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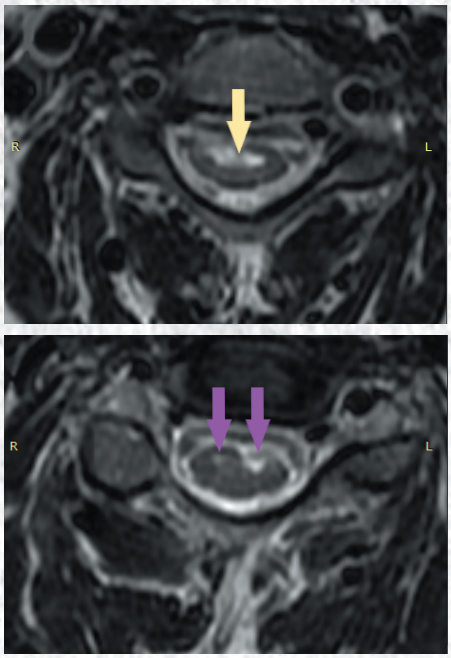

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Spectrum of Cognitive Impairment in Patients with Multiple Sclerosis

Alfiia H. Zabirova, Ilya S. Bakulin, Maria N. Zakharova, Elena V. Gnedovskaya, Natalia A. Suponeva

Research Center of Neurology, Moscow, Russia

Abstract

Introduction. *Cognitive impairment (CI) is a common manifestation of multiple sclerosis (MS), which significantly affects patients' daily life and professional activity. Despite the development of methods to screen MS patients for CI, data on its prevalence in the Russian population are still lacking.*
Aim*: to comprehensively assess cognitive functions in patients with different types of MS.*
Materials and methods. *The study included MS patients who did not have any other possible causes of CI and no diseases or conditions that confounded this assessment. CI was determined using the Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) test battery and the Stroop test as a decrease in the scores below the mean by at least 1.5 standard deviations. CI was subjectively assessed using the Perceived Deficit Questionnaire; fatigue was subjectively assessed using the Modified Fatigue Impact Scale (MFIS). The Mann–Whitney test and Fisher's exact test were used for comparison, and the Spearman test was used to evaluate correlations.*
Results. *We evaluated 77 MS patients (30 men; age 40 [30; 48] years; 47 with relapsing-remitting MS, 30 with progressive MS). CI incidence was 23.4% in patients with relapsing-remitting MS and 77% in patients with progressive MS, while multi-domain CI was statistically significantly more common in patients with progressive MS. Impairment of processing speed was the most common. Patients with relapsing-remitting MS and CI were statistically significantly older and had longer disease duration than those without CI. There was a statistically significant correlation of subjective CI severity with MFIS scores but not with testing results.*
Conclusion. *CI incidence in MS patients was relatively high with greater severity and involvement of more domains in patients with progressive MS. No correlation was found between subjective and objective CI assessment results, which may suggest that patients underestimated their deficit.*

Keywords: *multiple sclerosis; cognitive impairment; fatigue; cognitive test batteries*

Ethics approval. All patients provided their voluntary informed consent to participate in the study. The study protocol was approved by the Ethics Committee of Research Center of Neurology (Protocol 1-7/23, dated 25 January 2023).

Source of funding. This study was performed as part of the "Rehabilitation and adaptation of patients with nervous system damage: current possibilities for studying mechanisms and practice-oriented approaches" study (state registration number 122041800162-9).

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

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Спектр когнитивных нарушений у пациентов с рассеянным склерозом

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Аннотация

Введение. *Когнитивные нарушения (КН) являются распространённым проявлением рассеянного склероза (РС), значимо влияющим на повседневную и профессиональную активность пациентов. Несмотря на развитие методик скрининговой оценки КН при РС, сохраняется недостаток данных об их распространённости в российской популяции.*

Цель *исследования – комплексная оценка когнитивных функций у пациентов с разными типами течения РС.*

Материалы и методы. *В исследование включены пациенты с РС, не имеющие иных возможных причин развития КН и заболеваний или состояний, затрудняющих тестирование. КН определяли с помощью батареи тестов Brief International Cognitive Assessment in Multiple Sclerosis и теста Струпа как снижение показателей ниже среднего на 1,5 и более стандартных отклонения. Субъективную оценку КН проводили с помощью опросника Perceived Deficit Questionnaire, утомления – шкалы Modified Fatigue Impact Scale (MFIS). Для сравнения использовали критерий Манна–Уитни и точный критерий Фишера, для оценки корреляций – критерий Спирмена.*

Результаты. *Обследованы 77 пациентов с РС (30 мужчин, возраст 40 [30; 48] лет, 47 – с ремиттирующим РС, 30 – с прогрессирующим РС). Частота КН у пациентов с ремиттирующим РС составила 23,4%, с прогрессирующим РС – 77%, при этом у пациентов с прогрессирующим РС статистически значимо чаще встречались мультидоменные КН. Наиболее часто регистрировались нарушения скорости обработки информации. Пациенты с ремиттирующим РС и КН были статистически значимо старше и имели бóльшую длительность заболевания по сравнению с пациентами без КН. Субъективная выраженность КН статистически значимо коррелировала с показателями MFIS, но не с результатами тестирования.*

Заключение. *Показана достаточно высокая частота КН у пациентов с РС, при этом бóльшая выраженность и вовлечение большего числа доменов наблюдались при прогрессирующем РС. Обнаружено отсутствие корреляции субъективной и объективной оценки КН, что может свидетельствовать о недооценке пациентами дефицита.*

Ключевые слова: *рассеянный склероз; когнитивные нарушения; утомление; батареи когнитивных тестов*

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

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Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system with a relatively high prevalence. MS prevalence is estimated to be 2 to 165 cases per 100 thousand population in different geographical areas [1] and 50 to 80 cases per 100 thousand population in Russia [2, 3]. Depending on MS type, activity, and duration, neuroinflammation or degeneration mechanisms can predominate in its pathogenesis [4–6]. Despite significant development of treatment options for MS and improvement in its course, disability due to MS remains high [7, 8]. Affecting mostly patients of young or middle age, MS significantly worsens their professional and daily activities and decreases their quality of life [9].

Cognitive impairment (CI) in MS patients is quite challenging to diagnose, often ignored by patients themselves, and, therefore, often classified as a "hidden" MS symptom [10, 11]. In the Expanded Disability Status Scale (EDSS), the assessment of cognitive functions is limited to the subjective impression of the assessor, so CI is often not taken into account when disease activity is assessed, although its detection can further increase the sensitivity of relapse detection [12]. CI can also be a marker of aggressive disease [13].

Possible mechanisms underlying CI in MS patients include demyelination and gray matter atrophy. Several authors suggested that CI in MS patients can result from neuronal network disruption due to white matter lesions [14]. An important role in CI pathogenesis can be attributed to the atrophy of the gray matter in the thalamus, basal ganglia, hippocampal cortex, several areas of the cerebral cortex, and cerebellum [15, 16].

In recent years, increasing attention has been paid to studying cognitive functions using specialized scales and questionnaires, such as screening assessment tools and expanded neuropsychological test batteries. Most common screening tools include Symbol-Digit Modalities Test (SDMT) and its modifications, Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) battery, and more detailed ones such as Brief Repeatable Battery of Neuropsychological tests in multiple sclerosis (BRB-N), Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS), Battery Evaluating Cognitive Functions in Multiple Sclerosis (BCcogSEP), etc. [17]. Several questionnaires have been developed to subjectively assess cognitive functions, such as Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) [18] and Perceived Deficit Questionnaire (PDQ). It is assumed that screening tools can be used in all MS patients to assess them for CI and its changes over time, while expanded scales are feasible for selected groups of patients, in particular, those who have complaints of cognitive decline, or when CI is detected using screening tools [19].

Both overall incidence and phenotype of CI depend on the MS type. For instance, mild single-domain verbal memory/semantic fluency CI is more typical for relapsing-remitting MS (RRMS). Patients with progressive MS (PMS) more often have multi-domain CI or severe attention/executive CI [20]. However, data on incidence of CI in different domains depending on MS type remain inconsistent [21].

Study aim. This study aimed to comprehensively assess cognitive functions in patients with different types of MS.

Materials and methods

This cross-sectional study involved MS patients who received inpatient treatment at Research Center of Neurology (Moscow, Russia) from 2021 to 2024. The study was approved by the Ethics Committee of Research Center of Neurology (Protocol 1-7/23 dated 25 January 2023) and was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria:
- voluntary informed consent to participate in the study;
- age over 18 years;
- MS diagnosis confirmed according to the McDonald criteria, 2017.

Exclusion criteria:
- Diagnosed diseases or conditions that can be associated with CI (such as concomitant neurological disorders that result in deterioration of cognitive functions; clinically significant depression; use of medications with a known effect on cognitive functions; alcohol or drug abuse).
- Diagnosed diseases or conditions that can confound cognitive test results (uncorrectable visual or hearing impairment, severe dysarthria, tremor in the dominant hand, paresis in the dominant hand with a decrease in muscle strength corresponding to a decrease by up to MRC Weakness Scale score 2 or lower).
- Diagnosed severe medical or neurological concomitant conditions.

An MS relapse (clinical manifestations or disease activity detected using contrast-enhanced MRI) was not an exclusion criterion for the study.

Once the patients signed the informed consent form, demographic data, general and medical history were recorded, severity of neurological deficit was assessed using the EDSS scale, and severity of depression was assessed using the corresponding subscale of the Hospital Anxiety and Depression Scale. Severity of subjective cognitive impairment was assessed using the PDQ questionnaire; fatigue was assessed using the Russian version of the Modified Fatigue Impact Scale (MFIS) [22]. Objective assessment of CI was performed using the Russian version

of BICAMS test battery [23], which included the following tests [24, 25]:

- *SDMT*, which assesses processing speed. Individuals tested should quickly pair geometric shapes to one of nine numbers, based on a provided key, for 90 seconds. The outcome is total number of correctly paired shapes. To prevent upper motor extremity weakness from confounding the written version of this test, the oral version is used, when the patient calls the numbers out loud, and the assessor writes them down under the corresponding symbols.
- *Californian Verbal Learning Test – Second Edition (CVLT-II)*, which assesses short-term verbal memory and learning. The BICAMS battery allows 5 consecutive trials, which test immediate recall. The researcher reads a list of 16 words from 4 semantic groups to the patient, who should memorize them and recall in any order immediately after their presentation. The presentation is repeated 5 times, and the final score is the total number of items recalled over 5 trials.
- *The Brief Visuospatial Memory Test – Revised (BVMT-R)*, a test for non-verbal visual memory and learning. As with CVLT-II, only trials that test immediate recall are evaluated. Individuals tested are asked to study a figure with six geometric shapes for 10 seconds. The figure is removed and the participant is asked to accurately draw as many of the geometric shapes as they can remember, while simultaneously placing them in the correct location on the page. The three learning trials are scored based on accuracy (1 point) of each shape and location (1 point). A total score is derived from summing up the total number points across all three learning trials.

Since PMS patients often have impairment of executive functions, the BICAMS battery was supplemented with a Russian verbal version of *the Stroop test* to assess inhibition. The test consists of 3 parts: in part 1, the participant reads a sequence of color names (red, blue, yellow, and green) printed in black ink; in part 2, a sequence of hexagons printed in the same ink is presented, and the participant names the color of the geometric shapes. In part 3, the participant is given a card with color names written in an incongruent ink colour. The participant should voice the ink colours, ignoring the written word. Only part 3 is used to evaluate executive functions; the number of correct responses in 45 seconds is recorded [26].

In this study, the patient was considered to have CI if at least one cognitive test from the BICAMS battery or the Stroop test differed by at least 1.5 standard deviations from the mean cut scores [25, 26]. These cut scores have the highest sensitivity and adequately high specificity [26]. Therefore, processing speed impairment was recorded if SDMT score decreased to 44 or less (sensitivity 0.95; specificity 0.848), verbal memory impairment was recorded if CVLT-II score decreased to 39 or less (sensitivity 0.93; specificity 0.875), and spatial memory

Table 1. Characteristics of RRMS and PMS patients

Parameter		RRMS (n = 47)	PMS (n = 30)	p_{unc}	p_{corr}
Gender (M : F)		14 : 33	16 : 14	0,055	
Age		34 [27; 42]	47 [40; 58]	**< 0,001**	
Higher education		27	18	1,0	
Disease duration, months		22 [9; 60]	156 [75; 204]	**< 0,001**	
Relapse		45	14	–	
EDSS		3 [2,5; 3,5]	6 [4,5; 6,0]	**< 0,001**	
DMT use (yes : no)		11 : 36	15 : 14	**0,014**	
SDMT	test results	52 [49,00; 58,00]	38 [31,00; 46,75]	**< 0,001**	**< 0,001**
	number of patients with CI	7	20	**< 0,001**	**< 0,001**
CVLT-II	test results	55 [50,25; 61,00]	45 [38,25; 50,75]	**< 0,001**	**< 0,001**
	number of patients with CI	2	9	**0,003**	**0,015**
BVMT-R	test results	25 [21,50; 28,50]	23 [15,75; 26,00]	**0,022**	0,11
	number of patients with CI	7	9	0,15	0,6
Stroop test	test results	43 [38,50; 49,50]	34 [26,25; 39,75]	**< 0,001**	**< 0,001**
	number of patients with CI	1	10	**< 0,001**	**< 0,001**
Number of patients with CI	total	11	23	**< 0,001**	**< 0,001**
	single-domain CI	7	9	0,15	0,6
	CI in ≥ 2 domains	4	14	**< 0,001**	**< 0,001**
PDQ		17 [10; 29]	26 [15; 34]	0,311	1,0
MFIS	total score	27 [7,0; 45,0]	80 [61,5; 104,5]	**0,002**	**0,01**
	cognitive function subscale	12 [5,75; 17,00]	15 [7,25; 21,25]	0,475	1,0

Note. p_{unc}, significance level without correction; p_{corr}, significance level with Bonferroni correction for multiple comparisons. DMTs, disease-modifying therapies.

impairment was recorded if BVMT-R score decreased to 17 or less (sensitivity 0.946; specificity 0.933) [25]. A score of 30 and lower was used as a cut score for the Stroop test [26].

Descriptive statistics were calculated using IBM SPSS Statistics v. 27. Distribution of data was not normal (Shapiro–Wilk test; $p < 0.05$), so non-parametric statistical methods were used for analysis. Cognitive test scores and questionnaire data were compared between the groups using the Mann-Whitney test; differences in CI incidence were assessed using Fisher's exact test; correlations were assessed using the Spearman coefficient. Differences were considered statistically significant if $p < 0.05$. Adjustment for multiple comparisons was performed using the Bonferroni correction.

Results

The study included 77 MS patients (30 men, age 40 [30; 48] years) (hereinafter data are presented as Me [Q1; Q3]); of those, 47 patients had RRMS and 30 patients had PMS (26 secondary progressive MS, 4 primary progressive MS). Clinical and demographic characteristics and cognitive test results are shown in Table 1.

CI was observed in 11 (23.4%) RRMS patients; of those, 7 patients had single-domain CI, and 2 patients each had CI in 2 and 3 domains, respectively. It should be noted that RRMS patients with multi-domain CI had MS relapse at the time of inclusion in the study and did not receive DMTs, and in patients with 3-domain CI, MS duration was more than 7 years. In PMS patients, CI was reported in 23 (77%) patients, with 9 of them having single-domain CI, 6 CI in 2 domains, 5 in 3 domains, and 3 in 4 domains. Overall incidence of CI and multi-domain CI in PMS patients was statistically significantly higher than in RRMS patients (Fisher's exact test, $p < 0.001$) with no statistically significant differences in incidence of single-domain CI (Table 1).

RRMS and PMS patients did not have any statistically significant differences in gender or education level but differed in age and MS severity (Mann–Whitney test, $p < 0.001$), as well as frequency of DMT use (Fisher exact test, $p < 0.05$; Table 1). When RRMS and PMS patients were compared, statistically significant differences were found in SDMT, CVLT-II, BVMT-R, and Stroop test scores with no statistically differences in PDQ and cognitive fatigue scores. After Bonferroni correction for multiple comparisons, all differences remained statistically significant except for BVMT-R scores. When the incidence of CI in different domains was compared, statistically significant differences were also shown for SDMT, CVLT-II, and Stroop test (Fisher's exact test, $p < 0.05$).

Considering statistically significant differences between the RRMS and PMS patients in their age, MS duration and severity, we also evaluated a relationship between cognitive test results and these parameters using the non-parametric Spearman coefficient. Mean negative statistically significant correlations were shown for SDMT with age, for SDMT and

Table 2. Correlations between test parameters and questionnaires

Parameter		Age	Duration	EDSS	PDQ	MFIS	$MFIS_{cogn}$
SDMT	ρ	**–0,402**	**–0,554**	**–0,618**	–0,087	–0,270	–0,111
	p	**< 0,001**	**< 0,001**	**< 0,001**	0,459	0,020	0,911
CVLT-II	ρ	–0,272	**–0,471**	**–0,509**	–0,225	–0,371	–0,257
	p	0,017	**< 0,001**	**< 0,001**	0,054	0,001	0,027
BVMT-R	ρ	–0,339	–0,334	–0,260	–0,092	–0,200	–0,077
	p	0,003	0,003	0,023	0,437	0,087	0,514
Stroop test	ρ	–0,286	–0,255	**–0,544**	–0,149	–0,278	–0,193
	p	0,012	0,026	**< 0,001**	0,204	0,017	0,099
PDQ	ρ	0,002	0,097	0,198	–	**0,726**	**0,828**
	p	0,985	0,415	0,091	–	**< 0,001**	**< 0,001**

Note. *p*, significance level; ρ, Spearman correlation coefficient. $MFIS_{cogn}$, Modified Fatigue Impact Scale, Cognitive Subscale.

CVLT-II with disease duration, and for SDMT, CVLT-II, and Stroop test with MS severity according to EDSS (Table 2).

Differences in cognitive test results and questionnaire scores were evaluated in patients who used and did not use DMTs at the time of inclusion in the study. No statistically significant differences were found for subjective CI severity and fatigue in the total population and separate subsets.

We evaluated differences between patients with or without CI in subsets of RRMS and PMS patients by their age, MS duration and severity. RRMS patients with CI were statistically significantly older than those without CI (Mann–Whitney test, $p = 0.010$) and had more severe disease ($p = 0.043$), while no statistically significant differences were found in disease duration. There were no statistically significant differences in patients' age, MS duration or severity in PMS patients.

We also evaluated a correlation of subjective CI severity with cognitive test results and fatigue score (total score and cognitive fatigue score). When the relationship between cognitive test results and total PDQ score was evaluated, no statistically significant correlations were found. In contrast, the assessment of fatigue (general and cognitive) had a statistically significant strong correlation with the subjective CI severity according to PDQ. We also assessed a relationship between overall fatigue and cognitive fatigue scores with cognitive test results. However, only a moderate statistically significant negative correlation was shown between the total fatigue score and CVLT-II results (Table 2).

Discussion

CI was observed in approximately a quarter of RRMS patients, while in PMS patients its incidence was significantly higher (i.e. 77%). CI severity was also higher in PMS patients; however, this may be partly explained by the older age and MS duration in patients in this group. CI spectrum was different: RRMS patients had single-domain CIs, most often decreased processing speed or visuospatial memory, while PMS patients more often had multi-domain CIs. In PMS patients, a decrease in processing speed was also predominantly observed; impairments in other domains were less common and had a similar incidence. No statistically significant correlation was shown for subjective CI and fatigue assessment with cognitive test results regardless of the MS type.

CI incidence in RRMS patients in our study (23.4%) was consistent with some previous studies [27, 28]. In contrast, other authors showed a higher incidence of CI, i.e. 30–45% [29–31]. It should be noted that among RRMS patients in our study patients with MS relapse predominated, while in several studies in RRMS patients with a similar or higher CI incidence, patients were in remission [27, 30, 31], or in other studies MS activity was not specified [28, 29]. Since patients during relapses were shown to have a higher severity of CI [32, 33], this inconsistency requires further investigation.

The incidence of CI in PMS patients in our study was generally consistent with literature data [21, 31]. The differences in CI spectrum in RRMS and PMS patients were consistent with previous data summarized in a review by B. Brochet et al. [21]. The higher incidence of single-domain CI in RRMS patients and multi-domain CI in PMS patients is consistent with a large study by E. De Meo et al. [20], where patients with early RRMS most often had mild single-domain impairment in verbal memory/semantic fluency. In our group, impairment of processing speed was the most common among single-domain CIs. On the other hand, the highest incidence of impairment in processing speed in our study is consistent with the pre-viously proposed model of cognitive impairment, according to which the earliest impairment is seen in proces-sing speed, followed by impairment in visuospatial cognition, verbal cognition, working memory/attention, and executive functions [34].

An association of CI and patients' age, MS severity and duration found in our study was also shown in previous studies [21, 31, 35]. Evidence remains conflicting as to whether MS type is an independent risk factor for CI or whether patients' age and disease severity contribute more to the differences [29, 31]. Although a meta-analysis by N.C. Landmeyer et al. [36] showed that cognitive function parameters improved in patients receiving DMTs, we did not detect any statistically significant differences between patients who received DMTs and those who did not. This may be related to the high proportion of patients with early RRMS who started their DMTs recently.

Along with previous studies, we did not found any statistically significant correlation between subjective CI severity and objective test results [37]. Severity of subjective CI was previously shown to be more influenced by depression and fatigue [38], which is consistent with our results. The statistically significant moderate correlation of the overall fatigue score with CVLT-II verbal memory test results is similar to the results of a study that showed a relationship between BICAMS battery scores and subjective fatigue, in which fatigue had the most significant effect on CVLT-II scores [39]. Consistent with another recent study, we found a correlation between cognitive fatigue with subjective CI but not with objective test data [40].

Limitations of our study include small sample size and relatively high heterogeneity of patients; however, our results reliably showed the incidence of CI in real-world clinical practice when assessed using standardized screening tools. In addition, the use of cut scores for determination of CI may be considered as an important limitation of the study, and therefore, in future studies, it may be advisable to

assess the reliability of CI determination using other normal values for the Russian-speaking population, such as those based on regression. Finally, further studies would be useful to investigate changes in CI depending on disease activity, assess other cognitive domains, and compare patients with benign and highly active MS.

To summarize, our study was the first to provide a comprehensive assessment of CI prevalence in patients with different types of MS and different MS activity using the standardized Russian version of the BICAMS test battery and the Stroop test. Clinical and demographic differences between patients with CI and intact cognitive functions were also assessed. A relationship between subjective CI severity with both cognitive test results and fatigue severity was evaluated for the first time in the Russian-speaking population.

Conclusion

When cognitive functions were assessed in patients with different MS types using standardized test batteries, CI was shown to be a rather common symptom in patients with different MS types, with processing speed being affected most frequently. CI is associated with both clinical and demographic characteristics of patients (age, MS severity and duration) and with its type; PMS patients had higher severity of CI and impairment in several cognitive domains. No significant correlation was found between subjective CI assessment results and testing results, which suggests that patients underestimated their deficit. Therefore, CI is a rather common manifestation of MS, and its identification requires the active use of standardized test batteries for the objective assessment of CI in clinical practice.

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Clinical and Neuroimaging Patterns of Ischemic Stroke in Ph-negative Myeloproliferative Neoplasms

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Abstract

Introduction. *Philadelphia-negative myeloproliferative neoplasms (MPNs) are a rare blood disorder characterized by pancytosis and thrombohemorrhagic complications.*

The ***aim*** *of this article is to describe clinical and neuroimaging patterns of brain changes in patients with MPN.*

Materials and methods. *The study included 152 patients with an established diagnosis of MPN (according to WHO criteria 2008, 2016). A clinical and neurological examination, laboratory tests, and magnetic resonance imaging of the brain were performed.*

Results. *In patients with polycythemia vera and primary myelofibrosis, neuroimaging patterns are represented by small (up to 1.5 cm) post-infarction lesions in the brainstem, cerebellum, and cortex in adjacent perfusion territories after hemorheological microocclusive stroke. In patients with essential thrombocythemia, the neuroimaging pattern is more often represented by massive post-infarction changes in cortical-subcortical brain tissue with atherosclerotic lesions of the major head arteries, which appear to be atherothrombotic. Stroke preceded hematologic diagnosis in 30% of polycythemia vera cases, 40% of essential thrombocythemia cases, and 25% of primary myelofibrosis cases.*

Keywords: *blood disorders; myeloproliferative neoplasms/diseases; thrombosis; stroke; magnetic resonance imaging of the brain*

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. 11/14, dated November 19, 2014).

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Клинико-нейровизуализационные паттерны нарушений мозгового кровообращения на фоне гематологической патологии (Ph-негативных миелопролиферативных новообразований)

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Аннотация

Введение. *Ph-негативные миелопролиферативные новообразования (МПН) – редкая патология крови, характеризующаяся панцитозом и тромбогеморрагическими осложнениями.*

Цель *статьи – описание клинико-нейровизуализационных паттернов изменений вещества мозга у пациентов с МПН.*

Материалы и методы. *В исследование были включены 152 пациента с установленным диагнозом МПН (согласно критериям ВОЗ 2008, 2016 гг.). Проводились клинико-неврологический осмотр, лабораторное обследование, магнитно-резонансная томография головного мозга.*

Результаты. *У пациентов с истинной полицитемией и первичным миелофиброзом нейровизуализационные паттерны представлены небольшими (до 1,5 см) постинфарктными изменениями в стволе, мозжечке, области коры в зонах смежного кровоснабжения после нарушения мозгового кровообращения по типу гемореологической микроокклюзии. У пациентов с эссенциальной тромбоцитемией нейровизуализационная картина чаще представлена массивными постинфарктными изменениями вещества мозга корково-подкорковой локализации на фоне атеросклеротического поражения магистральных артерий головы, вероятно, по типу атеротромбоза. Инсульт предшествовал постановке гематологического диагноза в 30% случаев при истинной полицитемии, в 40% – при эссенциальной тромбоцитемии, в 25% – при первичном миелофиброзе.*

Ключевые слова: *заболевания крови; миелопролиферативные новообразования/заболевания; тромбоз; инсульт; магнитно-резонансная томография головного мозга*

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Introduction

Ph-negative myeloproliferative neoplasms/diseases (MPN/MPD) include the three most common clinical entities such as polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The incidence rate is 0.5 to 4.0 cases, 1.0 to 2.0, and 0.3 to 2.0 per 100,000 person-years for PV, ET, and PMF, respectively. The etiology of MPD remains unclear, and the leading hypothesis is the influence of environmental factors. The emergence of one of the driver mutations in the *JAK2*, *MPL*, or *CALR* genes is a key factor in the development of MPN. Despite distinct clinical entities, these disorders are linked by morphological similarities and propensity to thrombotic complications and leukemic transformation [2].

The prognosis for the disease course is variable and depends on the location and grade of the thrombotic event. Thrombosis with cerebral infarction is one of the major consequences of MPN that may significantly limit life expectancy and quality of life.

The **aim** of this study was to describe clinical and neuroimaging patterns of brain changes in patients with MPN/MPD.

Materials and methods

The study was conducted at the Research Center of Neurology and the National Medical Research Centre (NMRC) for Hematology from November 2014 to April 2024. The study included 152 patients with an established diagnosis of MPN (according to WHO criteria 2008, 2016). To confirm the diagnosis, data from clinical examination, complete blood count, core biopsy and molecular genetic testing were used, including mutation detection in *JAK2 (V617F), MPL, CALR, BCR/ABL1* genes (NMRC for Hematology).

Inclusion and exclusion criteria

The study included patients with a confirmed diagnosis of one of the clinical entities of Ph-negative MPN, who signed an informed consent form and had post-infarction brain changes as assessed by magnetic resonance imaging (MRI). Exclusion criteria included missing informed consent, absence of post-infarction brain changes, presence of severe somatic comorbidities, and contraindications to MRI (e.g., pacemakers).

All patients underwent a comprehensive clinical and neurological evaluation, as well as laboratory tests including complete blood count and blood chemistry (cholesterol, triglycerides, low- and high-density lipoprotein, glucose). To confirm an ischemic brain lesion, all patients with MPN underwent brain MRI at 3 T (Magnetom Verio, Siemens) in the sagittal, coronal, and axial planes in T2, T1, T2-FLAIR, and DWI sequences.

Study design

A cross-sectional, non-randomized, single-center interventional study.

The sample was formed by continuous inclusion of observations (after diagnosis, patients were offered additional examination at the Research Center of Neurology). After brain MRI, a study group was formed for further analysis (Figure 1).

Statistical analysis

Data analysis was performed in the RStudio environment (v. 2023.12.1, R Programming Language v.4.2.1) using the tidyverse, finalfit, and ggalluvial packages. Non-parametric methods of descriptive statistics were used. For continuous variables, data are presented as median and lower and upper quartiles; for discrete values, data are presented as frequencies. Alluvial plots (like a Sankey diagram) are used to visualize the relationships between groups of categorical variables in the study population with MPN, with each stratum indicating the size of the relationship (in this case, the number of patients/frequency in each category). Comparisons were made using the Mann–Whitney U test for two independent groups, the ANOVA test for three independent groups, and the χ^2 test for categorical variables. The null hypothesis was rejected at $p < 0.05$.

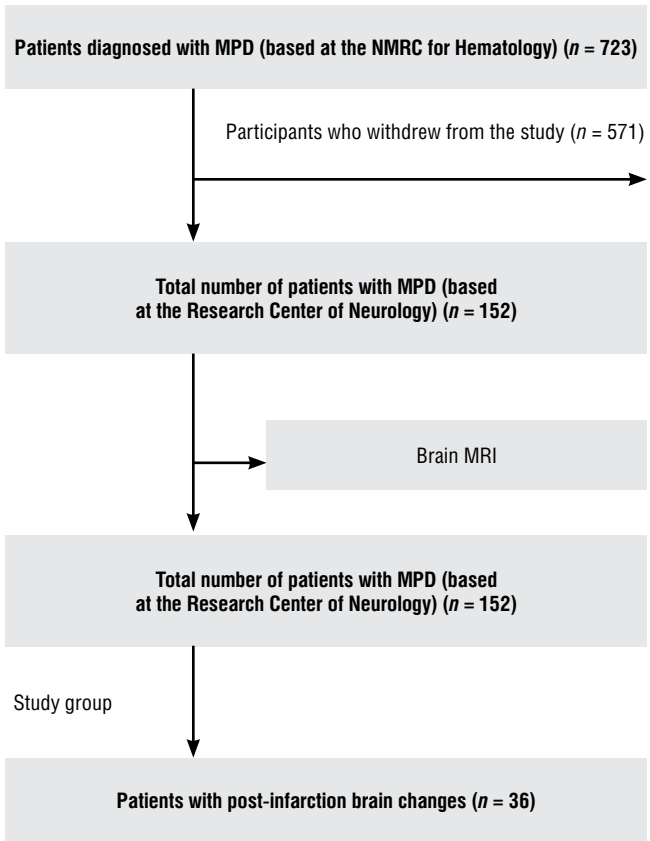

Fig. 1. Patient selection.

Results

The patients were comparable in age and distribution of major risk factors for ischemic stroke. In all groups, hydroxyurea in combination with acetylsalicylic acid was the main regimen of cytoreductive therapy.

Significant differences in hemoglobin levels, red blood cell count, and the *V617F* mutation status of the *JAK2* gene were not compared between the groups because MPD represents a heterogeneous group of clinical entities, and only PV is necessarily associated with an increase in these parameters.

Table 1. Clinical and laboratory characteristics of the study patients

Parameter	All patients (*n* = 152)	With post-infarction changes (*n* = 36)	No post-infarction changes (*n* = 116)	*p*
Male/female, *n* (%)	52 (34)/100 (66)	23 (64)/13 (36)	29 (25)/87 (75)	< 0,010
Age, years, Me [Q_1; Q_3]	48 [36; 55]	52 [39; 57]	47 [35; 55]	0,080
Hypertension, *n* (%)	51 (34)	14 (39)	37 (32)	0,565
Diabetes mellitus, *n* (%)	9 (6)	3 (8)	6 (5)	0,765
Myocardial infarction, *n* (%)	7 (5)	3 (8)	4 (3)	0,443
History of venous thrombosis, *n* (%)	19 (12,5)	8 (22)	11 (9)	0,083
JAK2 V617F, *n* (%)	117 (77)	27 (75)	90 (78)	0,924
CALR, *n* (%)	8 (5)	3 (8)	5 (4)	0,605
Cytoreductive therapy, *n* (%)	Hydroxyurea — 84; interferon — 8) (61%)	26 (72)	Hydroxyurea — 58) (57%)	0,147
Headache	88 (58)	12 (33)	76 (66)	0,001
Carotid atherosclerosis	51 (34)	18 (50)	33 (28)	0,028
Hemoglobin, g/L	141 [127; 157]	150 [136; 163]	140 [125; 153]	0,014
Red blood cells, × 10^{12}	4,8 [4,2; 5,5]	4,7 [4,2; 5,4]	4,9 [4,3; 5,5]	0,414
White blood cells, × 10^9	7,1 [5,7; 9,0]	7,3 [5,5; 8,9]	7,1 [5,7; 9,1]	0,764
Platelets, × 10^9	476 [308; 594]	429 [256; 546]	490 [324; 601]	0,099
Low-density lipoprotein, mmol/L	1,95 [1,42; 2,36]	1,98 [1,40; 2,68]	1,89 [1,42; 2,29]	0,452

The following data were analyzed to evaluate potential stroke factors in patients with MPD: results of molecular genetic testing of *JAK2* and *CALR* genes, data on comorbidities, history of venous thrombosis, blood tests, cardiovascular diseases, prevalence of carotid atherosclerosis according to the presence of stroke in the general population, and post-infarction brain changes (Table 1).

No statistically significant differences were found between the two groups relative to the presence of mutations in the *JAK2* and *CALR* genes or in the prevalence of venous thrombotic events. There were no significant differences between the groups in terms of specific therapy and hypertension. Stroke was more often associated with male gender. The higher prevalence rate of cephalgic syndrome was re-

Table 2. Clinical and laboratory characteristics of MPN patients with post-infarction brain changes

Parameter	PV (*n* = 17)	ET (*n* = 15)	PMF (*n* = 4)	*p*
Male, *n* (%)	14 (82)	6 (40)	3 (75)	0,04
Age, years, Me [Q_1; Q_3]	49 [43; 57]	51 [38; 58]	54 [48; 56]	0,995
Hypertension, *n* (%)	5 (29)	7 (47)	2 (50)	0,540
Diabetes mellitus, *n* (%)	1 (6)	2 (13)	0 (0)	0,610
Myocardial infarction, *n* (%)	3 (18)	0 (0)	0 (0)	0,160
History of venous thrombosis, *n* (%)	4 (24)	4 (27)	0 (0)	0,514
JAK2 V617F, *n* (%)	15 (88)	10 (67)	2 (50)	0,175
CALR, *n* (%)	0 (0)	2 (13)	1 (25)	0,174
Cytoreductive therapy, *n* (%)	12 (71)	11 (73)	3 (75)	0,976
Headache	5 (29)	5 (33)	2 (50)	0,734
Carotid atherosclerosis	9 (53)	9 (60)	0 (0)	0,097
Hemoglobin, g/L	162 [147; 174]	131 [126; 148]	154 [150; 158]	< 0,0001
Red blood cells, × 10^{12}	5,3 [4,5; 5,9]	4,3 [3,8; 4,9]	4,4 [4,0; 4,9]	0,006
White blood cells, × 10^9	7,7 [5,7; 8,6]	6,2 [4,7; 7,8]	10,2 [9,3; 10,8]	0,098
Platelets, × 10^9	259 [211; 499]	436 [319; 587]	578 [387; 746]	0,123
Low-density lipoprotein, mmol/L	1,79 [1,35; 2,02]	2,4 [1,4; 2,7]	3,15 [2,67; 3,50]	0,022

Note. Comparisons were made using a one-way ANOVA test for continuous variables (the null hypothesis was that the means of all groups were equal) and Fisher's exact test without continuity adjustment for frequencies. Due to the descriptive nature of the study, no further pairwise comparisons were made at $p < 0.05$.

ported in patients without post-infarction changes. Carotid atherosclerosis was more common in stroke patients (50% vs. 28%; $p = 0.0285$). Statistically significant differences were reported in hemoglobin levels; patients with stroke had higher hemoglobin levels (150 vs. 140 g/L; $p = 0.014$) and slightly lower platelet counts (429 vs. 490; $p = 0.099$).

Given the heterogeneity of laboratory parameters, we further analyzed each clinical entity of MPD separately, including clinical and neuroimaging features of stroke (Table 2; Figures 2, 3).

Polycythemia vera

Typical clinical and neuroimaging signs of stroke in PV included cortical infarct lesions in adjacent perfusion territories, brainstem, and cerebellum, corresponding to a prior hemorheological microocclusive stroke with an incidence of 65%. In a retrospective review, the clinical picture was characterized by nonspecific complaints of dizziness, sometimes vomiting, and fatigue. Patients primarily thought of food poisoning or, in the absence of vomiting, an exacerbation of the underlying hematologic disease and often did not seek medical attention. Post-infarction brain changes were found in the vertebral-basilar system (40%) and in the carotid system or adjacent perfusion territories (60%). Thrombotic occlusion of major head arteries followed by the stroke was detected in 3 patients (2 patients with thrombosis of one vertebral artery, 1 patient with internal carotid artery thrombosis). Follow-up FAT-SAT brain MRI did not confirm vascular dissection.

Two patients had concomitant ischemic stroke and hemorrhage (1 patient with the subarachnoid hemorrhage and 1 patient with the left thalamic hemorrhage). In the total group of PV patients examined, venous sinus thrombosis occurred in 1.5% of cases. In one case, thrombosis of the right transverse and sigmoid sinuses was complicated by a venous infarction on day 3.

In 30% of patients with PV, the hematologic disease was diagnosed after the stroke. Of them, one patient with moderate thrombocytosis and erythrocytosis developed a portal vein thrombosis as the first clinical event. Follow-up examination allowed diagnosing PV and specific cytoreductive and antiplatelet therapy was initiated. Considering the development of portal hypertension, it was decided to perform a mesenterico-caval anastomosis. During the 15-year follow-up period, a toxic (hepatic) encephalopathy developed, leading to cognitive decline, self-discontinuation of treatment, and subsequent recurrence of ischemic stroke.

In addition to the above cortical post-infarction changes in adjacent perfusion territories, 35% of patients with PV also had extensive hemispheric infarction lesions with severe neurological deficit (gross hemiparesis, aphasia, hemianopsia) with persistent loss of legal capacity and disability (mean age of patients was 54 years).

The main neuroimaging findings in stroke patients with PV were presented as two patterns (Figure 3):

- small (up to 1.5 cm) post-infarction lesions in the brainstem, cerebellum, deep white matter, and basal ganglia, cortical post-infarction lesions, cystic and gliotic changes without basal ganglia involvement, including adjacent perfusion territories, probably after hemorheological microocclusive stroke;
- large cortical post-infarction changes in the middle cerebral artery system and adjacent perfusion territories without basal ganglia involvement.

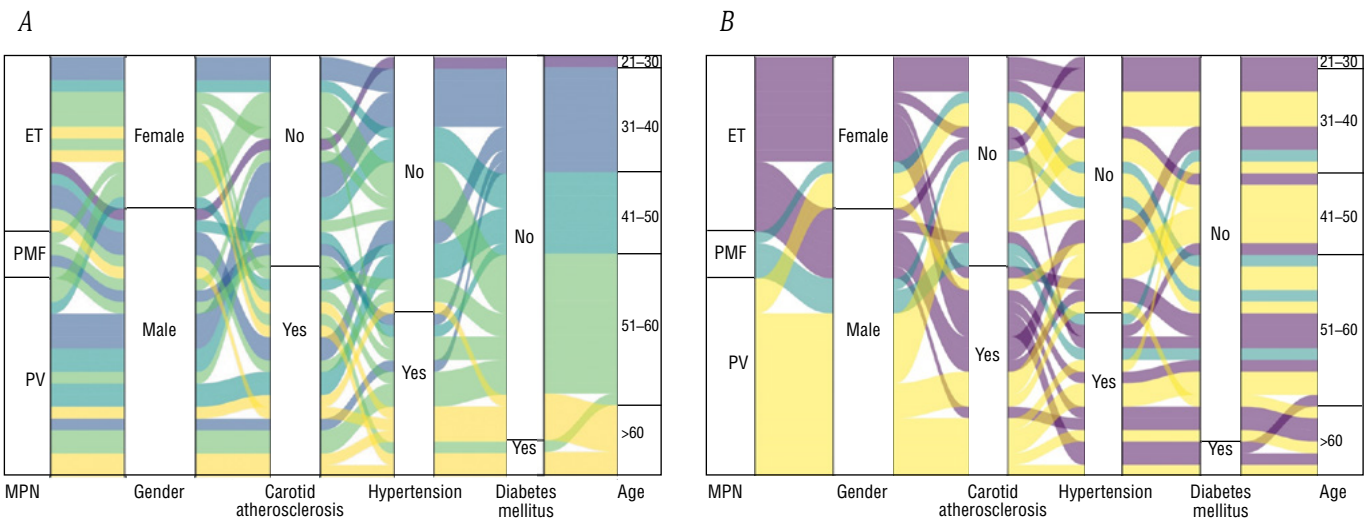

Fig. 2. Clinical patterns in post-stroke patients with MPN (alluvial plots).
A: color scheme by age category (right column); *B*: color scheme by MPN subgroup (left column).

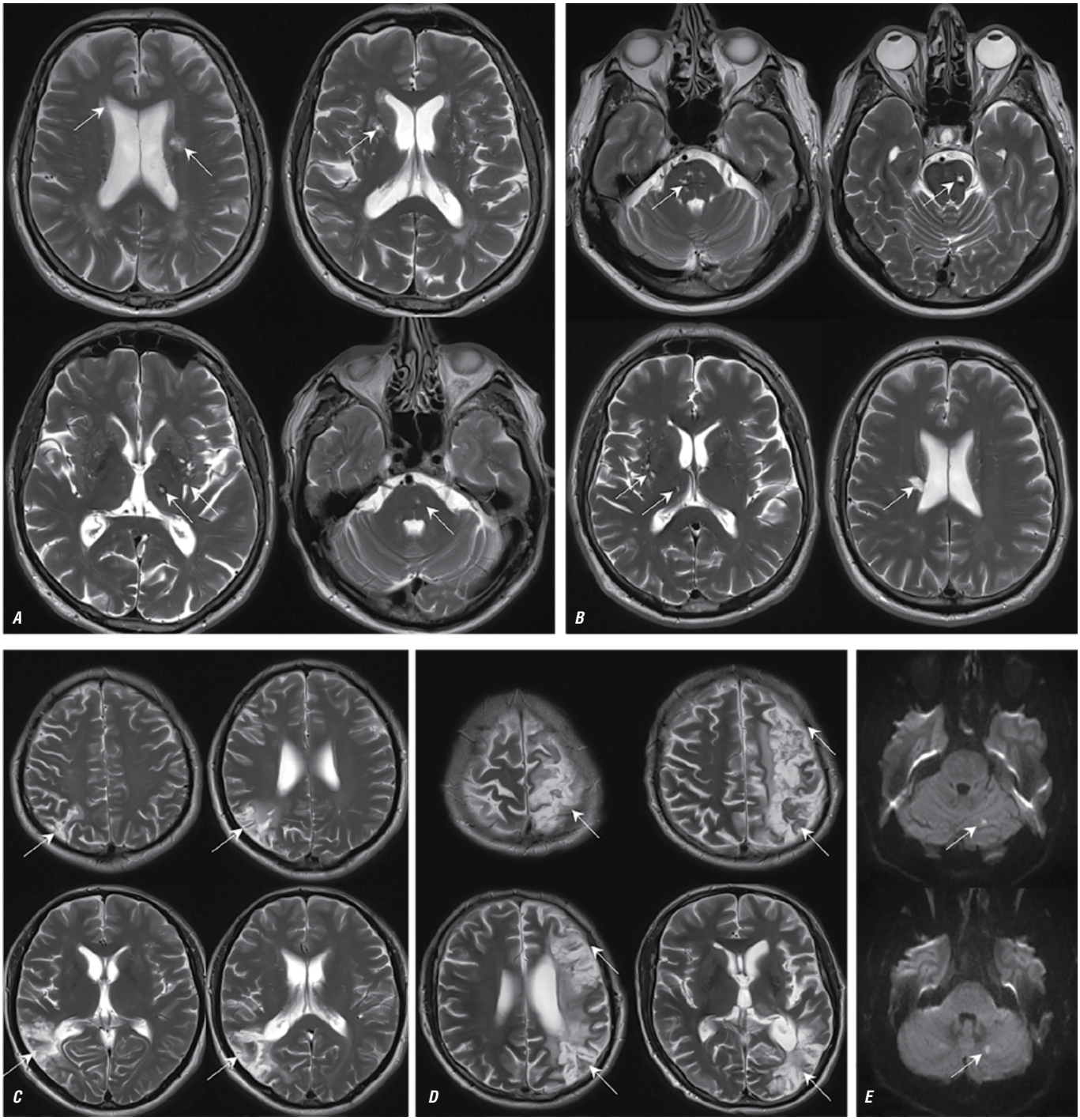

Fig. 3. Brain MRI of patients with PV in axial T2 (*A–D*) and DWI sequences with a b-value of 1,000 s/mm^2 (*E*).
Two main involvement patterns are visualized: small post-infarction lesions in the deep white matter, basal ganglia, and brainstem (*A*, *B*); one patient had lesions of acute ischemia in the left cerebellar hemisphere (*E*); large cortical post-infarction changes in the middle cerebral artery system and adjacent perfusion territories without basal ganglia involvement (*C*, *D*); post-infarction changes (*A–D*) and acute ischemic lesions (*E*) are indicated by arrows.

Essential thrombocythemia

Typical neuroimaging patterns of stroke in ET included massive post-infarction changes in the cortex, underlying and deep white matter, and basal ganglia with an incidence of 67%. In 26% of cases, stroke was associated with thrombotic occlusion of the internal carotid artery followed by formation of a massive ischemic lesion in the brain. Most cases were characterized by an acute onset with a gross neurological deficit. Post-infarction brain changes were found in the vertebral-basilar system (26%) and in the carotid system (74%). In 33% of the cases, the stroke resulted in permanent loss of legal capacity and disability (the mean age of the patients was 32 years).

In 1 patient with a history of right middle cerebral artery stroke followed by the left hemiparesis, the disease was complicated by thrombosis of the right jugular vein, lower extremity veins, recurrent pulmonary embolism with consequent myocardial remodeling, and persistent pulmonary hypertension.

In 40% of patients with ET, the stroke preceded the hematologic disease, including 1 patient with posterior reversible encephalopathy associated with extreme thrombocytosis (> 1 million platelets), which was the reason for the expanded hematologic examination leading to the diagnosis of ET.

An extensive cortical-subcortical lesions were the predominant neuroimaging pattern of stroke in ET (Figure 4).

Primary myelofibrosis

In most of PMF patients examined, the typical clinical signs of stroke included recurrent transient numbness in arms/legs, fine motor clumsiness that resolved spontaneously within a few hours, depending on the type of transient ischemic attack (TIA). Some patients described having TIAs several weeks or months before the stroke. Several patients reported episodes of significant, atypical headache with aura (visual snow, abnormal color perception), followed by focal changes (for several weeks).

The mean age of PMF patients with stroke was 50 years; there were no cases with post-infarction changes leading to persistent disability with significant motor deficit.

One patient did not receive cytoreductive antithrombotic therapy after PMF diagnosis (no history of thrombosis, age < 60 years), but developed a stroke in the right middle cerebral artery system 7 years after PMF diagnosis. In another patient, stroke preceded diagnosis of asymptomatic hematologic disease.

The predominant neuroimaging pattern of post-infarction changes in patients with PMF included small lesions in the deep brain substance, most likely after the hemorheological microocclusive stroke (Figure 5).

Discussion

Arterial and venous thrombosis of various locations is the leading cause of mortality and disability in ET, PV, and PMF [3, 4]. The diagnosis of Ph-negative MPN is based on the clinical picture and clinical laboratory data (peripheral blood tests, histology features in bone marrow core biopsy, and molecular genetic markers such as *JAK2*, *CALR*, *MPL*).

The goal of PV and ET therapy is to inhibit disease progression and preserve patients' quality of life. With proper management, the life expectancy of patients with PV and ET should not differ from that of the general population. The goal of PMF treatment is to increase life expectancy and prevent complications that can severely impact a patient's quality of life. All Ph-negative MPNs are treated using a risk-adapted strategy.

Arterial thrombosis accounts for two-thirds of thrombotic complications in patients with MPD, with stroke, TIA, and coronary thrombosis being the most clinically relevant [5–7]. Recent recommendations use objectively validated thrombotic risk factors [8]. On the one hand, such an approach reduces the long-term toxic effects of cytoreductive, anticoagulant, and antiplatelet therapies. On the other hand, existing thrombotic risk scales mainly consider only age, prior thrombotic events, cardiovascular diseases (hypertension), and mutation status (*V617* in the *JAK2* gene), and do not include factors such as the presence of atherosclerotic lesions in the major head arteries, cardiac pathology (atrial fibrillation, valve disorder, coronary atherosclerosis), obesity, oral contraceptive use, thrombophilia, low physical activity, and alcohol abuse.

J. Bogousslavsky first described cerebrovascular compli-cations in MPN patients in 1983, emphasizing that early diagnosis is essential to prevent the development and progression of cerebrovascular disease [9]. Subsequently, several publications described stroke, myocardial infarction, extensive atherosclerosis, deep vein thrombosis, and pulmonary embolism as the most common causes of death in MPN patients. The main factors of thrombotic complications have also been identified, such as the *V617F* mutation in the *JAK2* gene, leukocytosis, age, and vascular factors (hypertension) [10, 11].

In the European population, the cumulative incidence of ischemic stroke (mean follow-up of 3 years) was 25% in the PV group and 21% in the ET group [12]. This is generally comparable to our results, where the incidence of ischemic stroke was 24% in PV and 25% in ET.

A population-based cohort study by M. Hultcrantz et al. showed that patients with MPN have an approximately 1.5 times

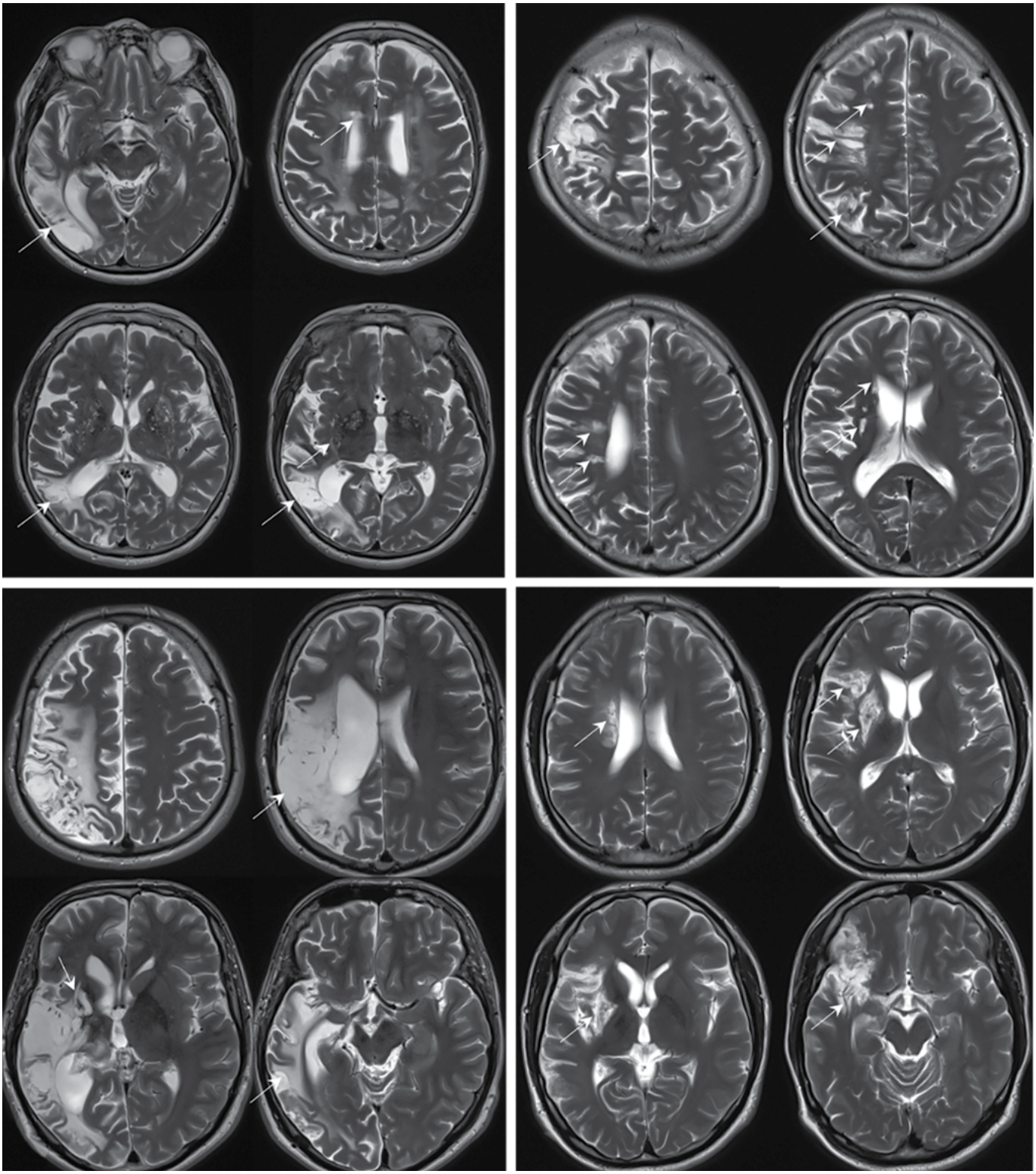

Fig. 4. Brain MRI of patients with ET; axial plane T2-weighted images.
In all cases, massive post-infarction changes are found in the cortex, underlying and deep white matter, and basal ganglia (post-infarction changes are indicated by arrows).

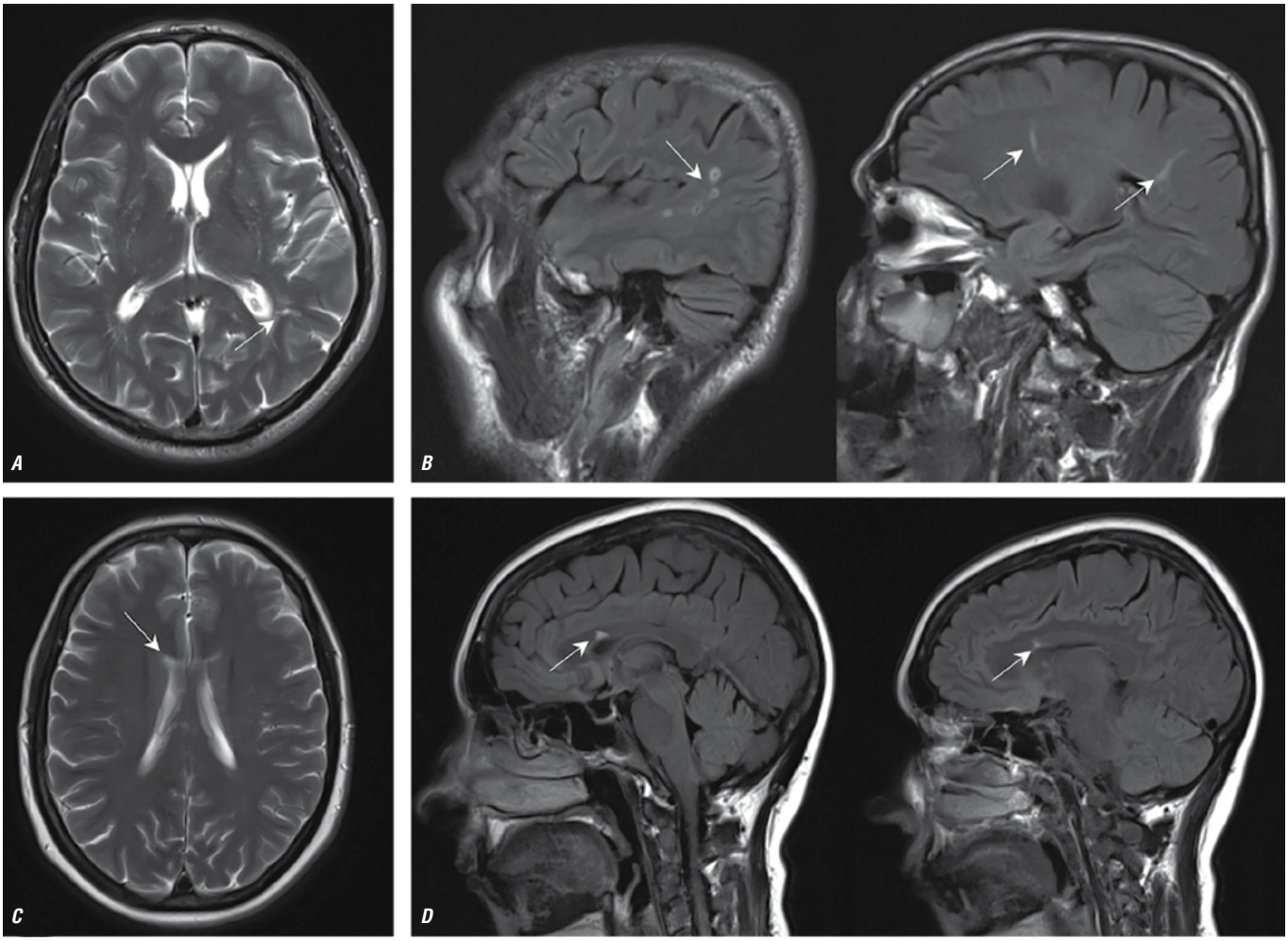

Fig. 5. Brain MRI of patients with PMF in axial T2 images (*A*, *C*) and in sagittal T2 FLAIR images (*B*, *D*).
Small post-infarction periventricular lesions are visualized (as indicated by arrows).

higher risk of ischemic stroke 5 years after diagnosis compared to age- and gender-matched controls [13]. These data support MPN as a group of diseases that require more careful monitoring and control of the underlying disease.

Cerebral and especially carotid atherosclerosis are known to play a key pathogenetic role in the development of ischemic stroke [14]. A. Drofenik et al. showed comparable prevalence and characteristics of carotid atherosclerosis in patients with ET and in the control group. However, the level of coronary calcium was higher in patients with ET [15], indicating greater vessel wall stiffness in these patients and therefore a potentially higher embolic risk. S. Kwon et al. described the epidemiology of cerebral atherosclerosis in patients with MPD associated with chronic inflammation (including *JAK2*-mediated) and demonstrated a higher neutrophil-lymphocyte ratio and carotid plaque burden compared to the general population [16]. The authors concluded that inflammation probably plays a critical role in the pathogenesis of MPD and that proinflammatory factors not only induce a prothrombogenic activity of blood, but also contribute to the progression of atherosclerosis, increasing cardiovascular risk. Abnormal activation of leukocytes, platelets, and vessel walls in ET and PV may lead to earlier development of atherosclerosis.

In our study, the higher detection rate of carotid athero-sclerosis was reported in stroke patients with ET (60%). However, extensive cortical-subcortical post-infarction changes were observed in patients with ET, indicating an atherothrombotic pathogenetic stroke, whereas brain tissue involvement was more likely in the PV and PMF groups, corresponding to a hemorheological microocclusive stroke.

In the study by M. Burattini et al., ischemic stroke was the presenting manifestation of PV in 16.2% of cases. The overall incidence of cerebrovascular complications was 5.5 per 100 persons per year, and stroke accounted for 8.8% of all PV-related deaths. The main risk factors were age, mutations, and history of thrombosis [17]. In our study, the incidence of stroke as the first manifestation of PV was 30%,

which can be explained by the characteristics of the population; some patients with hemorheological microocclusive stroke had no history of neurological symptoms, and only brain MRI according to the study protocol detected post-infarction changes.

Strokes associated with PV often remain unrecognized, in part due to the low prevalence of this clinical entity. Early diagnosis can lead to more effective treatment (with the use of phlebotomy, cytoreduction, and low-dose aspirin) and can reduce the risk of recurrence.

Data on the prevalence of stroke associated with ET as the first sign of an underlying hematologic disease are often limited to case series. T. Kato et al. described 10 patients with ET and ischemic stroke. In 8 patients (80%), the stroke preceded the diagnosis of ET [18]. In our study, stroke was the first manifestation of ET in 40% of cases.

M.I. Stefanou et al. at the University of Tübingen in 2014-2017 studied the medical records of 3,318 patients with cerebrovascular diseases, including 17 patients with MPD and ischemic stroke. In 58% of cases, stroke/TIA was the first manifestation of MPD [19].

Such variability in the available data may be explained by limitations in patient recruitment and enrollment. However, despite the variability of the parameters used, this underscores the relevant issue of the prevalence of stroke in patients with MPD, especially at a young age.

Sinus thrombosis has also been described in the literature as the first manifestation of MPD [20]. In our study, the incidence of venous sinus thrombosis was 7% (all patients had PV), but no hematologic disease was subsequently diagnosed.

One of the steps in this study was to evaluate erythrocyte/platelet aggregation parameters and their association with cerebrovascular disease in patients with MPD, which we have previously described [21, 22]. The neuroimaging pattern in hematologic patients is characterized by a relatively high frequency of so-called silent cerebral infarction lesions in addition to symptomatic stroke. Despite the absence of clinical manifestations, the consequences of previous silent MRI infarction lesions in patients with MPD may significantly and directly affect cognitive function and increase the risk of dementia in future [23, 24].

The rare hemorrhagic strokes described in this study are the subject of debate regarding the appropriateness of continuing aggressive antiplatelet therapy, particularly in cases of unrecognized resistance to certain antithrombotic drugs.

Management strategies, clinical outcomes, and life expectancy may be significantly affected in patients with established hematologic disease with or without adequate cytoreductive therapy when neurologic manifestations (headache, fatigue, transient hemi-/monoparesis of extremities, dysarthria, mild coordination disorders, cerebral ischemic lesions on MRI, sometimes silent) are present and the major features of MPD are underestimated. MPD should be recognized as a risk factor for stroke by all clinicians, not just neurologists. An expanded hematologic and neurologic examination may reduce the incidence of cryptogenic stroke.

Limitations of the study A relative limitation of this study is the recruitment of patients from a single clinical center; this cannot exclude a low representativeness of the sample.

Conclusion

A heterogeneous group of MPDs with persistent blood abnormalities is an important risk factor for cerebrovascular disease. The described clinical, laboratory, and neuroimaging patterns of cerebrovascular diseases in MPD may guide further examination of patients with unexplained and/or cryptogenic stroke.

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Ischemic Stroke and Coronavirus Infection: Complications of Endovascular Thrombectomy

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Abstract

The objective of our study was to compare complications of endovascular thrombectomy (EVT), in ischemic stroke (IS) patients admitted with or without COVID-19 to hospitals converted to deliver COVID-19-specific care.

Materials and methods. *A retrospective analysis of 817 clinical cases of IS patients aged 25–99 years treated in regional vascular centers of Saint Petersburg from 1 January to 31 December 2021, with confirmed thrombotic occlusion of cerebral vessels and subsequent EVT intervention.*

Results. *The EVT number per bed was significantly higher (1.6) in the non-converted hospitals compared to the COVID-19-converted hospitals (0.49; $p < 0.001$). At the same time, more intraoperative complications (12% vs. 7.1%; $p = 0.03$) were reported in non-converted hospitals compared to COVID-19 converted hospitals. The likelihood of a favorable functional outcome was higher in younger patients with less severe neurological deficits on admission and without concomitant COVID-19 or post-operative complications.*

Conclusion. *COVID-19 is a limiting factor for the effectiveness of an IS treatment in patients who underwent EVT, affecting thereby functional outcomes in this cohort of patients. The impact of the COVID-19 pandemic on intra-operative EVT complication rate was associated with disrupted triage of IS patients and an uneven distribution of the workload among surgical teams in the city hospitals.*

Keywords: *ischemic stroke; endovascular thrombectomy; cerebral artery thrombosis; novel coronavirus infection; complications*

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 Pavlov First Saint Petersburg State Medical University (protocol No. 2, dated November 18, 2022).

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Ишемический инсульт и коронавирусная инфекция: анализ осложнений внутрисосудистой тромбэкстракции

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Аннотация

Цель *исследования: сравнительный анализ осложнений внутрисосудистой тромбэкстракции (ВСТЭ) при ишемическом инсульте (ИИ) у пациентов при сочетании с COVID-19 и без него в условиях перепрофилирования стационаров под лечение COVID-19.*

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 1 января по 31 декабря 2021 г., с подтверждённой тромботической окклюзией церебральных сосудов и последующим выполнением ВСТЭ.*

Результаты. *Количество процедур ВСТЭ в расчёте на 1 койку в группе неперепрофилированных стационаров значимо выше (1,6) по сравнению с группой перепрофилированных стационаров (0,49; $p < 0,001$). При этом в неперепрофилированных стационарах зарегистрировано большее количество интраоперационных осложнений (12% против 7,1%; $p = 0,03$), чем в перепрофилированных. Вероятность благоприятного функционального исхода была выше у пациентов молодого возраста, без сопутствующего COVID-19, с небольшим неврологическим дефицитом при поступлении и при отсутствии послеоперационных осложнений.*

Заключение. *COVID-19 представляет собой фактор, лимитирующий эффективность лечения ИИ у пациентов с выполненной ВСТЭ, и влияет на функциональные исходы данной когорты пациентов. Влияние пандемии COVID-19 на развитие интраоперационных осложнений ВСТЭ было опосредовано нарушением общей логистики пациентов с ИИ и неравномерным распределением нагрузки на хирургические бригады стационаров.*

Ключевые слова: *ишемический инсульт; внутрисосудистая тромбэкстракция; тромбоз церебральных артерий; новая коронавирусная инфекция; осложнения*

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Introduction

Endovascular therapy has significantly expanded pathogenetic treatment options and time window for patients with acute ischemic stroke (IS) caused by large vessel occlusion (LVO) [1–3]. In regional vascular centers of Saint Petersburg, the number of endovascular thrombectomy (EVT) interventions for acute stroke increased annually from 2014 to 2020. While in 2014 only 8 EVTs were performed in Saint Petersburg (with the total number of 19,340 stroke patients admitted to regional vascular centers), in 2020 there were 624 interventions (with a total number of 17,832 stroke patients admitted to regional vascular centers) [4]. With the establishment of network of vascular centers in St. Petersburg, the hospital mortality was steadily decreasing from 26% and reached 15.8% in 2019, and stroke mortality has decreased 1.5-fold over the past 12 years, which is probably partly due to the increased availability of high-tech care[1].

The COVID-19 pandemic resulted in limited triage opportunities affecting availability of medical interventions, especially those where the time is critical [5]. For patients with cardiovascular diseases, this factor has complicated diagnostic, treatment and triage algorithms, hence increasing the risk for unfavorable outcomes [6–8]. Moreover, since the beginning of the pandemic, an increasing number of acute cerebrovascular accidents in patients with COVID-19 have been reported. Stroke may be the first clinical manifestation of this infection, which made the triage procedure more challenging due to the need of emergency screening for SARS-CoV-2. A large pool of evidence suggests that SARS-CoV-2 infection exacerbates both the IS course and a triage procedure, leading to unfavorable functional outcomes in these patients [9–12]. Growing number of unfavorable outcomes could also be caused by delays in health care-seeking behavior. For example, an article on a retrospective analysis of LVO stroke described a clinical case of a late call for emergency medical care due to the fear of SARS-CoV-2 infection [13, 14].

World experience shows that even despite the challenging triage and the need to follow additional protocols of service interaction, the number of EVT interventions in IS patients during the pandemic could remain at a fairly high level. In a retrospective review of the treatment of 126 IS patients with COVID-19 in vascular centers in the United States, Canada, and Iran, EVT was performed in 15 patients (12.1%) [15]; a review of the treatment of 202 patients in the same category from December 2019 to October 2020 reported EVT in 19 patients (9.4%), which seems rather modest; however, the combination of thrombolytic therapy and EVT was reported in 47 patients (23.3%), which together represents a significant proportion of 30% (66 patients) [16]. According to the Danish registry [18], of 23,688 stroke patients in Denmark, 552 patients underwent EVT between 1 January 2019 and 28 February 2021. The study revealed a decrease in the total number of IS patients admitted within 1 week after the implementation of quarantine measures, but the mean number of intravascular interventions remained constant throughout the study [9, 17].

The **objective** of this study was to compare EVT complication rates and outcomes in IS patients with and without COVID-19 treated in regional vascular centers of St. Petersburg, some of which were converted to deliver COVID-19 specific care.

Materials and methods

We retrospectively analyzed 817 medical records of all IS patients (365 males and 452 females) aged 25–99 years who underwent EVT from 1 January 2021 to 31 December 2021 in 11 vascular centers of Saint Petersburg (Pokrovsky City Hospital No. 1, Hospital for War Veterans, Mariinsky City Hospital No. 16, Nikiforov's All-Russian Center for Emergency and Radiation Medicine, Almazov National Medical Research Center, Alexandrovsky City Hospital No. 17, City Hospital No. 40, City Multidisciplinary Hospital No. 2, Dzhanelidze Research Institute of Emergency Medicine, City Hospital No. 26, St. Elizabeth City Hospital).

The inclusion criteria were:
- 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 intervention;
- no history of thrombolytic therapy within the comprehensive treatment plan.
- The exclusion criteria were:
- no polymerase chain reaction test for SARS-CoV-2;
- no indications for EVT;
- no control CT performed 24 hours post-surgery.

Demographic and clinical data, the nature of the stroke lesion, angiographic reperfusion assessment results, EVT complication rate, intracranial hemorrhage rate, and treatment outcomes were recorded. Surgical interventions were performed according to routine clinical indications[2]. 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. Complications were evaluated by control

[1] Official website of the Health Committee of St. Petersburg. In Saint Petersburg, the stroke mortality decreased one and a half times over the last 12 years.
URL: http://zdrav.spb.ru/ru/news/1970 (accessed on: 21.04.2024).

[2] Ischemic Stroke and Transient Ischemic Attack in Adults: National Clinical Guidelines, 2021.
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CT scans according to The Heidelberg Bleeding Classification [18]. The intraoperative complications to study were selected based on the practice of multicenter studies [19].

Functional outcome was considered favorable if modified Rankin score (mRS) was 0 to 2 and unfavorable if mRS was 3 to 5; death corresponded to mRS of 6. We also assessed mortality on day 90 after the stroke onset in a cohort of discharged patients based on cases registered in the Saint Petersburg State Information System. Death causes were reported based on autopsy results (for in-hospital deaths).

Quantitative data were presented as medians, Q1 (25%) and Q3 (75%) quartiles; categorical (qualitative) data were presented as rates and percentages; 95% confidence intervals (CI) were calculated for proportions. For all numerical data, preliminary testing for normality of distribution was performed using Shapiro-Wilk test, as well as skewness-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 and Mann–Whitney tests were used for data significantly deviating from normal distribution. The association between categorical variables was evaluated using Fisher's exact test and Pearson's χ^2 test. Multivariate analysis by binary logistic regression was used to assess correlation between clinically relevant factors and favorable outcomes. All reported *p* values were based on two-sided tests of significance. Differences were considered significant at $p < 0.05$. All calculations were performed using R package version 4.3.1.

Results

Distribution of patients to vascular centers of Saint Petersburg during the COVID-19 pandemic is presented in Table 1. The triage of stroke patients during this period was based on the presence or absence of COVID-19. Hence, in Saint Petersburg, only three (Dzhanelidze Research Institute of Emergency Medicine, City Hospital No 26, St. Elizabeth City Hospital) of 11 regional vascular centers were not converted to COVID-19 care, but the total number of patients who underwent EVT in these hospitals was higher (479 vs 338).

There were no significant differences in age, gender, NIHSS score, 90-day mortality, and functional outcomes in patients treated in both types of hospitals (Table 2). At the same time, statistically significant differences by the same parameters were found between patients with and without COVID-19 regardless of treatment site (Table 3). Thus, the NIHSS score at admission and mortality were higher in the COVID-19 patients, whereas the functional outcomes in COVID-19-free patients were significantly more favorable (mRS of 4 vs 3, respectively; $p < 0.001$).

The data on EVT complications in the patients treated in COVID-19 converted and non-converted hospitals are presented in Table 4. There is a trend for an increased incidence of the new emboli in the same territory in the patients treated in non-converted hospitals. However, in general, the rate of these complications was low, and the correction for multiple comparisons was not performed in the statistical analysis, so, it cannot be excluded that this difference is random.

No statistically significant differences were revealed by control CT scans 24 h after EVT (Table 2). We noted a trend for an increased incidence of intracerebral hematomas type 1 in the patients treated in COVID-19-converted hospitals, as well as in the COVID-19 patients (Table 3); however, this difference was below statistical significance threshold in both groups.

There was a trend for an increased incidence of arterial perforation in the patients with concomitant COVID-19 (Table 3), but due to extremely low incidence of this complication the statistical significance of this intergroup difference could not be evaluated. The incidence of subarachnoid hemorrhages in the patients with concomitant COVID-19 also tended to increase, but the inter-group difference was below statistical significance threshold, as in the case of arterial perforations.

Cumulatively, we found a statistically significant increase in intraoperative complication rate in the patients treated in non-converted hospitals (Table 2).

Table 1. Distribution of patients to regional vascular centers based on an adjusted triage procedure

Parameter	COVID-19 converted hospitals	Non-converted hospitals	*p*
Beds, *n*	693	300	< 0,001
EVT interventions, *n*	338	479	
EVTs/bed, *n*	0,49	1,6	
EVT proportion in total number of IS cases, %	4,1	5,3	
Treated IS cases, *n*	8165	8973	
Treated IS cases/bed, *n*	11,7	29,9	

Table 2. Main clinical characteristics and outcomes in IS patients who underwent EVT in COVID-19-converted and non-converted hospitals

Parameter	COVID-19-converted hospitals (*n* = 338)	Non-converted hospitals (*n* = 479)	*p*
Age	73 (63; 82)	74 (65; 83)	0,2
Males	155 (46% [40%; 51%])	210 (44% [39%; 48%])	0,6
COVID-19	80 (24% [19%; 29%])	139 (29% [25%; 33%])	0,089
NIHSS score at admission	15 (10; 18)	16 (12; 19)	0,011
In-hospital mortality	112 (33% [28%; 38%])	182 (38% [34%; 43%])	0,2
90 days post-stroke mortality	108 (36% [30%; 41%])	167 (39% [35%; 44%])	0,3
Intraoperative complications			
new emboli in the same territory	16 (4,7% [2,8%; 7,7%])	44 (9,2% [6,8%; 12,0%])	0,016
arterial dissection	7 (2,1% [0,91%; 4,4%])	9 (1,9% [0,92%; 3,7%])	0,8
arterial perforation	1 (0,3% [0,02%; 1,9%])	3 (0,6% [0,16%; 2,0%])	0,6
vasospasm requiring treatment	4 (1,2% [0,38%; 3,2%])	5 (1,0% [0,38%; 2,6%])	> 0,9
emboli in a new territory	1 (0,3% [0,02%; 1,9%])	1 (0,2% [0,01%; 1,3%])	> 0,9
Post-operative complications			
hemorrhagic infarction type 1	6 (1,8% [0,72%; 4,0%])	14 (2,9% [0,72%; 4,0%])	0,3
hemorrhagic infarction type 2	28 (8,3% [5,7%; 12,0%])	34 (7,1% [5,0%; 9,9%])	0,5
parenchymal hematoma type 1	23 (6,8% [4,5%; 10,0%])	19 (4,0% [2,5%; 6,2%])	0,072
parenchymal hematoma type 2	26 (7,7% [5,2%; 11,0%])	25 (5,2% [3,5%; 7,7%])	0,2
intraventricular hemorrhage	1 (0,3% [0,02%; 1,90%])	2 (0,4% [0,07%; 1,7%])	> 0,9
subarachnoid hemorrhage	11 (3,3% [1,7%; 5,9%])	23 (4,8% [3,10%; 7,20%])	0,3
Total complication rate			
intraoperative complications	24 (7,1% [4,7%; 11,0%])	56 (12,0% [9,0%; 15,0%])	0,030
post-operative complications	83 (25,0% [20,0%; 30,0%])	92 (19,0% [16,0%; 23,0%])	0,066
intra- and post-operative complications	5 (2,3% [0,84%; 5,5%])	18 (3,0% [1,8%; 4,8%])	0,6
Functional outcome			
Parameter	**COVID-19 converted hospitals (*n* = 226)**	**Non-converted hospitals (*n* = 297)**	***p***
Functional outcome at discharge, mRS excluding in-hospital mortality	3 (2; 4)	3 (2; 4)	0,8

Table 3. Main clinical characteristics and outcomes in groups of IS patients with or without COVID-19

Parameter	COVID-19 patients (*n* = 219)	COVID-19-free patients (*n* = 598)	*p*
Age	75 (67; 84)	73 (63; 82)	0,023
Males	103 (47% [40%; 54%])	262 (44% [40%; 48%])	0,4
NIHSS score at admission	17 (13; 20)	15 (10; 18)	< 0,001
In-hospital mortality	114 (52% [45%; 59%])	180 (30%; [26%; 34%])	< 0,001
90 days post-stroke mortality	98 (51% [44%; 59%])	177 (33% [29%; 37%])	< 0,001
Intraoperative complications			
new emboli in the same territory	16 (7,3% [4,4%; 12%])	44 (7,4% [5,5%; 9,8%])	> 0,9
arterial dissection	3 (1,4% [0,35%; 4,3%])	13 (2,2% [1,2%; 3,8%])	0,6
arterial perforation	3 (1,4% [0,35%; 4,3%])	1 (0,2% [0,01%; 1,1%])	0,061
vasospasm requiring treatment	2 (0,9% [0,16%; 3,6%])	7 (1,2% [0,51%; 2,5%])	> 0,9
emboli in a new territory	0 (0,0% [0,00%; 2,1%])	2 (0,3% [0,06%; 1,3%])	> 0,9
Post-operative complications			
hemorrhagic infarction type 1	4 (1,8% [0,59%; 4,9%])	16 (2,7% [1,6%; 4,4%])	0,5
hemorrhagic infarction type 2	19 (8,7% [5,4%; 13,0%])	43 (7,2% [5,3%; 9,7%])	0,5
parenchymal hematoma type 1	16 (7,3% [4,4%; 12,0%])	26 (4,4% [2,9%; 6,4%])	0,091
parenchymal hematoma type 2	14 (6,4% [3,7%; 11,0%])	37 (6,2% [4,5%; 8,5%])	> 0,9
intraventricular hemorrhage	0 (0,0% [0,00%; 2,1%])	3 (0,5% [0,13%; 1,6%])	0,6
subarachnoid hemorrhage	14 (6,4% [3,7%; 11,0%])	20 (3,4% [2,1%; 5,2%])	0,054
Total complication rate			
intraoperative complications	22 (10% [6,5%; 15,0%])	58 (9,7% [7,5%; 12,0%])	0,9
post-operative complications	53 (24,0% [19,0%; 31,0%])	122 (20,0% [17,0%; 24,0%])	0,2
intra- and post-operative complications	10 (3,0% [1,5%; 5,5%])	13 (2,7% [1,5%; 4,7%])	0,8
Functional outcome			
Parameter	**COVID-19 patients (*n* = 105)**	**COVID-19-free patients (n = 418)**	***p***
Functional outcome at discharge, mRS excluding in-hospital mortality	4 (3; 5)	3 (2; 4)	< 0,001

Table 4. Multiple correlation coefficients between the rates of favorable functional outcomes (mRS 0–2) and clinically significant variables in the study group

Parameter	Odds ratio	95% CI	*p*
Age	0,97	0,96–0,98	< 0,001
Treated in non-converted hospital	1,22	0,84–1,78	0,300
COVID-19-free patients	7,39	4,13–14,3	< 0,001
NIHSS score at admission	0,89	0,86–0,92	< 0,001
Absence of intraoperative complications	1,08	0,58–2,07	0,800
Absence of postoperative complications	2,20	1,31–3,84	0,004

The analysis of the factors associated with favorable functional outcomes showed no significant influence of treatment site or intraoperative complication rate (Table 4). Thus, the factors associated with favorable functional outcomes include younger age, milder neurological deficits on admission, and the absence of post-operative complications or COVID-19.

Discussion

We studied a population representative for the extended COVID-19 pandemic: a continuous sampling of IS patients underwent EVT in metropolitan vascular centers during 2021. We found that concomitant COVID-19 had no significant effect on the intraoperative or postoperative complication rate. However, when comparing the groups of patients treated in COVID-19-converted and non-converted hospitals, there was a statistically significant increase in the overall intra-operative complication rate in patients treated in non-converted hospitals.

This may be caused by organizational factors (i.e. suboptimal pre-hospital and in-hospital logistics for IS patients) limiting the success of specialized treatment techniques. On a per-bed basis, three times more IS patients were treated in non-converted hospitals and three times more EVT interventions were performed compared to per-bed load in the COVID-19-converted hospitals. The in-flow of patients during the pandemic increased while hospital staffing remained unchanged, which possibly led to an excessive staff workload, especially for surgical teams resulted in the higher rates of intraoperative complications.

The negative impact of organizational challenges is consistent with a worldwide trend; for example, less favorable outcomes in stroke patients treated during the COVID-19 pandemic have been reported in most cohort studies [20, 21].

We would like to emphasize that this study was not designed to evaluate the effectiveness of EVT compared to other treatment options, as this analysis does not include data on IS patients who did not undergo any surgery. Noteworthy, there was no significant difference in the proportion of COVID-19 patients in both COVID-19-converted and non-converted hospitals. Thus, the COVID-19 diagnosis and the treatment site could not directly influence the decision to choose surgery as a treatment option.

In IS patients with concomitant COVID-19, no statistically significant increase in both intraoperative and postoperative complication rates was reported despite the specific anticoagulant prophylaxis (according to COVID-19 management protocols).

Nevertheless, according to multivariate analysis data, concomitant COVID-19 turned out to be a predictor of unfavorable outcomes, regardless of the patient's age, stroke severity, and intra- and post-operative complications. At the same time, the hospital profile (converted or non-converted) had no effect on the disease outcomes. These findings confirm that COVID-19 worsens the IS outcome not only by indirectly affecting the organization of health care and logistics, but also by directly complicating the course of the disease.

Limitations of the study

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 damage that complicated COVID-19 course. It is also known that COVID-19 itself can contribute to an overall increase in NIHSS score [22], therefore, it cannot be excluded that in some COVID-19 patients, NIHSS scores above optimal cut-offs precluded EVT, while patients with an equivalent volume of brain lesion but without COVID-19 underwent the intervention, and thus the brain damage in patients without COVID-19 was initially more extensive. We did not consider cases with reduced EVT availability due to organizational challenges, including administrative issues and delays due to inter-hospital transfers.

Conclusions

In patients who underwent EVT in regional vascular centers of Saint Petersburg in 2021, concomitant COVID-19 did not affect the complication rates during interventional treatment of patients with hyperacute ischemic stroke. Nevertheless, the COVID-19 pandemic had an indirect negative impact on the IS course after EVT due to logistical disruption, uneven patient-bed allocation, triage challenges and, as a consequence, increased medical staff workload (especially in surgical teams). This factor may contribute to an increase in intra-operative complication rate in the hospitals with a large number of patients allocated to a smaller number of beds (non-converted hospitals in our study).

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Temporal Lobe Epilepsy with Bitemporal Interictal Epileptiform Discharges: Effects of Sleep and Wakefulness

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Abstract

Introduction. *Independent bitemporal interictal discharges are often found in patients with temporal lobe epilepsy. The likelihood of registering epileptiform activity (EA) is higher during sleep. Assessment of bitemporal interictal epileptiform discharges (BIEDs) with various discharge predominance ratio is used for presurgical evaluation of epilepsy patients and prediction of surgical outcomes.*

Our ***objective*** *was to determine the predominant side (PS) in patients with bitemporal epilepsy using the incidence of epileptiform discharges for each sleep stage.*

Materials and methods. *We analyzed 45 recordings of 10–24 h long-term video-EEG monitoring (LTM) in patients with bitemporal EA. For each recording, the total incidence of EA (IEA) and EA incidence for wakefulness and for each sleep stage were calculated individually. We also assessed the discharge predominance index (DPI) as a ratio of IEA in the predominant and contralateral sides for the entire recording and for each sleep stage.*

Results. *We observed an IEA increase with sleep deepening, with maximum values observed during N2 and N3 sleep stages. The minimum IEA values were recorded during REM sleep; nevertheless, most of the REM sleep discharges were detected on the PS. DPI values were the highest and the most stable during N2 and N3 stages.*

Conclusion. *The findings of our study demonstrate an increase in DPI values with non-rapid eye movement (NREM) sleep deepening in patients with bitemporal localization of EA. Despite the protective effects of REM sleep (i.e., reducing the likelihood of EA), it may be pivotal in lateralization of EA in patients with BIEDs. The PS is generally determined by a higher DPI during N2 and N3 stages.*

Keywords: *temporal lobe epilepsy with bitemporal discharges; sleep; electroencephalography; sleep stages*

Ethics approval. All patients provided their voluntary informed consent to participate in the study. The study protocol was approved by the Ethics Committee of the Research Center of Neurology (Protocol No. 11-6/22, dated 21 December 2022).

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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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Височная эпилепсия с битемпоральными интериктальными разрядами: влияние сна и бодрствования

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Аннотация

Введение. *У пациентов с височной эпилепсией нередко выявляются независимые битемпоральные разряды в межприступном периоде. Вероятность регистрации эпилептиформной активности (ЭА) увеличивается во сне. Наличие битемпоральных интериктальных эпилептиформных разрядов с различным соотношением количества разрядов по сторонам учитывается для определения исхода хирургического лечения.*

Цель: *на основании расчёта индекса эпилептиформных разрядов для каждой стадии сна выявить доминирующую сторону у пациентов с битемпоральной эпилепсией.*

Материалы и методы. *В исследование были включены 45 записей видео-ЭЭГ-мониторинга длительностью 10–24 ч у пациентов с битемпоральной ЭА. Для каждой записи рассчитывали общий индекс ЭА и индекс ЭА для бодрствования и каждой стадии сна отдельно. Также определяли индекс доминирования разрядов (ИДР) в процентах как соотношение разрядов на доминирующей и контралатеральной сторонах для всей записи и отдельно для каждой стадии.*

Результаты. *Отмечено увеличение индекса ЭА по мере углубления сна, максимальные значения выявлены в стадиях сна N2 и N3. Минимальное значение индекса ЭА было в фазе REM-сна, тем не менее в большинстве случаев разряды в REM-фазе выявлялись на доминирующей стороне. ИДР был наиболее высоким и стабильным в стадиях N2 и N3.*

Заключение. *Результаты исследования пациентов с битемпоральной локализацией ЭА свидетельствуют о возрастании ИДР по мере увеличения глубины не-REM-сна. Несмотря на то что REM-сон обладает протективными свойствами, снижая вероятность появления ЭА, для пациентов с битемпоральными интериктальными эпилептиформными разрядами он может иметь латерализующее значение. Доминирующая сторона в значительной степени определяется высоким значением ИДР в стадиях N2 и N3.*

Ключевые слова: *височная эпилепсия с битемпоральными разрядами; сон; электроэнцефалография; стадии сна*

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Introduction

Focal temporal lobe epilepsy (TLE) is the most common form of structural epilepsy and one of the most common neurological diseases, diagnosed in 1/3 of patients with epilepsy [1]. In 30% of cases, it is drug-resistant, so the patients become candidates for a surgical treatment [2]. Long-lasting focal TLE increases the probability of development of secondary epileptogenic focus in the contralateral cerebral hemisphere. EEG data demonstrate that the prevalence of bitemporal interictal epileptiform discharges (BIEDs) in patients with focal TLE can reach up to 60% [3, 4].

When both temporal lobes are involved, the predominance of epileptogenic focus is challenging to determine, and bilateral resection options are limited due to the risk of the Kluver–

Bucy syndrome. The search for clinical and neurophysiological markers of the predominant side (PS) in TLE patients with bitemporal discharges is of particular interest to achieve favorable surgical outcomes. It has been previously shown that the effectiveness of surgical treatment in patients with BIEDs correlates with higher discharge predominance index (DPI) on one side, and the most favorable outcomes were observed in patients with over 80–90% of unilateral discharges [5, 6].

In patients with focal TLE, the likelihood to find epileptiform activity (EA) is largely determined by the level of wakefulness and depth of sleep [7, 8]. EA is more often detected during sleep, especially in slow-wave sleep. Thus, an absolute count of discharges is insufficient without considering the duration of wakefulness and individual stages of sleep. To this end, incidence of epileptiform activity (IEA) may be employed, which is calculated as the number of discharges occurring over a specified time interval (e.g., 1 h) during which the patient has been either awake or asleep. So, the absolute count of discharges without indicating wakefulness or sleep stage at the time of EEG recording may not suffice.

The **objective** of the study was to assess the variability of DPI calculated with IEA values depending on the level of wakefulness and sleep depth in TLE patients with bitemporal discharges.

Materials and methods

Out of a total of 2086 patients who underwent long-term video-EEG monitoring (LTM) in the laboratory of the Research Center of Neurology between February 2018 and February 2024 [9], the recordings of 10–24 h LTM in 1063 patients with temporal lobe localization of EA were selected. BIED were registered in 203 cases. To identify the structural causes of epilepsy, brain magnetic resonance imaging (MRI) was performed using Magnetom Prisma 3T (Siemens Healthineers, Germany).

Inclusion criteria [9]:
1) bitemporal EA;
2) recording of all stages of sleep and wakefulness;
3) manual count of epileptiform discharges without using the algorithm of automatic discharge detection;
4) total number of BIEDs ⩾ 10;
5) brain MRI performed according to the HARNESS-MRI protocol using 3T MR scanner.

Non-inclusion and exclusion criteria [9]:
1) recordings with extratemporal EA;
2) recordings with ictal patterns, due to their possible effects on IEA;
3) recordings with more than 2000 discharges due to their challenging manual labeling;
4) DPI < 60%.

We analyzed 45 recordings of 20 females and 25 males aged 25–67 years (median 44.6 years). The disease duration at the time of admission ranged from 6 months to 43 years (median 29.8 years), and the age of epilepsy onset ranged from 4 months to 67 years (median 14.9 years). We performed surface EEG with scalp electrodes according to the international 10–20 system, with additional inferior temporal chain (F9, F10, T9, T10, P9, P10) and with simultaneous one-channel electrocardiogram recording.[9] Equipment used for the recording: Xltek Brain Monitor (Natus, USA) and BE Plus LTM amplifier (EBNeuro, Italy). At the beginning of study and after morning awakening, patients underwent activation procedures with eye closure, intermittent photic stimulation, and hyperventilation for 5 min.

In accordance with the recommendations of the American Association of Sleep Medicine (2017) [10], sleep scoring was done manually at 30 second epochs. REM sleep was scored based on oculomotor artifacts in frontal leads (under electrodes Fp1–F7, Fp2–F8), myographic artifacts in EEG channels, and EEG waveforms specific for REM sleep. We used traditional designations for sleep and wakefulness stages: N1 – sleep stage 1; N2 – sleep stage 2; N3 – sleep stage 3 (slow-wave sleep); REM – REM sleep; Wake – wakefulness [9]. A sample hypnogram with EA labels is presented in Figure 1.

The number of BIEDs during the recording ranged from 11 to 1920 discharges (median 299.6 discharges). For each recording, after building a hypnogram with BIED labels, we assessed the total IEA (the ratio of total number of discharges to the duration of recording in hours), IEA for wakefulness and each

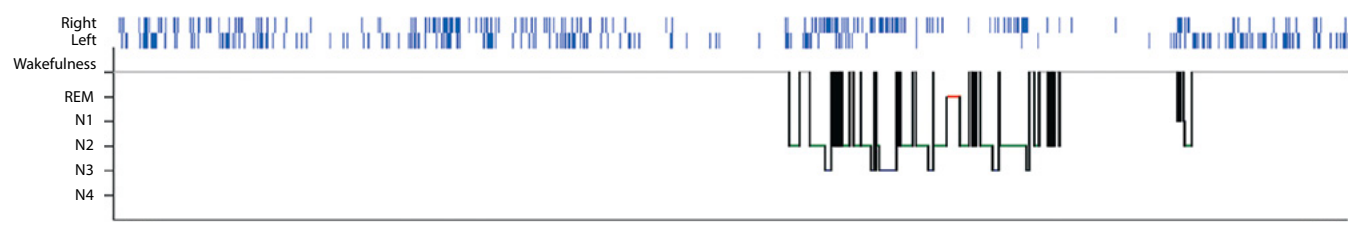

Fig. 1. Hypnogram with EA labels in the right (top row) and left (bottom row) temporal regions.

sleep stage (the ratio of number of BIEDs to the duration of stage in hours) [9]. The side with the predominance of discharges during the entire recording was defined as the PS, the opposite side was defined as the contralateral side (CS).

The DPI (%) for the entire recording and for wakefulness and each sleep stage was calculated using the formula: (number of discharges on PS)/(number of discharges on both sides) × 100. The amplitude of discharges was measured in the average reference montage. The highest discharge amplitude on each side was selected regardless of the level of vigilance (sleep and wakefulness).

To evaluate the DPI trends associated with specific sleep stages and wakefulness, additional normalization was performed via calculation of relative DPI for each stage on the PS (the ratio of the DPI of each stage to the total DPI).

When EEG data were compared with brain MRI findings according to the HARNESS-MRI protocol, potentially epileptogenic findings were identified in 17 cases: 9 cases of hippocampal sclerosis; 2 benign tumors associated with long-term epilepsy (LEAT); 3 meningiomas; 2 cases of temporal encephalocele; 1 cerebral hemiatrophy. Non-specific changes (cerebral microangiopathy, poststroke changes, and venous anomalies) not corresponding to EA localization were found in 23 cases. In 5 cases focal and diffuse changes in the brain were absent.

Results

In 21 patients the discharges predominated in the left temporal region and 24 patients had a right temporal predominance. Analysis of the BIED amplitude revealed that in 32 (71.1%) cases the maximum amplitude of discharges corresponded to PS. Bitemporal slowing was observed in 27 EEG recordings, unilateral slowing was detected in 13 recordings (11 out of 13 recordings on PS), and in 5 recordings slowing was absent.

The distribution of EA in temporal regions across wakefulness and sleep stages is presented in Table 1. During wakefulness epileptiform discharges were found in 33 (73.3%) cases. In 32 (71.1%) cases EA was detected on PS and in 18 (40%) it was found on CS (Table 1).

Table 2 presents the IEA ratios for the sleep stages, where BIEDs were detected, as well as the distribution of EA across wakefulness and sleep stages. The patients, whose recordings showed no significant differences in IEA values between two sides, were referred to a separate group. The PS/CS discharge ratios > 40% and < 60% were considered approximately equal.

In one MR-negative patient, EA was detected on the CS (Table 2). In N1 sleep stage, EA was detected in 25 (55.6%) recordings: 22 (48.9%) with EA on PS and 14 (30.4%) on CS (Table 1), while in 3 cases it was found on CS only (Table 2).

In sleep stage N2, EA was detected in 45 (100%) recordings: 45 (100%) with EA on PS and 42 (93.3%) on CS. In sleep stage N3, epileptiform discharges were found in 44 (97.8%) recordings on PS and in 36 (80%) recordings on CS. Only in one patient's recording EA was not found in N3, although detected in stage N2 (Table 1).

In the majority of recordings, BIEDs had the highest IEA during N3 stage (43 recordings; 95.5%), including 26 (57.8%)

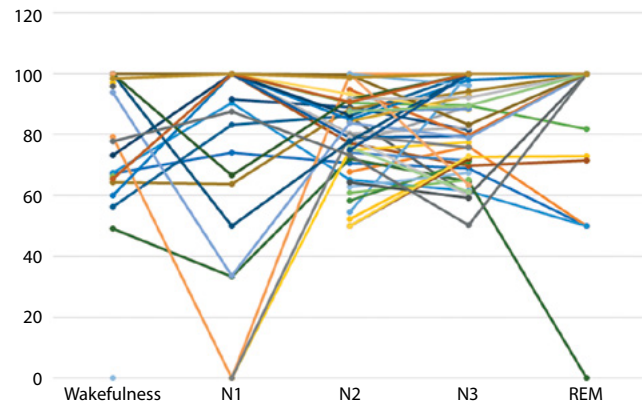

Fig. 2. Distribution of DPI values (%).
The X-axis presents sleep and wakefulness stages, the Y-axis – normalized DPI values. DPI values < 50% indicate the predominance of discharges on CS.

Table 1. Distribution of EA in temporal regions across sleep stages and wakefulness, *n* (%)

Sleep stage	Recordings with EA	Recordings with BIEDs	Recordings with EA on PS	Recordings with EA on CS
Wakefulness	33 (73,3%)	17 (37,8%)	32 (71,1%)	18 (40,0%)
N1	25 (55,6%)	11 (24,4%)	22 (48,9%)	14 (30,4%)
N2	45 (100,0%)	42 (93,3%)	45 (100,0%)	42 (93,3%)
N3	44 (97,8%)	36 (80,0%)	44 (97,8%)	36 (80,0%)
REM	19 (42,2%)	7 (15,5%)	18 (40,0%)	8 (17,8%)

Table 2. Distribution of EA across sleep stages and wakefulness, *n* (%)

Stage	EA on PS only	EA on CS only	Higher IEA on PS*	Higher IEA on CS	IEA with no significant differences between sides
Wakefulness	15 (33,3%)	1 (2,2%)	13/17 (76,5%)	2 (4,4%)	3 (6,7%)
N1	11 (24,4%)	3 (6,7%)	7/11 (63,6%)	5 (11,1%)	2 (4,4%)
N2	3 (6,7%)	0	37/42 (88,1%)	0	5 (11,1%)
N3	8 (17,8%)	0	33/36 (91,7%)	0	3 (6,7%)
REM	11 (24,4%)	1 (2,2%)	3/7 (42,9%)	1 (2,2%)	4 (8,9%)

Note. * — % of recordings with BIEDs during sleep or wakefulness.

recordings with BIEDs in both temporal regions. In 7 (15.5%) cases, EA with maximal IEA was recorded on the CS and in 10 (22.2%) cases — on the PS. In REM sleep EA was found in 19 (42.2%) recordings: in 18 (40%) cases on the PS and, in 8 (17.8%) cases on the CS, while in one recording EA was detected exclusively on the CS (Table 2).

We analyzed wakefulness and sleep stages with maximum IEA registered on PS during this study. The highest values were detected in the period of slow-wave sleep (N3 stage), amounting to 36 (80%) recordings. In 3 cases the leading stage was N2, in 5 cases — N1, in 1 case the maximum IEA was recorded during wakefulness. No cases with predominance of EA in REM sleep were detected.

Figure 2 shows the distribution of DPI values across wakefulness and each sleep stage. Maximum density of DPI values in N2 and N3 stages, where DPI was always > 50% (i.e., discharge predominance on PS) was of particular interest.

Discussion

The results of our study demonstrated that the highest IEA values were characteristic of the slow-wave sleep stage in the temporal region of PSDH. N2 sleep stage was the most significant in recordings with no EA detected during the delta sleep. A comparison of sleep stages revealed that the maximum number of discharges in N3 stage were found in 80% of recordings for PS and in 71.3% for CS. The IEA increased with sleep deepening (maximum values were detected in N2 and N3 stages). The minimum IEA was obtained in REM sleep.

Earlier studies also showed that the highest IEA values were characteristic of the delta sleep [8, 9, 11–14]. The distinctive features of our study are the analysis of patients exclusively with bitemporal discharges, manual labeling of discharges throughout the entire recording, and count of discharges by each sleep stage. The PS was determined by the total number of discharges on the left or right side, whereas, for example, Z. Clemens et al. determined it by the seizure onset side [13]. In other studies, the discharge count was often performed on fragments with different duration (5–20 min for each stage of sleep and wakefulness). High IEA in N2 and N3 stages can be explained by a high degree of neural synchronization in the cerebral cortex [15–17].

It is believed that EA in REM sleep is important for seizure-onset zone localization in TLE patients [18]. Our data partly confirm this statement. EA was recorded on PS in 19 (42.2%) cases and on CS in 8 (17.8%) cases. In 3 cases, IEA was higher on PS, while in 4 cases there was no significant difference between sides. In 1 case EA was found only in the contralateral temporal region (Table 2). There are conflicting opinions on this hypothesis. S. Singh et al. showed a lower localizing value of REM sleep compared to non-REM sleep when quantifying EA [14]. At the same time, it remains certain that REM sleep asa part of healthy sleep structure has protective effects, inhibiting not only EA but also epileptic seizures [19, 20].

While performing presurgical evaluation of patients with a drug-resistant focal TLE, one should take into account the lateralizing and localizing seizure symptoms. The data of ictal and interictal EEG and neuroimaging should correspond to each other [21]. However, in patients with BIEDs, which may occur due to secondary epileptogenesis often associated with a long-lasting epilepsy, it is necessary to assess IEA ratio in the temporal regions on both sides. Correlation between this ratio and surgical outcomes has been previously evaluated [5, 6]. The most favorable outcomes were achieved with a ratio of > 80% of discharges on the PS.

Various studies demonstrated that the prevalence of BIEDs varies in a wide range, from 21% [22] to 61% [3]. High variability of these data is primarily explained by the duration of recordings. The low prevalence values are associated with the relatively short duration of recordings. For example, in study [22], the duration of recording was ⩽ 2 h. In study [3], on the contrary, patients with only unitemporal discharges detected by a routine EEG were initially selected. These patients were subsequently monitored daily and BIEDs were also detected in 61% of recordings.

The results of our study demonstrate not only an increase in likelihood of finding EA with the sleep deepening, but

also considerable variability in DPI values during wakefulness and in the light sleep. DPI in these stages is unreliable and may be misleading, whereas it is the most stable in a deep sleep.

The results of this study justify the need for LTM with delta sleep assessment in patients with suspected focal epilepsy, because standard EEG is a short-term screening method of diagnosis, and daytime EEG monitoring of no more than 4 h does not always allow reaching a deep sleep stage. In structural forms of focal epilepsy, it is also necessary to count discharges in temporal regions and compare these data with MRI epilepsy protocol findings to substantiate the need for surgical treatment and to predict favorable surgical outcomes.

Conclusion

The findings of our study demonstrate an increase in DPI values with non-rapid eye movement (NREM) sleep deepening in patients with BIEDs. The ratio of IEA in a deep sleep is the most reliable indicator to determine the PS. Although REM sleep has protective properties reducing the likelihood of EA occurrence, it has significant localizing value for patients with BIEDs. In studies with short-term EEG recordings, the necessary depth of sleep is often not achieved, therefore reducing their diagnostic value. Count of epileptiform discharges in the right and left temporal regions is necessary to substantiate the need for surgical treatment and to predict favorable surgical outcomes in patients with focal TLE.

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Glymphatic System Assessment Using DTI-ALPS in Age-Dependent Neurodegenerative Diseases

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Abstract

Introduction. *Dysfunction of the glymphatic system glymphatic system of the brain is considered a pathogenetic factor in some age-dependent neurodegenerative diseases, including Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease (PD), and normal pressure hydrocephalus (NPH). The innovative method for calculating DTI-ALPS (Diffusion Tensor Image Analysis ALong the Perivascular Space) allows non-invasive assessment of the glymphatic system status using magnetic resonance imaging (MRI).*

The ***aim*** *of the study is to compare DTI-ALPS in patients with AD, DLB, PD, and NPH and to evaluate its potential use as a biomarker of the glymphatic system status in these diseases.*

Materials and methods. *The study included 116 subjects: 32 patients with AD, 15 patients with DLB, 31 patients with PD, 11 patients with NPH, and 27 healthy volunteers. Cognitive testing was performed for patients in the main groups using the Montreal Cognitive Assessment (MoCA) score. All subjects underwent diffusion tensor imaging (DTI) of the brain. DTI-ALPS was then calculated.*

Results. *DTI-ALPS index significantly differed across groups ($p < 0.001$). Patients with AD, DLB, and NPH had a significantly lower DTI-ALPS index on both sides compared to the PD group and healthy volunteers ($p < 0.01$). Analysis of the entire sample showed a direct correlation between MoCA score and DTI-ALPS index ($p < 0.05$).*

Conclusion. *This is the first comparison of DTI-ALPS across such a broad range of age-dependent neurodegenerative diseases. Since our DTI-ALPS results were comparable to previously reported data, we believe that this parameter can be used as an indirect marker of the glymphatic system status.*

Key words: *glymphatic system; diffusion tensor imaging; magnetic resonance imaging; neurodegenerative diseases; cognitive impairment; Alzheimer's disease; Lewy body dementia; Parkinson's disease; normal pressure hydrocephalus*

Ethics approval. All patients provided their voluntary informed consent to participate in the study. The study protocol was approved by the Ethics Committee of the Research Center of Neurology (protocol No. 1-2/22, dated January 19, 2022).

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Оценка глимфатической системы методом DTI-ALPS при возраст-зависимых нейродегенеративных заболеваниях

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Аннотация

Введение. *Дисфункция глимфатической системы мозга считается одним из патогенетических факторов некоторых возраст-зависимых нейродегенеративных заболеваний, таких как болезнь Альцгеймера (БА), деменция с тельцами Леви (ДТЛ), болезнь Паркинсона (БП) и нормотензивная гидроцефалия (НТГ). Инновационный метод расчёта индекса DTI-ALPS (диффузионно-тензорные изображения с оценкой периваскулярных пространств) позволяет неинвазивно оценивать состояние глимфатической системы посредством магнитно-резонансной томографии.*

Цель исследования *– сравнить результаты показателя DTI-ALPS у пациентов с БА, ДТЛ, БП и НТГ, а также оценить возможность его использования в качестве биомаркера состояния глимфатической системы при этих нозологиях.*

Материалы и методы. *В исследовании приняли участие 116 человек: 32 пациента с БА, 15 пациентов с ДТЛ, 31 пациент с БП, 11 пациентов с НТГ и 27 здоровых добровольцев. Пациентам основных групп проводили когнитивное тестирование с использованием Монреальской шкалы оценки когнитивных функций. Всем испытуемым была проведена магнитно-резонансная томография головного мозга в режиме диффузионно-тензорной томографии с последующим вычислением индекса DTI-ALPS.*

Результаты. *Значения индекса DTI-ALPS значимо различались между группами ($p < 0,001$). Пациенты с БА, ДТЛ и НТГ имели значимо более низкий индекс DTI-ALPS с обеих сторон по сравнению с группой БП и здоровыми добровольцами ($p < 0,01$). Анализ всей выборки выявил прямую корреляцию между баллом по Монреальской шкале оценки когнитивных функций и значениями DTI-ALPS ($p < 0,05$).*

Заключение. *Сравнение значений индекса DTI-ALPS среди такого широкого спектра возраст-зависимых нейродегенеративных заболеваний было проведено впервые. Учитывая, что полученные значения DTI-ALPS сопоставимы с ранее опубликованными данными, мы полагаем, что предложенный метод может быть использован в качестве косвенного маркера состояния глимфатической системы.*

Ключевые слова: *глимфатическая система; диффузионно-тензорные изображения; магнитно-резонансная томография; нейродегенеративные заболевания; когнитивные нарушения; болезнь Альцгеймера; деменция с тельцами Леви; болезнь Паркинсона; нормотензивная гидроцефалия*

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Introduction

Considering constant increase of the life expectancy, it is extremely important to understand the mechanisms of age-dependent neurodegenerative diseases [1, 2]. This paper considers one of these mechanisms and the method of its noninvasive integral assessment.

In 2012, a group of scientists at the University of Rochester experimentally described a new system for removing toxic substances from the brain substance. This system was called the glymphatic system or perivascular/paravascular transport system. It is represented by perforating arteries dividing into smaller arterioles, which pulsate and ensure the movement of cerebrospinal fluid-like intercellular fluid between the sur-

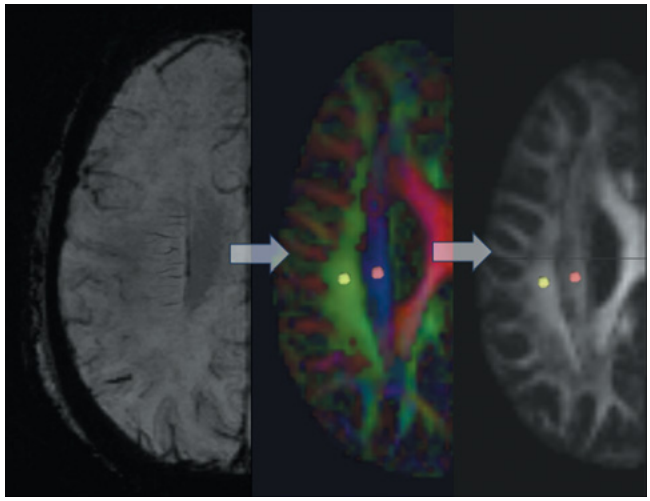
rounding glial cells, astrocytes. At the same time, metabolites are flushed out and absorbed into small venules that form large cerebral veins [3]. The glymphatic system is named after the body's lymphatic system because of the similar action.

The mechanisms of the glymphatic system are still being studied, but its several important functions have already been identified. These are elimination of metabolites and toxic agents, regulation of intracranial pressure, maintenance of intracellular and extracellular fluid balance, general homeostasis, and development of the immune response [4]. Dysfunction of the glymphatic system is thought to play important role in the pathogenesis of Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease (PD), and normal pressure hydrocephalus (NPH) [5].

The glymphatic function may be impaired due to endothelial changes, depolarization of aquaporin-4 channels, hyperlipidemia, sleep disturbances, and deposition of beta-amyloid and other pathologic proteins that accumulate in age-dependent neurodegenerative diseases. Abnormal protein deposition may be both a cause and a consequence of the glymphatic dysfunction [6–10]. Some authors suggest that additional factors inhibiting the glymphatic system activity may include a decrease in vascular pulsatility and a decrease in cardiac activity [11, 12].

In 2017, a group of Japanese scientists led by T. Taoka proposed an innovative technique to assess the status of the glymphatic system – diffusion tensor image analysis along the perivascular space (DTI-ALPS) [13]. DTI is used to record the movement of water molecules in the direction of perivascular spaces. At the level of the lateral ventricular bodies, the medullary veins are perpendicular to the lateral wall of the lateral ventricles. The perivascular spaces are in the same plane from right to left. In this region, the projection fibers run craniocaudally and the superior longitudinal fascicle of association fibers runs anteroposteriorly. Therefore, the perivascular spaces in this region are perpendicular to the projection fibers and the superior longitudinal fascicle (Fig. 1). This structure allows an almost independent analysis of the diffusion coefficient in the direction of the perivascular spaces, where the main tracts do not run parallel to the direction of the perivascular spaces. T. Taoka et al. found a significant decrease in DTI-ALPS index in the region of interest in patients with cognitive impairment, and a positive correlation between this parameter and the severity of cognitive impairment [13]. DTI-ALPS is the ratio between the averaged sum of the tensor values in the Dxx, Dyy, and Dzz directions in the region of the projection (proj) and association (assoc) fibers, which is calculated by the formula:

$$\text{DTI-ALPS} = \frac{\text{mean (Dxx–proj, Dxx–assoc)}}{\text{mean (Dyy–proj, Dzz–assoc)}}.$$



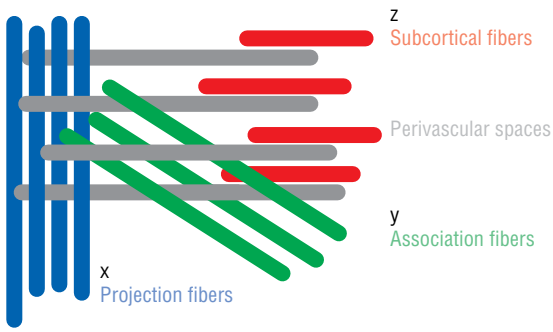


Fig. 1. Calculation of DTI-ALPS.
The region of interest (ROI) highlighted in yellow corresponds to the association fibers represented by the superior longitudinal fascicle. The ROI highlighted in red corresponds to the projection fibers represented by the pyramidal tract (adapted from T. Taoka et al. [13]).

The **aim** of this study was to compare AD, DLB, PD, and NPH using DTI-ALPS as an indirect parameter of glymphatic system function and to evaluate its potential use as a biomarker for these diseases.

Materials and methods

Subjects and clinical assessment

The study conducted at the Research Center of Neurology, included 116 patients from Neurology Department No. 5 with a molecular genetics laboratory (Table 1). Thirty-two patients were diagnosed with AD at the stage of mild cognitive impairment (n = 21) and dementia (n = 11) according to the criteria of the National Institute on Aging and Alzheimer's Association [14]. The median age was 71.5 [63.5; 75.5] years, median Montreal Cognitive Assessment Scale (MoCA)

Table 1. Demographic characteristics of the study groups

Parameter		Normal (*n* = 27)	AD (*n* = 32)	DLB (*n* = 15)	PD (*n* = 31)	NPH (*n* = 11)
Gender	male, *n* (%)	5 (18,5%)	5 (15,6%)	9 (60,0%)	5 (16,1%)	8 (72,7%)
	female, *n* (%)	22 (81,5%)	27 (84,4%)	6 (40,0%)	26 (83,9%)	3 (27,3%)
Age	Me [Q_1; Q_3]	63,0 [57,0; 67,0]	71,5 [63,5; 75,5]	71,0 [66,0; 78,0]	65,0 [59,0; 70,0]	68,0 [64,0; 75,0]

was 17.0 [10.3; 20.8] [15]. Fifteen patients were diagnosed with DLB at the stage of mild cognitive impairment (*n* = 11) and dementia (*n* = 4) according to criteria by I.G. McKeith et al. [16]. The median age was 71.0 [66.0; 78.0] years. The median MoCA score was 19.0 [17.3; 23.3]. As a comparison group, 31 patients diagnosed with PD at stage 2 (*n* = 5) and stage 3 (*n* = 26) according to the Hoehn and Yahr scale [17] were examined. They had no cognitive impairment and were diagnosed according to the clinical criteria of the International Parkinson and Movement Disorder Society [18]. The median age was 65.0 [59.0; 70.0] years. The median MoCA score was 27.0 [26.0; 28.0]. The study also included 11 patients diagnosed with NPH according to the criteria by N. Relkin et al. [19]. The median age was 68.0 [64.0; 75.0] years. The median MoCA score was 19.5 [17.8; 21.8]. The control group included 27 subjects without cognitive impairment (Mini-Mental State Examination score ⩾28 [20]; the median age was 63.0 [57.0; 67.0] years).

MRI scan

MRI was performed using a Siemens MAGNETOM Prisma 3T (Siemens Healthineers). In addition to conventional T1, T2, T2 FLAIR, and SWI sequences, the scan also included a 2D EPI (echo planar images) diffusion tensor sequence (TR = 5,600 ms, TE = 82 ms, b-values of 0, 1000 and 2500 s/mm^2, 64 diffusion directions in both AP (anterior to posterior) and PA (posterior to anterior) directions. The slice thickness was 2 mm.

Image post-processing

DSI Studio (Chen release) was used to post-process the DTI images[1]. Magnetic susceptibility artifacts were eliminated with b = 0 data using TOPUP correction. EDDY correction[2] was performed using FSL EDDY. The Population-average atlas was used to adjust the consistency of the DTI data [21].

We further identified regions of interest corresponding to projection and association fibers at the level of the posterior parts of the lateral ventricular bodies and extracted tensor values in the Dxx, Dyy, and Dzz directions. The values obtained were tabulated to calculate and statistically process the left and right DTI-ALPS results.

Statistical analysis

Statistical analysis was performed using SPSS Statistics v. 26.0 (IBM). In all cases, two-sided tests were used.

The null hypothesis was rejected at a significance level of $p<0.05$. Due to the sample size (*n* = 116), both parametric and non-parametric methods of comparative statistics were used.

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[2] Github.com [Internet]. The Tiny FSL package. URL http://github.com/frankyeh/TinyFSL (accessed on 8 March 2024).

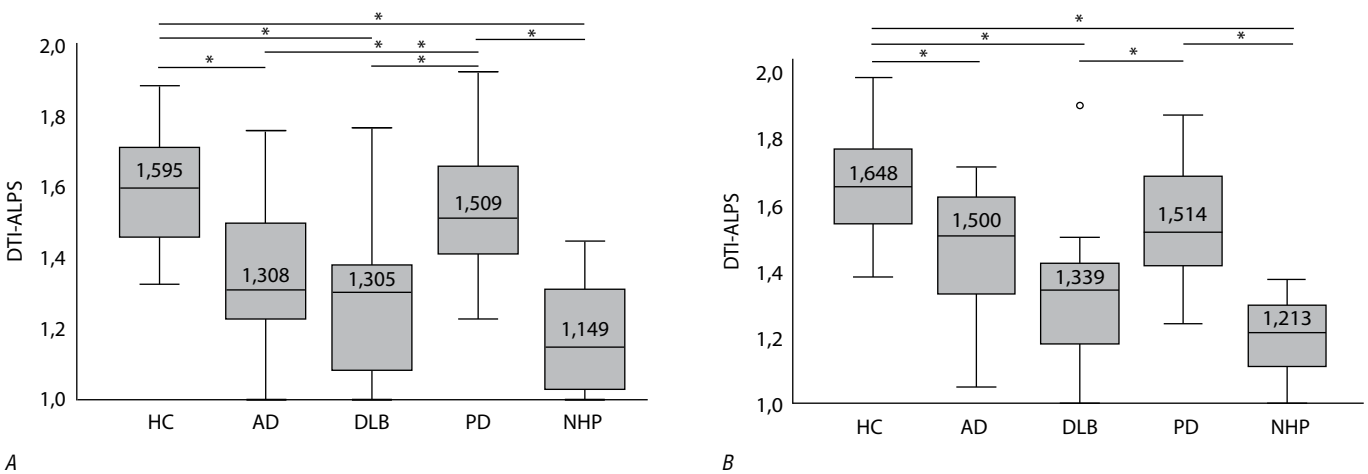

Fig. 2. Distribution of DTI-ALPS index between groups on the left (*A*) and right (*B*) sides. **p adj* < 0.01.

Table 2. Adjusted significance level for post hoc pairwise comparisons between study groups

Pair of groups to compare	DTI-ALPS left	DTI-ALPS right
HC *vs* AD	*p adj* < 0,001	*p adj* = 0,001
HC *vs* DLB	*p adj* < 0,001	*p adj* < 0,001
HC *vs* PD	*p adj* = 1,000	*p adj* = 0,102
HC *vs* NPH	*p adj* < 0,001	*p adj* < 0,001
AD *vs* DLB	*p adj* = 1,000	*p adj* = 0,064
AD *vs* PD	*p adj* = 0,003	*p adj* = 1,000
AD *vs* NPH	*p adj* = 0,099	*p adj* < 0,001
DLB *vs* PD	*p adj* = 0,001	*p adj* = 0,001
DLB *vs* NPH	*p adj* = 1,000	*p adj* = 0,758
PD *vs* NPH	*p adj* < 0,001	*p adj* < 0,001

To assess relationship between quantitative variables, a Pearson correlation coefficient was used. A Chaddock scale was used to determine the strength of significant associations. For all post hoc pairwise comparisons, the Bonferroni method was used to adjust for multiple comparisons. In addition, the association between diagnosis group and DTI-ALPS штвуч was assessed using a general linear model adjusted for gender and age.

Results

Significant differences in DTI-ALPS index were reported across groups on both right and left sides (Fig. 2). After adjustment for gender and age, these differences remained significant ($p < 0.001$).

The post hoc analysis showed that patients with AD, DLB, and NPH had significantly lower DTI-ALPS index on both sides compared to healthy volunteers (Table 2). The differences between AD patients and normal subjects were not statistically significant.

Patients with DLB and NPH had significantly lower DTI-ALPS index on both sides compared to patients with PD. Patients with AD also had significantly lower left DTI-ALPS index compared to patients with PD. On the right side, the differences were not statistically significant. In addition, patients with AD had a significantly higher right DTI-ALPS index compared to patients with NPH. On the left side, the differences were not statistically significant. Patients with DLB and NPH were not statistically significantly different.

Analysis of the entire sample showed a significant direct moderate correlation between MoCA scores and DTI-ALPS index on the left side ($r = 0.332$; $p = 0.002$) and a significant direct weak correlation on the right side ($r = 0.225$; $p = 0.035$). These data are represented in Figure 3.

Discussion

Since DTI-ALPS is a relatively new parameter for the glymphatic system assessment, literature on this topic is limited.

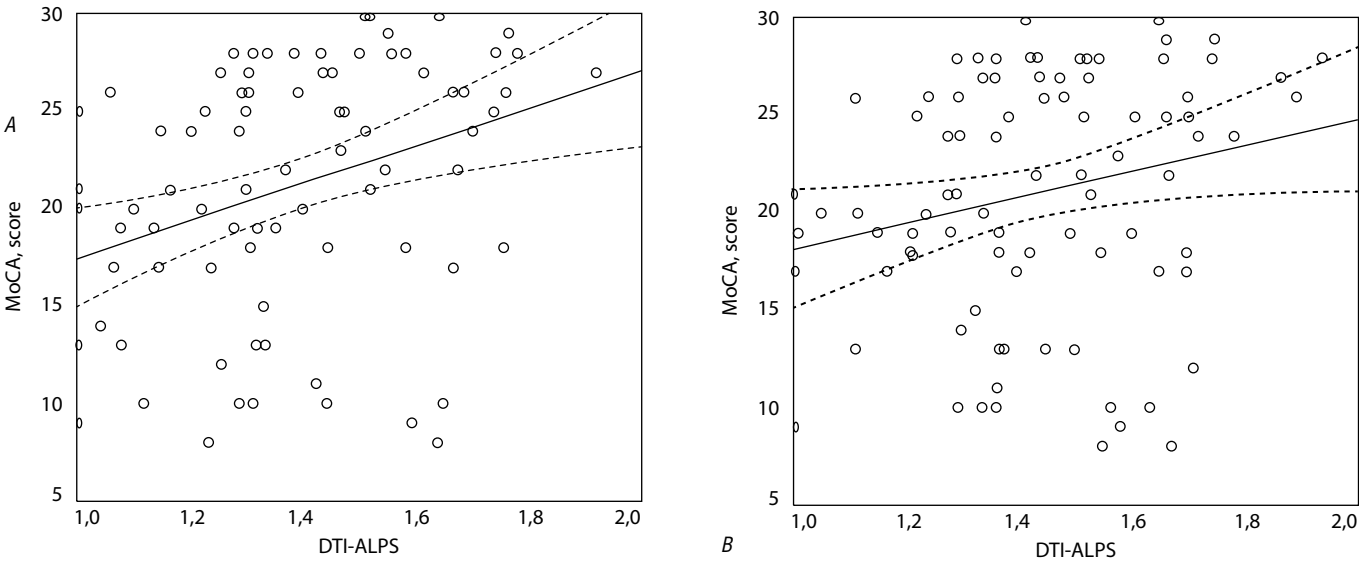

Fig. 3. Correlation of the left (*A*) and right (*B*) DTI-ALPS index with MoCA score.

Our study is the first in Russia to evaluate DTI-ALPS in patients with neurodegenrative diseases.

In our study, the lowest DTI-ALPS index was reported in patients with cognitive impairment (including AD) and the highest DTI-ALPS index was reported in controls and PD patients without cognitive impairment. When evaluating the decline in the glymphatic system activity as a factor of cognitive deficit, the data of T. Lian et al. [22] can be used. This study evaluated DTI-ALPS index in patients with AD (18 with moderate cognitive impairment, 38 with dementia), vascular dementia (n = 21), and healthy subjects (n = 28). As in our study, the highest DTI-ALPS index was reported in healthy subjects. The results in AD patients at the moderate cognitive impairment and vascular dementia stages were comparable, but significantly lower than those in the control group.

The correlation found between DTI-ALPS index and the severity of cognitive impairment (MoCA) is consistent with the data from the pivotal study by T. Taoka et al. [13] and the study by T. Lian et al. [22] described above. In a similar study, B.W. Williams et al. also reported a significant correlation between DTI-ALPS index and cognitive tests such as the Boston Naming Test [23]; Digit Span Test [24]; Route Construction Test, Part A [25, 26].

We observed the more significant differences in DTI-ALPS index in the left cerebral hemisphere, which were comparable to the data reported by T. Shen et al. who studied DTI-ALPS in a group of patients with PD at different stages according to the Hoehn and Yahr scale (n = 76) and in a control group (n = 48) [27]. The authors suggested that the left hemisphere, which is dominant in a larger percentage of the population, is involved in the pathological process earlier than the contralateral right hemisphere. Therefore, in early stages of PD (up to Hoehn and Yahr stage 2), changes in DTI-ALPS index were found only on the left side, and at later stages (Hoehn and Yahr stage 3 and higher), changes were bilateral. This mechanism may possibly be applicable not only to PD, but also to other neurodegenerative processes. X. Zhang et al. [23] and Y.J. Bae et al. [28, 29] showed lower DTI-ALPS index in the left cerebral hemisphere. However, T. Taoka et al. [13] only measured the left hemisphere, and T. Lian et al. [22] did not report for which hemisphere DTI-ALPS index was presented.

We found no statistically significant differences in DTI-ALPS index between the PD and control groups. Possible reasons may be that the study included earlier stage PD patients (Hoehn and Yahr stages 2–3) without cognitive deficit or that the sample size was small compared to the study by T. Taoka et al. [13]. However, in the study by Y.J. Bae et al., which also included 54 PD patients and 54 healthy volunteers, the authors reported significant differences in DTI-ALPS index between these groups ($p < 0.001$), as well as correlations between motor symptoms and cognitive test scores and DTI-ALPS index [28]. However, the authors did not report whether DTI-ALPS was evaluated only in one cerebral hemisphere or whether an average index was calculated. They also did not mention whether patients with PD had cognitive impairment.

Unfortunately, we did not find any papers that evaluated DTI-ALPS in patients with DLB, so we could not perform a comparative analysis of our data.

Across all study groups, the lowest DTI-ALPS index were reported in the NPH group, which is consistent with data from other studies. In another study, Y.J. Bae et al. evaluated DTI-ALPS in 16 patients diagnosed with NPH and compared the results with those of 16 control subjects [29]. DTI-ALPS index was extremely low in the NPH group, and the difference from the control group was significant ($p < 0.0001$). C. Georgiopoulos et al. also evaluated changes in DTI-ALPS index in 13 NPH patients and 27 healthy volunteers [30]. Considering the significance of DTI-ALPS differences, the authors propose this parameter as a marker of severity for both radiologic and clinical manifestations of this disease.

It should be noted that DTI-ALPS is an indirect marker of glymphatic system function. For a more accurate and direct assessment, contrast-enhanced invasive techniques are used. Limitations of interpreting results for this technique are discussed in the literature [31]. They also include the small number of patients in the DLB and NPH groups compared to the AD and PD groups, probably due to the lower prevalence of these diseases. Furthermore, DTI-ALPS cannot be used as a marker for the differential diagnosis of these disease due to the lack of significant differences between the AD, DLB, and NPH groups and between the PD and control groups.

Conclusion

We evaluated changes in DTI-ALPS index in different age-dependent neurodegenerative diseases, identified correlation with clinical manifestations (MoCA results), and evaluated differences in DTI-ALPS index across study groups. Unlike other papers, our study compared changes in a relatively wide range of degenerative diseases of the nervous system. For the first time, data for AD, DLB, PD, and NPH were compared. Since our results of DTI-ALPS index assessment were comparable to previously published results, we believe that this parameter can be used as an indirect marker of the glymphatic system status. However, its use in the differential diagnosis of individual diseases remains debatable.

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Blood Glucocerebrosidase Activity and α-Synuclein Levels in Patients with GBA1-Associated Parkinson's Disease and Asymptomatic *GBA1* Mutation Carriers

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Abstract

Introduction. *Mutations in a GBA1 gene, which encodes a lysosomal enzyme called glucocerebrosidase (GCase), are the most common genetic risk factor for Parkinson's disease (PD). The pathogenesis of PD results from the death of dopaminergic neurons in the substantia nigra of the brain, which is associated with the aggregation of α-synuclein protein. However, not all GBA1 mutation carriers develop PD during their lifetime.*

*The **aim** of this study was to evaluate GCase activity and α-synuclein levels in CD45⁺ blood cells of patients with PD associated with GBA1 mutations (GBA1-PD), asymptomatic carriers of GBA1 mutations (GBA1-carriers), and patients with sporadic PD (sPD), as well as correlation between the study parameters in the study groups.*

Materials and methods. *The study included patients with GBA1-PD (n = 25) and sPD (n = 147), and GBA1-carriers (n = 16). A control group included healthy volunteers (n = 154). The level of α-synuclein in CD45⁺ cells was measured by enzyme-linked immunosorbent assay, and GCase activity in dried blood spots was detected by high-performance liquid chromatography with tandem mass spectrometry.*

Results. *Increased level of α-synuclein protein was detected in CD45⁺ blood cells of patients with GBA1-PD, sPD, and GBA1-carriers compared to controls ($p = 0.0043$; $p = 0.0002$; $p = 0.032$, respectively). Decreased GCase activity was reported in GBA1-PD patients and GBA1-carriers compared to sPD patients ($p = 0.0003$; $p = 0.003$, respectively) and controls ($p < 0.0001$; $p < 0.0001$, respectively). However, negative correlation between α-synuclein levels and GCase activity was observed only in GBA1-PD patients, but not in GBA1-carriers.*

Conclusion. *Our data suggest a possible functional relationship between the activity of GCase and the metabolism of α-synuclein in PD associated with GBA1 mutations.*

Keywords: *Parkinson's disease; GBA1 gene; α-synuclein; glucocerebrosidase; glucocerebrosidase activity; blood*

Ethics approval. All procedures performed in human studies comply with the ethical standards of the National Committee on Research Ethics and the Helsinki Declaration or comparable standards of ethics. The research protocol was approved by the Ethics Committee of the N.P. Bekhtereva Institute of the Human Brain of the Russian Academy of Sciences (LEK Protocol No. 1, dated November 26, 2020). Informed voluntary consent was obtained from each of the participants included in the study.

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Активность глюкоцереброзидазы и уровень α-синуклеина в крови у пациентов с GBA1-ассоциированной болезнью Паркинсона и бессимптомных носителей мутаций в гене *GBA1*

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Аннотация

Введение. *Мутации в гене GBA1, кодирующем лизосомный фермент глюкоцереброзидазу (GCase), являются наиболее распространённым генетическим фактором риска развития болезни Паркинсона (БП), в основе патогенеза которой лежит гибель дофаминергических нейронов чёрной субстанции головного мозга, ассоциированная с агрегацией белка α-синуклеина. Однако не у всех носителей мутаций в гене GBA1 развивается БП в течение жизни.*

Целью *настоящего исследования являлась оценка активности GCase и уровня α-синуклеина в CD45⁺-клетках в крови пациентов с БП, ассоциированной с мутациями в гене GBA1 (GBA-БП), бессимптомных носителей мутаций в гене GBA1 (GBA-носители) и пациентов со спорадической формой БП (сБП), а также корреляции между изучаемыми параметрами в исследуемых группах.*

Материалы и методы. *В исследование включены пациенты с GBA-БП (n = 25) и сБП (n = 147), GBA-носители (n = 16). Контрольную группу составили здоровые лица (n = 154). Уровень α-синуклеина в CD45⁺-клетках определяли путём иммуноферментного анализа, активность GCase в сухом пятне крови — высокоэффективной жидкостной хроматографии в сочетании с тандем-масс-спектрометрией.*

Результаты. *Выявлен повышенный уровень белка α-синуклеина в CD45⁺-клетках крови в группе пациентов с GBA-БП, сБП, а также GBA-носителей по сравнению с контролем (p = 0,0043; p = 0,0002; p = 0,032 соответственно). Активность GCase была снижена у пациентов с GBA-БП и GBA-носителей по сравнению с пациентами с сБП (p = 0,0003; p = 0,003 соответственно) и контролем (p < 0,0001; p < 0,0001 соответственно). Однако обратная корреляция уровня α-синуклеина и активности GCase наблюдалась только у пациентов с GBA-БП, но не у GBA-носителей.*

Заключение. *Полученные данные свидетельствуют о возможной функциональной взаимосвязи между активностью GCase и метаболизмом белка α-синуклеина при БП, ассоциированной с мутациями в гене GBA1.*

Ключевые слова: *болезнь Паркинсона; ген GBA1; α-синуклеин; глюкоцереброзидаза; активность глюкоцереброзидазы; кровь*

Этическое утверждение. Все процедуры, выполненные в исследованиях с участием людей, соответствуют этическим стандартам Национального комитета по исследовательской этике и Хельсинкской декларации или сопоставимым нормам этики. От каждого участника исследования было получено информированное добровольное согласие. Протокол исследования одобрен Этическим комитетом Института мозга человека им. Н.П. Бехтеревой РАН (протокол № 1 от 26.11.2020).

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

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by the death of dopaminergic neurons in the brain and associated with aggregation of a α-synuclein protein inside them. PD is generally a sporadic disease. However, in 10% of cases, there is a positive family history. A number of genes have been described with mutations leading to the development of inherited forms of PD [1, 2]. *GBA1* mutations are a high PD risk factor leading to the development of GBA-associated PD (GBA-PD). Depending on the population, the prevalence of GBA-associated PD is up to 10% in patients with PD [3–5].

The GBA1 gene encodes a lysosomal enzyme called glucocerebrosidase (GCase). GCase is involved in cleaving the lysosphingolipid glucosylceramide into glucose and ceramide. Biallelic mutations in the *GBA1* gene result in a rare autosomal recessive disorder, Gaucher disease, associated with decrease in the GCase activity (5% to 30% depending on the mutation) as well as accumulation of its substrate [3, 6, 7]. In heterozygous carriers of *GBA1* mutations, both in GBA-PD patients and asymptomatic carriers of *GBA1* mutations (GBA carriers), decreased enzymatic activity of GCase and increased concentration of the lysosphingolipid glucosylceramide are also reported but to a lesser extent compared to patients with Gaucher disease [8–10]. It should be noted that not all *GBA1* carriers develop PD during their lifetime, and the mechanism of pathogenesis of the disease remains unclear.

Currently, the bidirectional effect of GCase dysfunction on α-synuclein levels via a feedforward/feedback mechanism is suggested [11, 12]. *In vitro* experiments have shown that α-synuclein can directly interact with GCase, leading to decrease in GCase activity [13].

Several other studies have shown that GCase dysfunction can cause α-synuclein to accumulate in neurons derived from induced pluripotent stem cells [11]. Increased α-synuclein levels have been reported in animal models of GCase dysfunction [14], as well as in dopaminergic neurons from induced pluripotent stem cells, and peripheral blood mononuclear cells obtained from GBA-PD [15, 16] and Gaucher patients [15, 17].

The **aim** of the study is to evaluate levels of α-synuclein in $CD45^+$ blood cells and GCase activity in GBA-PD patients, GBA carriers, sPD patients, and controls, as well as the correlation between these parameters in the study groups.

Materials and methods

Study groups

The study included patients with GBA-PD (heterozygous carriers of *GBA1* mutations; $n = 25$), patients with sPD ($n = 147$), GBA carriers ($n = 16$), and controls ($n = 154$). Diagnosis was based on the criteria of the Parkinson's UK Brain Bank [18] and the International Parkinson and Movement Disorder Society [19]. PD patients were examined at the N.P. Bekhtereva Institute of the Human Brain of the Russian Academy of Sciences and Pavlov First Saint Petersburg State Medical University. The study included L-DOPA-naïve patients with sPD. Patients with GBA-PD received L-DOPA therapy.

The group of GBA carriers ($n = 16$, neurologically healthy individuals with heterozygous *GBA1* mutations) included relatives of patients with Gaucher disease. Direct Sanger sequencing was used to confirm the presence of mutations. To rule out neurodegenerative diseases, all study participants underwent a clinical neurological examination. The controls ($n = 154$) were examined at the Pavlov First Saint Petersburg State Medical University. In all patients with sPD and controls, polymerase chain reaction and restriction analysis were used to confirm the absence of the common *GBA1* mutations (*L444P*, *N370S*, *E326K*) [5]. The control and experimental groups did not differ in age or gender.

All study procedures involving human subjects complied with the ethical standards of the National Research Ethics Committee and the Declaration of Helsinki or equivalent ethical standards. All subjects provided their voluntary informed consent to participate in the study. The study protocol was approved by the Local Ethics Committee of N.P. Bechtereva Institute of the Human Brain of the Russian Academy of Science (Protocol #1 dated 26 November 2020).

Determination of α-synuclein levels in $CD45^+$ cells

$CD45^+$ cells were isolated from 8 mL of peripheral blood by Ficoll density gradient centrifugation (Ficoll-Paque PLUS, GE Healthcare) followed by magnetic sorting using microparticles conjugated with antibodies to $CD45^+$ receptors and

miniMACS MS columns (Miltenyi Biotec). The cell suspension was aliquoted and frozen at –70°C.

Cells were lysed using the Chemicon Total Protein Extraction Kit (Millipore). Total protein concentration was measured using the Pierce BCA Protein Assay Kit (Thermo Scientific). The level of α-synuclein in $CD45^+$ cells was measured using Human alpha Synuclein ELISA kit (Thermo Fisher Scientific). All samples were adjusted for total protein (6 μg) and assayed in triplicate. Absorbance was measured using an XMark microplate spectrophotometer (Bio-Rad).

Measurement of blood GCase activity

GCase activity was measured by high performance liquid chromatography with tandem mass spectrometry in dried blood spots [10]. Enzymatic activity was evaluated by measuring the concentration of the product obtained as a result of the reaction of the enzyme with the following substrate: enzyme (E) + substrate (S) + (ES complex) E + product.

Mass spectrometry was performed using an API 3200 QTrap tandem mass spectrometer (ABSciex) in the multiple reaction monitoring mode. Activity was calculated by assuming that the amount of product obtained is directly proportional to the activity of lysosomal enzymes in the dried blood spot. As a control, samples with known levels of enzyme activity were added to each plate. Enzymes were provided by U.S. Centers for Disease Control and Prevention.

Statistical analysis

Statistical analysis was performed using R 3.6.2 software. The Shapiro–Wilk test was used to test the normality of the data. The Mann–Whitney U test was used for pairwise comparisons of variation series. $P < 0.05$ was considered statistically significant. The Spearman's rank correlation coefficient was used to assess the correlation between study groups. Clinical and experimental data are presented as mean ± standard deviation (M ± SD) and median (minimum-maximum), respectively.

Results

The clinical characteristics of the patients and controls enrolled in the study are shown in the table. Since the risk of PD is 6–7 times higher in carriers of the *N370S* and *L444P* mutations of the *GBA1* gene and 2 times higher in carriers of the *E326K* mutation, the levels of α-synuclein and GCase activity were evaluated both in the group of patients with the *N370S*, *L444P* mutations (GBA-PD – *N370S*, *L444P*) and in the general group including

Clinical characteristics and study parameters of participants in study groups

Parameter	Control	sPD	GBA carriers	GBA-PD, mutations	
				N370S, L444P, E326K	*N370S, L444P*
N	154[a] 68[g]	147[a] 40[6]	16[a] 15[g]	25	15
Gender (M/F)	75/79[a] 32/36[g]	61/86[a] 16/24[g]	5/11[a] 5/10[g]	15/10	9/6
Age, years (*M* ± *SD*)	62,02 ± 9,06[a] 59,68 ± 8,76[g]	63,36 ± 9,26[a] 61,57 ± 8,56[g]	53,93 ± 8,19[a] 53,26 ± 8,31[g]	61,74 ± 9,91	62,71 ± 11,19
Age of onset, years (*M* ± *SD*)	N/A	59,32 ± 10,00[a] 57,17 ± 8,91[g]	N/A	57,32 ± 9,91	57,00 ± 11,20
GBA1 mutations	N/A	N/A	5 L444P/N[a, g], 4 N370S/N[a, g], 1 L326P/N[a, g], 1 N227S/N[a, g], 1 R159W/N[a, g], 4 E326K/N[a]/3 E326K/N[g]	8 *L444P/N*, 7 *N370S/N*, 10 *E326K/N*	8 *L444P/N*, 7 *N370S/N*
Levels of α-synuclein, ng/mL	6,56 (0,46–45,70)	9,28 (0,63–65,60) p^* = 0,0002	12,80 (1,22–41,30) p^* = 0,032	10,80 (0,68–51,40) p^* = 0,0043	12,90 (2,92–37,50) p^* = 0,0014
Gcase activity, mM/L/h	8,14 (1,55–32,10)	7,60 (3,33–14,70)	4,67 (2,33–10,40) p^* = 3,9e-05 p^{**} = 0,003	4,28 (1,51–13,20) p^* = 5,1e-06 p^{**} = 0,00027	4,40 (1,51–6,13) p^* = 1,5e-06 p^{**} = 9,9e-05

Note. [a]Assay of α-synuclein levels; [g]Assay of GCase activity. N/A, not assessed. **p* compared to the control group; ***p* compared to sPD patients.

PD patients with the *N370S*, *L444P* and *E326K* mutations (all_GBA-PD).

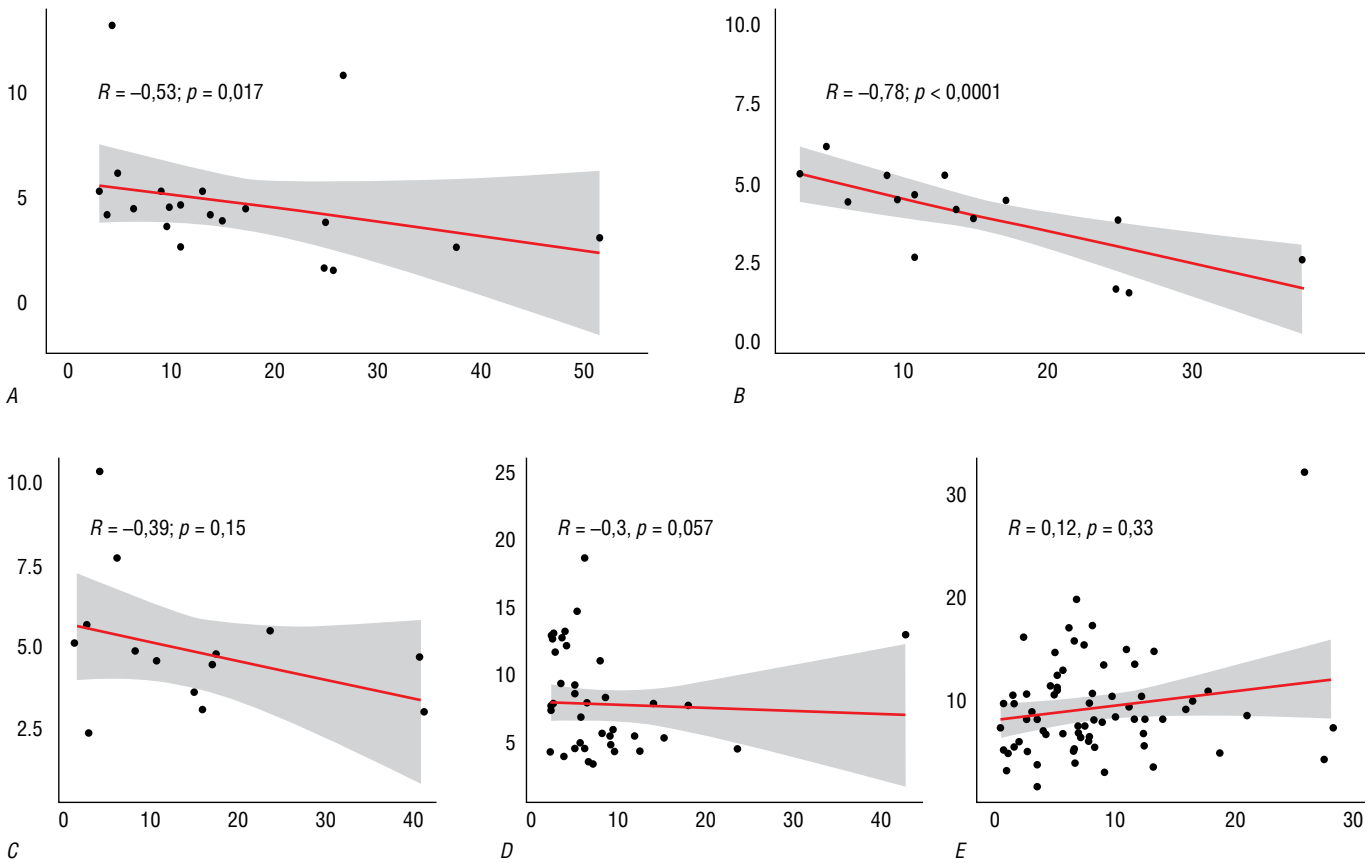
The study showed that the level of α-synuclein in CD45⁺ cells in all_GBA-PD and GBA-PD groups as well as in GBA carriers was increased compared to the control group ($p = 0.0043$; $p = 0.0014$; $p = 0.032$, respectively; Table). Levels of α-synuclein were also increased in patients with sPD compared to the control group ($p = 0.0002$). Decrease in GCase activity was observed in patients with GBA-PD and GBA carriers compared to patients with sPD ($p = 0.0003$; $p = 0.003$) and the control group ($p < 0.0001$; $p < 0.0001$) (Table), which is consistent with our previous results [2].

A negative correlation was found between GCase activity and α-synuclein levels in blood CD45⁺ cells in the all_GBA-PD group ($R = –0.53$; $p = 0.017$), the GBA-PD group ($R = –0.78$; $p < 0.0001$), but not in GBA carriers ($R = –0.39$; $p = 0.15$; Figure). In the sPD group, a negative correlation between GCase activity and α-synuclein levels in CD45⁺ cells were found at the threshold of statistical significance ($R = –0.3$, $p = 0.057$; Figure). At the same time, no correlation was found between the study parameters in the control group.

Discussion

The molecular mechanism underlying GBA-PD remains unclear. However, GCase dysfunction and intracellular α-synuclein oligomerization appear to be interrelated. However, the following questions are poorly understood. Whether a decrease in GCase activity and accumulation of lysosphingolipids, as well as changes in peripheral blood α-synuclein levels, precede disease development in *GBA1* mutation carriers, or is this a consequence of disease development, remains unknown. At the same time, it is crucial to study PD with a known etiology, as well as factors that precede and/or influence disease development in *GBA1* mutation carriers. This would allow identifying disease biomarkers and PD risk groups for *GBA1* mutation carriers in order to include this cohort in clinical trials of targeted therapies that increase the GCase activity [3].

For the first time, we showed that with increased α-synuclein levels and decreased blood GCase activity in patients with GBA-PD and GBA carriers, a negative correlation between α-synuclein levels and GCase activity was typical only for patients with GBA-PD, but not for GBA carriers.



Correlation between the level of α-synuclein in CD45⁺ blood cells and GCase activity in the all-GBA-PD group (*A*; *n* = 25), the GBA-PD group (*B*; *n* = 15), GBA carriers (*C*; *n* = 15), sPD patients (*D*; *n* = 40) and controls (*E*; *n* = 68).Abscissa: level of α-synuclein, ng/mL; ordinata: GCase activity, mM/L/h.

Increase in α-synuclein levels and decrease in peripheral blood GCase activity have previously been reported in PD patients with *GBA1* mutations [8, 10, 15]. For example, M. Avenali *et al.* found increased levels of α-synuclein in peripheral blood lymphocytes in the GBA-PD group compared to patients with sPD and controls [15]. Previously, we found increased plasma levels of oligomeric α-synuclein in patients with Gaucher disease and in PD patients with GBA1 mutations and polymorphic *GBA1* mutations compared to controls [9].

A link between GCase dysfunction and α-synuclein accumulation is being discussed [11]. *In vitro* studies demonstrated a direct effect of lysosphingolipids on α-synuclein aggregation [12, 20]. So, using α-synuclein isolated from dopaminergic neurons derived from induced pluripotent stem cells, it was shown that the GCase substrate called glucosylceramide induces aggregation of α-synuclein and promotes the conversion of its oligomeric forms into toxic aggregates of a specific conformation [21]. It is noteworthy that cyclic amplification of proteins with disrupted conformation has been used increasingly to evaluate such α-synuclein conformers in biological fluids of patients with synucleinopathies [22]. For example, M. Shahnawaz *et al.* used this technique to detect specific conformers of α-synuclein in cerebrospinal fluid samples obtained from patients with synucleinopathies compared to control samples without these conformers [23]. Therefore, the presence of abnormal α-synuclein forms, sensitive to decrease in GCase activity, in biological samples of PD patients may explain the observed negative correlation between GCase activity and the level of α-synuclein in blood $CD45^+$ cells in patients with GBA-PD and its absence in the group of GBA carriers. This assumption may also be supported by the negative correlation we found between the GCase activity and blood α-synuclein levels at the threshold of statistical significance in patients with sPD, but not in the control group.

Data on blood GCase activity in sPD are inconsistent [8, 24]. We found no differences in GCase activity in sPD patients compared to controls.

However, increased levels of α-synuclein were found in $CD45^+$ cells of sPD patients compared to controls, which is consistent with our previous findings [16]. In recent decades, the role of peripheral tissue levels of α-synuclein as a potential biomarker for PD has been discussed [25]. However, numerous studies had conflicting results, which may be explained by the differences in the methods and antibodies used, and other experimental factors. Despite the increased levels of α-synuclein in $CD45^+$ cells of patients with sPD shown in our study, the use of this marker for the differential diagnosis of PD does not seem possible because of the overlapping values obtained across the study groups. In healthy carriers of *GBA1* mutations, an even higher level of α-synuclein was detected in $CD45^+$ cells than in patients with sPD. Previous studies evaluating α-synuclein levels in peripheral blood mononuclear cells found no differences in patients with sPD compared to the control group [15, 26, 27]. In this context, further studies are required to assess the impact of α-synuclein levels in peripheral blood mononuclear cells on the development and progression of PD.

Our study had some strengths and weaknesses. The main strength of our study is the inclusion of asymptomatic *GBA1* mutation carriers, which allowed us to perform a comparative analysis of study parameters in the group of GBA carriers with and without PD. A homogeneous fraction of peripheral blood $CD45^+$ cells of study participants was used to assess α-synuclein levels, so it was possible to neutralize the effect of erythrocyte hemolysis on α-synuclein. It has been previously shown that peripheral blood mononuclear cells obtained by Ficoll gradient centrifugation may contain a mixture of red blood cells that include over 99% of the total α-synuclein in all blood cells [28]. Furthermore, our study included L-DOPA-naïve patients with sPD, which allowed us to exclude the potential influence of these agents on α-synuclein gene expression [29]. Most of the previous studies evaluating α-synuclein levels in mononuclear blood cells in PD patients have not considered effects of erythrocyte α-synuclein and use of L-DOPA-containing agents by PD patients.

The small size of the GBA-BP and GBA carrier groups is the major limitation of our study. Although there was no difference in the mean age between subjects with PD and subjects without PD, we cannot rule out the possibility that some GBA carriers may develop clinical symptoms of PD later in the lifetime.

Conclusion

Our data on the negative correlation between blood α-synuclein levels and GCase activity in GBA1 mutation carriers with PD, but not in asymptomatic GBA carriers, suggest that changes in blood α-synuclein levels and GCase activity in GBA1 mutation carriers may be observed with clinical manifestations of developing PD.

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Oxytocin and Vasopressin in Emotional Memory and "Face Reading": a Neurobiological Approach and Clinical Aspects

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Abstract

The ability to adequately perceive and recognize emotions is a key and universal tool in interpersonal communication, which allows people to understand feelings, intentions, and emotional reactions of themselves and others. Throughout their life, people have to make inferences about mental state of others by interpreting subtle social signals, such as facial expressions, to understand or predict others' behavior, which is crucial in constructive social interactions. Therefore, emotional memory associated with the ability to identify emotions based on one's life experience is the cornerstone of social cognition and interpersonal relationships. Oxytocin and vasopressin are neurohypophysial peptides that have attracted scientific attention due to their role in the emotional and social aspects of behavior. Variable and contrasting effects of oxytocin and vasopressin may be related to the sites of the brain where they exert their activity.

Aim. *This review aimed to evaluate neural mechanisms underlying oxytocin-mediated and vasopressin-mediated modulation of emotional memory; to assess how cerebral oxytocin-signal and vasopressin-signal transduction mediates emotional and social behavior; to discuss the role of the two neuropeptides in non-verbal interpersonal communication; and to present their cerebral effects in relation to an ability for "face reading" in patients with mental disorders.*

Keywords: *oxytocin; vasopressin; emotions; memory*

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Роль окситоцина и вазопрессина в эмоциональной памяти и «чтении мыслей по лицу»: нейробиологический подход и клинические аспекты

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Аннотация

Способность правильно воспринять и распознать эмоции является ключевым и универсальным инструментом в межличностном общении, который позволяет понять чувства, намерения и эмоциональные реакции – свои и другого человека. На протяжении всей жизни людям приходится делать выводы о психическом состоянии путём интерпретации тонких социальных сигналов, таких как выражение лица, чтобы осознать или предсказать поведение другого человека, что, несомненно, имеет решающее значение в выстраивании конструктивных социальных взаимодействий. В этой связи эмоциональная память, сопряжённая со способностью идентифицировать эмоции, базируясь на приобретённом жизненном опыте, является краеугольным камнем социального познания и межличностных отношений. Окситоцин и вазопрессин – два нейрогипофизарных пептида, которые привлекают внимание учёных за счёт их роли в реализации эмоциональных и социальных аспектов поведения. Установленные разнообразные и контрастирующие эффекты окситоцина и вазопрессина могут быть связаны с местом их активности в головном мозге.

***Цель** обзора – рассмотреть нейронные механизмы, лежащие в основе окситоцин- и вазопрессин-опосредованной модуляции эмоциональных воспоминаний, как церебральная окситоцин- и вазопрессин-сигнальная трансдукция опосредует эмоциональное и социальное поведение; обсудить роль двух нейропептидов в невербальном межличностном общении, а также представить их церебральные эффекты в отношении способности «чтения мысли по лицу» в контексте развития психоэмоциональных расстройств.*

***Ключевые слова:** окситоцин; вазопрессин; эмоции; память*

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Until the XX century, the emotional domain was the subject of close attention of philosophers. However, over the last few decades, new highly informative methods to investigate brain structure and function have emerged, in particular, powerful neuroimaging tools to study local brain functions during well-defined tasks. This significantly improved current understanding of the neural substrates involved in emotion processing [1, 2]. From the neurobiological perspective, emotions are a program of complex actions that are triggered by certain external or internal stimuli that activate the nervous system [3]. Emotion as a basic biological program implies an innately programmed mechanism that connects the processing of a sensory stimulus with the development of a coordinated behavioral response pattern [4]. These emotional processes are mediated and transmitted by certain hormones, such as oxytocin (OXT) and vasopressin (VP), which can be considered key ones [5, 6].

From the evolutionary perspective, OXT and VP are highly conserved neuropeptides. They are of high scientific interest due to the discovery of the fascinating behavioral functions they regulate, especially in the context of social

interactions. For example, OXT was shown to modulate a gamut of behavior types such as maternal care [7] and aggression [8], pair bonding [9], sexual behavior [10], social memory [11] and support [12], anxiety behavior and coping with stress [13, 14].

In contrast, VP was shown to have a strong influence on complex social behavior and emotional states that are more typical for men, such as aggression, fear, and anxiety [15], as well as hypervigilance and arousal [16].

Initially considered as a "prosocial" neuropeptide that enhances social closeness, attachment, and affiliative behavior, OXT has been recently shown to be an effective regulator of social and emotional behavior aspects such as social fear, anger, and envy [17, 18]. It is of interest that only few studies investigated the influence of OXT and VP on the development of emotional memory and, in particular, fear memory [19–22]. However, memory is a fundamental cognitive function that allows people to have constant access to relevant information and appropriately adjust our behavior after encoding our experience.

Emotions are known to reflect our internal emotional state, and an emotional reaction allows us to connect current events with our individual specific previous experience. In this context, emotional memory, which is associated with the ability to identify emotions, plays an important role in interpersonal relationships [23, 24]. "Face reading", i. e. the ability to infer mental state of others, which is also called cognitive empathy, is a cornerstone of all social interactions. The ability to track other people's emotional state over time and draw conclusions about their internal state based on external signals, such as facial expressions, allows us to predict corresponding behavioral responses [25].

OXT and VP effects on social cognition have received considerable attention over the past two decades. In particular, several studies showed that OXT administration improved the ability to identify a wide range of emotions [26–28], while the effects of VP were selective for emotional perception with a pronounced predominance in recognizing negative emotions over positive ones [29].

These important discoveries raised the question on how the local release of OXT and VP and subsequent effects mediated by their receptors in the target brain regions are reflected in the emotional and social aspects of brain function with an emphasis on emotion recognition and perception and memorization of emotionally salient signals.

Aim. This review aimed to examine the neural mechanisms underlying OXT-mediated and VP-mediated modulation of emotional memory and how OXT and VP signaling in specific neural circuits of certain brain regions mediates emotional and social behavior. We also presented the role of OXT and VP in non-verbal interpersonal communication and reviewed recent cutting-edge studies that evaluate OXT and VP local effects in different brain regions on "face reading" in the development of mental disorders.

Neural mechanisms underlying oxytocinergic modulation of emotional memory

The ability of OXT to modulate higher brain functions such as prosocial behavior, social recognition, reward, learning and memory, is determined by the neural network in the hypothalamic nuclei, an important structural basis for coordinated activity of OXT neurons in response to external stimuli. Moreover, the extrahypothalamic regions of the forebrain such as the amygdala, the bed nucleus of the stria terminalis, and the nucleus accumbens of the septum pellucidum also contain OXT-expressing neurons, which mediates local OXT-ergic regulatory effects [30]. OXT receptors are found in brain regions that are crucial for processing and encoding of information and formation of memory, such as hippocampus, striatum, amygdala, hypothalamus, nucleus accumbens, and midbrain [31].

In a clinical study by A.J. Guastella et al., OXT was shown to enhance encoding for predominantly positive social stimuli (happy faces), making the information more meaningful and therefore more memorable, with reducing memory consolidation for angry or neutral faces [32]. A subsequent study showed that salivary OXT levels correlated with formation of memory about specific social events with other people. Mothers with high salivary OXT levels recalled previous positive social events related to their children with great detail, which contributes to formation of warm and trustful relationship between parents and their children and helps foster positive attachment with children [33].

According to a comprehensive study by G. Plasencia et al. [34], women had higher plasma OXT levels than men, and older adults had higher plasma VP levels than younger adults. Functionally, higher VP levels were associated with severe anxiety, while increased OXT levels and low VP levels correlated with more rapid processing of sensorimotor information and formation of verbal memory, with these effects being especially pronounced in young men. Differences in plasma levels of the endogenous neuropeptides depending on gender and age demonstrated their significant opposite effects on affection expression and formation of social cognition (Figure 1).

Of interest are data showing that vaginocervical stimulation enhanced olfactory social recognition memory in female rats via oxytocin release in the olfactory bulb and modulatory actions on noradrenaline release [35].

Animal studies showed that exogenous OXT can have both promnestic and amnestic effects depending on gender, dose, and context [36]. In particular, intranasal OXT impaired

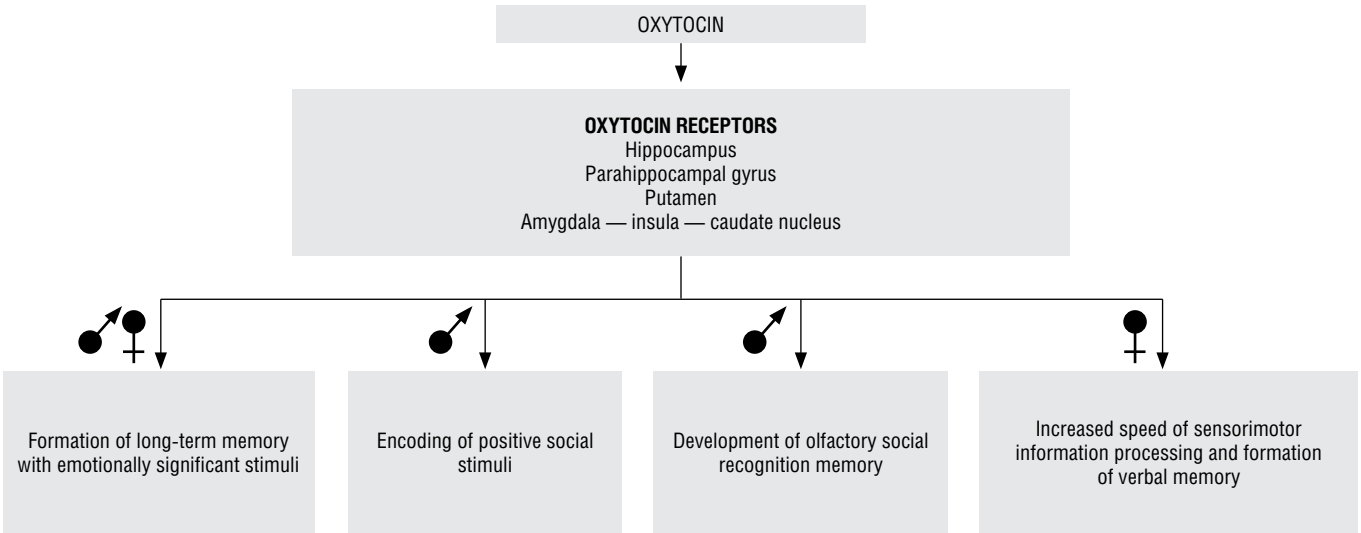

Fig. 1. Oxytocin-mediated modulation of emotional memory.

semantic association for words with reproduction-related but not neutral meaning, thus suggesting that OXT has selective effects on memory formation depending on the psychobiological salience of the stimuli [37]. Effects of intranasal OXT on human memory are ambiguous and depend on the OXT dose and its administration time, as well as the nature of the stimuli used (i. e. emotional or non-emotional). Specifically, data on the long-term memory of non-emotional stimuli showed either no effect or even worsening in memory, while studies using emotional stimuli showed an improvement in long-term memory performance with exogenous OXT [38].

Such a selective OXT-induced improvement in learning and memory triggered by emoticon stimuli was likely to be associated with increased activation and formation of functional connections in the brain regions that are responsible for the formation of emotional memory such as amygdala, hippocampus, parahippocampal gyrus and putamen, as well as between the amygdala and the insula and caudate [39].

Furthermore, in mice, OXT reversed β-amyloid-induced impairment of synaptic plasticity in the hippocampus via phosphorylation of extracellular regulated protein kinase-1 and protein kinase-2 (pERK1/2) and Ca2+-permeable receptors of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [40], which suggests that OXT can neutralize β-amyloid-mediated toxic effects on synapses. H.M. Latt et al. reported that OXT inhibited corticosteroid-induced apoptosis in hippocampal neurons by influencing OXT receptors, thus maintaining synaptic plasticity and memory during stress [41].

Vasopressin-mediated memory modulation

The hippocampus is a critical center for memory formation and a key structural target for VP because of high VP receptor density [42, 43]. The activation of vasopressin V1a receptors increased the functional activity of both pyramidal neurons in the subiculum (i. e. the base of the hippocampus with a branched neural network that processes sensory and motor signals to form a cognitive map that encodes spatial, contextual and emotional information) [44] and interneurons in the CA1-region of the hippocampus [45]. However, the highest density of VP receptors, especially V1a, was found in the dentate gyrus of the hyppocampus, which serves as a gate or filter at the entrance to the hippocampus, blocking or filtering incoming information [46]. At the cellular level, nanomolar VP levels were shown to cause a long-lasting increase in the amplitude of field excitatory postsynaptic potentials in neurons of the dentate gyrus in the hippocampus mediated by V1a receptors [47]. Moreover, intracerebroventricular administration of VP increased long-term potentiation in the dentate gyrus of intact anesthetized rats [48], which suggests that VP can increase neural excitability. This was confirmed by a recent study by X. Zhang et al., who showed that the intranasal administration of VP effectively improved the synaptic plasticity and related working and long-term memory in the APP/PS1 mouse model of Alzheimer's disease [49]. Non-clinical and clinical studies showed that VP was directly involved in the regulation of memory consolidation during sleep, which is mediated by activation of V1a receptors in the hippocampus [50].

Besides VP effects on hippocampal neurons in remodeling synaptic plasticity and long-term memory formation, a possible relationship between VP and the perception of emotional information, memory, and activation was reported (Fig. 2).

In particular, A.J. Guastella et al. showed that VP significantly enhanced the encoding of happy and angry male faces in comparison with neutral ones, which suggests that emotionally expressed stimuli are the most significant and priority

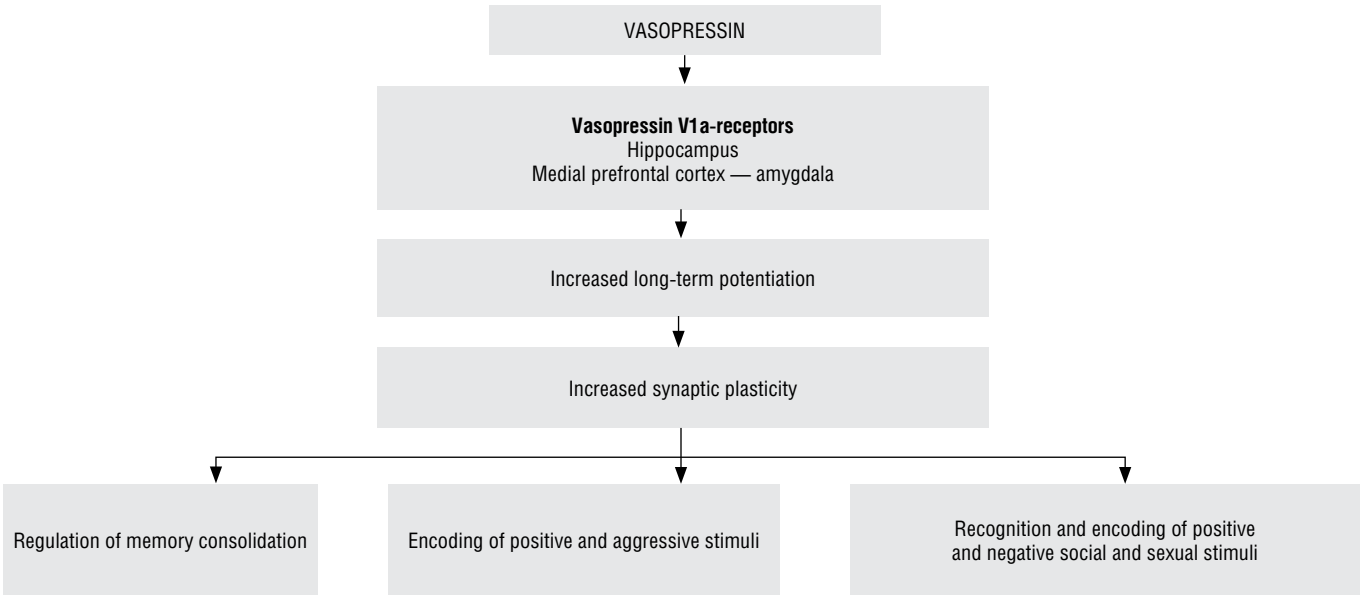

Fig. 2. Vasopressinergic memory modulation.

for memorization [51]. This specific effect of VP on social cognition, which is manifested by increased encoding of both positive and aggressive signals, may represent a mechanism by which VP may increase the variability and plasticity of behavioral responses in interpersonal relationships [52]. In a related study, exogenous VP facilitated recognition of positive and negative social and sexual stimuli over non-social stimuli, which demonstrated the possible participation of VP in cognitive mechanisms aimed at improving the perception and implementation of complex social behavior [53].

As suggested by several authors, these social and emotional VP effects are mediated by V1a receptors in target brain structures such as the lateral septum, hypothalamus, bed nucleus of the stria terminalis, hippocampus, amygdala, and brainstem [54–57]. Of those, the amygdala is considered the key structure involved in processing of a wide range of emotions, especially fear reactions [58]. Sensory information from external stimuli that are predictors of the fear reaction was shown to reach the amygdala through thalamic and cortical pathways. They are projected into the basolateral nuclei of the amygdala, i. e. areas of neural networks where fear memory develops due to long-term modification of synapses [59]. Available evidence shows that the basolateral region of the amygdala controls autonomic responses to fear via close connections with the periaqueductal gray matter of the midbrain, reticular formation and hypothalamus, thus triggering reactions inherent to a perceived threat such as defensive behavior, activation of the sympathetic nervous system, hypoalgesia, and release of stress hormones [60, 61].

D. Huber et al. recorded spontaneous spiking activity in acute brain slices of the central amygdala and found two distinct neurone populations: the first one was excited by OXT receptor activation, while the second was inhibited by OXT receptor activation but excited by VP receptor stimulation [62]. Neural cells excited by VP were located both in and beyond the central nucleus of the amygdala.

K. Motoki et al. showed that higher VP plasma levels positively correlated with activation of the amygdala in men but not in women [6]. Such an evident polarity can be explained by the fact that VP-positive neurons are located in the amygdala, where higher levels of VP receptors were found in males but not in females [63]. Reports on intense VP release in the amygdala and prefrontal cortex of male rats in response to low-intensity stress were also quite unexpected [64]. A lower degree of anxiety response was recorded in rats after high-intensity stress with no visible changes after low-intensity stress. O.J. Bosch et al. found intensive VP release in the central amygdala of lactating female rats with high anxiety, which positively correlated with aggressive behavior [8].

These gender differences in VP levels and their relationship with emotionally charged events remain unclear due to available inconsistent data and their unknown molecular cellular mechanism.

VP was shown to directly influence activation of the stress state, which is the key factor contributing to the consolidation of fear memory and associative learning [65, 66]. VP levels were shown to be increased in the central amygdala [67].

Not only did VP modulate associative learning and fear expression during stress but also fear-conditioned learning [22].

The amygdala is also involved in the reconsolidation and extinction of fear memory [68], i.e. two opposing functions

for contextual fear memory: reconsolidation maintains or strengthens fear memory, while extinction represents learning that generates inhibitory biochemical pathways that suppress fear response [69]. The pathway from the medial prefrontal cortex to the amygdala is the most likely neural pathway that mediates fear extinction response [59]. According to C.F. Zink et al., VP modulates the medial prefrontal cortex-amygdala circuit and connectivity patterns, which is reflected in social behavior related to fear and anxiety (Figure 2) [70]. Available data indicate that OXT promotes social fear extinction, while VP prevents this [71]. Prolonged fear can become a predictor for the development of anxiety disorders.

Considering a well-studied causal relationship between chronic stress and mood disorders, significant efforts have been made to find medication treatment options for anxiety and depression. R.A. Hodgson et al. proposed V1B-30N as a highly selective antagonist of V1b receptors with good oral bioavailability, which decreased plasma levels of the stress hormone and had an anxiolytic effect by reducing V1b-receptor activity [72]. This further confirms the significant role of VP in the formation of emotionally charged behavioral reactions in the context of stress-induced events, which are encoded by the hippocampus-amygdala-medial prefrontal cortex neural network with subsequent transformation of emotionally charged events into long-term memory.

Oxytocin as a neuropeptide modulator of non-verbal interpersonal communication

Visual perception of faces in the context of interpersonal relationships is usually unconscious and allows the extraction of socially relevant information such as gender, age, and emotions, thus regulating social interactions (i. e. approach and avoidance) [73]. Substantial evidence supports the hypothesis of OXT influence on the perception of social information, which is reflected in the regulation of social behavior, inducing processing of positive stimuli and attenuating negative ones, as well as increasing the salience of both social and emotional stimuli [74–76] (Figure 3).

In primates, exogenous OXT enhanced the perceptual salience of the eyes and the propensity to interact with a social partner in response to naturalistic social stimuli [77]. These OXT effects can be seen after its single administration. L.A. Parr et al. showed that OXT after repeated administration significantly increased the time monkeys spent viewing the lipsmack and threat videos (i. e. dynamic facial expressions) but selectively reduced attention to the eyes in neutral faces in a dose dependent manner [78]. The authors suggested that this unexpected non-prosocial effect of OXT may be explained by the suppression of OXT receptor expression in the brain regions responsible for regulation of social attention as a result of repeated administration of the neuropeptide. This calls into question the efficacy of exogenous OXT used in the long-term as a medication therapy for social behavior disorders.

Any face image has at the same time signs of identity and expression, i.e. who the person is and what feelings they experience. This clearly distinguishes visual stimuli from others, where at any given time a face will convey multiple independent signals that are thought to be processed by a neural network distributed in interconnected face-selective brain regions [79, 80].

In a clinical study, intranasal OXT improved recognition memory for neutral and angry faces with no effect for happy faces,

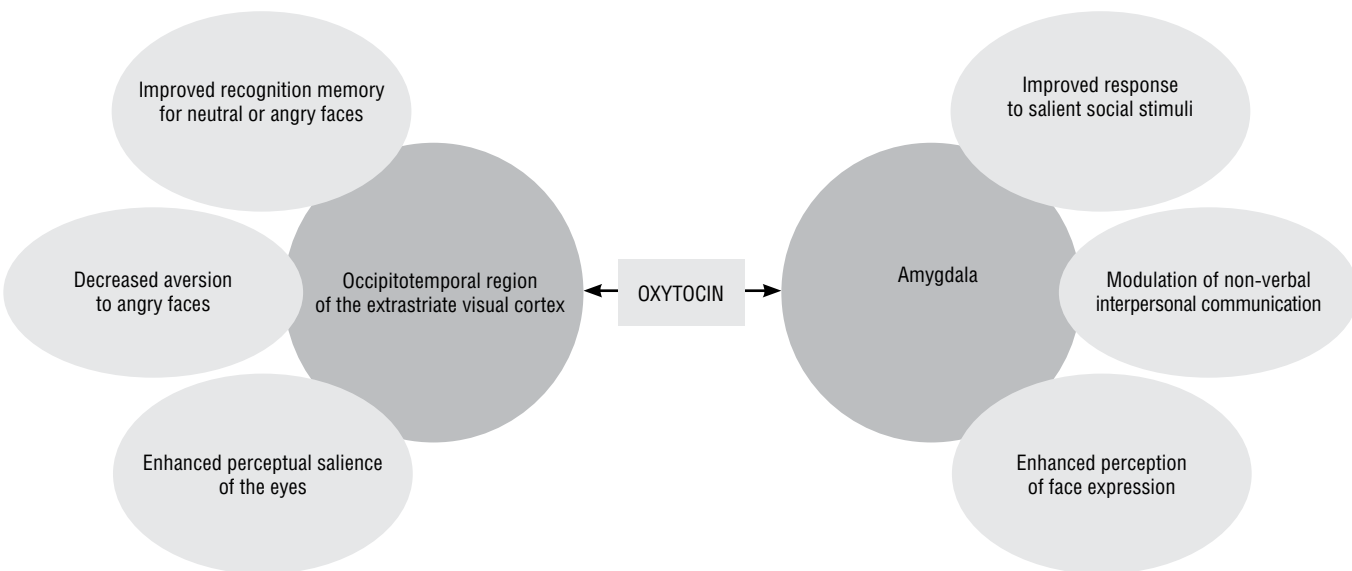

Fig. 3. Oxytocinergic regulation of social interaction.

regardless of participants' gender. However, OXT had no effect on the formation of facial expression memory. This selective influence of OXT on identity and facial expression memory may contribute to the modulation of social behavior [81].

It is noteworthy that OXT was able to modulate the awareness of socially salient emotional information in the environment even with short-term stimulus presentation (i.e. 18, 35 or 53 ms), which was manifested in an improvement in performance for facial stimuli with a more pronounced effect on happy faces [82].

Moreover, OXT specifically decreased the aversive aspects of angry faces, while having no effect on sad faces, which also have negative emotional valence. Financial feedback (reward), either positive (win) or negative (lose), did not have any significant effect on social preferences [83].

These effects of OXT are likely to be mediated by an activated neural network in the occipitotemporal regions of the extrastriate visual cortex, which are involved in visual analysis of faces, as well as the fusiform gyrus and superior temporal sulcus, which are involved in the representation of invariable and variable aspects of facial expressions, respectively [84–86].

Another perspective regarding the impact of OXT on social behavior is associated with social salience. It was hypothesized that OXT improves response to salient social stimuli [87, 88]. In other words, this is interpreted as the "social salience hypothesis", which is consistent with reports of several authors who suggested OXT-induced improvements in "face reading" with the eyes and an increase in eye contact [75, 89, 90], thereby contributing to the modulation of non-verbal interpersonal communication.

Although detailed understanding of the neural mechanisms underlying OXT effects on attention to the eyes is not yet fully developed, neuroimaging data suggest the involvement of the amygdala in attention to facial features in general [91–94] and the role of the superior colliculus in modulation of attention to facial features mediated via OXT [95].

According to J. Taubert et al. intranasal administration of OXT in rhesus monkeys improved perception of face expressions to a greater extent than face identity [96]. A subsequent detailed analysis showed that this was mainly related to the presence of a stimulus expressing fear or aggression (i. e. negative emotions). Accuracy in perceiving lip-smacking facial expressions as a sign of appeasement and submission, which has a positive social value, was noticeably lower in rhesus monkeys. This selective influence of exogenous OT on behavioral responses to facial expressions with negative valence supports the theory that OT effects are tuned to the socioemotional value of a visual stimulus that signals about fear or aggression as a sign of potential danger or hostility. These effects are mediated by activation of the OXT signaling pathway, which contributes to the manifestation of social cognition [96].

Current evidence regarding OXT effects on visual scanning of emotional faces is inconsistent. According to A. Lischke et al., OXT promoted emotion recognition from dynamic facial expressions regardless of modulation of visual attention to specific face areas [28]. OXT-induced improvement in emotion recognition was related to its direct involvement in the formation of memory for faces and expressions [97], which allows identifying whether the facial expression corresponds to those previously remembered. No OXT involvement in visual attention to the eye is likely to be related to its participation in prioritization, i. e. initial allocation of attention to social stimuli. This was confirmed by a more recent study where OXT reduced face processing time but had no effect on eye-gaze patterns when viewing static emotional faces [98].

However, Sosnowski M.J. et al., who investigated effects of endogenous and exogenous OXT on visual attention to facial features, did not found any significant differences in the visual attention of capuchin monkeys to the eye or mouth area in the categorization test (i.e. classifying males depicted in photographs as "dominant" or "subordinate"), regardless of OXT administration method [99]. The latter influenced the frequency and duration of the gaze at the entire face: endogenous OXT, in contrast to exogenous one, increased the test gaze parameters, which suggests their different influence on the gaze.

The effects of OXT were highly dependent on individual personality traits and context [100, 101]. OXT does not always promote positive social behavior in everyone and in all situations [18], so it may increase visual attention to the eye under certain conditions only. In this context, deep mechanisms underlying OXT effects depending on the person's characteristics and the situation remain unknown. The "social significance hypothesis" cannot fully explain the inconsistence of OXT-induced effects.

Modulatory effects of vasopressin on perception and social behavior

Instant, efficient, and accurate recognition of facial expressions represents a fundamental and unique ability of humans to participate in interpersonal communication. A growing body of experimental brain neuroimaging evidence demonstrates that the neural circuits responsible for empathy and emotion recognition are located primarily in the limbic system, prefrontal cortex, and frontoparietal regions [101–103]. Therefore, VP is an important neuromodulator that activates brain areas that are directly involved in the regulation of emotions, in particular, the limbic system (cingulate gyrus, amygdala) [70]. According to R.R. Thompson et al., VP exhibited dual effects on social communication in men and

women [104]. In men, exogenous VP stimulated agonistic facial motor patterns in response to the faces of unfamiliar men and decreased perceptions of the friendliness of those faces. In women, in contrast, AVP stimulated affiliative facial motor patterns in response to the faces of unfamiliar women and increased perceptions of the friendliness of those faces. It is also possible that VP effects on autonomic, motor, and psychological responses each resulted from its independent actions in different brain regions. If so, the orthogonal effects of VP on social communication patterns in men and women may be the result of sex differences in receptor distributions in the brain, such that VP directly activates specific fight or flight circuits in men and tend and befriend circuits in women.

In a study by F. Uzefovsky et al., exogenous VP significantly reduced the ability of male participants to recognize emotions of other men (this effect was restricted to recognition of negative emotions only), which may further promote aggression due to lack of empathy [29]. R. Polk et al. evaluated the VP-social cognition link in aging and showed that higher plasma VP levels did not correlate with the accuracy of dynamic emotion identification [105].

On the other hand, some authors suggested that VP was directly involved in pair-bonding behavior. In particular, intranasal administration of VP increased the willingness for mutually beneficial cooperation between strangers [106, 107] and selectively enhanced human cognition for sexual stimuli, regardless of valence [53]. VP-induced inhibition of activity in the left dorsolateral prefrontal cortex (i. e. an area responsible for decision-making under risk conditions) and increased functional connectivity of the left dorsolateral prefrontal cortex with the ventral medial striatum can be possible neural mechanism underlying the increased tendency to collaborate [108]. In the latter, as a structural component of the basal ganglia, where both V1a VP receptors and dopamine receptors are concentrated with a sufficiently high density, a reward system forms as a result of social interaction. Therefore, the interaction of the dopaminergic and vasopressinergic systems in the ventral medial striatum was shown to encode a beneficial component of social interactions by facilitating social recognition and pair bonding [109, 110].

X. Wu et al. showed gender-specific effects of VP in response to same-gender and other-gender facial expressions among males and females; males rated lower approachability scores to neutral and positive male faces, while females rated higher approachability scores to negative female faces [111]. VP is likely to modulate the perception of emotional stimuli to a greater extent than neutral ones. Such distinctive effects of VP on socio-emotional stimuli directly depend on gender and context.

This also demonstrates that VP has gender-specific effects on social behavior and associated emotional response.

Effects of oxytocin on "face reading" in patients with mental disorders

Considering the critical role of OT in social cognition (perception of social signals, identification of emotional body gestures, recognition of facial emotions, handling of emotionally charged situations, approach-avoidance behavior) and interpersonal interaction, the oxytocinergic system is a promising target for the treatment of mental disorders.

It should be considered that "face reading" requires the rapid and accurate perception of primary social stimuli as the primary communication tools for conveying necessary social and contextual information, emotional feedback, understanding of social norms, and the ability to recall and attribute different emotions to others. These aspects of social cognition are fundamentally impaired in patients with mental disorders.

A. Vehlen et al. reported that despite largely preserved basic facial emotions recognition, attention in social perception may be altered in patients with chronic depression disorders, and the latter was sensitive to intranasal treatment with oxytocin [112].

Evaluating an association between endogenous oxytocin levels and facial emotion recognition accuracy in individuals with schizophrenia, MJ. Spilka et al. showed that lower plasma OXT levels were associated with a significant reduction in accuracy of identifying high-intensity fearful facial expressions and low-intensity sad expressions [113]. This did not affect visual attention to salient facial features.

According to B.B. Averbeck et al., single low doses of OXT (24 IU) administered intranasally to patients with schizophrenia improved their ability to identify most emotions, whether the images presented to the patients depicted neutral or emotional faces (i.e. with happiness, surprise, fear, sadness, aversion, or anger) [114]. However, this contradicts to a recent randomized double-blind study [115] where such low acute doses of OXT had a limited and modest effect on social emotional face processing and did not affect eye gaze duration or gaze dwell time on faces. This is consistent with the data of J.K. Wynn et al., who, using electroencephalography and pupillometry, demonstrated that moderate OXT doses (36–48 IU) were optimal and effective for enhancing emotion recognition in patients with schizophrenia [116].

In this context, long-term (4-month) therapy with OXT in patients with schizophrenia improved the patients' ability to recognize and understand the emotional state of others, which is crucial in interpersonal communication and social behavior [117].

According to R. Wigton et al., OXT-induced improvement in social cognition in patients with schizophrenia is based on

attenuated neural activity in the brain regions that support mentalizing, processing of facial emotions, salience, aversion, uncertainty and ambiguity in social stimuli, including amygdala, temporo-parietal junction, posterior cingulate cortex, precuneus, and insula [118].

As shown by L.R. Horta de Macedo et al., exogenous OXT did not improve performance of patients with schizophrenia in a facial emotion matching task [119]. According to the authors, such unexpected results could have been caused by high doses of OXT (i.e. 48 IU) and the use of the facial emotion matching task contrasting with previous studies using emotion labeling tasks.

A. Schmidt et al. showed that OXT administration did not have any significant effects on inferring others' beliefs and social emotions in people at clinical high risk for psychosis [120]; this result was quite unexpected. Moreover, there was a decrease in neural activity in the bilateral inferior frontal gyrus while inferring others' beliefs and social emotions. Inhibition of activity in this brain region was seen in individuals at clinical high risk for psychosis with high social-emotional abilities. This demonstrates selective effects of OXT on emotions in pathophysiological conditions and directly depends on the ability to have emotional empathy.

The inferior frontal gyrus is an important part of the mirror neuron system, which is involved in significant aspects of social interaction, from imitation to emotional empathy [121]. Being a key target for the neurophysiological effects of OXT, the inferior frontal gyrus is directly involved in emotion recognition tasks, such as sentence processing guided by intonation [122] and discriminating facial expressions [123].

OXT modulates impairments in emotion perception and the ability to draw conclusions about others' thoughts and beliefs; these impairments can be considered predictors of mental disorders. This is done through selective OXT effects on certain brain regions, which can be considered in the development of new strategies for targeted therapy of social emotional disorders.

Role of vasopressin in the selective activation of brain activity during the recognition of emotions in patients with mental disorders

B. Bloch et al. demonstrated that the effects of exogenous VP on emotion recognition in individuals with schizophrenia were multidirectional and directly dependent on gender [124]. VP resulted in a significant decrease in the ability to recognize angry faces in men and sad faces in women. A VP-induced improvement in the perception of fearful facial expressions was found in women.

Levels of endogenous VP in patients with schizophrenia were significantly reduced, which correlated with the severity of symptoms and impaired recognition of others' emotions [125].

Considering neuroimaging data, L.H. Rubin et al. showed that basal VP levels in men and women with schizophrenia were associated with activity in the middle, medial and superior frontal gyri, as well as the cingulate cortex [126]. VP differentially modulated brain networks in the brain regions important for social cognition and emotion processing in women and men with schizophrenia. VP-mediated reductions in functional network connectivity of the frontal cortex (superior frontal gyrus) were found in women, while men had increased functional network connectivity in the middle frontal gyrus/cingulate gyrus. L.H. Rubin et al. showed a relationship between selective modulatory activity of VP, brain region and gender, which determines the different role of this neuropeptide in the recognition of emotions in male and female patients with schizophrenia.

An unexpected conclusion was made by D.S. Carson et al., who showed that VP blood levels in people with autism spectrum disorder aged 4–64 years significantly and positively correlated with VP levels in the cerebrospinal fluid. In addition, VP levels in the blood predicted severity of symptoms in the context of the theory of mind performance as the ability of adequate perception and understanding of others' emotions, thoughts, beliefs, and desires [127]. These results clearly demonstrated that VP levels in blood samples can be used not only as a reliable tool for a routine assessment of its activity in the brain but also as a biomarker for impaired social cognition in children with autism spectrum disorder.

In their neuroimaging study, X.J. Shou et al. found evidence that the development and progression of autism spectrum disorder is associated with pathological changes in the morphology and functionality of the brain regions where VP neurons are mostly localized [128]. Children with autism spectrum disorder had a decrease in the volume of the gray matter in the hypothalamus and an increase in the volume of the left amygdala and left hippocampus. The reduction in the volume of the hypothalamus might suggest dysplasia of neurons and/or neuropil in the hypothalamus that leads to decreased VP levels and the manifestation of autistic symptoms. Moreover, the degree of abnormal expansion of the amygdala was positively correlated with the severity of social and communication impairment.

Therefore, VP can be considered a promising neuropeptide that influences the social and emotional functions of the brain in the context of interpersonal relationships, which may be useful for understanding the etiology and neurobiological basis of mental disorders.

Conclusion

Research to investigate the multifaceted effects of OXT and VP remains an exciting direction for deeper understanding of the structure and functioning of the so-called "emotional

and social brain". Data accumulated over the past few decades have significantly enriched our understanding of OXT-ergic and VP-ergic regulation for processes that are vital for socialization, effective and flexible interpersonal communication, such as social cognition, social behavior, emotion recognition, and attention and memory to emotionally salient stimuli. However, data on OXT and VP effects on emotions and memory are sometimes inconsistent, so further studies are needed to investigate how context-dependent intracellular signaling cascades produce specific behavioral responses. Solving this scientific problem will allow obtaining unique knowledge about OXT-induced and VP-induced cellular response and signaling mechanisms in the neural networks of the brain structures that are responsible for the implementation of behavior. This will undoubtedly be decisive in the development of more effective therapeutic strategies using OXT, VP and their analogs for the treatment of mental disorders.

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Spectrum of Non-Motor Symptoms in Parkinson's Disease — a Review

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Abstract

Motor and non-motor symptoms of Parkinson's disease (PD) and their management have been evaluated in numerous studies. Four classical symptoms, including bradykinesia, tremor, rigidity, and postural abnormalities, are used to establish a clinical diagnosis of PD. However, this research is aimed at exploring the range of non-motor symptoms with an emphasis upon their ability to affect the patients with PD and their quality of life.

With a slow onset of the known symptoms like tremor or rhythmic shaking of limbs called "pill-rolling tremor", slowed movement (bradykinesia), muscle rigidity, stooped and altered posture, loss of the ability to blink or smile, and various speech and writing changes; the disease takes a leap into the non-motor symptoms like dementia, drooling, swallowing issues, difficulty urinating, and constipation. The dopaminergic pathophysiology of PD explains the anxiety, slowness of thought, fatigue, and dysphoria. Knowing the non-motor symptoms is crucial to help the clinician to make early diagnosis and to better understand the prognosis of the spectrum of this disease.

Keywords: *Parkinson's disease; non-motor symptoms; dementia; cognitive impairment; sleep disorders*

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Немоторные симптомы болезни Паркинсона: обзор

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Аннотация

Моторным и немоторным симптомам болезни Паркинсона (БП) и их лечению посвящён целый ряд исследований. Клинический диагноз «болезнь Паркинсона» устанавливается по наличию четырёх классических симптомов: брадикинезии, тремора, ригидности мышц и постуральных нарушений. Цель настоящего исследования состоит в изучении спектра немоторных симптомов и их влияния на качество жизни пациентов с БП.

В то время как такие симптомы болезни, как тремор по типу «скатывания пилюль», замедленность движений (брадикинезия), ригидность мышц, сутулость и постуральные нарушения, нарушение способности моргать или улыбаться, а также различные изменения речи и письма, развиваются медленно, на более ранних стадиях БП возникают немоторные симптомы: деменция, слюнотечение, нарушения глотания, затруднённое мочеиспускание и запор. Патофизиологические процессы, связанные с дофаминергической системой, обусловливают возникновение тревоги, замедление мышления, утомляемость и дисфорию у пациентов с БП. Знание немоторных симптомов необходимо для постановки диагноза на ранней стадии и улучшения прогноза для нарушений этого спектра.

Ключевые слова: *болезнь Паркинсона; немоторные симптомы; деменция; когнитивные нарушения; нарушения сна*

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

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Introduction

Dr. James Parkinson defined Parkinson's disease (PD) as a chronic neurodegenerative disorder of the extrapyramidal system. The disease is characterized by both motor and non-motor symptoms. The motor symptoms like bradykinesia, pill-rolling tremors, rigidity, etc. develop due to the degeneration of dopaminergic neurons in nigrostriatal pathway [1]. A progressive degeneration of dopaminergic neurons occurs in the pars compacta region of substantia nigra which projects to the striatum via the nigrostriatal pathway leading to a decline of dopaminergic functions in the patients. Most patients are reported to develop PD when there is 50% to 80% loss of dopaminergic neurons. The increased activity in globus pallidus internus segment and substantia nigra pars reticulata circuit is observed when there are decreased levels of dopamine in the striatum of PD patients, which contributes to abnormal functioning of gamma aminobutyric acid, resulting in inhibition of thalamus and reduced ability of thalamus to stimulate frontal cortex, leading to the reduced motor activity that is a feature of PD [1]. With no conclusive tests to confirm the diagnosis of PD, clinicians must rule out other diagnoses by assessing the history and symptoms.

The classical triad includes bradykinesia, rigidity and tremor at rest. Dysarthria, postural instability, and dystonia are other motor features of PD. Besides, further diagnostic workup including neuropsychiatric testing, sleep analysis, and assessment of vision should be carried out in suspected PD cases. Abnormal colour vision is, for instance, a non-motor symptom occurring due to the changes in intraretinal dopaminergic transmission. Thus, it becomes very important to be aware of the non-motor symptoms and consider them during clinical diagnosis [1].

The disease is generally managed by oral levodopa. With rehabilitation and physiotherapy as established therapeutic options to manage symptoms of PD, there are other new rehabilitation modalities used nowadays. In light of the necessity to underscore the significance of non-motor symptoms in patients with PD, this review has been prepared. It addresses various questions around the unchartered territory of non-motor manifestations and the approaches to their management.

Non-motor symptoms of Parkinson's disease

Depression

As described above, treatment of PD is complex. Besides movement disorders, it revolves around diminishing the behavioural abnormalities. The patients are prone to psychiatric conditions seen in the rest of the population like depression and cognitive impairment. As per B. Scott et al., out of a sample of 948 patients, about 36% presented with depression [2]. A meta-analysis pointed out that about one third of patients have clinically significant depression [3]. Another review mentions that around 50% of PD patients are affected by depression that may take a progressive course, with the development of anxiety and panic attacks [4]. Depression and anxiety may occur long before diagnosis is even made [5]. In a 2008 review article, it was implied that depression is common in patients with PD and it was found in 35% of PD patients [6]. However, depression is milder in patients with PD in contrast to those unaffected with PD; the PD patients with depression also present with apathy and anhedonia. Moreover, depression is seen early before the onset of motor symptoms and is linked to the duration and severity of motor symptoms. It also depends on the fluctuations of these symptoms and the dosage variations of dopaminergic medications. Factors like psychosis, sleep disturbances, anxiety and so on can lead to an increased risk of developing depression in PD. Loss of cortical cholinergic neurons may cause depression in patients with PD [7].

Anxiety

60% of patients with PD are affected by anxiety, which in general includes fear, worry, and apprehension and may not always be accompanied by depression [7]. It is more frequent in females and patients with very early disease onset. Associated with periods of low dopamine levels, anxiety levels proportionally increase with motor fluctuations and freezing (no movements) [8]. In a study conducted with 105 PD patients PD, anxiety was prospectively assessed based on the Parkinson Anxiety Scale, and Parkinson's Disease Questionnaire. Results showed that 56 patients had anxiety: episodic anxiety (50%) and persistent anxiety (15%). Higher prevalence of episodic anxiety is a PD-specific symptom and stems from the dopaminergic pathway [9]. Such anxiety episodes are often

related to verbal memory loss in PD patients with no symptoms of dementia. As such, the anxiety exerts an adverse influence on the quality of life and proper timely screening is a must to ensure the efficient delivery of care and management to PD patients and their close ones [9].

Cognitive impairment and dementia

Cognitive impairment and dementia may complicate PD. I. Galtier et al. conducted a study which included 43 patients with idiopathic PD and 20 neurologically normal controls who were followed up for the MDS (Movement disorder society) Task Force criteria for PD-MCI (mild cognitive impairment) diagnosis [10]. 96.2% was the maximum frequency for the multiple domain impairment and around 42.3% of PD-MCI patients had dementia when followed up. The logistic regression had clearly shown that the Hoehn–Yahr stage and education significantly contributed to the prediction of PD-MCI while Hoehn–Yahr stage and memory domain predicted dementia. Neurological deterioration, level of education, and loss of memory were prognostic factors for the progression of intellectual impairment [10]. The general trend which is seen in PD patient is an impairment of the executive dysfunctions) and visuospatial function, with less prominent memory deficits and preserved language function. Unstable set shifting, attention and planning comprising the executive dysfunction are seen early in the course of the disease, and this may even include impaired face recognition. Other measures of visuospatial functions degrade over the progress and severity of PD and dementia. Finally, the brain higher level functions get abnormal even before the patients gets diagnosed with dementia [10].

The percentage of dementia in population due to PD is 3–4%. Cross-sectional studies have shown that the mean prevalence of dementia is 40%. In prospective cohort studies, the incidence rates of dementia in patients with PD approximate 100 per 1000 patient-years which is five to six times higher than in controls without PD [11]. Memory deficits are not too rare in PD dementia but are adjoined to retrieval of information that is learned and known. Aphasia, apraxia, and severe memory loss are mostly seen in Alzheimer disease. Neuropsychiatric symptoms may occur in PD without dementia; however, they are increasingly more common in patients with more drastic cognitive impairment [12].

Hallucinations

Visual hallucinations affect up to 75% of PD patients. It not only impacts patient's life but also affects their family. One of the common hallucinations type is visual hallucinations. They were shown to be the strongest predictor of earlier placement in care homes, cognitive decline, and increased mortality. They occur mostly in the evening and involve perception of animals, people etc. [13]. The affected person experiences minor hallucinations and misinterprets objects, such as pile of clothes, dogs and cats and hears muffled and distorted sounds (auditory hallucinations). Some patients experience tactile, gustatory, or olfactory hallucinations. They feel the presence of someone and illusion of objects passing across the peripheral vision [14]. The prevalence estimate of visual hallucinations is 8.8% to 44%. The feeling of a presence of odd things, complex frightening visions, and some vague feelings is the entire visual phenomena span in visual hallucinations. Underreporting is a potential problem since patients fear of being labelled as "mad" [15].

Generally, it occurs to the patient in dim surroundings when they are alert and usually the eyes are open. It has been reported that a blurry image appears suddenly around the visual field without any voluntary effort. This episode persists for few seconds and vanishes out suddenly. These hallucinations were complex and contained inanimate objects or persons, but they were transient and perceptual. Usually there are five or less images, sometimes being meaningful to the patient, happening in dim areas, recurrent and non-threatening. How much the patient remembers of these hallucinations can change over time and depends on the cognitive impairment.

21.5% of the participants out of a total of 191 patients without dementia who were administered the Parkinson Psychosis Rating Scale had psychosis. In this sample, 13.6% had visual hallucinations, 6.8% of these had auditory hallucinations, 7.3% presented with illusions and 4.7% with paranoid ideation. Auditory hallucinations were also found in PD patients even though they were less common than visual hallucinations [16]. In a study with 121 PD patients, 8% had auditory hallucinations. The reports also show occurrence of erotomania, jealousy, and persecutory delusions. Unique entities such as Cotard Syndrome and Capgras syndrome have been also seen in PD patients [16].

Constipation

A non-motor symptom of constipation can occur early before the motor symptoms. The gastrointestinal symptoms are very common during all stages of PD, with 30% patients reporting drooling, dysphagia, gastroparesis, and constipation [17]. The reported constipation prevalence is 8% to 70% and is steadily rising as the disease progresses [17, 18]. The median prevalence of 44% was noted if the criterion of less than three bowel movements per week or straining is considered. The data points out that as compared to the general population the prevalence of constipation raises by a median of 30 percentage points in PD patients.

The difficult rectal evacuation seen in PD patients is not because of rectal hyposensitivity, and rather it is caused by the abnormal tone of the striated external sphincter and puborectalis muscles [19]. In cross-sectional studies, small intestine bacterial overgrowth is more often seen in patients with PD compared to healthy controls with a prevalence of 25% to 54% [20].

Gastrointestinal dysfunction with drooling

In the study conducted in PD patients in Charles Nicolle Hospital of Tunis during 2013 to 2014, 73% subjects had gastrointestinal symptoms as most common non-motor symptoms diagnosed with endoscopy and immunohistochemical study; these symptoms can be looked upon as a marker of PD [21]. The incidence of dysphagia ranges from 9% to 82% but has been noted up to 97% in objective studies [22]. In advanced PD patients who have severe bradykinesia and rigidity it leads to the oropharyngeal dysphagia. The incidence of gastroparesis is somewhere between 70% to 100% in mild PD patients with a mean half emptying time of 46 to 149 minutes and 55 to 221 minutes in moderate PD compared to 43 to 107 minutes in healthy controls. The distal oesophageal transit times and colonic transit times were both extended in early to moderate PD [20].

A non-motor symptom that affects more than half of patients with PD, excessive salivation, has a negative impact on their lives, especially in advanced stages. Along with drooling, the patients also presented with the lower swallowing capability, poorer functional swallowing, more severe facial hypokinesia and severe involuntary mouth opening. The incidence of drooling in PD ranges from 10% to 84% [21, 22]. The droolers showed more stooped posture. The presentation relates to abnormal swallowing in the oropharyngeal phase and an increased frequency of secretions of the parotid gland.

Till now, the pathophysiology of drooling in PD is not fully understood with reduced intra-oral salivary clearance expected to be the major cause of it [21]. Of all factors contributing to drooling, hypomimia was most strongly linked to and more seen in men with advanced PD and dysphagia [22]. Dysphagia is considered an important component in the multifactorial model which explained drooling. In fact, latest findings seem to prove that tongue bradykinesia is related to both oropharyngeal dysphagia and drooling [22].

In a study conducted in 84 patients at Mayo Clinic, ten showed delayed gastric emptying, another ten had slow colonic transit, sixteen had accelerated gastric emptying and 49 had normal transit time [23].

Dysphagia

Dysphagia was reported to affect 68% of late-stage PD patients (Hoehn–Yahr stages 4 and 5) in Barcelona and Lisbon cohort. A relevant unexplained weight loss or BMI (body mass index) below 20 suggests dysphagia [24]. During the course of disease around 20% of PD patients develop malnutrition. Sialorrhea or drooling is a predictor of dysphagia and aspiration pneumonia [24].

Rhinorrhoea

Rhinorrhoea refers to the presence of nasal discharge which is the “presence of nasal drainage in the absence of sinus problems, respiratory infections, and allergies”. In a systematic review for determination of rhinorrhoea incidence in PD in 451 patients and 233 controls, pooled prevalence of the symptom was 45%, and a greater number of patients with rhinorrhoea self-reported disturbances in smell compared to those without abnormal nasal disharge. The mean age of patients with PD and rhinorrhoea was significantly greater than those with PD without rhinorrhoea. No difference in disease duration, disease severity, or gender between the cohorts was identified [25].

Hyposmia

More than 90% of PD patients develop hyposmia or anosmia which is generally bilateral and occurs before motor symptoms due to dopamine deficiency. Patients generally do not report it but if the development or progression of hyposmia is associated with other early clinical, imaging and/or biochemical markers it could be viewed as a biomarker for detection of early pre-motor PD [26].

Othello syndrome

Of 805 patients with PD, 20 had delusional jealousy, which was associated with treatment with a dopamine agonist, and in five patients it can be treated by reducing the dose of dopamine agonist [27]. The patient can exhibit delusional jealousy in the evening or midnight or while indoors, but it can also sometimes happen during daytime or while outdoors. In the study review, the DSM-IV-TR (The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision) criteria were used. Unlike visual hallucinations, patients did not see persons or animals and were fully oriented. There was no abnormal odd or repetitive behaviour. These patients did not have any premorbid personality disorder prior to Othello syndrome, or any family history of psychiatric or personality disorders [28].

There are limited studies of Othello syndrome in PD and one such study identified eleven Othello syndrome subjects (nine males; two females) out of 153 patients who were found to have PD as per the Movement Disorders Society Criteria [29]. It was noted that Othello syndrome is more frequently seen in males; however, the incidence of this syndrome is 7.2% only [28].

Sexual dysfunction

Often neglected non-motor symptom, sexual dysfunction (SD) in PD patients is attributable to numerous social and cultural factors which is why it is still under-recognised. PD affects libido and there is orgasmic dysfunction in men

and women [30]. A multidisciplinary approach for diagnosis and treatment must be undertaken to assess the plethora of symptoms of SD in PD. More so, prevalence of SD in women is approximated around 25% to 63% with a greater prevalence in post-menopausal women [31]. Diminished libido and erectile dysfunction can occur in 80% of male PD patients and orgasmic dysfunction may reach up to 84% and 75% in female PD patients [32]. In 15% of cases symptoms appear early in PD developing over 65 years of age [33]. But even the young PD patients get affected by the symptoms of SD. They show decreased sexual desire and are feel discontented with sexual life.

Male sexual dysfunction is relatively more prevalent, and men have difficulties reaching orgasm and experience premature ejaculation. Women show predominant decrease in sexual desire and difficulties with arousal and orgasm. Decreased libido along with vaginal tightness, involuntary urination, and displeasure in sexual intercourse is also observed in females with PD [32].

Sleep disturbances

Sleep disturbances are one of the major non-motor symptoms in PD, including rapid eye movement (REM) sleep behaviour disorder (RBD), restless leg syndrome, and sleep apnoea. High percentages of people with sleep disorders are expected to develop PD, even though RBD is found to be in the best association with PD development. The probable risk is substantially greater for acquiring PD in patients with RBD compared to the general population, and once PD is initiated, the progression of motor symptoms is quicker than in patients with no RBD [5].

Urinary symptoms

Urinary frequency and retention is generally seen in patients with PD. This occurs due to disturbances in cholinergic parasympathetic nervous system. It has been noted that nigrostriatal degeneration might be responsible for urinary symptoms. Frequent nocturia is seen in 60% of patients and is caused by detrusor overactivity [34].

Conclusion

This review discusses all the non-motor symptoms of PD. The aim of this review was to present major non-motor symptoms that affect PD patients. Knowing the non-motor symptoms is crucial to help the clinician to make early diagnosis and for better prognosis of disease. These non-motor symptoms are treated specifically (Table) to ensure better relief and improve the quality of patients' life. Hyposmia, is a biomarker for the early pre-motor PD, and when combined with imaging and non-motor tests for diagnosis, it can help identify PD early.

Treatment aspects related to non-motor symptoms of Parkinson's disease

Non-motor symptoms	Treatment
Depression	• Use of antidepressants: selective serotonin reuptake inhibitors remain the drug of choice [35]; • cognitive behavioural therapy; • monoamine oxidase type B inhibitors, tricyclic antidepressants, and dopamine agonists can also be used to treat depression [36–40]
Anxiety	Clonazepam, benzodiazepines, and selective serotonin reuptake inhibitors [41–43]
Cognitive impairment and dementia	• Non-pharmacological approaches: — cognitive interventions, non-invasive brain stimulation, physical exercise [44]; • rivastigmine is approved for PD: available as capsules and transdermal patch [45]; • donepezil improves cognitive performance
Hallucinations	Hallucinations can be treated with clozapine in PD patients [46]
Constipation	• Macrogol; • lubiprostone; • cisapride; • mosapride; • tegaserod; • relamorelin [47]
Gastrointestinal dysfunction and drooling	• Catechol-O-methyl transferase inhibitors, monoamine oxidase type B inhibitors and amantadine are used to treat gastrointestinal dysfunction in PD patients [45]; • domperidone, 10 mg; • mosapride, 15 mg with dose titration from 10–15 mg/week to 45 mg; • non-pharmacological options: regular physical activity for overall benefit to the PD patients [48]
Rhinorrhea	• Antihistamines; • anticholinergic sprays; • topical steroid nasal sprays; • vidian neurectomy, cryotherapy; • radiofrequency ablation [25]
Dysphagia	• Dysphagia can be decreased by asking PD patients to do swallow manoeuvres [49]; • dietary modifications can also help to reduce dysphagia; • oral motor exercises [50]
Hyposmia	Deep brain stimulation can reduce hyposmia [51]
Othello syndrome	Discontinuing or reducing dose of dopamine agonists in PD patients with Othello Syndrome plus aripiprazole and quetiapine [52]
Sexual dysfunction	• Newly diagnosed PD patient — first start with dopaminergic drugs and ensure a follow up; • use of antidepressants like clomipramine; selective serotonin reuptake inhibitors such as sertraline may be successful; • sildenafil is an effective treatment option along with tadalafil and vardenafil; • sublingual apomorphine; • prostaglandin E1, papaverine and papaverine-phentolamine mixture are also effective [53]
Sleep disturbances	• Levodopa/carbidopa-controlled release (CR), eszopiclone, melatonin 3 to 5 mg can be used for the treatment of insomnia and modafinil for the treatment of excessive daytime sleepiness [54]
Urinary disturbances	Anticholinergics are used for urinary retention. Diazepam, baclofen or dantrolene may be useful in relaxing striated muscle in patients with hyper-reflexic external sphincters. Serotonergic agents such as duloxetine may be used to treat overactive bladder in PD [34]

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Magnetic Resonance Imaging Diagnostics of Vascular Myelopathies: from Basic Sequences to Promising Imaging Protocols

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Abstract

Magnetic resonance imaging (MRI) is the method of choice in diagnostics and differential diagnosis of spinal cord arterial infarction and venous insufficiency. However, imaging of vascular myelopathy is complicated by the lack of clear diagnostic criteria. Basic MRI sequences have low sensitivity at disease onset, and described MR patterns do not sufficiently increase imaging specificity for spinal cord ischemia, so imaging protocols are to be elaborated.

Diffusion-weighted imaging is a key additional sequence that allows establishing the ischemic nature of myelopathy.

Inclusion of spinal MR angiography in comprehensive MR examination allows visualization of aorta abnormalities, its large branches or spinal arteriovenous fistulas, so that they can be treated early.

We presented an optimal MRI protocol for patients with suspected ischemic spinal stroke. Promising high-tech MR sequences for visualization of vascular myelopathies were reviewed.

Keywords: *spinal cord; infarction; vascular myelopathy; diagnostics; magnetic resonance imaging; angiography*

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МРТ-диагностика сосудистых миелопатий: от базовых последовательностей к перспективным протоколам исследования

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Аннотация

Магнитно-резонансная томография (МРТ) является методом выбора в диагностике и дифференциальной диагностике артериального инфаркта спинного мозга и его венозной недостаточности. Однако визуализация сосудистой миелопатии осложнена отсутствием чётких диагностических критериев. При этом базовые последовательности МРТ обладают низкой чувствительностью в дебюте заболевания, а описанные МР-паттерны недостаточно повышают специфичность радиологической картины ишемии спинного мозга, что требует расширения протокола обследования.

Дополнительной последовательностью, позволяющей установить ишемическую природу миелопатии, в первую очередь является диффузионно-взвешенное изображение.

Включение в комплексное МР-обследование спинальной МР-ангиографии позволяет визуализировать патологию аорты, её крупных ветвей или спинальные артериовенозные фистулы, способствуя их ранней коррекции.

Представлен оптимальный технический протокол МР-исследования при подозрении на ишемический спинальный инсульт. Рассмотрена роль перспективных высокотехнологичных МР-последовательностей в визуализации сосудистой миелопатии.

Ключевые слова: *спинной мозг; инфаркт; сосудистая миелопатия; диагностика; магнитно-резонансная томография; ангиография*

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

Конфликт интересов. Авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Current challenges in diagnostics of non-compression vascular myelopathies

A search for effective methods for diagnosing myelopathies to differentiate various mechanisms of spinal cord (SC) damage has been ongoing for decades. The imaging methods that were described and introduced in the second half of the 20th century, such as angiography, expanded our understanding of blood supply to the SC and vascular myelopathies [1]. Widespread introduction of magnetic resonance imaging (MRI) into clinical practice and use of various MRI modalities and sequences have revealed many differential diagnostic aspects of central nervous system damage [2–4]. However, most MRI protocols that are successfully used for diagnostics of brain lesions are not used for myelopathies due to the anatomy and physiology of the SC. At the same time, development of neuroimaging methodology and consistent accumulation of knowledge about the pathophysiology of non-compressive vascular myelopathies allows considering the capabilities of MR technologies from new perspective.

Supplementing the definition proposed by the American Heart Association [5], we can say that ischemic spinal stroke (acute SC infarction, subheading G95.1 "Vascular myelopathies" of ICD-10, subheadings 8B43 "Non-compressive vascular myelopathy" of ICD-11[1]) is a severe damage of the SC substance that is manifested by a sudden or rapidly increasing persistent neurological deficit, which is established based on pathological, imaging, or other objective evidence of SC focal ischemic injury in a defined vascular distribution if other intra- or extramedullar abnormalities are excluded. Therefore, the current model for diagnosing vascular myelopathy is based primarily on the rapid exclusion of other acute myelopathies that require immediate surgery (such as compressive myelopathy, SC tumors) or conservative treatment (such as myelitis) [6, 7]. In other words, "vascular myelopathy" is still a diagnosis of exclusion.

[1] Not used in Russia.

Unfortunately, we do not have exact epidemiology data available on prevalence of SC vascular disorders. Rare publications on this topic reported a few studies with small sample size and heterogeneous inclusion criteria. According to them, vascular myelopathies account for 5% to 8% of all acute myelopathies and 1% to 2% of all vascular neurological pathologies [8]. A.I. Qureshi et al. in a population-based study suggested that the incidence may vary from 1.6 to 7.2 per 100,000 person-years [9].

The lack of uniform diagnostic protocols may be a reason for a relatively small number of registered cases of vascular myelopathy. Therefore, we can assume that patients with SC infarction are often misdiagnosed. The lack of diagnostics criteria has also hampered overall progress in spinal angioneurology [10]. However, early diagnostics of SC infarction is crucial for identifying and eliminating potentially manageable causes, as well as early initiation of rehabilitation measures [11].

Both clinical and imaging signs of vascular myelopathy largely depend on the mechanisms and causes of SC hypoperfusion, which are associated with either reduced arterial blood supply or venous dysregulation [12].

Most common causes of arterial spinal cord infarction (SCI) include aortic disease (atherosclerosis, dissection, coarctation), vertebral artery disease, atherosclerosis and mechanical compression of the radicular arteries, and hypotension due to heart failure [13–15]. According to various authors, the proportion of idiopathic SCI varies from 7% to 50% [8, 16]. Venous congestion due to abnormal arteriovenous shunts in the presence of spinal dural or epidural arteriovenous fistulas is a major cause of spinal venous insufficiency [6].

Iatrogenic causes of SC infarction should be mentioned separately. According to N.L. Zalewski et al., aortic aneurysm repair is the most common procedure that is complicated

by SCI (49% of cases) [17]. Other surgical interventions and procedures on the aorta account for 15% of cases; surgical and manual procedures on the spine, endovascular surgery, epidural anesthesia, and blockade of the cervical or lumbar roots of the spinal cord account for 36%.

It should be also noted that the studies mainly included patients after aortic surgery. Therefore, the pathogenesis and natural history of spontaneous or non-iatrogenic SC infarction remain largely unknown [18].

Thus, neuroimaging is a pivotal diagnostics step because it allows narrowing differential search and establishing a specific diagnosis.

Aim. This review aimed at summarizing available information on the sequences and MRI markers that are used in diagnostics of vascular myelopathies.

Materials and methods

A review of publications indexed in PubMed, Scopus, and RSCI databases was carried out using the key words "spinal cord", "ischemia", "infarction", "non-compressive myelopathy", "MRI", "sequences", "DWI", "DTI", "spinal angiography", "vascular malformations".

MRI methods for visualization of ischemic spinal stroke

Due to physical limitations of X-ray diagnostic modalities and spatial resolution of computed tomography (CT), MRI has become the gold standard for visualization of vascular and other lesions of the spinal cord. Crucial for a good-quality spinal examination is the use of magnetic resonance scanners with optimal spatial resolution and signal-to-noise ratio (SNR) [19].

However, available spine and SC MR protocols are less standardized than those for brain imaging. Spinal "visualization barriers" are most challenging for sequence optimization. Artifacts caused by lung excursion and respiratory movements of the chest, CSF dynamics and aortic pulsation, swallowing, can lead to distortion of MR images to a certain extent [17–19].

In addition, 3T MR scanners for SC imaging compared with 1.5T ones are more prone to artifacts caused by field inhomogeneity [20].

However, there are sequences that are used for any spine MRI protocol. These sequences are fast spin echo T2 and spin echo T1; investigations should have sequences in both sagittal and axial planes in the field of view that does not exceed the area of interest and slice thickness of up to 3 mm, which helps identify the exact location of the lesion [21].

Widely used in spinal neurology, T2-weighted imaging (WI) with the spin-echo inversion-recovery method (Short-Tau Inversion Recovery, STIR) is manifested by SC hyperintensity, since it enhances abnormal processes due to the short time inversion value, which suppresses the signal from fat. However, T2-STIR sequence has a lower signal-to-noise ratio and greater susceptibility to the spinal "imaging barriers" mentioned above. Therefore, this sequence has high sensitivity but low specificity for spinal lesions [19, 20].

As with cerebral infarction, T2-weighted images are sensitive to the total volume of tissue fluid in the SC. Therefore, signal intensity change appears only once significant vasogenic edema of the infarcted tissue has developed. Therefore, the SC ischemia lesion is not seen on T2-weighted MR images at the onset of clinical symptoms [6, 22]. In a study by K. Nedeltchev et al., only 45% of patients with acute SC ischemia had signal intensity changes on T2-weighed MR images performed on day 1 of the onset of clinical symptoms [8].

M.M. Thurnher et al. assessed MRI findings in 23 patients with SCI: MR signals on T2-weighted MR images were not visualized in 3–4 hours but were seen in 8 hours after the onset of clinical symptoms [23]. According to S. Weidauer et al., slight signal change on T2-weighted MR images can be seen as early as in 3 hours but significant signal change is seen only in 12–24 hours after the onset of clinical symptoms [24]. Based on these observations, the authors suggested that MRI should be performed not earlier than 12 hours from the onset of clinical signs of myelopathy or later, since the infarction lesion is best visible in the subacute stage of its development [11].

Thus, basic MRI sequences have low sensitivity at the onset of SCI, when the accuracy of the differential diagnosis of myelopathy is especially important and critical. On the other hand, low sensitivity of T2-weighted images at the onset of SCI (i. e. no signal enhancement from the lesion and the development of edema) can be itself a useful differential diagnostic sign [16, 24].

However, T2 signal hyperintensity and SC edema are non-specific findings that can be also seen in patients with myelitis of various origin. In this context, diffusion MRI sequences are of key relevance [6, 23, 24].

Diffusion-weighted imaging (DWI) sequence, which has a high sensitivity to cerebral cytotoxic edema, is widely used in angioneurology to determine the most acute stage of cerebral infarction [2, 25]. High sensitivity of DWI for acute ischemic processes in the brain has been demonstrated in multiple studies. Diffusion and perfusion MRI is an important investigational tool in the acute phase of ischemic stroke, as it may differentiate reversible brain tissue damage from irreversible [25].

Experience with DWI in patients with SCI is limited. This is mainly related to technical difficulty with DWI in the spinal

canal. Pulse sequences specifically designed for the spine and spinal cord are not commonly available and require optimization [23].

For DWI of the SC, single echoplanar imaging is used with a maximum b-factor of 600–1000 sec/mm^2 and a slice thickness of 3 mm. In SCI patients, apparent diffusion coefficient varied from 0.23 to 0.9 × 10^3 mm^2/s (Figure 1) [23].

None of the studies established the exact time frames for the manifestation of diffusion changes in the SC substance. According to different authors, the average time between the onset of clinical symptoms and signal change on DWI is 3 to 4 hours [26]. In a study by M.M. Thurnher et al. in 23 SCI patients, persistent hyperintensity of the SC ischemia lesion on DWI was reported when MR images were obtained between 2 and 9 days [23]. In a study in 11 patients by N. Yadav et al., diffusion limitation was not seen during imaging on day 17 to 21 from the onset of clinical symptoms [27]. Therefore, larger studies are needed to establish the temporal threshold for diffusion changes on MRI in patients with SCI.

There is no doubt that DWI-MRI can help in identifying SCI at early stage. However, despite the use of techniques to reduce spatial distortion and improve the quality of the images, some technical challenges persist for DWI of the SC [26].

Quality of echoplanar DWI is reduced due to susceptibility artifacts and those related to spine magnetic field, which may result in false positive results [28]. Throughout the long echo sequence, phase errors will accumulate, resulting in spatial inconsistency in the reconstructed image. The longer the echo sequence and the higher the resolution, the more pronounced the distortions will be, which will be also amplified due to differences in the susceptibility of various spinal tissues (bones, intervertebral discs, cerebrospinal fluid, etc.) [16, 27].

Susceptibility distortions around the SC can lead to “pile-up” artifacts (hyperintensities) that can mimic cord infarction [23, 29]. To maintain sensitivity to ischemia, it was proposed to use higher b-factor values (> 600) [28].

Due to possible false-positive DWI results, it is recommended to supplement subsequent control MR studies with standard sequences (T2-WI, T2-STIR) [11].

According to M.X. Wang et al., diffusion weighted images at the spinal level are preferred in sagittal planes, as this view allows for larger coverage, shorter acquisition time, and less artifact [12].

Key MR features of vascular myeolpathy

Due to small size of the SC, its lesions are relatively small and visually indistinguishable on MRI, which definitely complicates the differential diagnosis of myelopathies. However, for some demyelinating disorders (multiple sclerosis, neuromyelitis optica spectrum disorder, acute disseminated encephalomyelitis), systemic inflammatory disorders (sarcoidosis), dysmetabolic disorders (vitamin B12 deficiency) and other processes, specific MR patterns have been described, which, together with the clinical and laboratory findings, allow establishing the correct diagnosis [30–33]. Accuracy of imaging can be improved by considering MR patterns typical for the acute and subacute stages of vascular myelopathy of arterial or venous origin.

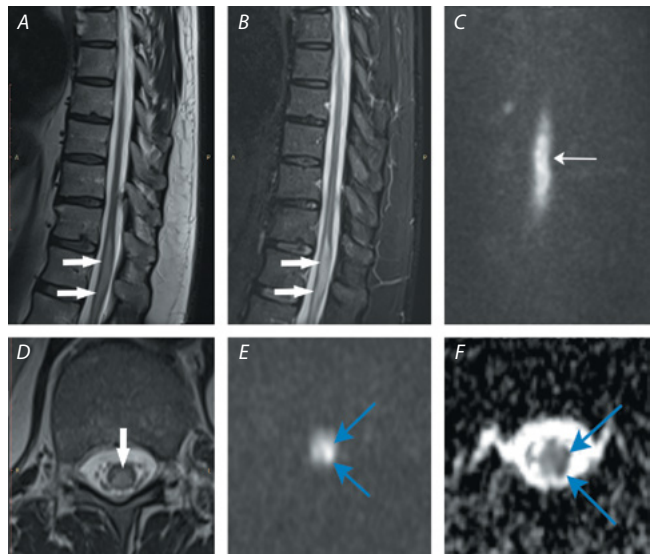

Fig. 1. MR image of patient P. with SC infarction at Th11–Th12.
A) T2-weighted image, sagittal plane: intramedullary hyperintense elongated lesion (white arrows) at Th11–Th12;
B) T2-STIR, sagittal plane: intramedullary hyperintense elongated lesion (white arrows) at Th11–Th12;
C) DWI, coronal plane: intramedullary hyperintense lesion of irregular shape at Th11–Th12 (white arrow), b = 800;
D) T2-weighted image, axial plane: hyperintense intramedullary lesion at Th11–Th12;
E) DWI, axial plane: intramedullary hyperintense lesion on the right at Th11–Th12 (blue arrows), b = 800;
F) DWI, axial plane, ADC map: diffusion restriction corresponding to the lesion on DWI (blue arrows), b = 800.

MR features of spinal cord arterial infarction

Arterial infarction of SC tends to occur in “watershed” areas where collateral circulation is poor, which is likely to explain delayed signal increase on T2-WI and T2-STIR in the acute phase of SCI [34]. However, a literature review demonstrated the lack of consensus on the most common location of such areas (lower cervical segments, middle, lower thoracic segments, conus medullaris).

Studies by A.A. Skoromets et al. [1], J. Novy et al. [18], S. Weidauer et al. [24, 31] illustrated various models (types) of arterial ischemia of the SC, which reflect the vascular territory involved: the area of the anterior spinal artery (ASA) limited by the anterior horns and adjacent white matter on

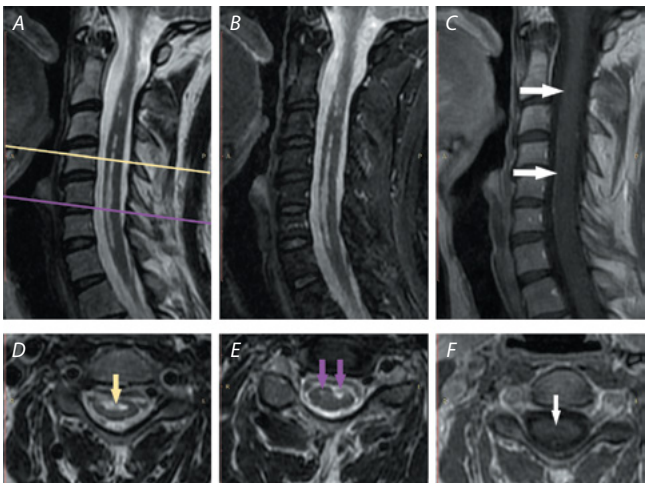

Fig. 2. MR image of patient A. with arterial infarction of spinal cord at C2–C3, C3–C7.
A) T2-weighed image, sagittal plane: multifocal intramedullary hyperintense elongated lesion at C2–C3, C3–C7; the light-yellow line indicates the section at C3 (*D*), the purple line indicates the slice at the C5–C6 intervertebral disc level (*E*);
B) T2-STIR, sagittal plane: intramedullary hyperintense elongated lesion (white arrows) at C2–C3, C3–C7;
C) T1-WI, sagittal plane: multifocal intramedullary hypointense elongated lesion at C2–C3, C3–C7 (white arrows);
D) T2-weighed image, axial plane: intramedullary hyperintense lesion at C3 occupying the gray matter area (hologrey phenomenon, light yellow arrow);
E) T2-weighed image, axial plane: intramedullary hyperintense lesions at the intervertebral disc at C5–C6 (snake eyes phenomenon, purple arrows);
F) T1-WI, axial plane: intramedullary hypointense lesion at C3 (white arrow).

both sides (anterior type); the area of the posterior spinal arteries limited by the posterior columns, adjacent areas of the lateral columns and part of the posterior horns (posterior type); rarer sulcocommissural, central and transverse types.

In some cases of reduced collateral blood supply to the SC, the ischemic lesion can involve only the gray matter of the anterior horns due to a greater sensitivity of motor neurons to anoxia and the presence of a "watershed" area between the pial and sulcocommissural arteries. Over time, this morphological pattern leads to a typical MRI pattern described as "owl eye" or "snake eye" appearance on axial T2-weighed images [27, 31]. On sagittal T2-weighed images, this hypointense lesion corresponds to a pin-like or pencil-like appearance and usually involves more than 2 spine segments (Figure 2) [19].

However, the "snake eye" appearance is not typical for SCI. Some other diseases that involve anterior horn motor neurons, such as motor neuron disease, spinal muscular atrophy [35], Hirayama disease [36], poliomyelitis and tick-borne encephalomyelitis, may also be associated with this MR sign [31–33].

It should be noted that the identification of specific MR patterns may have limitations in differential diagnosis, for example, with demyelinating lesions of the SC [34, 37]. In such cases, i. v. contrast enhanced brain MRI must be performed [24].

N.L. Zalewski et al. in their series of articles evaluated incidence of different MR patterns in 75 SCI patients [10, 17]. Signs of ischemia in the territory of the ASA with involvement of the anterior 2/3 of the SC and the "snake eye" or "pin" appearance was quite common (63–70% of cases). In almost half of the cases (46%), the hologrey phenomenon was observed on axial images, which corresponds to an increase in the T2 signal from the gray matter of the SC and, probably, reflects its greater vulnerability to hypoxia. Atypical T2-hyperintense anteromedial U- or V-shaped lesions were seen in 15–20% of cases. Lesions were often (68%) vertically extended (⩾ 3 vertebral segments), extending from the thoracic region to the conus and were accompanied by edema of the SC substance (25%). In some cases, a perifocal increase in T2-weighted signal from the ASA indicated the presence of a thrombus or slow blood flow [10, 17].

N. Yasuda et al. demonstrated different MR patterns depending on the location and extent of aortal surgery (thoracic/abdominal/aortic arch replacement) [38], thus showing the importance of neuroimaging monitoring in this population.

Besides medullary ones, we should note extramedullary MR signs of arterial ischemia of the SC, such as vertebral body infarction, which is manifested by abnormal high signal from the bone marrow on T2-weighed images. This phenomenon can be explained by proximal occlusion of the artery leading to the vertebral body, intervertebral disc, and spinal cord [26, 37, 39]. According to S. Weidauer, this MR sign can appear from 8 hours to several days or weeks after the onset of clinical symptoms [31]. Its prevalence ranges from 14% to 44%, and it is more common with lesions in the territory of the ASA [27].

MR features of spinal venous insufficiency

Spinal arteriovenous fistulas are the most common vascular malformations of the spine (70%). Among those, the most common are spinal dural arteriovenous fistulas (SDAVFs) of thoracolumbar localization, which account for 70–85% of cases with an annual incidence of 5–10 cases/1 million [32].

The fistula drains directly into the intradural radicular vein and then into the perimedullary venous plexus. Enlarged serpentine perimedullary veins ascend along the SC. Due to insufficient venous egress into the epidural plexus, venous congestion develops, followed by medullary edema, which later can lead to decreased arterial perfusion and subacute/chronic ischemia with very non-specific clinical manifestations such as gait disturbances (myelogenous intermittent claudication), "saddleback" hypoesthesia, pain in the lower extremities, and dysfunction of pelvic organs [1, 19, 40].

MR signs of SDAVF reflect the pathophysiological pattern of venous hypertension: key signs include swelling of the lower thoracic and caudal segments of the SC with hyperintensity on T2-WI and hypointensity on T1-WI together with tortuosity of the dilated perimedullary veins of the SC usually on its dorsal surface. These serpentine veins appear as linear areas of flow void phenomenon on T2-WI or contrast-enhancing structures on post-contrast T1-WI (Figure 3). In case of severe edema of the SC, the veins may not be visualized due to the mass effect [40]. Limited, often well-defined lesions with a hypointense rim due to hemosiderin deposits can also be detected, and they are characterized by a heterogeneous hyperintense intralesional signal depending on the stage of hemorrhage on T2-weighted images [31, 41].

N.L. Zalewski et al. demonstrated an additional MR pattern for SDAVF (termed the missing-piece sign), which is defined as an area of missing contrast enhancement in at least one or several SC segments amidst an intense area of contrast enhancement [42]. According to the authors, missing contrast enhancement in individual segments was likely to be related to the intact blood-cord barrier and better venous egress routes.

MR imaging of spinal cord vessels

Based on characteristics of the spinal cord ischemic lesion obtained using standard (T2, STIR) and diffusion MRI sequences, it should be considered whether the patient needs MR angiography of the CS.

In this context, selective spinal angiography (SSA) remains the diagnostic gold standard. SSA allows visualization of both normal angioarchitecture and various abnormalities of the arteries and veins of the SC. This method allows dynamic assessment of arterial inflows to the vascular myelopathy lesion, condition of the vessels directly in the lesion, and the features of the venous egress [1, 43, 44]. However, this invasive procedure can only be carried out in specialized centers by specialists in X-ray surgical diagnostics and treatment. Due to its technical difficulty and potential complications, the indication for SSA should be well considered and reserved for the cases where a vascular malformation is suspected (flow void phenomenon, i.e. a typical SC edema on T2, STIR), or secondly for preoperative imaging of the vascular anatomy or supply in cases of spinal or medullary tumors, or aortic disease [44].

Contrast spinal MR angiography (CMRA) can be an alternative option or a method preceding SSA that allows clarifying the origin, location, and volume of previously identified vascular change [45]. With comparable sensitivity to SSA, this method can be used for dynamic SC MR-angiography, including perioperative setting [44]. Angiodynamic analysis of the vascular myelopathy lesion is an advantage of CMRA. Dynamic CMRA is also useful in detecting dissection and thrombosis of large (aorta) and small (vertebral) arteries (Figure 4) [21, 45].

CMRA allows visualization of blood flow in the arterial, venous and delayed phases. Therefore, 3D and 4D CMRA is an effective technique for visualization of vascular malformations and arteriovenous fistulas, such as SDAVFs [45]. These sequences allow determining the exact location of the arteriovenous fistula, its interaction with other vascular structures, and the course of serpentine perimedullary vessels [33]. In a study by A. Lindenholz et al., CE-MRA correctly localized the SDAVF in 43 of the 53 cases (81%) [46].

In some cases, such as in patients with artificial pacemakers, other MR-incompatible devices, or severe claustrophobia, MRI cannot be performed for diagnostics of vascular myelopathy. These patients should have CT angiography of the aorta and its branches, which allows identifying atherosclerotic damage to the walls of the major vessels, the presence of local narrowings and dissections that impede the SC blood supply [12, 43, 44].

Promising approaches in MR imaging of vascular myelopathy

Analysis of intramedullary lesions is challenging if standard MR sequences are used. Determining the nature of myelopathy and distinguishing acute ischemic lesions from hyperacute and subacute ones remains challenging from the clinical and radiological points of view.

Use of ultra-high-field MRI scanners (⩾ 3 T) has an obvious advantage of more detailed imaging of small structures, which is especially valuable in visualization of the SC and its vessels for primary or preoperative diagnostics [20]. However, the choice of a 3 T MR scanner for SCI is controversial, as more detailed visualization of the lesion may be attenuated by the presence of the aforementioned “imaging barriers” [47].

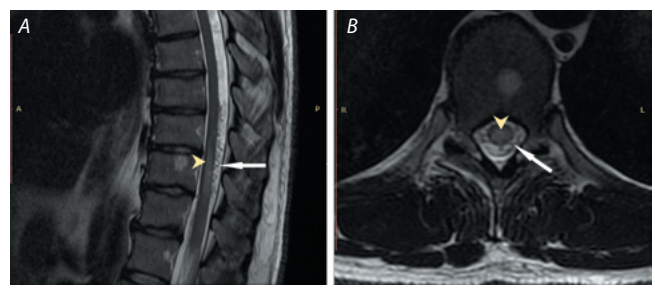

Fig. 3. MR image of patient V. with spinal venous insufficiency at Th9–Th11.
A) T2-WI, sagittal plane; *B)* T2-WI, axial plane: intramedullary hyperintense lesion of predominantly dorsal location at Th9–Th11 (light yellow arrow), hypointense dilated perimedullary vessels, mainly along the posterior surface of the SC at Th8–Th11 ("flow voids" phenomenon, white arrow).

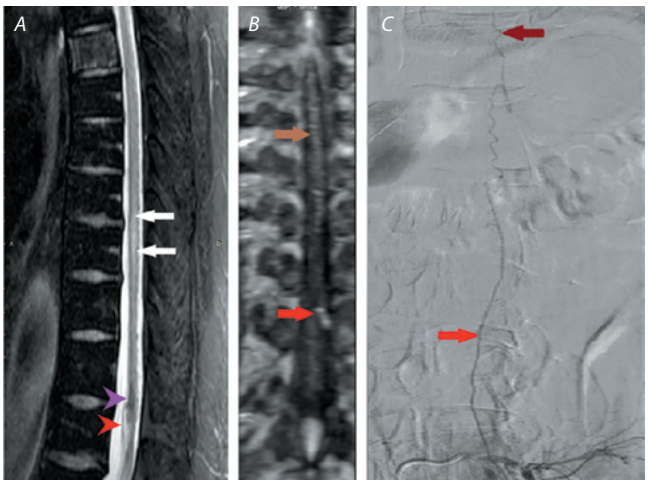

Fig. 4. MRI and angiography of patient S. with spinal venous insufficiency at Th8–Th10, Th11–Th12.
A) T2-SPAIR (SPectral Attenuated Inversion Recovery), sagittal plane: centromedullary hyperintense lesion at Th8–Th10 (white arrows), sharply hypointense lesion probably caused by hemosiderin deposition at Th11–Th12 (purple arrow), dilated straight vessel adjacent to the spinal cord conus (red arrow);
B) SMRA, coronal plane: under contrast enhancement along the entire posterior surface of the SC, a dilated convoluted vessel (brown arrow) is seen, into which the wide radicular vein flows from the left intervertebral foramen Th10–Th11 (red arrow);
C) selective spinal angiography of the left common lumbar artery (L4, L5): early arteriovenous discharge from the radiculospinal artery into the dilated vein of the cauda equina (red arrow) with contrasting of the spinal veins in the cranial direction (brown arrow).

Diffusion tensor imaging (DTI) is an additional sequence that can be performed at 1.5 and 3 T. This method allows non-invasive mapping of molecular diffusion in biological tissues. Similarly to DWI, DTI uses a b-factor range of 600–800 mm/sec, mainly because of the cranial-caudal direction of water molecule diffusion in the SC [21, 29, 48].

The relatively small transverse dimensions and elongated shape of the SC is a major diagnostic challenge for DTI in SCI imaging. The limited volume of fiber tracts naturally leads to the need for high spatial resolution [47].

The above-mentioned studies demonstrated the increasingly important diagnostic role of DTI owing to its ability to assess the white matter microstructural integrity via measurements of quantitative diffusion indices, such as cross-sectional area as an indicator of SC atrophy, fractional anisotropy to assess axonal integrity, magnetization transfer coefficient as an indicator of demyelination, and mean diffusion in the ischemic lesion and perifocal areas [49]. At 3T or higher field strengths, T2-weighted imaging of the SC provides high resolution and strong contrast between gray matter and white matter, allowing segmentation between these structures and calculation of their cross-sectional area (Figure 5) [50].

For the axial imaging of SC several authors suggested supplementing the MRI protocol with T2*-gradient recalled echo,

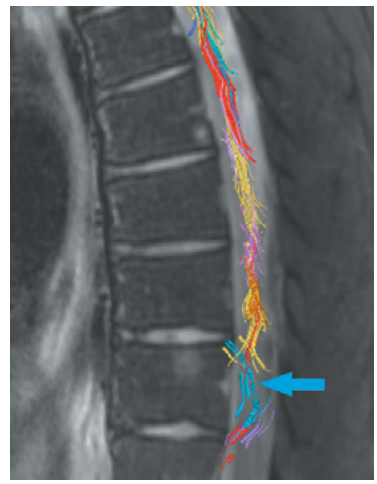

Fig. 5. 3D DTI color-coded tractography map of patient V. with spinal venous insufficiency at Th9–Th11.
Conducting fibers at Th9–Th11 are highlighted in blue, demonstrating abnormal spatial orientation of the fibers in the ischemic lesion (blue arrow), fractional anisotropy 0.46 ± 0.18, apparent diffusion coefficient 0.79 ± 0.15 × 10^3 mm^2/sec.

which has a high sensitivity to paramagnetic blood products (hemosiderin) [19].

Conclusion

Despite the lack of uniform diagnostic protocols, MRI is the method of choice for the diagnosis and differential diagnosis of vascular and other myelopathies. Diagnostic efficacy of MRI directly depends on spatial resolution and signal/noise ratio of the scanner.

Patterns described do not sufficiently increase the specificity of the radiological picture of the acute period of SC infarction, so the MR examination protocol should be elaborated. DWI is an additional sequence that allows establishing the ischemic nature of myelopathy. Average time to normalization of DWI signal is 2 to 3 weeks, which is essentially a "diagnostic window" for confirming/excluding the diagnosis and starting treatment.

If included in a comprehensive diagnostic protocol, dynamic angiographic methods, such as CMRA, allow visualization of thrombosis of the aorta and its large branches or SDAVF and other spinal arteriovenous fistulas, contributing to their early surgical correction.

Thus, the optimal technical protocol for MRI for 1.5 and 3 T scanners in patients with suspected arterial vascular myelopathy is the following [19, 21, 44]:
- Sagittal spin-echo T2-WI;
- Axial spin-echo T2-WI;
- Sagittal spin-echo T2 STIR;
- Sagittal and axial DWI (b = 600–800);
- Axial T2*-gradient recalled echo;

- Pre-contrast sagittal spin-echo T1-WI;
- 3D dynamic three-phase contrast CMRA;
- Post-contrast sagittal spin-echo T1-WI.

Slice thickness is 3 mm.

Differential diagnostic aspects of identifying vascular lesions necessitate comparison of sagittal and axial images of the SC. The advantage of the sagittal plane is greater coverage with shorter acquisition times. The axial plane allows visualizing the specific location of the lesion across the diameter of the SC and the symmetry of MR signal change in the case of ischemia in the territory of the ASA.

We should highlight the issue of introducing mandatory neuroimaging monitoring including diffusion and angiodynamic MR scanning modes, in particular, during surgery on the aorta. This approach seems to be extremely important, since it will allow timely preventive measures to be taken against potential myeloischemic disorders in this patient population.

Investigation of microstructural ischemic lesions of the SC with DTI is of great clinical interest. Assessing the integrity of the SC tracts under the influence of various causes of myeloischemia will facilitate the selection of an appropriate treatment. Additional studies to investigate capabilities of DTI with substantiated results will allow including this method in an expanded examination protocol.

In general, there are still many unresolved issues regarding the visualization of ischemic lesions of the SC. There are no generally accepted approaches and protocols for MRI diagnostics of vascular myelopathies, and differential diagnostics is challenging. The information presented in this review can be a guideline in routine clinical practice and a basis for further research and development of a unified approach to diagnosing vascular myelopathy in Russia.

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Deep Brain Stimulation Withdrawal Syndrome, a Rare Life-Threatening Condition in Neurology and Neurosurgery

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Abstract

The article addresses an acute condition associated with an abrupt cessation of neurostimulation of deep brain structures, which is manifested by acute hypokinesia and rigidity with further development of akinesia, anarthria and dysphagia. This may result in the need for emergency hospitalization and admission to an intensive care unit. The article presents literature review and clinical case reports. We discuss causes and approaches to the prevention and management of acute decompensation in patients with Parkinson's disease associated with abrupt deep brain stimulation cessation.

Keywords: *neurostimulation of deep brain structures; Parkinson's disease; akinesia; parkinsonian hyperpyrexia syndrome; malignant neuroleptic syndrome; withdrawal syndrome; deep brain stimulation*

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Синдром отмены нейростимуляции у пациентов с болезнью Паркинсона – редкое неотложное состояние в неврологии и нейрохирургии

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Аннотация

Статья посвящена острому состоянию, связанному с внезапным прекращением стимуляции глубоких структур головного мозга, которое проявляется резким нарастанием гипокинезии и ригидности с развитием обездвиженности, анартрии и нарушений глотания, в результате чего пациенты могут быть экстренно госпитализированы, в том числе в отделение реанимации. Представлены обзор литературы и клинические наблюдения. Обсуждаются причины, пути профилактики и способы коррекции острой декомпенсации состояния у пациентов с болезнью Паркинсона, связанной с внезапным прекращением глубокой стимуляции мозга.

Ключевые слова: *нейростимуляция глубоких структур головного мозга; болезнь Паркинсона; акинетический криз; синдром паркинсонизма-гиперпирексии; злокачественный нейролептический синдром; синдром отмены; deep brain stimulation*

Этическое утверждение. Исследование проводилось при добровольном информированном согласии пациентов.

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

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Introduction

The deep brain stimulation (DBS) technique has a long history of success in treating complications of long-term dopamine replacement therapy (DRT) and tremor in patients with Parkinson's disease (PD) [1].

Patients with advanced PD may develop acute worsening of the condition with rapidly progressing hypokinesia and rigidity, immobility, anarthria, dysphagia (akinetic crisis, acute akinesia), in some cases accompanied by hyperthermia (akinetic-hyperthermic syndrome, parkinsonian hyperpyrexia syndrome). The main cause is errors in antiparkinsonian medication regimen. Dopamine receptor-blocking agents, gastrointestinal diseases, COVID-19, hospitalization due to exacerbation of concomitant diseases, traumas, surgery, especially accompanied by electrolyte disorders, can also cause decompensation in PD patients [2, 3].

Acute decompensation associated with withdrawal or excessively reduced doses of antiparkinsonian agents, perioperatively or during selection of the primary neurostimulation options, was described in patients who underwent DBS surgery [4–9]. At the same time, effective DBS without reducing high doses of antiparkinsonian agents can also be accompanied by decompensation triggered by abrupt tapering or stopping dopaminergic agents [10, 11].

However, with an increasing number of operated patients worldwide, the main challenge is acute DBS discontinuation, which can be potentially life-threatening [12]. The first two clinical case reports of unintentional unilateral DBS hardware turn-off resulted in severe parkinsonism syndrome close to akinesia were presented by M.I. Hariz et al. in 2001 [13]. Already with their first experience in DBS technique, the authors noticed that abrupt withdrawal of effective stimulation of subthalamic nucleus (STN-DBS) resulted in an emergency requiring immediate hospitalization of the patient. Subsequently, a number of clinical case reports on various causes of implantable pulse generator (IPG) failure have been published.

Discontinuation of effective DBS, as well as withdrawal of antiparkinsonian medication, will always cause an increase in the severity of motor impairment in PD patients, but it does not always cause severe DBS withdrawal syndrome (DBS-WDS).

DBS-WDS is regarded as a rare condition, although there is currently no data available regarding its actual incidence. S. Reuter et al. report the following data: 8 cases of DBS-WDS per 434 DBS implantations between 1999 and 2014 and 216 IPG changes between 2008 and 2015 [14]. M. Anheim et al. observed 10 clinical cases over the period of 13 years, in which patients exhibited severe worsening in PD symptoms following the IPG battery depletion [15]. K. Fakhar et al. reported symptom improvement in 38 patients from a cohort of 320 patients (including 131 patients with PD) who underwent IPG battery replacement between 2002 and 2012 [16]. A.K. Helmers et al. presented results for 6 patients with a high risk of DBS-WDS who were followed up over a period of 2017–2020 [17].

Some studies used stimulation OFF mode (STIM OFF) on purpose to evaluate the results of PD treatment in patients with DBS, but it did not lead to severe decompensation.[18] In one of the key studies, M. Fabbri et al. analyzed the effects of STN-DBS in patients with late-stage PD (Hoehn Yahr score $\geqslant 4$ and Schwab and England score $< 50\%$) [19]. The DBS was switched off with subsequent assessment of the motor impairment severity. Most of the patients did not experience serious adverse events, but the DBS response was significant in 80% of patients; 5% could not tolerate the DBS OFF mode for more than 10 min because of the pronounced discomfort and worsening of parkinsonism. In 4 (11%) patients, stimulation was switched

back on because of delayed worsening of their condition (up to 10 days). In total, 92% of patients show a meaningful response to STN-DBS and only 3 (8%) patients remained with STIM OFF with no symptoms of DBS-WDS [20].

We searched the PubMed database for "parkinsonism-hyperpyrexia syndrome after DBS", "neuroleptic malignant syndrome after DBS", and "deep brain stimulation withdrawal syndrome". We then selected articles that provided comprehensive clinical observations of severe decompensation following the abrupt cessation of neurostimulation, necessitating hospitalization and intensive care [11, 14, 21–32]. Fourteen articles describing 27 clinical cases are presented in Table 1.

In the majority of the described clinical cases, this condition was caused by IPG battery depletion, infection in the area

Table 1. Published cases of severe DBS withdrawal syndrome (WDS)

No.	Author, year	Age, years	PD duration/DBS duration, years	Reasons for stimulation discontinuation	Hyperthermia/ hyperpyrexia	Reimplantation	Outcome
1	K. Chou et al., 2004 [21]	63	17/4	Depletion of IPG on one side	No	Yes	Alive
		76	17/3		No	Yes	Alive
2	T. Kadowaki et al., 2011 [22]	60	11/2	Switch-off of the stimulator due to mental disorders	Yes	IPG was not removed, low-frequency mode	Alive
3	J. Neuneier et al., 2013 [23]	77	18/5	Depletion of IPG	Yes	Yes	Died
4	S. Hocker et al., 2013 [24]	74	–/4	Switch-off of the stimulator	Yes	No	Alive
5	C.A. Artusi et al., 2015 [25]	63	18/5	Depletion of IPG	Yes	Yes	Alive
6	S. Reuter et al., 2015 [26]	52	20/8	IPG removal due to infection	No	Yes	Alive
		74	24/10		No	Нет I No	Died
		75	19/9		Yes	Нет I No	Died
7	R. Rajan et al., 2016 [27]	51	18 /7	Depletion of IPG	Yes	Yes	Alive
		54	22 /11		No	Yes	Alive
8	C.J. Liu et al. 2017 [28]	69	12/3	Depletion of IPG	Yes	Yes	Alive
9	S. Reuter et al., 2018 [14]	77	19/4	IPG removal due to infection	No	Yes, in 23 days (range 3–45 days)	Alive
		62	26/13		No		Alive
		71	37/15		No		Alive
		68	23/10		No		Alive
		67	18/15		No		Alive
10	J. Azar et al., 2019 [29]	67	23/7	Depletion of IPG	Yes	Yes	Alive
11	W.A. Kamel et al., 2019 [30]	73	21/12	Depletion of IPG	No	Yes	Alive
12	V. Holla et al., 2020 [31]	67	17/4	Depletion of IPG	No	Yes	Alive
		60	17/4		No	Yes	Alive
13	J. Azar et al., 2022 [11]	76	14/9	Depletion of IPG	Yes	Yes	Alive
14	S. Grimaldi et al., 2023 [32]	71	24/12	Depletion of IPG	No	Yes	Alive
		68	20/3	Depletion of IPG	No	Yes	Alive
		64	26/15	Depletion of IPG	No	Yes	Alive
		71	25/20	IPG removal due to infection	No	Yes, in 80 days	Alive
		54	24/16	Depletion of IPG	No	Yes	Alive

Table 2. Characteristics of patients with severe DBS WDS (own data)

No.	Age, years; sex	Duration of PD/duration of DBS, years	DBS target	LED before DBS/ LED DBS, mg	Hyperthermia/ hyperpyrexia	Reimplantation	Outcome
1	56; male	19/8	STN	2450/1750	Yes	Yes	Died
2	60; male	22/3	GPi	1700/1050	No	Yes	Alive
3	63; male	19/7	(DBS in other center)	No data available	Yes	No	Died
4	65; female	13/5	STN	5450/950	Yes	No	Died
5	67; female	17/4,5	STN	850/850	Yes	No	Died
6	63; male	17/4	STN	1250/525	No data available	No	Died

Note. LED — levodopa equivalent dose.

of DBS hardware that required removal of its components, and accidental turn off of the neurostimulator. In all of the described clinical cases, the patients were treated with STN-DBS. With the advent of rechargeable neurostimulation systems, DBS-WDS can also be caused by untimely IPG battery charging or malfunction of the charger.

In this article, we report 6 clinical cases of PD patients with severe DBS-WDS accompanied by impaired vital functions with various outcomes. The general characteristics of the patients are presented in Table 2. In all of these cases, WDS was triggered by IPG battery depletion.

Outpatient cases of neurostimulation discontinuation with growing severity of parkinsonism syndrome without vital disorders were observed significantly more often. These cases were caused by accidental turn off of the neurostimulator by the patient or caregiver, depletion of IPG battery, malfunction of the charger causing IPG battery drain, or DBS hardware infection with subsequent removal of the neurostimulator. In most cases, short-term or long-term DBS discontinuation caused no vital disorders and was not included into this study.

Only two patients with acute DBS-WDS were treated in the Burdenko National Medical Research Center for Neurosurgery. They underwent urgent IPG replacement (clinical cases 1 and 2). One patient (clinical case 3) was followed up by the specialists of the Neurology Department at the Russian Medical Academy of Continuous Professional Education. The patient was admitted to the Botkin State Clinical Hospital, and the DBS hardware was implanted in another medical facility. These 3 clinical cases are described below.

Clinical case 1

Patient aged 56 years had been suffering from PD for 19 years. He had been receiving levodopa for 13 years. Eight years after the treatment initiation, at the peak of levodopa action, violent movements appeared, which were accompanied by a gradual decrease in the time of drug action. Further, during 2 years at the start of levodopa action, the patient had painful leg dystonia and trunk muscle pain in the OFF-period. Eleven years after the onset of motor disorders, a bilateral STN-DBS system was implanted at the Burdenko National Medical Research Center for Neurosurgery. With the start of neurostimulation, a significant decrease in the severity of parkinsonism syndrome was observed throughout the entire follow-up period. After 4.5 years, the first scheduled IPG replacement was performed.

The patient was admitted to the Burdenko National Medical Center of Neurosurgery on an emergency basis. As reported by the patient's wife, the patient's motor status, speech disorders (dysarthria), dysphagia, and consciousness decline occurred within two days of complete discharge and turning off the neurostimulator. Additionally, the patient exhibited hyperthermia. Due to dysphagia, the patient practically did not take any water, food or antiparkinsonian drugs.

With acute akinesia symptoms, the patient was admitted to an intensive care unit (ICU). Levodopa/carbidopa administration via nasogastric tube was initiated at a dosage of 250/50 mg every 4 hours (6 times per day). Due to an emergency, the subcutaneous pulse generator was replaced on the admission day. The DBS was set with the previous parameters. Further, despite infusion of antibacterial agents, inotropic support, and resumed DBS, the symptoms of consciousness decline and motor disorders persisted. Rhabdomyolysis with rhabdomyolysis-induced acute kidney injury, secondary somatic (bilateral pneumonia, urinary tract infection, sepsis) and neurological (hypoxic encephalopathy) complications were diagnosed. Brain MRI revealed multiple new ischemic foci in the deep parts of the cerebral hemispheres. Once the patient's condition had stabilized on day 44 of the treatment, he was referred for further therapy and rehabilitation to the hospital at the place of residence, where he died within a month.

Clinical case 2

Patient aged 60 years has been ill for 22 years. PD was diagnosed five years after the onset of motor disorders (tremor) and a treatment was prescribed. Five years after the PD diagnosis, levodopa was introduced as an additional treatment. The levodopa wearing-off was associated with the gradual progression of motor fluctuations and dyskinesia, and further

with patient's falls. 14 years after the diagnosis was established, bilateral implantation of DBS system in the internal segment of the globus pallidus (GPi) resulted in motor symptom improvement and a decrease in motor fluctuations and dyskinesia. Walking disorders with propulsive gait and rare falls remained.

After 3 years of effective GPi neurostimulation, an acute increase in the severity of parkinsonism syndrome, pronounced stiffness, immobility, speech and swallowing disorders were noted. The patient was admitted to a city hospital, then transferred to an ICU, where IPG battery depletion and cessation of stimulation were detected. Levodopa/carbidopa administration via nasogastric tube at a dosage of 250/50 mg every 3 hours was initiated.

The patient was transferred to the Burdenko National Medical Center of Neurosurgery on day 5 after cessation of neurostimulation. On the day of admission the subcutaneous IPG was replaced. As neurostimulation was resumed, the severity of bradykinesia decreased, motor activity and speech improved, independent swallowing/feeding restored. On the following day, the patient was placed in a vertical position. Two days later, his motor activity returned to normal, and antiparkinsonian medication was restarted at the previously administered doses. The patient was discharged on day 6 in satisfactory condition with full recovery of neurological status and daily activity.

Clinical case 3

Patient aged 63 years, duration of PD 19 years. Motor fluctuations and drug-induced dyskinesia gradually progressed. 11 years after the disease onset bilateral STN-DBS system was implanted with positive effect. Further, according to the relatives, the patient neither consulted neurologists, nor came for correction of neurostimulation parameters, nor controlled the IPG battery charge level. However, he constantly took antiparkinsonian agents (levodopa/carbidopa at the dose of 250/50 mg, 1/2 tablets 5 times a day).

The patient was admitted to the intensive care unit (ICU) of Botkin State Clinical Hospital three days after the stimulator was turned off. At the time of admission, the patient was in a severe condition, presenting with hyperthermia, immobility, and dysphagia. Despite the administration of therapeutic measures, the patient continued to experience hyperthermia. Additionally, the patient developed acute renal failure, and four days after admission, the patient died from multi-organ failure. Due to the extremely severe condition of the patient, IPG replacement was not considered.

Clinical cases 4–6

Three patients were treated at their place of residence, and their data were obtained from their relatives. Two of them died in the acute period of DBS-WDS (clinical cases 4 and 5).

In patient 5, rechargeable neurostimulator failure occurred 4.5 years after surgery. The cause of the malfunction remained unidentified. The patient died on day 3 after admission to the hospital at her place of residence.

Patient 6 was admitted to an ICU at his place of residence. He survived the acute period. After a long period of conservative treatment, the patient was discharged with severe motor and cognitive impairment. The relatives refused to replace the IPG. Much later, the patient died at the place of residence in a state of severe disability.

In case of acute parkinsonism in a patient with DBS, other predisposing factors and triggers must be ruled out!

Dopamine replacement therapy-induced acute parkinsonism

- **Termination/change of DBS**
- **Therapy tapering (dose reduction) or abrupt discontinuation:**
  - suboptimal treatment adherence;
  - mental disorders (mental confusion, hallucinations);
  - severe dyskinesia;
  - post-operative period
- **Malabsorption:**
  - gastrointestinal disorders (severe constipation, intestinal obstruction)
- **Additional therapy with dopamine blockers (haloperidol, pimozide, sulpiride, etc.)**

Not related to dopamine replacement therapy

- Aggravating factors;
- Infection;
- Trauma;
- Subdural haematoma (if the condition worsening is preceded by a fall);
- Stress;
- Dehydration;
- Excessively hot weather

Fig. 1. Factors leading to acute decompensation in Parkinson's disease patients receiving DBS.

Discussion

Despite the fact that DBS technique has a long history of use in PD patients, including in Russia, the conditions associated with abrupt DBS discontinuation remain poorly defined. Thus, DBS-WDS is an emergency condition arising from abrupt neurostimulation turn off and characterized by acute hypo/akinesia, rigidity and/or tremor, accompanied by levodopa wearing-off phenomenon. The main causes of DBS-WDS are IPG battery depletion or rechargeable battery drain, accidental turn off, hardware failure, or infection in the implantation area. They all require DBS system removal (Figure 1) [11].

Provisional scale of DBS-WDS severity: severe (inpatient) – antiparkinsonian therapy ineffective, severe decompensation, dysphagia requiring nasogastric feeding, life-threatening complications requiring hospitalization; moderate (outpatient) – only motor and non-motor parkinsonism worsening without hyperpyrexia, immobility and vital disorders.

Clinical manifestations of severe DBS-WDS include acute rigidity with or without tremor, accompanied by severe akinesia [11, 14, 21–32]. In most cases, this occurs within 1 day after DBS cessation. The most frequent symptom of severe DBS-WDS is dysphagia, which leads to difficulty taking liquids and levodopa. Further, there is a change in mental status (from arousal and mental confusion to stupor) with concurrent development of autonomic symptoms (tachypnea, tachycardia, blood pressure fluctuations, increased sweating, pallor, and urinary incontinence/retention). In some patients, hyperthermia (hyperpyrexia) may be observed over the next few days, probably indicating a more severe course of decompensation. Blood tests in hyperpyrexia reveal leukocytosis, which may lead to misdiagnosis of septicemia. In this case, elevated creatinine kinase levels ranging from 260 to 50,000 U/L may be indicative of rhabdomyolysis [28].

Main characteristics of DBS-WDS:
- DBS-WDS in PD patients is a rare condition caused by abrupt cessation of neurostimulation;
- cessation of stimulation may be due to IPG battery depletion, accidental turn off, DBS hardware failure, or infection in the implantation area;
- abrupt cessation of stimulation does not always lead to DBS-WDS, but always causes worsening of parkinsonism symptoms;
- patients with a disease duration > 15 years and a long period of neurostimulation (> 5 years), elderly patients are at risk;
- hypothetically, DBS-WDS has a different pathogenetic mechanism compared to withdrawal of dopaminergic agents;
- DBS cannot be adequately replaced by DRT, even at the highest doses;
- intensified DRT should be considered as a temporary solution;
- early replacement of the neurostimulator improves clinical outcomes and should be considered as a first-line therapy to prevent lethal outcomes.

Typically, patients develop a medication-refractory akinetic state. A UPDRS motor score decrease is more than 2-fold [11, 14, 21–32]. Despite a significant increase in the levodopa equivalent dose in some patients (10-fold or more, average LED up to 3,200 mg/day), no adequate response to therapy was observed.[14] Thus, DBS withdrawal after long-term stimulation is not fully compensated by DRT, even at high doses [12, 29]. Even intrajejunal administration of levodopa/carbidopa-intestinal gel and subcutaneous administration of apomorphine fail to compensate DBS withdrawal [14, 32]. The reason for this remains unclear.

Complications of DBS-WDS include aspiration pneumonia, rhabdomyolysis-induced acute renal failure, disseminated intravascular coagulation, and venous thromboembolism. The differential diagnosis can be challenging. CJ. Liu et al. reported a clinical case of a patient with a 12-year PD duration, who developed DBS-WDS during the preparation period for routine IPG replacement [28]. The surgery was postponed due to hyperthermia and suspected sepsis. Only after significant worsening of clinical symptoms and despite the administration of broad-spectrum antibiotics, the source of sepsis could not be identified and then DBS-WDS was suspected. Treatment with dantrolene and bromocriptine along with intensive supportive therapy were started, and the dose of dopaminergic agents was increased. The conservative treatment proved ineffective, so the IPG was replaced, which led to regression of hyperthermia.

The outcome prediction in DBS-WDS treatment is complex. Severe DBS-WDS without IPG reimplantation has a high mortality rate. The only efficient treatment option is urgent IPG replacement and restoration of stimulation. In most cases, early IPG reimplantation allows preventing decompensation even in the presence of hyperpyrexia. If the patient survives, recovery may take from a few days to weeks to months. S. Reuters et al. reported that 3 of 4 patients recovered the initial motor level, which they had weeks or months prior to IPG explantation. Nevertheless, one year later, a decrease in daily activities was noted, which could be caused either by prolonged recovery or by disease progression [14]. Even with the earliest possible reimplantation, DBS-WDS treatment may be inhibited by extremely severe condition of the patient due to secondary complications (ischemic brain damage), as described in our clinical case 1.

Risk factors for the severe DBS-WDS are a long-standing PD (> 15 years) and a long-term STN stimulation (> 5 years). Additional risk factors may include advanced age, severe

motor impairment prior to DBS, and progression of disease symptoms since the initial surgery [11, 14, 32].

The exact mechanism of DBS-WDS is yet to be determined. A growing pool of evidence points to an acute neurotransmitter imbalance in the hypothalamus, the nigrostriatal system, and the mesocortical dopaminergic system [26]. Some authors believe that poor response to receptor stimulation by levodopa in patients with advanced PD along with motor improvement after restoration of neurostimulation are suggestive of possible different mechanisms of action in the nigral pathways for the DBS versus oral dopaminergics. Such observations imply possible neuroprotective effect of DBS, which is yet to be confirmed [29].

The mechanism of action of levodopa is aimed at restoring impaired dopaminergic transmission in the nigrostriatal system, while DBS specifically inhibits transmission of electrical signals by hyperactive STN. Electrical stimulation of STN affects cortical activity either by inhibiting activity of indirect pathway or via the hyperdirect pathway of the basal ganglia [33–35]. P. Zsigmond et al. suggested that STN-DBS may indirectly increase dopamine release in the putamen by affecting the pars compacta in the substantia nigra, subsequently reducing the need for levodopa in PD patients receiving neurostimulation [36].

Nowadays, functional MRI (fMRI) studies evaluating the effects of STN-DBS and levodopa, demonstrate modulatory effects of levodopa on brain activity in the putamen during certain motor tests. These effects were not observed in patients receiving DBS [37]. Resting-state fMRI data confirm that modulatory effects of levodopa and STN-DBS on brain connectivity are different. Levodopa increases dopamine availability thereby inducing broad changes in functional brain connectivity both within and outside the motor network [38]. This effect has been confirmed even in healthy volunteers [39]. As to STN-DBS, a simple model was first proposed in which STN inhibition by electrical stimulation leads to a decrease in glutamatergic transmission, supporting activity of the direct pathway of the basal ganglia [40]. More recent studies have shown that the effects of STN-DBS are mediated by complex modulation of brain networks, for example, via antidromic activation of input structures. We have described these mechanisms in detail previously [41].

In any case, poor response to high doses of dopaminergic agents in PD patients after discontinuation of chronic DBS remains an enigma. Could it be caused by postsynaptic changes in dopamine receptor affinity in striatal neurons and degeneration of striatal dendrites with loss of dopaminergic synapses? Understanding the observed changes may be important to improve the results of DBS treatment and to learn more about the pathophysiology of PD. The precise mechanism by which DBS affects neurotransmission in the brain is yet to be elucidated.

Diagnostic algorithm for patients with suspected DBS-WDS is presented in Figure 2. It is important to acknowledge that due to the rarity of DBS-WDS, there is a dearth of vigilance among intensive care physicians and neurologists in diagnosing this condition.

Approaches to DBS withdrawal syndrome therapy

There is a lack of consensus as to whether acute DBS-WDS is the same condition as acute akinesia in PD. Nevertheless, given the similar clinical presentation, it is reasonable to assume that DBS-WDS in PD patients should probably be treated in the same way as akinesia or akinetic-hyperthermic (malignant) syndrome.

According to the literature, the main agents to treat DBS-WDS are dopaminergic agents: levodopa, dopamine receptor agonists – pramipexol, transdermal rotigotine, ropinirole, as well as bromocriptine (7.5–15.0 mg/day), amantadine orally and intravenously, subcutaneous infusions of apomorphine (not available in Russia), methylprednisolone intravenously (1 g), dantrolene sodium (2–3 mg/kg per day intravenously) [42, 43].

Dantrolene is a skeletal muscle relaxant, its mechanism of action is associated with inhibition of intracellular calcium release from sarcoplasm. It is effective in treatment of malignant hyperthermia [44]. Dantrolene can reduce rigidity in individual patients, so it might be used in patients with DBS-WDS accompanied by hyperpyrexia.

Bromocriptine (5–10 mg 3 times a day) is also traditionally recommended for the treatment of acute akinesia, although there are no studies demonstrating its efficacy. However, according to recent publications, bromocriptine has still been prescribed despite the fact that newer non-ergoline dopamine receptor agonists with less side effects are now available. It remains unclear whether a newer generation dopamine receptor agonist or bromocriptine should be preferred [44, 45].

In some cases, patients received parenteral amantadine sulfate (PK-Merz) at a dose of 200 mg (500 mL) 2–3 times daily for 5–14 days. Amantadine sulfate is a blocker of NMDA-type of glutamate receptors, and also exhibits additional dopaminergic effects. These include stimulation of dopamine synthesis in nigral neurons; enhanced release of dopamine (and other monoamine) vesicles into the synaptic cleft and inhibited dopamine reuptake by presynaptic terminals; increase in dopaminergic receptor sensitivity to the neurotransmitter; mild cholinolytic effect [2, 45, 46]. Prior to prescribing amantadine sulfate, it is necessary to assess creatinine, urea levels, and renal function. Amantadine sulfate is contraindicated for patients with acute renal failure.

Hydration, body temperature control, and respiratory support in the ICU should be carried out in a due manner. Undoubtedly,

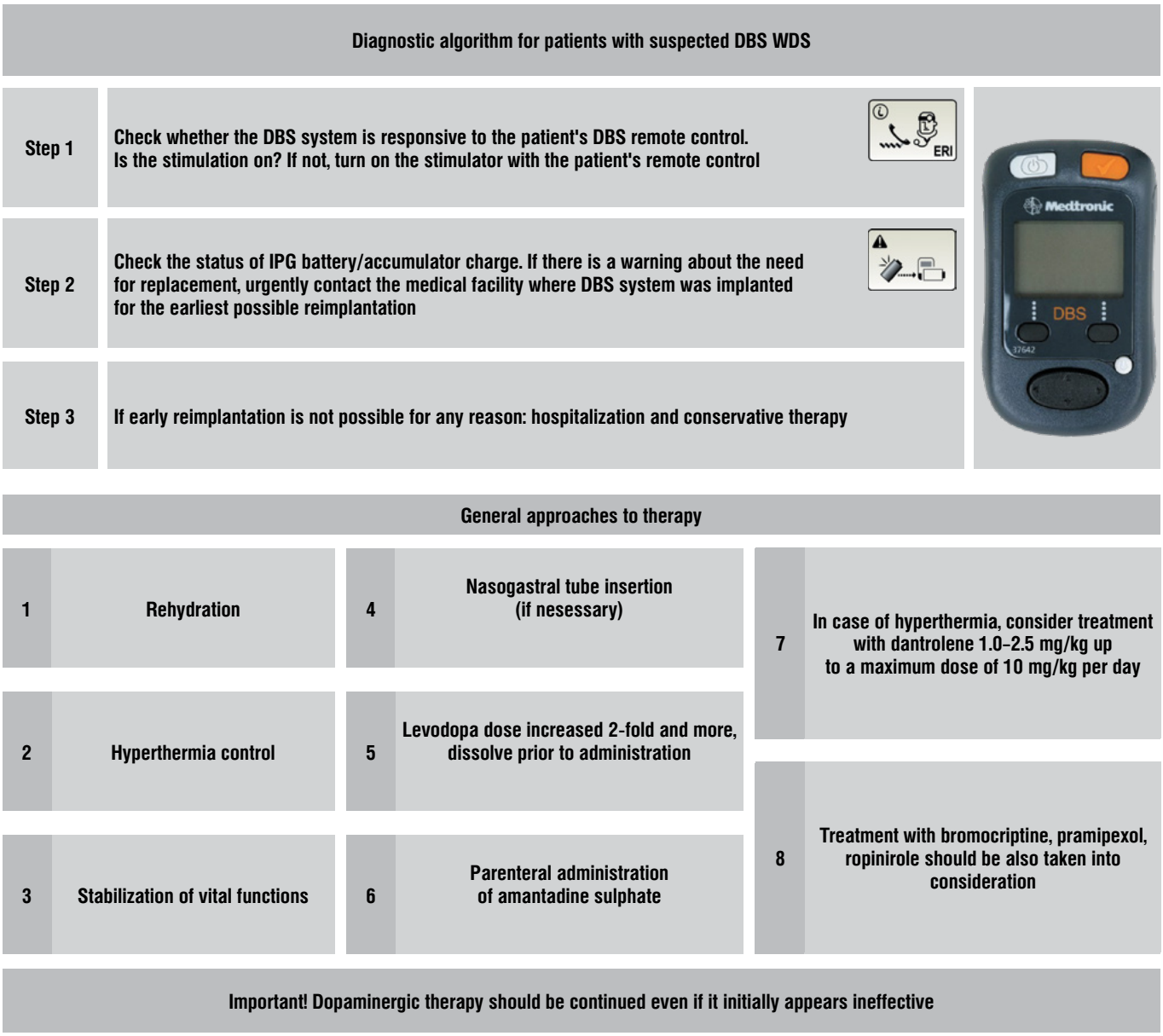

Fig. 2. Diagnostic algorithm for patients with suspected DBS WDS.

reintroduction of agents containing levodopa, which the patient took in the past (if they were withdrawn due to DBS), or the agent dose augmentation is of paramount importance. It is necessary to resume dopaminergic therapy in increased doses (2-fold or more) as early as possible, regardless of the clinical response (a proper response may develop only 7–11 days later or not develop at all) [2].

Nevertheless, in most of the described cases, only early IPG reimplantation promptly reversed akinesia and autonomic instability in patients, which was not achieved with pharmacotherapy. A number of authors believe that dopaminergic therapy during [post-implantation] week 1 may contribute to the favorable outcome [14]. A.K. Helmers et al. suggested that in patients with expected delay in neurostimulation restoration, such pharmacological support can be considered as extreme [17].

When DBS cessation was a result of infections in the IPG area, treatment traditionally includes antibiotic therapy, sanitation of the infection site, and removal of the infected implant with subsequent reimplantation or destructive surgery on deep brain structures. The incidence of such infections is about 2% after primary implantation and ranges from 0.7% to 6% after IPG replacements. In the majority of cases, the infection rate grows with the number of previous IPG replacement procedures, which adds to the benefits of rechargeable neurostimulation systems [47–49]. In this case, a gradual decrease in DBS level and levodopa dose

augmentation prior to neurostimulator removal should prevent the DBS-WDS.

Although early reimplantation would be a logical option, it is often delayed due to the current standards for reimplantation of implantable systems after bacterial infections. Even though the time between explantation and reimplantation is not standardized, reported periods range from 6 weeks to 6 months. It is believed that once the infection is cleared, IPG can be safely reimplanted after 2–3 months [47, 50, 51]. However, if the patient is at high risk of developing DBS-WDS, the infected IPG and extensions can be removed, and a new IPG and extensions on the contralateral side can be implanted during the same surgery with appropriate antibiotic support [14, 17]. For patients with high energy-consuming DBS settings requiring frequent IPG replacement, a switch to rechargeable stimulators is recommended [47, 52].

In the literature, DBS-WDS is described predominantly in patients with STN stimulation. It is assumed that GPi stimulation may be a safer option, because doses of dopaminergic agents for GPi stimulation usually remain high and more stable, in contrast to a significant dose decrease with STN stimulation. At the same time, we presented a clinical case of DBS-WDS in a patient with GPi stimulation (clinical case 2), which suggests the possibility of DBS-WDS development in such patients as well.

Conclusion

Thus, according to the Guidelines on Subthalamic Nucleus and Globus Pallidus Internus Deep Brain Stimulation for the Treatment of Patients with Parkinson's Disease published in 2018, the IPG expiration can be considered a movement disorder emergency [53]. IPG battery drain, accidental turn off, or removal of infected IPGs rapidly worsen parkinsonian symptoms and may cause life-threatening DBS-WDS similar to acute akinesia and hyperthermia. Delayed replacement of subcutaneous IPG should be minimized to avoid potential complications associated with abrupt DBS cessation. If immediate IPG replacement is not possible, the use of intestinal levodopa/carbidopa gel or apomorphine infusion (not available in Russia) may be considered as adjuvant therapy.

Physicians should remain alert to the development of DBS-WDS in high-risk PD patients (long-standing PD, long-term DBS, elderly patients). In these patients, thorough monitoring of battery level is required. The urgent IPG replacement or hardware troubleshooting, especially in high-risk patients, should be the first priority for neurosurgical centers dealing with DBS.

In Russia, IPG replacement is included in Section II of the List of types of high-tech medical care, but not included in the Basic program of compulsory medical insurance. Therefore, urgent IPG replacement in critical situations is challenging. This is why it is advisable to include subcutaneous IPG replacement into the Basic program of compulsory medical insurance (Section I of the List of types of high-tech medical care), in order to increase the availability of this type of medical care, taking into account that rare but potentially dangerous DBS withdrawal syndrome can lead to patient's death.

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Clinical Case of Atypical Botulism with Pseudointernuclear Ophthalmoplegia Syndrome

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Abstract

Botulism is a rare cause of bulbar and oculomotor syndromes. A late diagnosis and, therefore, late initiation of specific therapy may lead to multiple life-threatening complications. Epidemiological history and clinical findings are key to the correct diagnosis, but if these data are not available due to atypical clinical findings, botulism identification is challenging.

In our clinical case, a 31-year-old man was admitted to the hospital with double vision, impaired eye movements, and difficulty swallowing rapidly developing for 2 days. Ocular motility dysfunction included disturbed conjugate eye movements. In young patients, this is most often caused by demyelinating disease with medial (posterior) longitudinal fasciculus damage and symmetrical bilateral ptosis. The patient denied eating foods that could cause botulism and did not have any gastrointestinal symptoms. Differential diagnoses included demyelinating disease onset and Miller–Fisher syndrome. The next morning, completely identical clinical signs appeared in the patient's mother who had eaten canned mushrooms, so botulism was suspected. Over the next few hours, despite the administration of anti-botulinum serum, acute respiratory failure developed, and the patient was placed on a ventilator for 28 days. The patient and his mother were discharged in a satisfactory condition, and their symptoms completely resolved within a few months. The diagnosis of botulism was confirmed by toxicological examination.

Keywords: *botulism; myasthenia gravis; bulbar syndrome; internuclear ophthalmoplegia; ptosis; Miller–Fisher syndrome*

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Клиническое наблюдение ботулизма с атипичным течением и развитием синдрома псевдомежъядерной офтальмоплегии

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Аннотация

Ботулизм является редкой причиной развития бульбарного и глазодвигательного синдромов. Несвоевременно установленный диагноз и, соответственно, поздний старт специфической терапии может привести к многочисленным жизнеугрожающим осложнениям. Ключом к верному диагнозу служат эпидемиологический анамнез и клиническая картина, однако при отсутствии этих данных или атипичности клинических проявлений картины постановка диагноза затруднительна.

В описанном клиническом случае 31-летний мужчина поступил в клинику с острым развитием двоения, нарушением движений глаз и затруднением глотания в течение 2 дней. Дисфункция со стороны глазодвигательных нервов характеризовалась нарушением сочетанных движений глазных яблок, которая чаще всего у молодых пациентов обусловлена демиелинизирующим заболеванием с поражением медиального (заднего) продольного пучка, а также симметричным двусторонним птозом. Пациент отрицал употребление в пищу продуктов, способных вызвать ботулизм, признаки гастроэнтерического синдрома отсутствовали. Дифференциальный диагноз проводился между дебютом демиелинизирующего заболевания и синдромом Миллера–Фишера. Утром следующего дня полностью идентичная клиническая картина возникла у матери пациента, которая употребляла в пищу консервированные грибы, на основании чего был заподозрен ботулизм. В течение последующих нескольких часов, несмотря на введение противоботулинической сыворотки, развилась острая дыхательная недостаточность, ввиду чего пациент был переведён на искусственную вентиляцию лёгких, длительность которой составила 28 сут. Пациент и его мать были выписаны в удовлетворительном состоянии с полным регрессом симптоматики в течение нескольких месяцев. Диагноз «ботулизм» был подтверждён токсикологической экспертизой.

Ключевые слова: *ботулизм; миастения; бульбарный синдром; межъядерная офтальмоплегия; птоз; синдром Миллера–Фишера*

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Introduction

Botulism is a serious life-threatening disease with neurological symptoms being key ones, and, therefore, patients often visit or are referred to a neurologist. Typical botulism is diagnosed on the basis of epidemiological history and characteristic clinical pattern.

Foodborne botulism accounts for more than 99% of all botulism cases[1]. Typically, patients eat home-cooked canned foods such as mushroom, meat, fish, or vegetables. If having suitable conditions for reproduction in an anaerobic environment, the bacterium called *Clostridium botulinum* produces toxins that

[1] Botulism in children: Clinical guidelines (approved by the Ministry of Health of Russia in 2021). URL: https://cr.minzdrav.gov.ru/schema/697_1 (assessed: 07/28/2024).

cause botulism. The bacteria get into contaminated products due to their poor processing; botulinum toxin is odorless, colorless, and tasteless, making it impossible to identify, especially if the cans with the product are not swollen [1]. There are several types of botulinum toxins. Serotypes A, B, and E are the most pathogenic for humans and the most common; serotype F is less common [1, 2]. There have been rare cases of botulism due to bacterial colonization of a wound (wound botulism) or the intestines (infant botulism and adult intestinal colonization botulism) and botulism due to injection of high-concentration botulinum toxin for cosmetic or therapeutic purposes (iatrogenic botulism) [2].

In typical cases, the clinical picture of botulism includes a combination of gastrointestinal and paralytic symptoms. The incubation period ranges from 2–4 hours to 2–3 days, rarely up to 5 days [2]. Gastrointestinal symptoms often develop early and include nausea, vomiting, abdominal pain and/or bloating with non-profuse diarrhea being less common. Paralytic symptoms include neurological symptoms involving striated and smooth muscles. The following neurological signs of botulism can be identified [2–4]:

- Internal and external ophthalmoplegia, i. e. mydriasis with decreased/no photoreactions, accommodation paralysis with a feeling of "fog before the eyes", ptosis, strabismus, diplopia, and nystagmus;
- Bulbar syndrome: dysphagia, dysarthria, dysphonia, nasolalia, with possible hypoglossal nerve damage;
- Damage to other cranial nerves such as paresis of facial muscles and head drop syndrome due to accessory nerve damage;
- Tetra- or paraparesis, i. e. weakness or fatigue in the limbs, abnormal muscle fatigue syndrome, hypo- or areflexia of tendon reflexes, muscle hypotonia;
- Paresis of the respiratory muscles with acute respiratory failure;
- Autonomic nervous system symptoms such as dry mouth, difficulty urinating, constipation, lack of intestinal motility, heart rhythm disturbances (most often sinus tachycardia), and fluctuations in blood pressure.

Key points to consider when assessing the patient's neurological status:

a) Symmetrical symptoms;
b) The patient is fully conscious with no abnormalities in vital signs;
c) Damage to the skeletal muscles and autonomic parasympathetic system due to acetylcholine transmission blockade.

The diagnosis is confirmed by biological assays on white mice infected with patient's serum, extracts of their feces or suspicious food. Besides detecting botulinum toxin, this assay allows identifying the type of toxin [2, 5].

Of key importance is making prompt decision and starting anti-botulinum therapy as early as possible (before receiving biological assay results), as a delay or wrong diagnosis can cause long-term therapy in the intensive care unit and/or patient's death. Anti-botulinum serum used in Russia contains toxoids against the major toxin types (A, B, E) that cause the disease. Botulism caused by toxin F is extremely rare; there is no toxoid against it in routine Russian sera, and this can negatively affect the patients' prognosis [2]. In another article, we presented a clinical case of severe type F botulism with an unfavorable outcome [6].

Given its rare incidence, diagnosing botulism is challenging, especially in big cities, where industrial production of vegetables and pickles has almost completely replaced home production. However, even with alertness to this disease, doctors may make a mistake when making a diagnosis in the case of atypical botulism. The clinical case presented below fully illustrates this point.

Clinical case

A 31-year-old man was admitted to a hospital by an ambulance with complaints of difficulty swallowing, double vision, unstable gait, and diffuse headache of VAS score 7 to 8. He considered himself ill for 24 hours. The morning before, he started to have headaches, blurred vision, and unstable gait. On the day of admission, his condition got worse (i.e. swallowing disturbance developed, vision and gait unsteadiness worsened), so an ambulance was called. The patient denied abdominal pain, nausea/vomiting, and dry mouth. He was asked many times by different doctors whether he had eaten canned foods, mushrooms, pickles or fish and said he had not eaten any of these products. All his family members were healthy.

Neurological status: completely alert, oriented, adequate. The patient had asthenia and got tired upon examination. Visually, the axis of the eyeballs was not disturbed but the patient noted the "blurriness" of objects in all directions and called this double vision. No restrictions in the range of eye movements were recorded. Disturbed conjugate eye movements with diplopia were seen; when assessing gaze in the horizontal plane, asymmetry and asynchrony of eye movements in both directions were observed: the eye going to the medial corner of the eye (adduction) "lagged behind" the eye going to the lateral corner (abduction). When looking up, he had vertical nystagmus, which "faded" when the gaze was fixed. An assessment of convergence showed slowness and limitation of adductor movements of the eyeballs. No abnormal photoreactions, abnormal accommodation, or mydriasis were observed. Mild bilateral ptosis to the upper edge of the pupil was seen. Bulbar symptoms were also seen such as dysphagia, mild dysphonia and dysarthria; however, palatal and pharyngeal reflexes were of normal vivacity, and the soft palate was symmetrical and mobile. There were abnormalities considered to be cerebellar signs: gait with a wide base of support, instability in the Romberg position, diffuse decrease in muscle tone. In the finger-nose test, tremor was observed,

which persisted in postural position. Tendon reflexes were significantly decreased. All symptoms were symmetrical. No paresis, sensory disorders, meningeal signs, or respiratory failure were seen.

Considering brainstem focal symptoms (especially internuclear ophthalmoplegia [INO] and vertical nystagmus), no epidemiological history or gastrointestinal symptoms, and preserved photoreactions, brain demyelinating disease was suspected. For differential diagnosis, brain magnetic resonance imaging was planned with further decision on the diagnosis the next day. The acute onset of the symptoms, a combination of ocular motility dysfunction, ataxia and a sharp decrease in tendon reflexes also suggested Miller-Fisher syndrome. The patient was transferred to the emergency neurology department.

The next morning, the patient's 49-year-old mother, who had eaten home-canned mushrooms, was admitted to the hospital with similar symptoms. The diagnosis of food botulism became obvious, so the patient with his mother were transferred to the Republican Clinical Infectious Disease Hospital in Kazan. Immediate therapy for botulism was initiated: gastric lavage, cleansing enema, and polyvalent anti-botulinum serum. On the same day, both patients had bulbar disorders worsened with weakness of the neck muscles and acute respiratory failure developed, which required mechanical ventilation. Only at the end of the 3rd day after the disease onset did the patient develop mydriasis, a typical sign of botulism, with no photoreactions (i. e. delayed inhibition of photoreactions). Limitation of eye movements persisted without deterioration.

A biological assay on white mice confirmed botulism and showed type A toxin in both patients. Due to prolonged mechanical ventilation, both patients underwent tracheostomy, and measures were taken to maintain their vital functions. The patient was on a ventilator for 29 days and his mother for 31 days. Both patients were discharged home in satisfactory condition, and all their neurological symptoms resolved over the next few months. The patient's ocular motility dysfunction completely resolved.

Only before discharge to the outpatient stage, the patient said that "he may have tried little mushrooms prepared by his mother".

Discussion

According to Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor), in 2021, 148 people suffered from botulism in Russia; of those, 22 (14.9%) cases were fatal[2]. A significant portion of these deaths might have been associated with late diagnosis. In literature, a high percentage of errors in diagnosing botulism has been highlighted. In a large review of botulism diagnostics in 332 patients in the US, the treating physician provided alternative diagnostic considerations for 83% of cases, most frequently Guillain–Barré syndrome [2]. Botulism may be also misdiagnosed as stroke, Lambert-Eaton syndrome, meningitis, encephalitis, or functional disease [2, 7]. In atypical cases, it becomes even more challenging to suspect botulism, as illustrated by our clinical case.

The primary diagnostic challenge in this case was the absence of a typical epidemiological history for botulism. In the majority of cases, the patient's consumption of canned foods is the primary indicator that prompts the physician to suspect botulism. However, the absence of an epidemiological history does not rule out the possibility of botulism, as the patient may not be aware of eating contaminated food or may forget about it (as our patient). In addition to foodborne botulism, there are wound botulism and infant botulism, in which there is no food history. In 1% to 4% of cases, there are no epidemiology data at all, and patients are diagnosed with "botulism of unknown origin" [8]. Another epidemiological point to consider is that several individuals may get sick simultaneously, which occurred in our clinical case, but our patients fell ill with an interval of about 2 days. The "clustered" distribution of the toxin in food consumed was reported, when the entire amount of toxin can be concentrated in a minimal amount of the food contaminated, so only one person can get sick, although several persons consume the same products [9].

Our patient did not have any gastrointestinal symptoms at disease onset. In foodborne botulism, gastrointestinal symptoms are typical but not obligatory. No gastrointestinal symptoms can be seen in over 50% of cases [2]. For example, vomiting was reported by only 50% of patients, and abdominal pain by only 25% [2]. Vomiting is known to be a protective reaction in case of poisoning with any types of toxins. The absence of vomiting in our patients may have contributed to complete absorption of the toxin from the gastrointestinal tract and more severe disease.

The absence of symptoms from the autonomic nervous system was also unusual. Acetylcholine is the key transmitter not only in neuromuscular transmission but also in postganglionic parasympathetic nerve endings and nerve ganglia. Therefore, botulism can be associated with decreased or no photoreactions, mydriasis, constipation, inhibited intestinal motility, and impaired urination. Mydriasis is the most common of the above symptoms; it is included in the clinical criteria for diagnosis [10]. However, the incidence of autonomic symptoms in the early stages does not exceed 50%, and the prevalence of mydriasis is only 37% [2]. Our clinical case demonstrated that internal ophthalmoplegia can be delayed, as in our patient, who

[2] Federal Service for Supervision of Consumer Rights Protection and Human Welfare. On prevention of botulism.
URL: https://www.rospotrebnadzor.ru/about/info/news/news_details.php?ELEMENT_ID=22031 (assessed: 07/28/2024).

had mydriasis and suppression of photoreactions only 72 hours after the onset of botulism, when he was already on a ventilator.

The most interesting in our clinical case is the nature of ocular motility dysfunction, as well as vertical nystagmus, which, in most cases, is associated with damage to the central brainstem structures. A unilateral or bilateral lesion of the medial longitudinal fasciculus of the brain stem is an anatomical substrate for INO. In patients with INO, adduct of one eye is slowed down, limited, or impossible, while the other abducting eye has nystagmus. In case of unilateral INO, the lesion is on the same side as the eye with the adduction weakness [11]. Ophthalmoparesis in INO is occult and unnoticeable with fast and unfixed gaze, and paresis is detected in the muscles of one eye only with slow tracking eye movements. This is why patients do not have obvious strabismus [12]. Convergence adduction is preserved in most patients. This can help differentiate INO from partial medial rectus palsy. Convergence disturbance in INO can be observed only in cases with a lesion in the medial longitudinal fasciculus at the level of oculomotor nuclei, since the tracts that form the near vision reflex pass here [13–15]. INO is often associated with monoocular nystagmus in the abductor eye. One of the hypotheses explaining abduction nystagmus is associated with an adaptive response to overcome weakness of the contralateral medial rectus muscle (Hering's law). Since the medial longitudinal fasciculus contains tracts involved in the regulation of vertical eye movements, patients with INO often exhibit disturbances in vertical eye movements, including vertical nystagmus [13, 16]. In young people, INO is most often caused by multiple sclerosis [17, 18].

Our patient had disturbed smooth tracking of the eyeballs in the form of slow adduction and asynchrony of eye movements, which is similar to INO in patients with demyelinating disease. However, there were contradictions in the clinical pattern of ocular motility dysfunction: there was no nystagmus in the abductor eye, the ability to converge was impaired, bilateral symmetrical ptosis was seen, and vertical nystagmus was attenuated. These signs suggested peripheral damage and weakness of external eye muscles. Thus, the patient had pseudointernuclear ophthalmoplegia.

Isolated cases of pseudointernuclear ophthalmoplegia in myasthenia gravis and in Miller-Fisher syndrome have been described in literature [19–21]. Nystagmus and disturbed conjugate movements of the eyeballs in patients with botulism can be explained by weakness of the eye muscles due to neuromuscular transmission blockade by botulinum toxin. The "fading" nystagmus was most likely associated with weakness of the superior rectus muscles. The diagnosis must have been slowed down and misled by delayed paralysis of the internal, smooth muscle structures of the eye [21]. Botulism-related pseudointernuclear ophthalmoplegia syndrome has not been described in the literature before.

Conclusion

In patients with acute symmetrical oculomotor and/or bulbar symptoms, differential diagnoses should include botulism. In doubtful cases, immediate administration of anti-botulinum serum is recommended. No epidemiological history, gastrointestinal symptoms or symptoms from the autonomic nervous system does not rule out botulism. In patients with botulism, development of impaired pupillary reactions can be delayed and pseudointernuclear ophthalmoplegia may be observed. However, a thorough assessment of the symptoms allows suspecting peripheral weakness of the ocular muscles such as convergence disorder, attenuated nystagmus, and ptosis together with a limitation of ocular movements.

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Atypical Presentation of Dysembryoplastic Neuroepithelial Tumor

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Abstract

Dysembryoplastic neuroepithelial tumor (DNET) is a benign glioneuronal neoplasm, usually found in children and adolescents, in the vast majority of cases associated with drug-resistant epilepsy. Typically, epileptic seizures are the main, and in most cases, their only clinical manifestation. Although DNET is a benign, biologically stable tumor with few reports of malignancy, it is one of the most common reasons for epileptic surgery. The epileptogenic potential of this tumor is so high that DNET s, along with ganglioglioma, have received the informal term "epileptomas" and are by far the leaders in the group of low-grade tumors associated with long-term epilepsy-associated tumors (LEAT). It is believed that this epileptogenicity is due to localization in the neocortex and frequent association with focal cortical dysplasias (FCD). In the world literature, there are only a few mentions of DNET s not associated with epilepsy. The article presents the experience of complex, interdisciplinary diagnosis of DNET in a child without epilepsy who complained of frequent headaches. During a comprehensive MRI examination, a cortical-subcortical pathological substrate was discovered in the left temporal lobe with radiological signs of DNET. During video-EEG monitoring of night sleep, no epileptiform signs were recorded. There was no history of epileptic seizures or other paroxysms. A control MRI revealed a slight increase in the size of the pathological substrate, which was the reason for surgical treatment. Pathological examination revealed microscopic features of DNET. This case of absence of epilepsy in a child with cortical DNET in the temporal lobe cortex suggests that the spectrum of its clinical manifestations and biological behavior is not fully understood and requires further comprehensive study.

Keywords: *DNET; glioneural tumors; patient without epilepsy; neuroimaging epilepsy.*

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Атипичное клиническое проявление дизэмбриопластической нейроэпителиальной опухоли

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Аннотация

Дизэмбриопластическая нейроэпителиальная опухоль (ДНЭО) – доброкачественное глионейрональное новообразование, как правило, встречающееся у детей и подростков, в подавляющем большинстве случаев ассоциированное с фармакорезистентной эпилепсией. Обычно эпилептические приступы являются основным и в большинстве случаев единственным клиническим проявлением ДНЭО. Несмотря на то что ДНЭО – доброкачественная, биологически стабильная опухоль с единичными упоминаниями о случаях малигнизации, она является одной из наиболее частых причин хирургического лечения эпилепсии. Эпилептогенный потенциал этой опухоли настолько высок, что ДНЭО, наряду с ганглиоглиомой, получили неофициальный термин «эпилептомы» и с большим отрывом лидируют в группе опухолей низкой степени злокачественности, ассоциированных с длительным течением эпилепсии. Есть мнение, что такая эпилептогенность обусловлена локализацией опухоли в неокортексе и частой ассоциацией её с фокальными кортикальными дисплазиями. Нами обнаружены единичные упоминания о ДНЭО, не ассоциированных с эпилепсией.

В статье представлен опыт комплексной междисциплинарной диагностики ДНЭО у ребёнка без эпилепсии, который обратился с жалобами на частые приступы головной боли. В ходе комплексного обследования при магнитно-резонансной томографии головного мозга был обнаружен кортикально-субкортикальный патологический субстрат в левой височной доле, имеющий радиологические признаки ДНЭО. При видео-ЭЭГ-мониторинге ночного сна не было зарегистрировано эпилептиформных знаков. В анамнезе не отмечалось эпилептических приступов или иных пароксизмов. При повторной магнитно-резонансной томографии головного мозга обнаружено увеличение размеров патологического субстрата, что послужило поводом для хирургического лечения. Патоморфологическое исследование выявило микроскопические признаки ДНЭО. Этот случай отсутствия эпилепсии у ребёнка с кортикальной ДНЭО в коре височной доли позволяет предположить, что спектр её клинических проявлений и течения раскрыт не полностью и требует дальнейшего всестороннего изучения.

Ключевые слова: *дизэмбриопластическая нейроэпителиальная опухоль; глионейрональные опухоли; пациент без эпилепсии; нейровизуализация эпилепсии*

Этическое утверждение. Исследование проводилось при добровольном информированном согласии законных представителей пациента.

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

The term "dysembryoplastic neuroepithelial tumor" (DNET) was first proposed in 1988 by C. Daumas-Duport et al., who identified a group of tumors with unique morphological features such as intracortical location, multinodular architecture, heterogeneity in cellular composition, and presence of a specific glioneuronal element [1]. Three forms of DNETs have been identified: simple, complex, and non-specific. Regardless of such polymorphism, DNETs are low-grade tumors with isolated reports of anaplastic transformation [2, 3]. DNETs are the second most common tumors associated with chronic intractable epilepsy and, along with gangliogliomas, are conventional representatives of low-grade long-term epilepsy-associated tumors (LEATs) [2, 4]. LEATs have common clinical, morphological, and radiological features such as association with drug-resistant or intractable epilepsy, age of onset below 20 years, frequent location in the temporal lobe, no marked neurological deficit, and extremely rare cases of anaplastic transformation [2, 3, 5]. Gangliogliomas and DNETs are by far the leaders in the LEAT group. In a very large cohort of patients who had epilepsy surgery, over 70% of all tumors were LEATs [6]. In many studies, the epileptogenicity of DNETs was up to 100%, and there is no surprise that specialists studying tumors of the LEAT group gave them an unofficial name "epileptomas" [7, 8].

In our article we described a case of DNET with atypical clinical course reported in a child without epilepsy, who underwent surgical treatment for the tumor.

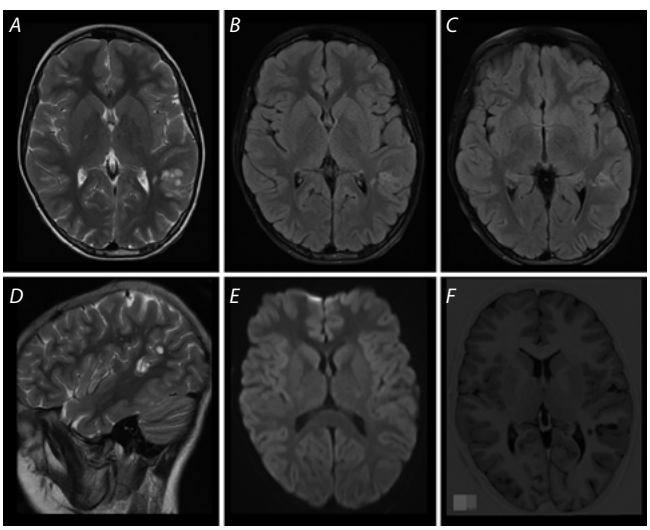

Fig. 1. Brain MRI of patient G. at his first examination.
A lesion is seen in the posterolateral area of the left temporal lobe with involvement of the parietal lobe, with a multicystic structure ("soap-bubble pattern") typical for DNET, with subcortical/cortical location and transmantle spread to the posterior horn of the homolateral lateral ventricle (*A, B, C*). On sagittal slices, involvement of the parietal lobe of the left hemisphere is clearly seen (*D*). The lesion does not demonstrate restricted diffusion or perifocal reaction (*E*). T1 SPC ISO images with a slice thickness of 1 mm clearly show the multicystic structure of the lesion and its predominant location in the corticomedullary area (*F*).

Clinical case report

Patient G., 12 years old, consulted a neurologist with complaints of periodic headaches, which had been seen for about one year after a closed craniocerebral injury, and speech impairment, which his parents described as quiet inarticulate speech during periods of excitement. Brain magnetic resonance imaging (MRI), which was conducted as part of the patient's comprehensive examination, showed a lesion in the left temporal lobe. Based on radiological findings and location, a tumor, presumably DNET, was suggested with a differential diagnosis of another representative of the LEAT group (Figure 1).

Considering the patient's complaints of headaches and the polymorphism of possible atypical manifestations of temporal lobe epilepsy, he was referred to an epileptologist and administered with overnight video EEG monitoring (VEEG). VEEG monitoring showed slow and diffuse biopotentials of residual organic background with a focus of slow pathological activity in the left frontal-central area in the form of frequent bursts of high-amplitude paroxysmal theta rhythm. No clear local or interhemispheric asymmetry was identified. Typical epileptic activity was not recorded. Tolerance to hypoxia was intact. Cortical epileptogenesis was consistent with the patient's age.

The neurological status showed no abnormalities of higher mental functions, motor domain, sensory domain, or cranial nerves.

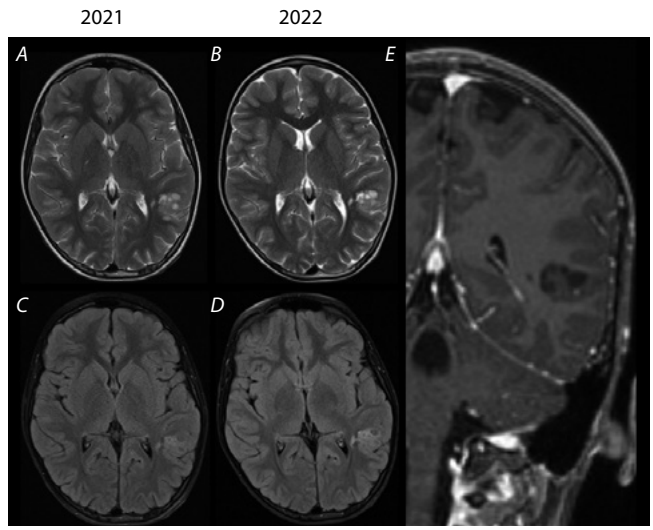

Fig. 2. Follow-up brain MRIs of patient G. 1 year later.
When images from 2021 and 2022 are compared, higher relaxation properties of the lesion are determined in the T2 and FLAIR MRI sequences. The multicystic structure and transmantle spread to the posterior horn of the left lateral ventricle are visualized more clearly. The retrospective comparison shows no signs of enlargement, perifocal reaction, or mass effect (*A* to *D*). No abnormal accumulation of an intravenous MRI contrast agent is seen in the structure of the lesion (*E*).

His personal or family history did not include any noteworthy episodes of loss of consciousness or seizures. Considering the changes in the left temporoparietal lobe, no epileptic seizures, changes in the neurological status, and VEEG monitoring findings, the interdisciplinary team discussed the patient's management, diagnosed him with "Neuroepithelial tumor of the left temporal lobe, presumably DNET", and recommended follow-up over time.

Follow-up MRI 1 year later showed non-obvious signs of biological instability of the lesion (Figure 2); therefore, the patient's neurosurgeons recommended surgical treatment.

The tumor in the left temporal lobe of the brain was removed by microsurgery with intraoperative neurophysiologic monitoring. Morphological examination of the resected tissue showed microscopic and immunohistochemical signs of simple low-grade DNET (Figure 3). A detailed examination of resected cortical fragments did not provide any evidence of an association with focal cortical dysplasia (FCD). Molecular genetic testing of the tumor tissue was performed by FISH with DNA probes; *BRAF V600E* mutations and *KIAA1549-BRAF* At the time of the publication, the post-operative follow-up of patient G. lasted 11 months; no epileptic seizures or abnormal changes in his neurological status were found.

Discussion

Epileptic seizures that are difficult to control with antiepileptic therapy are the main and, in many cases, the only clinical sign of DNET. A single case of DNET in an adult patient without seizures has been described in generally available medical literature. The authors associated this atypical pattern with the absence of FCD in the peritumoral cortex [9]. However, the association with FCD is considered one of the main but far from the only factor contributing to the high epileptogenicity of DNET [6, 10]. There are three key hypotheses that explain tumor-associated epilepsy. Two of them (i.e. epileptocentric and tumor-centric) emphasize the key role of the tumor, while the third one gives preference to the role of molecular genetic aberrations found in tumor tissue [3, 6, 11, 12].

According to the epileptocentric approach, changes leading to hyperexcitability in the peritumoral cortex play a key role in the development of epilepsy. This is associated with metabolic, morphological, neurotransmitter or immunological changes in the tumor and peritumoral tissue [11, 13]. Various abnormalities of cortical development, especially FCD, are often found adjacent to pediatric brain tumors and play an important role in the development of epilepsy. These are usually type I FCDs, which have a high epileptogenic poten-

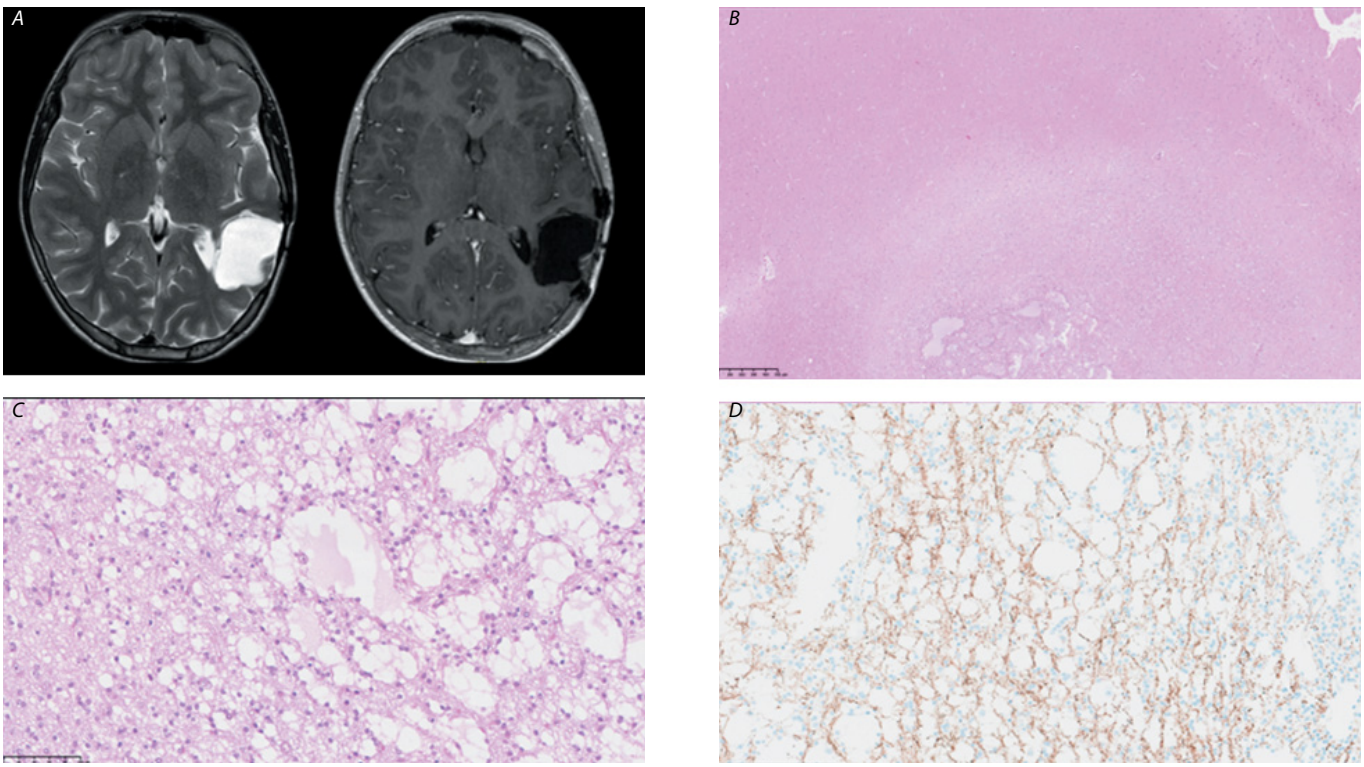

Fig. 3. Postoperative MRI and morphological findings of patient G.

MRI demonstrated total removal of the tumor from the left temporoparietal region with the transmantle track and adjacent cortex (*A*). At the border of the gray and white matter, tumor tissue was seen, which consisted of cells morphologically similar to oligodendrocytes, which formed unidirectional chains. Microcysts filled with mucoid substrate were observed in these chains (*B*). In individual microcysts, there were neurons located in the mucoid material ("floating" neurons) (*C*). In DNETs, neuronal axons form parallel cords that have the same direction as the columns of oligodendroglial cells. These structures are called specific glioneuronal elements, and they are typical for this tumor. Immunostaining with anti-neurofilament protein antibody (*D*).

tial themselves, and the association with a tumor from the LEAT group makes this substrate superepileptogenic. A literature review suggested a wide range of detection rates for the association of neuroepithelial tumors with FCD (i. e. 20–80%) [6, 10, 14]. In patient G., no abnormalities in the architecture of the peritumoral cortex were found in the materials submitted for morphological examination. We considered this argument to be a possible factor contributing to the fact that the patient did not have epilepsy. However, this cannot be considered the only correct hypothesis because some tumors from the LEAT group associated with FCD or other cortical dysgenesias are increasingly found in patients without epilepsy [14, 15]. Therefore, the role of peritumoral FCD in the development of epileptic seizures is not fully understood, and studies in this area should be continued.

According to the tumor-centric approach, epileptic activity is triggered by the tumor itself and develops due to its direct mechanical effect. The tumor and edema cause increased intracranial pressure, leading to cerebral hypoperfusion. This results in local tissue destruction, ischemia, necrosis, neovascularization, microhemorrhages, and inflammation [11, 13]. In the case of patient G., there were no typical signs of a neoplastic process such as mass effect, perifocal edema, or neovascularization. Differences in relaxation characteristics and more distinct boundaries of the cystic component, without a significant increase in size, which were considered by the experts as progression, may be explained by the fact that different models of MRI scanners were used for the initial and follow-up examinations.

Therefore, the tumor found in the patient was relatively biologically stable, which, based on the tumor-centric theory, may have affected its epileptogenicity. However, it should be noted that the tumor-centric hypothesis was tested on gliomas and is more applicable to highly aggressive forms of these tumors with rapid progression [6].

There are increasing number of reports in the literature about a potential association of certain genetic mutations found in tumors with the occurrence of epileptic seizures. A new classification of tumors that was introduced in 2021 considers not only their histological structure but also specific genetic mutations [16]. Studies identified several genetic factors associated with the development of epilepsy in patients with brain tumors, such as *1p/19q* co-deletion and *IDH1/IDH2* mutations. They suggested that these mutations may affect the balance between inhibition and excitation in the brain, which can cause epileptic seizures [17, 18]. However, conventional LEATs are not associated with these mutations, which questions this hypothesis. Genetic changes responsible for tumor-associated epileptogenesis in LEATs are likely to be in the rat sarcoma mitogen-activated protein kinase (RAS/MAPK) and phosphoinositide 3-kinase protein kinase B mammalian target of rapamycin (PIK3-AKT/mTOR) pathways [19]. For example, *FGFR1* and *BRAF V600E* mutations, which are associated with these pathways, were detected in patients with DNET [3, 16]. Several publications indicated that the *BRAF V600E* mutation detected in tumor tissue may correlate with a worse prognosis for the postoperative outcome of epilepsy and provoke relapses of the neoplastic process [20].

Availability of molecular genetic testing of the tumor tissue in our case was limited. Testing for *BRAF V600E* mutations and *KIAA1549-BRAF* fusion was available using FISH with DNA probes, which was negative. We were unable to search for the *FGFR1* mutation, which is the most typical for DNET; however, we did not find any literature data on its role in tumor epileptogenesis, in contrast to *BRAF V600E* mutations and *KIAA1549-BRAF* fusion.

Patient's young age was yet another possible factor contributing to the absence of epilepsy. Although epilepsy occurs before the age of 20 years in over 90% of patients with DNET, there have been reports of late-onset seizures associated with this tumor [2, 21]. In one of the largest studies in patients with DNET, the mean age of epilepsy onset was 14.6 years (range, 3 months to 54 years) and age at surgery was 30.5 years (range, 6 to 65 years) [22]. The age of patient G. at the time of his surgery was 12 years, so epilepsy could develop at an older age. However, in another study in children, the mean age of onset of epileptic seizures was 8.1 years (range, 2 months to 14 years) and age at surgery was 12.4 years (range, 3.25 to 18.5 years), which also questions this hypothesis [23].

Epilepsy is known to have polymorphism of its clinical manifestations, especially if its structural cause is located in the temporal lobe. Quite often, symptoms differ from typical manifestations of epilepsy, which can be misinterpreted by specialists unfamiliar with this problem; therefore, the patients may not receive proper diagnostics and treatment. VEEG monitoring, which was conducted as part of the comprehensive examination of patient G., did not show any typical epileptic activity while awake and asleep, neither did functional tests. The patient did not have a personal or family history of epileptic seizures or other paroxysms. No abnormal symptoms were found in the patient's neurological status, and complains of headaches were the main clinical sign. Therefore, we can say with a certain degree of confidence that the patient did not have epilepsy at the time of his surgery.

Conclusion

Although epileptic seizures are the main and, in some cases, the only clinical symptom of DNET, which justifies its unofficial term "epileptoma," this tumor may be detected in patients without seizures. Such an atypical course requires more thorough investigation of the conventional mechanisms that induce LEAT-associated epileptogenesis and possible contribution of molecular genetic aberrations.

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