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Regional cerebral hypoperfusion as a cause of symptoms and progression of multiple sclerosis

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ABSTRACT

Background. Neurodegenerative processes play an important role in the development of clinical features of multiple sclerosis (MS) as well as in the progression of the disease. At the same time, neurodegenerative mechanisms of MS are not completely clear, which makes researchers pay special attention to pathogenetic aspects of the disease that have not been studied before.

Previously it was shown that MS patients can have alterations in the local cerebral blood flow, however, the meaning of the detected abnormalities is still not clear.

The aim of our work is to evaluate the perfusion character in the demyelinating lesions and normal-appearing brain structures, and to determine their relation to clinical features of MS.

Material and methods. 49 patients with relapsing-remitting and secondary progressive MS with clinical and MRI remission were included in the study. The patients underwent contrast-enhanced MR perfusion of the brain on the 3 Tesla MR-tomograph, as well as the Functional System Score, Expanded Disability Status Score and Fatigue Status Score evaluation. The data analysis included automatic construction of perfusion maps of the cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit time (MTT) values in the normal-appearing brain structures and in the demyelinating lesions and statistical analysis.

Results. The received results allow to presume that variation of CBV values in MS lesions can indicate heterogeneity of processes in these lesions – from reactivation of inflammation to remyelination.

Significant reduction of perfusion in nucleus lenticularis was revealed. This reduction did not depend on the severity of the disease and correlated negatively with the fatigue score. This allows to suppose that the therapy focused on brain perfusion improvement can be used as symptomatic therapy of MS. Considering the fact that regional hypoperfusion precedes the development of brain structure atrophy, it is hypothesized that the improvement of perfusion may prevent neurodegeneration in MS. The obtained findings need further investigation.

Key words: multiple sclerosis, fatigue, cerebral perfusion, regional hypoperfusion, neurodegeneration.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients included in the study signed an informed consent. The study was approved by the Ethics Committee at IHB RAS (Protocol No. 1 of 19.02.2015).

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Локальная церебральная гипоперфузия как причина развития симптомов и прогрессирования рассеянного склероза

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РЕЗЮМЕ

Введение. Нейродегенеративные процессы играют важную роль в развитии клинических проявлений рассеянного склероза (РС), а также в прогрессировании заболевания. В то же время механизмы нейродегенерации при РС не вполне ясны, что заставляет исследователей обращать внимание на ранее не изученные патогенетические аспекты заболевания. Было показано, что у больных РС могут наблюдаться изменения локального кровотока в головном мозге, однако значение выявленных нарушений изучено недостаточно.

Целью нашей работы являлись оценка особенностей перфузии в очагах демиелинизации и внешне неизмененных структурах головного мозга и определение их взаимосвязи с клиническими проявлениями РС.

Материалы и методы. В исследовании приняли участие 49 пациентов с ремиттирующим и вторично-прогрессирующим РС в стадии ремиссии (клинической и по данным магнитно-резонансной томографии (МРТ)), которым проводились МР-перфузия головного мозга с контрастным усилением на томографе с индукцией магнитного поля 3 Тл, а также оценка по шкале функциональных систем (FS), расширенной шкале нетрудоспособности (EDSS), шкале утомляемости (FSS). Анализ данных включал в себя автоматическое построение перфузионных карт для показателям: объем мозгового кровотока CBV, объемная скорость кровотока CBF и среднее время циркуляции MTT в очагах демиелинизации и внешне неизмененных структурах головного мозга.

Результаты. Большой разброс показателей CBV в очагах может свидетельствовать о гетерогенности происходящих в них процессов – от реактивации воспаления до ремиелинизации. Выявленное нами значимое снижение перфузии в лентикулярных ядрах вне зависимости от тяжести заболевания, которое отрицательно коррелировало с выраженностью утомляемости, позволяет предположить, что терапия, направленная на улучшение перфузии головного мозга, может использоваться в качестве симптоматической терапии РС. Учитывая то, что регионарная гипоперфузия опережает развитие атрофии, мы считаем, что лечение, направленное на улучшение перфузии, способно предотвращать развитие нейродегенеративных изменений при РС, что требует дальнейших исследований.

Ключевые слова: рассеянный склероз, утомляемость, церебральная перфузия, регионарная гипоперфузия, нейродегенерация.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследовательская работа выполнена в рамках поисковых научных исследований согласно госзаданию ИМЧ РАН.

Соответствие принципам этики. Все участники исследования подписали информированное согласие. Исследование одобрено комиссией по этике ИМЧ РАН (протокол № 1 от 19.02.2015).

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INTRODUCTION

A decrease in cerebral perfusion in patients with multiple sclerosis (MS) was demonstrated more than 30 years ago using single-photon emission computed tomography (SPECT) and positron emission tomography (PET) [1–4]. For a long time, these data had not been in demand. However, due to research of neurodegenerative processes in MS and the lack of effective therapy to prevent their development, interest in studying the changes in local blood flow in the brain of MS patients has increased again. The widespread implementation and enhancement of magnetic resonance imaging (MRI), which allows to compare structural changes in the brain and local hemodynamics in individual zones of interest, have greatly expanded the possibilities of studying local cerebral perfusion. Currently, both contrast and non-contrast perfusion MRI techniques are used. Quantitative indicators of local blood flow are: cerebral blood flow (CBF) – the rate at which a certain amount of blood flows through 100 g of the brain substance per unit time (ml / 100 / min), cerebral blood volume (CBV) – the total amount of blood in the specific volume of the brain (ml / 100 g of brain tissue), mean transit time (MTT) – the time it takes for blood to pass through 100 g of the brain tissue.

Changes in brain perfusion in MS have been studied both in foci of demyelination and in unaltered white matter (UWM) and unaltered grey matter (UGM). Some researchers noted that the foci in MS are mainly located in areas with low perfusion rates [5, 6], and their volume negatively correlates with regional CBF [7]. An increase in CBF and CBV was found in the foci accumulating contrast medium in T1 weighted images (WI), which, according to researchers, may indicate inflammation-induced vasodilation [8]. Y. Ge et al. examined 17 patients with relapsing-remitting type of MS (RRMS) using contrast MR perfusion imaging. When comparing the main perfusion parameters in the foci with contralateral UWM, the authors identified three types of foci: foci that accumulate the contrast medium; foci that do not accumulate the contrast medium, in which perfusion characteristics are similar to those in the foci of the first type; foci that do not accumulate the contrast medium and have perfusion characteristics that are different from those in the first type. In the first and second types of foci, an increase in CBF and CBV was noted. The results obtained led to the conclusion that a perfusion study allows to identify the foci with no significant breach in the blood-brain barrier (there is no accumulation of the contrast medium on T1 weighted images), but nevertheless, reactivation of inflammation can take place [9].

Studies using contrast MR perfusion imaging found a decrease in CBF in UWM with clinically isolated syndrome, with suspicion of development of RRMS and primary progressive (PP) MS, compared with healthy controls [10–13]. The results obtained allowed the authors to suggest that cerebral hypoperfusion of UWM develops in patients with MS already at early stages of the disease, regardless of the type of the disease course and, possibly, is one of the important pathogenetic links in the development of MS. Hypoperfusion in patients with MS was also detected in the cortex and subcortical gray matter [14, 15]. Some researchers identified a relationship between cognitive impairment and hypoperfusion of the cortex and subcortical gray matter in patients with RRMS and secondary progressive (SP) MS [15-17]. However, in the study by M. Ingrisch et al. (2017) [18], which included 24 MS patients and 16 people from the control group, no significant hypoperfusion of UWM in the thalamus and pons was detected. Thus, the findings of studies on local cerebral perfusion in patients with MS, recommenced over the past decade, are often contradictory, which makes further work in this direction relevant.

The purpose of the study was to assess the features of local blood flow in the foci of demyelination and unaltered gray and white matter of the brain and to determine their relationship with the clinical manifestations of multiple sclerosis.

MATERIALS AND METHODS

The study involved 52 patients with MS, including three who were excluded from the study due to the signs of the active process on MR images. The study included patients with RRMS and SPMS, defined according to the McDonald criteria (2010). The exclusion criteria were clinical exacerbation and (or) MRI activity (the presence of foci accumulating a contrast medium on the MRI) of the disease, systemic corticosteroid therapy over the past 30 days, and changes in the scheme of pathogenetic and (or) symptomatic therapy over the past three months. The control group included ten sex- and age-matched healthy volunteers. All patients and healthy volunteers before the study and any manipulations signed an

informed consent to participate in the study and the procedures.

Examination program. Clinical neurological examination was carried out using the functional systems (FS) score, the Expanded Disability Status Scale (EDSS) and the Fatigue Severity Scores (FSS). To compare the clinical manifestations of MS with the results of the MR perfusion analysis, the patients were divided into groups according to the degree of disability according to the EDSS scale: 1 – mild disability (0–3.0 points); 2 – moderate disability (3.5–6.0 points); 3 – severe disability (more than 6.0 points).

MRI was performed on the ACHIEVA 3T system (Philips, Japan) using an eight-channel head coil. The scanning protocol included T2 TSE images (TR / TE = 3000/80 ms, 28 slices, slice thickness 3 mm), axial and sagittal FLAIR images (TR / TE = 11000/125 ms, TI = 2 800 ms, 28 slices, slice thickness 3 mm), pre-contrast T1 SE images (TR / TE = 700/10 ms, 28 slices, slice thickness 3 mm), post-contrast 3D FFE T1 sequences (TR / TE = 500/50 ms, 96 slices, slice thickness 1 mm). MR perfusion imaging with contrast enhancement was used to determine CBF, CBV, and MTT values. The parameters of contrast MR perfusion imaging were measured manually in the foci of demyelination and in the unaltered white matter, located contralaterally. In addition, perfusion values were assessed at the level of the pons, midbrain, thalamus, lenticular nuclei, genu and splenium of the corpus callosum, in the white matter of the basal parts of the frontal lobes, in the semioval centers, and at the base of the pre- and postcentral gyri in both cerebral hemispheres (Fig. 1).

Statistical analysis. Correlation analysis (Spearman's rank correlation coefficient, significance at $p < 0.01$), one-way analysis of variance with a post-hoc test using Fisher criterion and Shapiro-Wilk and Levene's tests for testing the normality of distributions and homogeneity of variances ($p < 0.05$), and non-parametric Kruskal-Wallis test ($p < 0.05$) were used. The results are given that are detected by both parametric and nonparametric methods of analysis. Statistical processing was performed using the Statistica 10.0 software for Windows (serial number AXAR208F-447913FA-B).

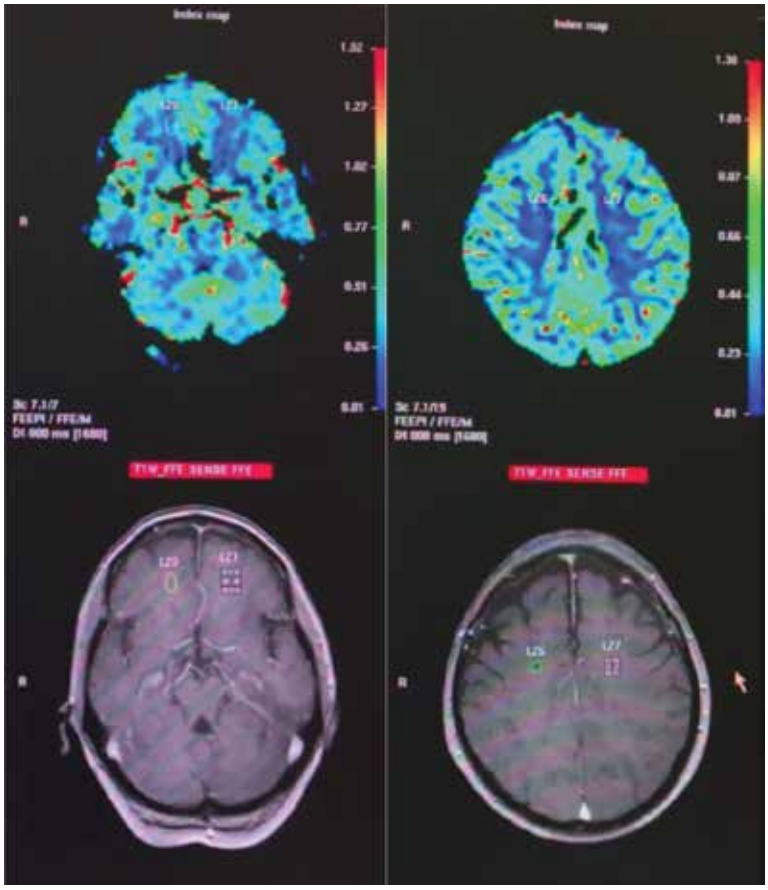

Fig. 1. Areas of interest on the post-contrast T1-WI and perfusion maps

RESULTS AND DISCUSSION

No statistically significant differences in CBV, CBF and MTT values in hypointensive lesions on T1 weighted images were detected, as opposed to the symmetric UWM area in the contralateral hemisphere both in the group of MS patients and in separate groups with mild, moderate and severe disability (Fig.2).

A big difference in the CBV and CBF values in the foci may indicate heterogeneity of the lesions that are hypointensive on T1 weighted images, including both truly inactive foci and foci in which reactivation of inflammation can develop, which does not cause a significant breach in the blood-brain barrier integrity [19]. Thus, the absence of contrast-accumulating foci on T1 weighted images does not always imply true remission. This fact may explain clinical situations in which an increase in neurological deficit without MR activity on contrast T1 weighted images is observed. In this case, it may not be the beginning of steady progression of the disease, but subacute exacerbation, which requires appropriate therapy (Fig. 3, 4).

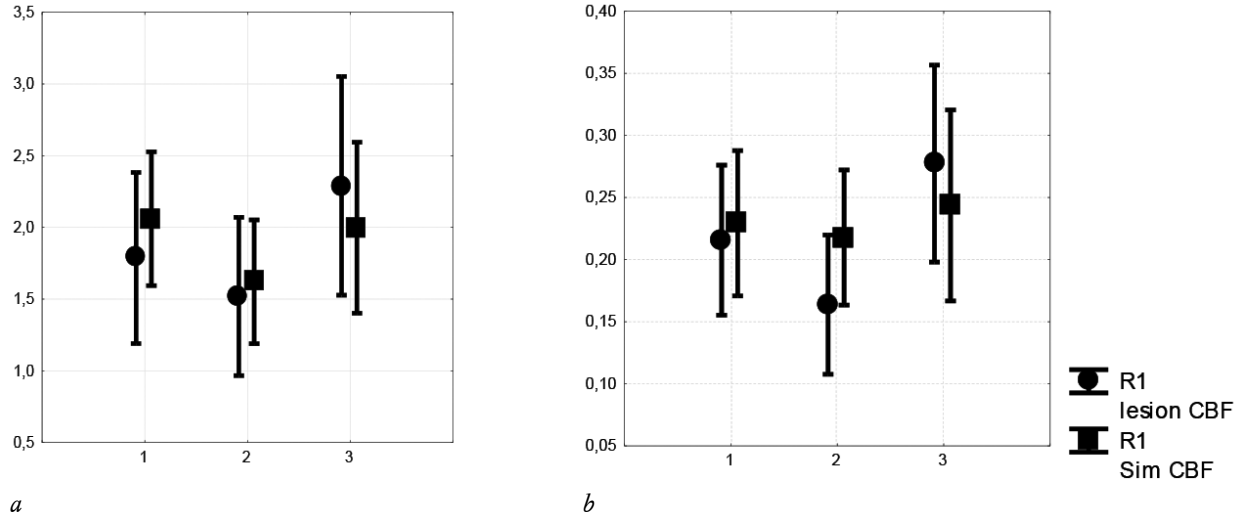

Fig. 2. CVB (*a*) and CBF (*b*) values in contrast-negative T1-WI hypointensive lesions and contralateral normal-appearing white matter (NAWM) in patients with different disability scale: 1– mild disability, 2 – moderate disability, 3 – severe disability; *m* ± confidence interval 95%

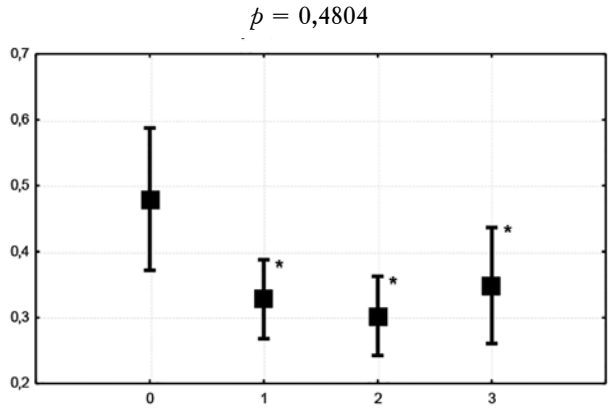

Fig. 3. Significant decrease in the *nucleus lenticularis* CBF values in MS patients in comparison with healthy controlsss: 0 – healthy control, 1 – mild disability, 2 – moderate disability, 3 – severe disability, *m* ± 0.95 confidence intervals. * significant difference from the control group

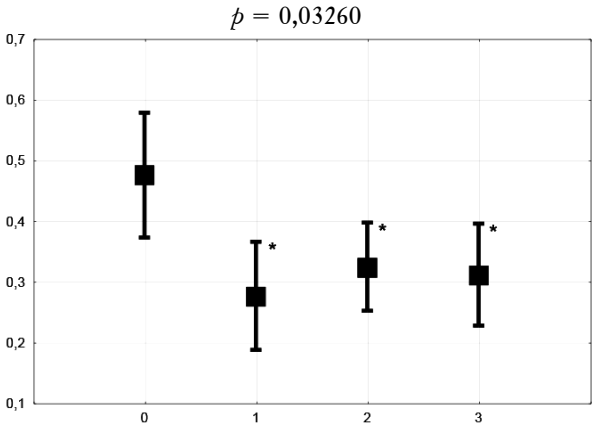

Fig. 4. Interrelation between the perfusion values and the severity of cerebellar disfunction. ANOVA, m ± 0.95 confidence intervals, * – significant difference from the control group. 0 – without cerebellar disfunction: 1 – mild disability, 2 – moderate disability, 3 – severe disability

The obtained findings indicate a decrease in perfusion in the lenticular nuclei bilaterally in the whole group of patients, even with minimal disturbances in the functional systems scores. Anatomically, lenticular nuclei include two structures: the putamen and the globus pallidus. R.B. Postuma and A. Dagher in a meta-analysis of 126 studies (83 using PET and 41 using functional MRI) identified different patterns of coactivation of the cortical regions and structures of the striatum, which, in particular, confirmed the previously existing concept that the putamen is the main " motor "structure of the striatum [20]. In our previous studies [21, 22], it was found that the presence of minimal clinical signs of damage to functional systems, with the exception of visual disturbances, is accompanied by the development of general atrophy and neurodegenerative changes in the putamen and, to a lesser extent, in the thalamus. In addition, when analyzing changes in groups of patients with different degrees of disability, it was shown that global and regional atrophic disorders (the putamen, the thalamus, individual regions of the cortex) significantly differ from the normal values in moderate and severe disability (3.5 points or more). In morphometric analysis, the volume of the structures that make up the lenticular nucleus significantly decreases in the group of RRMS patients with disease duration of more than 5 years and with congenital heart disease. Thus, as in the studies conducted by other authors [8, 10–12], the results of the present study suggest that cerebral hypoperfusion develops in patients with MS already at early stages of the disease and, possibly, is one of the important pathogenetic links in the development of neurodegenerative changes in the brain of such patients.

A correlation analysis of clinical parameters and local perfusion values revealed a significant negative correlation between fatigue and CBF in the left and right lenticular nuclei (Spearman's rank correlation coefficients $p = -0.568$ and $p = -0.569$, respectively, Fig. 5).

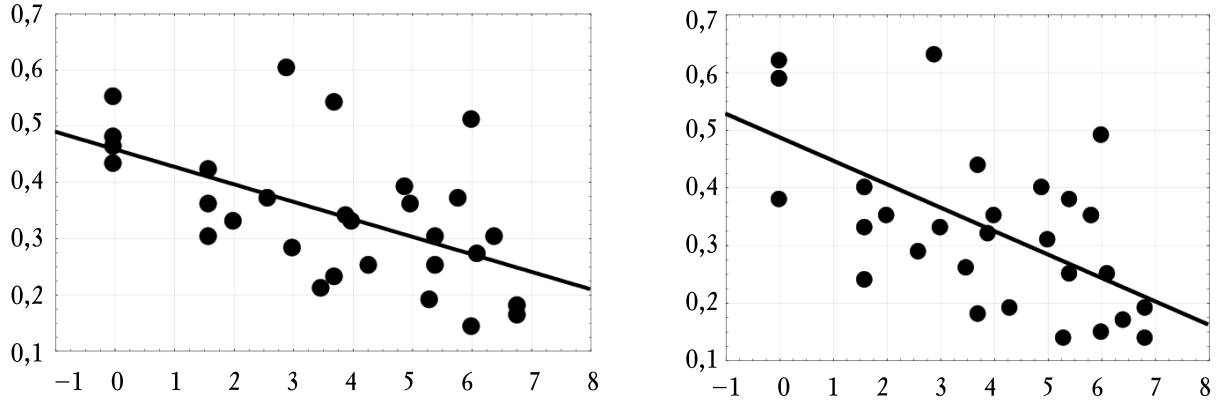

Fig. 5. Correlation between the CBF value in the left ($p = -0.568$) and right ($p = -0.569$) lenticular nuclei and FSS scale, $p < 0.01$

CONCLUSION

Fatigue in multiple sclerosis occurs in 75–92% of patients and is one of the key symptoms that affects the quality of life and may be the first sign of MS exacerbation. The pathogenesis of fatigue in multiple sclerosis has so far been the subject of numerous studies. Fatigue in MS is not directly related to the severity of paresis, but is more common in patients with pyramidal insufficiency [23]. Considering that the putamen, which is a part of the lenticular nucleus, is the main "motor" structure of the striatum [20], the data of this study can explain more frequent observations of increased fatigue in patients with pyramidal insufficiency. This suggests that therapy aimed at improving cerebral perfusion can be used as symptomatic treatment of fatigue in patients with MS. In addition, given the fact that regional hypoperfusion develops ahead of atrophy, it can be assumed that treatment aimed at improving perfusion can prevent the development of neurodegenerative changes, which requires further research.

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