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Quantitative susceptibility mapping (QSM) in deep gray matter as a neurodegeneration marker in relapsing-remitting and secondary-progressive multiple sclerosis

© **Maria S. Matrosova[1]*, Vasiliy V. Bryukhov[1], Ekaterina V. Popova[2, 3], Galina N. Belskaya[1], Marina V. Krotenkova[1]**

[1] Research center of neurology; 80-1, Volokolamskoye shosse, Moscow 125367, Russian Federation

[2] Pirogov Russian National Research Medical University of the Ministry of Healthcare of the Russian Federation; house 1, Ostrivityanova str., Moscow 117997, Russian Federation

[3] City Clinical Hospital №24 of Moscow Healthcare Department; 10, Pistsovaya str., Moscow 127015, Russian Federation

Purpose. The aim of the study was to investigate changes in iron distribution in the brain of patients with multiple sclerosis (MS) using magnetic resonance imaging (MRI) technique – quantitative susceptibility mapping (QSM) – in comparison with clinical data.

Materials and methods. Three groups of patients were included in this prospective study: 47 patients with relapsing-remitting MS (RRMS), 20 patients with secondary progressive MS (SPMS) and 39 healthy controls. For all patients we collected clinical data, including history of present illness (H&P) and disability degree, and performed brain MRI followed by QSM maps obtaining and assessing relative magnetic susceptibility in subcortical structures.

Results. We found an increase in magnetic susceptibility in the heads of the caudate nuclei and in putamen in patients with SPMS as compared to RRMS. At the same time, a decrease in magnetic susceptibility in the thalamic pulvinar was detected in patients with MS in the long term, but a sharp hyperintensity in conjunction with decreasing volume was observed in some patients.

Conclusion. Increased magnetic susceptibility on the QSM in subcortical structures of the brain, reflecting iron content, is more typical for patients with SPMS, which may indicate the prognostic value of these changes.

Keywords: multiple sclerosis, magnetic resonance imaging, iron, quantitative susceptibility mapping, secondary progressive multiple sclerosis

Conflict of interest. The authors declare no conflict of interest. The study had no sponsorship.

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Introduction

Multiple sclerosis (MS) is a common inflammatory and degenerative demyelinating disease of the central nervous system (CNS), affecting mostly people of reproductive age. There are more than 2 million people worldwide suffering from this pathology, which is the fourth most common of all neurological diseases in the world [1, 2]. Despite this fact, the exact pathogenesis of the disease is still not fully understood, and the existing treatment is primarily aimed at the immunological, inflammation-mediated component of the disease [3–6]. In turn, the neurodegenerative component plays an equally important role in the development of the disease. However, it is particularly characteristic of progressive forms of MS, it begins in the early stages of the disease, gradually escalating over time [7–9].

Magnetic resonance imaging (MRI) is a “gold standard” for MS diagnosis. It assesses dissemination of the process in space and over time [10–11]. However, progressive forms of MS don't usually result in the appearance of new foci in the brain and spinal cord on MRI, while the patient's symptoms steadily increase [12]. At the same time, there are no clear criteria for the conversion of relapsing-remitting MS (RRS) into secondary-progressive MS (SPMS), and the mechanisms by which disease progression occurs remain unexplored [13–14]. Confirmation of progression is established clinically based on the persistent increase in neurological deficits or a score on the Expanded Disability Status Scale (EDSS) only after 6 months from the appearance of neurological deficits [15–16].

Assessment of the disease progression on MRI also requires long-term dynamic monitoring. Thus, it is now known that the neurodegenerative process in MS is accompanied by the development of brain substance atrophy (both cortical and global), which is difficult to measure in the early stages. Standard MRI sequences assess it indirectly in the form of expansion of the liquor spaces, which cannot be seen in a short dynamic observation [17]. Morphometric MRI also allows assessment of atrophic changes retrospectively when they have occurred [18–19].

Consequently, the search for possible biomarkers (including neuroimaging markers) that can detect the transfer of RRMS to SPMS and evaluate the neurodegenerative component of the disease can play an important role in the early diagnosis of progressive forms of MS and possibly identify a new target for the therapy [20].

Iron can potentially be such predictor, as its abnormal metabolism and accumulation in certain areas of the brain, accompanies the development of many neurodegenerative diseases. However, it is important to remember that this process is also, although at a lower degree, typical for the aging process of the brain [21–25]. In addition, it has been found that a large amount of it is contained in microglia cells, which are involved in the pathogenesis of MS, as well as in oligodendrocytes, the destruction of which can also release it [26–29]. However, quantification of iron is not possible using both standard MRI sequences and susceptibility-weighted images (SWI). A modern MRI technique, quantitative susceptibility mapping (QSM), can be used for this purpose. QSM allows quantitative assessment of the magnetic susceptibility of chemical compounds in the human body, including iron, calcium, and hemoglobin breakdown products [30–32].

Over the last years, scientific interest in the patterns of iron accumulation in MS remains high, and studies are being actively carried out on this topic [33–35]. Our aim in this work was to study iron accumulation in the brain substance of MS patients using QSM, as well as to explore the relationship of iron content with the clinical presentation and the disease type.

Material and Methods

Patients

This prospective randomized study was approved by the local Research Center of Neurology ethics committee.

Forty-seven patients with RRMS (including 35 women) between 18 and 57 years old (34 [27;41]) and 20 patients with SPMS (including 15 women) between 24 and 66 years old (49 [39;55]) from Moscow multiple sclerosis departments were included in the study. Exclusion criteria, in addition to claustrophobia and metal implants in the body (including a pacemaker), were pregnancy, comorbid brain pathology on MRI, and pulse therapy within one month before the study. The control group consisted of 39 healthy volunteers (including 27 women) aged 23 to 58 years without brain pathology on MRI, comparable in sex and age to RRMS patients (33 [27;46]) without CNS complaints.

All patients were informed about the upcoming study and signed an informed voluntary consent for the study in advance.

Clinical evaluation

The following clinical data were preliminarily collected for all patients: age, disease duration, onset symptoms, and age at onset (Table). In addition, the neurologist determined an EDSS score.

MRI protocol

All images were acquired using a 3 Tesla Siemens Magnetom Prisma scanner with a 64-channel head coil.

The MRI protocol included T2-weighted turbo spin-echo pulse sequence, 3D T2 FLAIR (fluid attenuation inversion recovery), and an additional 3D T2* GRE sequence (for QSM acquisition).

Standard T2-weighted images were obtained using the following parameters: TR/TE = 6000/99 ms, turbo factor (TF) 17, ETL 13, slice thickness 4 mm, flip angle 150°, voxel size 0.3 × 0.3 × 4.0 mm, bandwidth 220 Hz/pixel, acquisition time (TA) 1 min 26 s.

A 3D T2FLAIR sequence was obtained using the following parameters: TR/TE/TI = 7000/390/2200 ms, TF 278, slice thickness 0.6 mm, voxel size 0.5 × 0.5 × 0.6 mm, bandwidth 751 Hz/pixel, TA 7 min 58 s.

A 3D T2* GRE sequence with multiple echo signals (multi-TE) was used to obtain initial phase and magnitude images for further QSM acquisition: first

Table. Demographic and clinical characteristics of patients in all groups and quantitative values of magnetic susceptibility in brain structures

		Group		
		RRMS (n = 47)	**SPMS (n = 20)**	**Control (n = 39)**
Sex	Male, % Female, %	12 (25.5%) 35 (74.5%)	5 (25%) 15 (75%)	12 (30.8%) 27 (69.2%)
Age, years	Median [Q1; Q3]	34.0 [27.0; 40.0]	48.5 [39.0; 57.0]*	30.5 [27.0; 45.5]
Disease duration, years	Median [Q1; Q3]	8.0 [5.0; 12.0]	15.0 [10.0; 20.0]*	–
EDSS score	Median [Q1; Q3]	1.5 [1.0; 2.0]	5.5 [4.5; 6.0]*	0.0 [0.0; 0.0]
Heads of caudate nuclei (ppb, mean)	Mean ± SD	66.0 ± 17.0	68.0 ± 30.0	59.0 ± 13.0
Putamen (ppb, mean)**	Mean ± SD	43.8 ± 21.5	51.9 ± 30.8*	36.2 ± 15.2
Globus pallidus (ppb, mean)	Mean ± SD	145.8 ± 32.8	150.9 ± 73.3	136.0 ± 27.2
Pulvinar (ppb, mean)	Mean ± SD	35.0 ± 28.5	17.1 ± 31.0*	38.1 ± 24.2
Dentate nuclei (ppb, mean)**	Mean ± SD	119.9 ± 39.2	120.3 ± 78.5	95.2 ± 40.2
Red nuclei (ppb, mean)**	Mean ± SD	114.8 ± 39.5	121.1 ± 42.4	107.5 ± 31.3
NAWM1 (ppb, mean)	Mean ± SD	–20.6 ± 7.4	–22.2 ± 4.3	–20.3 ± 8.0
NAWM2 (ppb, mean)	Mean ± SD	–26.1 ± 8.6	–28.5 ± 7.0	–25.5 ± 8.3
Motor cortex (ppb, mean)**	Mean ± SD	24.8 ± 12.5	29.1 ± 14.4	23.0 ± 12.9

Note: * p-value < 0.05; ** Age-adjusted values; NAWM1 – normal-appearing white matter in frontal lobes; NAWM2 – normal-appearing white matter in parietal lobes.

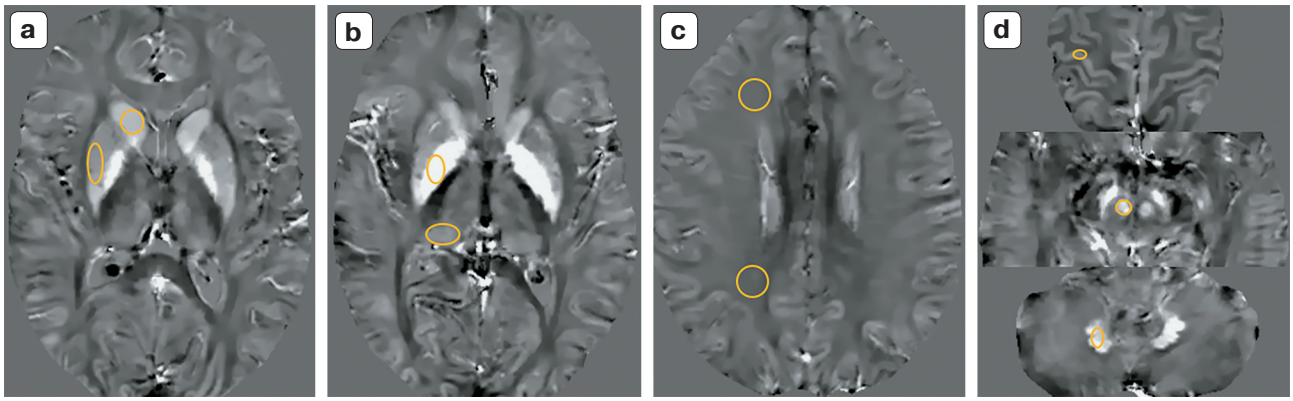

Fig. 1. Regions of interest (ROIs) on the QSM map in which magnetic susceptibility was measured (top to bottom). **a** – head of caudate nucleus and putamen; **b** – globus pallidus and thalamic pulvinar; **c** – normal-appearing white matter of frontal and parietal lobes; **d** – motor cortex, red nucleus, dentate nucleus.

TE 6.1 ms, TE interval 4.02 ms, number of echoes 10, TR time 47 ms, slice thickness 1 mm without slice gap, flip angle 15°, voxel size 0.5 × 0.5 × 1.0 mm, TA 4 min 38 s.

Postprocessing and analysis

To obtain QSM, we used MEDI Toolbox, a program based on the MatLab with MEDI algorithm (Morphology Enabled Dipole Inversion) [36–37].

Using ROI analysis, we measured magnetic susceptibility (in ppb) on QSM of the following locations: heads of caudate nuclei, putamen, globus pallidus and thalamic pulvinar, red nuclei, dentate nuclei, precentral gyrus (motor cortex), and normal-appearing white matter (NAWM) of frontal (NAWM1) and parietal (NAWM2) lobes (Fig. 1). The thalamus was examined in pulvinar, as this structure is the most visually homogeneous part of it, which allows a more reliable quantitative assessment.

Statistical analysis

Statistical analysis was performed using StatTech v. 2.6.7 (developer – Stattech Ltd.), as well as using SPSS 23.0 software package (developer – IBM).

The median and quartiles, as well as the mean and standard deviation (with a normal distribution) were used to describe quantitative variables. Quantitative variables were assessed for normality using the Shapiro–Wilk criterion (for less than 50 patients) or the Kolmogorov–Smirnov criterion (for more than 50 patients).

Frequency and proportion (as a percentage) were used to describe the categorical variable.

Since the sample size exceeded 100 participants, we compared the groups by quantitative variables using a parametric method, using analysis of variance (ANOVA). For posterior (post hoc) pairwise comparisons of groups, Bonferroni or Dunnett methods were used to adjust for multiple comparisons.

Categorical variables were compared by Pearson's χ^2 test or Fisher's exact test.

In all cases, two-sided versions of statistical criteria were used.

The direction and closeness of the correlation between the two quantitative variables were assessed using the Spearman rank correlation coefficient (for a distribution other than normal).

For comparisons between three groups the null hypothesis was rejected at the significance level $p < 0.05$, for pairwise comparisons – at the adjusted significance level $p_{adj} < 0.05$.

Results

It was found that the magnetic susceptibility in putamen, dentate nuclei, and red nuclei, as well as in the motor cortex significantly correlated with age: that is, the older the patient, the higher the iron content in these structures. In this regard, a normalization factor was introduced when comparing the parameters of the groups due to differences in the average age of the patients (Table, marked with "**"). Despite this, there was a statistically significant ($p = 0.018$) increase in the magnetic susceptibility in putamen and its decrease in pulvinar in patients with SPMS compared to RRMS and the controls by an average of 20 units (Fig. 2a). However, there was no correlation between these changes and the duration of the disease (Fig. 2b). Moreover, despite the general trend, the correlation of these changes with the EDSS disability score was statistically insignificant, $p = 0.09$ (Fig. 2c).

In addition, all groups of patients showed differences in visualization of pulvinar on QSM, caused by magnetic susceptibility and visible volume of this structure. These differences were divided into three patterns (Fig. 3): "normal" pattern (Fig. 3a) as a well-visible pulvinar with a slightly hyperintense MR signal on QSM compared to the rest of thalamus, "hyperintense" pattern as a highly hyperintense MR signal in the pulvinar region with an apparent decrease in its volume (Fig. 3b) and a "hypointense" pattern showing decreased magnetic susceptibility in pulvinar and the absence of its clear visualization (Fig. 3c).

Normal pattern occurred in most healthy controls (>90%), except three patients of older age (approximately 50 years old). In turn, in the RRMS group, a normal pattern was detected in 81% of subjects, and in the SPMS group – only in 38%. At the same time, 33% of patients with SPMS and only 6% of patients with RRMS had a hypointense pattern, while another 13% of RRMS and 29% of SPMS patients, in contrast, had a hyperintense pattern (Fig. 4a).

These patterns did not depend on the disease duration, but demonstrated significant correlation with the EDSS score (Fig. 4b,c).

Differences in magnetic susceptibility in the remaining subcortical structures, as well as in NAWM and in the motor cortex, were statistically insignificant (Table).

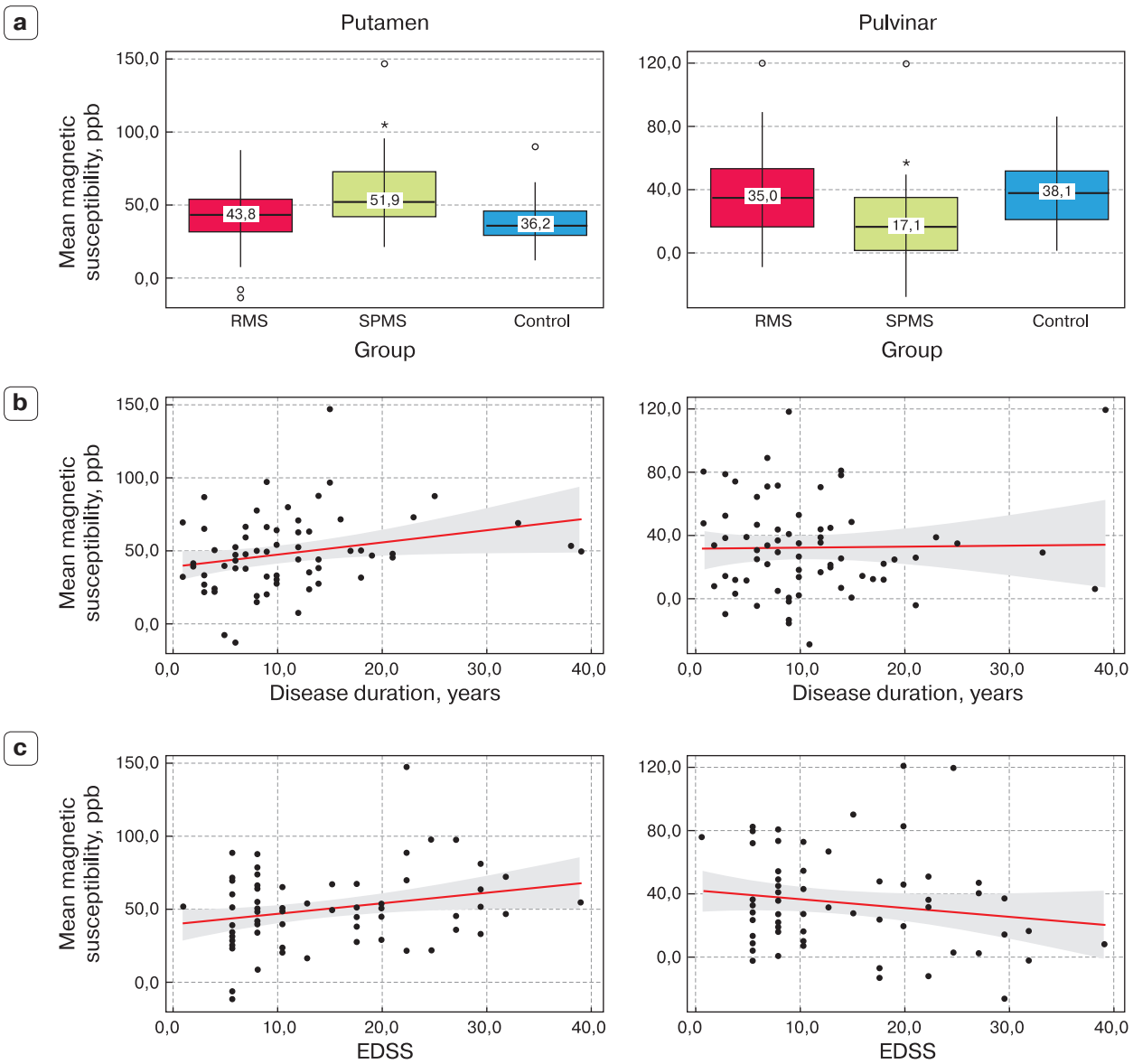

Fig. 2. Dependence of magnetic susceptibility in putamen (left plots) and in the thalamic pulvinar (right plots) on group (**a**), disease duration (**b**) and EDSS scale (**c**). Colors match groups: red – RRMS (**a**, left row), green – SPMS (**a**, middle row), blue – control (**a**, right row).

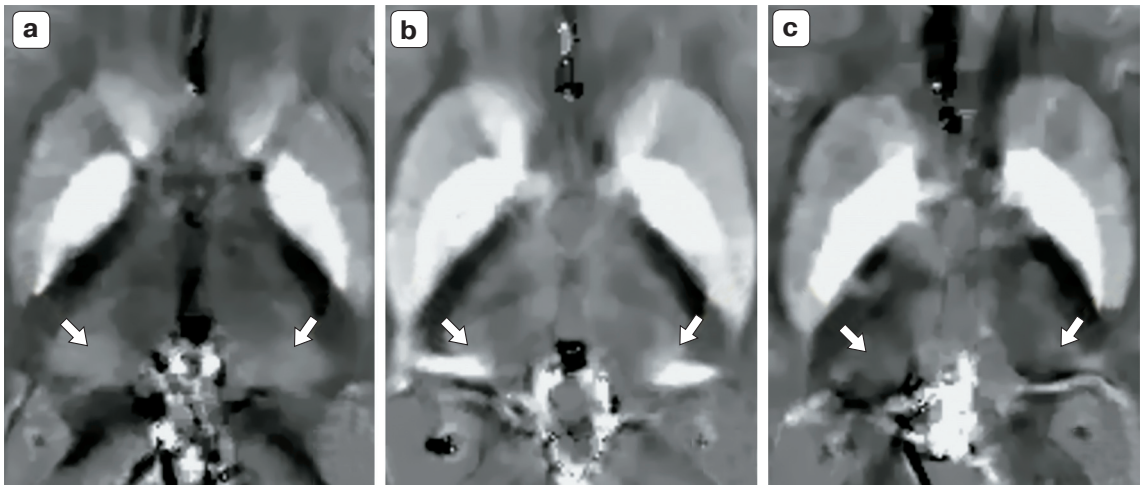

Fig. 3. Magnetic susceptibility patterns in the pulvinar (arrows) on QSM maps in three patients of the same age: **a** – normal pattern in a healthy control; **b** – hyperintense signal in a patient with RMS; **c** – iso/hypointense signal in a patient with SPMS.

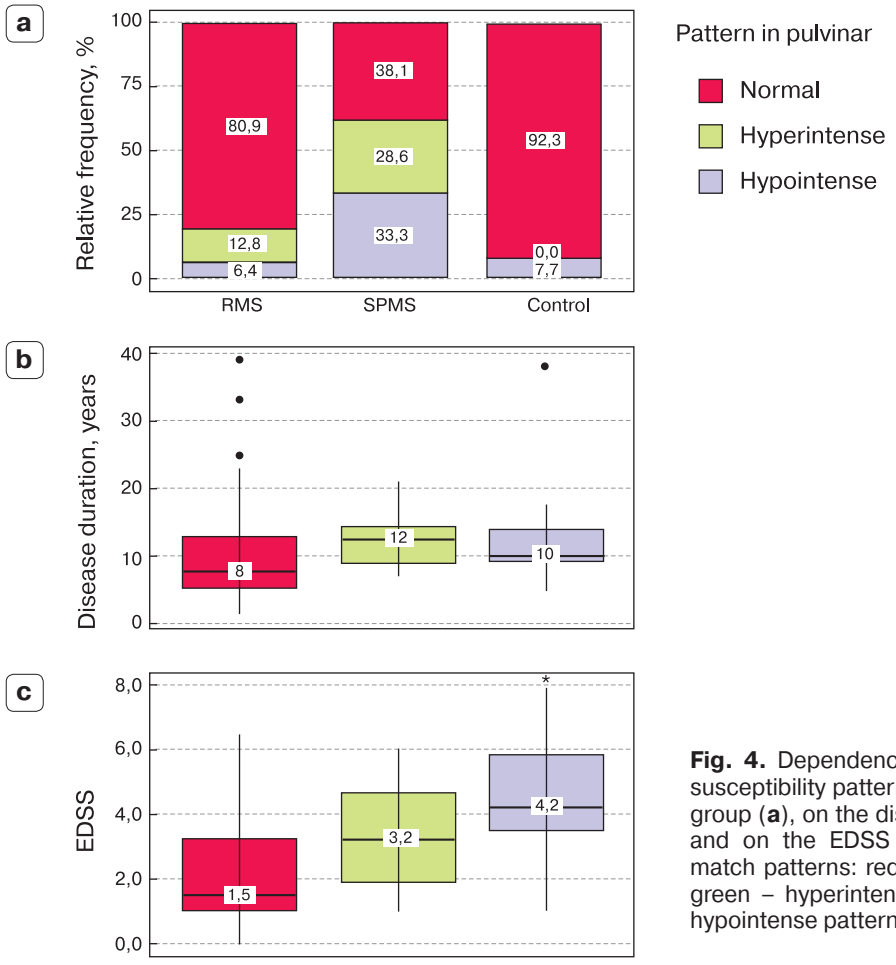

Fig. 4. Dependence of the magnetic susceptibility pattern in pulvinar on the group (**a**), on the disease duration (**b**), and on the EDSS score (**c**). Colors match patterns: red – normal pattern, green – hyperintense pattern, blue – hypointense pattern.

Discussion

According to the literature, the thalamus, as well as the lenticular nuclei, is one of the first structures affected by atrophic changes in MS [19, 38, 39]. It agrees with the changes we have identified in putamen and pulvinar region. Some authors associate thalamic atrophy with the duration of the disease [40]. At the same time, another study showed that disease duration had no effect on the brain volume loss, which agrees with the lack of correlation of these parameters in our study [7].

The absence of significant changes in other structures does not prove the absence of involvement of these structures in the pathological process. Alterations occur, although, possibly, a bit later – a larger sample of patients is required to estimate these changes. In our study, the number of patients with SPMS was two times lower than in the other groups, so it can affect the significance of the results.

Taking into consideration the revealed differences between the disease types and a weak connection between pulvinar pattern and the degree of disability (Fig. 4c), we can suggest at least two mechanisms responsible for the detected changes formation.

At first, we can assume a nonlinear change in iron content in the thalamus with the progression of the disease. Probably, the initially triggered degenerative process leads to activation of iron-loaded macrophages and microglia cells and, consequently, to accumulation of iron in this area [41]. In turn, free iron itself can take part in reactions resulting in the formation of toxic free radicals, causing oxidative stress and mitochondrial damage, only exacerbating the situation [22]. As a result, atrophy of this area occurs, and iron ions are gradually being eliminated.

A second more likely hypothesis is based on the results of the study, according to which an increase in magnetic susceptibility is not necessarily an evidence of iron inflow into the affected area of the brain. It can also be explained by atrophic changes, in which a decrease in brain structure volume due to the loss of neurons leads to a local increase in the concentration of iron, which was previously distributed equally over a larger area [33]. In this case, the increase in magnetic susceptibility, which we detected in pulvinar in some patients, may not be the cause, but only a consequence of an atrophy, which is currently taking place, but still cannot be identified with existing techniques.

Conclusion

In summary, quantitative susceptibility mapping revealed MRI patterns in subcortical structures that were more typical for secondary-progressive multiple sclerosis than for relapsing-remitting MS. The revealed changes may indicate the potential possibility of iron assessment in these structures to determine the probable progression of the disease. Obviously, further studies on a larger sample of patients are needed to determine the significance of these findings, while simplification of the postprocessing procedure would allow the QSM technique to be integrated into routine clinical practice.

Authors' participation

Matrosova M.S. – conducting research, collection and analysis of data, review of publications, statistical analysis, analysis and interpretation of the obtained data, writing text.

Bryukhov V.V. – concept and design of the study, analysis and interpretation of the obtained data, text preparation and editing, participation in scientific design.

Popova E.V. – participation in scientific design.

Belskaya G.N. – participation in scientific design, responsibility for the integrity of all parts of the article, approval of the final version of the article.

Krotenkova M.V. – participation in scientific design, responsibility for the integrity of all parts of the article, approval of the final version of the article.

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Contact*: Maria S. Matrosova – 125367 Moscow, Volokolamskoye shosse, 80. Phone: +7-495-490-22-05. E-mail: kmari-s@yandex.ru

Maria S. Matrosova – graduate student, Radiologist, Research center of neurology, Moscow. https://orcid.org/0000-0003-4604-7288

Vasiliy V. Bryukhov – Cand. of Sci. (Med.), Senior Research Associate, Radiologist of Research center of neurology, Moscow. https://orcid.org/0000-0002-1645-6526

Ekaterina V. Popova – Doct. of Sci. (Med.), Head of Multiple Sclerosis Center in Moscow City Clinical Hospital 24; Assistant professor, Pirogov Russian National Research Medical University Department of Neurology, Neurosurgery and Medical Genetics, Moscow. https://orcid.org/0000-0003-2676-452X

Galina N. Belskaya –Doct. of Sci. (Med.), Professor, Head of Multidisciplinary Clinical and Diagnostic Center, Research center of neurology, Moscow. https://orcid.org/0000-0001-9831-8970

Marina V. Krotenkova – Doct. of Sci. (Med.), Head of Department of Radiology, Main Researcher, Research center of neurology, Moscow. https://orcid.org/0000-0003-3820-4554

Для корреспонденции*: Матросова Мария Сергеевна – 125367 Москва, Волоколамское шоссе 80. Тел.: +7-495-490-22-05. E-mail: kmari-s@yandex.ru

Матросова Мария Сергеевна – аспирант, врач-рентгенолог ФГБНУ “Научный центр неврологии”, Москва. https://orcid.org/0000-0003-4604-7288

Брюхов Василий Валерьевич – канд. мед. наук, старший научный сотрудник, врач-рентгенолог ФГБНУ “Научный центр неврологии”, Москва. https://orcid.org/0000-0002-1645-6526

Попова Екатерина Валериевна – доктор мед. наук, заведующая межокружного отделения рассеянного склероза ГБУЗ “ГКБ 24 ДЗМ”; доцент кафедры неврологии, нейрохирургии и медицинской генетики лечебного факультета ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России, Москва. https://orcid.org/0000-0003-2676-452X

Бельская Галина Николаевна – доктор мед. наук, профессор, заведующая многопрофильным клинико-диагностическим центром, ФГБНУ “Научный центр неврологии”, Москва. https://orcid.org/0000-0001-9831-8970

Кротенкова Марина Викторовна – доктор мед. наук, главный научный сотрудник, руководитель отдела лучевой диагностики ФГБНУ “Научный центр неврологии”, Москва. https://orcid.org/0000-0003-3820-4554

Количественная оценка магнитной восприимчивости (QSM) в подкорковых структурах головного мозга как маркер нейродегенерации при ремиттирующем и вторично-прогрессирующем рассеянном склерозе

© **Матросова М.С.[1]*, Брюхов В.В.[1], Попова Е.В.[2, 3], Бельская Г.Н.[1], Кротенкова М.В.[1]**

[1] ФГБНУ "Научный центр неврологии"; 125367Москва, Волоколамское шоссе, д. 80, стр. 1, Российская Федерация

[2] ФГАОУ ВО "Российский национальный исследовательский медицинский университет им. Н.И. Пирогова" Минздрава России; 117997 Москва, ул. Островитянова, д. 1, Российская Федерация

[3] ГБУЗ города Москвы "Городская клиническая больница № 24 ДЗ города Москвы" (ГБУЗ "ГКБ № 24 ДЗМ"); 127015 Москва, ул. Писцовая, д. 10, Российская Федерация

Цель исследования. Целью исследования стало изучение изменений в распределении железа в веществе головного мозга с помощью методики магнитно-резонансной томографии (МРТ) – количественного картирования восприимчивости (quantitative susceptibility mapping QSM) – в сопоставлении с клиническими данными у пациентов с рассеянным склерозом (РС).

Материал и методы. В данное проспективное исследование вошли три группы пациентов: 47 пациентов с ремиттирующим РС (РРС), 20 – с вторично-прогрессирующим РС (ВПРС) и 39 здоровых добровольцев (группа контроля). Для всех пациентов были собраны анамнестические данные и проведена МРТ головного мозга, включающая последовательность мульти-эхо 3D T2* GRE, после чего были получены карты QSM и рассчитана относительная магнитная восприимчивость в области подкорковых структур.

Результаты. Были выявлены более высокие показатели магнитной восприимчивости в скорлупе у пациентов с ВПРС по сравнению с РРС, что может отражать избыточное накопление железа в данных структурах. При этом было выявлено понижение магнитной восприимчивости в подушке таламуса у пациентов с ВПРС, однако у части пациентов отмечалось ее резкое повышение при уменьшении объема подушки таламуса.

Заключение. Повышение магнитной восприимчивости на карте QSM в области подкорковых структур головного мозга, преимущественно, в области скорлупы, отражающее накопление железа, а также ее снижение в области подушки таламуса, являются более характерными для пациентов с ВПРС, что может иметь прогностическую значимость в оценке прогрессирования заболевания.

Ключевые слова: рассеянный склероз, магнитно-резонансная томография, железо, количественное картирование восприимчивости, вторично-прогрессирующий рассеянный склероз

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