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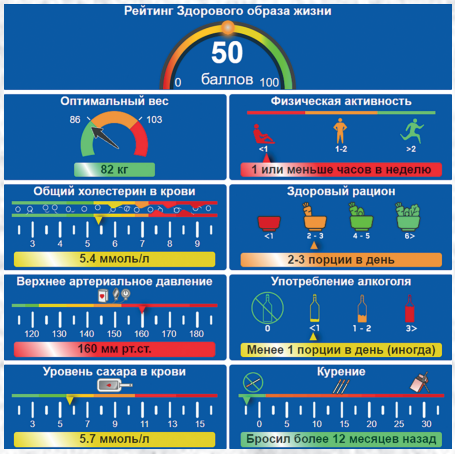

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On the front cover: part of the Figure 3 from the article of M.A. Kravchenko et al. (P. 88).

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РЕЦЕНЗИРУЕМЫЙ НАУЧНЫЙ МЕДИЦИНСКИЙ ЖУРНАЛ

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Key Risk Factors for Intracerebral Hemorrhage According to Regional Population-Based Stroke Registry

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Abstract

Introduction. *Intracerebral hemorrhage (ICH) registry data allow assessing epidemiological parameters and risk factors in different age, gender, race, ethnicity, and other subgroups.*
This study ***aimed*** *to evaluate the prevalence of key risk factors in a group of Yakutsk residents with primary hypertensive ICH included in the regional population-based stroke registry from 2015 to 2017.*
Materials and methods. *This study of risk factors was conducted in patients with hypertensive ICH (n = 251) from the regional population-based stroke registry, including 133 (53%) men and 118 (47%) women of Asian or Caucasian races. We performed statistical analysis of data.*
Results. *The analysis of risk factors showed that the prevalence of smoking and excessive alcohol consumption was higher in men with ICH compared with women (p < 0.001). There were no statistically significant differences in the incidence of hypertension, history of myocardial infarction, dyslipidemia, or diabetes mellitus in patients with ICH in gender or ethnicity subgroups. Fibrillation and other heart diseases were more common in Caucasian patients than in Asian (p = 0.005). ICH was associated with high levels of low-density lipoproteins and triglycerides with low levels of total cholesterol and high-density lipoproteins compared with healthy individuals.*
Conclusions. *We described gender and ethnic differences in the prevalence of risk factors in patients with hypertensive ICH.*

Keywords: *intracranial hemorrhage; risk factors*

Ethics approval. The study was approved by the Ethics Committee of the Yakut Scientific Center for Complex Medical Problems (protocol No. 37, November 28, 2014).

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Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

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Основные факторы риска внутримозговых кровоизлияний (по данным территориально-популяционного регистра инсульта)

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Аннотация

Введение. *Анализ данных регистра внутримозговых кровоизлияний (ВМК) предоставляет уникальную возможность изучения особенностей эпидемиологических показателей и факторов риска в зависимости от возрастных, гендерных, расово-этнических и других факторов.*

Цель *исследования – изучить распространённость основных факторов риска в группе пациентов с гипертензивными ВМК – резидентов г. Якутска, включённых в территориально-популяционный регистр инсульта за 2015–2017 гг.*
Материалы и методы. *Исследование факторов риска проведено у пациентов с гипертензивными ВМК (n = 251), включённых в территориально-популяционный регистр инсульта, в том числе у 133 (53%) мужчин и 118 (47%) женщин, принадлежащих к азиатской и европеоидной расам. Выполнен статистический анализ данных.*
Результаты. *Анализ факторов риска показал, что при ВМК распространённость курения и чрезмерного потребления алкоголя была выше среди мужчин по сравнению с женщинами (p < 0,001). Частота артериальной гипертензии, инфаркта миокарда в анамнезе, дислипидемии, сахарного диабета при ВМК не имела статистически значимых различий в зависимости от пола и этнической принадлежности. Фибрилляция предсердий и другие болезни сердца выявлялись чаще среди пациентов европеоидной расы по сравнению с пациентами азиатской расы (p = 0,005). Развитие ВМК характеризовалось высокими показателями липопротеинов низкой плотности и триглицеридов, низкими показателями общего холестерина и липопротеинов высокой плотности по сравнению со здоровыми лицами.*
Заключение. *Установлены гендерные и этнические особенности в распространённости факторов риска среди пациентов с гипертензивными ВМК.*

Ключевые слова: *внутримозговые кровоизлияния; факторы риска*

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Introduction

A concept for risk factors and areas for preventive activities for cerebrovascular disease was formed based on the results of epidemiological studies [1].

Hemorrhagic stroke (HS) is one of the most severe acute cerebrovascular accidents; most often, it complicates the course of hypertension and is associated with high case fatality rate (mortality rate is up to 50%) and severe disability [2]. According to a prospective population-based study (27,702 subjects without a history of stroke in the Swedish population), relative risk of developing massive cerebral hematomas in patients with high blood pressure exceeds the risk of developing ischemic stroke (IS) [3].

S.R. Martini et al. studied risk factors for intracerebral hemorrhage (ICH) in 597 patients and 1548 controls [4]. Hypertension, warfarin use, heredity (i.e. ICH in close family members), history of IS, no higher education, ε2 or ε4 alleles of the *APOE* gene were associated with the risk of developing ICH. A relationship was established between non-lobar hematomas and hypertension with hypercholesterolemia, while lobar hematomas were associated with ε2 or ε4 alleles of the *APOE* gene.

The relationship between cholesterol levels and the development of HS is controversial [5]. Low cholesterol levels were reported to be associated with an increased risk of ICH [6]. However, several studies gave opposite results. For example, I. Suh et al. did not find any relationship between low cholesterol levels and the risk of developing ICH [7].

Distribution of IS risk factors in different ethnic groups was thoroughly studied using a regional population-based registry. However, few studies investigated ethnic aspects of risk factors for HS [8–11].

A recent study by C.F. Tsai et al. [8] to assess key risk factors for stroke among patients with HS or IS in the Chinese population was conducted using hospital registry data from 2006 to 2011. A total of 1373 patients with HS and 4953 patients with IS were assessed. The mean age of patients with HS was significantly lower than that of

patients with IS (61 years vs. 68 years; $p < 0.001$) without significant age differences in gender groups. Hypertension (OR = 2.23; 95% CI 1.74–2.87) and alcohol abuse (OR = 1.44; 95% CI 1.16–1.77) had more significant associations with HS than with IS, while diabetes mellitus, atrial fibrillation, coronary artery disease, hyperlipidemia, smoking, and transient ischemic attacks were more frequent in patients with IS than in patients with HS. The authors concluded that hypertension and alcohol abuse in the Chinese population had a stronger association with the risk of HS compared with IS, especially in younger patients.

N.A. Khan et al. studied ICH prevalence in the Canadian population [12]. The proportion of ICH was the highest among representatives of East Asian ethnic groups (30% in the total structure of stroke), followed by patients from South Asia (17%) and the Caucasian population (15%) ($p < 0.001$).

N.C. Smeeton et al. showed that the incidence of hypertension before hemorrhagic stroke was the highest in young black patients [9].

A study was conducted to evaluate the prevalence of risk factors in patients with stroke according to the regional population-based register in Yakutsk from 2002 to 2004. Hypertension was detected in 88.9% of patients, smoking in 43.1%, dyslipidemia in 39.5%, coronary artery disease in 38.6%, atrial fibrillation in 14.8%, myocardial infarction in 14.0%, diabetes mellitus in 11.9%, alcohol abuse in 4.5%, stress in 19.9%, and family history of stroke in 60.7%. In stroke patients from the non-indigenous Yakutian population, smoking, diabetes mellitus, and alcohol abuse were more common [13]. When comparing the frequencies of risk factors for stroke, the authors showed that diabetes mellitus and overweight were less common in the Yakutian population compared to the Moscow one: 7.7% and 21.9% ($p = 0.005$), 49.5% and 72% ($p = 0.004$), respectively. Key risk factors for IS in the Moscow and Yakutian populations included hypertension (84.5% and 74.0%), heart disease (75% and 65.4%), and smoking (43% and 42.3% respectively) [14].

Therefore, ICH registry data allowed assessing epidemiological parameters in different age, gender, race, ethnicity, economic, climate, geographical, and other subgroups.

This study **aimed** to evaluate the prevalence of key risk factors in a group of Yakutsk residents with primary hypertensive ICH included in the regional population-based stroke registry from 2015 to 2017.

Materials and methods

This study of risk factors was conducted in 251 patients with primary hypertensive ICH from the regional population-based stroke registry, including 133 (53%) men and 118 (47%) women of Asian or Caucasian races. Ethnicity was determined by patients' self-identification. Subjects were considered as the native ethnic population of Asian race if their ethnicity was indicated as Yakuts, Evenks, Evens, or Yukaghirs or as Caucasian if they indicated that they belonged to the Caucasian race.

Brain computed tomography (CT) was performed using 64-slice SOMATOM Definition AS scanner (Siemens), and magnetic resonance imaging (MRI) was performed using Magnetom Espree 1.5 T (Siemens).

The following risk factors for ICH were evaluated: hypertension, cigarette smoking, excessive alcohol consumption, atrial fibrillation, history of myocardial infarction, other heart disorders (i.e. stable coronary artery disease, valvular heart disease, and cardiomyopathies), dyslipidemia, and diabetes mellitus.

Patients who smoked at least 1 cigarette per day during at least 1 year were considered smokers. Excessive alcohol consumption was defined as systematic intake of more than 21 standard drinks per week (1 standard drink corresponds to 30 mL of distilled spirits) or more than 70 g of pure ethanol per day.

Atrial fibrillation according to ECG data was recorded in 28 patients without a history of cardiac arrhythmias.

Standard blood biochemistry parameters were measured using Konelab PRIME 30i (Thermo Fisher Scientific).

A case-control study was conducted to evaluate a possible relationship of blood lipid parameters and the risk of ICH.

Inclusion criteria for the test group: patients under the age of 60 years with acute ICH.

Inclusion criteria for the control group: healthy individuals under the age of 60 years without a history or clinical data of acute cerebrovascular accidents.

Statistical analysis was conducted using IBM SPSS Statistics v. 22 software package. Quantitative characteristics without normal distribution were described as median values (Me) with lower and upper quartiles [Q1; Q3]. Mann–Whitney U-test was used to compare samples with distribution other than normal. Descriptive statistics for categorical variables were presented as rates (n) and percentages (%). A relationship between qualitative characteristics was assessed using contingency tables. Significance of differences was assessed using Pearson χ^2 test. χ^2 test with Yates' correction and Fisher's exact test were used when several expected frequencies in the tables were less than 10. The power of associations was evaluated using

odds ratios (ORs). ORs with 95% confidence intervals (CI) were presented; associations with CI that included 1 were not considered statistically significant.

Results

Smoking and excessive alcohol consumption in patients with ICH were more common in men than in women ($p < 0.001$; $\chi^2 = 14.111$; df = 1; OR = 3.048; 95% CI 1.682–5.523). The incidence of hypertension, atrial fibrillation, history of myocardial infarction, dyslipidemia, and diabetes mellitus in patients with ICH did not have any statistically significant differences in gender subgroups (Table 1).

In patients with ICH, incidence of hypertension ($p = 1.000$), tobacco smoking ($p = 0.556$), history of myocardial infarction ($p = 0.120$), dyslipidemia ($p = 0.437$), and diabetes mellitus ($p = 0.886$) did not have statistically significant differences in ethnic subgroups (Table 2). Asian patients less frequently had atrial fibrillation ($p = 0.005$; $\chi^2 = 7.858$; df = 1; OR = 0.328; 95% CI 0.146–0.735) and other heart diseases ($p = 0.014$; $\chi^2 = 6.089$; df = 1; OR = 0.392; 95% CI 0.185–0.831) compared with Caucasian patients.

In patients with ICH, total cholesterol and high-density lipoprotein (HDL) levels were significantly lower (4.98 ± 1.26 and 5.21 ± 0.98 ($p = 0.015$), 1.18 ± 0.44 and 1.52 ± 0.48 ($p < 0.0001$), respectively), while triglyceride and low-density lipoprotein (LDL) levels were significantly higher than in healthy individuals (1.35 ± 0.86 and 1.04 ± 0.59 ($p = 0.000001$), 3.50 ± 1.13 vs. 2,90 ± 0.88 ($p < 0.0001$), respectively; Table 3). No differences in lipid parameters were seen in ethnic subgroups (Table 4).

Discussion

Hypertensive ICH accounts for 10% of all stroke types [1, 15, 16]. ICH prevalence varies depending on geographic regions. Particularly high incidence of ICH was shown in Japan and Korea [15, 17].

Modifiable risk factors include smoking, excessive alcohol consumption, and lipid levels. Non-modifiable risk factors for ICH include older age and male gender [15, 17–19]. Over the past 30 years, the incidence of hypertensive ICH has decreased, while the incidence of ICH associated with antithrombotic agents has increased [20].

Our study showed that in patients with ICH, atrial fibrillation and other heart diseases (stable coronary artery disease, valvular heart disease, cardiomyopathies) were detected more often in Caucasian men than in Asian men. There were no significant differences in the incidence of hypertension, history of myocardial infarction, diabetes mellitus, or dyslipidemia in gender or ethnicity groups.

Risk factors for developing ICH that are of major concern include smoking and excessive alcohol consumption. Nicotine, the main toxic agent in cigarette smoke, which con-

Table 1. Prevalence of risk factors in patients with ICH in different gender subgroups, *n* (%)

Risk factor	Male (*n* = 133)	Female (*n* = 118)	*p* (χ^2; df)	OR (95% CI) for significant differences
Arterial hypertension	131 (98.5)	116 (98.3)	1.000**	–
Cigarette smoking	51 (38.3)	20 (16.9)	< 0.0001* (14.111; df = 1)	3.048 (1.682–5.523)
Excessive alcohol consumption	51 (38.3)	20 (16.9)	< 0.0001* (14.111; df = 1)	3.048 (1.682–5.523)
Atrial fibrillation	14 (10.5)	14 (11.9)	0.737* (0.113; df = 1)	–
History of myocardial infarction	12 (9.02)	16 (13.6)	0.254* (1.298; df = 1)	–
Other heart diseases	66 (49.6)	61 (51.7)	0.743 (0.107; df = 1)	–
Dyslipidemia	56 (42.1)	56 (47.5)	0.395* (0.725; df = 1)	–
Diabetes mellitus	9 (6.8)	12 (10.2)	0.331* (0.944; df = 1)	–

Note. Here and in Table 2, other heart diseases include stable coronary artery disease, valvular heart disease, cardiomyopathies; *Pearson χ^2 test; **Fisher's exact test.

Table 2. Prevalence of risk factors in patients with ICH by their ethnicity, *n* (%)

Risk factor	Asian race (*n* = 159)	Caucasian race (*n* = 92)	*p* (χ^2; df)	OR (95% CI) for significant differences
Arterial hypertension	156 (98.1)	91 (98.9)	1.000**	–
Cigarette smoking	47 (29.6)	24 (26.1)	0.556* (0.346; df = 1)	–
Excessive alcohol consumption	47 (29.6)	24 (26.1)	0.556* (0.346; df = 1)	–
Atrial fibrillation	11 (6.9)	17 (18.5)	0.005* (7.858; df = 1)	0.328 (0.146–0.735)
History of myocardial infarction	14 (8.8)	14 (15.2)	0.120* (2.418; df = 1)	–
Other heart diseases	28 (41.8)	33 (64.7)	0.014* (6.089; df = 1)	0.392 (0.185–0.831)
Dyslipidemia	68 (42.8)	44 (47.8)	0.437* (0.604; df = 1)	–
Diabetes mellitus	13 (8.2)	8 (8.7)	0.886* (0.021; df = 1)	–

Table 3. Lipid parameters in patients with ICH

Parameter	Patients with ICH (*n* = 251)	Healthy controls (*n* = 537)	*p**
Total cholesterol. mmol/liter	4.90 [4.05; 5.75]	5.15 [4.53; 5.77]	0.012
Low-density lipoproteins. mmol/liter	3.44 [2.74; 4.13]	2.82 [2.29; 3.43]	< 0.0001
Triglycerides. mmol/liter	1.13 [0.79; 1.68]	0.89 [0.64; 1.26]	0.001
High-density lipoproteins. mmol/liter	1.11 [0.92; 1.35]	1.44 [1.16; 1.72]	< 0.0001

Note. *Mann–Whitney U-test.

Table 4. Lipid parameters in patients with ICH by their ethnicity

Parameter	Asian race (*n* = 159)	Caucasian (*n* = 92)	*p**
Total cholesterol. mmol/liter	4.9 [4.1; 5.8]	5.0 [4.0; 6.2]	0.166
Low-density lipoproteins. mmol/liter	3.4 [2.8; 4.0]	3.7 [2.8; 4.7]	0.061
Triglycerides. mmol/liter	1.1 [0.8; 1.6]	1.2 [0.9; 1.7]	0.189
High-density lipoproteins. mmol/liter	1.1 [0.9; 1.4]	1.2 [0.4; 1.6]	0.240

Note. *Mann–Whitney U-test.

tains over 9,000 different chemicals, increases the risk of cardiovascular and cerebrovascular disease [21]. Smoking and excessive alcohol consumption were shown to increase the risk of ICH across different populations [22]. ICH incidence is higher in men than in women [23, 24]. Compared with non-smokers, the risk ratio for ICH in men and women who smoke is 1.82 and 1.3, respectively [25]. In our study, smoking and excessive alcohol consumption were more common in male patients with ICH compared with female.

Data on the relationship between lipid parameters and the risk of cerebrovascular disease, including stroke, are contradictory [6, 26–28]. Multiple studies showed that hypercholesterolemia was associated with the risk of IS [6, 29], while the role of lipid parameters for the development of HS was not so obvious.

According to several studies, low TC levels were associated with ICH risk [6] and unfavorable outcome [5]. However, other studies showed that increased cholesterol and LDL levels and low HDL levels were associated with ICH risk [30].

Our study showed that patients with ICH had statistically significant decreases in TC and HDL and statistically significant increases in TG and LDL compared with healthy controls.

Our data are consistent with another study [30], which showed that increased TG levels were not associated with the risk of primary ICH, while increased LDL and TC levels and low HDL levels were associated with ICH. In addition, previous studies [6, 31, 32] showed that low TC levels were a predictor for ICH.

Conclusion

The analysis of risk factors showed no statistically significant differences in the incidence of hypertension, history of myocardial infarction, diabetes mellitus, or dyslipidemia in patients with hypertensive ICH in gender or ethnicity subgroups. Atrial fibrillation and other heart diseases were more common in Caucasian patients compared with Asian. Smoking and excessive alcohol consumption were more common in men than in women. ICH was associated with high LDL and TG levels and low TC and HDL levels compared with healthy controls.

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Cell-Mediated Immunity in Multiple Sclerosis Patients Who Discontinued Therapy with an Integrin Inhibitor

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Abstract

Introduction. *Natalizumab (NTZ) is a humanized monoclonal antibody (mAb) that selectively inhibits α4-integrin adhesion molecule located on the surface of lymphocytes and prevents their trafficking into the central nervous system (CNS).*

The aim *of this study was to identify characteristics of lymphocyte population and subpopulation pattern in the peripheral blood (PB) of multiple sclerosis (MS) patients who discontinued NTZ due to an increased risk of developing developing progressive multifocal leukoencephalopathy.*

Materials and methods. *We conducted an open-label prospective observational study in 26 MS patients. Of those, 6 patients had rapidly progressive MS, 10 patients discontinued NTZ and had confirmed relapses afterwards, and 10 patients received NTZ and had no relapses during the washout period. Ten apparently healthy individuals were used as controls. Cell-mediated immunity parameters were evaluated by flow cytometry using a panel of mAbs to differentiation antigens of PB lymphocytes.*

Results. *Patients who discontinued NTZ had significantly decreased absolute lymphocyte counts in PB, decreased T-cytotoxic, NKT and B1 lymphocyte subpopulation levels, and decreased activated T-cell ($CD3^+HLA^-DR^+$) levels, which may be related to their redistribution, passing through the blood-brain barrier, and trafficking into the central nervous system. $CD20^+$ B-cell levels did not differ from normal. Additional immune predictors of MS relapses after NTZ discontinuation can include decreased absolute count of PB lymphocytes and decreased percentage of $CD3^+CD8^+$ T-cell, NKT-cell, and B1-cell ($CD19^+CD5^+$) subpopulations. Significantly increased levels of $CD25^+$- and $CD38^+$-activated B-cells compared with the normal levels in naïve patients and subjects without relapses after NTZ discontinuation may suggest a high activation potential of the circulating B-cell pool and, therefore, a high risk of MS relapses.*

Conclusions. *The changes in the lymphocyte subpopulation pattern in the PB of MS patients after NTZ discontinuation may have a prognostic value for assessing the risk of relapses; they justified switching patients to anti-B-cell therapy.*

Keywords: *natalizumab, immune reconstitution inflammatory syndrome, rebound phenomenon, T-cells, B-cells*

Ethics approval. The study was approved by the Independent Ethics Committee at the M.F. Vladimirsky Moscow Region Research Clinical Institute (Protocol No. 8, June 13, 2019).

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Особенности клеточного иммунитета у больных рассеянным склерозом, прервавших терапию ингибитором интегрина

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Аннотация

Введение. *Натализумаб (НАТ) – гуманизированное моноклональное антитело (МАТ), селективный ингибитор молекулы адгезии α4-интегрина, располагающейся на поверхности лимфоцитов, – предотвращает проникновение лимфоцитов в центральную нервную систему (ЦНС).*

Целью *исследования было выявление особенностей популяционного и субпопуляционного состава лимфоцитов периферической крови (ПК) у пациентов с рассеянным склерозом (РС), прекративших терапию НАТ в связи с повышенным риском развития прогрессирующей мультифокальной лейкоэнцефалопатии.*

Материалы и методы. *Проведено открытое проспективное наблюдательное исследование 26 пациентов с РС, из них 6 – с быстро прогрессирующим РС; 10 – прервавших терапию НАТ с подтверждённым в дальнейшем обострением заболевания; 10 – получавших терапию НАТ без обострений заболевания в отмывочный период. В качестве референсных значений использованы аналогичные показатели 10 практически здоровых лиц. Параметры клеточного иммунитета оценивали методом проточной цитометрии с использованием панели МАТ к дифференцированным антигенам лимфоцитов ПК.*

Результаты. *У пациентов, прекративших терапию НАТ, обнаружено значительное снижение абсолютного числа лимфоцитов ПК, снижение содержания Т-цитотоксической, NKT- и В1-субпопуляций лимфоцитов, а также уровня активированных Т-лимфоцитов ($CD3^+HLA^-DR^+$), что может быть связано с их перераспределением, преодолением гематоэнцефалического барьера и проникновением в ЦНС. Уровень $CD20^+$-В-лимфоцитов не отличался от нормальных значений. Иммунологическими дополнительными предикторами обострения РС после отмены НАТ могут служить снижение абсолютного количества лимфоцитов ПК; снижение содержания субпопуляций $CD3^+CD8^+$-Т-лимфоцитов, NKT-лимфоцитов, В1-лимфоцитов ($CD19^+CD5^+$). Кроме того, обнаруженные данные о выраженном увеличении содержания активированных по $CD25^+$- и $CD38^+$-В-лимфоцитов по сравнению с нормальными величинами у «наивных» пациентов и лиц без обострения заболевания после отмены НАТ могут свидетельствовать о высоком активационном потенциале циркулирующего пула В-лимфоцитов, а следовательно, о высоком риске обострения РС.*

Выводы. *Выявленные изменения субпопуляционного состава лимфоцитов ПК у пациентов РС после отмены НАТ могут иметь прогностическое значение для оценки степени риска развития обострения заболевания и подтверждают адекватность перевода пациентов на анти-В-клеточную терапию.*

Ключевые слова: *натализумаб; воспалительный синдром восстановления иммунитета; ребаунд-феномен; Т-лимфоциты; В-лимфоциты*

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Introduction

It is commonly accepted that multiple sclerosis (MS) is a heterogeneous multifactorial immune-mediated disease with both T-cells and B-cells playing a key role in its pathogenesis. The initiating stage of MS development is thought to be due to the activation of peripheral autoreactive effector $CD4^+$ T-cells, which migrate to the central nervous system (CNS) and initiate the disease process by producing cytokines (interferon-γ, tumor necrosis factor, interleukins 17, 21, and 22), thus leading to activation of resident immune cells (microglia, astrocytes, and macrophages), increased function of antigen-presenting cells, and increased production of reactive oxygen and nitrogen species [1–3].

Drug therapies for MS that are based on its pathogenesis include several approaches such as reducing levels of Th1/Th17-cells that potentiate the disease, activating regulatory T-cells, suppressing lymphocyte transport in the nervous system, and targeting B-cells. Medications with such different mechanisms of action are classified as disease-modifying therapies (DMTs).

Natalizumab (NTZ) is a humanized monoclonal antibody (mAb) that selectively inhibits α4-integrin adhesion molecule, which is expressed on the surface of lymphocytes and required for binding to brain capillary endothelium of the blood-brain barrier; NTZ prevents lymphocytes from adhering to the endothelium and penetration into the central nervous system. NTZ significantly reduced clinical relapse rate, occurrence rate of new T2 hyperintense lesions and gadolinium enhancing lesions on MRI, and disability progression in patients with remitting MS [4, 5].

As shown in pharmacokinetic studies, CD49d molecules (i.e. integrin α-subunits) were bound to NTZ molecules on the surface of lymphocytes in 76–84% of patients. Extended dosing intervals were associated with an increased CD49d expression [6]. Á. Cobo-Calvo et al. showed that 2 months after NTZ discontinuation, the expression of CD49d and other lymphocyte adhesion molecules (CD29 and CD11a) continuously increased, CD49d expression up to Month 3 after NTZ discontinuation was related to MS activity at the end of the study, and CD49d expression, both in $CD45^+CD4^+$ and $CD45^+CD8^+$, at Month 6 after NTZ withdrawal correlated to NTZ treatment duration [7]. The authors found that "molecular rebound" after NTZ discontinuation was more pronounced in patients on long-term NTZ treatment and suggested that testing for CD49d should be used to closely monitor MS activity in patients after NTZ discontinuation.

Over the decade of its use in clinical practice in Russia, the safety profile of NTZ has been well studied. Usually, NTZ is well tolerated with rare adverse events. However, NTZ increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic infection which is characterized by the death of oligodendrocytes and some astrocytes, and development of large secondary demyelination lesions. Considering initial seropositivity to John Cunningham virus (JCV), prior history of immunosuppression, and duration of NTZ therapy, a PML risk management plan has been developed[1] , according to which, if the risk increases, patients should discontinue NTZ and switch to another therapy. However, 38% of patients experienced relapses after NTZ discontinuation, which can be explained by immune reconstitution inflammatory syndrome (IRIS) and, in some cases, by rebound phenomenon (i.e. exacerbation of existing MS symptoms and onset of new MS symptoms, often resembling acute disseminated encephalomyelitis) [8–10]. A short washout period after NTZ discontinuation reduced the risk of IRIS but increased that of PML [11, 12].

R. Planas et al. [13] studied changes in peripheral blood (PB) T-cell populations in patients receiving NTZ and showed increases in the levels of T-cells, NK-cells, and especially B-cells. While the percentage of naïve, effector, and memory T-cells that left lymphoid organs remained unchanged during the treatment, the authors showed an increase in activated (similar to memory or marginal zone cells) but not naïve B-cells. T. Plavina et al. [14] showed that total lymphocyte counts in the PB of patients receiving NTZ increased more than 1.5-fold compared with the levels before the initiation of the treatment, decreased after the end of the treatment starting from Week 8, and returned to normal levels (i.e. those before the treatment) by Week 16. However, the authors did not evaluate lymphocyte subpopulations more thoroughly.

Treatment with NTZ was also associated with decreases in the levels of $CD4^+$ and $CD8^+$ T-cells, B-cells ($CD19^+$) and plasma cells in the cerebrospinal fluid due to the inhibition of their trafficking into the cerebrospinal fluid from the PB, while high levels of $CD4^+$ and $CD8^+$ T-cells were seen in patients with clinically manifested relapses after NTZ discontinuation, which was considered as IRIS [15, 16].

Since the risk management strategy for treating MS patients with NTZ involves its discontinuation if the chances of PML increase, it is necessary to identify the signs that would allow evaluating the risk of exacerbations or the development of IRIS in such patients.

The aim of our study was to identify characteristics of PB lymphocyte population and subpopulation pattern in MS patients who discontinued NTZ due to an increased risk of PML.

[1] Clinical Guidelines for Multiple Sclerosis, 2022. URL: https://cr.minzdrav.gov.ru/recomend/739

Materials and methods

This was an open-label prospective observational study. The conduct of the study was approved by the Local Ethics Committee at M.F. Vladimirsky Moscow Region Research Clinical Institute (Protocol 8, June 13, 2019).

Inclusion criteria:
- male or female patients aged 18 to 60 years who signed informed consent;
- highly active MS or rapidly progressing remitting MS;
- patients with anti-JCV antibody index > 1.5 or inadequate response to NTZ.

Exclusion criteria:
- contraindications for anti-B-cell therapy;
- pregnancy;
- lactation;
- refusal to use contraception during the treatment.

Withdrawal criteria:
- patient's refusal to continue to participate in the study;
- patient's non-compliance to study procedures.

We examined 26 MS patients who were followed at Moscow Region MS Center from 2019 to 2022. Group 1 included patients with rapidly progressive MS (RPMS): 2 men and 4 women with a mean age of 27.0 ± 4.6 years and a mean disease duration of 2.6 ± 0.8 years, who had not previously received DMTs. They had 2 or more clinical relapses within a year, at least 1 gadolinium enhancing lesion or new T2-weighed lesions and confirmed disability progression, i.e. Expand Disability Status Scale (EDSS) score increased by 1 or more within the last year.

Treatment adjustment was required in 20 MS patients (8 men and 12 women aged 19–44 years; mean age 35.7 ± 9.5 years) who received NTZ: in 17 patients, this was due to high anti-JCV antibody titer indexes, treatment duration of more than 24 months and a high risk of PML; 3 patients had relapses recorded in the second year of therapy with a confirmed increase in their EDSS scores in the next 24 weeks of follow-up, and their MS was classified as secondary progressive MS with relapses. Therefore, the patients were candidates for being switched to ocrelizumab. Age of disease onset was 22.3 ± 4.6 years, and duration of the disease from the onset of first symptoms was 14.4 ± 4.9 years. Their mean baseline EDSS score was 3.2 ± 0.7, which corresponded to moderate disability. Group 2 included 10 patients who received NTZ, discontinued it and then had a relapse that was confirmed both by clinical evaluation and neuroimaging. Group 3 included 10 patients who discontinued NTZ and had no signs of relapses afterwards.

A total of 10 apparently healthy individuals tested for the same parameters were used as controls (group 4).

Cell-mediated immunity parameters in MS patients were evaluated by flow cytometry using a mAb panel to differentiation antigens of PB lymphocytes (Becton Dickinson). We studied lymphocyte population and subpopulation pattern within the lymphocyte gate ($CD45^+$): $CD3^+$, $CD19^+$, $CD20^+$, $CD3^-CD16^+CD56^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD3^+HLA^-DR^+$. B-cell subpopulation pattern (B1-cells, memory B- cells), expression of co-stimulatory and activation antigens (CD40, CD25, CD38, CD95) were determined within the $CD19^+$ vs SSC gate.

Statistical analysis was carried out using StatPlus Pro 7.6.5.0 software package. Quantitative data were presented as mean values with standard deviation ($M \pm SD$). Given small sample sizes, distribution was tested for normality using Shapiro–Wilk test [17]. For quantitative data with non-normal distribution, we compared three independent samples with the group of apparently healthy individuals using Mann–Whitney test with Bonferroni correction ($p < 0.017$) and performed multiple comparison of independent samples using Kruskal–Wallis test [18]. Statistical tests were conducted for a two-sided hypothesis with the level of statistical significance set at 0.05.

Results

We examined 26 MS patients (10 men and 16 women aged 21 to 52 years), who underwent an assessment of cell-mediated immunity parameters by flow cytometry before starting ocrelizumab therapy. When being switched from NTZ to another DMT, patients should have a safety washout period of 12 weeks to 6 months depending on the treatment option that has been chosen for further treatment. The mean duration of the treatment-free period in the examined group was 7.9 ± 1.9 months. Its duration was related to availability of the medications and timelines for further examinations to minimize risks due to the adjusted therapy. However, as the washout period duration increased, the risk of relapses also increased; clinically manifested relapses with neuroimaging confirmation were recorded in 10 (50%) patients.

Cell-mediated immunity parameters in our patients are presented in Table 1.

In all patients, total leukocyte count and percentage of lymphocytes were within normal limits: 7.290 ± 1.277 × 10^9/liter and 26.3 ± 2.3% (group 1), 7.229 ± 1.256 and 26.1 ± 6.6 (group 2), 6.431 ± 2.328 and 30.8 ± 10.3 (group 3), 6.500 ± 1.859 and 33.3 ± 5.6 (group 4), respectively.

In group 1, levels of T-cells, B NK-cells, T-helpers, cytotoxic T-cells and NKT-cells ($CD3^+CD16^+CD56^+$) did not differ from the control values. Patients in group 2 had their absolute lymphocyte counts significantly decreased

Table 1. Cell-mediated immunity parameters in MS patients (percentage of cells within $CD45^+$-cell gate)

Parameter	Group				*p*
	1 (*n* = 6)	2 (*n* = 10)	3 (*n* = 10)	4 (*n* = 10)	
Total lymphocyte count. × 10^9/liter	1.933 ± 2.160	1.774 ± 0.432	1.652 ± 0.613	2.070 ± 1.013	$p = 0.009$ $p_{2-4} = 0.005$
Cell percentage. %					
$CD3^+$	76.90 ± 6.06	71.9 ± 16.8	69.86 ± 12.29	74.33 ± 7.83	$p = 0.117$
$CD3^+CD4^+$	40.47 ± 5.64	48.0 ± 12.1	42.79 ± 11.22	41.0 ± 5.01	$p = 0.525$
$CD3^+CD8^+$	34.26 ± 7.01	22.87 ± 6.67	25.41 ± 8.24	33.00 ± 4.2	$p < 0.001$ $p_{2-4} < 0.001$
$CD3^-CD16^+CD56^+$	11.33 ± 2.36	16.6 ± 18.5	13.01 ± 5.97	12.47 ± 2.99	$p = 0.831$
$CD3^+CD16^+CD56^+$	6.13 ± 1.98	4.93 ± 3.23	2.52 ± 2.18	10.50 ± 4.51	$p < 0.001$ $p_{2-4} = 0.003$ $p_{3-4} = 0.002$
$CD3^+HLA^-DR^+$	11.8 ± 0.47	6.6 ± 3.21	8.26 ± 2.75	13.30 ± 5.35	$p < 0.001$ $p_{2-4} = 0.002$ $p_{3-4} = 0.012$
$CD19^+$	11.16 ± 2.83	12.0 ± 5.57	14.16 ± 7.33	11.79 ± 2.31	$p = 0.417$
$CD20^+$	10.24 ± 2.17	10.66 ± 6.1	12.81 ± 6.53	11.19 ± 1.41	$p = 0.219$
$CD19^+HLA^-DR^+$	9.80 ± 1.34	11.75 ± 5.57	13.09 ± 6.80	10.32 ± 1.41	$p = 0.348$

Note. Here and in Table 2 *p* indicates significance of differences between the groups (Kruskal–Wallis test); p_{1-4} between groups 1 and 4; p_{2-4} between groups 2 and 4; p_{3-4} between groups 3 and 4.

Table 2. Parameters of B-cell immunity in MS patients (percentage of cells within $CD19^+$-B-lymphocyte gate, %)

Cells	Group				*p*
	1 (*n* = 6)	2 (*n* = 10)	3 (*n* = 10)	4 (*n* = 10)	
$CD40^+$	51.13 ± 8.26	39.68 ± 27.13	55.76 ± 28.59	49.20 ± 3.69	$p = 0.168$
$CD95^+$	19.27 ± 1.67	18.9 ± 10.84	33.29 ± 22.27	19.89 ± 1.41	$p = 0.094$
$CD5^+$	19.30 ± 6.36	9.63 ± 3.3	19.08 ± 15.99	17.29 ± 4.47	$p < 0.001$ $p_{2-4} < 0.001$
$CD27^+$	25.97 ± 5.22	32.08 ± 18.31	30.53 ± 14.18	28.30 ± 2.28	$p = 0.441$
$CD38^+$	29.43 ± 6.96	20.8 ± 9.56	44.13 ± 18.18	16.10 ± 4.47	$p < 0.001$ $p_{1-4} < 0.001$ $p_{3-4} < 0.001$
$CD25^+$	21.93 ± 5.51	16.37 ± 7.45	27.58 ± 8.05	13.79 ± 3.69	$p = 0.003$ $p_{1-4} = 0.004$ $p_{3-4} = 0.016$

compared with healthy subjects. This parameter was not decreased in patients of group 3, who discontinued NTZ and did not have any relapses.

Although absolute PB lymphocyte counts in patients who discontinued NTZ was lower than in the control group and in patients with RPMS, the percentage of B-cells for both pan-B cell markers ($CD19^+$ and $CD20^+$) in these patients did not differ significantly from naïve patients and apparently healthy individuals.

A similar pattern was seen with B-cells expressing class 2 histocompatibility antigens ($CD19^+HLA^-DR^+$), which reflect their antigen-presenting ability. In contrast, activated T-cell ($CD3^+HLA^-DR^+$) counts in groups 2 and 3 were significantly decreased compared with the control group. The percentage of cytotoxic T-cells ($CD3^+CD8^+$) was significantly reduced (1.5-fold) in patients of group 2, who had MS relapses, while the percentage of the NKT-cell subpopulation was significantly reduced in groups 2 and 3 compared with healthy subjects.

The group of naïve patients with RPMS had a significant increase in the levels of B-cells expressing activation markers CD38 and CD25 compared with the control group (Table 2). For other parameters (expression of co-stimulatory molecule CD40, memory B-cell ($CD27^+$) levels, expression of CD5 and CD95 antigens), no significant differences were found with the control group.

Patients who discontinued NTZ and did not have MS relapses had a significant increase in activated B-cell levels (as measured by the expression of CD25 and CD38 markers) compared with the control group. Patients with MS relapses after NTZ discontinuation had a significant decrease in B1-cell ($CD19^+CD5^+$) subpopulation compared with the treatment-free patients and control group.

No significant differences were found in other parameters (expression of co-stimulatory molecule CD40, memory B-cell ($CD27^+$) count, CD95 expression) in patients who discontinued NTZ vs. naïve patients and the control group.

Discussion

Literature data on cell-mediated immunity in MS patients are inconsistent because there is a wide variety of disease types, clinical manifestations, changes in neurological deficit progression over time, as well as treatment options for MS patients.

B. Arneth showed a high degree of inter-individual variability in the levels of all lymphocyte subpopulations in 290 MS patients, especially those on DMTs [19]. The author showed increased counts of PB T-cells ($CD3^+$) and T-helpers ($CD4^+$), including activated ones ($CD4^+HLA^-DR^+$), and an increased percentage of NKT-cells ($CD3^+CD16^+CD56^+$). An increased count of activated cytotoxic $CD8^+$ T-cells suggests an important role of this subpopulation in MS.

Multiple experimental and clinical studies showed a pro-inflammatory encephalithogenic effect of $CD8^+$ T-cells, which was enhanced after contacting with myelin basic protein molecules [20]. Myelin-specific $CD8^+$ T-cells may exacerbate brain inflammation in MS. $CD8^+$ T-cells were found in brain lesions in mice with experimental encephalomyelitis and in the brain matter in patients with MS.

In our study, we did not find any significant disturbances of NKT-cell immunity parameters in naïve patients with RPMS compared with control values. In naïve patients, T-cell immunity parameters paradoxically seemed to be within normal limits. This fact might be explained by an insufficient number of observations.

As for B-cell subpopulation pattern of naïve patients, they had a significant increase in activated B-cell percentage (both for CD25 and CD38 expression).

In contrast, patients who discontinued NTZ had higher changes in T-cell and B-cell immunity parameters such as decreased total lymphocyte count, significantly reduced percentage of cytotoxic T-cell ($CD3^+CD8^+$) and NKT-cell subpopulations with specific killer effector activity, significantly decreased percentage of activated T-cells ($CD3^+HLA^-DR^+$).

We cannot exclude that decreased counts of cytotoxic T-cells ($CD3^+CD8^+$), activated T-cells ($CD3^+HLA^-DR^+$), and NKT-cells circulating in the PB in patients who discontinued NTZ in our study could be related to their redistribution, passing through the blood-brain barrier, and penetration into the central nervous system. This hypothesis can be indirectly confirmed by the high levels of such cells in the PB of patients without relapses.

On the other hand, C.A. Wagner et al. showed a significant increase in the counts of circulating memory $CD8^+$ T-cells specific to myelin antigens vs. control [21].

An initial view of MS as a T-cell-mediated disease is currently being reconsidered as there is increasing evidence of B-cell involvement in the pathogenesis of the disease. The mechanism underlying CNS damage in MS is thought to be related to aberrant stimulation of plasma cells and B-cells, which leads to the development of autoantibodies to specific myelin antigens. B-cells were shown to interact with $CD4^+$ T-cells and initiate an adaptive immune response to myelin antigens; reduced inflammation and alleviated clinical signs were shown after inhibiting B-cell immunity [22, 23].

Ya.A. Lomakin et al. evaluated the repertoire of B-cell receptors in regulatory B-cells in PB of MS patients and showed that the incidence rate of several regulatory B-cell genes was different from immunoglobulin gene distribution in healthy individuals, and this shift was more pronounced in patients with highly active MS [24]. These data allowed the authors suggesting that the repertoire of regulatory B-cells in MS changes at early stages of B-cell maturation.

An assessment of B-cell population in the PB of MS patients who discontinued NTZ therapy in our study demonstrated that levels of B-cells with linear antigens ($CD19^+$, $CD20^+$) persisted together with maintaining their functional activity (antigen-presenting ability).

Having evaluated B-cell subpopulation pattern in patients who discontinued NTZ, we found some differences between the patients with or without relapses. In patients with relapses after NTZ discontinuation, we found a significant decrease in B1-cell subpopulation ($CD19^+CD5^+$), i.e. cells that are associated with autoantibody development in autoimmune disorders.

In contrast, patients without MS relapses after NTZ discontinuation had a significant increase in subpopulations of interleukin-2 receptor (CD25) and CD38 activated B-cells compared with control values. The data indicate a significant increase in the activation potential of B-cells, which may be expressed as their increased proliferation and differentiation into plasma cells that secrete autoantibodies against specific myelin antigens.

Conclusion

Our study showed that MS patients who were candidates for switching to ocrelizumab, a therapeutic mAb (anti-CD20), did not have any decreases in $CD20^+$ B-cell count after long-term therapy with NTZ; in contrast, they maintained their levels.

The following criteria can be used as additional immune criteria (predictors) for MS relapses after NTZ discontinuation:
- decreased absolute lymphocyte counts in PB;
- reduced percentage of effector $CD3^+CD8^+$ T-cell subpopulation in PB;
- reduced percentage of NKT-cell subpopulation;
- reduced percentage of B1-cell subpopulation in PB.

On the other hand, increased levels of $CD25^+$ and $CD38^+$ activated B-cells in patients with RPMS and subjects without clinically diagnosed relapses after NTZ discontinuation in our study may suggest a high activation potential of the circulating B-cell pool and, therefore, a high risk of MS relapses.

These data confirmed that switching these patients to anti-B-cell therapy is justified.

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Neuroimaging Markers for Differential Diagnosis Between Multifocal Motor Neuropathy and Multifocal Acquired Demyelinating Sensory and Motor Neuropathy

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Abstract

Introduction. *Similar asymmetric patterns of motor disorders and neurophysiological changes complicate the differential diagnosis between multifocal motor neuropathy (MMN) and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) as two chronic dysimmune neuropathies with significantly different treatment approaches. The lack of specific paraclinical markers often result in misdiagnosis and selection of ineffective specific therapy. Identification of specific neuroimaging biomarkers to differentiate these conditions may improve diagnostic approaches.*
Objective: *To identify neuroimaging markers for the differential diagnosis between MMN and MADSAM.*
Materials and methods. *The study included 65 participants, particularly 30 individuals with MMN and 35 individuals with MADSAM followed up in the Center of Peripheral Nervous System Diseases, Research Center of Neurology, Moscow, Russia. We retrospectively analyzed their clinical and epidemiological characteristics as well as ultrasonography and magnetic resonance imaging (MRI) findings.*
Results. *Ultrasonography was performed on the peripheral nerves of the upper extremities, the spinal nerves, and the brachial plexus. The results showed that participants with MADSAM had significantly greater cross-sectional areas (CSAs) and a higher incidence of intraneural ultrasonographic abnormalities compared to participants with MMN. CSA thresholds of the median nerves were identified using ROC analysis to differentiate between MMN and MADSAM. MRI scans of the brachial plexus revealed no abnormalities in 41.4% of the individuals with MMN and 27.3% of the individuals with MADSAM. Meanwhile, STIR hyperintense signal from the brachial plexus was most typical (> 70%) for the MADSAM group.*
Conclusions. *This was the first detailed comparative analysis of neuroimaging findings in a large sample of patients with either MMN or MADSAM in Russia. Ultrasonographic markers for differential diagnosis have been determined. The advantages and limitations of ultrasonography and MRI of the brachial plexus and the spinal and peripheral nerves in diagnosing multifocal chronic dysimmune neuropathies have been demonstrated.*

Keywords: *multifocal motor neuropathy, multifocal acquired demyelinating sensory and motor neuropathy, ultrasonography of peripheral nerves, magnetic resonance imaging of the brachial plexus, dysimmune neuropathies*

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of the Research Center of Neurology (protocol No. 10-4/21, November 17, 2021).

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Нейровизуализационные дифференциально-диагностические маркеры при мультифокальной моторной нейропатии и мультифокальном варианте хронической воспалительной демиелинизирующей полинейропатии

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Аннотация

Введение. *Одинаковый асимметричный паттерн двигательных нарушений и однонаправленные нейрофизиологические изменения, регистрируемые при мультифокальной моторной нейропатии (ММН) и мультифокальном варианте хронической воспалительной демиелинизирующей полинейропатии (мХВДП), усложняют проведение дифференциального диагноза между этими двумя хроническими дизиммунными нейропатиями, терапевтическая тактика которых существенно различается. Отсутствие отличительных специфических параклинических маркёров зачастую приводит к ошибочному суждению о диагнозе и выбору неэффективной патогенетической терапии. Актуален прицельный поиск внутригрупповых нейровизуализационных различий.*

Цель *исследования: определить нейровизуализационные дифференциально-диагностические маркеры при ММН и мХВДП.*

Материалы и методы. *В исследование были включены 65 пациентов: 30 – с диагнозом ММН и 35 – с диагнозом мХВДП, наблюдающиеся в Центре заболеваний периферической нервной системы ФГБНУ «Научный центр неврологии». Проведены ретроспективный анализ клинико-эпидемиологических характеристик пациентов, сонографическое и магнитно-резонансное (МРТ) обследования.*

Результаты. *У пациентов с мХВДП по сравнению с ММН при УЗИ длинных периферических нервов рук, спинномозговых нервов и стволов плечевых сплетений отмечены значимо бóльшие величины площади поперечного сечения и частота регистрации интраневральных сонографических изменений. С помощью ROC-анализа определены пороговые величины площади поперечного сечения срединного нерва, значимые для дифференциальной диагностики ММН и мХВДП. В 41,4% случаев у пациентов с ММН МРТ-картина исследования плечевых сплетений была сопоставима с нормой, при мХВДП патологические изменения не выявлены в 27,3% случаев. При этом наличие STIR-гиперинтенсивного сигнала от плечевых сплетений наиболее характерно для пациентов с мХВДП и встречалось более чемв 70% случаев.*

Заключение. *В ходе настоящего исследования впервые в России на большой выборке пациентов проведён детальный сравнительный анализ данных нейровизуализационных методов исследования у пациентов с ММН и мХВДП; определены сонографические дифференциально-диагностические маркеры, показаны преимущества и ограничения ультразвукового и МРТ-исследований плечевых сплетений, спиномозговых и периферических нервов в диагностике мультифокальных хронических дизиммунных нейропатий.*

Ключевые слова: *мультифокальная моторная нейропатия; мультифокальный вариант хронической воспалительной демиелинизирующей полинейропатии; ультразвуковое исследование периферических нервов; магнитно-резонансная томография плечевых сплетений; дизиммунные нейропатии*

Этическое утверждение. Исследование проводилось при добровольном информированном согласии пациентов. Протокол исследования одобрен Этическим комитетом Научного центра неврологии (протокол № 10-4/21 от 17.11.2021).

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

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

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Introduction

Similar asymmetric patterns of motor disorders and neurophysiological changes complicate the differential diagnosis between multifocal motor neuropathy (MMN) and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) as two chronic dysimmune neuropathies (CDNs) with significantly different treatment approaches [1, 2]. Despite continuous improvement of the chronic inflammatory demyelinating polyneuropathy (CIDP) and MMN diagnostic criteria, the lack of specific paraclinical markers result in misdiagnosis and selection of ineffective specific therapy [1–3].

The significance of neuroimaging, namely ultrasonography (USG) and magnetic resonance imaging (MRI) of peripheral nerves and brachial plexus (BP), for CIDP diagnosis has been demonstrated [4–6]. However, possible use of the methods for differential diagnosis between MMN and MADSAM and their interchangeability are still being discussed.

Objective: To identify neuroimaging markers for the differential diagnosis between MMN and MADSAM.

Materials and methods

The study included individuals with MMN (n = 30) and with MADSAM (n = 35), followed up in the Center of Peripheral Nervous System Diseases, Research Center of Neurology, Moscow, Russia.

Inclusion criteria:
- age > 18 years;
- CIDP diagnosed according to the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) 2021 diagnostic criteria;
- MMN diagnosed according to EFNS/PNS 2010 diagnostic criteria;
- signed informed consent to participate in the study.

Exclusion criteria:
- age < 18 years;
- the diagnosis did not comply with MMN or CIDP diagnostic criteria;
- contraindications for USG and MRI;
- decompensated severe medical conditions;
- patient refused to provide an informed consent.

We retrospectively analyzed clinical and epidemiological characteristics of the participants (sex, age at onset and enrollment, disease duration, and onset-to-treatment duration).

USG was performed in B mode with 4–18 MHz frequency on PhilipsElite scanner with a linear probe. We assessed long peripheral nerves of the upper extremities (median, ulnar, and radial nerves) at 23 points bilaterally and BPs in 7 areas bilaterally. At each point, we measured the nerve cross-sectional area (CSA) either elliptically or, in irregular cross section, manually along the internal hyperechoic nerve border. We considered CSA parameters published by A. Kerasnoudis et al. [7] and A. Grimm et al. [8]. At each point, we also evaluated intraneural abnormalities classified according to L. Padua et al. [9].

MRI scan was performed under the standard protocol with 3T induction by Magnetom Siemens Prisma. We used high-resolution STIR 3D sequence to measure slice thickness and signal intensity (TR = 3000 msec, TE = 281 msec, TI = 230 msec, reconstructed voxel size 0.4 × 0.4 × 0.9 mm, FOV = 350 mm, number of slices 144, scan time 7 min 27 sec). In each participant, we measured thickness of C4–C7 (N5–N7) anterior branches equidistantly from the ganglia on both sides and at maximum and used the highest result for statistical analysis. We also assessed BP MR signal intensity qualitatively at the entire visible level. MRI assessment was based on EAN/PNS guidelines (2021), with threshold coronary thickness of 5 mm. This paper presents an assessment of this parameter (thickened or not) based on the generally accepted reference. In addition, we performed a qualitative assessment of MRI signal intensity (hyperintense/not hyperintense) from BPs, based on the clinical radiologist's experience, without using quantitative methods.

Statistical analysis was performed using SPSS Statistics 23.0 (IBM). We used paired tests for all comparisons. Distribution of quantitative data was estimated using frequency histogram analysis. Quantitative variables were described using medians (Me), quartiles [Q1; Q3], means, and standard deviations (in Gaussian distribution), while categorical variables were described using frequencies and percentages.

We used independent samples t-test to compare two independent data groups by quantitative variables in Gaussian distribution and Mann–Whitney U test to compare them in non-Gaussian distribution. We used Pearson's χ^2 test to compare two independent data groups by categorical variables and Fisher's exact test under constraints. We performed ROC analysis to assess the possible use of median nerve CSA as a diagnostic marker. We determined optimal thresholds with the Youden's index calculated as sensitivity and specificity sum minus 1.

Results

The study included 65 participants, particularly 30 individuals, of them 12 (40%) women and 18 (60%) men aged 34–68 (Me = 49.0 [41.0, 56.0]), with MMN (Group 1) and 35 individuals, of them 9 (25.7%) women and 26 (74.3%) men aged 25–78 (Me = 52.0 [40.0, 61.0]), with MADSAM (Group 2) (Table 1). No gender or age differences was documented. The disease duration was significantly higher in the MMN population than in the MADSAM population (p = 0.001). Both groups included pre-treated and treat-

Table 1. Epidemiological, clinical and medical history data of patients included in the study

Characteristic		Patients with MMN	Patients with MADSAM	*p*
Number of participants		30	35	–
Sex	male. *n* (%)	18 (60.0%)	26 (74.3%)	0.290
	female. *n* (%)	12 (40.0%)	9 (25.7%)	
Enrollment age. years	*M* ± *SD*	49.7 ± 10.1	51.5 ± 12.4	0.519
	Me [Q_1; Q_3]	49.0 [41.0; 56.0]	52.0 [40.0; 61.0]	
Disease duration. years	Me [Q_1; Q_3]	10.0 [7.0; 13.0]	6.0 [4.0; 8.0]	0.001

ment-naive patients. The MMN group included 24 (80%) pre-treated individuals and 6 (20%) treatment-naive patients, while the MADSAM group included 20 (57%) pre-treated individuals and 15 (43%) treatment-naive patients.

Comparative evaluation of USG findings on the long peripheral nerves of the upper extremities in patients with MMN and MADSAM

Comparative evaluation of USG findings at 23 points on each side of the long peripheral nerves of the upper extremities revealed intergroup differences in 34 (73.9%) of 46 possible points with a threshold significance < 0.05. Therefore, the significance threshold was elevated to 0.005, which enabled us to decrease the number of the points with statistically significant intergroup differences to 12 (26%) (Table 2).

Compared to the patients with MMN, the mean unilateral CSA of the median nerve in the patients with MADSAM was significantly higher at the antecubital fossa, the lower and upper brachium thirds, and bilaterally in the axillary area ($p < 0.005$). Ulnar nerve imaging demonstrated similar changes at the upper antebrachium third, the brachium, and in the axillary area unilaterally ($p < 0.005$), while radial nerve imaging showed them at the middle and upper brachium thirds unilaterally ($p < 0.005$; Table 2).

Considering that intergroup difference was most often found in the median nerve at various levels, we performed ROC analysis to evaluate the possible use of the median nerve CSA for differential diagnosis between MMN and MADSAM. We took the models with area under the ROC curve (AUC) > 0.700 into account. The CSA thresholds of the median nerve, assessed unilaterally and significant for the differential diagnosis between MMN and MADSAM, in favor of the latter, were the following:

- ⩾ 8.10 mm² at the lower antebrachium third (AUC = 0.741, sensitivity 74%, specificity 73%; Fig. 1, *A*);
- ⩾ 7.25 mm² at the upper antebrachium third (AUC = 0.766, sensitivity 71%, specificity 70%; Fig. 1, *B*);
- ⩾ 9.9 mm² at the antecubital fossa (AUC = 0.731, sensitivity 63%, specificity 73%; Fig. 1, *C*);
- ⩾ 11.65 mm² at the lower brachium third (AUC = 0.712, sensitivity 71%, specificity 70%; Fig. 1, *D*);
- ⩾ 12.55 mm² at the upper brachium third (AUC = 0.707, sensitivity 71%, specificity 77%; Fig. 1, *E*);
- ⩾ 12.6 mm² in the axillary area (AUC = 0.760, sensitivity 71%, specificity 70%; Fig. 1, *F*);

USG changes were asymmetric in both groups as expected with the pathophysiology and the clinical characteristics of the studied CDNs.

Comparative evaluation of the USG patterns of intraneural changes in the assessed arm points based on L. Padua's classification demonstrated that the above changes were significantly more often revealed in the patients with MADSAM though only in isolated MMN cases. So, in the MADSAM patients, class 1/2 intraneural changes (enlarged CSAs, enlarged single fascicules) were significantly more often revealed on the medial nerves at the antecubital fossa ($p = 0.003$), at the lower brachium third ($p = 0.012$), and in the axillary area ($p = 0.019$); on the ulnar nerves in the lower (right: $p = 0.013$; left: $p = 0.007$) and middle ($p = 0.008$) brachium third and in the axillary area ($p = 0.003$); and on the radial nerves in the middle ($p = 0.013$) and upper ($p = 0.017$) brachium thirds.

Thus, USG of the long peripheral nerves of the upper extremities showed a significantly larger CSA and a higher incidence of documented intraneural USG abnormalities in the patients with MADSAM than in the MMN patients. We determined significant thresholds of the median nerve CSA at various levels for differential diagnosis between MMN and MADSAM.

Comparative evaluation of USG findings of the spinal nerves and the BPs in patients with MMN and MADSAM

USG detected enlarged diameters of the spinal nerves and BP trunks in 26 (87%) patients with MMN and 32 (94%) patients with MADSAM, including unilateral ones in 6 (23%) of 26 patients with MMN and 3 (9%) of 32 patients with MADSAM (Fig. 2).

As compared to the patients with MMN, the mean unilateral diameters of the spinal nerves and CSAs of the BP

Table 2. Comparative evaluation of USG findings on the long peripheral nerves of the upper extremities in patients with MMN and MADSAM, mm² (Me [Q_1; Q_3])

Nerve and assessment level			Reference CSAs	Side	Patients with MMN	Patients with MADSAM	*p*
Peripheral nerves	Median nerve	radiocarpal joint	< 10	Right	8.35 [7.50; 9.70]	8.90 [7.30; 11.30]	0.598
			< 10	Left	8.45 [7.50; 9.90]	9.30 [7.90; 10.30]	0.298
		antebrachium lower third	< 10	Right	7.45 [6.30; 8.70]	8.60 [7.00; 10.10]	0.120
		antebrachium lower third	< 10	Left	6.60 [5.80; 8.50]	9.30 [7.80; 11.10]	0.001
		antebrachium middle third	< 10	Right	6.75 [6.00; 8.20]	7.70 [6.70; 10.70]	0.011
		antebrachium middle third	< 10	Left	7.45 [6.30; 8.80]	8.90 [7.10; 12.40]	0.036
		antebrachium upper third	< 10	Right	6.35 [5.20; 7.40]	8.70 [6.70; 13.20]	< 0.001
		antebrachium upper third	< 10	Left	7.50 [6.10; 9.20]	9.10 [6.70; 12.20]	0.039
		antecubital fossa	< 12.5	Right	8.30 [7.10; 10.70]	11.00 [8.10; 13.30]	0.006
			< 12.5	Left	8.10 [6.90; 10.10]	12.20 [7.90; 16.60]	0.001
		brachium lower third	< 12	Right	11.00 [9.00; 15.20]	13.70 [9.80; 20.00]	0.040
		brachium lower third	< 12	Left	10.75 [8.60; 12.30]	14.30 [11.30; 23.00]	0.003
		brachium middle third	< 12	Right	12.50 [9.10; 15.20]	14.30 [10.10; 20.30]	0.069
		brachium middle third	< 12	Left	10.70 [8.70; 12.80]	13.80 [9.80; 20.10]	0.006
		brachium upper third	< 12	Right	11.10 [9.80; 12.40]	14.70 [12.10; 20.40]	0.004
		brachium upper third	< 12	Left	10.55 [9.70; 12.60]	13.70 [8.70; 19.80]	0.035
		axillary fossa	< 12	Right	12.05 [10.20; 15.30]	17.10 [12.30; 26.70]	0.004
			< 12	Left	10.30 [9.10; 13.10]	16.60 [11.10; 22.20]	< 0.001
	Ulnar nerve	radiocarpal joint	< 6	Right	5.35 [4.30; 6.60]	5.40 [4.60; 6.70]	0.693
			< 6	Left	5.30 [4.20; 6.30]	6.10 [5.20; 6.90]	0.053
		antebrachium lower third	< 8.5	Right	6.10 [4.70; 6.90]	6.60 [4.90; 7.60]	0.241
		antebrachium lower third	< 8.5	Left	5.40 [4.70; 6.60]	6.60 [5.30; 8.90]	0.015
		antebrachium middle third	< 8.5	Right	6.30 [5.30; 7.50]	7.60 [5.50; 9.00]	0.047
		antebrachium middle third	< 8.5	Left	6.00 [5.10; 6.70]	6.90 [5.30; 10.70]	0.033
		antebrachium upper third	< 8.5	Right	6.00 [5.20; 8.30]	7.10 [5.80; 8.70]	0.107
		antebrachium upper third	< 8.5	Left	5.90 [5.10; 7.00]	7.50 [6.30; 10.00]	0.001

End of the Table 2.

Nerve and assessment level				Reference CSAs	Side	Patients with MMN	Patients with MADSAM	*p*
Peripheral nerves	Ulnar nerve	antecubital fossa		< 10	Right	8.15 [6.70; 11.00]	9.30 [7.10; 10.40]	0.608
				< 10	Left	8.35 [6.20; 9.50]	9.80 [6.80; 12.00]	0.016
		brachium	lower third	< 9.5	Right	7.65 [6.50; 9.30]	9.90 [6.80; 15.20]	0.024
		brachium	lower third	< 9.5	Left	7.40 [5.80; 9.60]	8.70 [7.10; 13.00]	0.017
		brachium	middle third	< 9.5	Right	8.40 [6.70; 9.20]	10.70 [7.30; 14.40]	0.045
		brachium	middle third	< 9.5	Left	8.40 [6.30; 10.60]	9.90 [6.80; 13.30]	0.100
		brachium	upper third	< 9.5	Right	7.60 [6.30; 9.80]	10.90 [7.70; 15.60]	0.003
		brachium	upper third	< 9.5	Left	8.10 [7.00; 9.10]	10.10 [7.80; 13.70]	0.007
		axillary fossa		< 9.5	Right	7.75 [6.40; 11.00]	11.60 [7.90; 17.90]	0.002
				< 9.5	Left	8.55 [6.60; 9.80]	10.80 [8.10; 17.20]	0.008
	Radial nerve	antecubital fossa			Right	6.70 [5.00; 7.80]	8.60 [5.70; 10.10]	0.010
					Left	8.10 [6.00; 11.40]	9.70 [7.40; 12.00]	0.041
		brachium	lower third	< 3	Right	6.80 [5.40; 8.40]	8.30 [5.70; 9.20]	0.111
		brachium	lower third	< 3	Left	7.30 [5.60; 8.40]	8.10 [6.30; 11.20]	0.067
		brachium	middle third	< 3	Right	6.30 [5.00; 8.10]	7.70 [5.50; 10.50]	0.039
		brachium	middle third	< 3	Left	6.00 [5.30; 7.40]	8.60 [6.30; 11.00]	0.002
		brachium	upper third	< 3	Right	7.85 [6.10; 9.90]	9.40 [7.90; 14.20]	0.004
		brachium	upper third	< 3	Left	7.70 [6.40; 8.90]	9.60 [7.10; 13.30]	0.044
		axillary fossa			Right	7.80 [6.70; 10.70]	10.80 [7.00; 16.10]	0.031
					Left	7.75 [6.70; 10.30]	9.60 [8.20; 15.30]	0.006

trunks were statistically significantly larger in the MADSAM population (Table 3). USG revealed significant differences of the mean CSAs at the middle and lower BP trunks unilaterally and in the cross-scanned supraclavicular fossa ($p < 0.01$).

Thus, USG of the spinal nerves and the BP trunks revealed significantly larger diameters and CSAs respectively in the patients with MADSAM than in those with MMN.

Comparative evaluation of BP MRI findings in the patients with MMN and MADSAM

BP MRI was conducted in 29 patients with MMN and 33 patients with MADSAM. The most common reason for refusal was claustrophobia (i.e. a fear of confined spaces). BP MRI findings were apparently normal in 41.4% of the patients with MMN and no changes were found in 27.3% of the patients with MADSAM (Table 4). Enlarged BP trunks were detected with the same frequency in both groups ($p > 0.05$). Documented in 70% of the cases, STIR hyperintense BP signal was more typical for the patients with MADSAM.

Qualitative evaluation showed several changed BP trunk patterns in the assessed sample:

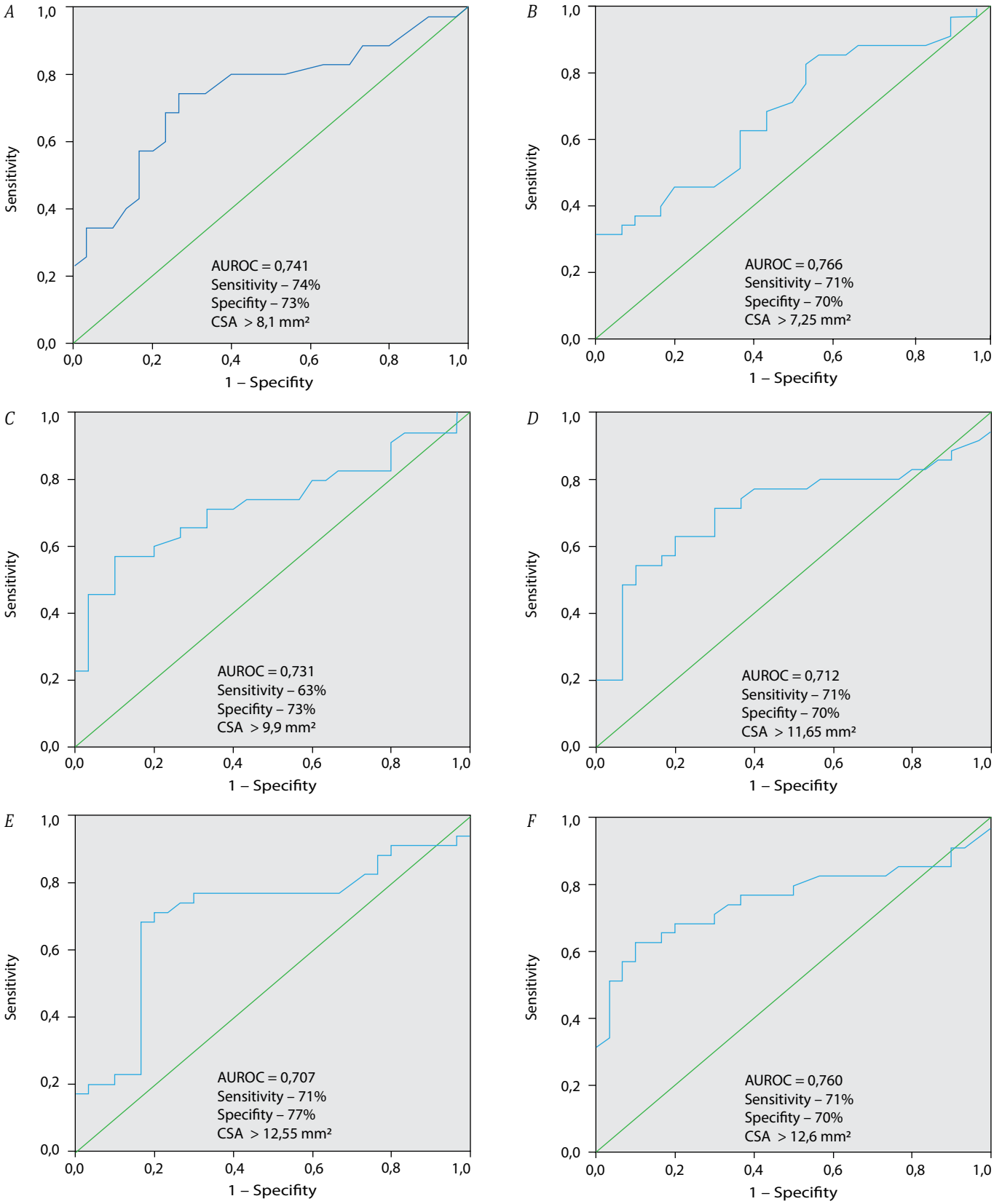

Fig. 1. ROC analysis of the significance of the median nerve CSA at various levels for the differential diagnosis between MMN and MADSAM.

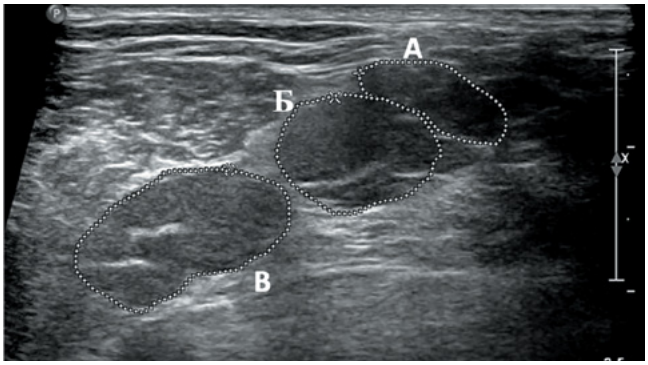

Fig. 2. USG of BP trunks in a patient with MADSAM (8-year follow-up history, pre-therapy assessment).
In the cross section, three primary trunks are seen in the scalene part, with enlarged upper (⩽ 33.6 mm²; *A*), middle (⩽ 68.9 mm²; *B*), and lower (⩽ 94.8 mm²; *C*) primary trunks (reference < 8 mm²).

- significant symmetric bilateral diffuse BP thickening in 10 (34.5%) patients with MMN and 17 (51.5%) patients with MADSAM (Fig. 3);
- asymmetric diffuse BP thickening in 3 (10.3%) patients with MMN and 2 (6%) patients with MADSAM (Fig. 4);
- local BP thickening in 4 (13.8%) patients with MMN and 5 (15.2%) patients with MADSAM (Fig. 5);
- isolated hyperintense STIR MRI signal without enlarged BP trunks in 5 (17.2%) patients with MMN and 6 (18.2%) patients with MADSAM (Fig. 6)

Therefore, qualitative evaluation of the BP MRI findings demonstrated rather uniform changes that did not differentiate reliably between MADSAM and MMN.

Discussion

N. Taniguchi et al. were first to describe a CIDP USG pattern [10]. Routine thyroid USG found thickened peripheral nerves and BP proximal parts in a patient with a 3-year follow-up CIDP history [10]. Being widely available and non-invasive, peripheral nerve USG was then further investigated in a cohort of patients with polyneuropathies of various origin.

First studies were conducted in limited samples. In 2004, N. Matsuoka et al. assessed 13 patients with CIDP and documented enlarged cervical nerves in 69% cases [11]. In 2009, C. Zaidman et al. assessed 36 patients with CIDP, found over 2-fold diffusely enlarged median and ulnar nerves as compared to controls, and discovered direct correlation between the USG pattern and disease duration, with inverse correla-

Table 3. Comparative evaluation of USG findings of the spinal nerves and the BPs in patients with MMN and MADSAM, Me [Q_1; Q_3]

Assessed level		Side	Patients with MMN	Patients with MADSAM	*p*
Spinal nerves. mm	C5	Right	8.15 [7.50; 9.40]	9.30 [8.20; 14.80]	0.022
Spinal nerves. mm	C5	Left	8.65 [7.30; 11.20]	10.20 [7.00; 16.70]	0.171
Spinal nerves. mm	C6	Right	11.40 [9.00; 17.70]	14.70 [10.00; 20.50]	0.134
Spinal nerves. mm	C6	Left	12.60 [9.50; 14.50]	14.20 [11.90; 26.60]	0.023
Spinal nerves. mm	C7	Right	10.75 [9.40; 16.40]	13.50 [10.90; 19.80]	0.040
Spinal nerves. mm	C7	Left	13.20 [9.60; 15.70]	15.60 [12.00; 27.20]	0.039
BP trunk CSA. mm²	upper trunk (*n* < 8)	Right	7.80 [6.20; 11.10]	9.80 [7.10; 15.60]	0.124
BP trunk CSA. mm²	upper trunk (*n* < 8)	Left	7.15 [5.40; 11.60]	11.00 [6.90; 21.30]	0.069
BP trunk CSA. mm²	middle trunk (*n* < 8)	Right	12.10 [9.30; 15.70]	16.50 [11.20; 26.10]	0.040
BP trunk CSA. mm²	middle trunk (*n* < 8)	Left	10.25 [8.40; 15.90]	16.70 [11.70; 29.10]	0.009
BP trunk CSA. mm²	lower trunk (*n* < 8)	Right	12.05 [9.10; 14.70]	15.40 [10.10; 20.80]	0.095
BP trunk CSA. mm²	lower trunk (*n* < 8)	Left	13.25 [9.90; 15.30]	17.50 [11.70; 26.50]	0.004
Supraclavicular fossa CSA. mm²		Right	66.15 [58.80; 98.00]	83.50 [66.20; 115.00]	0.024
Supraclavicular fossa CSA. mm²		Left	70.35 [54.90; 90.60]	101.0 [74.60; 125.00]	0.002

Table 4. Comparative evaluation of BP and spinal nerve MRI changes in the patients with MMN and MADSAM, *n* (%)

Characteristic		Side	Patients with MMN	Patients with MADSAM	*p*
Enlarged BP trunks	upper trunk	Right	9 (31.0%)	16 (48.5%)	0.200
Enlarged BP trunks	upper trunk	Left	8 (27.6%)	17 (51.5%)	0.072
Enlarged BP trunks	middle trunk	Right	13 (44.8%)	20 (60.6%)	0.308
Enlarged BP trunks	middle trunk	Left	13 (44.8%)	20 (60.6%)	0.308
Enlarged BP trunks	lower trunk	Right	13 (44.8%)	18 (54.5%)	0.611
Enlarged BP trunks	lower trunk	Left	12 (41.4%)	17 (51.5%)	0.456
STIR hyperintense BP signal (total)		Right	16 (55.2%)	24 (72.7%)	0.188
STIR hyperintense BP signal (total)		Left	14 (48.3%)	27 (81.8%)	0.007
STIR hyperintense BP signal without enlarged BP trunks		–	5 (17.2%)	6 (18.2%)	1.000
No changes		–	12 (41.4%)	9 (27.3%)	0.289

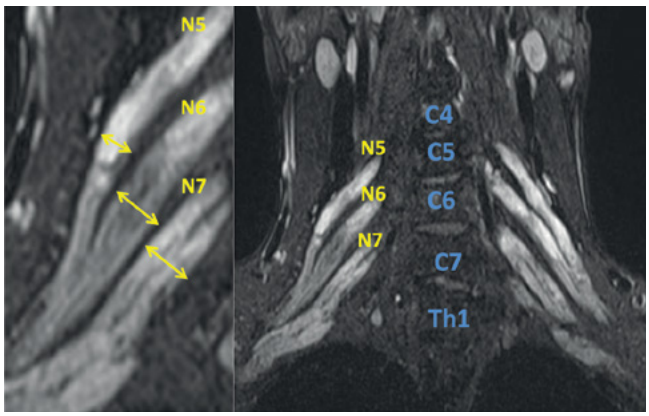

Fig. 3. MRI of BPs in a MMN patient (13-year follow-up history; assessed on maintenance therapy: intravenous immunoglobulin 1 g/kg every 4 weeks).
The coronal STIR MRI showed significant (⩽ 8 mm) bilateral uniform symmetric BP thickening, with hyperintense signal.

tion between assessed peripheral nerve CSA and motor fiber conduction velocity [12]. Several studies were limited as small case series with an idea to establish correlation between enlarged peripheral nerve CSA on one hand and CIDP and MMN symptom severity, electroneuromyographical conduction blocks, and response to specific therapy on the other hand [13–18]. There were no reliable evidence that USG and electoneuromyography abnormalities correlate with neurological deficit distribution and severity [19, 20]. A number of studies showed that the peripheral nerve CSA is smaller in relapsing disease than in progressive disease [16]. Besides, the patients with peripheral nerve CSAs that exceed reference values and with hypoechoic USG signal tended to be better responders to specific treatment than those without any enlarged CSA and with hyperintense USG signal [9, 21].

L. Padua et al. established enlarged CSAs and described three patterns of intraneural USG abnormalities in patients with CIDP: the thickened nerve with hypoechoic fascicules (Class 1); the thickened nerve with hypo- and hyperechoic fascicules (Class 2); the normal nerve CSA with the hyperechoic signal (Class 3) [9].

Further research was aimed at developing USG protocols for differential diagnosis between polyneuropathies of various origin with disease follow-up [17, 22–25]. Particularly, the S. Goedee et al., showed that the median nerve CSA enlarged at the antebrachium > 13 mm^2 and at the brachium > 10 mm^2 as well the enlarged CSA of any BP bundle > 8 mm^2 is 99% specific for CIDP diagnosis [4].

Additionally, D.S. Druzhinin et al. obtained noteworthy findings by peripheral nerve USG in patients with MMN (n = 13) and CIDP (n = 7) [26]. They showed that similarly enlarged BP and peripheral nerve CSAs were detected in both CIDPs, while asymmetric USG changes were more typical for patients with MMN and symmetric and diffuse changes were seen in those with CIDP.

In 2021, as a result of 20-year retrospective analysis of accumulated data, EAN and PNS recognized peripheral nerve USG as a significant supportive modality of CIDP diagnosis [1]. The MMN criteria have not included USG yet [2].

MR neuroimaging traces back to the early 1990s. First publications were focused on the MRI of the cauda equina [27–29]. In 1997, the Netherlandic clinicians were first to demonstrate BP MRI diagnostic performance in patients with DNs [30].

A study published in 1999 included 14 patients with CIDP

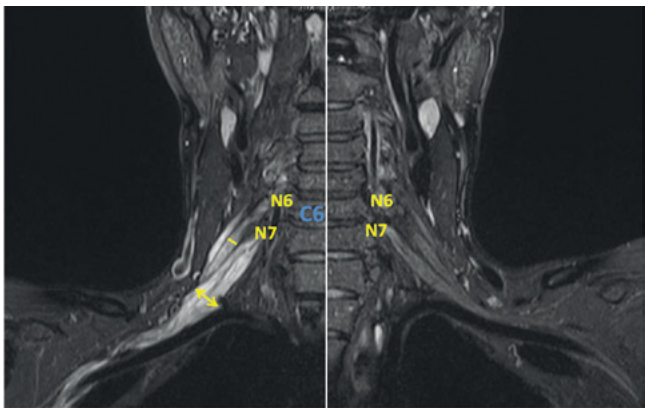

Fig. 4. MRI of BPs in a MADSAM patient (6-year follow-up history; assessed on maintenance therapy: intravenous immunoglobulin 1 g/kg every 12 weeks for 2 years).
The coronal STIR MRI showed right-sided significant (⩽ 12 mm) diffuse N7 thickening, with hyperintense signal. Hyperintense MRI signals from other right-sided BP elements were registered at the entire visible level with unchanged thickness. No changes on the left side.

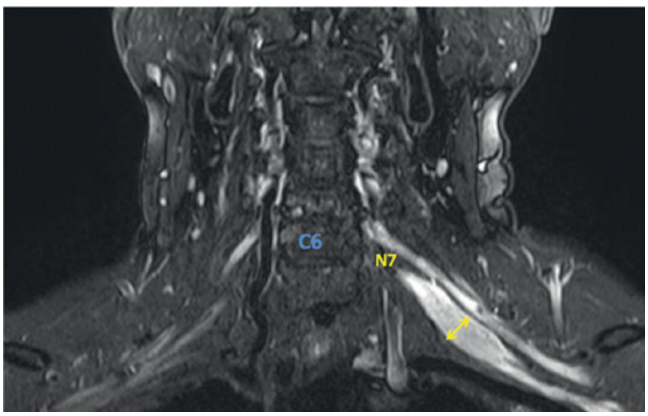

Fig. 5. BP MRI in a MMN patient (10-year follow-up history, pre-therapy assessment).
The coronal STIR MRI showed left-sided local N7 (⩽ 11 mm) primary trunk thickening, with hyperintense signal. Thickness of other BP elements remained unchanged; however, hyperintense MRI signal was registered bilaterally.

[31]. Brachial and lumbar plexus MRI showed enlarged BPs in 8 (57%) patients and enlarged lumbar plexus in 6 (43%) patients. Further, enhanced MRIs revealed signal hyperintensity in 5 patients with hypertrophic plexus and 1 patient without any signs of hypertrophy for researchers to conclude contrast agent accumulation directly depended on disease activity [31].

Currently the use of an intravenous contrast agent in MR neuroimaging has lost its diagnostic value and might be utilized in few peripheral nerve abnormalities (primary masses, metastases) [32]. Sequences that suppress fat signals (e.g. STIR) have become methods of choice to assess changed peripheral nerves. With good signal/noise ratios (SNRs), optimal contrast parameters, and sufficient spatial resolution ob-

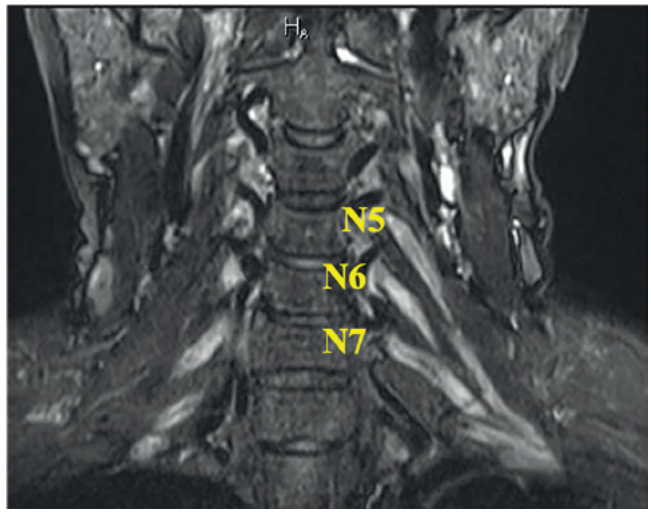

Fig. 6. MRI of BPs in a MADSAM patient (6-year follow-up history; assessed during 2-year glucocorticosteroid therapy).
Hyperintense STIR MRI signal bilaterally at the entire visible level without any thickened BP trunks.

tained on modern high-field (⩾ 1.5T) scanners, we can obtain high-quality selective images of tiny or tortuous structures, minimize respiration and vasculature/musculature artifacts, and come closer to BP qualitative description and DN differential diagnosis [33].

Thus, USG and MRI have been shown to provide accurate information for the diagnosis of CDN. However, intra-group neuroimaging differences are still a current target. Thus, the differential diagnosis between two multifocal CDNs, MMN and MADSAM, remains a challenging issue.

Unlike D.S. Druzhinin et al. [26], we complicated our task with comparison of MMN and multifocal (atypical) CIDP, having increased the number of patients and adding MRI findings.

We demonstrated that mean nerve CSAs in the MADSAM group were larger than those in the MMN group. Established USG patterns must be based on relevant CDN underlying mechanisms including demyelination and, as a consequence, more apparent edema of the peripheral nerves in the patients with MADSAM and affected though less edematic nodal and paranodal areas of the nerve trunks in the patients with MMN.

Like H.S. Goedee et al. [4], we found that it is the median nerve, particularly its proximal part (above the antecubital fossa), that it is the most diagnostically informative among three upper-extremity peripheral nerves including the median, ulnar, and radial nerves. We were first to conduct ROC analysis and calculate median nerve CSAs in the assessed levels that can be used for differential diagnosis between the investigated CDNs. Noteworthily, sensitivity and specificity of the obtained CSA thresholds varied, depending on the assessed points and

the side. Therefore, AUC [95% confidence interval] was < 0.7 in the median-nerve CSA ROC model for the antebrachium and brachium middle thirds. However, these points constitute the basis of the Ultrasound Pattern Sum Score [22] and the abbreviated ultrasound protocol [4] widely used for the diagnosis of dysimmune neuropathies. Considering these results, we recommend broadening the scope of assessment with antebrachium and brachium lower and upper thirds for MMN and MADSAM differential diagnosis.

USG typically revealed full-length thickened peripheral nerves in the patients with MADSAM and mostly asymmetrically changed segments in the patients with MMN, which was described above [26, 34, 35].

Spinal nerve and BP MRI did not demonstrate any significant differences between the patients with MMN and MADSAM. Furthermore, MRI BP qualitative characteristics (thickened or not; STIR-hyperintense signal or not) have a low diagnostic value in patients with CDN, especially with non-pronounced changes. In USG, qualitative analysis is cheaper and enables us to assess changes quantitatively (as diameters and CSAs) unlike that in MRI. Therefore, further research should focus on the determination of quantitative MRI-parameters and evaluation of their significance for differential diagnosis between multifocal CDNs.

As demonstrated earlier, combined USG and MRI increased diagnostic value of both methods up to 83% in patients with MADSAM while, according to the authors, the methods are substitutable [4]. Our study showed that the patients with normal peripheral-nerve CSAs on USG can demonstrate only isolated hyperintense MRI signal from the BP trunks in the STIR mode (2/29 [6.9%] in the MMN population, 1/33 [3.0%] in the MADSAM population), which can indirectly indicate CDN.

Conclusion

This is the first study in Russia's that provided a detailed comparison of neuroimaging findings obtained in a large sample of patients with MMN and MADSAM; determined ultrasonographic markers for differential diagnosis; and demonstrated advantages and limitations of USG and MRI of BPs, spinal and peripheral nerves in the diagnosis of multifocal chronic dysimmune neuropathies.

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Changes in Clinical and Network Functional Connectivity Parameters in Motor Networks and Cerebellum Based on Resting-State Functional Magnetic Resonance Imaging Data in Patients with Post-Stroke Hemiparesis Receiving Interactive Brain Stimulation Neurotherapy

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Abstract

Introduction. *Interactive brain stimulation (IBS) neurotherapy is an advanced neurofeedback technology (NFB) that involves the organization of a feedback "target" based on signals recorded by functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). The NFB allows patients to volitionally self-regulate their current brain activity and may therefore be a useful treatment option for diseases with altered activation and functional connectivity (FC) patterns.*

Our ***objective*** *was to assess the effects of IBS on the FC changes in motor networks and correlations between clinical and network parameters in patients with post-stroke hand paresis.*

Materials and methods. *Patients with a history of stroke < 2 months were randomized into a main group (n = 7) and a control group (n = 7). All the patients followed the stroke physical rehabilitation for 3 weeks. The main group received IBS training, where the patients learned to imagine movements of the paretic hand trying to amplify the fMRI signal from the primary motor cortex (M1) and the supplementary motor area (SMA) on the lesion side with simultaneous desynchronizing the μ- and β-2 EEG rhythms in the central leads. Clinical tests and MRI were performed prior to and immediately after the treatment. FC matrices were constructed using CONN software based on resting-state fMRI data.*

Results. *By the end of the training, M1–M1 functional connectivity in the control group weakened, while no changes were observed in the main group. The FC strength was positively correlated with the grip strength ($\rho = 0.69$; $p < 0.01$) and with the results of the Box and Blocks test (BBT score, $\rho = 0.72$; $p < 0.01$) and the Fugl-Meyer assessment for upper extremity (FM-UE score, $\rho = 0.87$; $p < 0.005$). Ipsilesional SMA connectivity with contralesional cerebellum weakened ($p < 0.05$ in the main group). Its strength was negatively correlated with the BBT and FM-UE scores (both tests $\rho = -0.44$; $p < 0.05$).*

Conclusions. *Volitional control of M1 and SMA activity in the lesion hemisphere during the post-stroke IBS training alters the architecture of the entire motor network affecting clinically significant FC types. We studied a possible mechanism of this technology and its potential use in treatment programs.*

Keywords: *interactive brain stimulation neurotherapy; neurofeedback; stroke rehabilitation; motor cerebral networks; functional connectivity*

Ethics approval. The study was approved by the Ethics Committee of Federal Research Center of Fundamental and Translational Medicine (protocol No. 8 dated March 15, 2021), all the patients signed informed consent prior to treatment.

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Клинико-сетевая динамика функциональных связностей моторной сети и мозжечка по данным функциональной магнитно-резонансной томографии покоя у пациентов с постинсультным гемипарезом в курсе интерактивной терапии (стимуляции) мозга

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Аннотация

Введение. *Интерактивная терапия (стимуляция) мозга (ИСМ) – это развитие технологии нейробиоуправления (НБУ), предполагающее организацию обратной связи по сигналам функциональной магнитно-резонансной томографии (фМРТ) и электроэнцефалографии. НБУ позволяет испытуемым произвольно регулировать текущую мозговую активность и потому может быть полезным лечебным инструментом при заболеваниях с изменёнными паттернами активации и функциональных связностей (ФС).*

Цель *исследования – оценить влияние ИСМ на динамику ФС моторной сети и клинико-сетевые корреляции у больных с постинсультным парезом руки.*

Материалы и методы. *Больные с инсультом давностью до 2 мес рандомизированы в основную (n = 7) и контрольную (n = 7) группы. Все проходили курс физической реабилитации в течение 3 нед; основная группа в курсе ИСМ обучалась воображать движение паретичной руки так, чтобы добиться усиления сигнала фМРТ первичной моторной коры (M1) и дополнительной моторной области (SMA) на стороне поражения с одновременной десинхронизацией μ- и β-2 ритмов электроэнцефалограммы в центральных отведениях. Клинические и МРТ-исследования проводили до и сразу после лечения. Матрицы ФС строили в программе «CONN» по данным фМРТ покоя.*

Результаты. *К концу курса ФС M1–M1 в контрольной группе стала слабее, в основной – не изменилась. Сила её прямо коррелировала с динамометрией ($\rho = 0{,}69$; $p < 0{,}01$), результатом тестов «Box-n-Blocks» ($\rho = 0{,}72$; $p < 0{,}01$) и Фугл-Мейера для руки ($\rho = 0{,}87$; $p < 0{,}005$). Связность ипсилатеральной SMA с противоположным мозжечком ослабла (в основной группе – $p < 0{,}05$); сила её обратно коррелировала с результатом тестов «Box-n-Blocks» и Фугл-Мейера для руки (для обоих $\rho = -0{,}44$; $p < 0{,}05$).*

Заключение. *Волевое управление активностью M1 и SMA поражённого полушария в курсе ИСМ после инсульта меняет архитектуру всей моторной сети, влияя на клинически значимые ФС. Рассматривается возможный механизм действия технологии и перспектива освоения её в лечебных программах.*

Ключевые слова: *интерактивная терапия (стимуляция) мозга; нейробиоуправление; реабилитация после инсульта; моторная церебральная сеть; функциональная связность*

Этическое утверждение. Исследование одобрено локальным этическим комитетом Федерального исследовательского центра фундаментальной и трансляционной медицины (протокол № 8 от 15.03.2021), все пациенты подписали добровольное информированное согласие перед началом процедур.

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Introduction

Modern methods of neuroimaging and statistical analysis expand the possibilities to study the network mechanisms of the brain functioning in general and its plasticity in particular. Studying the effects of stroke lesions on the interactions between distant brain regions is possible using functional connectivity (FC), which is defined as a measure of the temporal correlation of the activation patterns in spatially separated cortex areas. Cerebral network modelling has shown that post-stroke changes in the neural activity are widely distributed throughout the whole brain [1], and cognitive and neurological recovery is associated with restoration of activation patterns and intra- and inter-network connectivity [2–7].

Stroke motor rehabilitation is typically focused on the affected limb, assuming that special exercises and sensory stimulation enhance innate structural and functional neuroplasticity, which compensates for lost functions. However, the existing approaches provide satisfactory rehabilitation results only in 30% of stroke survivors.[8] So, in the search of the ways to control neuroplasticity and to enhance the rehabilitation effects, brain-computer interface technology, namely neurofeedback (NFB) method [9–12] based on ideomotor learning, shows a lot of promise. Movement imagery activates various nodes of the brain's motor system [13], and targeted training in this mental skill helps restore motor function in stroke patients. Feedback on actual changes in the neural ensemble activity makes such training more efficient, enhancing its effects on local neuroplasticity.

Since desynchronization in μ- (8–13 Hz) and β-2 (18–26 Hz) EEG rhythms in central leads indicates the sensorimotor cortex activity, these rhythms are typically used as EEG-NFB targets in post-stroke rehabilitation [14]. However, mapping the activation area based on recordings from the scalp surface is imprecise because it records a cumulative signal from a large number of neurons, which is distorted by the transmission and resistance of the underlying tissues. In this regard, functional magnetic resonance imaging (fMRI) is the most adequate tool for visualizing spots from 1 mm^3, including those located in the deep parts of the brain. The fMRI technology is based on registering miniature magnetic field disturbances that depend on the level of blood oxygenation (blood oxygenation level dependent, BOLD). Activation of neurons is thought to increase local blood flow, a phenomenon known as neurovascular coupling, and alters the ratio of oxyhemoglobin to deoxyhemoglobin in the drainage venules. The BOLD signal amplified by increased oxyhemoglobin concentration is believed to indirectly indicate the activity of specific neural ensembles [15].

The NFB was proposed as a potentially useful tool for post-stroke rehabilitation over a decade ago [16]. Subsequent pilot studies demonstrated that patients can use the real-time fMRI signals to self-regulate the activity of various motor areas [17, 18]. However, the clinical effect and mechanism of this phenomenon are insufficiently studied.

The advancements in the systems for recording and processing electromagnetic signals allowed recording EEG directly in the magnetic field of an MR scanner. So, a new tool for research and rehabilitation emerged. It simultaneously captures electrical (EEG) and hemodynamic (fMRI) neuronal activity signals built in neurofeedback contour, and it serves as the basis for bimodal fMRI-EEG neurofeedback platform [19–21]. We address this NFB method as interactive brain stimulation neurotherapy (IBS) [22–24]. Several studies examined the feasibility of this method for chronic stroke patients [22, 25, 26], its potential for rehabilitation [27], changes in hierarchical communication within the motor networks [28], as well as their functional connections with non-motor structures involved in learning [29].

The objective of our randomized clinical study was to analyze the effects of IBS on FC parameters in motor networks and evaluate the correlations between clinical and network characteristics in patients with hand paresis in the early post-stroke recovery period.

Patients and methods

The study included 14 patients (12 males and 2 females) with middle cerebral artery (MCA) stroke hemiparesis with hand paresis of $\geqslant$ 2 points (Medical Research Council Scale), and onset > 2 weeks and < 2 months, with Montreal Cognitive Assessment (MoCA test) $\geqslant$ 26. The patients were all right-handed and had an average age of 58.6 ± 8.7 years. All the patients were treated at the clinic of the Federal Research Center of Fundamental and Translational Medicine for three weeks. After the screening, they were randomized into the main (n = 7) and the control group (n = 7) in a blinded manner (Table 1). The treatment included massage to the paretic limb, physical therapy, reflex therapy, and therapeutic exercises (axial static load to the articular-ligamentous apparatus and dynamic aimed random movements) 3–5 times a week for 15–20 min depending on the patient's state determined by pulsoxymetrics. Rehabilitation in the main group was supported by 6 IBS sessions, where the patients followed movement imagery training to activate the primary motor cortex (M1) and supplementary motor area (SMA) and desynchronize the μ- (8–13 Hz) and β-2- (18–26 Hz) EEG rhythms in the central leads on the lesion side. The treatment strategy was generally presented as movement imagery training of the paretic limb. Each training session consisted of 16 parts: movement imagery/visual feedback (displayed on a digital scale from 0 to 100)/resting periods of 40/10/20 sec, respectively.

Table 1. Clinical and demographical characteristics of the study participants (n = 14)

Group	Index	Age, years	Gender	Stroke onset, weeks ago	Hemisphere	Lesion site	NIHSS score	Rankin score	MRC prox/ MRC dist*	Grip strength, kg*	BBT*, blocks/min	FM-UE* score	KVIQ vis/kin
Main group	P1	59	M	2	Right	Put; CE; LT	5	3	3/3	20,5	18	46	5/5
	P2	75	M	2	Right	CR; GP	2	3	4/3	21,4	47	44	10/5
	P3	58	M	3	Right	LF; LP	4	3	1/2	24,2	13	14	5/5
	P4	64	M	4	Left	GP	4	2	4/3	27,4	44	56	9/10
	P5	48	M	5	Right	NL; CE; Ins; LF; LP	3	3	4/3	20,6	41	49	8/5
	P6	48	M	2	Left	CR	5	3	3/3	24,6	31	49	8/8
	P7	47	F	4	Right	CR	3	4	4/2	8,8	16	38	15/10
Control group	P8	55	M	6	Left	Put; CE	5	4	1/1	3,7	8	19	21/22
	P9	65	M	2	Left	GP	5	3	4/2	9,1	17	34	5/5
	P10	71	M	6	Right	LF; LP; NB	3	3	3/3	0	8	32	5/5
	P11	55	M	6	Right	LF (lac)	3	3	3/2	8,5	27	34	5/5
	P12	65	M	3	Right	GP	3	3	3/2	1,6	0	38	20/16
	P13	51	F	2	Left	CR	3	3	3/4	14,6	45	55	20/20
	P14	59	M	6	Left	LP	4	3	3/2	14,5	19	32	5/5

Note. M — male; F — female; CE — *capsula externa*; CR — *corona radiata*; GP — *gyrus precentralis*; Ins — *insula*; KVIQ vis/kin Kinaesthetic and Visual Imagery Questionnaire, vis — visual subscale, kin — kinaesthetic subscale; lac — lacunar stroke; LF — *lobus frontalis*; LP — *lobus parietalis*; LT — *lobus temporalis*; MRC — Medical Research Council (MRC) Scale for Muscle Strength; MRC_{dist} — grip strength by MRC scale; MRC_{prox} — deltoid muscle strength by MRC scale; NB — *nuclei basales*; NIHSS — National Institutes of Health Stroke Scale; NL — *nucleus lentiformis*; Put — *putamen*; * — for the affected hand.

The fMRI was performed in the International Tomography Center of the Siberian branch of Russian Academy of Sciences (ITC SBRAS) using Ingenia 3.0T MR system (Philips). A reference anatomical brain image was obtained with T1-TFE sequence, voxel size of $1 \times 1 \times 1$ mm^3. Basic T2*-weighted images were obtained with EPI-FFE sequence (TR/TE = 2500/35 msec, voxel size of $2 \times 2 \times 5$ mm^3). FMRI neurofeedback sessions were supported by parallel EEG recording using BrainAmp128-channel EEG system (Brain Products). To pre-process the real-time fMRI images online, to compute the averaged signal level from the region of interest, and to organise the NFB target, OpenNFT software was used.

Test sessions with clinical assessment and MRI (3D T1 MP-RAGE sequences; resting state fMRI of real and imaginary hand movement) were conducted prior to and after the treatment (test 1 [T1] and test 2 [T2], respectively). Muscle strength was evaluated using Medical Research Council (MRC) Scale, where grade 0 means no movement and grade 5 means full strength, and grip strength dynamometer (normal values for males > 45 kg, for females > 31 kg). To assess motor functioning of the hand the Fugl-Meyer assessment (FM-UE) [30], Box and Blocks test (BBT), and the modified Rankin scale were used [31]. The Kinaesthetic and Visual Imagery Questionnaire (KVIQ-10) [32] was applied for diagnosis and daily self-training of the patients to develop correct and efficient motor imagery strategy.

For offline pre-processing of the results and display of the fMRI images Standard preprocessing pipeline of Matlab-based CONN software was used. The CONN Standard preprocessing pipeline enables functional frame realignment to eliminate motion artifacts, normalize images to the standard MNI brain , to correct motion artifacts, input of white matter and CSF signals profoundly, to remove the pronounced outliers with ASR function, and to smooth the data using isotropic Gaussian kernel. The data obtained from the patients with right-sided paresis were mirrored. FC matrices were generated using CONN toolbox with an a priori set of the regions of interest [23]: SMA, M1, and cerebellum (Cer) bilaterally. The FC matrices generated with the resting state fMRI data were compared within and between the groups using the Student's t-test. To identify general trends in the changes of clinical test results and FC parameters, Spearman's rank correlation coefficient was applied. Clinical data was computed in Microsoft Excel and Statistica v. 12.0 using descriptive statistics. To characterize the groups, median values (Me), 25th and 75th percentiles, mean values (M), and standard deviation (σ) were calculated. The groups were compared using the Mann–Whitney U test and the Pearson's χ^2 test. The intragroup changes of parameters were assessed using the Wilcoxon signed-rank test. The differences were recognized as significant at $p < 0.05$.

The study was approved by the Local Ethics Committee at the Federal Research Center of Fundamental and Translational Medicine (Protocol No. 8 dated March 15, 2021). All the patients signed informed consent prior to treatment.

Results

Clinical data

There were no intergroup differences by gender, age, stroke onset, Rankin, NIHSS and MRC scores for proximal and distal parts of the arm, nor in BBT and FM-UE scores prior to treatment (test 1). However, the baseline grip strength scores were lower in the control group (Table 2).

By the end of rehabilitation (test 2), all the clinical parameters in the main group, except MRCprox score, improved ($p < 0.05$). An increase in MRCprox and the BBT scores in the control group were recognized as significant ($p < 0.05$). We noticed that by the end of the treatment 4 patients (1 from the main group and 3 from the control group) lost 1.4–2.7 kg (1.9 kg in average) of their grip strength. The same patients showed either 1 point improvement or no improvement in their MRCdist scores (grip strength). Other test results showed no negative trends for individual values (Table 3). At the end of the treatment, the groups differed by the grip strength and BBT scores (Table 4).

Functional connectivity between motor network nodes

The motor network in the resting state (rs-fMRI) prior to treatment demonstrated medium intra-network connectivity: 0.18 in the main group and 0.15 in the control group ($p > 0.05$). There were no baseline intergroup differences in connectivity between specific nodes within the network. By the end of the treatment (test 2), the FC between ipsilesional SMA and contralesional Cer was significantly weaker in the main group; for other parameters only trends were observed (see the Figure). In the control group, we noticed the trend to diminished connectivity between ipsilesional M1 and contralesional M1, and between ipsilesional M1 and ipsilesional SMA (the upper row in the Figure). No changes in M1–M1 connectivity were observed in the main group; the connectivity between ipsilesional M1 and SMA in both hemispheres, and contralesional Cer became stronger (middle row in the Figure).

Correlations between clinical and network parameters

Correlation analysis of test 2 data revealed positive correlation between interhemispheric M1-M1 connectivity levels and FM-UE ($\rho = 0.87$; $p < 0.005$), BBT ($\rho = 0.72$; $p < 0.01$) and grip strength scores ($\rho = 0.69$; $p < 0.01$) in all the patients. Test 1 data demonstrated low correlation between M1–M1 connectivity levels and BBT score ($\rho = 0.45$; $p < 0.05$). By the end of the treatment, the connectivity between right-side

Table 2. Demographic and clinical characteristics of patients in the main and control groups prior to the treatment, median values [Q_1–Q_3]

Parameter	Main group (*n* = 7)	Control group (*n* = 7)	*p*
Age, years	58.0 [48.0; 61.5]	59.0 [55.0; 65.0]	0.381
Males: Females	6 : 1	6 : 1	1.02
Stroke onset, weeks ago	3.0 [2.0; 4.0]	6.0 [2.5; 6.0]	0.211
Affected hand (left/right)	2/5	4/3	0.282
Modified Rankin score	3.0 [3.0; 3.0]	3.0 [3.0; 3.0]	0.461
NIHSS score	4.0 [3.5; 4.5]	3.0 [3.0; 4.5]	0.711
MRC_{prox} score*	4.0 [3.0; 4.0]	3.0 [3.0; 3.0]	0.261
MRC_{dist} score*	3.0 [2.5; 3.0]	2.0[2.0; 2.5]	0.261
Grip strength, kg*	21.4 [20.4; 24.4]	8.5 [2.7; 11.8]	0.0041
BBT, blocks/min*	31.0 [17.0; 42.5]	17.0 [8.0; 23.0]	0.211
FM-UE score*	46.0 [41.0; 49.0]	34.0 [32.0; 36.0]	0.131
KVIQ vis score	8.0 [6.5; 9.5]	5.0 [5.0; 20.0]	1.01
KVIQ kin score	5.0 [5.0; 9.0]	5.0 [5.0; 18.0]	0.621

Note. Here and in Tables 3 and 4: *values for the affected hand; MRC_{dist} — grip strength by MRC scale; MRC_{prox} — deltoid muscle strength by MRC scale; NIHSS — National Institutes of Health Stroke Scale. [1] — comparison using the Mann–Whitney U test; [2] — using the χ^2 test.

SMA and left-side Cer showed negative correlation with BBT and FM-UE scores (both $\rho = -0.44$; $p < 0.05$).

Discussion

We present the results of the first randomized study on the FC changes in the motor cerebral network compared with the hand mobility tests taken during interactive brain stimulation neurotherapy (fMRI-EEG-neurofeedback) in the ischemic stroke patients during the early recovery period.

By the end of the treatment, the patients in both groups showed clinical improvement, which was slightly more pronounced in the IBS group. The sample size allows no statements about specific impact of IBS on the success of motor learning; however, the trend appears promising. Previous fMRI-NFB [16–18] and fMRI-EEG-NFB [22–29] studies demonstrated that the participants were able to volitionally activate motor regions in the cortex, despite the stroke onset more than 6 months ago. Several studies [16, 27, 29] also demonstrated improvements in hand motor function in some patients. The IBS neurotherapy looks as an attractive treatment option because the BOLD-signal built in the neurofeedback contour allows to focus on a specific cerebral structure and to regulate its activity for treatment/research purposes in the assumption that long-term clinical effects would be mediated by structural and functional plasticity in the brain systems associated with learning. The concept of volitional reconstructing the neural networks during the post-stroke recovery period is based on this assumption.

The resting state fMRI registers basic activity of the brain caused by continuous transmission of neuronal signals at rest without any specific stimulation or active task execution. This registration is based on low-frequency filtration of spontaneous oscillations of the BOLD-signal [33]. Thus, this technology can be employed in the studies of network organization of the brain in patients with the broad range of neurological disorders.

Longitudinal observational studies showed that post-stroke motor executive networks become more complex and chaotic, inter- and intrahemispheric FC between motor regions in the lesioned hemisphere weakens, while intrahemispheric connectivity between motor regions on the "intact" side strengthens. In the meanwhile, the improvement in motor function correlates with the restoration of activity in the motor regions and an increase in their interhemispheric FC levels [2–4, 34, 35].

In our study, interhemispheric M1-M1 FC weakened in the control group by the end of the physical rehabilitation,

Table 3. Clinical data changes by the end of the treatment, median values [Q_1–Q_3]

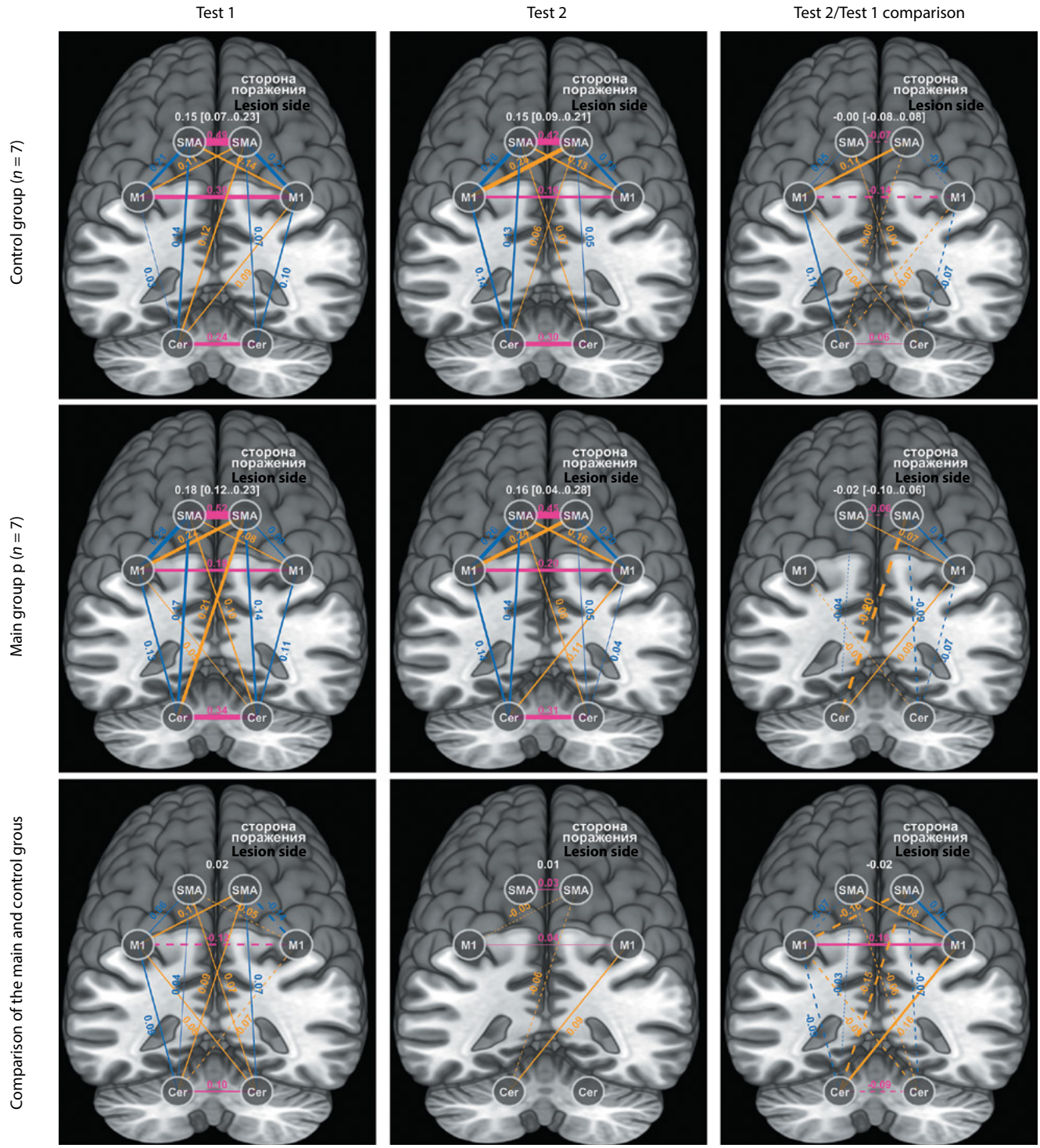
Parameter	Main group (*n* = 7)		Control group (*n* = 7)	
	test 1	test 2	test 1	test 2
Modified Rankin score	3.0 [3.0; 3.0]	2.0# [2.0; 2.0]	3.0 [3.0; 3.0]	2.0 [2.0; 3.0]
NIHSS score	4.0 [3.5; 4.5]	3.0# [1.5; 3.0]	3.0 [3.0; 4.5]	2.0 [2.5; 3.5]
FM-UE score*	46.0 [41.0; 49.0]	51.0# [45.5; 55.0]	34.0 [32.0; 36.0]	36.0 [31.5; 44.0]
MRC_{prox} score*	4.0 [3.0; 4.0]	4.0 [4.0; 4.0]	3.0 [3.0; 3.0]	4.0# [3.5; 4.0]
MRC_{dist} score*	3.0 [2.5; 3.0]	4.0# [3.5; 4.0]	2.0 [2.0; 2.5]	3.0 [2.5; 3.5]
Grip strength, kg*	21.4 [20.4; 24.4]	27.6# [22.8; 28.6]	8.5 [2.7; 11.8]	5.8# [5.0; 15.1]
BBT, blocks/min*	31.0 [17.0; 42.5]	47.0# [38.5; 52.0]	17.0 [8.0; 23.0]	27.0 [15.0; 34.0]
KVIQ vis score	8.0 [6.5; 9.5]	17.0# [13.5; 20.0]	5.0 [5.0; 20.0]	14.0 [7.5; 18.0]
KVIQ kin score	5.0 [5.0; 9.0]	15.0# [12.5; 17.5]	5.0 [5.0; 18.0]	5.0 [5.0; 17.0]

Note. #$p < 0.05$ compared with test 1 results (Wilcoxon signed-rank test).

Table 4. Clinical data in the main group vs.control group at the end of the treatment, median values [Q_1–Q_3]

Parameter	Main group (*n* = 7)	Control group (*n* = 7)	*p*
Modified Rankin score	2.0 [2.0; 2.0]	2.0 [2.0; 3.0]	0.26
NIHSS score	3.0 [1.5; 3.0]	2.0 [2.5; 3.5]	0.32
MRC_{prox} score*	4.0 [4.0; 4.0]	4.0 [3.5; 4.0]	0.80
MRC_{dist} score*	4.0 [3.5; 4.0]	3.0 [2.5; 3.5]	0.21
Grip strength. kg*	27.6 [22.8; 28.6]	5.8 [5.0; 15.1]	0.001#
BBT. blocks/min*	47.0 [38.5; 52.0]	27.0 [15.0; 34.0]	0.026#
FM-UE score*	51.0 [45.5; 55.0]	36.0 [31.5; 44.0]	0.13
KVIQ vis score	17.0 [13.5; 20.0]	14.0 [7.5; 18.0]	0.38
KVIQ kin score	15.0 [12.5; 17.5]	5.0 [5.0; 17.0]	0.32

Note. #$p < 0.05$ compared with test 1 results (Wilcoxon signed-rank test).



FC matrices of motor networks in the main and the control groups prior to and after the treatment.
The white circles designate the regions of interest, the colored lines indicate their connections. The rose lines represent interhemispheric cross-lateral connections, the orange lines represent interhemispheric diagonal connections, and the blue lines represent intrahemispheric connections. The strength of the functional connections is proportional to the width of the lines, with weaker connections indicated by dotted lines. The correlation coefficient (ρ) is shown above the lines. The results of FC comparison before and after the treatment are presented on the right and on the lower panels, within and between the groups, respectively.
Digits in white above each matrix reflect the mean value of the intranetwork connectivity or the difference in its level within or between the groups: on the right and on the lower panels, respectively. The confidence interval of 0.95 for this mean value is shown in the brackets. *$p < 0.05$ (using Student's t-test).

while in the main group it did not change or tended to increase. At the same time, the intrahemispheric functional connectivity M1–SMA on the lesion side became stronger in the IBS group, while in the control group no similar trend was observed (see the Figure). The functional test results (BBT, FM-UE, and grip strength scores) showed positive correlation with M1–M1 interhemispheric connectivity levels.

The cerebellum is involved in the motor learning and further in motor control of the developed movement imagery skills [36]. We observed an increase in connectivity between ipsilesoinal M1 and contralesional Cer in the main group and a decrease in FC between the ipsilateral SMA and both Cer in all the patients (see the Figure). To what extent such trends determine the success of post-stroke motor learning is not entirely clear, although we have found a negative correlation between the results of functional tests and the levels of connectivity between SMA in the lesioned hemisphere and the contralesional Cer.

There is a controversy between the results obtained in our study and in the previous studies, and the data of some recent studies, where the clinical improvement was not associated with the changes in the motor network FC [37, 38]. In one of the studies [38], the activation patterns and FC in stroke patients showed no difference from the same parameters in healthy controls in none of the recovery stages for one year. These data may indicate that cortical reorganization is not the only (and, possibly, not the main) mechanism for restoring lost movements. This assumption is supported by our data showing no significant intragroup changes in connectivity matrices by the end of the treatment, while the improvement in hand motor function during the treatment was obvious. Perhaps, it can be explained by a relatively short duration of the study (3 weeks). However, this time was sufficient to notice the trends in the changes of interactions between certain motor network nodes, and these trends were different in the main and in the control groups. Apparently, IBS additionally recruits cerebral structures associated with motor learning, and this, together with volitional control of the activity of the motor network cortical nodes on the lesioned side, leads to secondary changes in the pyramidal tracts. We came to this assumption based on the results of the recent study carried out by Z.B. Sanders et al.: after three sessions of real-time fMRI NFB in the remote period of stroke onset, the patients learned to increase the laterality of motor cortex activity in the lesioned hemisphere during movements of the stroke-affected hand. No differences in FM-UE scores were observed between the groups receiving real or sham neurofeedback, although real fMRI-NFB group demonstrated better gross hand motor performance in subtasks in the Jebsen–Taylor hand function test [39]. In the same group, the data of diffusion tensor imaging tractography collected one month after the treatment showed decreased corticospinal tract asymmetry, which was positively correlated with participants neurofeedback performance [39]. It can be assumed that volitional modulation of cortical activity might have a specific impact on both functional and structural neuroplasticity, potentially leading to favorable clinical outcomes.

Study limitations. The study enrolled patients with a wide range of stroke localizations and individual differences in screening results, so we aimed to focus on intragroup changes avoiding inter-group comparisons. Analysis of EEG data recorded during the training sessions, where possible effects of the treatment on each modality of bimodal fMRI-EEG platform were assessed separately and/or interchangeably, was not included in this article, although it was a significant part of the study. The fMRI-EEG-NFB sessions were carried out in the early post-stroke recovery period, when the innate neuroplasticity mechanisms are still active. On one hand, drawing conclusions about the real effects of our intervention is difficult. On the other hand, this supports the hypothesis that targeted self-regulation of activity in motor cortical regions through IBS neurotherapy during this period can provide the necessary impulse for neural network improvement. A small sample size (in our case, n = 14) is a common weak point of an fMRI and fMRI-EEG research. However, the NFB neurotherapy based on bimodal fMRI-EEG platform is a conceptual trend that allows accumulating data in order to achieve correlations sufficient to serve the needs of practical medicine. A larger sample size might provide conclusive evidence of the effects of IBS on motor learning efficacy. However, we have found correlations between clinical parameters and changes in specific connectivities within the motor networks, and these changes differed between the study groups.

Conclusion

Neurological deficits and post-stroke recovery depend on the intensity of processes running all over the brain. This is the reason why the search for cerebral structures, which can respond to non-invasive treatment allowing directly or indirectly optimize the neuroplasticity of the brain, is so much in trend nowadays. One of such research and therapeutic tools is neurofeedback neurotherapy based on BOLD-signal (that is, interactive brain stimulation based on fMRI- or fMRI-EEG-neurofeedback). It allows patients to evolve from a passive recipients of therapeutic intervention into active participants capable of reconstructing neural connections between distant areas of their own brain, resulting in efficient clinical progress.

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Efficacy and Safety of PEGylated Interferons for Relapsing-Remitting Multiple Sclerosis in Adult Patients: Results of Matching-Adjusted Indirect Comparison

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Abstract

Introduction. *Beta interferons are effective and safe agents for the treatment of relapsing-remitting multiple sclerosis (RRMS). PEGylated interferons have been developed in order to increase patient adherence. Direct comparisons of the efficacy and safety of PEGylated interferons have not yet been conducted.*

Our ***objective*** *was to evaluate the efficacy and safety of SamPEG-IFN-β1a versus PEG-IFN-β1a in adult patients with RRMS.*

Materials and methods. *We conducted a systematic search of randomized clinical trials (RCTs) using the PubMed, Embase and eLIBRARY.RU databases. Efficacy was assessed based on the proportion of patients with disease relapses and the annualized relapse rate (ARR) during the 1st and the 2nd years of treatment. Safety was assessed by the number of patients with adverse events (AEs), serious AEs (SAEs), and any AEs that led to the treatment discontinuation. We conducted pairwise matching-adjusted indirect comparison (MAIC) to assess comparative efficacy of PEGylated IFNs. To evaluate the efficacy, hypotheses of non-inferiority of SamPEG-IFN-β1a to PEG-IFN-β1a and superiority of SamPEG-IFN-β1a over PEG-IFN-β1a were tested.*

Results. *Based on results of the systematic review, four articles were selected wherein the results of phase 3 clinical trial of PEG-IFN-β1a and phase 2–3 clinical trial of SamPEG-IFN-β1a were described. In PEG-IFN-β1a group (n = 512) the agent was administered once every 2 weeks, in SamPEGIFN-β1a group (n = 114) the agent was administered at a dose of 240 μg. The analysis results confirmed the hypothesis of SamPEG-IFN-β1a non-inferiority to PEG-IFN-β1a in efficacy, while SamPEG-IFN-β1a superiority over PEG-IFN-β1a in efficacy was not confirmed. The hypothesis of SamPEG-IFN-β1a superiority over PEG-IFN-β1a in safety was also confirmed based on a significantly lower incidence of SAEs and any AEs that led to treatment discontinuation.*

Conclusions. *The proportion of patients with relapses and the ARR in 1 year and in 2 years of therapy indicates that SamPEG-IFN-β1a is non-inferior to PEG-IFN-β1a in efficacy. SamPEG-IFN-B1a demonstrated a more favourable safety profile than PEG-IFN-B1a as showing less odds of SAEs and AEs leading to treatment discontinuation.*

Keywords*: multiple sclerosis; immunomodulatory therapy; DMDs; PEGylated interferons; PEG-IFN-β1a; SamPEG-IFN-β1a; indirect comparison; efficacy; safety*

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Эффективность и безопасность пегилированных форм интерферона в лечении ремиттирующего рассеянного склероза у взрослых пациентов: результаты скорректированного непрямого сравнения

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Аннотация

Введение. *Препараты интерферона-β зарекомендовали себя как эффективные и безопасные препараты в лечении ремиттирующего рассеянного склероза (РРС). С целью повышения приверженности пациентов разработаны пегилированные формы интерферона. Прямого сравнения эффективности и безопасности пегилированных интерферонов между собой не проводилось.*

Цель: *оценка эффективности и безопасности применения сампэгинтерферона-β1а (СПИ) по сравнению с пэгинтерфероном-β1а (ПИ) у взрослых пациентов с РРС.*

Материал и методы. *Проведён систематический поиск рандомизированных клинических исследований в электронных базах данных PubMed, Embase и eLIBRARY.RU. Эффективность оценивали по доле пациентов с обострениями и среднегодовой частоте обострений на 1-м и 2-м годах терапии; безопасность – по числу пациентов с нежелательными явлениями (НЯ), серьёзными НЯ, любыми НЯ, приведшими к отмене терапии. Сравнительная оценка клинической эффективности пегилированных форм ИФН проводилась попарно методом скорректированного непрямого сравнения. Для оценки эффективности были выдвинуты гипотезы неменьшей эффективности и превосходства СПИ по сравнению с ПИ.*

Результаты. *По результатам систематического обзора были отобраны 4 статьи, описывающие результаты исследования III фазы для ПИ и исследования II–III фазы для СПИ. Общее количество участников в группе ПИ с режимом применения 1 раз в 2 нед – 512 человек, в группе СПИ в дозе 240 мкг – 114 человек. По результатам проведённого анализа подтверждена гипотеза неменьшей эффективности, но не гипотеза превосходства по эффективности препарата СПИ по сравнению с ПИ. Также подтверждена гипотеза превосходства СПИ над ПИ по безопасности, выражающаяся в значимо меньшей частоте серьёзных и любых НЯ, приведших к отмене терапии.*

Выводы. *По доле пациентов с обострениями и среднегодовой частоте обострений за 1 и 2 года терапии СПИ не менее эффективен, чем ПИ. Применение СПИ является более безопасным, чем ПИ, поскольку характеризуется существенно меньшими шансами развития серьёзных НЯ и любых НЯ, приводящих к отмене терапии.*

Ключевые слова*: рассеянный склероз; иммуномодулирующая терапия; препараты, изменяющие течение рассеянного склероза, пегилированные интерфероны; пэгинтерферон-бета 1а; сампэгинтерферон-бета 1а; непрямое сравнение; эффективность; безопасность*

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Сапожников К.В., Толкачева Д.Г., Соколова В.Д., Саблева Н.А., Мироненко О.Н., Химич Т.В. являлись сотрудниками АО «Биокад» на момент проведения исследования.

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Introduction

Beta interferons (IFN-β) are effective and safe agents for the treatment of relapsing-remitting multiple sclerosis (RRMS). However, the need of frequent dosing along with known adverse reactions (AR), including injection site reactions, make patients less adherent to the therapy, which results in higher risk of the disease relapse. To increase patient adherence, PEGylated IFNs were developed: peginterferon-β1a (PEG-IFN-β1a) and sampeginterferon-β1a (SamPEG-IFN-β1a). Both agents have the mechanism of action similar to that of IFN-β, belong to the class of disease-modifying drugs (DMDs) and may be prescribed as the first-line therapy for the RRMS patients aged ⩾ 18 [1–3].

IFN PEGylation significantly increases the hydrodynamic radius of the IFN molecule improving its pharmacokinetics, reducing fluctuations of IFN concentration in the blood due to lower levels of receptor- and antibody-mediated clearance and proteolysis, increasing the half-life of the molecule in the body and its general activity *in vivo* (along with decreased activity *in vitro*). PEGylated IFN-β are characterized by conjugation with a PEG molecule with a molecular weight increased to 30 kDa, so that IFN-β lasts longer in the body and can be used once in 14 days. SamPEG-IFN-β1a is characterized by the intramuscular route of administration [1, 2]. Moreover, IFN PEGylation might potentially decrease the antigenicity of the protein because PEG can inhibit recognition of antigenic epitopes in the IFN molecule by the immune system. Furthermore, PEGylation contributes to higher solubility and stability of the proteins, which is especially useful for the manufacturing and storage of the finished therapeutic proteins [1].

PEG-IFN-β1a is the first PEGylated IFN used for the treatment of RRMS patients. Its introduction into the clinical practice allowed not only to reduce the incidence of reported ARs, but also to increase patient compliance [3]. At the moment of systematic search and data synthesis, only subcutaneous dosage form of PEG-IFN-β1a was authorized in Russia (Plegridy, Biogen IDEC, Ltd.). Intramuscular dosage form was approved in 2023 and, according to its SmPC, is bioequivalent to the subcutaneous PEG-IFN-β1a[1].

SamPEG-IFN-β1a, the next in the line of PEGylated IFNs [1], was authorized in 2023 (Tenexia, JSC BIOCAD). This agent demonstrated superiority over low dose IFN-β [2]; however, there is no direct comparison with PEG-IFN-β1a, and this lack of evidence determines the relevance of our study.

The **objective** of the study was to evaluate clinical efficacy and safety of SamPEG-IFN-β1a vs PEG-IFN-β1a in adult patients with RRMS using matching-adjusted indirect comparison (MAIC).

Materials and methods

Systematic literature review

To gather the evidence on clinical efficacy and safety of SamPEG-IFN-β1a and PEG-IFN-β1a, three independent researchers conducted a systematic search of RCTs in PubMed, Embase and eLIBRARY.RU electronic databases. Date of the systematic search: February 4, 2022. The search strategy is presented in Appendix 1. Publications were selected by two independent researchers using EndNote X9.2 and MS Excel software.

The systematic review and further evidence synthesis were performed on publications describing the results of phases II and III clinical trials of SamPEG-IFN-β1a and PEG-IFN-β1a. The efficacy endpoints include the proportion of patients with the disease relapse and annualized relapse rate (ARR) for years 1 and 2 of the therapy. The safety outcomes are the proportion of patients with adverse events (AE), serious adverse events (SAE), and any AE led to treatment discontinuation over the first year of therapy. Additionally, data on the same parameters for 2 years of treatment were analyzed.

Target population consisted of the adult patients with the signs of active RRMS according to the clinical examination and diagnostic imaging data. The patients were either IFN (IFN-β1a, IFN-β1b)-naive or discontinued the IFN therapy at least 6 months prior to RCT.

In the selected publications, clinical and methodological heterogeneity was evaluated. Risk of bias was assessed by the Cochrane risk-of-bias tool (RoB2) [4].

If the total number of relapses in the comparator agent group was unavailable, it was calculated from the ARR confidence interval (CI) using the formula for its standard error.

Evidence synthesis

Due to the absence of the common comparator efficacy endpoints were compared between PEGylated IFNs by the pairwise unanchored MAIC. Hypotheses of non-inferiority of SamPEG-IFN-β1a to PEG-IFN-β1a and superiority of SamPEG-IFN-β1a over PEG-IFN-β1a at years 1 and 2 were tested. Confidence limits from ADVANCE clinical trial [5, 6] for the relative PEG-IFN-β1a efficacy versus placebo and versus delayed treatment were used as pre-specified margins for non-inferiority and superiority, respectively (Table 1). Superiority hypothesis without a margin was tested for each safety endpoint.

[1] Plegridy, 125 μg, solution for intramuscular injection. Summary of Product Characteristics (SmPC) ЛП-№ (003419)-(РГ-RU). URL: https://lk.regmed.ru/Register/EAEU_SmPC

Table 1. Margins for non-inferiority of SamPEG-IFN-β1a to PEG-IFN-β1a and for superiority of SamPEG-IFN-β1a over PEG-IFN-β1a at year 1 and year 2 of the treatment

Parameter	Assessment time point	Non-inferiority margin	Superiority margin
ARR ratio	1 year	≤ 2.0	≤ 0.5
	2 years	≤ 2.0	≤ 0.5
Relapse Odds Ratio	1 year	≤ 2.5	≤ 0.4
	2 years	≤ 2.5	≤ 0.4

For data analysis, R-Studio 2022.07.2 software was used (R version 4.2.1, maic package). Individual patient data on the efficacy and safety of SamPEG-IFN-β1a, as well as on therapy effect modifiers, were obtained in the clinical trial BCD-054-2 (RCT register No. 237 from April 28, 2017). Effect modifiers included all possible predictors of the ARR in RRMS patients, and their list was prespecified before the analysis. The SamPEG-IFN-β1a study population was weighted for the values of these effect modifiers derived from the selected trials for the comparator (PEG-IFN-β1a) using the Newton–Raphson method. Adjusted (weighted) and unadjusted odds ratios (OR) of relapse or AEs for years 1 and 2 of the treatment were estimated using logistic regression with robust CIs. The adequacy of the adjustment for the effect modifiers was assessed by comparing the effective sample size to the initial sample size of the SamPEG-IFN-β1a study population.

Results

Systematic search results

Systematic search yielded five articles (three in English and two in Russian) reporting the results of phase III ADVANCE clinical trial for PEG-IFN-β1a [5–7] and phase II–III clinical study for SamPEG-IFN-β1 (Clinical trial ID: NCT02744222) [1, 2]. The search strategy is available on the journal website in Appendix 1, article selection results are presented in the form of a PRISMA diagram in Appendix 2.

Overview of the selected trials and target population

In ADVANCE randomized, double-blind, controlled clinical trial of PEG-IFN-β1a vs placebo, the PEG-IFN-β1a

Table 2. Population parameters in SamPEG-IFN-β1a and PEG-IFN-β1a trials

Parameter	Patients receiving SamPEG-IFN-β1a	Patients receiving PEG-IFN-β1a
Number of participants	114	512
Age, years; *M* ± σ	33.8 ± 9.0	36.9 ± 9.8
Females, *n* (%)	75 (65.8%)	361 (70.5%)
Screening EDSS score; *M* ± σ	2.43 ± 1.00	2.47 ± 1.26
Confirmed MS diagnosis, years ago; *M* ± σ	1.5 ± 2.2	4.0 ± 5.1
MS symptom onset, years ago; *M* ± σ	5.5 ± 5.5	6.9 ± 6.6
DMD-experienced patients, *n* (%)	29 (24.6%)	95 (18.6%)
Relapse rate in the last year; *M* ± σ	1.3 ± 0.6	2.6 ± 1.0
T2-weighted MRI lesions; *M* ± σ	50.7 ± 41.5	48.1 ± 36.8
Contrast-enhancing lesions in T1-weighted MRI; *M* ± σ	1.3 ± 3.4	1.2 ± 3.4
Patients without GD^+ MRI lesions at screening, *n* (%)	73 (64.0%)	334 (65.2%)

Note. *M* — mean value, σ — standard deviation.

Table 3. Primary efficacy endpoints for PEGylated IFNs

Parameter	Assessment time point	Patients receiving SamPEG-IFN-β1a	Patients receiving PEG-IFN-β1a
ARR, relapses/year (95% CI)	1 year	0.13 (0.08–0.23)	0.26 (0.21–0.32)
	2 years	0.11 (0.07–0.17)	0.22 (0.18–0.27)
Proportion of patients with relapses, *n/N* (%)	1 year	13/114 (11.4%)	90/512 (17.6%)
	2 years	19/114 (16.7%)	124/512 (24.2%)
Proportion of patients with any AE, *n/N* (%)	1 year	108/114 (94.7%)	481/512 (93.9%)
	2 years	109/114 (95.6%)	699/740 (94.5%)
Proportion of patients with any SAE, *n/N* (%)	1 year	1/114 (0.9%)	55/512 (10.7%)
	2 years	4/114 (3.5%)	120/740 (16.2%)
Proportion of patients with AEs/SAEs led to treatment discontinuation, *n/N* (%)	1 year	2/114 (1.8%)	25/512 (4.9%)
	2 years	2/114 (1.8%)	41/740 (5.5%)

Note. *n* — number of patients with a registered event; *N* — total number of observations; % – proportion of patients with a registered event in the total number of patients.

group (n = 512) received study agent once every 2 weeks. NCT02744222 is a randomized, double-blind clinical trial aimed at comparison of two doses of SamPEG-IFN-β1 vs placebo and vs intramuscular IFN-β1a injection. 114 participants were assigned to SamPEG-IFN-β1 240 μg group.

Baseline clinical parameters of each trial participant are presented in Table 2.

Assessment of selected efficacy endpoints

Baseline efficacy and safety data for PEGylated IFNs are presented in Table 3. In the SamPEG-IFN-β1a group, ARR was calculated as the ratio of the total number of relapses during the period to the total number of patient years for patients who received at least 1 dose of the agent. In year 1 of the treatment there were 14 events per 104.26 patient years; in year 2 – 22 events per 194.49 patient years.

Risk of bias assessment

The risk of bias in both RCTs (NCT00906399[2] and NCT02744222[3]) was considered low [7, 8]. See Appendix 3 on the journal website.

[2] Efficacy and Safety Study of Peginterferon Beta-1a in Participants with Relapsing Multiple Sclerosis (ADVANCE). URL: https://clinicaltrials.gov/study/NCT00906399

[3] Comparative Clinical Trial to Evaluate Efficacy, Safety and Tolerance of BCD-054 and Avonex® for Treatment of Patients with Remitting-relapsing Multiple Sclerosis. https://clinicaltrials.gov/study/NCT02744222

Effect modifiers

To achieve comparability between populations, the following baseline characteristics were considered as effect modifiers: patient age, EDSS scores, and the relapse rate over the last year. The list of effect modifiers was prespecified based on the clinical guidelines for multiple sclerosis.

The choice of the first-line DMD therapy for each patient is determined by the clinical course of MS, patient's age, and EDSS score. The first-line DMDs are not recommended for the fulminate MS determined, inter alia, by the relapse rate in year 1 of follow-up. For this reason, relapse rate in the last year was classified as a balancing criterion. Descriptive statistics for all effect modifiers were presented in in the ADVANCE clinical trial, as well [5, 7].

Results of matching-adjusted indirect comparison

Target values for descriptive statistics for effect modifiers, as well as their values in the SamPEG-IFN-β1a group before and after adjustment are presented in Table 4. The effective sample size (n = 77) can be considered as slightly different from the SamPEG-IFN-β1a initial sample size (n = 114).

MAIC results for efficacy endpoints are presented in Figures 1 and 2.

Table 4. Target and mean values of effect modifiers in SamPEG-IFN-β1a group prior to and after adjustment

Effect modifier	Target value	Unadjusted value	Adjusted value
EDSS score	2.47	2.4	2.4699
Age, years	36.9	33.8	36.8997
Relapse rate in the last year	1.6	1.3	1.6000

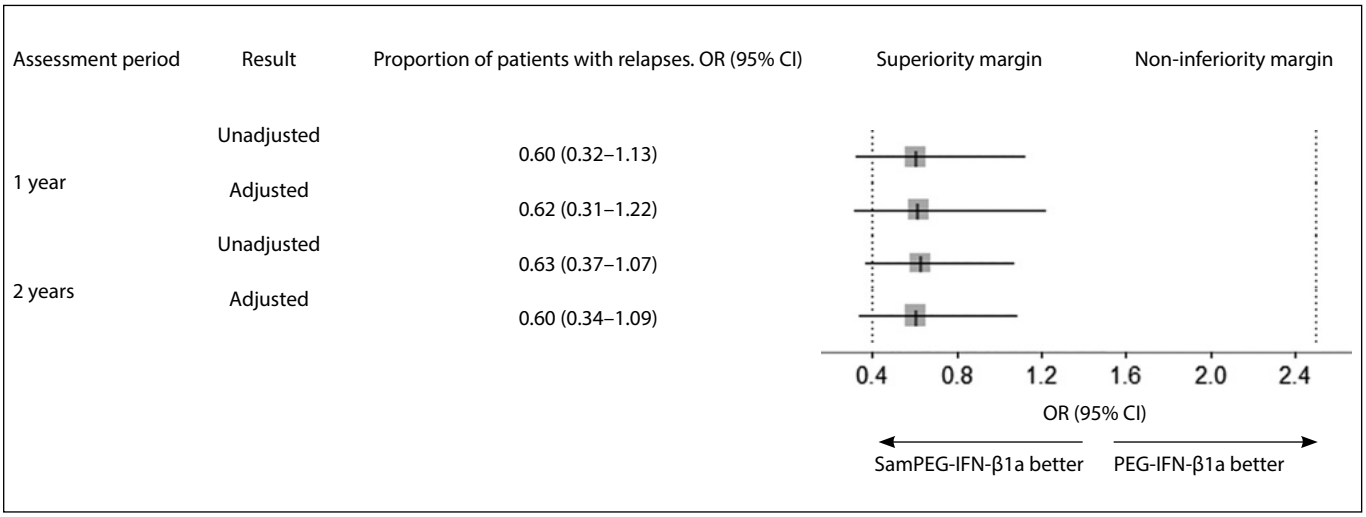

Fig. 1. SamPEG-IFN-β1a vs PEG-IFN-β1a: odds ratio for relapses of multiple sclerosis.
Note: CI – confidence interval; OR – odds ratio.

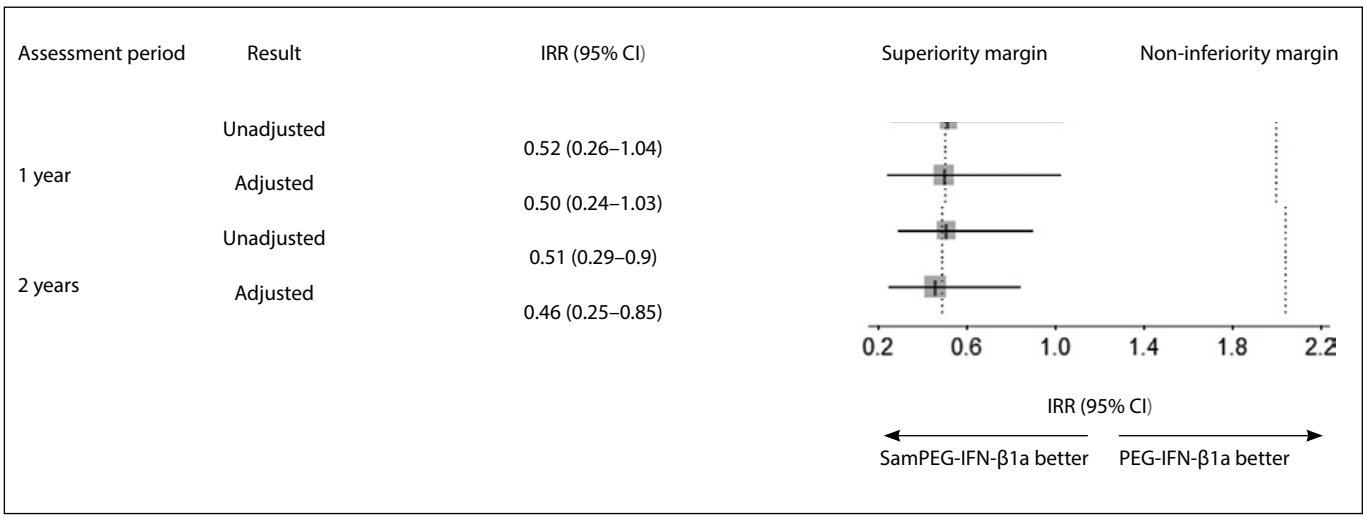

Fig. 2. SamPEG-IFN-β1a vs PEG-IFN-β1a: annualized relapse rate.
IRR – incidence rate ratio.

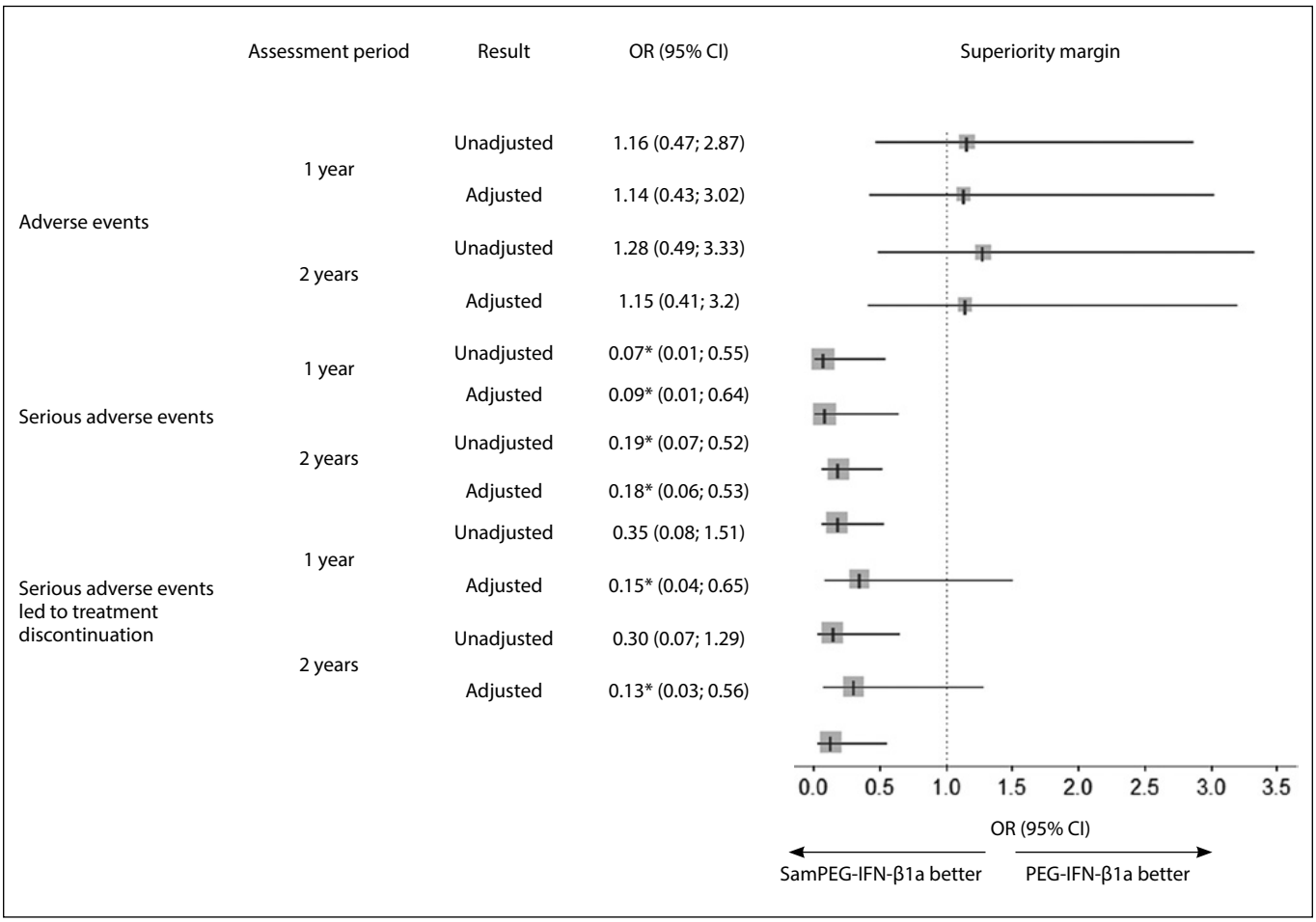

Fig. 3. SamPEG-IFN-β1a vs PEG-IFN-β1a: odds ratio for various categories of adverse events.
*Statistically significant difference.

MAIC results for safety endpoints are presented in Figure 3.

Based on the results of our study, the hypothesis of non-inferiority of SamPEG-IFN-β1a to PEG-IFN-β1a was confirmed, while the hypothesis of superiority of SamPEG-IFN-β1a over PEG-IFN-β1a in efficacy was not confirmed. We also confirmed the hypothesis of SamPEG-IFN-β1a superiority over PEG-IFN-β1a in safety, based on a significantly lower odds of SAE and any AE led to treatment discontinuation.

Discussion

Beta interferons are effective and safe agents playing an important role in the treatment of RRMS[4]. All IFN-β types share the same mechanism of action, but differ in dosing regimen and route of administration. IFN-β1b and IFN-β1a administered subcutaneously require frequent high-dose administration (high-dose IFN-β), while IFN-β1a administered intramuscularly can be used in a relatively small dose (low-dose IFN-β). PEG-IFN-β1a can be administered either subcutaneously or intramuscularly once every 2 weeks [3]. SamPEG-IFN-β1a is administered intramuscularly once every 2 weeks, which allows for longer intervals between injections increasing patient adherence due to a lower incidence of injection site AEs [1, 2].

MAIC was used to estimate clinical efficacy and safety of SamPEG-IFN-β1a vs PEG-IFN-β1a in adult patients with signs of RRMS activity as evidenced by clinical examination or diagnostic imaging results. Patients were either IFN-experienced (IFN-β1a, IFN-β1b) or had discontinued IFN therapy for at least 6 months prior to the enrollment in an RCT. The results of our analysis demonstrated non-inferiority of SamPEG-IFN-β1a to PEG-IFN-β1a in this patient population. Efficacy endpoints included the proportion of patients with relapses and ARR in 1 year and in 2 years of treatment. These estimands are used for DMD efficacy evaluation according to NEDA criteria (No Evidence of Disease Activity), according to which the optimal response to DMD therapy is determined by the

[4] Ministry of Health of the Russian Federation, Guidelines for Multiple Sclerosis, 2022, published on July 13, 2022.

absence of relapses, absence of progression of neurological deficit during the follow-up period, and absence of the MRI signs of disease activity. Safety endpoints included the number of patients with AEs, SAEs, and AE led to the treatment discontinuation. In the SamPEG-IFN-β1a trial, the severity of any registered AE or deviation in laboratory results was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) recommended by the National Cancer Institute of the United States and used in European RCTs [2].

There is no literature available on the direct comparison of PEGylated interferons-β for RRMS, which makes it relevant to continue the research to obtain results of direct comparison. Existing data from comparative meta-analyses on the use of non-PEGylated IFN-β demonstrates their comparable clinical efficacy. So, meta-analysis data presented by T.R. Einarson et al. showed that clinical profiles of Avonex (low-dose IFN-β1a), Rebif® (high-dose IFN-β1a), and Betaseron® (high-dose IFN-β1b) were similar [9]. At the same time, there is data indicating that the high-dose IFN-β therapy is more effective compared to low-dose IFN-β therapy. A systematic review of comparative trials conducted by B.J. Oliver et al. demonstrated that high-dose IFN-β treatment was superior to low-dose IFN-β treatment for relapse control and stability of MRI results [10]. The results of the direct comparative EVIDENCE study showed that treatment with subcutaneous high-dose IFN-β1a was associated with the significant decrease in clinical and imaging signs of disease activity over 1–2 years compared to intramuscular low-dose IFN-β1a treatment [11]. Recent data on SamPEG-IFN-β1a 240 μg confirmed its superiority over low-dose IFN-beta1a in efficacy, as evidenced by a longer period till the next relapse [2].

Non-PEGylated IFN-β are effective and safe agents playing an important role in the treatment of RRMS [3]. However, frequent dosing leads to the decrease in patient adherence. SamPEG-IFN-β1a and PEG-IFN-β1a allow to increase intervals between the injections and require less frequent dosing: once every 2 weeks [1, 2]. It is also known, that IFN-β agents (IFN-β1a and IFN-β1b) are immunogenic and their use is associated with an increased level of neutralizing antibodies (NAbs) to IFN-β. It has been proven that neutralizing antibodies can reduce the clinical effectiveness of IFN-β agents in patients with multiple sclerosis. The NAb development rate in patients receiving non-PEGylated IFN-β ranges from 5.6% to 44% [12]. PEGylated IFNs are known to cause less NAb development. According to the ADVANCE study, 4.63% of patients[5] treated with SamPEG-IFN-β1a and less than 1% patients treated with PEG-IFN-β1a develop NAbs [5].

The subcutaneous route of administration is associated with the lower incidence of injection site adverse reactions [1, 2, 13]. Direct comparative study on effects of subcutaneous vs intramuscular PEG-IFN-β1a showed that intramuscular administration was associated with a lower incidence of injection site events, which are a key factor of the non-adherence or therapy discontinuation among RRMS patients receiving DMD injections [13].

Limitations. Any indirect comparison is inevitably associated with limitations. Although using individual patient data was the only way to adjust for differences between studies in the conducted indirect comparison, the lack of a common comparator group is a significant limitation, as it makes validation of matching and assessment of relative effects impossible. At the same time, this method of analysis is widely recognized both in Russia[6] and worldwide.

Matching-adjusted indirect comparison allowed to take into account only observable and measurable effect modifiers, excluding any unobservable ones. Nevertheless, the effective sample size after weighting showed sufficient statistical power of the comparisons made.

We compared the data on efficacy and safety of intramuscular SamPEG-IFN-β1a vs subcutaneous PEG-IFN-β1a due to insufficient evidence database on intramuscular administration of a comparator agent: our systematic review only yielded phase I clinical trial on bioequivalence of two PEG-IFN-β1a dosage forms in healthy volunteers conducted by Y. Zhao et al. [13], which did not meet inclusion criteria of the review.

Compared to the number of patients included in the ADVANCE RCT, data for SamPEG-IFN-β1a from BCD-054-2 RCT was obtained for relatively smaller sample, which may limit the power of statistical inference. The analysis is to be updated after post-marketing studies of SamPEG-IFN-β1a. We will use hybrid individual patient data for MAIC, as it was done in the study of treatment options for patients with melanoma [14].

In clinical trials conducted in Russia and Eastern Europe, AEs are reported reluctantly [15], which may also affect the BCD-054-2 trial results. At the same time, registration of SAEs and AEs led to treatment discontinuation depends much on the medical personnel qualification, thus, including them into the analysis compensates this limitation.

The approach we used for setting up the margins for non-inferiority for ARR ratio and odds ratio of relapse (inverse value of the lower 95% CI limit for respective

[5] Summary of Product Characteristics TENEXIA®, ЛП-N=(002167)-(РГ-RU) from 13.04.2023. URL: https://tenexia.ru/v1_1.3.1%20Проект%20ОХЛП_SPC.054.1.EAEU-RU.01.07%20(1467910531)%20штамп%20М3.pdf

[6] Methodological guideline for indirect comparison of drug products. Approved by the Center for Healthcare Quality Assessment and Control of the Ministry of Health of the Russian Federation, order No.181-од. from December 29, 2017.

endpoints from clinical trial of PEG-IFN-β1a vs placebo or vs delayed treatment) cannot be considered conservative, as according to this approach any SamPEG-IFN-β1a superiority over placebo or delayed treatment would mean its non-inferiority to PEG-IFN-β1a. On the other hand, less conservative approach is acceptable if a study agent is superior in safety, which was expected for SamPEG-IFN-β1a, namely in the lower incidence of injection site AE due to intramuscular administration instead of PEG-IFN-β1a subcutaneous administration. Moreover, the results obtained in our study show that SamPEG-IFN-β1a non-inferiority could have also been confirmed with the more conservative margin for non-inferiority, as if we compared this parameter with a certain positive effect of PEG-IFN-β1a.

The studied therapy options were not compared by any secondary efficacy endpoints, namely, by the duration of period till the next relapse and by confirmed disability progression. This can be considered as another limitation of this study. Due to the limited number of patients, no comparison in subgroups was conducted (i.e., DMT-naive and DMT-experienced patients, etc.).

Despite the stated limitations, we expect the results of this indirect comparison to be reliable and justified due to the high quality of the data and due to the fact that all the assessments were adjusted for clinically significant effect modifiers.

Conclusion

This study presents the results of the unanchored matching-adjusted indirect comparison of SamPEG-IFN-β1a and PEG-IFN-β1a as the first-line therapy in adult patients with signs of RRMS activity based on data collected during a 2-year follow-up period.

The results of indirect comparison indicate that first-line SamPEG-IFN-β1a therapy is non-inferior to PEG-IFN-β1a first-line therapy. This conclusion is based on the proportion of patients with MS relapses and ARR over 1 year and 2 years of the treatment. In addition, the odds of SAEs and any AE led to discontinuation of the treatment is significantly smaller for SamPEG-IFN-β1a in comparison to PEG-IFN-β1a.

This study might help clinicians in choosing first-line therapy for adult patients with the signs of RRMS activity based on clinical examination or diagnostic imaging results.

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Ischemic Stroke and COVID-19 Infection: an Analysis of Treatment Outcomes in Patients who Underwent Endovascular Thrombectomy

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Abstract

Aim. *This study aimed to compare and evaluate treatment outcomes in groups of ischemic stroke patients with or without COVID-19 infection who underwent endovascular thrombectomy (EVT).*

Materials and methods. *We conducted a retrospective analysis of 817 case records of IS patients aged 25 to 99 years with confirmed thrombotic occlusion of cerebral arteries and subsequent EVT who were treated in regional vascular centers in St. Petersburg from January 01, 2021 to December 31, 2021.*

Results. *Patients without COVID-19 had favorable outcome more often than patients with confirmed COVID-19 (35.0% vs. 7.3%, $p < 0.001$); mortality rate was 30% vs. 52%, respectively ($p < 0.001$).*

Conclusions. *Intercurrent COVID-19 significantly worsened prognosis and increased risk of death in ischemic stroke patients who underwent EVT.*

Keywords*: ischemic stroke; endovascular thrombectomy; cerebral artery thrombosis; COVID-19 infection; severe respiratory infection*

Ethics approval. The study was conducted with the voluntary informed consent of the patients. The research protocol was approved by the Ethics Committee of the First St. Petersburg State Medical University named after Academician I.P. Pavlov (protocol No. 2, dated 11.18.1022).

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Ишемический инсульт и коронавирусная инфекция: анализ исходов лечения у пациентов с выполненной внутрисосудистой тромбоэкстракцией

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Аннотация

Цель *исследования – сравнительный анализ исходов лечения в группах пациентов с ишемическим инсультом, перенёсших внутрисосудистую тромбоэкстракцию (ВСТЭ) на фоне актуальной коронавирусной инфекции и без неё.*
Материалы и методы. *Проведён ретроспективный анализ 817 историй болезни пациентов с ИИ в возрасте 25–99 лет, проходивших лечение в региональных сосудистых центрах Санкт-Петербурга с 01.01.2021 по 31.12.2021, с доказанной тромботической окклюзией церебральных сосудов и последующим выполнением ВСТЭ.*
Результаты. *У пациентов без COVID-19 чаще отмечался благоприятный функциональный исход – 35% против 7,3% у пациентов с COVID-19 ($p < 0,001$), доля летальных исходов составила 30% против 52% ($p < 0,001$).*
Заключение. *Интеркуррентная COVID-19 значимо ухудшает прогноз и увеличивает вероятность летального исхода у пациентов с ишемическим инсультом и выполненной ВСТЭ.*

Ключевые слова*: ишемический инсульт; внутрисосудистая тромбоэкстракция; тромбоз церебральных артерий; новая коронавирусная инфекция; тяжёлая респираторная инфекция*

Этическое утверждение. Исследование проводилось при добровольном информированном согласии пациентов. Протокол исследования одобрен Этическим комитетом Первого Санкт-Петербургского государственного медицинского университета им. акад. И.П. Павлова (протокол № 2 от 18.11.2022).

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Introduction

Endovascular therapy has significantly expanded pathogenetic treatment options for patients with acute ischemic stroke (IS) caused by occlusion of proximal cerebral arteries and allowed decreasing hospital mortality and improving functional outcomes [1–4]. Reperfusion treatment in cerebral artery thrombosis has become more accessible with the combined use of endovascular intervention and intravenous thrombolytic therapy, expanding the "therapeutic window" for restoring blood flow from 4.5 to 6 and even up to 24 hours, increasing the rates of successful recanalization [5–7].

An established and well-equipped network of vascular centers sharing common triage principles was a key factor that allowed introducing advanced specialized medical care, including high-tech one, for stroke patients in the regions of Russia. Intensive recruitment of personnel experienced in endovascular surgery and regular training of new specialists have been performed since 2011, and this has significantly accelerated introducing endovascular thrombectomy (EVT) into routine practice of regional vascular centers. By 2014, there were 20 radiology surgeons in Saint Petersburg with up to 10 cerebral endovascular procedures in their professional journey [7–9], while today there are 77 of them. Twenty-four surgeons have performed up to 10 EVT procedures, and 10 to 100 surgeons up to 38 EVT procedures. Fourteen surgeons have performed over 100 procedures, and one of them has performed over 150 cerebral endovascular procedures for acute thrombosis and cerebral artery occlusion. The expertise gained in patient triage in St. Petersburg together with adequate staffing has led to an exponential increase in the number of endovascular procedures (i.e. from 25 in 2014 to 1123 in 2022). In 2019, 26% of the total number of EVT procedures performed in vascular centers of Russia was performed in St. Petersburg.

Considering the complex nature of the surgical interventions, regional registries to access the quality and success of the interventions were established in Moscow and St. Petersburg at the beginning of the introduction of EVT. According to the Moscow Stroke Registry, in 2019, successful recanalization (Modified Treatment in Cerebral Ischemia (mTICI) score of 2b–3) was achieved in 75% of patients; thromboaspiration, which was used in 51.6% of patients, was the most common procedure for thrombectomy; good functional recovery by the end of Day 20 (Rehabilitation Triage Scale score of 0–2) was observed in 29.2% of patients. 20-day mortality rate in the cohort of surgically treated patients was 31.8% [8].

The COVID-19 pandemic created critical challenges, significantly affecting the specialized medical care system for stroke patients and limiting triage opportunities and care availability in most regions of Russia [10]. Stroke patients were more vulnerable if having signs of COVID-19 [11–15]. A dramatic role in increased frequency of more severe disease and increased mortality was played by the mutual aggravation of the two conditions and a loss of time caused by "rehospitalization" of patients from vascular centers to so-called "green zones" in repurposed hospitals, as well as limitations associated with more common contraindications to intravenous thrombolytic therapy and EVT due to the comorbidity.

This study aimed to compare and evaluate treatment outcomes in the ischemic stroke patients with or without COVID-19 infection who underwent EVT.

Materials and methods

We conducted a retrospective analysis of 817 case records of all patients (365 men and 452 women) aged 25–99 years who were treated for IS from January 01, 2021 to December 31, 2021 in 11 vascular centers in St. Petersburg (Pokrovskaya City Hospital No 1, Hospital for War Veterans, Mariinskaya City Hospital No 16, A.M. Nikiforov Russian Emergency and Radiation Medicine Center, Aleksandrovskaya City Hospital No 17, Almazov National Medical Research Center, City Hospital No 40, City Multi-Field Hospital No 2, I.I. Dzhanelidze Research Institute of Emergency Medicine, City Hospital No 26, St. Elizaveta City Hospital No 3).

Inclusion criteria for study population:
- Ischemic stroke confirmed by neuroimaging, i.e. computed tomography (CT) or magnetic resonance imaging (MRI);
- confirmed thrombotic occlusion of proximal cerebral arteries followed by EVT;
- no history of thrombolytic therapy;
- Exclusion criteria:
- no polymerase chain reaction test for SARS-CoV-2;
- no indications for EVT;
- no control CT performed 24 hours after the surgery.

All patients underwent standard clinical and neurological examination, and the clinical diagnosis of IS was established according to ICD-10 and TOAST criteria. Neurological deficit was assessed using the National Institutes of Health Stroke Scale (NIHSS). EVT success was determined by control angiography; result was considered as success if the lumen of the cerebral artery was restored with mTICI score of 2b to 3 and as failure if mTICI score was 0 to 2a. Functional outcomes after IS were assessed using the Modified Rankin Scale (mRS) at discharge. Functional outcome was considered favorable if mRs score was 0 to 2 and unfavorable if mRs score was 3 to 5; death corresponded to mRs score of 6. We also assessed mortality on Day 90 after the onset of stroke in a cohort of discharged patients based on cases registered in the St. Petersburg State Information System. Death causes were reported based on autopsy results (for hospital deaths).

Quantitative data were presented as medians and quartiles (Me [Q1; Q3]); categorical (qualitative) data were presented as rates and percentages; 95% confidence intervals (Cis) were calculated for proportions. For all numerical data, preliminary testing for normality of distribution was performed using Shapiro–Wilk test, as well as skewness and kurtosis test by calculating *p* value when testing the null hypothesis about normal distribution of the variable. Student's t-test for independent samples was used for statistical analysis of data with normal distribution. Non-parametric Wilcoxon–Mann–Whitney and Kruskal–Wallis tests were used for data without normal distribution. The association between categorical variables was evaluated using Fisher's exact test and Pearson's χ^2 test. The relationship between quantitative characteristics was deter-

mined by calculating Pearson linear correlation coefficient. Univariate and multivariate logistic regression models were generated to assess the association of favorable functional outcome (mRs score of 0–2) at discharge and the variables of interest and their confounder variables. All *p*-values were based on two-sided tests. Differences were considered significant with $p < 0.05$. All calculations were performed using R package version 4.3.1.

Results

Demographics and clinical characteristics of the study population are presented in Table 1.

Based on the selection criteria, we identified a cohort of 219 patients with confirmed COVID-19 (according to PCR and chest CT results) from all 817 patients who underwent EVT; no documented confirmation of COVID-19 was obtained in 598 cases. Outcome assessment results are presented in Table 2.

The data show that statistically significant differences were seen in 4 parameters:

- neurological deficit severity (NIHSS score);
- mortality rate by the end of acute IS period;
- functional outcome by mRS score by the end of treatment in the acute period;
- death number and percentage on Day 90 after disease onset.

When assessing the cohorts, we found that the neurological syndrome at admission and initiation of treatment was significantly more severe in patients with COVID-19, which supported the hypothesis on mutual aggravation of the conditions and demonstrated pathogenesis of COVID-19. NIHSS score was 17 and 15 in patients with or without COVID-19, respectively ($p < 0.001$).

Hospital mortality rate in the study population ($n = 817$) was 36% ($n = 294$), which was significantly higher than before the pandemic. Of those, mortality rate in patients without or with COVID-19 at the time of stroke was 30% *vs.* 52%, respectively ($p < 0.001$). A total of 89 (11%) IS cases were excluded from the analysis because their treatment did not comply with several provisions of the Procedure for provid-

Table 1. Demographics and clinical characteristics of IS patients with or without COVID-19

Parameter	Patients with COVID-19	Patients without COVID-19	*p*
Number of patients, *n*	219	598	
Age, years	75 [67; 84]	73 [63; 82]	0.023
Male gender, *n* (%)	103 (47)	262 (44)	0.4
NIHSS score at admission	17 [13; 20]	15 [10; 18]	< 0.001
ASPECTS score by CT at admission	10.00 [8.00; 10.00]	10.00 [8.00; 10.00]	0.5
Number and percentage of patients with 0 to 6 h from stroke to arterial puncture, *n* (%)	133 (61; 95% CI 54–67)	399 (67; 95% CI 63–70)	0.11
Successful angiographic reperfusion (mTICI score of 2a to 3), *n* (%)	164 (77; 95% CI 71–83)	492 (86; 95% CI 83–89)	0.004
Functional outcome at discharge, mRS score	6.00 [4.00; 6.00]	3.00 [2.00; 6.00]	< 0.001
Mortality rate on Day 90 from IS onset, *n* (%)	98 (51; 95% CI 44–59)	177 (33; 95% CI 29–37)	< 0.001

Note. *Quantitative data are presented as medians and quartiles (Me [Q1; Q3]). Qualitative data are presented as rates and percentages.

Table 2. Comparative analysis of outcomes at discharge after EVT in IS patients with or without COVID-19

Outcome group	Patients with COVID-19	Patients without COVID-19	*p*	Total, *n*
Discharged + died (total), *n*	219	598	–	817
During 3 months after IS:				
died, *n* (%)	98 (51%; 95% CI 44–59)	177 (33%; 95% CI 29–37)	< 0.001	275
survived, *n* (%)	93 (49%; 95% CI 42–56)	360 (67%; 95% CI 63–71)	< 0.001	
Number of missed values	28	61		89

ing specialized medical care for stroke patients[1] due to triage problems, lack of personnel or shortage of critical care beds. In these cases, the relationship between outcomes of hospital treatment was obviously not related to the treatment option and comorbidity.

In IS patients who underwent EVT and did not have confirmed COVID-19, favorable functional outcomes (mRS score of 0–2) at discharge were more common (35.0% *vs.* 7.3%; $p < 0.001$). By Day 90 from stroke onset, outcome was known in 728/817 patients, while in 89 patients it could not be established. Mortality rate on Day 90 after stroke onset was lower in patients without diagnosed COVID-19 compared with patients without it (33% *vs.* 51%).

Outcomes of endovascular surgery (successful/unsuccessful) were available in 784/817 patients; no information on mTICI recanalization score was available in 33 case records. Statistical analysis confirmed significant intergroup differences (Table 1): successful recanalization was achieved in 86% of patients without signs of COVID-19 *vs.* 77% of patients with concomitant COVID-19 ($p = 0.004$).

To identify the association between favorable functional outcome with endpoints and confounders in a cohort of IS patients who required endovascular surgery, a multiple logistic regression model was generated including age, neurological deficit (NIHSS score) at admission, degree of revascularization achieved, and absence of COVID-19 (Table 3).

Discussion

We studied a continuous sample of IS patients who underwent EVT in vascular centers of St. Petersburg in 2021; this population was representative for the period of the widespread COVID-19 pandemic. We found that IS patients without COVID-19 who underwent EVT had a better prognosis for favorable functional outcome, higher chances of good revascularization and a lower probability of death both during hospital treatment and within 3 months after IS onset.

This may be partly caused by administrative factors such as suboptimal pre-hospital and in-hospital triage and poor availability of specialized medical care. Stroke admissions and frequency of systemic thrombolysis and/or EVT dropped during the COVID-19 pandemic in many countries [16]. Door-to-puncture time increased in EVT candidates, which was associated with the performance of chest computed tomography [17]. In our population, there was a trend towards less frequent early (up to 6 hours from the onset) EVT in patients with COVID-19 (61% vs. 67% in patients without COVID-19), which, however, did not achieve statistical significance in either univariate or multivariate analysis.

Other possible causes may include aggravation of neurological deficit due to intercurrent SARS-CoV-2 infection. Neurological symptoms in COVID-19 are not uncommon: headache, paresthesias, impaired perception of smell and taste, impaired consciousness have been reported in patients with COVID-19, and, in some cases, COVID-19 manifested with stroke [18, 19]. In our population, COVID-19 was associated with more severe neurological deficit in the hyperacute stroke phase (NIHSS score at admission). It is important to note that differences in the severity of neurological deficit were not associated with inter-group differences in the ASPECTS score, suggesting that the higher NIHSS score in patients with COVID-19 was not explained by later hospitalization.

Therefore, COVID-19 appeared to be an independent factor to aggravate IS severity, which was confirmed by multivariate analysis results. In our population, the odds of an unfavorable stroke outcome in patients with COVID-19 increased 6.82-fold (95% CI 3.81–13.2) with adjustment for age, severity of neurological deficit, EVT outcome, and time. This ob-

[1] Decree 928n of the Ministry of Health of the Russian Federation dated November 15, 2012 "On approval of the Procedure for providing medical care to stroke patients".

Table 3. Coefficients of logistic regression equation to assess the association between favorable functional outcome (mRs score of 0–2) and clinically significant variables in the study group

Parameter	Univariate analysis			Multivariate analysis		
	odds ratio	95% CI	*p*	odds ratio	95% CI	*p*
Age	0.96	0.95–0.98	< 0.001	0.97	0.96–0.99	< 0.001
NIHSS score at admission	0.87	0.84–0.89	< 0.001	0.88	0.85–0.91	< 0.001
Over 6 h from stroke onset to arterial puncture	0.78	0.56–1.08	0.13	0.74	0.50–1.10	0.14
Successful recanalization	3.18	1.98–5.37	< 0.001	2.84	1.64–5.18	< 0.001
No COVID-19	6.77	4.08–12.0	< 0.001	6.82	3.81–13.2	< 0.001

servation is consistent with the global trend: less favorable outcomes in patients treated for stroke have been reported in most cohort studies during the COVID-19 pandemic [18, 20]. This might be directly related to COVID-19 severity. The advantage of our study compared with observational case series that compared IS outcomes before and during the COVID-19 pandemic is that our study considered the status of SARS-CoV-2 infection and IS severity. Our results confirmed a hypothesis on the pathophysiological role of COVID-19 *per se* and its complications in IS patients. It is important to note that administrative measures during a pandemic should aim not only at improving patient triage but also at carefully preventing secondary infection in IS patients admitted without COVID-19.

Limitations. Our study was based on a retrospective analysis of case records; it was observational and did not consider treatment outcomes of patients who did not undergo EVT due to extreme severity of their respiratory syndrome or multiple organ involvement that complicated COVID-19. We did not consider cases with reduced EVT availability due to administrative issues because deaths in this population were expected and would likely to worsen the outcomes in the general population of stroke patients.

Conclusion

Our results demonstrated with high confidence the negative impact of COVID-19 on outcomes in patients receiving endovascular treatment for acute cerebral artery thrombosis. COVID-19 significantly worsened survival and functional outcomes in IS patients who underwent EVT. Administrative issues, which reduced the availability of timely pathogenetic therapy, significantly contributed to hospital mortality in IS patients.

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3,5-Dimethyladamantan-1-amine Restores Short-term Synaptic Plasticity by Changing Function of Excitatory Amino Acid Transporters in Mouse Model of Spinocerebellar Ataxia Type 1

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Abstract

Introduction. *Memantine is an agent that used for treatment of Alzheimer's type dementia. Memantine considerably reduces the effects of neurodegeneration, may potentially slow down the neurodegenerative changes in the cerebellum and may act as treatment of choice for spinocerebellar ataxia type 1 (SCA 1).*

Our *objective was to study molecular mechanisms of the short-term synaptic plasticity improvement associated with long-term memantine use in SCA 1 transgenic mice.*

Materials and methods. *The experiments were performed on 12-week-old CD1 mice. We created a mouse model of cerebellar astrogliosis after expression of mutant ataxin-1 (ATXN1[Q85]) in the Bergmann glia (BG). To model the astrocyte-mediated neurodegeneration in the cerebellum, the mice were injected with LVV GFAP-Flag-ATXN1[Q85] lentiviral vector (LVV) constructs intracortically. Some of the mice received 0.35 mg/kg memantine dissolved in drink water once daily for 9 weeks. The control animals were administered LVV GFAP-ATXN1[Q2]-Flag. Changes of the excitatory postsynaptic currents amplitudes from Purkinje cells (PC) were recorded by patch clamp. Expression of anti-EAAT1 in the cerebellar cortex was assessed using immunohistochemistry.*

Results. *The reactive glia of the cerebellar cortex in SCA1 mice is characterized by a decrease in the immunoreactivity of anti-EAAT1, while chronic memantine use restores this capacity. The decay time of the excitatory postsynaptic current amplitude in the parallel fiber-Purkinje cell (PF-PC) synapses of the SCA1 mice is considerably longer, which indicates the slowing of glutamate reuptake and EAAT1 dysfunction. The prolonged presence of increased neurotransmitter levels in the synaptic cleft facilitates activation of the mGluR1 signaling and restoration of mGluR1-dependent synaptic plasticity in Purkinje cells of the SCA1 mice.*

Conclusions. *The slowing of neurotransmitter reuptake associated with long-term memantine treatment improves mGluR1-dependent short-term synaptic plasticity of the Purkinje cells in the SCA1 mice. Restoration of synaptic plasticity in these animals may underlie partial reduction of ataxic syndrome.*

Keywords*: short-term synaptic plasticity; astrogliosis; spinocerebellar ataxia type 1; glutamate reuptake*

Ethics approval. Authors confirm compliance with institutional and national standards for the use of laboratory animals in accordance with «Consensus Author Guidelines for Animal Use» (IAVES, 23 July 2010). The research protocol was approved by the Ethics Committee of Prof. V.F. Voino-YasenetskyKrasnoyarsk State Medical University (protocol No. 80/2017, December 27, 2017).

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3,5-диметил-адамантан-1-амин восстанавливает кратковременную синаптическую пластичность посредством изменения функции транспортёров возбуждающих аминокислот у модельных мышей со спиноцеребеллярной атаксией 1 типа

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Аннотация

Введение. *Мемантин – препарат для лечения деменции альцгеймерского типа, который значительно уменьшает явления нейродегенерации. Потенциально он может замедлить нейродегенеративные изменения в мозжечке и быть средством выбора в лечении спиноцеребеллярной атаксии 1 типа (СЦА1).*

Цель работы *– исследование молекулярных основ улучшения кратковременной синаптической пластичности при длительном потреблении мемантина модельными СЦА1-мышами.*

Материалы и методы. *Опыты проведены на 12-недельных мышах линии CD1. Мы создали модель астроглиоза мозжечка мыши после экспрессии мутантного атаксина 1 (ATXN1[Q85]) в глии Бергмана. Для моделирования астроцит-опосредованной нейродегенерации мозжечка данным мышам интракортикально в мозжечок вводили векторную конструкцию LVV GFAP-ATXN1[Q85]-Flag. Часть этих мышей получала мемантин в дозе 0,35 мг/кг в день, растворённой в питьевой воде, в течение 9 нед. Мышам контрольной группы вводили LVV GFAP-ATXN1[Q2]-Flag. Динамику амплитуд возбуждающих постсинаптических токов клеток Пуркинье регистрировали с помощью метода локальной фиксации потенциала. Экспрессию anti-EAAT1 в коре мозжечка изучали методом иммуногистохимии.*

Результаты. *Для реактивной глии коры мозжечка у СЦА1-мышей характерно снижение иммунореактивности анти-EAAT1, хроническое потребление мемантина восстанавливает этот показатель. У СЦА1-мышей в синапсах параллельных волокон с клетками Пуркинье время спада амплитуд возбуждающих постсинаптических токов значительно увеличено, что свидетельствует о замедлении обратного захвата глутамата и нарушении функции EAAT1. Повышенное продолжительное нахождение нейромедиатора в синаптической щели способствует облегчению активации mGluR1-пути передачи сигналов и восстановлению mGluR1-зависимой синаптической пластичности в клетках Пуркинье СЦА1-мышей.*

Заключение. *Замедление обратного захвата нейромедиатора при длительном потреблении мемантина оказывает положительное влияние на mGluR1-зависимую кратковременную синаптическую пластичность в клетках Пуркинье СЦА1-мышей. Восстановление синаптической пластичности у данных животных может лежать в основе частичного уменьшения атаксического синдрома.*

Ключевые слова*: кратковременная синаптическая пластичность; астроглиоз; спиноцеребеллярная атаксия 1 типа; обратный захват глутамата*

Этическое утверждение. Все исследования выполняли с учётом принципов гуманного обращения с животными, протоколы были утверждены решением Локального этического комитета КрасГМУ им. проф. В.Ф. Войно-Ясенецкого (протокол № 80/2017 от 27.12.2017).

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Introduction

Spinocerebellar ataxia type 1(SCA1) belongs to the group of polyglutamine diseases caused by an increased number of CAG nucleotide repeats in the coding region of the ataxin-1 gene (*ATXN1*). SCA1 is characterized by progressive cerebellar ataxia followed by bulbar paralysis and death in 10–15 years after the onset [1]. The pathogenesis can be explained by the toxic effect of a protein encoded by a mutant *ATXN1* gene, which forms aggregates in cells [2–4]. Studies of various SCA1 models showed that the main targets of this toxic effect are the cerebellar Purkinje cells (PC) [5–7]. The same models also demonstrated impairment of the short-term and long-term synaptic plasticity [8].

Glutamate is the neurotransmitter which predominantly mediates excitatory synaptic activity in the central nervous system. The concentration of glutamate in the synaptic cleft is strictly controlled by the balance between its release and clearance. This function is performed by excitatory amino acid transporter EAAT1, which is Na^+-dependent glutamate transporter mainly expressed in glial cells of the cerebellum [9]. Astrocytic EAATs play an important role in modulation of glutamatergic excitation, allow glutamate reuptake from the synapse and thereby protect neurons [10].

Dysfunction in these processes results in extracellular glutamate accumulation leading to excitotoxicity and damage of neurons [11]. Glutamate spillover from the synaptic cleft may activate extrasynaptic of N-methyl-D-aspartate (NMDA) receptors. Excessive Ca^{2+} influx through extrasynaptic NMDA-receptors induces signaling pathways activating programmed cell death [12].

The use of NMDA-receptor antagonists in neuroprotective pharmacotherapy for various neurodegenerative diseases is promising therapeutic approach [13]. One of such agents is 3,5-dimethyladamantan-1-amine (memantine). Memantine has been approved by FDA for the treatment of Alzheimer's disease [14, 15]. The neuroprotective effect of memantine has been also studied in other pathological conditions, i.e. ischemia, migraine, depression-like behavior, etc. [16–18]. Potential effects of memantine on SCA1 treatment are still unknown.

Another important role of NMDA receptors is their involvement in synaptic plasticity, which underlies learning and memory formation.

Previously, we described a model based on chronic optogenetic activation of Bergmann glia with the light-sensitive cation channel rhodopsin-2 (ChR2), where it was demonstrated a crucial role of EAAT mechanism dysfunction and further excitotoxicity in the pathogenesis of the cerebellar neurodegeneration [6]. We also described the short-term synaptic plasticity impairment in this model [19].

In this study we used a SCA1 mouse model with selective expression of mutant ataxin-1 to study the effects of long-term memantine administration on short-term synaptic plasticity.

Our **objective** was to explore the molecular mechanism of the short-term synaptic plasticity improvement associated with long-term memantine use in the SCA1 mouse model.

Materials and methods

AVV and LVV production

In order to increase the LVV expression level we used a GFAP promoter.[20] Sequences of non-pathogenic *ATXN1*[Q2] (encoding human ataxin-1 with 2 glutamine repeats) or pathogenic ATXN1[Q85] (with 85 uninterrupted glutamine repeats) were fused in frame with the sequence encoding the FLAG tag at their 5'ends. After that, Flag-ATXN1[Q2] and Flag-ATXN1[Q85] constructs were transferred into the pTYF lentiviral shuttle vector, under the control of the enhanced GFAP promoter. The detailed procedure for viral vector production was described previously [21]. Titers of LVV-GFAP-Flag-ATXN1[Q2] LVV and LVV-GFAP-Flag-ATXN1[Q85] were 7×10^9 transducing units (TU) per 1 mL. LVV were stored at −80ºC and used within 6 months.

Neurodegeneration modeling

Three-week-old wild type mice (P21) were anesthetized by 50 mg/kg Zoletil (Virbac) intraperitoneally. Mice were kept warm by a heated pad during surgical interventions. 3 μL of LVV or phosphate-buffered saline (PBS) were slowly injected

into the cortex of the cerebellar vermis (lobule VI) using a 10 μL Hamilton syringe. Stereotaxic coordinates relative to bregma were: AP: –2.5 mm, ML: 0 mm, DV: 2 mm. Mice were used for further experiments 9 weeks after the injection when expression of transgenic ataxin-1 was prominent. Some SCA1 mice received memantine at a dose of 0.35 mg/kg per day, dissolved in drinking water, for 9 weeks [22].

Immunohistochemistry

For immunohistochemistry, mice were perfused transcardially with a paraformaldehyde, 4% in 0.1 M PBS after being anesthetized by Zoletil (50 mg/kg) intraperitoneally. The whole brain was removed and postfixed in the same fixative overnight. The cerebellar vermis was cut into 50 μm sagittal slices. The slices were treated with rabbit monoclonal anti-EAAT1 antibodies (1 : 500, Cloud Clone Corp.) and then visualized with Alexa Fluor 594-conjugated donkey anti-rabbit IgG (1 : 1000, Life Technologies). The antibodies were dissolved in a PBS solution containing 2% normal donkey serum, 0.1% Triton X-100, and 0.05% NaN_3. For comparison, confocal fluorescence images of the cerebellar slices from the corresponding region of the cerebellum were obtained using the FV10i microscope (Olympus). Images were recorded as Z-stacks using × 10 objective and 1024 × 1024 resolution. Microphotographs converted to black and white were analyzed using ImageJ software. To avoid false positive results, we used the anti-EAAT1 signal fluorescence filter at 30% of maximal fluorescence intensity. To measure the EAAT1-positive area, the images of more than 30 pixels were selected.

The patch clamp method

Once the mice were deeply anesthetized by Zoletil, they were decapitated. The whole brain was dissected out and quickly immersed in ice-cold Ringer's solution, oxygenated by 95% O_2 and 5% CO_2. Parasagittal slices (250 μm) of the cerebellar vermis were made using a vibratome Microtom CU65 (Thermo Scientific). The slices were cut in a Ringer solution containing (in mM): 234 sucrose, 26 $NaHCO_4$, 2.5 KCl, 1.25 NaH_2PO_4, 11 glucose, 10 $MgSO_4$, and 0.5 $CaCl_2$ at 4ºC with continuous oxygenation by a mixture of 95% O_2 and 5% CO_2 [6]. The slices were maintained in an extracellular solution containing (in mM): 125 NaCl, 2.5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 1.25 NaH_2PO_4, 26 $NaHCO_3$, 10 D-glucose, and 0.05–0.10 picrotoxin. This solution was oxygenated continuously with a mixture of 95% O_2 and 5% CO_2 at room temperature for 1 h before starting the electrophysiological experiments.

For electrophysiological whole-cell recordings we used intracellular solution containing (in mM): 140 Cs-gluconate, 8 KCl, 10 HEPES, 1 $MgCl_2$, 2 MgATP, 0.4 NaGTP, 0.2 EGTA (pH 7.3). Electrophysiological data were analyzed using pClamp10 (Molecular Devices), Patchmaster (HEKA), and Clampfit 10.5 (Axon Instruments) software. Voltage of the PC membrane was clamped at –70 mV. To record the excitatory postsynaptic currents (EPSCs) during the stimulation of the parallel fibers (PF), the stimulating electrode was placed into the molecular layer of the cerebellar cortex. The assessment of the EPSC decay time constant (characteristic decay time τ) was performed in Clampfit by approximating the EPSC curve with an exponential function from the peak value (A) to the end of the signal recording.

For the short-term synaptic plasticity analysis (synaptically evoked suppression of excitation, SSE), the PC membrane voltage was clamped at –70 mV. The control PF-EPSC recording was made at 0.2 Hz during 40 sec. To evoke SSE, we applied high frequency PF stimulation (15 impulses at 100 Hz) in order to activate mGluR-mediated signaling pathway in PCs. The averaged PF-EPSC amplitudes over 10 s were normalized to the baseline values equal to the mean values prior to the SSE evoking. PF-EPSCs were then recorded for 100 s after the stimulation.

Statistical methods and data processing

The data were expressed as mean values ± standard error of the mean (*M* ± *SEM*) with 95% confidence interval. Statistical analysis was performed using basic statistical functions from the R open-source statistical software. Differences between the individual groups were analyzed using ANOVA and Tukey–Kramer test, which allows to correct *p* values when sample sizes are unequal. The differences were considered as significant at $p < 0.05$.

Results

Long-term memantine administration affects EAAT1 expression.

Changes in the cerebellar cortex caused by target expression of mutant ataxin-1 in the Bergmann glia were described in detail previously [23]. In this study, SCA1 mice were administered 0.35 mg/kg memantine for 9 weeks starting from postnatal day 21 to block neurodegenerative process.

Reactivation of the Bergmann glia with mutant ataxin-1 affected EAAT1 expression in mice. The mice with ATXN1[Q85] showed a decrease in expression of this gene: the area of anti-EAAT1 positive signal blot relative to the total area of the image was 15.2 ± 0.5% (9 areas studied in 3 mice – area/number (*a/n*) = 9/3 versus 17.0 ± 0.3% (*a/n* = 8/3) in mice expressing ATXN1[Q2] ($p = 0.007$; Fig. 1, *A*, *B*). Chronic memantine administration increased the area of anti-EAAT1 positive signal up to 17.5 ± 0.1% (*a/n* = 11/3) compared with mice without chronic memantine administration in mice expressing ATXN1[Q85] ($p = 0.002$).

An increased number of expressed EAAT1 positive spots in SCA1 mice after long-term memantine administration

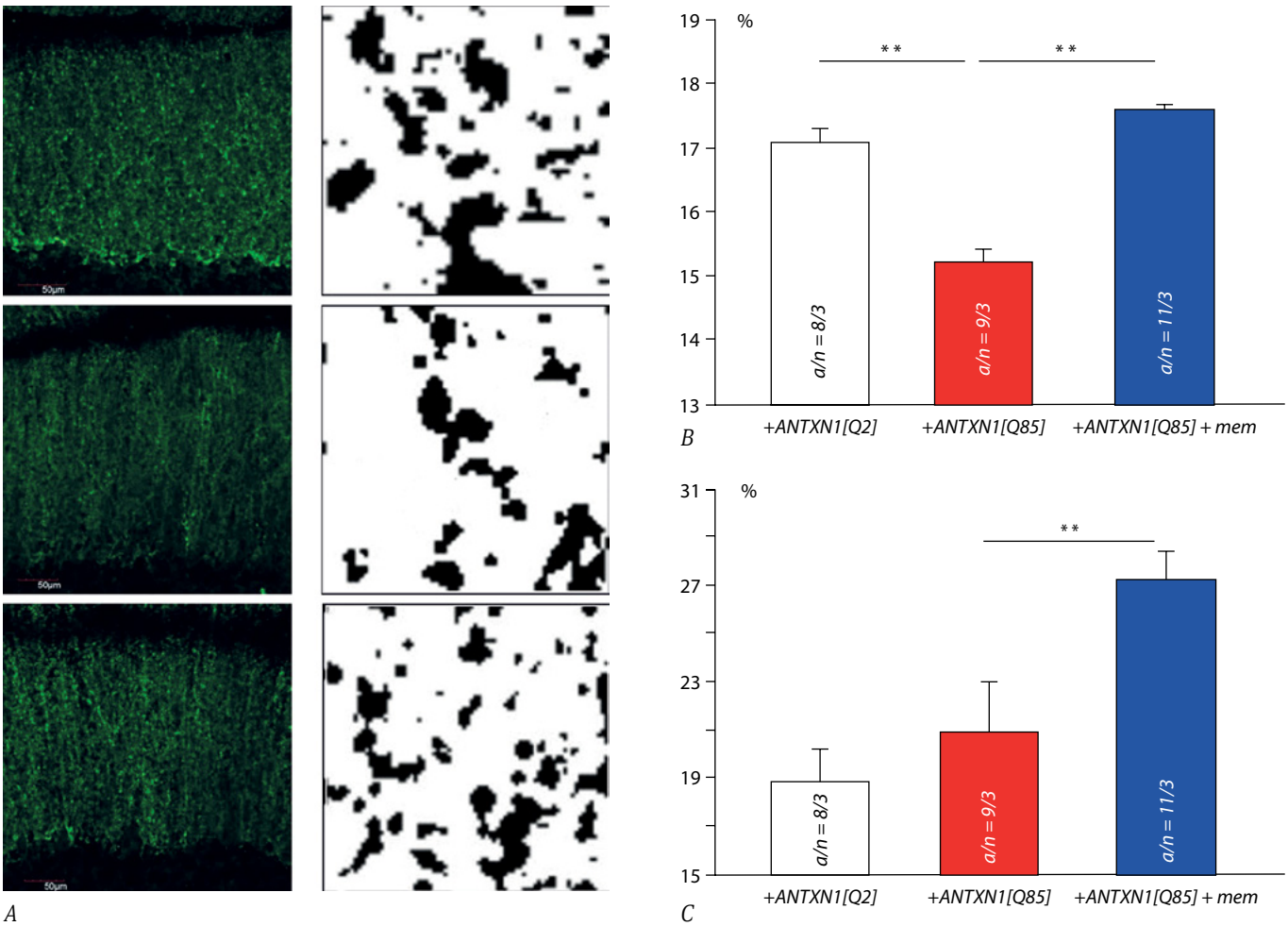

Fig. 1. EAAT1 expression in animals receiving and not receiving memantine.
A – fluorescent microphotographs of the cerebellar cortex slices labeled with anti-EAAT1 (left panel). The images processed with ImageJ software (right panel). Chart scales are 50 and 5 μm respectively. *B* – proportion of anti-EAAT1 positive signal area. *C* – total amount of anti-EAAT1 positive spots. *a/n* – number of examined areas/animals. $^{**}p < 0.01$.

turned out to be a more significant parameter: 27.1 ± 1.3 vs ATXN1[Q85] (21.0 ± 2.1) and ATXN1[Q2] (18.7 ± 1.7) in mice receiving vehicle ($p = 0.02$ and $p = 0.0001$ respectively; Fig. 1, *A*, *C*). These data indicate that memantine alters EAAT1 expression level by increasing the area and the number of transporters on the Bergmann glia cell membrane in the cerebellar cortex.

Long-term memantine administration affects synaptic transmission in PF-PC synapses

Altered EAAT1 expression levels change glutamate uptake from the synaptic cleft, which, in its turn, affects the synaptic transmission. To assess the effects of long-term memantine administration on synaptic transmission and plasticity, we studied electrophysiological characteristics of the PCs.

Decay time constant (τ) for PF-EPSC amplitudes recorded in PCs in SCA1 mice that did not receive memantine was not statistically different from the controls and was 14.5 ± 1.0 ms–1 (18 cells studied in 4 mice – cells/number (*c/n*) = 18/4) in ATXN1[Q2] mice and 15.1 ± 1.5 мс$^{-1}$ in ATXN1[Q85] mice (*c/n* = 19/4; $p = 0.75$; unpaired t-test). Long-term memantine administration increased τ-value for PF-EPSC amplitudes in SCA1 mice up to 21.0 ± 2.3 ms^{-1} (*c/n* = 14/4; $p = 0.048$; Fig. 2).

The mutant ataxin-1 expression in the Bergmann glia selectively affects SSE levels

Slow decay of PF-EPSC amplitudes may indicate a long-term effect of glutamate on postsynaptic receptors due to its accumulation caused by uptake dysfunction. This may create conditions for glutamate release from the synaptic cleft and for activation of perisynaptic receptors, such as mGluR1. Thus, we studied a certain type of short-term synaptic plasticity associated with activation of mGluR1 signaling in the PCs. Tetanic PF stimulation results in activation of mGluR1

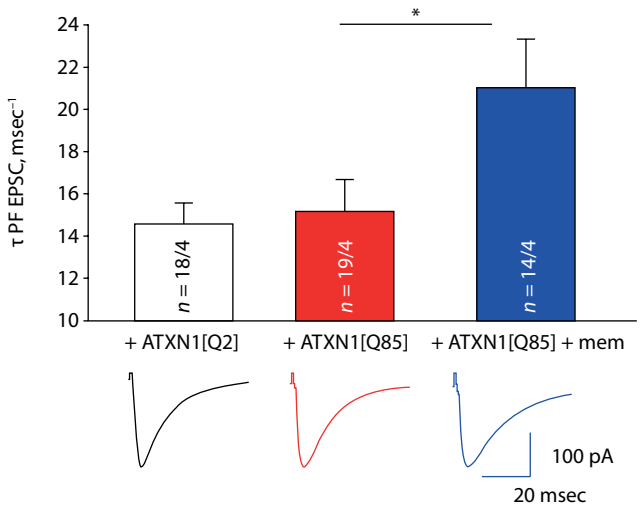

Fig. 2. Memantine increases the constant decay time (τ) of PF-EPSC amplitude in the PC of SCA1 mice.
Summary diagram of the PF-EPSCs mean constant decay time (τ). Representative curves are presented on the right panel. *c/n* is the number of cells/animals (*$p < 0.05$).

associated with a local increase in Ca^{2+} concentration in the PCs. Ca^{2+} influx triggers the synthesis of endocannabinoids, which signal retrogradely to inhibit the release of glutamate from the presynaptic PF terminals (SSE) [24–27].

In the presence of 25 μm CPCCOEt, an mGluR1-specific blocker, the amplitude PF-EPSC began to rise immediately after the tetanic stimulation: from 37.6 ± 5.9 to 63.5 ± 5.0% (*c/n* = 7/3; $p = 0.026$, the paired t-test; Fig. 3).

After the tetanic stimulation in ATXN1[Q85] mice the PF-EPSC amplitude increased (116.1 ± 8.9% [*c/n* = 8/3]). The amplitude inhibition was not detected, while in ATXN1[Q2] mice the PF-EPSC amplitude dropped after the stimulation and stayed reduced during the whole period of recording (79.1 ± 14.1%; *c/n* = 8/3; $p < 0.01$; Fig. 4). Long-term memantine administration restored the SSE level: the amplitude after the stimulation has dropped (44.9 ± 8.5%; *c/n* = 9/3; $p < 0.001$ versus the mice without memantine consumption); the changes of amplitude restoration were similar to those in ATXN1[Q2] mice (Fig. 4).

Discussion

We used SCA1 mouse model with LVV GFAP-ATXN1[Q85]-Flag target expression in the Bergmann glia [23] to assess the effects of memantine on the processes involved in short-term synaptic plasticity. Memantine was administered in drinking water for 9 weeks at 0.35 mg/kg.

Previously, we showed a decrease in expression and in the function of excitatory amino acid transporters EAAT1 in the optogenetic model of cerebellar neurodegeneration [6]. These changes are associated with dysfunction in astrocyte glutamate reuptake from the synaptic cleft and are well documented for various neurodegenerative conditions [13, 14, 16].

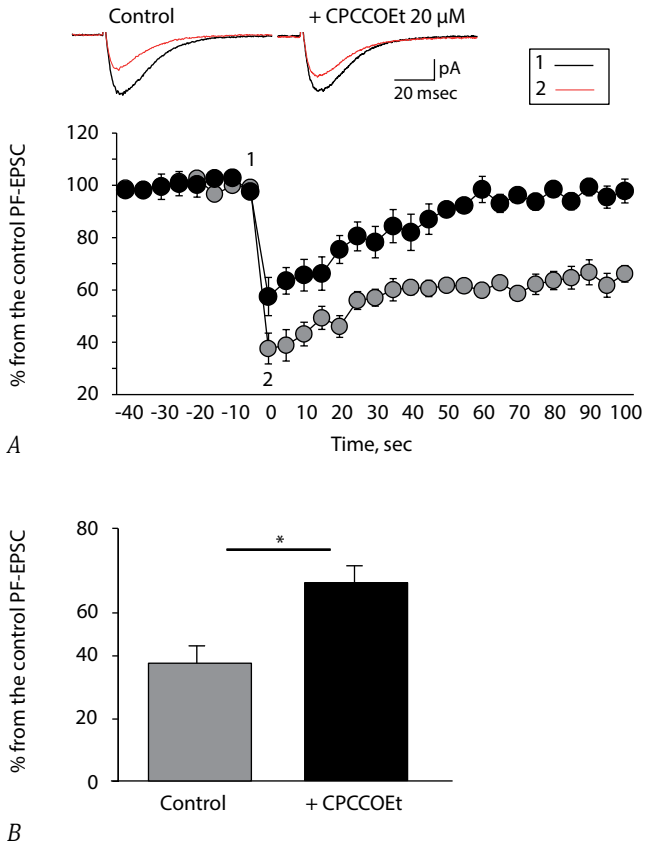

Fig. 3. The SSE impairment after the inhibition of mGluR1-dependent signaling pathway in the presence of CPCCOEt.
A – changes of PF-EPSC amplitudes after tetanic PF stimulation. Representative PF-EPSC curves above the chart: recorded immediately before the stimulation (point 1, 10 sec on the time axis) and after the stimulation (point 2, 0 sec on the time axis). *B* – amplitudes normalized to the pre-stimulation level immediately after the stimulation (point 2). *c/n* is the number of cells/animals. *$p < 0.05$.

In our SCA1 mouse model, a similar effect was observed: we found a decrease in EAAT1 expression in the cerebellar cortex. Memantine restored the expression levels up to the control values in both neurodegeneration models [6]; Fig. 1, *A, B*. There are data indicating that EAAT1 protein expression is activated by exogenous glutamate [10, 28]. S. Duan et al. have discovered that this glutamate-mediated mechanism of the augmentation in EAAT1 function is induced by the EAAT1 surface expression in cultured murine astrocytes without altering expression level of a membrane transport protein [29]. We speculate that such mechanism prorects neurons against excitotoxicity. We showed increased anti-EAAT1 positive blots in SCA1 model mice after memantine consumption (Fig. 1, *A, C*). It may indicate to altered clasterisation or transportation of these transmitters to cell membrane depending on glutamate presence in the synaptic cleft. It is important to continue studies to prove this hypothesis.

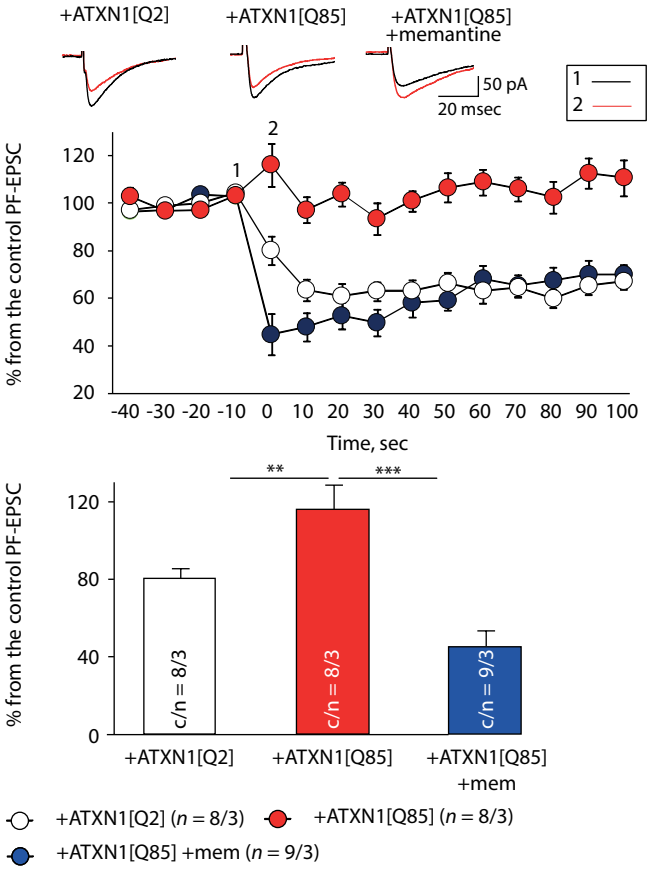

Fig. 4. SSE restoration in SCA1 mice after long-term memantine administration (mem).
A – changes of PF-EPSC amplitudes after tetanic PF stimulation. Representative PF-EPSC curves above the chart: recorded immediately before the stimulation (point 1, 10 s on the time axis) and after the stimulation (point 2, 0 s on the time axis).
B – amplitudes normalized to the pre-stimulation level immediately after the stimulation (point 2).
c/n is the number of cells/animals.
$^{**}p < 0.01$; $^{***}p < 0.001$.

At the same time, it was shown that memantine administration decrease glutamate uptake activity, both in the frontoparietal cortex and in the hyppocampus, with no effect on expression levels of the excitatory amino acid transporters [30].

The observed increase in EAAT1 expression might be a compensatory mechanism activated by decline in EAAT1 function. The EAAT1 dysfunction is also due to the increased τ-values for PF-EPSC observed in SCA1 mice receiving long-term memantine administration (Fig. 2).

One of the manifestations of the altered levels of gene expression and a result of astroglia reactivation in SCA1 mice is impaired glutamate signal transmission. There is a decrease of mGluR1 levels on the PC membranes, as well as the levels of glutamate symporters EAAT4 and of glutamate and aspartate transporter EAAT1 in the Bergmann glia [31–34], resulted in a number of electrophysiological PC dysfunctions, which compromises motor learning and synaptic plasticity [33, 34].

The most studied types of synaptic plasticity in PF-PC synapses are the paired pulse facilitation, impulse suppression after depolarization, SSE and long-term depression (LTD). Among these types, SSE and LTD are mGluR-dependent ones, but LTD is triggered by a combination of PF stimulation (mGluR activation) and Purkinje cell depolarization [35]. For this reason, LTD is not able to show selective changes of mGluR signaling in PCs. LTD induction is blocked not only in the presence of mGluR-specific blockers, but also in the absence of membrane depolarization [36]. So, the SSE was studied as a process completely dependent on mGluR activation [25]. The range of an increase in mGluR-signaling may be indirectly, but quite precisely determined based on restoration of EPSC curve after tetanic stimulation. With long-term memantine administration, an increase in neurotransmitter levels in the synaptic cleft allows glutamate accumulation, which causes mGluR1 activation and thereby contributes to SSE restoration (Fig. 4).

The decreased glutamate uptake from the synaptic cleft by PF-PCs is induced by long-term effects of memantine administration. This mechanism causes no neurodegradation, because NMDA receptors remain blocked by memantine. However, increased levels of glutamate in the synaptic cleft allow this neurotransmitter to reach the perisynaptic mGluR1 and induce synaptic plasticity, such as SSE (Fig. 4). Understanding this process would help to predict the effects of prescribed drugs on the glutamatergic system.

Achieving a balance between the release and clearance of glutamate may be the key to treating many neurodegenerative diseases. Understanding these mechanisms is of paramount importance for the planning of future clinical studies.

Conclusion

In neurodegenerative diseases affecting the cerebellum, such as SCA1, the impairment of SSE type of short-term synaptic plasticity is associated with mGluR degradation on the dendritic spines. In our study we demonstrated that memantine induced a decrease in neurotransmitter uptake by modulating EAAT1 function and an increase in mGluR signaling within PCs. Our research contributes to the picture of the impaired mechanisms of synaptic plasticity in the neuronal cells of the cerebellum, the understanding of which is a necessary element of the treatment strategy for neurodegenerative various conditions.

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Neuroplasticity, music, and human brain

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Abstract

Introduction. *Studying the influence of music on the human brain is one of the key topics in neuroscience as it allows extending our understanding of brain neuroplasticity.*
This study aimed *to investigate structural brain organization in professional musicians.*
Materials and methods. *We investigated 27 brains (i.e. 54 hemispheres) of male musicians, female musicians, male non-musicians, and female non-musicians by magnetic resonance imaging. All study participants were aged 20 to 30 years and did not have any mental or neurological disorders. Gray matter volume and cortex thickness in different cortical structures of the right and left hemispheres were measured.*
Results. *We found major changes in the brain structure in professional musicians (both male and female) vs. non-musicians. We found differences in the macroscopic structure of the triangular region in the Broca's motor speech area in musicians' brain. Increases in gray matter volume in the brain of musicians and its individual cortical structures were shown in the superior temporal region, Broca's motor speech area, hippocampus, superior parietal lobule, and other structures. We found increased thickness of cortical structures in musicians vs. non-musicians.*
Conclusions. *Practicing music regularly was shown to change structural brain organization; we found significant increases in gray matter volume and cortex thickness in various cortical structures in the right and left brain hemispheres of musicians vs. non-musicians.*

Keywords*: brain; male; female; music; cortical structures*

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of the Research Center of Neurology (protocol No. 7-4/22, August 29, 2022).

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Нейропластичность, музыка и мозг

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Аннотация

Введение. *Изучение влияния музыки на мозг человека является одной из важных проблем нейронауки, т.к. позволяет расширить наше представление о нейропластичности мозга.*
Цель *исследования – изучение особенностей структурной организации мозга профессиональных музыкантов.*
Материалы и методы. *С помощью магнитно-резонансной томографии исследовали 27 мозгов (54 полушария) мужчин-музыкантов, женщин-музыкантов и людей, не имеющих отношения к музыке. Все исследуемые были в возрасте 20–30 лет, без неврологических и психических заболеваний. Измеряли объём серого вещества и толщину коры различных корковых формаций в правом и левом полушариях мозга.*
Результаты. *Установлены принципиальные изменения строения мозга профессиональных музыкантов (мужчин и женщин) в сравнении с мозгом людей, не имеющих отношения к музыке. Отмечены особенности макроскопического строения триангулярной области речедвигательной зоны Брока мозга музыкантов. Установлено увеличение объёма серого вещества мозга музыкантов и его отдельных корковых формаций, в частности, верхней височной извилины, речедвигательной зоны Брока, гиппокампа, верхней теменной дольки и ряда других структур. Показано увеличение толщины коры корковых структур мозга музыкантов в сравнении с мозгом немузыкантов.*

Заключение. *Систематические занятия музыкой изменяют структурную организацию мозга, установлено значительное увеличение объёма серого вещества и толщины коры различных корковых формаций в правом и левом полушариях мозга музыкантов по сравнению с людьми контрольной группы.*

Ключевые слова*: мозг; мужчина; женщина; музыка; корковые формации*

Соблюдение этических стандартов. Исследование проводилось при добровольном информированном согласии пациентов. Протокол исследования одобрен Этическим комитетом Научного центра неврологии (протокол № 7-4/22 от 29.08.2022).

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

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

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Introduction

Neuroplasticity or brain plasticity is one of the key topics in neuroscience. The term neuroplasticity refers to the ability of the brain to change its function and structure under the influence of external environment, professional activity, or psychological stress [1–5].

Santiago Ramón y Cajal was one of the first researchers to use the term neural plasticity; however, he used it to describe the neuron as a key and fundamental brain unit. Afterwards, this term was used mainly to describe regeneration of peripheral nervous system [6].

The use of microelectrodes in neurophysiological studies allowed researchers to record electrical signals from neurons and, therefore, to elucidate interactions between individual neurons by drawing structural and functional maps of the brain. In the 1960s, D. Hubel and T. Wiesel studied animals' brain and showed that the brain had greater plasticity in younger animals, especially between Week 3 and Week 8 of the postnatal period. By showing changes in the functioning of cortical brain structures in animals with visual impairment, these authors also demonstrated for the first time that the functional map of the brain can change [7–9].

Further experimental studies showed the ability of structural and functional brain maps to change [10–12].

Studies to evaluate the brain of healthy human subjects and patients by magnetic resonance imaging (MRI) greatly contributed to understanding neuroplasticity. For the first time, changes in people's brain related to their professional activity were shown.

Music is an essential component of human emotional life. Many modern publications clearly demonstrated that music influenced human memory, rhythm, and perception of time. Listening to music, people can calm down and relax, or music can make them move or dance. Practicing music professionally can reshape a person's life [13, 14]; however, there are very few studies, if any, to evaluate musicians' brains.

This study aimed to investigate structural brain organization in professional musicians.

Materials and methods

A total of 27 brains (i.e. 54 hemispheres) of 9 male non-musicians, 9 female non-musicians, 5 male musicians, and 4 female musicians were studied by MRI. All study subjects were aged 20 to 30 years and did not have any mental or neurological disorders. All male and female musicians have been playing the piano since their childhood and had a university degree in music (i.e. piano). Currently they worked as piano teachers, accompanists or gave recitals.

Study subjects provided informed consent to participate in the study. The study protocol was approved by the Ethics Committee of Research Center of Neurology (Protocol 7-4/22, August 29, 2022).

We measured total volume of the gray matter, white matter, several cortical structures, inferior frontal gyrus,

opercular region of Broca's motor speech area, parahippocampal gyrus, superior temporal gyrus, temporal pole, and other brain structures, as well as cortex thickness in several brain regions.

The study was performed using an ultra-high-field Siemens MAGNETOM Prisma MRI scanner in T1 MP2RAGE sequence in the sagittal plane with 176 slices, slice thickness of 1 mm, scanning parameters TR = 5000.0 ms, TE = 2.74 ms, TI1 = 700 ms, TI2 = 2500 ms, flip angle$_1$ = 4°, flip angle$_2$ = 5° and matrix size of 256 mm. Brain surface was reconstructed by processing MRI images using CAT12 MRI data processing toolkit, which was created using Matlab package. The Segment module was used according to the standard procedure described in the CAT12 application manual. Gray matter volume and cortex thickness were measured using CAT12 in the ROI Tools module with neuromorphometrics and parc_a2009s_thickness atlases.

Data were processed statistically using Statistica v. 8 and Rver.4.x software packages. Differences between brain parameters of musicians and non-musicians were assessed for significance using non-parametric statistics with Mann – Whitney U-test. Differences were considered significant if the level of statistical significance p was less than 0.05. For the ease of data representation in the article, median values (M) and interquartile ranges (Q_1–Q_3) were provided.

Results

We found major changes in the brain structure of male musicians *vs.* male non-musicians and female musicians *vs.* female non-musicians. An analysis to compare the macroscopic structure of the Broca's area in the left hemisphere (LH) showed that female musicians had more complex structure of the triangular region in the brain cortex compared with female non-musicians. Additional grooves were seen in the brain of female musicians compared with female non-musicians (especially in the triangular region), as well as merging of the triangular region with the opercular region and the orbital region of the brain due to the presence of interstitial formations, which increased the size of both the triangular and opercular regions (Fig. 1, 2).

In male musicians, relative volume of the gray matter as a percentage of total brain volume was greater than in male non-musicians (p = 0.048): median relative volume of the gray matter as a percentage of total brain volume was 36.00% ± 4.05% in male non-musicians and 40.25% ± 3.68% in male non-musicians. In women, differences were not considered significant (p = 0.44; Fig. 3).

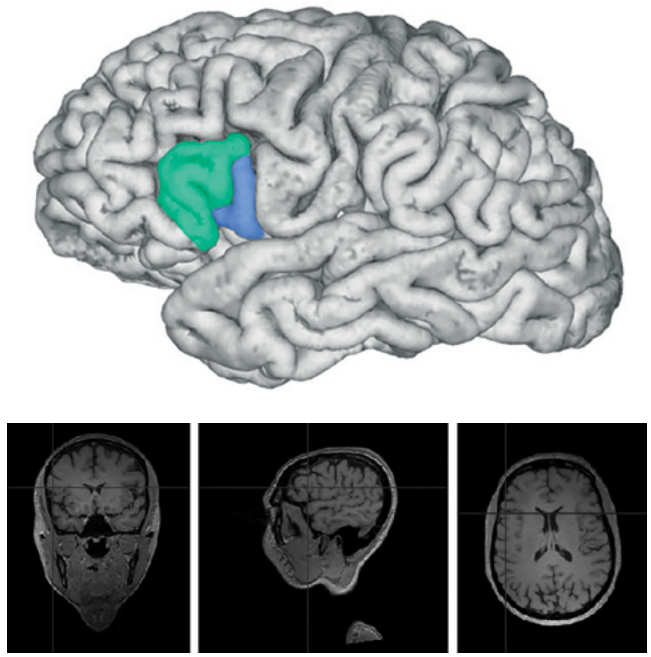

Fig. 1. Structure of Broca's area in the brain of a female musician, LH.
Triangular region is shown in green; opercular region is shown in blue.

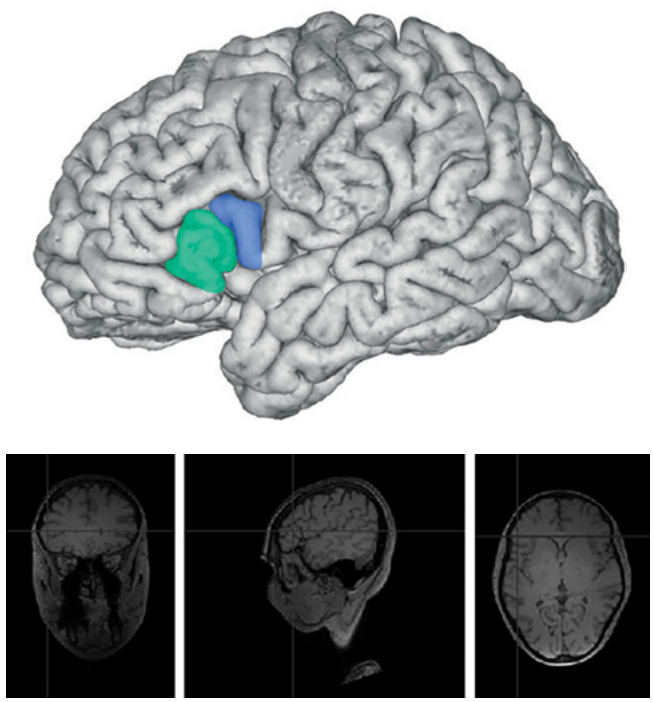

Fig. 2. Structure of Broca's area in the brain of a female non-musician, LH.
Triangular region is shown in green; opercular region is shown in blue.

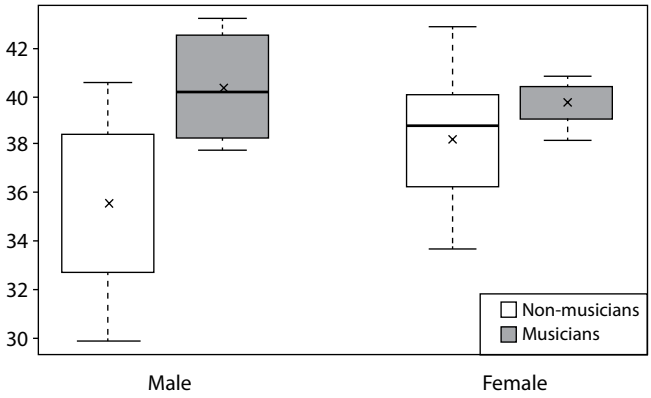

Fig. 3. Relative volume of gray matter in male and female non-musicians and musicians, % of total brain volume.

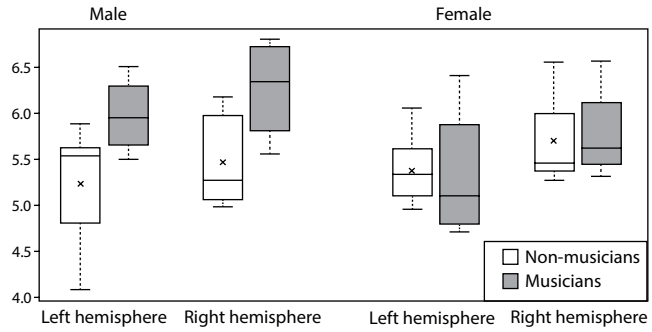

Fig. 4. Volume of superior temporal gyrus in musicians and non-musicians, cm³.

This study showed that the volume of several cortical structures in the brain of male and female musicians was bigger than that of male and female non-musicians, respectively. Median volume of the opercular region of Broca's motor speech area in the inferior frontal gyrus of the right hemisphere (RH) was 2.53 ± 0.94 cm³ and 2.82 ± 0.10 cm³ in male non-musicians and male musicians, respectively. Male musicians had the same trend in their brain LH. Median volume of the opercular region of Broca's motor speech area in the LH was 2.42 ± 0.62 cm³ and 2.72 ± 0.09 cm³ in male non-musicians and male musicians, respectively.

Hippocampus volume was slightly increased in musicians (p = 0.57), and median hippocampus volume in the RH was 3.25 ± 0.19 cm³ and 3.32 ± 0.36 cm³ in male non-musicians and male musicians, respectively.

Of note are changes in the volume of cortical structures in the temporal region of the brain in male musicians compared with these brain structures in non-musicians (Fig. 4). Median volume of the superior temporal gyrus in the RH was 5.27 ± 0.88 cm³ and 6.34 ± 0.72 cm³ in male non-musicians and male musicians, respectively (p = 0.048). Median volume of the superior temporal gyrus in the LH in male

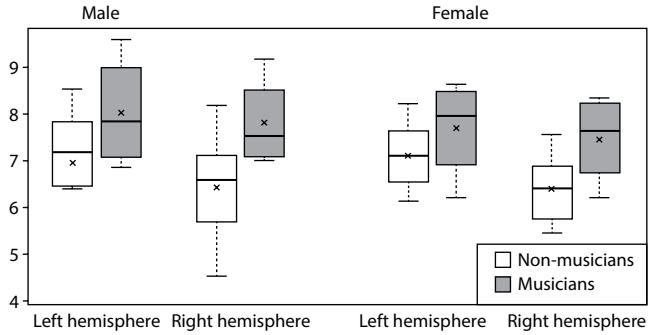

Fig. 5. The volume of the upper parietal lobule of the brain of musicians and people of the control group, cm³.

musicians (5.95 ± 0.45 cm³) was also higher than in male non-musicians (5.53 ± 0.73 cm³) (p = 0.110). In women, median volume of the superior temporal gyrus in the RH was 5.63 ± 0.38 cm³ and 5.46 ± 0.62 cm³ in female musicians and female non-musicians, respectively (p = 0.604). Median volume of the superior temporal gyrus in the LH was 5.10 ± 0.77 cm3 and 5.32 ± 0.51 cm³, respectively (p = 0.604).

A trend towards an increased volume of the superior parietal lobe was shown in musicians (Fig. 5). Median volume of the superior parietal lobe in the RH was 6.58 ± 1.33 cm³ in male non-musicians and 7.58 ± 2.20 cm³ in male musicians (p = 0.072); that in the LH was 7.21 ± 1.40 cm³ and 7.89 ± 1.61 cm³, respectively (p = 0.368). In women, median volume of the superior parietal lobe in the RH was 6.40 ± 1.19 cm³ and 7.71 ± 1.19 cm³ in female non-musicians and female musicians, respectively (p = 0.076). In the LH, median volume of the superior parietal lobe was 7.14 ± 1.16 cm³ and 8.04 ± 1.18 cm³ in female non-musicians and female musicians, respectively (p = 0.330).

This study demonstrated increased thickness of the cortex in several cortical structures in musicians. For example, median cortex thickness in the angular gyrus of the brain LH was 2.04 ± 0.29 mm and 2.20 ± 0.19 mm in male non-musicians and male musicians, respectively (p = 0.283). A similar increase in median cortex thickness in the angular gyrus was seen in male musicians (2.30 ± 0.18 mm) *vs.* non-musicians (2.13 ± 0.23 mm) (p = 0.048). Median cortex thickness in the angular gyrus in female musicians was also higher than in female non-musicians (p = 0.017 and p = 0.034) with the differences being statistically significant in both hemispheres, while differences in men were statistically significant only in the RH.

There was a trend towards increased cortex thickness in the superior temporal gyrus (lateral) of the LH in male musicians (2.68 ± 2.68 mm) *vs.* male non-musicians (2.42 ± 0.30 mm) (p = 0.109); that of the RH was 2.71 ± 0.11 mm in male musicians and 2.38 ± 0.22 mm in male non-musicians

(p = 0.073). In female non-musicians, median cortex thickness in the lateral part of the superior temporal gyrus was 2.55 ± 0.33 mm (LH) and 2.66 ± 0.18 mm (RH); in female musicians, median values were 2.63 ± 0.18 mm (LH) and 2.70 ± 0.27 mm (RH), respectively (p = 0.504 and p = 0.904).

We also showed changes in the volume of the *planum temporale* in musicians. Median volume of the *planum temporale* in the LH was 1.84 ± 0.19 cm^3 in male musicians and 1.60 ± 0.39 cm^3 in male non-musicians (p = 0.214), that in the RH was 1.71 ± 0.18 and 1.41 ± 0.17 cm^3, respectively (p = 0.048). In female musicians, median volume of the *planum temporale* was 1.62 ± 0.39 cm^3 and 1.57 ± 0.20 cm^3 in LH and RH, respectively. In female non-musicians, median volume of the *planum temporale* was similar: 1.45 ± 0.12 cm^3 (p = 0.604) and 1.42 ± 0.17 cm^3 (p = 0.199) in the LH and RH, respectively.

Discussion

Our study showed major differences in the brain structure in musicians *vs.* non-musicians. Increased volume of several cortical structures was found in both male and female musicians.

Our data are consistent with several experimental studies that clearly showed that constant training and mental activities can lead to changes in the structural organization of the human brain and increase the overall volume of cortical structures [15].

Musicians who play the piano and achieve great results in their professional life should work hard. According to Andreas Eriksson's theory, it takes at least 10,000 hours of deliberate practice to master a skill. This corresponds to about 3 hours of training every day, i.e. about 20 h every week. This hypothesis was named "a 10,000-hours rule" [13]. Such intensive systematic training and constant practice were shown to result in structural changes in the entire human brain and individual cortical structures. Several studies showed that constant training in people of other professions also led to changes in their brain structure. This was shown in a study to evaluate the brain of taxi drivers in London, which showed an increase in the posterior hippocampus, which is responsible for spatial perception and spatial memory. More experienced taxi drivers were shown to have a larger volume of the caudal hippocampus [16]. Meditation and learning foreign languages were also shown to be associated with changes in the structure of the human brain.

An analysis of changes in different brain regions of musicians compared with male and female non-musicians clearly showed an increase in the volume of the superior temporal gyrus in musicians.

Our data are consistent with other authors' data who also showed increased *planum temporale*, especially in musicians' brain [13, 17, 18].

Some authors showed that the volume of the auditory cortex in musicians was 30% higher than in non-musicians [19].

Publications also showed that absolute pitch had a great influence on restructuring of musicians' brain (plasticity), particularly on changes in the temporal regions. However, famous musicians who did not have absolute pitch, such as Igor Stravinsky and Miles Davis, were also described in literature [13].

A comparative analysis of the brain structure in musicians and non-musicians allowed us to show increases in the superior parietal region both in the RH and LH. This increase may be related to the fact that the superior parietal region is involved in the integration of sensory information and plays a key role in reading music scores [20, 21].

We showed increased volume of the parahippocampal gyrus, especially in the RH, in the brain of musicians *vs.* non-musicians. This can be explained by the fact that the parahippocampal gyrus is involved in the implementation of emotional and speech functions. Some authors showed activation and reorganization of the parahippocampal gyrus, especially in the RH, in subjects who were listening to music [22].

We showed increased Broca's speech motor area in male musicians *vs.* male non-musicians and in female musicians *vs.* female non-musicians. Music lessons were shown to improve speech functions and an ability to process sound signals [23–26]. Some researchers believe that Broca's speech motor area is actively involved in listening to and playing musical works [27]. Functional MRI was used to show activation of the Broca's speech motor area (fields 44 and 45) in people who were listening to any musical work; activation of the premotor cortex (field 6), orbital region of the inferior frontal gyrus (field 47), and superior temporal gyrus (fields 21, 37, and 22) was also seen [28–30]. All these studies confirmed that speech processing and practicing music are closely related, and music was shown to stimulate and improve verbal working memory [31, 32].

Of great interest are our data suggesting increases in the *planum temporale* in male and female musicians compared with male and female non-musicians, respectively. We showed increased volume of *planum temporale*, particularly in the brain LH.

In this study, practicing music regularly was shown to change structural and functional brain organization.

Available data suggest that music, which results in major plastic changes in human cognitive functions, can and should be used in the treatment of several neurological and psychiatric disorders. Music-supported therapy can be effective in post-stroke rehabilitation, motor activity disorders, anxiety disorders, and other disorders [33–36].

Conclusion

Our study, which investigated structural organization of the brain in musicians, clearly showed significant changes in many cortical structures of the brain, which generally contribute to the development of human musical abilities, speech, and cognitive functions.

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Surgical Treatment Options for Degenerative Lumbosacral Spinal Stenosis

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Abstract

Degenerative spinal stenosis is the most common type of degenerative and dystrophic spine disease. The clinical picture of stenosis, which may include axial pain syndrome, leg pain, intermittent claudication syndrome, weakness and loss of sensitivity in the legs, and impaired pelvic functions, can significantly worsen patients' quality of life and reduce their ability to work and lead an active lifestyle.

Degenerative spinal stenosis mostly affects the elderly. Therapeutic and neurological communities have stereotypes about spine surgery being too traumatic and invasive, and, therefore, they believe that their use should be contraindicated to and limited in elderly patients. However, surgeons are increasingly giving preference to minimally invasive interventions with high efficacy and safety together with a low risk of complications.

*We **aimed** at reviewing current treatment methods for degenerative lumbosacral spinal stenosis with an emphasis on surgical treatment methods.*

Keywords: *degenerative spinal canal stenosis; spinal canal decompression methods; endoscopic decompression*

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Варианты хирургического лечения дегенеративных стенозов пояснично-крестцового отдела позвоночника

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Аннотация

Стеноз позвоночного канала дегенеративной природы является самой распространённой нозологией среди дегенеративно-дистрофических поражений позвоночника. Клиническая картина стеноза, которая может включать аксиальный болевой синдром и боль в ногах, синдром перемежающейся хромоты, слабость и нарушение чувствительности в ногах, нарушение тазовых функций, существенно снижает качество жизни пациентов и приводит к потере ими трудоспособности и возможности вести активный образ жизни.

Дегенеративный стеноз позвоночника – это в основном болезнь пожилых людей. В терапевтическом и неврологическом сообществах сложился стереотип о чрезмерной травматичности и инвазивности хирургических вмешательств на позвоночнике и, следовательно, о противопоказаниях и ограничениях использования опций хирургического лечения у пациентов пожилого возраста. Однако в настоящее время хирурги всё чаще отдают предпочтение малоинвазивным вмешательствам, имеющим высокую эффективность и безопасность и характеризующимся низкими рисками осложнений.

***Целью** данной работы является обзор современных методов лечения дегенеративных стенозов пояснично-крестцового отдела позвоночника с акцентом на хирургических вариантах лечения данной патологии.*

***Ключевые слова**: дегенеративный стеноз позвоночного канала; способы декомпрессии позвоночного канала; эндоскопическая декомпрессия*

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

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

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Introduction

Spinal canal (SC) stenosis is defined as a diffuse or limited abnormal narrowing of the SC that results in compression of neurovascular structures such as the spinal cord, spinal roots, ganglia, arteries, and veins [1–3]. This concept is based on a multifactorial pathological mechanism that involves compression of intracanal neurovascular structures. The clinical picture of lumbar spinal stenosis was first described by H. Verbiest in 1954 [4, 5]. D. Onel et al. defined stenosis as any narrowing of the central spinal canal or intervertebral foramen [6]. Stenosis classifications were described in details by L.E. Antipko [2]. By its ethiology, SC stenosis can be primary (congenital), secondary (acquired), or combined. Congenital SC stenosis is developed as a result of congenital anomalies or postnatal developmental defects. Acquired SC stenosis can be caused by degeneration, infection, traumas, or post-operative changes.

Degeneration and dystrophic processes in the spine are irreversible and begin in humans around the age of 20. They are caused by the Kirkaldy–Willis cascade, which includes three stages: dysfunction, relative instability, and restabilization [7].

Prevalence of symptomatic degenerative spinal stenosis is 11% and 25% in the total population and in outpatient settings, respectively [8]. The need for surgical care for degenerative stenosis is 50 procedures per 100,000 population[1], which corresponds to 20% of patients seeking medical help for spinal stenosis. Prophylactic measures are important in preventing the development of any disease, which is also true for degenerative SC stenosis. However, in the case of stenosis, the aim is not to prevent it as such but rather to slow down degeneration and dystrophic processes with preserving maximal functionality of the spine, paravertebral muscles, and nervous structures such as the spinal cord and roots. Conservative treatment and rehabilitation are initiated if spinal stenosis becomes symptomatic [9]. And only if these treatment options turn out to be ineffective, the patient can proceed to radical surgery.

Clinical findings

Neurogenic (caudogenic) intermittent claudication is the most typical syndrome of SC stenosis; it includes the following symptoms:

- back pain occurs when walking and irradiates to legs;
- leg pain and paresthesia in specific spine positions. Symptoms become worse during extension, walking (especially down stairs), prolonged standing, i.e. in body positions with SC being narrowed yet more;
- pain decreases or disappears when sitting, bending, or squatting. There is no pain when walking up the stairs or riding a bicycle;
- bending or standing does not increase symptoms, unlike discogenic pain;
- pain increases in lying position;
- neurological symptoms (i.e. muscle weakness, loss or decreased reflexes, sensory disorders) are related to exercise;
- Lasegue's sign is more often negative.

Neurogenic claudication should be differentiated from true (vascular) intermittent claudication associated with occlusive disease.

In patients with SC stenosis, other complaints include pelvic dysfunction, which is manifested by bladder disturbances and impotence of various degree.

Neurological examination shows minimal to no abnormalities [10].

Magnetic resonance imaging (MRI) is a method of choice for diagnosing degenerative spinal stenosis. Fig. 1 shows

[1] Progress Report for 2020 by V.V. Krylov, Head External Neurosurgery Expert of the Ministry of Health of Russia. URL: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/056/647/original/Отчет_за_2020_год_Крылов.pdf

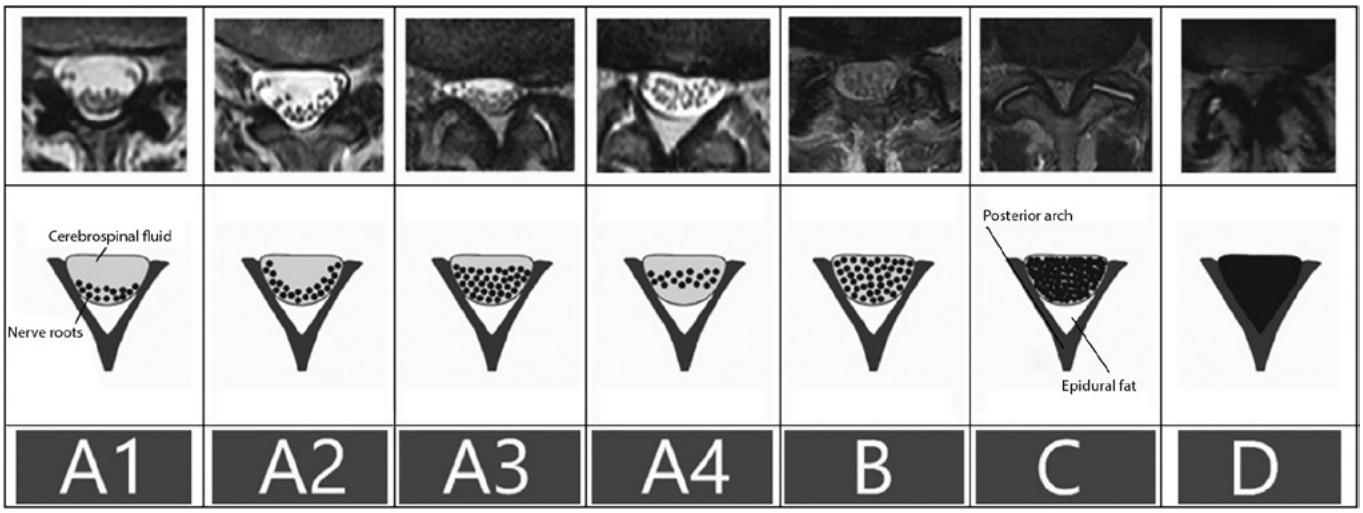


Fig. 1. Visual grading of stenosis according to C. Schizas [11].

visual grading of stenosis according to C. Schizas [11]. Significant stenotic changes on computed tomography or MRI in healthy people without complaints is a challenge related to imaging [12]. Therefore, significance of any imaging results in patients with SC stenosis is defined by their clinical findings.

Treatment methods

Conservative treatment

According to clinical guidelines, conservative stenosis treatment includes medication and non-medication methods [9, 13]. Medication treatment includes non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, muscle relaxants, antidepressants, and anticonvulsants [1, 9, 14–17]. Medication methods aim to reduce the intensity of chronic back pain. No NSAIDs were shown to be superior over the other ones in their analgetic activity. Long-term use of NSAIDs is associated with an increased risk of adverse effects, primarily gastrointestinal and cardiovascular disorders. Therefore, NSAIDs should be administered for a short period, i.e. for 5 to 10 days (according to European guidelines for the management of chronic nonspecific low back pain, treatment with NSAIDs should last not more than 3 months) [13].

In case of inadequate treatment response to NSAIDs or contraindications to their use, weak opioids are recommended to reduce pain intensity.

Their most common side effects include drug dependence, constipation, dizziness, increased sweating, and decreased potency [9]. The use of potent opioids is limited to transdermal therapeutic systems with gradual sustained release of the active ingredient. For mild chronic back pain, muscle relaxants can be used as an alternative to NSAIDs to reduce pain intensity; for severe pain, a combination of muscle relaxants with NSAIDs or other analgesics can be administered. Medications that aim to eliminate the neuropathic component of pain (antidepressants and anticonvulsants) can be used in the treatment of chronic back pain.

Psychological factors become more important as chronic back pain persists. According to the current concept, cognitive behavioral therapy can be used for management of chronic pain because pain and disability are caused not only by anatomical or physical abnormalities but also by psychological factors. Inclusion of cognitive behavioral therapy in multidisciplinary programs significantly increased treatment efficacy and decreased the number of lost workdays vs. standard care (evidence level A) [18].

Despite minimal risks associated with conservative treatment and apparent comparability of its efficacy with surgical treatment, conservative treatment is a symptomatic solution for stenosis, while anatomically, compression of the neurovascular structures still persists and can be completely eliminated only by decompression surgery in the degenerative SC segment.

A review (2016) to evaluate optimal non-surgical and surgical treatment options for SC stenosis had very little confidence to conclude whether surgical treatment or a conservative approach was better for lumbar spinal stenosis and could provide no new recommendations to guide clinical practice. However, the authors noted that no side effects were reported for any conservative treatment, and the rate of side effects ranged from 10% to 24% in surgical cases. No other differences were found between non-surgical and surgical treatment methods. The authors noted that clinicians should be very careful in informing patients about possible treatment options, especially given that conservative treatment options have resulted in no reported side effects.

There are no standard protocols for non-surgical treatment, which is challenging. Despite the availability of international and national clinical guidelines, treatment protocols are rarely followed in real-world clinical practice. This may suggest an individual approach to each clinical case (although guidelines usually indicate alternative treatment options if the patient has contraindications to a particular group of medications) or inadequate communication between surgeons and medical professionals who prescribe conservative treatment. In any case, the lack of standardization does not allow evaluating and further comparing treatment outcomes with various methods using the evidence-based approach. The authors stated that the concepts for comparing the methods were incorrect by default, and it would be more illustrative and effective to compare one type of surgical approach versus a specific physical exercise program or versus a defined medication protocol [19]. No clear protocols for non-surgery treatment and poor methodology of the studies that compared conservative and surgical methods were also mentioned by other authors [20, 21].

Surgical treatment

Currently there is an increasing number of surgical interventions performed for lumbar spinal stenosis. This is related to the fact that average life expectancy is increasing, and incidence of back pain increases with age. An increasing need for surgical treatment for back pain and increasing number of elderly patients necessitates searching for more effective and safe techniques and approaches.

Fig. 2 shows an algorithm for management of patients with lumbar spinal stenosis.

Open decompression and stabilization

Spinal column decompression is a conventional surgical procedure for lumbar stenosis; it can be performed with or without instrumental stabilization (interbody fusion, transpedicular fixation). SC decompression can be performed by open technique or through minimally invasive tubular

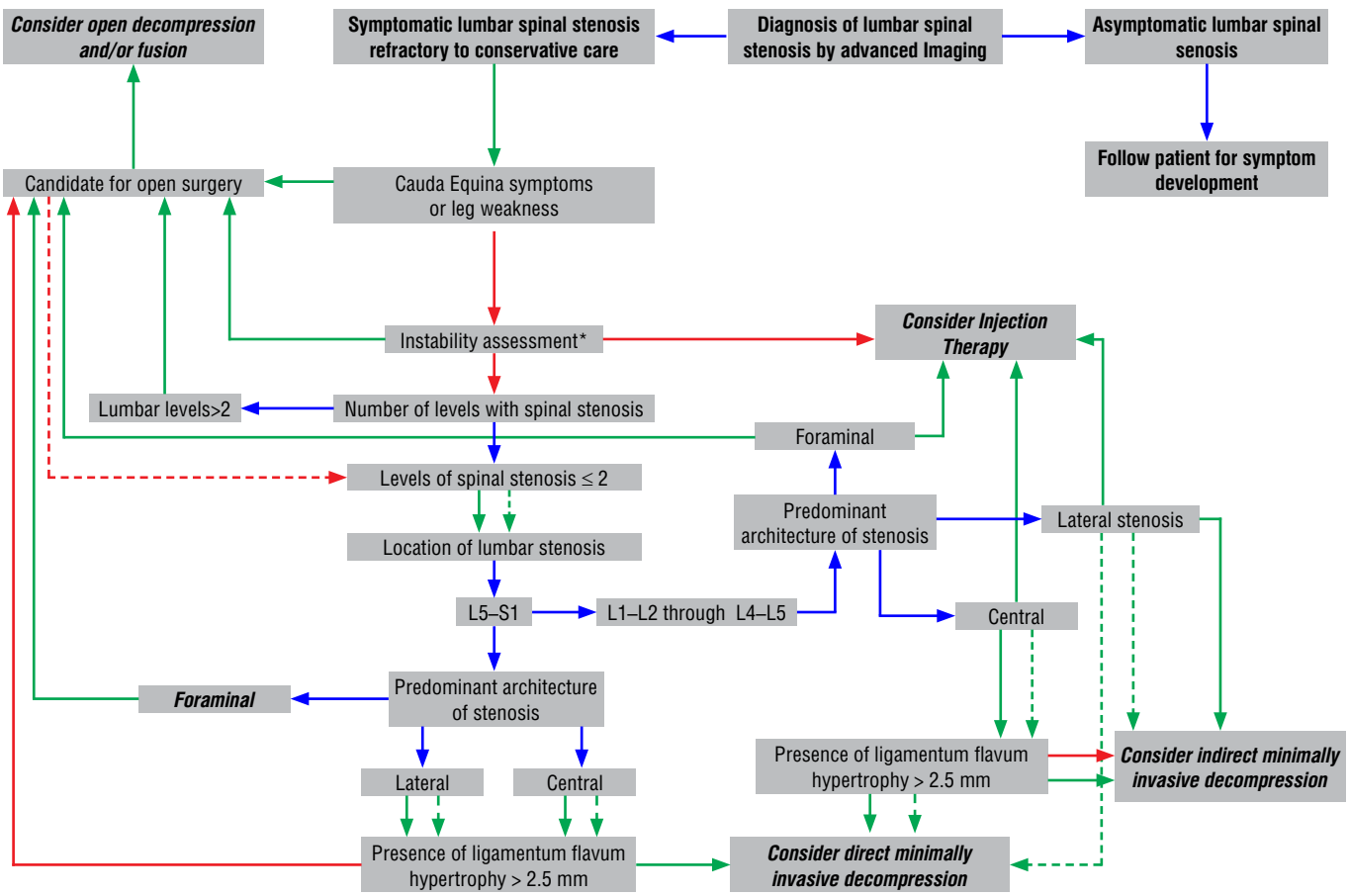


Fig. 2. Surgery treatment algorithm for degenerative stenosis according to T.R. Deer et al. [22].
Blue arrows, option chosen; green arrows, yes; dotted green lines, instability, hypertrophy of the ligamentum flavum, the patient is not a candidate for open surgery with or without stabilization; red arrows, no; dotted red lines, instability, no hypertrophy of the ligamentum flavum, the patient is not a candidate for open surgery with or without stabilization.
*In this algorithm, instability is defined as spondylolisthesis of grade 2 or more.

dilators, with or without microscopic or endoscopic assistance. Decompression includes laminectomy, hemilaminectomy, facetectomy, foraminotomy, which can be either unilateral or bilateral depending on the patient's clinical picture. Previously, open decompression was performed for SC stenosis; now more and more clinics can perform microscope-assisted decompression, which implies not only microsurgical visualization of the surgical wound but also use of microsurgical instruments for more precise and accurate procedures.

A.J. Caputy et al. [23] believed that stabilization should be used in the cases when laminectomy is performed together with discectomy and facetectomy, which lead to spine destabilization. Spine stabilization includes interbody fusion (installation of an implant [cage] in place of the intervertebral disc after its removal) and transpedicular fixation (installation of metal structures [screws] into the bodies of adjacent vertebrae through their pedicles and connection of the screws using a rod system). Decompressive and stabilizing interventions can be performed from the posterior, transforaminar (through the intervertebral foramen), lateral, anterior, and extralateral approaches (PLIF, TLIF, OLIF, ALIF, and XLIF, respectively; Fig. 3). TLIF and PLIF are used in most cases [24]. Recently, the KLIF abbreviation has appeared to designate Kambin's triangle for lumbar interbody fusion (Fig. 4).

Despite an increasing popularity of minimally invasive approaches, instability signs in the spinal motion segment that is involved in the degenerative process are an indication for stabilizing surgery.

Degenerative spondylolisthesis has always been considered a sign of instability, although no consensus on the definition of instability has been achieved yet. Several studies suggested that spondylolisthesis is iatrogenic in its nature and the degree of existing spondylolisthesis increases after surgical decompression [24–26]. Other studies supported a wide use of stabilization surgeries both for patients with or without spondylolisthesis [27]. A.R. Vaccaro et al., C.R. Martin et al. [28, 29], the authors of publications that were contested afterwards, advocated simultaneous decompression and stabilization to prevent restenosis or postoperative instability.

A. Goel believed that instability is the basis of any clinical problem with spine degeneration (whether cervical or lumbar), and, therefore, stabilization is the only possible approach and treatment method [30]. He explained this by the fact that compression cannot be primary but is a consequence of instability; therefore, decompression alone without stabilization cannot be a complete treatment.

The instability issue, like many other issues in medicine, is controversial and ambiguous and is unlikely to have a

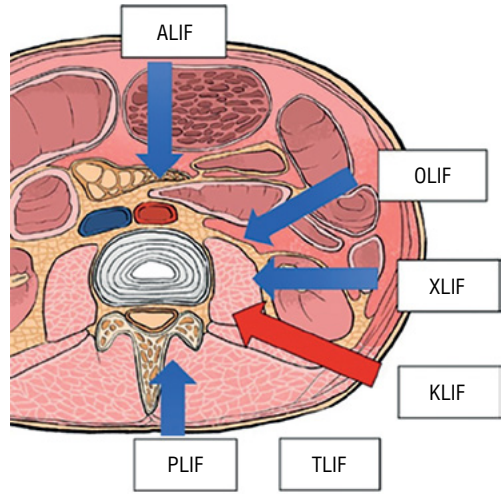


Fig. 3. Access types for interbody fusion.
ALIF, anterior lumbar interbody fusion; OLIF, oblique lumbar interbody fusion; XLIF, extralateral lumbar interbody fusion; KLIF, Kambin's triangle for lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion, PLIF, posterior lumbar interbody fusion.
Source: Morimoto M., Sairyo K. Full-endoscopic trans-Kambin's triangle lumbar interbody fusion (Fullendo-KLIF). In: Sairyo K. (eds.) Transforaminal full-endoscopic lumbar surgery under the local anesthesia. Singapore Springer; 2021.
DOI: 10.1007/978-981-15-7023-0_13

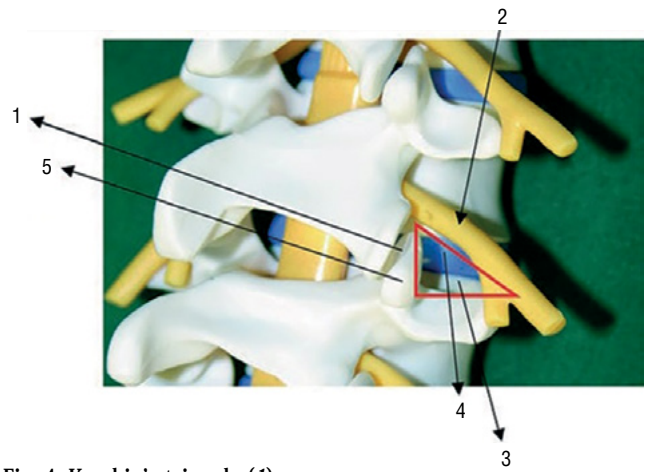


Fig. 4. Kambin's triangle (*1*).
2, nerve root forms the anterior border of the working area; 3, proximal plate; 4, intervertebral disc; 5 superior articular process.

universal solution that would work for all patients and satisfy all medical professionals [31–35]. Thus, it is most fair to believe that there is no one correct answer to the question whether stabilization is needed, and the decision should be made in each individual case in order to achieve most effective treatment outcomes and restore patients' functional status.

Endoscopic methods

In recent years, the surgical community has increasingly discussed the use of endoscopic approaches in lumbar stenosis surgery. This is explained by both a global trend

towards reducing the aggression of surgical interventions and expected better clinical outcomes such as improvement in symptoms, hospitalization duration, financial burden, rapid restoration of functional status, and ability to work. Endoscopy is particularly relevant in surgery for elderly and comorbid patients due to less intraoperative trauma to surrounding tissues, shorter surgery duration, no need to install implants, and rapid postoperative rehabilitation and recovery.

Endoscopy was introduced into the practice of spinal surgeons relatively recently (in the 1990s), when K.T. Foley et al. presented a tubular retractor system for endoscopic spine surgery. Endoscopic methods were gradually introduced in the practice of intervertebral disc decompression and removal of herniated intervertebral discs [36–39].

By their invasiveness, endoscopic methods are classified into percutaneous endoscopy (full-endoscopic methods) and tubular endoscopy (microendoscopy). Technically, percutaneous endoscopic approaches are classified as intralaminar, transforaminar, and posterolateral (Fig. 5) [1].

For surgical treatment of central stenosis formed by hypertrophic joints and the yellow ligament and stenosis of the lateral recess, there are percutaneous endoscopic systems with a 10-mm port, which allow adequate decompression even with severe compression of the nerve structures. Through unilateral access, decompression is carried out on one side of the SC and on the opposite side using the over-the-top technique (Fig. 6, 7).

A pilot, multicenter, randomized, double-blind study (2020) compared two minimally invasive approaches in the treatment of lumbar spinal stenosis: uniportal full-endoscopic interlaminar and tubular approaches [40]. The only significant difference found was a better improvement in Oswestry Disability Index (ODI) (i.e. in functional status) at 6 months in endoscopic group. All patients underwent MRI before and after surgery. Between-group differences were not statistically significant. Finally, clinical improvement was shown to be independent of the degree of increase in the cross-sectional area of the SC or dural sac. There were statistically significant between-group differences in intraoperative blood loss (lower in endoscopic group), while number of complications was similar in both groups (2 in each group).

Many studies showed advantages of endoscopy over microsurgery [41, 42]. When both techniques are compared, considering highly qualification and broad experience of operating surgeons, endoscopy would be superior to microsurgery since minimal intraoperative tissue trauma leads to faster patients' recovery and high efficacy of surgical treatment. We can say that such

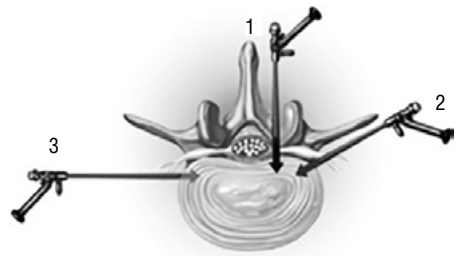


Fig. 5. Percutaneous endoscopic methods: intralaminar (1), posterolateral (2) and transforaminal (3).

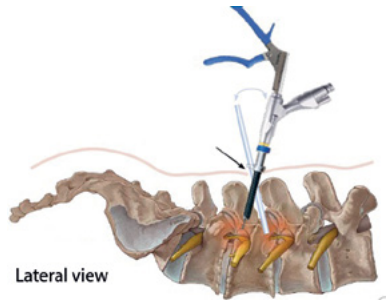


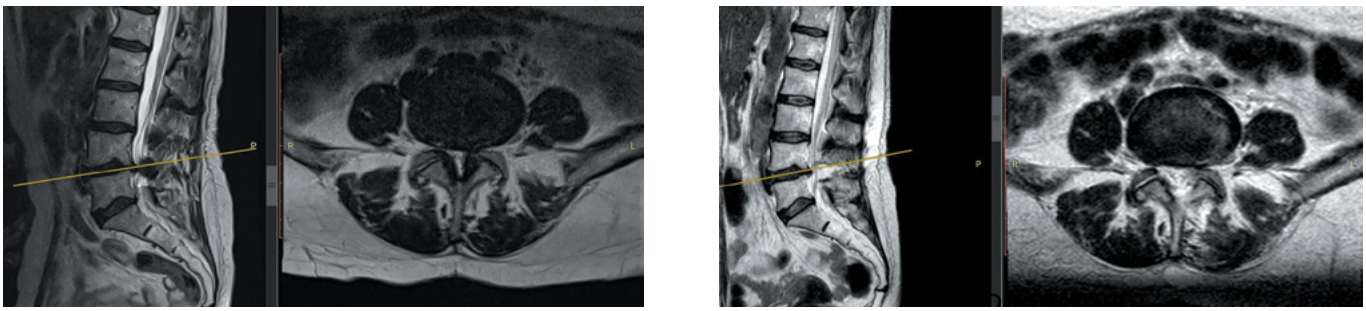
Fig. 6. System for percutaneous endoscopic surgery for degenerative spinal stenosis.
Arrow, one access for decompression at two levels.

promising results were expected and obvious. Efficacy and safety of endoscopy was also showed by H.S. Kim et al. [42–44].

Ralf Wagner (Germany) is a leading expert in endoscopic spinal neurosurgery. He has a broad experience in minimally invasive interventions and is actively involved in training specialists and international collaborative studies to investigate the efficacy of minimally invasive methods. For instance, he developed indications and contraindications for fully-endoscopic intralaminar lumbar decompression and described a step-by-step technique for performing this intervention [45]. R. Wagner is an author of several publications with technical notes about different spine endoscopies [45–48]. He conducted a randomized clinical trial together with surgeons from Spain and Argentina [40].

Several publications of C.J. Siepe et al. described full-endoscopic procedures for lumbar disc herniations and lumbar spinal stenosis [49, 50]. They mentioned a learning curve for new minimally invasive methods, which is one of the main and significant disadvantages of endoscopic interventions. However, benefits of endoscopic procedures can be seen not only in young patients but also in the elderly with comorbidities [51].

Therefore, many authors noted faster restoration of patients' functional status after endoscopic interventions, a long period of time needed to train in minimally invasive



A *B*

Fig. 7. MRI of a patient with central degenerative stenosis at L4–L5 level.
A, before surgery; *B*, after endoscopic decompressoin with DeltaJoimax.

methods, and heterogeneity of parameters used to compare conservative and surgical treatment methods [52, 53].

Conclusion

The microsurgical technique remains the gold standard in the surgical treatment of degeneration and dystrophic spine disease; it is clearer and has been tried and tested by more surgeons. Microsurgical decompression with stabilization is a treatment of choice for severe stenosis. However, surgery is evolving towards reduced invasiveness, and endoscopic methods, if performed by highly skilled specialists, are very effective, so operating surgeons can further develop their skills and improve clinical outcomes.

Compared with traditional decompression and stabilization procedures, endoscopic surgery is associated with a minimal risk of complications and allows patients to quickly restore their functional status and ability to work. This is relevant for patients without signs of obvious instability of the spinal motion segment, elderly patients with comorbidities, which can be relative contraindications for open traumatic surgery and complicate the postoperative recovery period.

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PreventS-MD®: a New Digital Technology to Maintain Cardiovascular Prevention in Routine Clinical Practice

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Abstract

Stroke, myocardial infarction (MI), and other main non-communicable diseases (NCDs) remain major causes of mortality and disability globally. Up to 80% of cardiovascular events and up to 60% of NCDs are associated with potentially controlled risk factors (RFs). State-of-the-art digital technologies can help bridge the gap between evidence-based prevention methods and their critically low availability in routine clinical practice.
An innovative digital platform named PreventS-MD® is a specially developed tool for healthcare professionals to be used under time constraints. With PreventS-MD®, clinicians can estimate patient's 10-year cardiovascular risk within several minutes. Then, they automatically get adapted results and recommendations to address identified RFs as well as graphical representation of specific RF contribution to overall stroke and MI risks. If some additional time is available, the clinician and the patient can collaboratively set customized achievable goals to correct modifiable RFs. An integrated analytical module provides healthcare managers with current digital risk profiles of the relevant population to evaluate prevention effectiveness and to forecast the load throughout the healthcare levels.
PreventS-MD® has several unique advantages, including time-saving design, the function to activate motivated RF correction, individually tailored recommendations, and information on personally changed digital profiles of vascular risks. As cardiovascular diseases and main NCDs have a lot of common RFs, PreventS-MD® implemented into routine clinical practice will utilize a complex approach to the prevention of main NCDs, decreasing both stroke and MI burden and addressing complications of chronic pulmonary and kidney disease, tumors of any type, dementia, etc.

Keywords: *stroke; myocardial infarction; risk factors; prevention; software*

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ПревентС-Врач® – новая цифровая технология поддержки мероприятий по профилактике сердечно-сосудистых заболеваний в рутинной клинической практике

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Аннотация

Инсульт, инфаркт миокарда и другие основные неинфекционные заболевания (НИЗ) продолжают оставаться ведущими причинами смерти и инвалидизации во всём мире. До 80% сердечно-сосудистых событий и до 60% НИЗ ассоциированы с потенциально контролируемыми факторами риска (ФР). Современные цифровые технологии способны помочь преодолеть разрыв между научно доказанными методами профилактики и катастрофически низкой степенью их внедрения в повседневную клиническую практику.
Инновационная цифровая платформа ПревентС-Врач® является инструментом, специально разработанным для применения в условиях ограниченного рабочего времени врача. С помощью системы ПревентС-Врач® у доктора появляется возможность в течение нескольких минут получить оценку 10-летних рисков развития у пациента основных сердечно-сосудистых заболеваний (ССЗ). В автоматическом режиме формируется адаптированное для неспециалиста описание результатов, рекомендации по коррекции выявленных ФР, а также графическое представление вклада отдельных ФР в суммарные риски инсульта и инфаркта миокарда. При наличии дополнительного времени врач совместно с пациентом могут воспользоваться функцией установки персонально приемлемых и достижимых целей по коррекции модифицируемых ФР. Встроенный в систему модуль аналитики предоставляет руководителям учреждений здравоохранения актуальную информацию о цифровом профиле риска обслуживаемой популяции, позволяет оценивать эффективность проводимых профилактических мероприятий и прогнозировать нагрузку на разные звенья медицинской службы.
ПревентС-Врач® имеет ряд уникальных преимуществ: экономящий рабочее время врача дизайн системы; функционал активации мотивационных механизмов коррекции ФР; гибкая персонализация рекомендаций; предоставление данных об индивидуальной динамике цифрового профиля сосудистого риска. В связи с тем что ССЗ и основные НИЗ имеют много общих ФР, внедрение ПревентС-Врач® в рутинную клиническую практику позволяет реализовать интегрированный подход к профилактике основных НИЗ – способствовать не только снижению бремени от инсультов и инфарктов миокарда, но и уменьшению последствий от хронических заболеваний лёгких и почек, онкологических заболеваний различной локализации, деменции и др.

***Ключевые слова**: инсульт; инфаркт миокарда; факторы риска; профилактика; программное обеспечение*

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Introduction

Cardiovascular disease (CVD) is a leading cause of early death and disability globally. Available prevention approaches are not sufficiently effective due to constantly increasing absolute burden of stroke and myocardial infarction (MI) despite improving relative CVD mortality and prevalence rates globally. With digitization and the methods of behavioral psychology, with the coverage of all the risk groups, and with time-saving design, the development

and the implementation of new technologies for preventive interventions can drastically decrease CVD and other main non-communicable disease (NCD) burden.

Major Issues of Prevention Delivery

Low availability of prevention measures in routine clinical practice is a global challenge. In prevention, primary clinician's limitation is insufficient amount of time. Other most common reasons include inadequate insurer's compensation of preventive visits, patients' refusal to discuss or follow recommendations, and low clinician's qualification in terms of preventive consulting [5, 8–11].

It appears that general prevention strategy needs to be reviewed by healthcare institutions. Nowadays, prevention is focused on identifying individuals already at high risk. Prevention guidelines aim to do this, and most risk assessment and stratification scales have been developed from this perspective. A high-risk strategy is intuitively clear for both clinicians and patients because it implies identifying significant health abnormalities that should be managed immediately. However, this approach results in 2 of 3 individuals with a low to moderate 10-year risk of cardiovascular events missing the time of a gradual risk increase for prevention. If the risk were calculated in individuals immediately before their stroke or a MI, most of them would be at high risk. The pool of risk factors (RFs) that determine the total risk is shaped as a result of long-term interaction between genetic, behavioral, environmental, and other factors rather than at once. Thus, there is an evident need to complement the high-risk strategy with methods that are independent of absolute risk for large-scale intervention in the continuum of cardiovascular risk development [13].

Many countries spend significant funds on preventive screenings [7]. Nevertheless, the literature suggests their low effectiveness [6]. The causes include focus on the above high-risk strategy in screening and almost no use of prevention methods psychologically based on health-related behavior.

Prevention is dramatically complicated by the population's lack of active interest in their health. According to the literature, up to 70% of patients seek medical care only in significant deterioration of their health [4]. An integral goal of prevention is people's indoctrination with an idea of the need to change their lifestyle. The task requires the repeated and versatile popularizaton of adapted information.

Brief history of PreventS-MD® development

The Research Center of Neurology (former Institute of Neurology under the Russian Academy of Medical Sciences) have studied epidemiology and prevention of brain vascular diseases for over 40 years. In 2014, the Center initiated collaboration with the National Institute for Stroke and Applied Neurosciences (Auckland, New Zealand) led by Prof. V.L. Feigin (Stroke Riskometer Project), which resulted in the free mobile application adapted for Russian-speaking individuals [3]. Further work in the area resulted in articulating the main limitations of current approaches to CVD prevention and in getting a new concept of the motivational preventive strategy covering the entire population and taking into account individual, relative rather than absolute vascular risk. This approach can reasonably cover a much larger proportion of the population by prevention in emerging vascular risk when prevention is the most effective [15].

In 2021, the Research Center of Neurology and Regional United System of Medical Informatization, a Russian company dealing with medical online technologies for years, launched pilot works to establish the concept of a software product for cardiovascular risk management across medical institutions, PreventS-MD®. Their objective was to complement and expand the preventive intervention options provided to the public via the Stroke Riskometer App.

In 2023, the development of the software product was completed. The Research Center of Neurology and the National Institute for Stroke and Applied Neurosciences tested system usability with clinicians from 27 countries [12]. Currently, the system is being clinically validated.

System functionality

PreventS-MD® is module-based software including an input module (questionnaire), a risk assessment module for clinicians, a summary module for patients, a behavior change support module, and an analytical module (Fig. 1). PreventS-MD® is an WEB application deployed on secure servers and accessed from authorized devices via an encrypted browser protocol. A desktop computer, a tablet, or a smartphone can be used to operate the system in various clinical scenarios.

Input module

In order to maximize obtained risk information, one should enter 24 parameters including: age (date of birth); sex; ethnicity; height; weight; smoking and alcohol consumption statuses; fruit and vegetable intake; physical activity level; average systolic blood pressure (SBP); continuous antihypertensive treatment status; presence of chronic stress or depression; family history of stroke or MI; levels of total cholesterol, high-density lipid cholesterol, and blood glucose; and history of diabetes, ischemic heart disease, and/or atherosclerosis of large peripheral arteries, left ventricular hypertrophy, atrial fibrillation, dementia, moderate cogni-

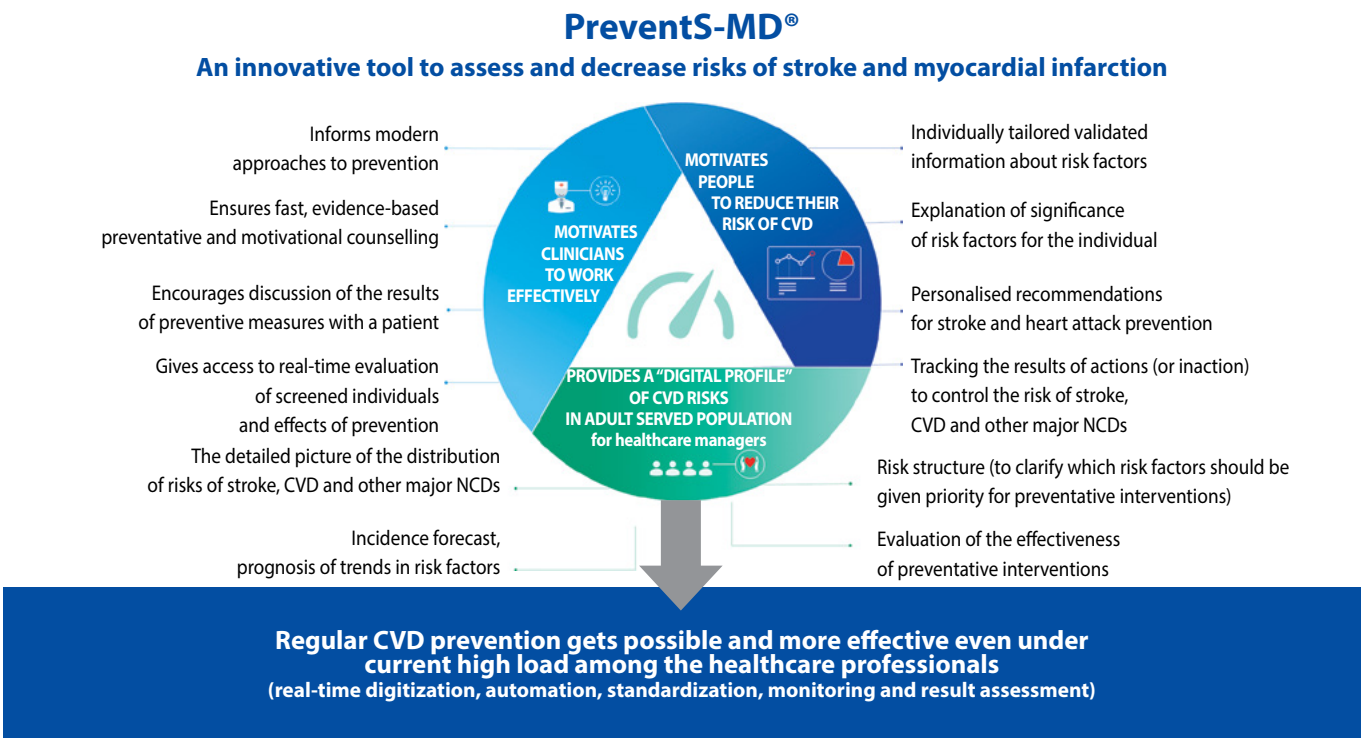

Fig. 1. PreventS-MD®'s main features.*

tive impairment, head injury, and stroke or transient ischemic attack. Additionally, the upper limit of the reference SBP level can be entered for display in the individual progress graph in the report materials.

In order to facilitate and speed up data entry, the mandatory fields include gender, age, ethnicity, and levels of the mean and upper limit of reference blood pressure. Other fields can be automatically filled with the value "Unknown". So, the questionnaire can be pre-filled, e.g. by nursing staff at the emergency department, or preliminary risk can be pre-assessed to be finally assessed once the remaining data have been entered. Another, preferable data entry option is integration with existing electronic medical records. In this case, most fields can be filled semi-automatically from existing Electronic Health Records (EHR). The ability and the extent of integration depends on the specifics of EHR software. The clinician only has to confirm the results of the automatic input and, if necessary, make some adjustments. The initial testing of the patient in the system is the most time-consuming (10–15 min) as, during repeated risk assessments, all the questionnaire fields are automatically filled with the results of the previous examination and the clinician only has to update the answers (3–5 min).

In order to facilitate data entry for each question, there are a brief summary on the entry form and an expanded one in the electronic user guide, with summary for each RF relationship to total cardiovascular risk and references to scientific publications. Therefore, active use of the PreventS-MD® may become an additional option to increase clinicians' awareness on the significance of certain RFs.

Risk assessment module for clinicians

PreventS-MD® incorporates a number of algorithms to get: 5-year and 10-year absolute and relative risks of stroke through the Stroke Riskometer [14]; 10-year absolute and relative risks of coronary events through the Framingham Risk Score [18]; Life's Simple 7 (LS7) scores [16], [14]; and original Healthy Lifestyle Scale scores (Fig. 2 and 3). Information on the stroke and MI risks is primarily needed as basic rationale to initiate preventive counseling. The concept of risk is difficult to understand for non-professionals on the whole. Additionally, absolute stroke and MI risks, even high-risk thresholds (> 10-15% over 10 years), appear to be slightly significant for general public. Recently, there has been increasing discussion about the need to refrain from using absolute risk indicators as the sole criterion for determining the need for preventive intervention [14]. When communicating with a patient, we suggest using a relative increase in absolute risk, which more clearly allows to show the necessity of controlling RFs even in young individuals and in the presence of few RFs.

Individual contribution of each RF is identified to the total stroke and MI risk is calculated in addition to absolute and relative vascular risks (Fig. 4). Thus, the clinician can discuss with the patient which of the RFs are the most

Results

Stroke risks		Coronary heart disease risks	
Absolute 10-year stroke risk	**2%**	Absolute 10-year coronary heart disease risk	**5%**
10-year stroke risk is increased*	**2.1 times**	10-year CHD risk is increased	**2.5 times**
Absolute 5-year stroke risk	**0.9%**		
5-year stroke risk is increased*	**2.6 times**		

*Shows risk of this individual compared to someone of the same age, sex, and ethnicity/race but without additional risk factors (relative risk); "not increased" message means that relative risk is equal to 1.0

Risk of other majon non-communicable diseases

Increased risk**

**Based on Life's Simple 7 score, which is closely correlated with excessive

Fig. 2. Risk assessment output for professionals.

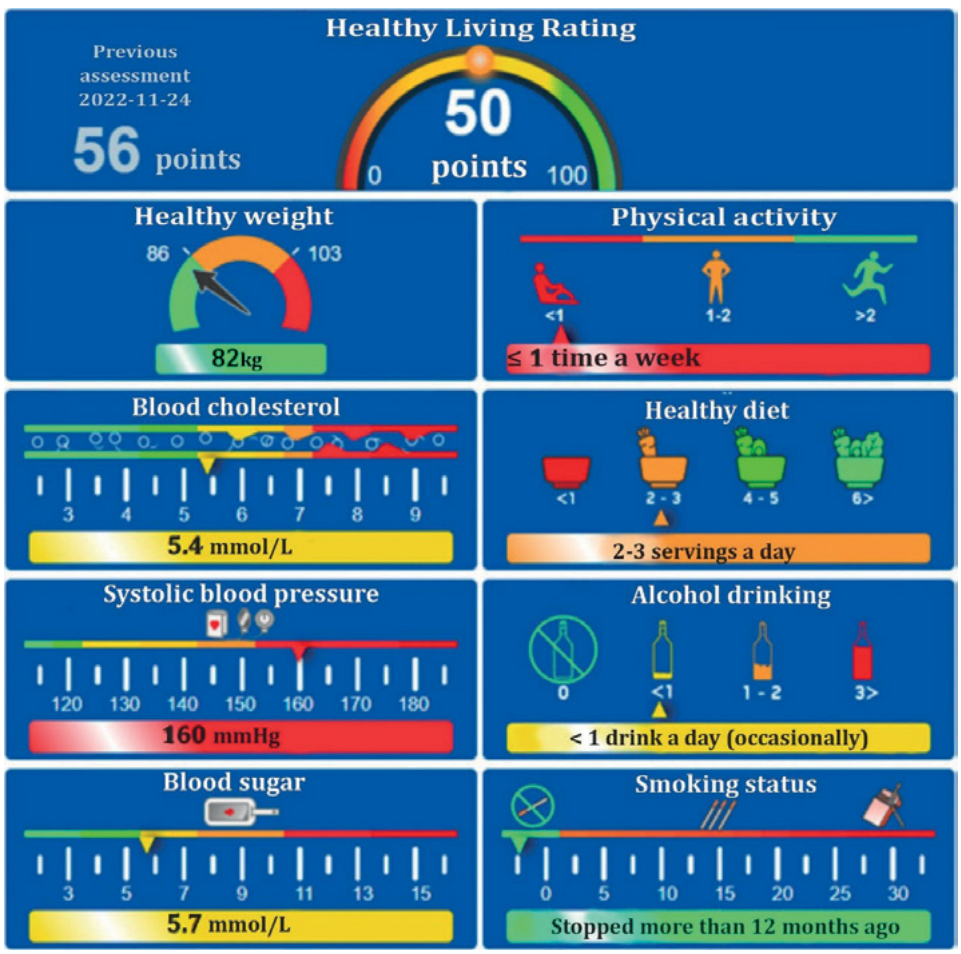

Fig. 3. Healthy Living Rating for patients.

important for them and to select those to correct for the greatest risk reduction, i.e. additional conditions for customization of preventive intervention.

PreventS-MD® also provides an opportunity to estimate relative risk of other significant NCDs including chronic obstructive pulmonary disease, pulmonary embolism, pneumonia, chronic kidney disease, deep vein thrombosis, cancer, hip fracture, and dementia. This calculation is based on the literature related to correspondence between LS7 scores and relative risk of the above conditions [17]. As these data are indicative, a color-coded chart with graphically represented NCD risks is to provide this information to patients (Fig. 5).

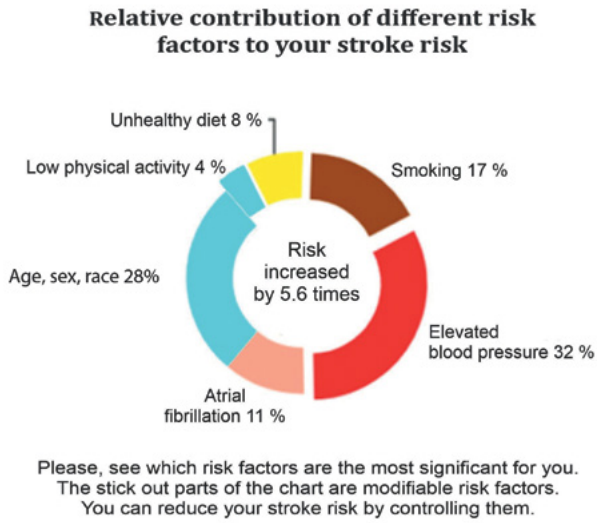

Fig. 4. Individual relative RF contribution to the total stroke risk.

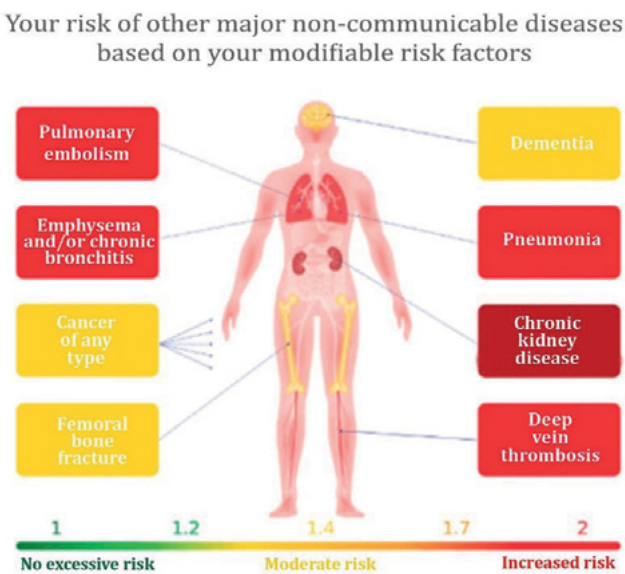

Fig. 5. Relative risks of other significant NCDs.

Summary module for patients

In order to save clinician's time, the final report for a patient is semi-automatically generated. The summary form includes textual description of the results, with an explanation of the identified increase in relative risks and a list of identified RFs (Fig. 4). For each of the identified RFs, recommendations are provided as adapted for non-professionals. The recommendations are based on international and national guidelines for cardiovascular prevention. The summary and recommendations can be edited to correspond with individual requirements. The clinician can select the recommendations to add to the printable summary form because excess of information can evidently have the same negative impact as lack of information.

In addition to textual information, the PreventS-MD® provides the results of current and previous examinations graphically, as charts and graphs. Therefore, the clinician gets an opportunity to discuss changes in patient's risks of stroke and MI and particular RFs with them. In addition to the changes in the considered indicators, the graphs contain information on the optimal (target) levels and repeated information related to the possible positive effect of the target levels achieved on the risk level (Fig. 6).

Maintenance of secondary stroke prevention

PreventS-MD® has been designed not only to maintain primary CVD prevention. Although there are currently no algorithms approved for wide use to calculate individual risks of recurrent stroke and MI, the incidence of recurrent vascular events is generally known. The main RFs targeted by preventive interventions in secondary prevention are the same. However, more attention should be paid to phar-

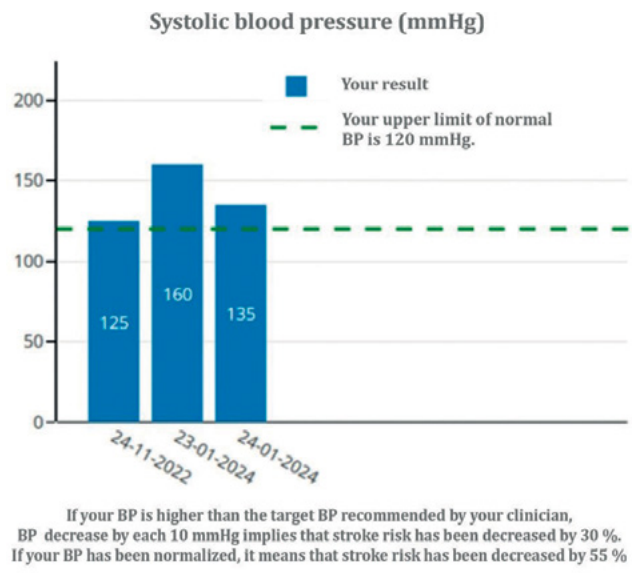

Fig. 6. Changes in the individual SBP levels.

maceutical therapy in such patients. Rationale for good treatment adherence can be added to the report as a separate recommendation (Fig. 7). A number of special phrases are provided to describe the effect of antihypertensive, hypolipidemic, antiaggregant, and anticoagulant therapies on risk levels. These phrases should always be added by clinicians at their discretion by selecting the appropriate options (check boxes). The relevant options are automatically highlighted in red in patients with elevated SBP (> 140 mmHg), elevated total cholesterol (> 6.2 mmol/L), atrial fibrillation, and history of coronary events.

If the patient has a history of stroke and/or manifestations of ischemic heart disease, the system generates a special summary and modified phrases on the effects of pharmaceutical prophylaxis. In addition to textual information on need for good treatment adherence, the system provides graphical representation of risk reduction as compared to that in treatment refusal. These graphs can also be customized depending on whether a particular category of pharmaceuticals is indicated.

Healthy Living Rating

This tool was designed to allow a clinician to focus patient's attention on modifiable RFs in an accessible and attractive manner (Fig. 3). This component is especially important in prevention of recurrent vascular events. As it is impossible to calculate the risks of recurrent events, it also becomes difficult to demonstrate a positive effect (risk reduction) when behavioral and metabolic RFs are corrected. Healthy Living Rating considers the presence and the severity of the main modifiable RFs. The maximum score is 100 units. The previous test result is also displayed in the report. We should note that the score can be used even if the data are partially absent. In this case, a warning is displayed and the number of points is also calculated with maximum possible value of 100 units but for the specified RFs only.

Behavior change support module

Cardiovascular disease prevention is a challenge mostly related to knowledge about the psychological features of health behavior management. Behavioral psychologists have been trying to find an effective solution for many years. Many models have been created and tested, primarily "motivational behavior models" [2]. Although no universal solution has been found to date, there is consensus that key elements of behavior regulation are aspects of motivation, self-regulation, and setting personalized, specific, and acceptable goals [1]. PreventS-MD® include two tools, a questionnaire for subjective assessment of motivation to initiate correction of identified RFs and a behavior change targeting tool with the Confidence in Achieving Goals questionnaire.

The motivation assessment questionnaire is generated automatically and based on the identified RFs. It is an 0 to 10 visual analog scale to grade desire of starting

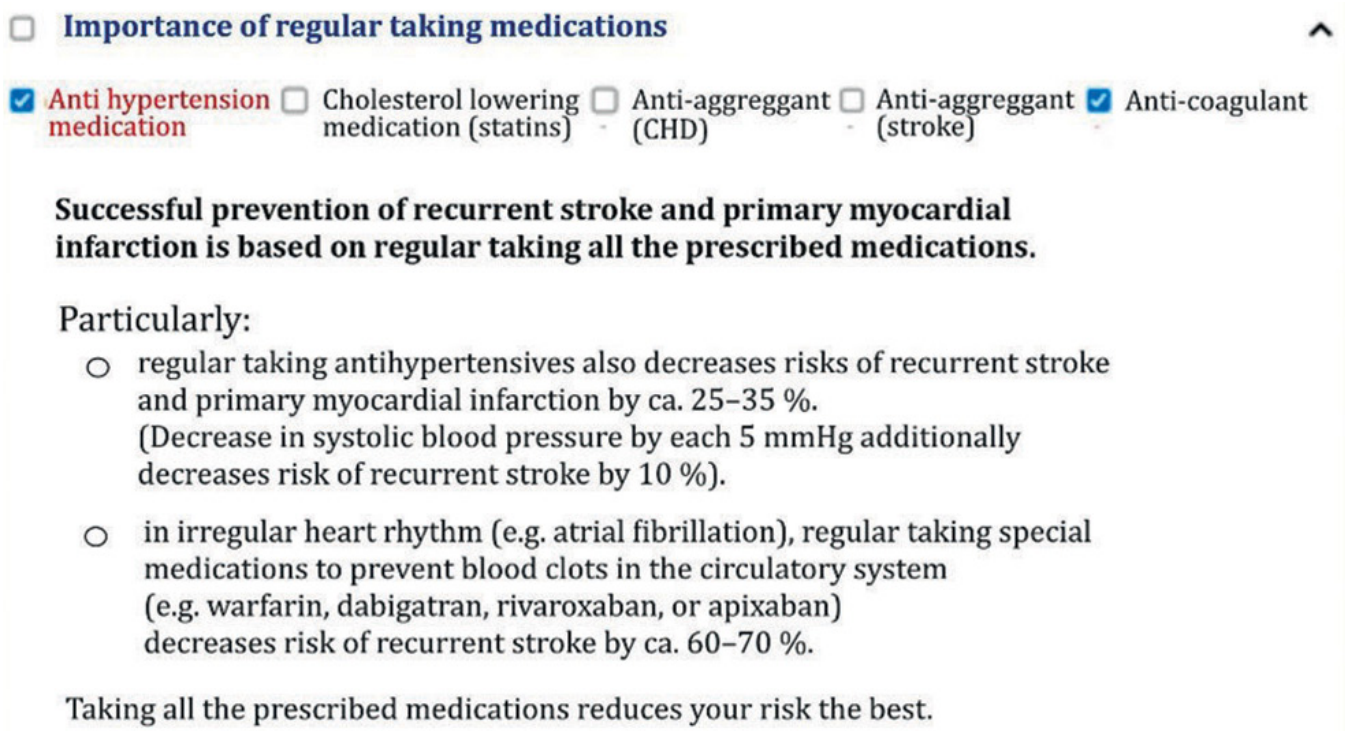

Fig. 7. Recommendation that emphasizes the importance of good treatment adherence.

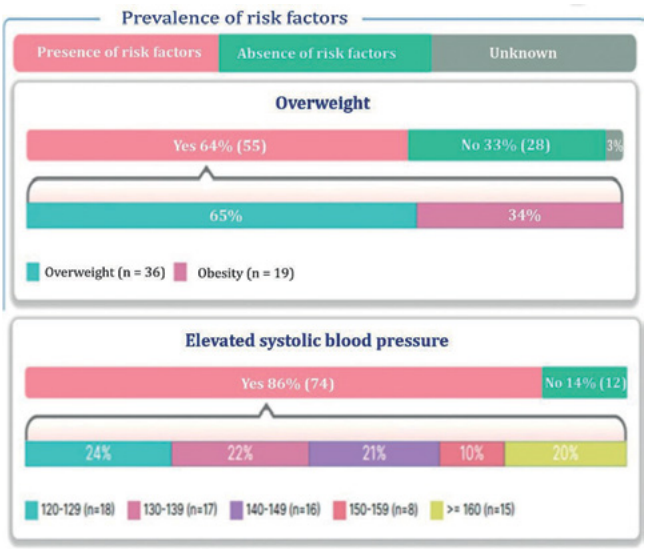

Fig. 8. Prevalence of risk factors represented in an analytical module.

to control certain RFs. Data can be entered immediately into the system via the online interface when interviewing a patient, or the questionnaire can be printed out for the patient to complete with following transfer the responses. According to the literature, further counseling on direct interventions for a specific RF is appropriate if the subjective motivation score is ⩾ 5 points. Otherwise, further discussion is necessary on the need to control this RF as a whole. In addition to current survey results, the clinician also has access to the history of motivation assessments at previous visits.

RFs with an entered motivation value of ⩾ 5 points are displayed in the interface to set individual goals. The system has several options for each RF, which can be additionally modified. It is possible to set one's own option of the goal entirely. The list of goal templates is planned to be expanded regularly in the future. Behavioral psychologists do not recommend setting over 3 goals per visit although the system allows you to do so.

The clinician can print out an individually generated questionnaire to give the patient a handout with the selected goals and to fulfil an additional, supporting technique, the assessment of confidence in achieving the goals. The questionnaire is an 0 to 10 visual analog scale. The output allows the clinician to determine when it is appropriate to schedule another visit for supportive preventive counseling and which RFs require additional support and are an additional way to support behavior change as they form of a "written agreement between a clinician and a patient."

Analytical module

PreventS-MD® is a software to support preventive intervention and a powerful tool for management decision-making, and a basis for scientific research. All the data entered into the system and the calculated indicators are available for analysis. The analytical module includes several sections (analytical models), with preset calculation indicators and diagrams grouped to solve the relevant task: assessment of system utilization activity, determination of RF burden in the population served (Fig. 8), assessment of risk changes, health behavior tool usage statistics, and risk estimate of other NCDs. For each analytical model, there is a number of filters to get data selected for a certain period, in a separate unit, for patients of selected age, sex, etc. For additional analysis, anonymized data can be uploaded to a file in a format that is compatible with statistical software.

Technology implementation options

PreventS-MD® can be accessed as a separate software product from authorized devices via the Internet or as part of an actual EHR software. The developed application programming interface (API), in fact, allows one to connect to any EHR system following all the requirements for personal data protection. The ability to semi-automatically prefill the questionnaire with EHR data depends on the system to be integrated with. Presently, there is experience of successful pilot integration with the Medialog medical information system.

Expected results of large-scale implementation into practice

Based on the literature data related to the proven positive impact of addressing major NCD RFs on morbidity and mortality rates, we can state that large-scale PreventS-MD® implementation in the routine practice of healthcare institutions can contribute to reducing the burden of CVDs and other major NCDs by up to 50%, namely:

- preserving the work capacity of experienced workers;
- reducing economic losses to employers and the state;
- reducing treatment and rehabilitation costs;
- increasing effectiveness of other prevention activities;
- improving the quality of life and longevity in the population.

These results can be achieved by the fact that:

1. Clinicians get an opportunity to perform standardized, evidence-based preventive counseling as part of their core activity.
2. The population gets motivated to control the RFs based on customized information and specific instructions.
3. Healthcare managers are able to make timely and targeted decisions based on objective information as the effectiveness of the strategy for RF correction all the international and national prevention guidelines is increased.

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Chronic Inflammatory Demyelinating Polyneuropathy Induced by Immune Checkpoint Inhibitors: Case Reports

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Abstract

Neurological immune-related adverse events (irAE) are rare but potentially fatal complications associated with the use of immune checkpoint inhibitors (ICI). Recently, there has been a trend towards an increase in the incidence of these cases.
We present two case reports of demyelinating polyneuropathy in patients with skin melanoma treated with pembrolizumab or nivolumab. Unawareness of neurological irAE induced by ICI leads to delayed diagnosis and medical treatment, and this may result in persistent neurological deficit or even patients' death. Neurological irAEs include myasthenia gravis, aseptic meningitis, encephalitis, myelitis, inflammatory demyelinating neuropathy, myositis or their combinations, etc. Considering their variability in patients treated with ICI and poor representation in publications, each case report can be of practical value.

Keywords: *monoclonal antibodies; immune checkpoint inhibitors; pembrolizumab; nivolumab; neurological complications; dysimmune polyneuropathy; chronic inflammatory demyelinating polyneuropathy*

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of the I. Kant BFU (protocol No. 34, September 29, 2022).

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Хроническая воспалительная демиелинизирующая полинейропатия на фоне применения ингибиторов контрольных точек: клинические наблюдения

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Аннотация

Неврологические нежелательные явления (ННЯ), связанные с применением ингибиторов контрольных точек (ИКТ), являются редкими, но потенциально фатальными осложнениями. За последние годы отмечается тенденция к росту регистрации данных случаев.
Мы приводим два клинических случая демиелинизирующей полинейропатии у пациентов с меланомой кожи на фоне лечения пембролизумабом и ниволумабом. Отсутствие осведомлённости о ННЯ при применении ИКТ ведёт к задержке постановки правильного диагноза,

вследствие этого – к отсроченному назначению лекарственной терапии и развитию стойкого неврологического дефицита, вплоть до летального исхода. Среди ННЯ выделяют миастению, асептический менингит, энцефалит, миелит, воспалительную демиелинизирующую нейропатию, миозит или их сочетания и др. С учётом их вариабельности при использовании ИКТ и малой представленности в мировой литературе описание каждого клинического случая при применении данных лекарственных средств имеет практическую ценность.

***Ключевые слова**: моноклональные антитела; ингибиторы контрольных точек; пембролизумаб; ниволумаб; неврологические осложнения; дизимунная полинейропатия; хроническая воспалительная демиелинизирующая полинейропатия*

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Этическое утверждение: Исследование проводилось при добровольном информированном согласии пациентов. Протокол исследования одобрен Этическим комитетом БФУ им. И. Канта (протокол № 34 от 29.09.2022).

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

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Introduction

Mechanisms underlying immune evasion of tumor cells include increased expression of immune checkpoints (ICs) and their ligands regulating signaling pathways that influence the magnitude and duration of immune response, as well as tolerance of immune cells to their own antigens. Besides conventional chemotherapy, advances in the development and implementation of immune therapies targeting ICs for cancer patients led to a new class of neurological complications, which often remain unrecognized by neurologists and oncologists. This type of monoclonal antibodies is used for the treatment of metastatic malignant tumors and melanoma by enhancing natural antitumor response [1, 2]. Experience with these agents is rapidly growing, and the most studied immune checkpoint inhibitors (ICIs) include agents that target cytotoxic T-lymphocyte associated protein 4 (CTLA-4), such as ipilimumab and tremelimumab; programmed cell death protein-1 (PD-1), such as nivolumab, pembrolizumab, cemiplimab, and dostarlimab; and its ligands (programmed cell death ligand PD-L1, PD-L2), such as atezolizumab and durvalumab. Monotherapy is more common, while combination therapy with anti-PD-1 and anti-CTLA-4 is used less often [3]. Lymphocyte activation and restoration of antitumor immune response occur due to blocking of IC signaling pathways [1, 4]. However, PD-1/PD-L1 and CTLA-4 are widely expressed not only by cancer cells but also by other cell types; therefore, a wide range of autoimmune reactions can occur if they are suppressed. Neurological immune-related adverse events (irAEs) occurred approximately in 1–6% of patients treated with ICIs and affected both the peripheral and central nervous systems [5]. Most neurological irAEs were reported in 2017–2018 (61–78% of cases), reflecting the substantially increased use of ICIs in recent years [6]. Describing neurological irAEs is necessary not only to promptly adjust therapy in cancer patients but also to accumulate knowledge for the medical community.

In this article, we present two case reports of dysimmune neuropathy that occurred during the treatment with pembrolizumab and nivolumab in patients with metastatic skin melanoma. Chronic inflammatory demyelinating polyneuropathy (CIDP) is usually associated with other causes such as respiratory viral infections, surgery, pregnancy, vaccination, etc. In our cases, PD-1 inhibitors triggered immune response, which resulted in CIDP.

Case report 1

Patient F., 73 years old, received 10 infusions of nivolumab 3 mg/kg in a total dose of 2610 mg for head and neck skin melanoma. First symptoms (i.e. burning sensation in the feet) appeared after the 9th infusion. Within 1.5 months after the 10th infusion, the patient complained of hand pain and leg weakness. Nivolumab was discontinued. Four months after the last infusion, the patient was unable to ambulate and could not turn over in bed without assistance. Examination showed flaccid tetraparesis with plegia in the feet, no tendon reflexes, hypoesthesia of pain sensitivity in the hands, in the legs from the knee level, no vibration sensitivity, atrophy of the distal and proximal arm and leg muscles.

Nerve conduction study (NCS) using Neurosoft 4 MVP micro at a temperature of at least 32ºC showed no sensory and motor responses from the lower limbs; unidirectional changes in the upper limbs, i.e. low-amplitude M-responses with conduction velocity decreased to 27 m/s (normal range: more than 50 m/s); and temporal dispersion of the response in the median nerve increased by 68% (Fig. 1). Sensory responses from the hands were not recorded. Needle electromyography (EMG) showed vigorous spontaneous denervation activity in lower leg and forearm muscles and moderate activity in proximal limb muscles. Clinical findings, NCS and EMG parameters were consistent with CIDP [7]. Routine blood tests did not show any abnormalities, and lumbar puncture data were not available because the patient refused to undergo this procedure. The patient was administered methylprednisolone 80 mg/day for 1 month followed by tapering-off and pregabalin 600 mg/day for neuropathic pain syndrome. During the treatment, consistent improvements were seen in foot extension, which improved to Medical Research Council (MRC) score of 3 [8].

Case report 2

Patient S., 85 years old, received pembrolizumab (2 mg/kg) for skin melanoma of the anterior chest wall with metastases to the lungs, left breast, and postoperative scars. The patient received a total of 5 infusions in a total dose of 1000 mg. First symptoms appeared 2 weeks after the 4th infusion; they included pain in the muscles of the thighs and lower back with Visual Analogue Scale scores of up to 6, which lasted for 1 week. After the 5th pembrolizumab infusion, feet burning sensation and paresthesia appeared with tetraparesis gradually developing. The patient presented with mild dysarthria, areflexia, peripheral tetraparesis with muscle strength decreased to MRC score of 3 in the distal muscles of the arms and legs and to MRC score of 2 in the hip flexors [8]. He had paretic gait with a walker. He lost all sensitivity types in the upper and lower limbs of polyneuritic type (up to knees and up to the middle of the forearm); hyperalgesia of the hands and feet was seen.

Routine laboratory tests showed creatine phosphokinase (CPK) increased to 871 U/L and protein-cell dissociation in the cerebrospinal fluid (cytosis 6 cells/mm^3, protein 2.019 g/L). NCS with Dantec Keypoint Focus at a temperature of at least 32°C showed demyelination signs that met the criteria for CIDP [7].

An example of conduction block in an atypical area in the ulnar nerve is shown in Fig. 2. Needle EMG showed single spontaneous activity and minimal neurogenic changes in motor unit potential parameters in the distal muscles of the lower limbs. Brain MRI did not show any significant abnormalities. The patient received 1 session of plasmapheresis with exchanged plasma volume of 35 mL/kg, which was tolerated without complications. However, he experienced general weakness, so further sessions were

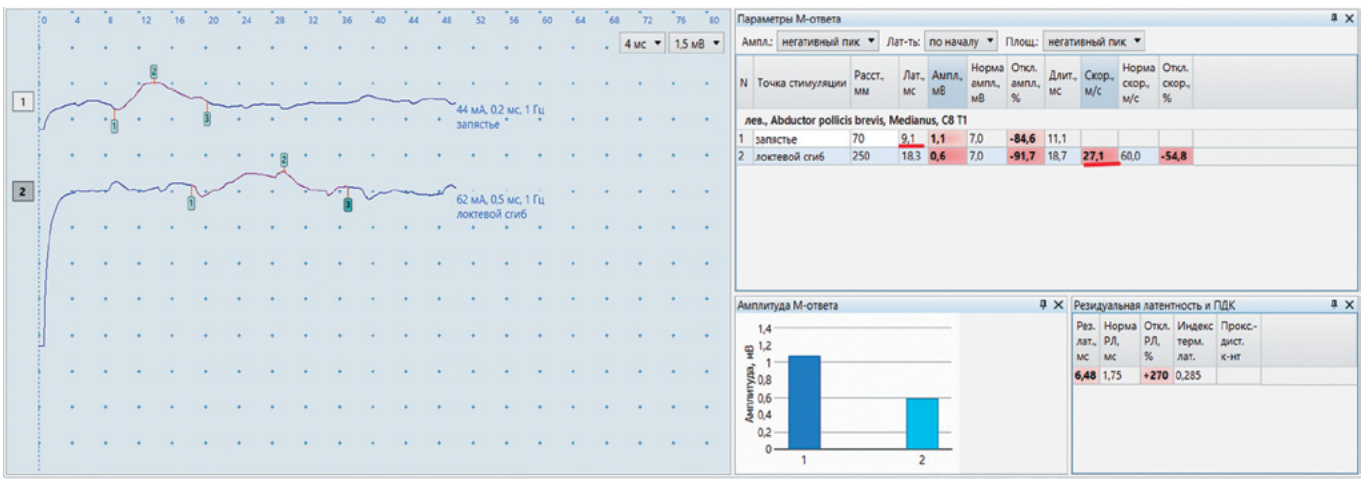

Fig. 1. Decreased conduction velocity in the median nerve in the forearm of patient F. to 27.1 m/s (normal range: > 49 m/s), prolonged distal latency to 9.1 ms (normal range: < 4.4 ms). Negative phase of proximal motor response lasted 18.7 ms. Dispersion of proximal motor response. Amplitude of distal motor response decreased to 1.1 mV (normal range: > 4 mV).

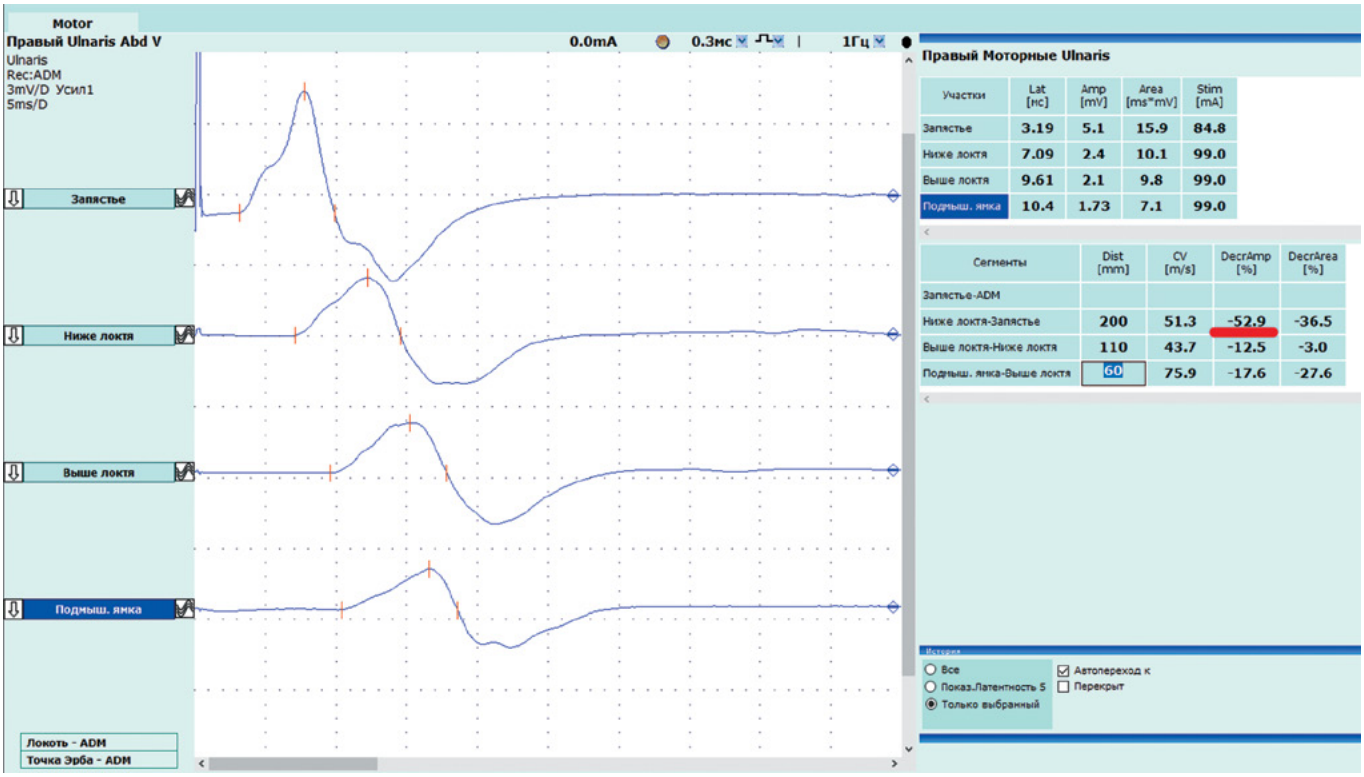

Fig. 2. Conduction block of 52.9% (normal range: no block) in an atypical area of compression in the ulnar nerve. Amplitude of distal motor response decreased to 5.1 mV (normal range: > 6.0 mV). Distal latency was 3.19 ms (normal range: < 3.3 ms).

Summarized patients' data

Parameter	Patient F.	Patient S.
Age, years	73	85
Sex	Male	Male
ICI agent	Nivolumab	Pembrolizumab
Number of infusions	10	5
Total dose, mg	2610	1000
Time to onset, weeks	18	4
NCS	Nerve conduction velocity decreased by 30% in more than 2 nerves	Conduction block of more than 50% in the ulnar nerve, lack of F-wave in the tibial nerves
Needle EMG	Spontaneous activity ++, neurogenic type of changes in motor unit potentials	Spontaneous activity +, minimal neurogenic changes
Treatment	Corticosteroids	Plasmapheresis, corticosteroids

not performed. Oral prednisolone was added with an alternating dosing regimen of 70/35 mg for 4 months, which was associated with a slight improvement with increased strength in the hip flexors and more stable gait. Other neurological parameters remained unchanged. CPK levels returned to normal with the treatment.

Summarized patients' data are presented in the Table.

Discussion

We described two rare cases of CIDP dysimmune neuropathy, which developed after the use of ICIs. According to literature, peripheral nervous system damage occurred 2–5 times more often than complications from the central nervous system [8]. A systematic review by A. Johansen et al. included 61 publications on 85 patients treated with PD-1 inhibitors that were identified from selected indexed literature databases until June 2018, and neuropathy was identified in 23% of cases. The authors noted many cases with atypical presentation, which included combinations of myasthenia gravis and myopathy, as well as common cardiac/respiratory complications, proximal weakness (35%) and muscle pain (28%), which was seen at the onset of the case in patient S. Describing and discussing such cases of ICI complications is important for neurological practice, since mortality in these patients remains high despite adequate treatment, including corticosteroids and intravenous immunoglobulins [9].

Mean time to onset of neurological complications was about 12 weeks after the initiation of ICI therapy [10]. In our patients it was different: 18 weeks in case 1 (after the 9th infusion of nivolumab every 2 weeks) and 14 weeks in case 2 (2 weeks after the 4th infusion of pembrolizumab every 3 weeks).

According to a post-marketing 10-year analysis of the European Pharmacovigilance Database conducted in 2023 and presented by R. Ruggiero et al., all peripheral neuropathies that were the most commonly associated with nivolumab and pembrolizumab included only 12 cases of CIDP. Dysimmune neuropathies included different clinical variants such as Miller–Fisher syndrome, acute inflammatory demyelinating polyneuropathy, etc. Cases of ICI-induced CIDP were reported much less often [11]. A publication suggested that melanoma patients may have a higher risk of developing ICI-induced demyelinating polyneuropathy due to epitopes shared by melanocytes and Schwann cells, as they are both derived from the neural crest [12].

In our cases, clinical findings included symmetrical tetraparesis with sensory impairment. According to literature data, the most typical manifestation of dysimmune neuropathies included symmetrical limb weakness (94% of cases), followed by cranial nerve involvement and bulbar disorders [9]. In both our cases, we found demyelinating neuropathy with secondary axonal changes. According to literature, patterns included demyelination (61%) and axonal (27%) patterns [10]. CSF test results were available only for patient S.; they showed protein-cell dissociation. Cerebrospinal fluid showed elevated protein levels in most patients (97%) with lymphocytic pleocytosis in 13 (36%) patients [13]. We did not have any data on anti-ganglioside antibodies in our patients; however, according to the literature, antibodies were positive only in 2 of 17 patients examined [13]. Facial nerve palsy and trigeminal neuralgia were the most frequently noted cranial neuropathies attributed to immune checkpoint inhibitors [14]. No cranial nerve involvement was found in our cases. Small-fiber/autonomic neuropathy was also reported, resulting in orthostasis, anhidrosis, gastrointestinal motility disorders and/or urinary retention [15], which was not seen in our patients. Predominantly demyelinating nature of polyneuropathy induced by ICIs differentiates it from axonal polyneuropathy that occurs in patients who receive conventional chemotherapy [16].

In our cases, ICI-induced CIDP was seen together with neuropathic pain syndrome, which occurred at the onset of the case in patient F. and after resolution of muscle pain in patient S. This was described as a unique manifestation and an early symptom of CIDP in 2 clinical cases when ipilimumab was used in combination with nivolumab in patients with metastatic melanoma [17] and is not typical for classical CIDP.

Causes of neurological irAEs in individual patients are unknown; recently, immunotoxicity has been increasingly associated with changes in the intestinal microbiome [18]. It is of interest that CPK levels in patient S. were increased, which was previously described only in 3 patients with CPK levels of above 1000 U/L with overlap syndromes together with myasthenia, polyneuropathy, and myositis [10]. Most often, increased CPK levels were seen in patients with isolated myositis or a combination of myositis and myasthenia [19]. However, we could not confirm myositis in patient S. because no ongoing process was found in his proximal muscles, and when studied over time, CPK returned to normal quite rapidly, which rather confirms that these changes were of random nature. It remains debatable whether treatment of neurological irAEs can suspend the effectiveness of cancer immunotherapy, thus requiring monitoring over time in this population.

Conclusion

Although ICI-induced neurological complications are rare, they can be serious or even life-threatening; therefore, patients should be continuously monitored during this

treatment. A history of ICI therapy and changes in NCS are the main diagnostic criteria in these cases. Our cases and cases reported in literature supported the hypothesis that compact myelin proteins are likely to be the primary target in ICI-associated neuropathy, particularly in that induced by PD-1-inhibitors. ICI-induced dysimmune neuropathies cannot be discriminated from classic dysimmune neuropathies by their clinical or neurophysiological signs, with the latter being associated with neuropathic pain. Further studies of these signs in larger cohorts of patients are needed. Key treatment options for neurological irAEs include ICI discontinuation with administration of other therapy based on the decision of the oncology team and prescription of immunosuppressive therapy [20].

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