extent of white matter lesion and increased risk of definite PSF domains in post-stroke period, but not early than 1 month after stroke onset. At the same time there were no robust associations between cerebral infarct volumes as well as between brain atrophy indexes and rates of any PSF domain within the whole 6 months post-stroke period.

In our study subcortical infarcts were associated with increased risk of those PSF domains which are related just to physical activity (physical PSF and activity-related PSF). Subcortical strokes in most cases are accompanied by motor pathway lesions, so physical PSF in these cases might result from a difference between greater effort produced by the patient and the actual motor output by paretic muscles [13]. Moreover, in patients with subcortical strokes PSF may occur due to a failure in the integration of the limbic input and the motor functions within the basal ganglia affecting the striatal–thalamic–frontal cortical system [14]. In other studies it has been also revealed associations between subcortical strokes and risk of PSF in different post-stroke periods. Acute caudate infarcts were an independent predictor of PSF in the multivariate analysis, with an OR of 6,4 [15]. Subcortical infarcts were the independent factors associated with PSF 3 months after stroke occurrence whereas the relationship between PSF and lesion location was not significant during the acute stage, so it has been suggested that, PSF is related to derangement of dopaminergic system secondary to strokes occurring in strategic areas and this redistribution of neurotransmitters may take some time [16]. Subcortical white matter infarcts were associated with persistent PSF 15 months after stroke occurrence with OR of 4,21 (p=0,01) [17].

Infratentorial infarcts were associated with increased risk of global PSF in 3 months and in 6 months after stroke onset. Our finding supports others who found an association between PSF and brainstem strokes [18, 19], in particular infratentorial infarcts were related to an increased risk for PSF (OR 4.69; 95% CI 1.03–21.47) [18]. So, this phenomenon may indicate a form of PSF related to pathophysiological mechanisms in the brainstem which may be linked to the interruption of neural networks involved in attention, such as the reticular activating system [19].

We have found that leukoaraiosis extension was directly associated with risk of mental PSF domain in 3 months after stroke and later. Naess H. et al. have reported that the presence of leucoareosis on CT was independently associated with PSF in patients with ischemic and hemorrhagic strokes [20]. The importance of white matter lesions in the pathophysiology of fatigue has been reported in non-stroke patient populations, for example reduced white matter volume was observed in chronic fatigue syndrome [21]. It's well known that white matter lesions are directly connected with cognitive decline [22]. Associations between leukoaraiosis severity and risk of mental PSF can be explained, at least partially, by the fact that persons with cognitive impairments try to compensate the cognitive deficits by making extra effort (so called «coping theory») [19]. The last phenomenon probably becomes more pronounced when patient tries to restore pre-stroke activity some time after stroke onset.

Conclusions.

1. There are no reliable associations between any neuroimaging variables and rates of any PSF domain within first month after ishemic stroke occurrence.

2. Subcortical brain infarcts are significantly associated with increased risk of PSF domains which are connected to physical activity (physical PSF and activity-related PSF) in 1 months after stroke onset and later, whereas infratentorial infarcts are significantly associated with increased risk of global PSF in 3 months after stroke onset and later.

3. White matter lesion extension according to Fazekas scale score is directly associated with significant higher risk of mental PSF in 3 months after stroke onset and later.

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SUMMARY

NEUROIMAGING CHARACTERISTICS AND POST-STROKE FATIGUE WITHIN THE FIRST 6 MONTHS AFTER ISCHEMIC STROKES

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Aim - identify neuroimaging characteristics associated with different post-stroke fatigue (PSF) domains within first 6 months after ischemic strokes.

There were enrolled in the study 107 patients with acute ischemic strokes. General PSF and certain PSF domains (global, physical, mental, motivational, activity-related) were measured by multidimensional fatigue inventory-20 (MFI-20) scale at hospital stay, in 1, 3 and 6 months after stroke occurrence. Brain MRI studies included cerebral infarct localization, planimetric measurements of infarct volumes, measurement of brain atrophy indexes (bifrontal, bicaudate, cortical atrophy indexes, width of third ventricle) and evaluation of leukoaraiosis severity, according to Fazekas scale.

In univariate logistic regression analysis infarcts volumes as well as brain atrophy indexes were not significantly associated with risk of any PSF domain at any time points within first 6 months after ischemic strokes. On the other hand, it had been found reliable associations between subcortical infarcts and increased risk of PSF domains which are related just to physical activity (physical PSF, activity-related PSF) in 1 month after stroke onset and later, as well as reliable associations between infratentorial infarcts and risk of global PSF domain in 3 months after stroke and later. Moreover, it have been revealed significant direct associations between severity of white matter lesions and risk of mental PSF in 3 months after stroke onset and later.

Subcortical infarcts may be risk factors for development of physical PSF domain, infratentorial infarcts – risk factors for development of global PSF domain, leukoaraiosis extension – risk factor for development of mental PSF domain but not early than 1 month after stroke occurrence.

Keywords: stroke, fatigue domains, neuroimaging.

РЕЗЮМЕ

НЕЙРОВИЗУАЛИЗАЦИОННАЯ ХАРАКТЕРИСТИКА И ПОСТИНСУЛЬТНАЯ УСТАЛОСТЬ В ТЕЧЕНИЕ ПЕРВЫХ 6 МЕСЯЦЕВ ПОСЛЕ ИШЕМИЧЕСКОГО ИНСУЛЬТА

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Цель - идентифицировать нейровизуализационные морфометрические характеристики с учетом данных магнитной резонансной томографии головного мозга, ассоциированных с определенными компонентами постинсультной усталости в течение первых 6 месяцев после инсульта.

В исследование включено 107 пациентов с острым ишемическим инсультом. С помощью многомерной шкалы усталости - MFI-20 проводилось обследование пациентов в определенных временных точках после развития инсульта: в стационаре, спустя 1, 3, 6 месяцев после развития инсульта. Нейровизуализационная характеристика включала определение локализации инсульта, измерение объема церебральных инфарктов, индексов церебральной атрофии (бифронтальный и бикаудальный индексы, ширина третьего желудочка, индекс корковой атрофии), оценку выраженности лейкоареоза по шкале Fazekas.

Универиантный логистический анализ каких-либо достоверных ассоциаций между объемами церебрального инфаркта, индексами церебральной атрофии и частотой развития какого-либо компонента постинсультной усталости (ПИУ) в течение всего 6-месячного периода наблюдения не выявил. Выявлены прямые статистически достоверные ассоциации между наличием субкортикальных инфарктов и риском развития физической ПИУ спустя месяц после инсульта и позже, между наличием субтенториальных инфарктов и риском развития глобальной ПИУ спустя 3 месяца после инсульта и позже, между выраженностью лейкоареоза и риском развития психического компонента ПИУ спустя 3 месяца после инсульта и позже.

Пациенты с субкортикальными инсультами являются группой риска относительно развития физического компонента ПИУ, пациенты с инфратенториальными инсультами — группой риска развития общей ПИУ, а степень выраженности лейкоареоза достоверно повышает риск развития психической ПИУ, но не ранее, чем спустя 1 месяц после развития инсульта.

რეზიუმე

ნეიროვიზუალიზაციური დახასიათება და პოსტინსულტური დაღლილობა იშემიური ინსულტის შემდეგ პირველი 6 თვის განმავლობაში

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კვლევის მიზანს წარმოადგენდა ნეიროვიზუალიზაციური მორფომეტრული დახასიათების იდენტიფიცირება თავის ტვინის მაგნიტურ-რეზონანსული ტომოგრაფიის მონაცენების გათვალისწინებით, რომლებიც ასოცირებულია პოსტინსულტური დაღლილობის გარკვეულ კომპონენტებთან პირველი 6 თვის განმავლობაში ინსულტის შემდეგ.

კვლევაში ჩართული იყო 107 პაციენტი მწვავე ინსულტის შემდეგ. დაღლილობის მრავალგანზომილებიანი სკალის - MFI-20 მეშვეობით ჩატარდა პაციენტების გამოკვლევა დროის გარკვეულ მონაკვეთებში იშემიური ინსულტის განვითარების შემდეგ: სტაციონარში, ინსულტის განვითარებიდან 1,3 და 6 თვის შემდეგ. ნეიროვიზუალიზაციური დახასიათება მოიცავდა ინსულტის ლოკალიზაციის განსახღვრას,ცერებრალური ინფარკტების მოცულობის და ცერებრალური ატროფიის ინდექსების (ბიფრონტალური, ბიკაუდალური ინდექსები, მესამე პარკუჭის სიგანე, ქერქოვანი ატროფიის ინდექსი) გაზომვას, ასევე, ლეიკოარეოზის გამოხატულების შეფასებას Fazekas-ს სკალის გამოყენებით. უნივარიანტულმა ლოგისიტკურმა ანალიზმა ცერებრალურ ინფარკტის მოცულობას, ცერებრალური ატრიფიის ინდექსებს და პოსტინფარკტულ დაღლოლობის კომპონენტების განვითარებას შორის 6 თვის დაკვირვების შედეგად არავითარი სარწმუნო ასოციაციები არ გამოავლინა.

გამოვლინდა პირდაპირი სტატისტიკურად სარწმუნო ასოციაციები სუბკორტიკალურ ინფარკტებსა და ფიზიკური პოსტინსულტური დაღლილობის განვითარების რისკებს შორის ინსულტის 1 თვის შემდეგ და მოგვიანებით,ასევე, სუბტენტორულ ინფარკტებს და გლობალურ პოსტინსულტურ დაღლილობის განვითარების რისკებს შორის, ლეიკოარეოზის გამოხატულებასა და პოსტინსულტური დაღლილობის ფსიქიკური კომპონენტის განვითარების რისკებს შორის 3 თვის შემდეგ და მოგვიანებით.

პაციენტები სუბკორტიკალური ინსულტებით წარმოადგენენ პოსტინსულტური დაღლილობის ფიზიკური კომპონენტის განვითარების რისკ ჯგუფს,პაციენტები ინფრატენტორული ინსულტებით კი - პოსტინსულტური საერთო დაღლილობის ჯგუფს; ლეიკოარეოზის გამოხატვის ხარისხი სარწმუნოდ აძლიერებს პოსტინსულტური ფსიქიკური დაღლილობის განვითარების რისკს ინსულტის განვითარების 1 თვის შემდეგ.