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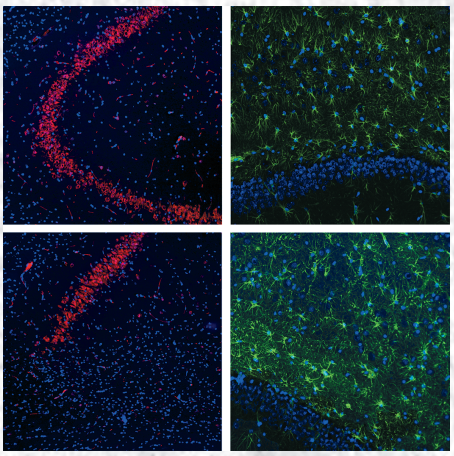

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On the front cover: part of the Figure 1 from the article of D.N. Voronkov et al. (P. 38).

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РЕЦЕНЗИРУЕМЫЙ НАУЧНЫЙ МЕДИЦИНСКИЙ ЖУРНАЛ

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Simultaneous Dual-Target Magnetic Resonance-Guided Focused Ultrasound Treatment for Patients with Tremor-Dominant Parkinson's Disease

Rezida M. Galimova[1, 2], Sergey N. Illarioshkin[3], Gulnara N. Akhmadeeva[1, 2], Dinara I. Nabiullina[2], Felix F. Kashapov[2], Shamil M. Safin[1], Igor V. Buzaev[1, 2], Dinara R. Teregulova[2], Yulia A. Sidorova[2], Olga V. Kachemaeva[1, 2]

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Abstract

Introduction. *Non-invasive magnetic resonance-guided focused ultrasound (MRgFUS) is a new neurosurgical treatment option for tremor-dominant Parkinson's disease (TDPD). Outcomes of ablation with dual targeting of two subcortical nuclei to improve functional treatment results are yet to be explored.*

Aim. *This study aimed to evaluate the safety and efficacy of MRgFUS with simultaneous unilateral ablation of two cerebral targets in patients with TDPD.*

Materials and methods. *A total of 82 TDPD patients (20 women, 62 men; median age 65.0 [52.5; 70,0] years) received unilateral MRgFUS, i.e. ventrointermedial (VIM) nucleus thalamotomy and/or pallidothalamotractotomy (PTT). Motor symptoms, including tremor, were assessed using MDS-Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III). VIM, PTT, and VIM + PTT ablation was received by 34, 12, and 36 patients, respectively.*

Results. *After surgery, MDS-UPDRS-III score improved by 40.1% (30.2; 51.7) without early or late-onset serious complications. Tremor returned in 18 patients (all after VIM thalamotomy); 9 of them successfully underwent re-treatment 9–12 months after the first procedure. Simultaneous dual-target (VIM + PPT) intervention was successfully received by 36 patients without any serious complications. A total of 89.3% and 69.7% of patients remained relapse-free in the dual-target and single-target groups, respectively (p = 0.039).*

Conclusion. *Simultaneous dual-target (VIM and PTT) MRgFUS showed favorable safety and efficacy profiles and can be considered a symptomatic treatment option for TDPD patients.*

Keywords: *magnetic resonance-guided focused ultrasound; Parkinson's disease, VIM-thalamotomy; pallidothalamotractotomy; tremor*

Ethics approval. All patients provided their voluntary informed consent to participate in the study. The study protocol was approved by the Local Ethics Committee of Bashkir State Medical University, Ufa, Russia (protocol No. 8, October 21, 2021).

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Одновременное воздействие на две мишени методом фокусированного ультразвука под контролем МРТ при лечении пациентов с дрожательными фенотипами болезни Паркинсона

Р.М. Галимова[1, 2], С.Н. Иллариошкин[3], Г.Н. Ахмадеева[1, 2], Д.И. Набиуллина[2], Ф.Ф. Кашапов[2], Ш.М. Сафин[1], И.В. Бузаев[1, 2], Д.Р. Терегулова[2], Ю.А. Сидорова[2], О.В. Качемаева[1, 2]

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Аннотация

Введение. *Неинвазивная технология воздействия фокусированным ультразвуком под контролем магнитно-резонансной томографии (МР-ФУЗ) является одним из новых методов нейрохирургического лечения преимущественно дрожательных фенотипов болезни Паркинсона (Д-БП). Возможность абляционного воздействия одновременно на две мишени в области подкорковых ядер с целью улучшения функциональных результатов лечения нуждается в изучении.*

Цель *работы – оценить безопасность и эффективность лечения пациентов с Д-БП методом МР-ФУЗ при одновременном одностороннем воздействии на две церебральные мишени.*

Материалы и методы. *Методом МР-ФУЗ 82 пациентам (20 женщин, 62 мужчин; медиана возраста – 65,0 [52,5; 70,0] лет) с Д-БП проведено одностороннее лечение – таламотомия вентроинтермедиального ядра (VIM) и/или паллидотрактотомия (PTT). Выраженность двигательных проявлений, включая тремор, оценивали по III части шкалы MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III). Воздействие на VIM осуществлено в 34 случаях, на PTT – в 12, комбинированное воздействие VIM и PTT – в 36.*

Результаты. *После операции у пациентов выявлено улучшение симптомов по шкале MDS-UPDRS-III на 40,1% (30,2; 51,7) без развития ранних и отдалённых серьёзных осложнений. У 18 пациентов наблюдался рецидив тремора (все случаи после VIM-таламотомии), 9 из них успешно выполнены повторные воздействия через 9–12 мес после первого лечения. Одновременное воздействие на 2 мишени (VIM и PPT) успешно проведено у 36 пациентов, без серьёзных осложнений. В результате комбинации 2 мишеней безрецидивное течение Д-БП на протяжении года имело место у 89,3% больных, в то время как в подгруппе с абляцией 1 мишени – у 69,7% (p = 0,039).*

Заключение. *Одновременное воздействие на две мишени (VIM и PTT) методом МР-ФУЗ может рассматриваться как один из вариантов лечения симптомов у пациентов с Д-БП при благоприятном профиле безопасности таких вмешательств.*

Ключевые слова: *фокусированный ультразвук под контролем МРТ; болезнь Паркинсона; VIM-таламотомия; паллидоталамотрактотомия; тремор*

Этическое утверждение. Исследование проводилось при добровольном информированном согласии пациентов. Протокол исследования одобрен локальным этическим комитетом Башкирского государственного медицинского университета (протокол № 8 от 21.10.2021).

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

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

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Introduction

Parkinson's disease (PD) is one of the most common progressive neurodegenerative disorders. The incidence of PD is 5 to 35 per 100,000 person-years [1–4]. In the next 20 years, the prevalence of PD is expected to double [5], and, without any new effective treatment options, this might lead to a significant increase in social and economic disease burden [6].

Medication therapy to manage symptoms of neurotransmitter imbalance in the brain is indicated to patients with tremor-dominant Parkinson disease (TDPD). If there no alternative medication treatment options, patients are usually administered functional neurosurgery with deep brain stimulation (DBS) or stereotactic ablation: radiofrequency ablation, gamma knife, or magnetic resonance guided focused ultrasound surgery (MRgFUS) [7–14]. Before widespread introduction of DBS, destructive surgery with an efficacy of 50–80% was the leading treatment option for PD symptoms [11, 15]. Since the end of the 20t^{h} century, DBS has become the leading neurosurgery option for PD [16–18]. Recently, ablative treatment methods have become popular again due to the introduction of MRgFUS, which allows managing movement disorders with high accuracy and avoiding any surgical incisions, anesthesia, long hospitalization, and pain [11, 19–21].

MRgFUS involves a combination of two procedures: high-intensity focused ultrasound and MRI, which are used to plan the target point and conduct thermometry in real time. Bond et al. in 2017 were one of the first to describe successful treatment of PD-associated tremor by MRgFUS in the ventral intermediate thalamic nucleus in 27 patients [22]. Among the authors who evaluated long-term results of MRgFUS in patients with PD, A. Sinai et al. reported the longest follow-up in 26 TDPD patients after VIM-ablation (median follow-up 36 months, range 12–60 months) [23]. Treatment resulted in 100% improvement in tremor in 23 patients and 90% improvement in 3 patients. In 2 patients tremor returned completely and in 8 patients there was partial return of tremor. This study demonstrated that unilateral MRgFUS VIM-thalamotomy in TDPD patients was effective and safe and provided long-term response. Heading to the premotor cortex, several important tracts (pallidothalamic, cerebellothalamic, and vestibulothalamic) converge in the VIM nucleus, and this makes it an optimal candidate for managing tremor and justifies intervention in this area [15, 24].

Attempts to perform MRgFUS ablation of the subthalamic nucleus (STN) were described by R. Martínez-Fernández et al. However, analysis of their results showed that this intervention, compared with other targets, was associated with a higher incidence of adverse effects (such as ballism, chorea, paresis, speech disturbances, and gait disturbances) with a similar efficacy [25]. With such adverse effects developing after subthalamotomy (with some of them persisting for up to one year or more), many medical centers prefer to target the VIM nucleus, which has become the key target for the treatment of essential tremor and the most common target for tremor in PD.

No effect on hypobradykinesia and muscle rigidity is a disadvantage of targeting the VIM nucleus [26]. Meanwhile, targeting the pallidothalamic tract (PTT) at the level where the Forel's fields H1 and H2 converge was shown to reduce tremor, rigidity, and hypobradykinesia by an average of 70–93% while leaving the thalamus intact [20]. M.N. Gallay et al. assessed MRgFUS pallidothalamic tractotomy results in 51 patients with late-stage TDPD and complications of levodopa treatment (dyskinesia and fluctuations) [27]. They found percentage reductions of 84% for tremor, 70% for rigidity, and 73% for hypokinesia with almost complete suppression of levodopa-induced dyskinesia. This study showed that pallidothalamic tractotomy is very promising for the treatment of TDPD and complications of levodopa treatment.

Numerous studies have been conducted to evaluate MRgFUS with ablation of one target, while the feasibility, safety, and efficacy of simultaneous dual targeting are barely represented in available literature. A single study published in 2023 described 3 TDPD patients who received stepwise dual-target MRgFUS with VIM and PTT ablation [28]. All patients tolerated the two treatment steps adequately without any complications.

Aim. Our study aimed to evaluate the safety and efficacy of simultaneous unilateral dual-target MRgFUS in TDPD patients.

Materials and methods

Treatment with a MRgFUS system (ExAblate 4000, Insightec) was received by 82 patients (20 women and 62 men) with TDPD. Median patients' age was 65.0 [52.5; 70] years. Mean age was 64.5 (55; 70.5) for men and 63.0 (61.0; 72.0) for women with no statistically significant gender differences (p = 0.95, Wilcoxon's test). This prospective study included patients who received MRgFUS treatment at V.S. Buzaev International Medical Center from May 05, 2020 to July 29, 2023.

PD was diagnosed based on the PD diagnostic criteria of the International Parkinson and Movement Disorder Society [29]; the stage was determined using the Hoehn–Yahr functional scale [30]; and disease severity was assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part III (MDS-UPDRS-III) [31, 32]. A total of 37 and 28 patients had Hoehn and Yahr Rating Scale stage 2 and 3, respectively. Median MDS-UPDRS-III score before treatment was 54 (43; 65).

Eligibility criteria for the neurosurgical intervention:
1) idiopathic PD lasting for 2 years or more;
2) age over 30 years;

3) persistence of tremor when using standard levodopa agents (at least 500 mg) or side effects with required doses of standard levodopa agents;
4) on-medication fluctuations (on-off phenomenon) or dyskinesia;
5) tremor intensity score at rest and/or hypokinesia score of ⩾ 3–4;
6) no significant cognitive impairment (i.e. total Montreal Cognitive Function Assessment Scale score of at least 20) and no psychotic disorders;
7) bone ultrasound permeability factor of ⩾ 0.35;
8) no current treatment with anticoagulants and/or antiplatelet agents, no brain tumors or vascular malformations;
9) no contraindications to MRI, such as claustrophobia or incompatible implants.

All patients were informed about DBS but did not consider it for several reasons (fear of a device in the brain; difficulties with access to medical centers that adjust DBS parameters due to remoteness of patients' place of residence, etc.). During the screening period for MRgFUS, all patients also underwent brain MRI with the SWI/SWAN sequence, which has a certain diagnostic value in PD [33, 34].

We described MRgFUS in detail before [12]. In all cases, unilateral intervention was performed; the side of intervention was chosen as a joint decision with the patient and their relatives, considering severity of their symptoms or dominant limb. Median bone ultrasound permeability factor was 0.48 (0.41; 0.58); median treatment duration was 97.2 (73.6; 126.4) min; median number of sonications was 11 (9.5; 13.0).

We chose two targets for MRgFUS: VIM and PTT. The VIM nucleus was used in first patients because this target was approved earlier (in 2018) [12]. After PTT tractotomy was approved in November 2021, targets were selected for each patient in accordance with their clinical status (presence of severe muscle rigidity, hypokinesia, or disabling tremor) [35]. Of 82 treated patients, 34 received VIM, 12 PTT, and 36 VIM + PTT thalamotomy. A total of 51 and 31 patients received left-sided and right-sided interventions, respectively.

After treatment, all patients were followed up according to the approved protocol with clinical neurological examination and brain MRI at Months 1, 3, 6, and 12.

Statistical analysis was performed in x86_64-apple-darwin17.0 platform under macOS Monterey v. 12.0.1 in R v. 4.2.1 software package distributed under open license. Continuous numerical variables were tested for normal distribution using the Shapiro–Wilk test. Non-parametric methods were used in case of a relatively small number of observations and no normal distribution. Dependent groups were compared using the paired Wilcoxon test, and independent groups were compared using the Wilcoxon test. If there were more than two groups, the Kruskal–Wallis comparison method was used. Spearman correlation analysis was performed. Data were evaluated visually using graphs plotted using functions built into R. Time to return of symptoms was analyzed by Kaplan–Meier survival methods using survival v. 0.4.9 and survminer v. 0.4.9 packages.

Results

Positive MDS-UPDRS-III response to MRgFUS was achieved in all TDPD patients. Median score before and after surgery was 54 (43; 65) and 31 (24; 39), respectively, $p < 0.00001$ (Fig. 1). No statistically significant differences were found in treatment results between men and women ($p = 0.68$).

Evaluation of MRgFUS results by target (Fig. 2) showed greater improvement with PTT or VIM + PTT targets ($p < 0.001$, Kruskal–Wallis method). Improvement was 32.0% (24.5; 40.2) in the VIM group, 50.0% (40.3; 57.5) in the VIM + PTT group, and 40.1% (37.2; 58.7) in the PTT group; differences were statistically significant ($p < 0.001$, Kruskal–Wallis test). If tremor persisted after a sufficient PTT lesion, the patient received a second ablation intervention in another target. Fig. 3 shows a TDPD patient's MRI scan after MRgFUS treatment in both PTT and VIM.

Statistically significant differences were found in percentage improvement (vs. baseline MDS-UPDRS-III score) between patients with isolated PTT and VIM ablation ($p = 0.000024$, Wilcoxon's test). However, no statistically significant differences were found between PTT + VIM and PTT ablation groups ($p = 0.9245$). Median improvement in MDS-UPDRS-III score was 47.9% (38.8; 57.6) and 32% (24.2; 40.2) in patients with and without PTT thalamotomy, respectively. Median absolute improvement in MDS-UPDRS-III was 29 (21; 34) and

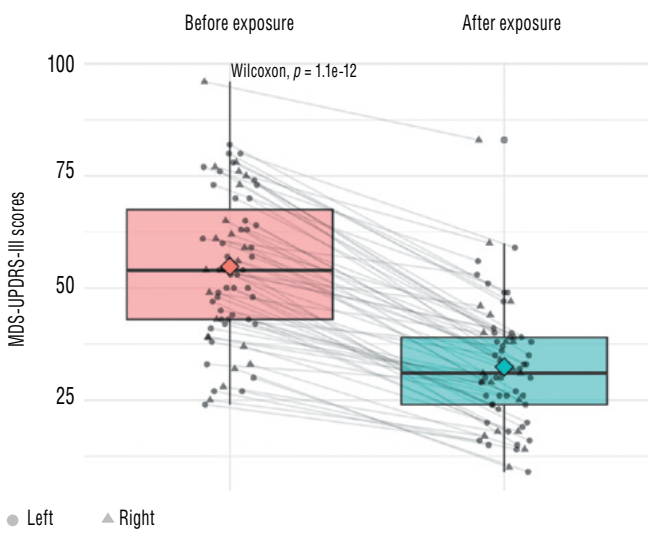

Fig. 1. MRgFUS treatment response (score, before and after) in TDPD patients.
*$p < 0.00001$, Wilcoxon's test.

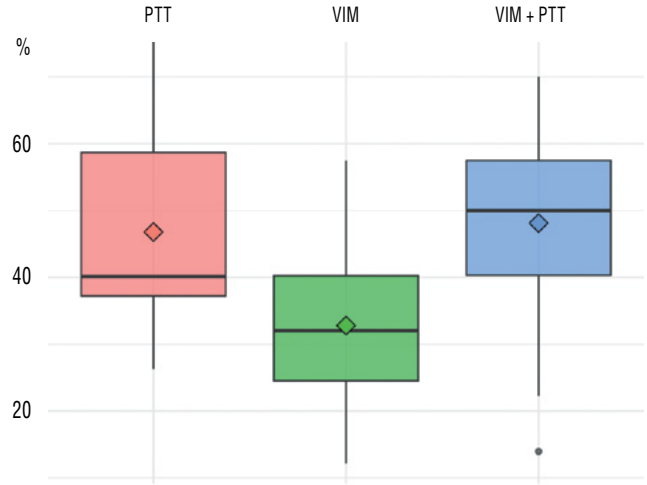

Fig. 2. Percentage improvement achieved in TDPD patients after MRgFUS (MDS-UPDRS, part III) vs. baseline by different targets.
*$p < 0.001$, Kruskal–Wallis method.

13.5 (10.2; 21) in patients with and without PTT ablation, respectively ($p < 0.0001$, Wilcoxon's test).

A total of 73 patients received MRgFUS without any adverse effects. During the procedure, few patients developed complications related to the procedure itself: headache ($n = 4$), which resulted in procedure discontinuation in 1 case; increased blood pressure ($n = 5$); transitory obtundation ($n = 1$); arterial hypotension in response to medication

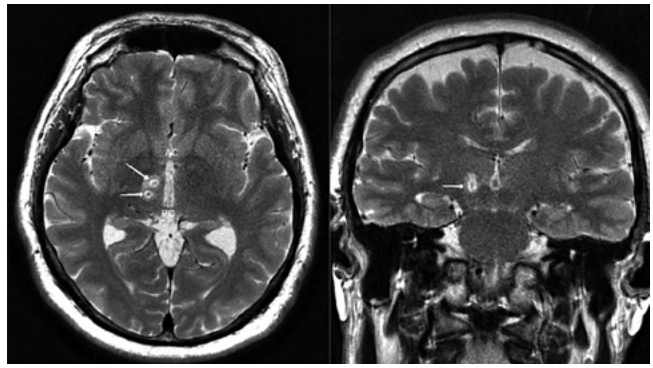

Fig. 3. Patient's MRI scan 2 h after simultaneous right-sided PTT + VIM ablation (axial and coronary planes).
Ablation lesions are shown with arrows.

administration during installation of the stereotactic frame ($n = 2$). No complications were observed after the end of treatment.

Several complications were observed in the early period after MRgFUS due to edema in the treatment target: apraxia within month 1 occurred in 6 out of 48 patients in the group with PTT ablation and 2 out of 34 in the group without PTT ablation ($p = 0.32$, χ^2 method): 2 patients had dysarthria, 1 had decreased flow of speech, and 1 had numbness of the tip of the tongue. Most of these symptoms improved by follow-up month 6. One year after surgery, apraxia persisted in 2 and 2 patients with and without PTT ablation, respectively.

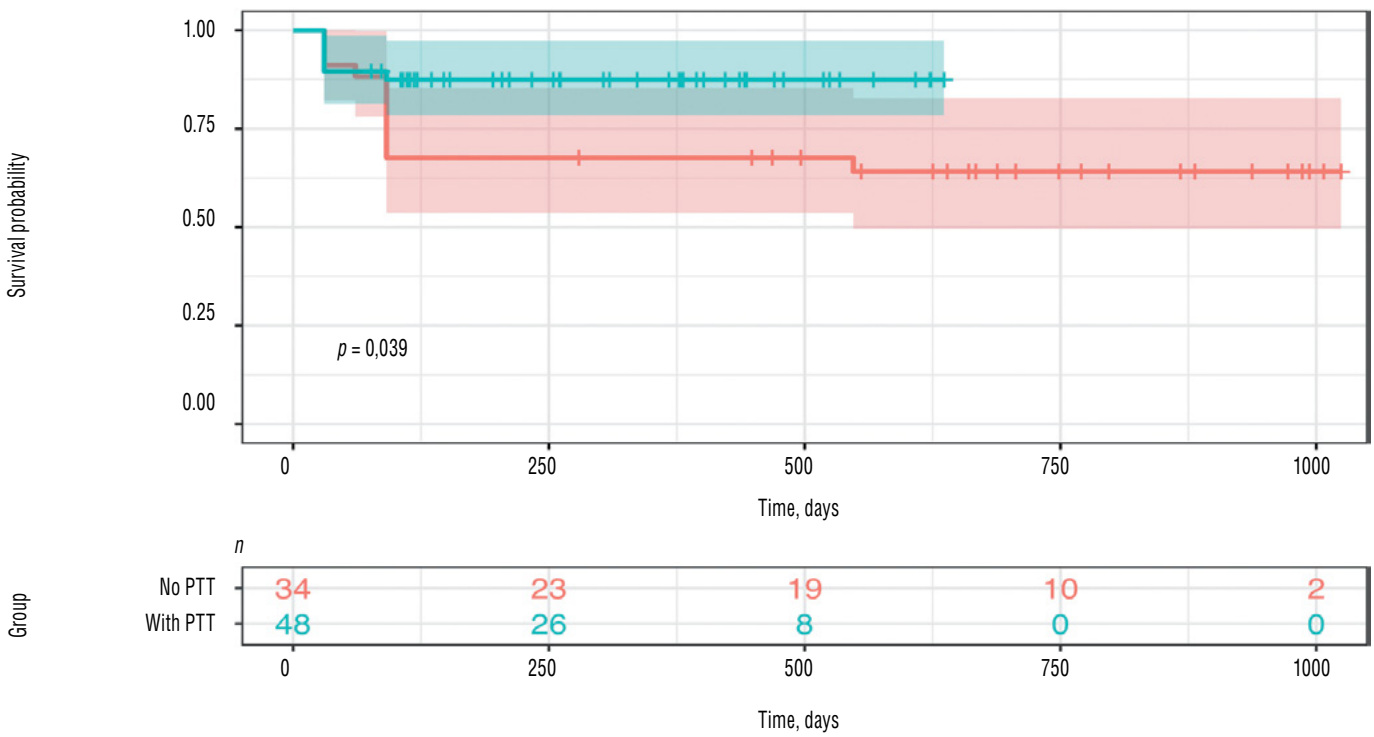

Fig. 4. Kaplan–Meier curve for symptom return depending on PTT targeting.

Median follow-up in TDPD patients after MRgFUS was 376 days (107.5; 612). Return of tremor (less pronounced compared with hyperkinesis before surgery) was recorded in 18 patients, including 5 and 13 patients with and without PTT ablation, respectively. Nine patients (2 women and 7 men; median age 63 (41; 69) years) of 18 received repeat treatment. All 9 patients did not receive PTT thalamotomy after specific targeting the VIM nucleus. During re-treatment, 5, 3, and 1 patient received PTT ablation, repeat VIM ablation, and PTT + VIM ablation, respectively. As a result, all patients achieved a satisfactory result without return of tremor throughout the entire follow-up period. In other 9 patients with tremor return, the symptoms were not significant enough to be an indication for re-treatment, and they remained being followed up.

We evaluated long-term treatment results after MRgFUS in men and women; no significant gender differences were found ($p = 0.64$; Kaplan–Meier method). However, when long-term treatment results were compared between single-target and dual-target treatment, long-term results were statistically significantly better in patients who received PTT + VIM ($p = 0.039$, Fig. 4).

Discussion

Treatment of TDPD patients is still a major challenge [1–3, 35]. The efficacy of conventional treatment with various groups of medications decreases over time, which is complicated by the development of persistent adverse effects [2, 8]. To date, DBS has been the best treatment option providing a significant reduction in tremor and other PD symptoms [10, 16–18]. However, DBS limitations include its invasive nature, complexity, implantation of the device into the body, insufficient availability, and the need for constant follow-up in large specialized medical centers in order to monitor the parameters of the generator.

In recent years, MRgFUS has been widely used to treat tremor-dominant Parkinson disease [12]. We reported our positive experience with MRgFUS in the treatment of 82 TDPD patients with a mean follow-up duration of 1 year or more, an improvement of MDS-UPDRS-III score of 40.1%, and no serious early or long-term complications. Here, we present a unique experience of dual-target MRgFUS in PTT and VIM. In 18 patients, tremor returned (all cases after VIM nucleus ablation); 9 of them successfully underwent re-treatment 6–9 months after the first procedure.

A thorough analysis of cases when tremor returned after MRgFUS and an assessment of treatment results in other centers allowed us to introduce MRgFUS PTT ablation (after its approval in 2021) in this category of patients in our clinical practice. According to our data, PTT ultrasound ablation in TDPD patients resulted in a greater improvement in early and long-term results compared with conventional VIM nucleus ablation, which is consistent to results of other authors [27]. Simultaneous dual-target (i.e. VIM and PTT) MRgFUS, which is reported in our publication, is a global priority since we have not found any previous studies on this topic, except for 3 cases of stepwise treatment [28].

Overall, an analysis of the early and long-term treatment results with MRgFUS showed that our data were comparable with efficacy and safety data in other studies [19–23, 27, 28]. In our opinion, simultaneous unilateral MRgFUS treatment can be considered an effective treatment option for patients with medication-resistant TDPD. To make a final decision on whether to include this method in the list of recommended treatment options for PD, determine precise criteria for patient selection, understand outcome variability, and assess the possibility of conducting bilateral interventions, multicenter studies in large cohorts of patients are needed.

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Phenotypes of COVID-19-Associated Dysautonomia in Patients Requiring Veno-Venous Extracorporeal Membrane Oxygenation

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Abstract

Background. *Patients with novel coronavirus infection (COVID-19) receiving veno-venous extracorporeal membrane oxygenation (VV-ECMO) are typically prone to hemodynamic disorders of various severity. Tachycardia, increased cardiac output, or arterial hypotension affect the effectiveness of VV-ECMO. One of the possible causes of hemodynamic disorders leading to ineffective VV-ECMO may be dysautonomia (DA), which refers to an imbalance of sympathetic and parasympathetic divisions of the autonomic nervous system (ANS). The development of DA in various critical conditions was described previously. Dysautonomia also develops in COVID-19 (COVID-19-associated DA), but it was studied only in stable non-ICU patients. The presented study focuses on COVID-19-associated DA in critical COVID-19 patients requiring VV-ECMO support.*
The study ***was aimed at*** *determining COVID-19-associated DA phenotypes, their impact on VV-ECMO effectiveness and disease outcomes.*
Materials and methods. *The study included 20 patients: 12 (60%) females, 8 (40%) males. The patients had an average age of 55 years. All the patients underwent 24-hour Holter monitoring with spectral analysis of heart rate variability (HRV) assessing low-frequency component of the spectrum (LF), the high-frequency component of the spectrum (HF), the LF/HF ratio on days 1, 3, and 5 of VV-ECMO. Diagnostic criteria for COVID-19-associated DA was a decrease in LF/HF < 2.28 or an increase in LF/HF > 6.94. The diagnostic criteria of predominant tone of sympathetic nervous system (sympathetic tone) was an increase in LF/HF > 6.94, while a decrease in LF/HF < 2.28 indicated predominant parasympathetic tone. Low sympathetic tone was determined by a decrease in LF < 15%, and an increase in LF > 40%. Low parasympathetic tone was determined by a decrease in HF < 15%, and an increase in HF > 25%. The criteria used were based on the results of previous studies.*
The following parameters were registered in the study population: VV-ECMO weaning, duration of respiratory and VV-ECMO support, length of stay in the intensive care unit (ICU) and in hospital, and disease outcomes.
Results. *COVID-19-associated DA was diagnosed in all the patients. LF/HF median value was 0.1. HRV spectrum parameters changed significantly over time: on day 5 of VV-ECMO support LF and HF values significantly decreased. The patients were divided into three groups according to the DA phenotype: group 1 (n = 4 [20%]) with normal sympathetic tone and high parasympathetic tone (nShP phenotype); group 2 (n = 14 [70%]) with low sympathetic tone and high parasympathetic tone (lShP phenotype); group 3 (n = 2 [10%]) with low sympathetic tone and normal parasympathetic tone (lSnP phenotype). The latter group was excluded from further statistical analysis due to the small sample size. In group 2, the mean HR was significantly higher compared with group 1. In group 1, VV-ECMO weaning was successful in 50% of cases, whereas in group 2 it was successful in 7.2% (p = 0.04).*
Conclusions. *To determine a dysautonomia phenotype, it is necessary to continuously monitor DA status in COVID-19 patients during VV-ECMO. Tachycardia in COVID-19 patients during VV-ECMO does not exclude the ANS imbalance with a significant predominance of parasympathetic tone over the sympathetic tone. It is this COVID-19-associated DA phenotype that is significantly associated with the unfavorable outcomes.*

Keywords: *COVID-19; novel coronavirus infection; dysautonomia; autonomic nervous system; extracorporeal membrane oxygenation*

Ethics approval. All patients provided their voluntary informed consent to participate in the study. The study was approved by the Ethics Committee of the Sklifosovsky Research Institute of Emergency Medicine (Protocol No. 11-22, dated 21 November 2022).

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Фенотипы COVID-19-ассоциированной дисавтономии у пациентов, нуждающихся в проведении вено-венозной экстракорпоральной мембранной оксигенации

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Аннотация

Актуальность. *При проведении вено-венозной экстракорпоральной мембранной оксигенации (вв-ЭКМО) у пациентов с новой коронавирусной инфекцией (COVID-19) типичны гемодинамические нарушения разной степени тяжести. Тахикардия, увеличение сердечного выброса или артериальная гипотензия влияют на эффективность вв-ЭКМО. Одной из возможных причин нарушений гемодинамики, приводящих к неэффективности вв-ЭКМО, может стать дисавтономия (ДА) – дисбаланс симпатического и парасимпатического отделов вегетативной нервной системы (ВНС). Ранее описано развитие ДА при различных критических состояниях. При COVID-19 также развивается ДА (COVID-19-ДА), но объектом исследований, её изучавших, были исключительно стабильные, нереанимационные пациенты. Представленное исследование посвящено проблеме COVID-19-ДА у пациентов с COVID-19, находящихся в критическом состоянии, требующем проведения вв-ЭКМО.*

Цель *исследования – определение фенотипов COVID-19-ДА, их влияния на эффективность вв-ЭКМО и исходы заболевания.*

Материалы и методы. *В исследование вошли 20 пациентов: 12 (60%) женщин, 8 (40%) мужчин. Средний возраст – 55 лет. Пациентам проводили суточное холтеровское мониторирование с оценкой спектральных параметров вариабельности сердечного ритма: низкочастотного (LF) и высокочастотного (HF) компонентов записи, отношения LF/HF на 1, 3, 5-е сутки проведения вв-ЭКМО. Критерием COVID-19-ДА являлось снижение LF/HF менее 2,28 или повышение LF/HF более 6,94. Критерием преобладающего тонуса симпатического отдела ВНС являлось увеличение LF/HF более 6,94, парасимпатического – снижение LF/HF менее 2,28. Критерием пониженного тонуса симпатического отдела ВНС являлось снижение LF менее 15%, повышенного – увеличение LF более 40%. Критерием пониженного тонуса парасимпатического отдела ВНС являлось снижение HF менее 15%, повышенного – увеличение HF более 25%. Используемые критерии были основаны на результатах ранее проведённых работ.*

У пациентов фиксировали факт отлучения от вв-ЭКМО, длительность респираторной терапии и вв-ЭКМО, длительность пребывания в отделении реанимации и интенсивной терапии и срок госпитализации, исходы заболевания.

Результаты. *COVID-19-ДА была диагностирована во всех наблюдениях. Медиана LF/HF составила 0,1. Параметры вариабельности сердечного ритма достоверно изменялись в динамике: на 5-е сут вв-ЭКМО достоверно снижались параметры LF и HF. В зависимости от тонуса симпатического и парасимпатического отделов ВНС пациенты были разделены на три группы: 1-я (n = 4; 20%) – фенотип с нормальным тонусом симпатического отдела и высоким тонусом парасимпатического отдела ВНС; 2-я (n = 14; 70%) – фенотип с пониженным тонусом симпатического отдела и высоким тонусом парасимпатического отдела ВНС; 3-я (n = 2; 10%) – фенотип с пониженным тонусом симпатического отдела и нормальным тонусом парасимпатического отдела ВНС (эта группа была исключена из дальнейшей статистической обработки, поскольку являлась малочисленной). Во 2-й группе средняя частота сердечных сокращений была достоверно выше по сравнению с 1-й группой. В 1-й группе отлучение от вв-ЭКМО было успешно в 50% случаев, тогда как во 2-й – в 7,2% (p = 0,04).*

Выводы. *При проведении вв-ЭКМО у пациентов с COVID-19 необходим продлённый мониторинг ДА для определения её фенотипа. Наличие тахикардии у пациентов с COVID-19 при проведении вв-ЭКМО не исключает наличия дисбаланса ВНС с существенным преобладанием тонуса парасимпатического отдела ВНС над симпатическим. Именно такой фенотип COVID-19-ДА достоверно ассоциирован с развитием неблагоприятного исхода.*

Ключевые слова: *COVID-19; новая коронавирусная инфекция; дисавтономия; вегетативная нервная система; экстракорпоральная мембранная оксигенация*

Этическое утверждение. Исследование проводилось при добровольном информированном согласии пациентов. Протокол исследования одобрен локальным этическим комитетом НИИ СП им. Н.В. Склифосовского (протокол № 11-22 от 21.11.2022).

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Introduction

Viral pneumonia caused by a novel coronavirus infection (COVID-19) leads to the development of acute respiratory distress syndrome (ARDS) in 8–15% of patients [1]. According to the current clinical guidelines, a veno-venous extracorporeal membrane oxygenation (VV-ECMO) should be initiated when a COVID-19 patient develops ARDS causing progressive refractory gas exchange impairment despite the use of lung-protective mechanical ventilation, adequate sedation, myorelaxation, and prone positioning [2].

COVID-19 patients requiring VV-ECMO are prone to hemodynamic disorders of various severity degrees: hypo- and hypertension, refractory tachycardia, which can affect the VV-ECMO effectiveness, causing a mismatch in minute volume between intrinsic and artificial blood circulation [3, 4]. Hemodynamic disorders in such patients may be caused by DA due to imbalance of sympathetic and parasympathetic divisions in the autonomic nervous system (ANS) [5]. DA develops in patients with critical conditions caused by a wide range of diseases. DA has also been described in COVID-19 patients (COVID-19-associated DA) [6–8]. Previously published studies on COVID-19-associated DA are mostly based on the data obtained from stable non-ICU patients. We were unable to find studies on COVID-19-associated DA in critical ICU-patients requiring VV-ECMO in available literature. Our study focuses on this issue.

The study **was aimed at** determining COVID-19-associated DA phenotypes, their impact on VV-ECMO effectiveness and disease outcomes.

Materials and methods

Inclusion criteria:
- aged 18 years and older;
- confirmed COVID-19 diagnosis;
- ARDS with refractory gas exchange impairment;
- need for VV-ECMO support.

Exclusion criteria:
- atonic coma;
- persistent or paroxysmal atrial fibrillation;
- sinoatrial block, sick sinus syndrome; atrioventricular block;
- high-grade premature ventricular contractions (Lown grade IVa, IVb, V);
- artificial cardiac pacemaker;
- dysautonomia diagnosed prior to COVID-19.

All patients were provided with the full range of necessary medical care approved by the temporary guidelines of the Ministry of Health of the Russian Federation on prevention, diagnosis and treatment of COVID-19, valid in the period of the treatment [9].

On admission, patients underwent chest computed tomography (CT) using Aquilion Prime CT scanner (Toshiba) with subsequent assessment of lung injury severity. In case of respiratory dysfunction, the patients were provided with respiratory support using SV300 ventilator (Mindray), non-invasive ventilation (NIV) with high-flow oxygen and mask ventilation, and invasive mechanical ventilation. Sedation and myorelaxation as indicated to patients were performed by prolonged intravenous infusion of propofol at a dose of 4–12 mg/kg per hour and

rocuronium bromide at a dose of 0.3–0.6 mg/kg per hour. If COVID-19-associated DA was suspected, we initiated intravenous or enteral administration of β-blockers (esmolol, metoprolol at appropriate doses) and intravenous infusion of dexmedetomidine (DMM, central α-sympathomimetic) at a dose of 0.7–1.4 μg/kg per hour. This therapy strategy was proposed by A. Rudiger et al. for managing dysautonomia symptoms in sepsis and was called decatecholaminization [20]. Myocardial contractility and volemic status were evaluated on transthoracic echocardiogram (TTE) using MyLab 70 ultrasound system (Esaote).

Indications for VV-ECMO [10]:
- ratio of arterial oxygen partial pressure and fraction of oxygen in inspired air (PaO_2/FiO_2) < 150 mm Hg, or
- PaO_2/FiO_2 < 60 mm Hg > 6 hours, or
- PaO_2/FiO_2 < 50 mm Hg > 3 hours, or
- pH < 7.20 and arterial partial CO_2 pressure ($PaCO_2$) > 80 mm Hg > 6 hours, or
- $PaO_2/FiO_2 \geqslant$ 150 mm Hg with pH < 7.20 and $PaCO_2$ > 80 mm Hg > 6 hours.

Contraindications for VV-ECMO [10]:
- patients over 70 years;
- duration of mechanical ventilation prior to VV-ECMO > 10 days;
- inability of cannulla placement;
- contraindications to anticoagulant therapy;
- concomitant incurable end-stage diseases.

DA was diagnosed by heart rate variability (HRV) parameters obtained during 24 h Holter monitoring using CardioMem CM 3000 Digital Recorder (GE). Holter monitoring allowed to assess heart rate (HR), low-frequency component of the HR variability spectrum associated with sympathetic tone (LF), high-frequency component associated predominantly with parasympathetic tone (HF), and LF/HF ratio.

Reference values for the monitored parameters [11–14, 28–31]:
1) average 24 h HR: 60–80 bpm;
2) LF percentage in total frequency spectrum: 15–40%;
3) HF percentage in total frequency spectrum: 15–25%;
4) LF/HF: 2.28–6.94.

Altered LF/HF ratio may indicate an ANS imbalance. HRV spectrum analysis allows to determine the dysautonomia phenotype based on the assessment of the sympathetic and parasympathetic tones. The LF/HF ratio below the reference values indicates the predominant parasympathetic tone [31], above the reference values – the predominant sympathetic tone [31].

Patients underwent 24 h Holter monitoring with the assessment of the above parameters on days 1, 3 and 5 of VV-ECMO. Data containing significant errors making more than 20% of the Holter recording and confounding HRV assessment were excluded from further analysis. The following parameters were registered in the study population: the results of the VV-ECMO weaning, duration of respiratory therapy and VV-ECMO, length of stay in the ICU and in hospital, and disease outcomes.

Statistical data were processed using Statistica 12 software (StatSoft). Data per group were compared using the Mann–Whitney method, qualitative inter-group variables were compared using Fisher's exact test, intra-group parameters (dependent variables) were assessed using Wilcoxon test.

Results

The study was conducted in the ICU of the infectious diseases department in Sklifosovsky Research Institute of Emergency Medicine, Moscow, Russia from September 2021 till February 2022. The study included 20 patients (12 (60%) females and 8 (40%) males) with COVID-19-associated ARDS requiring VV-ECMO. The average age of the patients was 55 years. Table 1 presents general characteristics of the patients included in the study at their ICU admission prior to VV-ECMO.

COVID-19-associated DA was diagnosed in all the patients. Table 2 presents HRV parameters reflecting the ANS balance.

The obtained data demonstrate significant changes of sympathetic and parasympathetic tones in COVID-19 patients. So, LF and HF values significantly decreased on day 5 of VV-ECMO. These data indicate the need to monitor HRV in COVID-19 patients during at least the whole period of VV-ECMO support.

Depending on COVID-19-associated DA phenotype, namely, on sympathetic and parasympathetic ANS activity, the patients were divided into three groups:
5) group 1, *n* = 4 (20%): normal sympathetic tone and high parasympathetic tone (nShP);
6) group 2, *n* = 14 (70%): low sympathetic tone and high parasympathetic tone (lShP);
7) group 3, *n* = 2 (10%): low sympathetic tone and normal parasympathetic tone (lSnP).

Since group 3 included only 2 patients, the analysis data would be considered not eligible for formal analysis. Therefore, data from group 3 were removed from further analysis and interpretation of its results. Only data from groups 1 and 2 were compared. These groups were statistically similar by age, gender, severity of condition at admission and at the time of VV-ECMO start, and concomitant diseases (Table 3).

Table 1. General characteristics of patients included in the study at their ICU admission prior to VV-ECMO

Parameter	Value
Age, years, Me (Q_1; Q_3)	55.00 (38.25; 60.00)
Gender, *n* (%)	
males	8 (40)
females	12 (60)
Concomitant diseases, *n* (%)	
arterial hypertension	13 (65)
diabetes mellitus	3 (15)
chronic heart failure	2 (10)
General data, Me (Q_1; Q_3)	
time from disease onset to admission, days	14.50 (11.00; 25.00)
time from admission to VV-ECMO start, days	1.50 (1.00; 3.00)
time from disease onset to VV-ECMO start	17.50 (15.00; 28.75)
Respiratory support, *n* (%)	
NIV	9 (45)
invasive mechanical ventilation	11 (55)
Gas exchange parameters (with respiratory support), Me (Q_1; Q_3)	
P/f	94.00 (89.25; 96.00)
SpO_2, %	92.00 (62.75; 110.00)
Lung injury CT score, *n* (%)	
CT-3	4 (20)
CT-4	16 (80)
Complications, *n* (%)	
bacterial inflammation	11 (55)
sepsis	3 (15)
septic shock	1 (5)

Note. Me — median; Q_1 — lower quartile; Q_3 — upper quartile.

Table 2. Changes in HR and HRV parameters, Me (Q_1; Q_3)

Parameter	VV-ECMO duration, days		
	1	3	5
n	20	20	19
24 h HR, bpm	84.50 (77.50; 97.75)	83.50 (75.00; 98.75)	84.00 (65.00; 101.00)
LF, %	5.60 (2.02; 9.22)	8.99 (2.92; 12.75)	2.98* (1.13; 6.48)
HF, %	53.50 (31.13; 70.57)	53.30 (45.88; 61.60)	29.95* (15.18; 43.23)
LF/HF	0.1 (0.04; 0.23)	0.12 (0.05; 0.3)	0.11 (0.03; 0.18)

Note. *$p < 0.05$ compared with day 3 of VV-ECMO.

Table 3. General characteristics of patients in group 1 and group 2

Parameter	Group	
	1	2
n	4	14
Age. years. Me (Q_1; Q_3)	46.50 (37.50; 58.50)	57.50 (40.20; 62.00)
Gender. *n* (%)		
males	1 (25)	6 (42.8)
females	3 (75)	8 (57.2)
Concomitant disease. *n* (%)		
arterial hypertension	3 (75)	10 (71.4)
diabetes mellitus	1 (25)	2 (14.2)
chronic heart failure	0	2 (14.2)
Respiratory support at admission. *n* (%)		
NIV	2 (50)	6 (42.8)
invasive mechanical ventilation	2 (50)	8 (57.2)
Respiratory support at VV-ECMO start, *n* (%)		
NIV	0	2 (14.2)
invasive mechanical ventilation	4 (100)	12 (85.7)
Lung injury CT score. *n* (%)		
CT-3	2 (50)	1 (7.1)
CT-4	2 (50)	13 (92.9)

Table 4. Comparative HR and HRV analysis in group 1 and group 2 on day 1 of VV-ECMO, Me (Q_1; Q_3)

Parameter	Group	
	1	2
n	4	14
24 h HR, bpm	74.00 (65.00; 82.25)	86.50* (79.75; 97.25)
LF, %	24.67 (17.55; 31.24)	5.30** (2.06; 7.52)
HF, %	54.42 (36.54; 57.14)	56.00 (41.96; 74.20)
LF/HF	0.47 (0.43; 0.58)	0.09** (0.03; 0.12)

Note. *$p < 0.05$; **$p < 0.001$ compared with group 1.

Results of comparative HR and HRV analysis in group 1 and group 2 on day 1 of VV-ECMO are presented in Table 4.

According to the presented data, HR in group 2 was significantly higher compared with group 1. Considering lower sympathetic tone in group 2 patients, such HR values make a data paradox.

The groups were statistically similar by the duration of VV-ECMO, mechanical ventilation, length of ICU and hospital stay, and the frequency of outcomes, except for the frequency of weaning patients from VV-ECMO (Table 5). In group 1 VV-ECMO weaning was successful in 50% patients, while in group 2 — in 7.2% patients ($p = 0.04$). From all the patients included in the study, a patient from group 2 was the only survivor. This fact suggests an importance of the said inter-group difference. However, statistical analysis revealed no significant difference in mortality between the groups.

There were no significant differences across the groups in myocardial contractility and volemic status based on TTE results (see Table 6). Importantly, the TTE results in both groups were within normal range.

Taking into account the data on the β-blockers and DMM effectiveness in the managing DA symptoms using decatecholaminization strategy, as well as the potential influence of sedatives and myorelaxants on the ANS balance, we performed a comparative analysis between the groups by the frequency of using these agents by all study time points (Table 7).

Table 5. Comparison of groups by outcomes

Parameter		Group 1	Group 2
n		4	14
Mechanical ventilation duration, days	Me (Q_1; Q_3)	20.50 (6.00; 35.00)	11.00 (6.75; 13.25)
VV-ECMO duration, days	Me (Q_1; Q_3)	6.00 (6.00; 7.50)	8.50 (5.00; 12.25)
Length of ICU stay, days	Me (Q_1; Q_3)	16.50 (8.00; 32.50)	12.00 (7.75; 16.50)
Length of hospital stay, days	Me (Q_1; Q_3)	21.50 (8.00; 35.00)	12.00 (7.75; 16.50)
VV-ECMO-weaning	*n* (%)	2 (50)	1* (7.2)
Survived	*n* (%)	0	1 (7.2)
Deceased	*n* (%)	4 (100)	13 (92.8)

Note. *$p < 0.05$ compared with group 1.

Table 6. Comparison of the groups by TTE parameters

Parameter		Normal	Group 1	Group 2
n			4	14
Left ventricular ejection fraction, %	Me (Q_1; Q_3)	55–65	58.50 (52.75; 68.75)	62.50 (53.00; 66.25)
Left ventricular end-diastolic volume, ml	Me (Q_1; Q_3)	55–149	109.50 (100.75; 149.00)	104.50 (95.50; 112.50)
Left ventricular end-systolic volume, ml	Me (Q_1; Q_3)	18–40	44.50 (32.75; 66.00)	39.00 (33.50; 48.50)
Left ventricular stroke volume, ml	Me (Q_1; Q_3)	50–70	74.00 (57.25; 84.75)	68.00 (60.75; 73.50)
Inferior vena cava collapsibility > 50%	*n* (%)		1 (25)	6 (42.8)

Table 7. Comparison of groups by frequency of using sedatives, myorelaxants, and β-blockers, *n* (%)

Indicated agent	VV-ECMO duration, days 1		3		5	
	group 1	group 2	group 1	group 2	group 1	group 2
n	4	14	4	14	4	14
β-Blockers	2 (50)	8 (57.2)	2 (50)	8 (57.2)	2 (50)	6 (42.8)
β-Blockers and DMM	1 (25)	3 (21.4)	2 (50)	5 (35.7)	2 (50)	7 (50)
Propofol	3 (75)	11 (78.5)	0	8* (57.2)	1 (25)	9 (64.2)
Myorelaxants	3 (75)	9 (64.2)	0	7 (50)	1 (25)	7 (50)

Note. *$p < 0.05$ compared with group 1.

The presented data indicate that group 2 patients significantly more often received intravenous propofol infusion only on day 3 of VV-ECMO (p = 0.04). The frequency of using β-blockers, DMM, myorelaxants, and propofol on day 1 and day 3 of VV-ECMO in both groups is statistically similar. Moreover, DA phenotype was determined on day 1 of VV-ECMO, when the frequency of using agents that might affect the ANS was similar in both groups.

Discussion

The main objective of the presented study is to define the problem of dysautonomia in ICU patients in general and in COVID-19 patients requiring VV-ECMO as one of the most demanding ICU patient populations in particular. Based on the data obtained, we could emphasize two basic points. First, dysautonomia was present in all the patients with severe COVID-19, advanced ARDS, and the need for VV-ECMO. Second, based on the tone of the sympathetic and parasympathetic divisions of the ANS, we distinguished three COVID-19-associated DA phenotypes: nShP; lShP and lSnP. In our opinion, such a methodological approach to the DA issue in critically ill patients is innovative and extremely practical. It may lead to conceptual changes in the management of patients with critical conditions. It clarifies the necessity to monitor the ANS status, to prevent the development of hemodynamic disorders, and to apply targeted management taking into account the personal phenotype of DA.

The DA issue is not new for intensive care practice. Dysautonomia is a frequent and typical manifestation of CNS failure in neurological ICU patients. HRV analysis data in patients with traumatic brain injury indicate DA development with predominant sympathetic tone in 8–20% cases [15]. HRV analysis in patients with aneurysmal subarachnoid hemorrhage demonstrates a pronounced increase in sympathetic tone [16]. High sympathetic tone is also typical for acute stroke patients [17]. In patients with combined trauma and sepsis, sympathetic tone also predominates significantly more often [18, 19].

Based on the results of these studies, the concept of decatecholaminization was developed, which subsequently successfully proved its effectiveness in ICU patients [20]. This concept is based on the combined use of DMM and esmolol. Combination of these agents inhibits the sympathoadrenal response developing in critical conditions. Septic shock treatment with DMM allows to reduce plasma concentrations of adrenaline by 40% [21]. Esmolol reduces mortality almost 2-fold (from 80.5% to 49.4%) in patients with septic shock and the need for high-dose vasopressor support.[22] All the decatecholaminization studies indicate that the combination of DMM and esmolol is effective in patients with DA associated with high sympathetic tone.

Subsequent studies have shown the heterogeneity of DA manifestations in ICU patients. For example, the predominance of sympathetic tone in sepsis, reflecting the activation of compensatory mechanisms to maintain homeostasis at the onset of bacterial inflammation, is subsequently replaced by the predominant parasympathetic tone. In this case, the severity of septic shock correlates with an increase in parasympathetic tone [23]. HRV analysis in stable non-ICU COVID-19 patients indicates predominance of parasympathetic tone [24]. Our study also demonstrated a significant and substantial predominance of parasympathetic tone over sympathetic tone in critical COVID-19 patients requiring VV-ECMO.

COVID-19 is known to cause both morphologic and functional damage to the central nervous system, where the ANS regulatory centers (paraventricular structures, the olfactory tract, the hippocampus) have been damaged earlier and more severely than the others [25]. It is the ANS regulation centers failure, as well as involvement of the vagus nerve in the COVID-19 pathogenesis, that might be the reason for the COVID-19-associated DA and, consequently, the predominance of parasympathetic tone.

The outcomes of VV-ECMO in COVID-19 patients are significantly and substantially worse compared to other ICU patients [26]. We believe that it is COVID-19-associated DA that plays an important, if not leading, role in those pathologic processes that trigger unfavorable disease outcomes in extremely severe COVID-19 patients. However, it remains unknown whether it is COVID-19-associated DA that causes severe disease course or it is an epiphenomenon.

Our study identified three COVID-19-associated DA phenotypes, which is a unique interpretation of the DA issue in the ICU patients. The most common lShP phenotype is significantly associated with failure to successfully complete VV-ECMO. On the contrary, successful VV-ECMO weaning was significantly more frequent in patients with nShP phenotype. Failure to wean the patient from VV-ECMO means inability to compensate for gas exchange impairment as a result of persisting hypoxemia, which eventually leads to the development of multi-organ dysfunction and lethal outcomes. In this regard, matching in minute volume between intrinsic and artificial blood circulation is one of the goals of intensive therapy, which allows to achieve adequate parameters of gas exchange and to avoid the development of multi-organ dysfunction and, consequently, an unfavorable outcome.

According to the data obtained, there were no significant inter-group differences in the frequency of using β-blockers and DMM for decatecholaminization. It is the concept of decatecholaminization proposed as an effective management strategy for DA with high sympathetic tone that is hypothetically promising for matching in minute

volume between intrinsic and artificial blood circulation due to reduction of a patient's cardiac output. However, our study showed that patients with COVID-19-associated DA and the need for VV-ECMO predominantly develop a DA phenotype with a depressed sympathetic tone, while the parasympathetic tone is dramatically elevated. At the same time, there is a lack of application of the decatecholaminization strategy for COVID-19-associated DA management. This also explains why the course of the disease associated with high parasympathetic tone is more severe, outcomes are unfavorable, and management methods are lacking.

An interesting result of the study is that patients with lShP phenotype significantly more often received prolonged intravenous propofol infusion on day 3 of VV-ECMO. A more pronounced ANS imbalance and worse outcomes in this group suggest that the use of propofol for pharmacological sedation should be avoided in this cohort of patients. Propofol is likely to adversely affect the ANS balance, thereby intensifying DA and worsening the disease outcomes. However, the lack of significant difference between these two groups on day 1 of VV-ECMO in the frequency of the propofol use (and the use of other agents theoretically affecting the ANS) suggests that the COVID-19-associated DA phenotype is independent of propofol.

Another unique finding of the presented study is a significantly higher HR in the lShP group compared with the nShP group. In our opinion, this phenomenon is worthy of a separate description and further study. To define this phenomenon, we propose a term 'the ANS paradox' referring to a condition in which patients with lShP phenotype develop persistent tachycardia or an overt tendency to tachycardia. The main issue of the 'ANS paradox' is that tachycardia leads to obvious complications (such as persistent hypoxemia in patients with VV-ECMO support), while pharmacological heart rate lowering with β-adrenoblockers and central α-adrenomimetics leads to even greater ANS imbalance and, consequently, to more severe DA. It is noteworthy that statistical analysis of TTE parameters in patients of both groups revealed no significant differences. Normal TTE values indicate that tachycardia is not associated with hypovolemia or a hyperdynamic circulation.

A major issue to be addressed in future studies is the choice of optimal therapy for DA with an lShP phenotype. Controlled hypothermia could become such a therapy option. It is well known that moderate hypothermia reduces a patient's cardiac output by developing bradycardia and depressing metabolism. This leads to matching in minute volume between intrinsic and artificial blood circulation under VV-ECMO without affecting adrenoreceptors and, consequently, without worsening of the already distorted ANS imbalance [27].

The presented study has a number of limitations. First, it is a monocenter study. Second, the study included only 20 patients. From a formal point of view, this is a small sample size. However, given the unique study population and the phenomenon under investigation – COVID-19-associated DA in VV-ECMO – the volume of clinical material is perceived as sufficient and unparalleled in world practice. Third, the main method of DA diagnostics is the analysis of Holter ECG monitoring. Critically ill patients received a large number of drugs that influenced the ANS tone: sedatives and narcotic drugs, β-blockers and central α-sympathomimetics. Although for most of these drugs (with the exception of propofol) the frequency and duration of use in the groups were similar, we still suspect that the use of these drugs may have influenced our findings. Because of the above limitations, further studies are needed to address the issue of DA in the ICU patients requiring VV-ECMO.

Conclusion

1. COVID-19-associated DA is observed in all COVID-19 patients receiving VV-ECMO support, making prolonged monitoring of ANS status with HRV analysis mandatory.

2. COVID-19-associated DA has three phenotypes: phenotype with normal sympathetic tone and high parasympathetic tone (nShP); phenotype with low sympathetic tone and high parasympathetic tone (lShP); phenotype with low sympathetic tone and normal parasympathetic tone (lSnP). In terms of VV-ECMO effectiveness and the possibility of weaning, the lShP phenotype is the worst.

3. COVID-19-associated DA is characterized by the 'ANS paradox': tachycardia associated with lShP phenotype. The use of decatecholaminization strategy (DMM and esmolol), widespread in modern intensive care, in patients with this DA phenotype is pathophysiologically incorrect. In this regard, further studies are needed to manage the ANS tone in patients with the 'ANS paradox' and the DA phenotype with predominant parasympathetic tone. Controlled hypothermia may become such a method of intensive therapy.

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Functional MRI-guided Repetitive Transcranial Magnetic Stimulation in Cognitive Impairment in Cerebral Small Vessel Disease

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Abstract

Introduction. *Cerebral small vessel disease (CSVD) is one of the leading causes of vascular and mixed cognitive impairment (CI). Treatment options for CSVD-associated CI are limited. Repetitive transcranial magnetic stimulation (rTMS) is a promising non-drug treatment option.*
The aim of the study was to evaluate the effects of 10 rTMS sessions of the left dorsolateral prefrontal cortex (DLPFC) on cognitive functions in CSVD patients.
Materials and methods. *The study included 30 patients with CSVD and moderate CI randomized to the active (DLPFC stimulation; n = 20) and control (vertex stimulation; n = 10) groups. Both groups received 10 sessions of high-frequency rTMS. The DLPFC target was selected based on the individual paradigm fMRI data with a focus on executive functions. Cognitive function was assessed using the Montreal Cognitive Assessment Scale (MoCA), the Trail Making Test (TMT), the Tower of London Test, and the Rey–Osterritz Complex Figure Test before, immediately after, and 3 months after the stimulation. Adverse events were assessed using standardized questionnaires.*
Results. *The active group showed a significantly better effect compared to the control group according to MoCA, TMT A and B, The Tower of London Test, delayed recall on the Rey–Osterrieth Complex Figure Test immediately after the stimulation and MoCA, TMT A and B and The Tower of London 3 months after the stimulation. Adverse events in the study were mild and did not affect treatment adherence.*
Conclusion. *rTMS is a promising, safe, and well-tolerated treatment option for mild cognitive impairment in CSVD. However, additional research is needed to make recommendations for its clinical use.*

Keywords*: repetitive transcranial magnetic stimulation; non-invasive brain stimulation; mild cognitive impairment; vascular cognitive impairment; cerebral small vessel disease*

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. 12-4/16, December 14, 2016).

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фМРТ-направленная ритмическая транскраниальная магнитная стимуляция в терапии когнитивных расстройств при церебральной микроангиопатии

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Аннотация

Введение. *Церебральная микроангиопатия (ЦМА)/болезнь мелких сосудов – основная причина сосудистых и смешанных с дегенерацией когнитивных расстройств (КР). Возможности терапии КР при ЦМА ограничены. Ритмическая транскраниальная магнитная стимуляция (рТМС) является перспективным методом их немедикаментозной терапии.*

Цель исследования *– оценить эффект 10 сессий рТМС левой дорсолатеральной префронтальной коры (ДЛПФК) на когнитивные функции у пациентов с ЦМА.*

Материал и методы. *В исследовании участвовали 30 пациентов с ЦМА и умеренными КР. Они были рандомизированы в активную (стимуляция ДЛПФК; n = 20) и контрольную (стимуляция вертекса; n = 10) группы. В обеих группах проведено 10 сессий высокочастотной рТМС. Мишень в пределах ДЛПФК выбиралась по индивидуальным данным фМРТ с парадигмой на управляющие функции мозга. Когнитивные функции оценивали по Монреальской шкале оценки когнитивного статуса (МоСА), тесту построения пути (ТМТ), «башне Лондона» и комплексной фигуре Рея–Остеррица до, сразу после и через 3 мес после стимуляции. Нежелательные явления оценивали по стандартизированным опросникам.*

Результаты. *Сравнение эффектов между группами показало статистически значимо лучший эффект в активной группе, чем в контрольной, по результатам шкалы МоСА, тестов построения пути А, В, «башня Лондона», отсроченному воспроизведению комплексной фигуры Рея–Остеррица сразу после стимуляции и шкалы МоСА, тестов ТМТ А, В и «башня Лондона» через 3 мес после стимуляции. Наблюдаемые в исследовании нежелательные явления были лёгкими по выраженности и не влияли на приверженность пациентов лечению.*

Заключение. *рТМС является многообещающим, безопасным и хорошо переносимым методом терапии умеренных КР при ЦМА, однако для формирования рекомендаций по применению в клинической практике необходимы дополнительные исследования.*

Ключевые слова*: ритмическая транскраниальная магнитная стимуляция; неинвазивная стимуляция головного мозга; умеренные когнитивные расстройства; сосудистые когнитивные расстройства; болезнь мелких сосудов; церебральная микроангиопатия.*

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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

Cerebrovascular disease is the second most common cause of cognitive impairment after Alzheimer's disease [1]. Cerebral small vessel disease (CSVD) is a leading cause of vascular cognitive impairment [2, 3]. Currently, treatment options for vascular cognitive impairment are limited [4].

Mild cognitive impairment (MCI) is a decline in cognitive function that exceeds that of normal aging but does not meet the clinical criteria for dementia [5]. In the population aged 65 years and older, the MCI prevalence is equal to or greater than that of dementia and may reach 42% [6]. However, MCI not only deteriorates quality of life [7], but is also an independent risk factor of dementia; 20–30% of cases of mild cognitive impairment progress to dementia within 6 years [1].

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method increasingly used to treat neurological disorders [8]. The mechanism of the therapeutic rTMS effect is usually associated with TMS-induced synaptic plasticity [9].

rTMS is best studied for treatment of Alzheimer's cognitive impairment. A meta-analysis included 12 studies (n = 231) with different rTMS protocols, including multi-target stimulation and stimulation of the dorsolateral prefrontal cortex (DLPFC). A statistically significant improvement in cognitive function was found in the active stimulation group compared to the control group. The effect was greater in milder forms of Alzheimer's disease [10]. The most compelling evidence for efficacy was obtained using a multi-target rTMS protocol combined with target-specific cognitive training, called rTMS-COG. In the international expert recommendations, this protocol was assigned a level of evidence C [8]. A randomized, placebo-controlled study showed a statistically significant effect of high-frequency rTMS of the left DLPFC on memory in elderly patients with amnestic MCI [11].

A relatively large number of studies evaluated the use of TMS in Alzheimer's disease and amnestic MCI (as a predementia stage of Alzheimer's disease). The use of TMS in vascular cognitive impairment has been less studied. Most studies evaluated the diagnostic use of TMS, while only few studies evaluated the therapeutic effect of rTMS [12–14]. Two studies investigated the effect of a single rTMS session on the left DLPFC. I. Rektorova et al. showed that executive functions (EF) measured with the Stroop test improved after 1 rTMS session [12]. S. Sedlackova et al. found no statistically significant differences between stimulation of DLPFC and M1 (control target) [13]. One of more recent studies showed the effect of supplementary motor area rTMS on cognitive functions in CSVD patients with MCI [14]. There are no studies on the efficacy of multiple sessions of the left DLPFC rTMS in CSVD patients.

It is important to explore the potential of personalized targets for rTMS due to the structural and functional heterogeneity and interindividual anatomical variability of the cerebral cortex. One way of personalization is to use structural neuroimaging to construct a 3D model of the head and then to overlay functional neuroimaging data such as resting-state fMRI and task fMRI [15]. For example, functional connectivity-based personalization is being actively studied in depression [16-19]. Task fMRI-guided navigated TMS is actively used in studies with healthy volunteers [20], but is rarely applied in clinical practice (J.P. Szaflarski et al. reported its use in patients with post-stroke aphasia [21]).

The **aim** of this study was to evaluate the immediate and delayed effects of 10 sessions of fMRI-guided high-frequency rTMS of the left DLPFC on cognitive functions in CSVD patients with MCI.

Materials and methods

This randomized, double-blind, placebo-controlled, parallel study was conducted at the Research Center of Neurology.

Inclusion criteria:
- Age of 45 to 80 years,
- CSVD diagnosed according to STRIVE guidelines (2013) [22],
- MCI diagnosed using VASCOG criteria [23],
- No changes in treatment for cognitive impairment or use of other central nervous system agents for 1 month before rTMS, during rTMS, and for 3 months after the stimulation.

Exclusion criteria:
- Contraindications to rTMS and/or MRI,
- History of stroke (except lacunar one),
- History of epilepsy or epileptiform discharges on EEG,
- Use of antidepressants and antipsychotics,
- Decompensation of severe somatic disease,
- Mental disorder or alcohol and/or drug abuse.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Federal State Budgetary Scientific Institution "Research Center of Neurology" (Protocol No. 12-4/16 dated 14 December 2016). Prior to enrollment, all patients signed an informed consent form.

Design of the study

After enrollment, all patients were randomized using sealed envelope method in a 2:1 ratio to active stimulation (left DLPFC) or control stimulation (vertex area).

Prior to stimulation (T0), cognitive functions were assessed, and patients underwent task fMRI. Subsequently, 10 rTMS sessions (5 sessions per week) were performed. Cognitive functions were reassessed immediately (T1) and 3 months (T2) after the rTMS treatment. The investigator performing the initial clinical assessment for eligibility and repeated cognitive assessments at each stage was blinded to the stimulation protocols.

Cognitive function tests

The Montreal Cognitive Assessment Test (MoCA) was used to assess general cognitive status. Additional tests were used to assess EF and visuospatial functions [24]. EF was assessed using the Trail Making Test (TMT), with the TMT-A subtest assessing psychomotor speed and the TMT-B subtest assessing divided attention, and the Tower of London test assessing cognitive control. Visuospatial functions were assessed by copying the Rey–Osterrith Complex Figure Test (ROCF), and nonverbal memory was assessed by delayed recall of the CF 30 min after copying [25].

Neuroimaging

All patients had structural MRI and task fMRI on a 3T Magnetom Verio (Siemens) for determination of the stimulation target. The anatomical structure was visualized using a 3D-T1 gradient echo with multiplanar reconstruction (3D-T1 MPR) sequence consisting of 176 sagittal slices (TR = 1940 ms; TE = 308 ms; interslice interval = 0.5 mm; field of view = 250 mm; matrix = 256×256; slice thickness = 1 mm). The paradigm fMRI used an axial T2* gradient echo sequence (TR = 3000 ms; TE = 30 ms; slice thickness = 3 mm).

The paradigm had a block design and consisted of 4 activation blocks and 4 rest blocks, with each block lasting 30 s. Before the start and at the end of each activation block, subjects were verbally instructed to start or stop the task. They were asked to count silently starting from 1 and skipping multiples of 3. When the next activation block began, the patient repeated counting from 1 [26]. Before the MRI, the patient was trained to perform the task outside the scanner under the supervision of the investigator.

SPM12 for MATLAB R2018a (Mathworks) was used for preprocessing and statistical analysis of individual fMRI data to determine the stimulation target[1]. The first level analysis used a regressor with a value of 1 in the activation block, 0 in the rest block, and a T-contrast corresponding to the regressor with a voxel-wise significance threshold of 0.001 without correction. The data obtained were co-registered with the structural data and uploaded to the navigation system. The rTMS target was positioned within the left DLPFC (corresponding to the middle frontal gyrus) according to the visually detectable maximum activation.

Transcranial magnetic stimulation

The navigation system of the NBS eXimia Nexstim stimulator (Nexstim Plc) was used for fMRI-guided navigation rTMS. The target for active stimulation was located in the DLPFC while the control group used the vertex detected by visible anatomical landmarks. For rTMS, a Magstim Rapid 2 stimulator (Magstim Company Ltd.) was used with a figure-of-eight coil calibrated for navigation. Stimulation was performed at an intensity of 100% of the resting motor threshold of *m. abductor pollicis brevis*, determined using the Rossini–Rothwell algorithm [27]. In both groups, high-frequency rTMS was performed with a stimulation frequency of 20 Hz, 2-second trains with a 28-second intertrain interval, 2400 stimuli per session, for a total of 10 sessions. Patients completed standardized TMS tolerability questionnaires (adverse events (AEs) during stimulation and within 24 hours after the stimulation).

Statistical analysis

MATLAB R2018a (Mathworks) was used for statistical analysis. Normal distribution was tested using the Shapiro–Wilk test. The data were non-Gaussian distributed, so non-parametric methods were used. The Friedman test was used to determine changes in cognitive test scores between the 3 intra-group measurements. The Wilcoxon test was used for paired intra-group comparisons. The Mann–Whitney test was used to compare quantitative characteristics between groups (comparison of effects). The Fisher's test (for binary characteristics) and the Fisher–Freeman–Halton test (for 3 levels of the Fazekas scale) were used for comparing qualitative parameters. Changes were considered significant at $p < 0.05$.

Results

Patients

A total of 96 patients were screened for the study, of which 30 patients were included into the final analysis (Figure 1). There were no statistically significant differences in gender, age, severity of neurological symptoms, or cognitive test scores between two groups (Table 1).

All patients underwent paradigm fMRI with a target identification in the left DLPFC. Figure 2 shows the stimulation target localization for the active group.

[1] Statistical Parametric Mapping; Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK. URL: http://www.fil.ion.ucl.ac.uk/spm

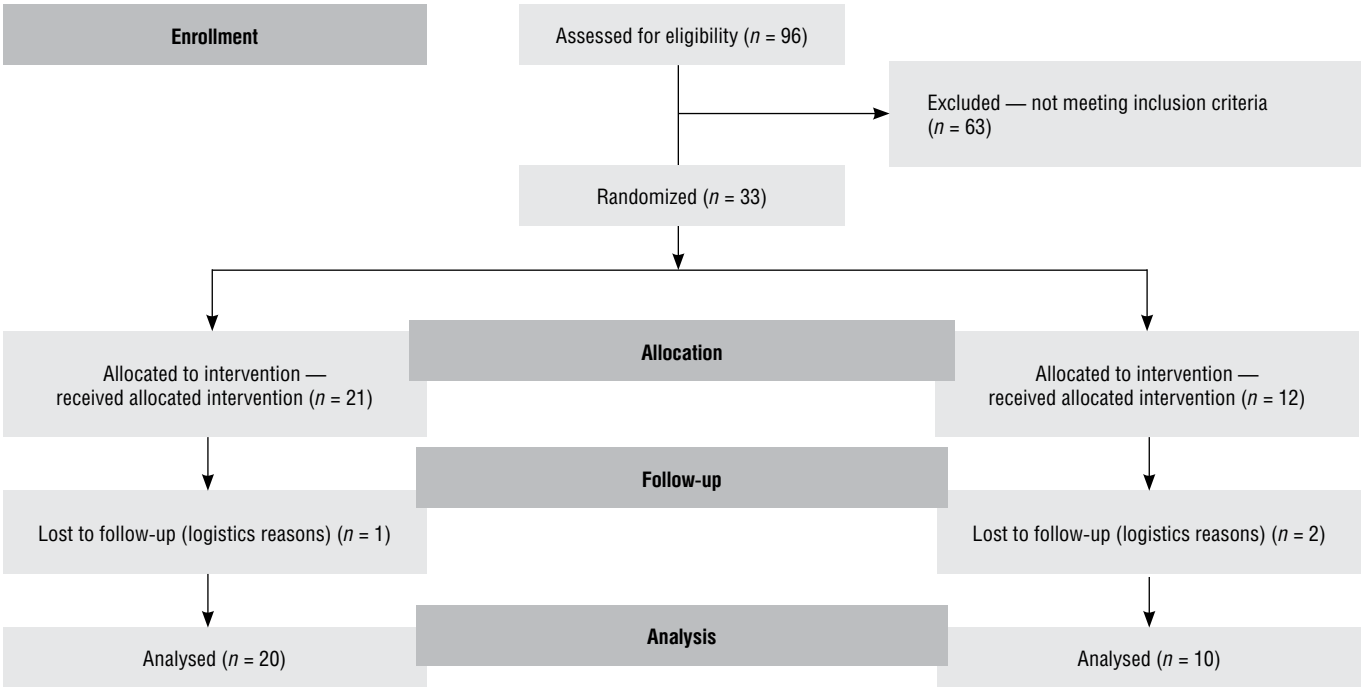

Рис. 1. Блок-схема отбора пациентов.
Fig. 1. Flow chart.

Table 1. Demographic, clinical, and neuroimaging characteristics of patients

Parameter	Active group (*n* = 20)	Control group (*n* = 10)	*p*
Sex (male), *n* (%)	10 (50%)	2 (20%)	0.24
Age, years, Me [Q1; Q3]	60 [57.5; 66.5]	58 [57.5; 69.0]	0.94
Gait disorder, *n* (%)	14 (70%)	6 (60%)	0.69
Pseudobulbar palsy, *n* (%)	5 (25%)	2 (20%)	1.00
White matter hyperintensity (Fazekas scale)			0.73
Fazekas I	2 (10%)	0	
Fazekas II	9 (45%)	4 (40%)	
Fazekas III	9 (45%)	6 (60%)	
White matter lacunes, *n* (%)	12 (60%)	4 (40%)	0.44
Lacunes in subcortical structures, *n* (%)	6 (30%)	5 (50%)	0.43
Brainstem lacunes, *n* (%)	9 (45%)	4 (40%)	1.00
Juxtacortical microbleeds, *n* (%)	5 (25%)	3 (30%)	1.00
Subcortical microbleeds, *n* (%)	11 (55%)	3 (30%)	0.26

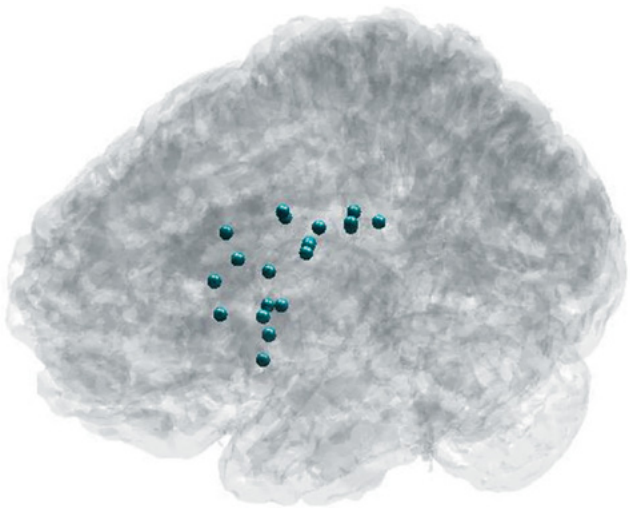

Fig. 2. Localization of stimulation target within the left DLPFC in the active group.

Assessment of the intra-group effect

In the active group, using the Friedman test, a statistically significant effect of time point was reported for MoCA test ($p < 0.001$), TMT-A ($p = 0.012$), TMT-B ($p < 0.001$), the Tower of London ($p < 0.001$), and delayed CF recall ($p = 0.009$) test. For CF copying, the effect was not statistically significant ($p = 0.929$). In the control group, the effect of time point was not statistically significant for all tests (MoCA, $p = 0.119$; TMT-A, $p = 0.368$; TMT-B, $p = 0.347$; the Tower of London, $p = 0.187$; copying and recall of CF, $p = 0.867$ and $p = 0.792$, respectively).

In a pairwise comparison using the Wilcoxon test, a statistically significant improvement was reported immediately after the stimulation and 3 months after the stimulation for the MoCA, TMT-B, and Tower of London tests, while for the TMT-A and delayed CF recall, a statistically significant improvement was reported only immediately after the stimulation, and no significant changes were observed when copying the CF (Table 2). In the control group, no statistically significant changes were observed in any of the tests used, either immediately or 3 months after the stimulation (Table 2).

Comparison of inter-group effects

When comparing the effects between the active and control groups, the active group showed a statistically significant greater effect on the MoCA, TMT-A, TMT-B, and the Tower of London tests immediately and 3 months after the stimulation. For delayed recall of CF, the active group showed a statistically significant greater effect only imme-

Table 2. Intra-group effect of rTMS, Me [Q_1; Q_3]

Test	Time points	Active group ($n = 20$)	p	Control group ($n = 10$)	p
MoCA, score	T0	24 [22; 26]	–	22 [22; 24]	–
	T1	26 [24; 28]	< 0.001	25 [22; 25]	0.094
	T2	26 [19.5; 27]	0.001	23 [21; 24]	0.329
TMT-A, sec	T0	69 [51.0; 91.5]	–	56 [47; 76]	–
	T1	53 [42.5; 72.5]	0.009	57 [52; 86]	0.91
	T2	58 [41; 87.5]	0.08	57 [52; 86]	0.093
TMT-B, sec	T0	162 [126.0; 256.5]	–	168 [135; 243]	–
	T1	138 [106.5; 219.5]	0.007	186 [109; 207]	0.071
	T2	119 [82; 173]	0.032	169 [138; 244]	0.889
The Tower of London Test, score	T0	12.5 [8.75; 16]	–	12 [11; 14].	–
	T1	13 [11.0; 18.5]	0.002	12 [11; 16]	0.083
	T2	14 [12.5; 16.5]	0.044	10 [9; 13]	0.724
Complex Figure, copying, score	T0	32 [27.5; 35]	–	34 [33; 34]	–
	T1	34 [27.5; 36]	0.279	33 [32; 35]	0.656
	T2	33 [28; 36]	0.612	27 [25; 31]	0.380
Complex Figure, delayed recall, score	T0	16 [8; 21.75]	–	15.5 [7; 21.5]	–
	T1	20 [10.25; 26.75]	0.003	17.5 [15.5; 26]	0.102
	T2	16 [9.75; 26.75]	0.690	14 [12; 21]	0.500

Note. T0, baseline testing; T1, testing immediately after the stimulation; T2, testing 3 months after the stimulation; p for T1 and T2 was calculated as a pairwise comparison for T1/T0 and T2/T0, respectively.

Table 3. Effect sizes of rTMS (difference in cognitive test scores between T1 and T0. T2 and T0) and comparison of active and control groups. Me [Q_1; Q_3]

Test	Time point	Active group (*n* = 20)	Control group (*n* = 10)	*p*
MoCA	T1	2 [1; 3]	1 [0; 2]	0.044
	T2	2 [0; 3]	1 [0; 1]	0.044
TMT-A	T1	–9 [–22.5; –3]	7 [–4; 12]	0.007
	T2	–5 [–26.5; 7.5]	7 [–4; 21]	0.041
TMT-B	T1	–15[–54; 6]	–5 [–10; 9]	0.014
	T2	–46 [–56.5; –18.5]	–5 [–10; 9]	0.006
The Tower of London Test	T1	2 [2; 3.5]	1 [0; 1].	0.019
	T2	3 [2; 5]	1 [0; 3].	0.046
Complex Figure. copying	T1	0 [–1; 3.5]	0 [–1; 1]	0.275
	T2	0 [–1.5; 3]	0 [–1; 1]	0.270
Complex Figure. delayed recall	T1	3 [0.75; 5.5]	1.5 [–0.5; 2.5]	0.043
	T2	1.5 [–1.75; 4]	0.5 [–0.5; 4]	0.480

Note. T0. baseline testing; T1. testing immediately after the stimulation; T2. testing 3 months after the stimulation. A negative value indicates a decline in the test scores. A positive score indicates an improvement for all tests except TMT. where improvements are indicated by a negative score and declines are indicated by a positive score.

diately after the stimulation. For copying CF, no statistically significant difference was found between the active and control groups (Table 3).

Tolerability

Data from 270 sessions were analyzed (180 sessions in the active group and 90 sessions in the control group). No serious adverse events were reported during rTMS in any group. Pain at the site of stimulation was observed in 11.7% of all rTMS sessions in the active group and in 9% of all rTMS sessions in the control group. Pain severity on the numerical rating scale was 1 in 61.9% of cases, 2 in 28.6%, 3 in 4.75%, and 5-6 in 4.75% in the active group and it was 2 in 62.5% of cases, 3 in 25%, 6 in 12.5% in the control group. Other discomfort sensations at the site of stimulation (muscle contractions, burning, itching, etc.) were observed in 15.5% of all sessions in the active group and in 2.2% in the control group. Patients reported somnolence in 11.7% of sessions in the active group and 17% of sessions in the control group. Headache within 24 hours of stimulation was reported in 3.9% of all sessions in the active group and 8.9% in the control group. When comparing the incidence of AEs between the active and control groups, there was no statistically significant difference for headache during ($p = 0.539$) and after the stimulation ($p = 0.08$), as for the somnolence ($p = 0.26$), and the statistically significant difference was found only for non-painful discomfort ($p < 0.001$).

Discussion

Our paper showed that 10 sessions of fMRI-guided rTMS of the left DLPFC significantly improved cognitive functions in CSVD patients with MCI. The active group showed the significantly greater effect compared to the control group, both at the general cognitive level and in specific domains (EF and non-verbal short-term memory), and this effect persisted across a range of tests for 3 months after the stimulation. The proposed rTMS protocol for MCI had a good safety and tolerability profile.

In our protocol, the left DLPFC was used as a stimulation target. The choice of the target area was based on the available data on the role of this area in vascular cognitive impairment [28, 29], as well as on previous studies showing the efficacy of stimulation of the left DLPFC in cognitive impairment of various etiologies [30]. The activity of the frontal lobes plays a key role in the EF, and in CSVD early decline in EF is observed [28]. Loss of frontal-parietal connectivity in white matter involvement is currently considered an important factor in the pathogenesis of cognitive impairment in CSVD [29]. A significant loss of interhemispheric and frontal connectivity in CSVD has been demonstrated by structural connectivity studies [28].

Along with the EF scores, nonverbal memory and overall cognitive level improved. However, no statistically significant changes in visuospatial functions (CF copying test) were found in our study, which may be due to the predominant role of the posterior parts of the cerebral cortex, such as the parietal and occipital cortex, for this domain [31]. Further studies are required to evaluate the efficacy of rTMS in cortical regions other than DLPFC or multisite TMS for the treatment of visuospatial deficits in MCI.

In our study, we analyzed individual paradigm fMRI data to determine target localization. fMRI-guided TMS is considered one of the potential methods to increase the efficacy of rTMS [32-34]. Comparing different approaches to

target detection (using a 10-20% electrode positioning system, using structural MRI, fMRI, or a target in Talairach space), determination of a significant effect of rTMS of the right DLPFC on fMRI reaction time requires a 10-fold smaller sample size compared to using the 10-20% system [33]. A recent meta-analysis showed that fMRI-guided navigation for rTMS in healthy volunteers had a higher online effect compared to other methods of target selection [20].

Our choice of paradigm is primarily based on the switching task, but also involves other components of EF and limits the effect of learning [35].

Limitations of target selection using individual paradigm fMRI data include the low reproducibility of fMRI results at the individual level [36]. It is unclear what impact this may have on clinical efficacy. However, we did not compare our method with other methods of target selection. Therefore, we cannot conclude on the advantage of a personalized approach and its appropriateness for real clinical practice.

It should be noted that the effect of rTMS on some of the tests persisted for at least 3 months after treatment. M. Sabbagh et al. reported a positive effect after TMS-COG treatment that was more significant 12 weeks after rTMS compared to that after 7 weeks, which is consistent with the data obtained in this study [37]. Given the progressive nature of cognitive impairment in CSVD, this suggests that rTMS may have an effect on the course of the disease. However, this statement requires further investigation in separate studies. It is also useful to study the effect of repeated rTMS courses or maintenance sessions after the main treatment. The latter approach has been shown to be effective in other conditions, such as depression and pain syndromes [38, 39].

One of the most promising areas for future research is the development of effective combined protocols for rTMS and cognitive training. The potential enhancement of neuromodulation effects by combining it with various methods of cognitive interventions is being actively studied in several neurological and mental disorders [40]. This approach has been shown to be effective in Alzheimer's disease [38] and requires further study in vascular cognitive impairment.

No serious AEs were reported during the rTMS treatment. The AEs reported by patients in the study were mild and did not affect treatment adherence. The profile of AEs was comparable to previously published data [41]. Therefore, our data confirm the safety and good tolerability of rTMS of the left DLPFC in vascular MCI.

Limitations of our study include the small sample size, therefore, our results should be validated in studies with larger samples. The diagnosis of vascular cognitive impairment was based on clinical and neuroimaging data according to the VASCOG criteria [23]; however, given the lack of cerebrospinal fluid testing for beta-amyloid, we cannot exclude the presence of mixed cognitive impairment in some patients. We used vertex TMS in the control group, which is a common approach in the study of cognitive function using TMS. However, it should be noted that one session of vertex theta burst stimulation had an effect on reaction time similar to that of stimulation of a functionally significant cortical area in the study by D. Pizem et al [42]. On the other hand, our study showed no significant differences in any of the test points in the control group, so we can to some extent ignore the significance of the effect of vertex stimulation. Another limitation of our study is the randomization procedure with unequal distribution ratio between groups. This resulted in a mismatch in number of subjects in the main and control groups. Such an approach increases the probability of the second type of error (reduces the probability of finding an effect, if any), but does not affect the probability of the first type of error (a false positive result). It should be noted that the aim of our study was not to identify the cognitive tests on which rTMS has the greatest effect, so the *p* values are given without adjustment for multiple comparisons. However, if the study results are used in work where such selection is required, a correction should be applied to control the possibility of false positives.

Conclusion

This study provides promising results on the potential efficacy of fMRI-guided rTMS for treatment of MCI in CSVD patients. However, given the above limitations, further larger studies are needed for more definitive conclusions.

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Immunomorphologic Assessment of Changes in Functional Astroglial Proteins in a Kainate-Induced Hippocampal Sclerosis Model

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Abstract

Introduction. *Astrocytes are involved in mediator metabolism, neuroplasticity, energy support of neurons and neuroinflammation, and this determines their pathogenetic role in epilepsy.*

Aim. *This study aimed at evaluating region-specific changes in the distribution of functional astroglial proteins in reactive astrocytes in a kainate-induced model of mesial temporal lobe epilepsy.*

Materials and methods. *The localization and expression of functional astroglial proteins (i.e. aquaporin-4, connexin-43, EAAT1/2, and glutamine synthetase) in the hippocampus CA3 region, dentate gyrus, and stratum lucidum layer were evaluated by immunofluorescence 28 days after intra-hippocampal administration of kainic acid to animals.*

Results. *Changes were heterogeneous in different hyppocampus subregions. Astrocytes of the stratum lucidum associated with mossy fibers showed the highest vulnerability and decreased content and/or disturbed localization of the channels and transporters that form membrane complexes in the processes. Disturbances in homeostatic functions of astrocytes aggravated the adverse processes both on the side where the toxin was injected and in the contralateral hippocampus.*

Key words*: hippocampal sclerosis; kainic acid; astrocytes*

Ethics approval. The experiment was carried out in compliance with bioethics standards for experiments with laboratory animals. The study was approved by the Ethics Committee of Research Center of Neurology (Protocol 5-3/22 dated 06/01/2022).

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Иммуноморфологическая оценка изменений функциональных белков астроглии на индуцированной каинатом модели склероза гиппокампа

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Аннотация

Введение. *Участие астроцитов в медиаторном обмене, нейропластичности, энергетической поддержке нейронов и нейровоспалении определяет их патогенетическую роль при эпилепсии.*

Цель *исследования – оценка регионально-специфических изменений распределения функциональных белков астроглии в реактивных астроцитах при каинат-индуцированной модели мезиальной эпилепсии височной доли.*

Материалы и методы. *Иммунофлуоресцентным методом оценивали локализацию и экспрессию функциональных белков астроглии: аквапорина-4, коннексина-43, EAAT1/2 и глутаминсинтетазы в поле CA3 гиппокампа, зубчатой извилине, слое stratum lucidum у животных через 28 сут после интрагиппокампального введения каиновой кислоты.*

Результаты. *Выявленные изменения носили неоднородный характер в исследованных субрегионах гиппокампа. Астроциты stratum lucidum, ассоциированные с мшистыми волокнами, демонстрировали наибольшую уязвимость и снижение содержания и/или нарушение локализации каналов и транспортёров, формирующих мембранные комплексы в отростках. Нарушение гомеостатических функций астроцитов отягощает патологический процесс как на стороне введения токсина, так и в противоположном гиппокампе.*

Ключевые слова*: склероз гиппокампа; каиновая кислота; астроциты*

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Introduction

About a third of epilepsy cases are drug-resistant [1]; therefore, mechanisms of epileptogenesis and new therapeutic targets are the most important objectives of translational neuroscience. At the molecular and morphological levels, epilepsy is characterized by neurodegeneration, abnormal neuroplasticity, impaired neurogenesis, changes in the topology of neuronal connections, neurotransmitter imbalance, abnormal functional ability of several receptor complexes, and modified molecular structure of ion channels [2].

Hippocampal sclerosis (HS) with neuronal death in several hippocampal regions is the most common histological diagnosis in adult patients who undergo surgery for focal structural drug-resistant epilepsy [3, 4]. Glutamatergic excitotoxicity caused by excessive release of glutamate during epileptic activity is considered to be the leading cause of neuronal death in HS [5]. Participating in homeostasis and regulating levels of extracellular glutamate, astroglia is directly involved in excitotoxic reaction cascades. By modulating synaptic transmission, astrocytes provide energy support to neurons and participate in neuroinflam-

mation and synaptic plasticity [6]. Impairment of astrocytic functions is a key cause of epileptogenesis [7].

In HS, there are several patterns of damage that are associated with astrogliosis (astrocyte proliferation and hypertrophy) of various severity. International League Against Epilepsy (ILAE) type 1 HS is the most common (i.e. 60–80% of cases); it is associated with severe damage in CA1 and CA3 regions and affects CA2 and *dentate gyrus* (DG) [4]. Type 2 HS is mostly associated with damage in CA1, while in type 3 HS hilus (also known as CA4) neurons are affected most significantly. Pre-operative seizure burden and outcome after hippocampal resection positively correlated with the degree of gliosis, in particular in the CA3 region [8].

No pronounced neuronal death is found in up to 20% of cases of temporal lobe epilepsy. This is explained by reactive changes in astroglia, which, according to A. Grote et al., does not precede types 1–3 HS but is a separate condition [9]. Relationship between reactive changes in astroglia and damage to hippocampal neurons has not been elucidated yet.

Epileptogenesis in temporal lobe epilepsy is associated with abnormal invasion of mossy fibers (i.e. DG granular cell axons) into the molecular layer of the DG and formation of new excitatory synapses. Reorganization of the hippocampal neural network results in oversynchronization and generation of epileptic discharges [10], where dysfunction of glial cells plays a key role.

Administration of kainic acid (KA), an agonist of kainate receptors (i.e. a subtype of ionotropic glutamate receptors), is a common chronic model of temporal lobe epilepsy that reproduces pathomorphological signs of HS. Besides increased excitability of CA3 glutamatergic pyramidal neurons and suppression of GABA release, effects of KA, depending on its interaction with presynaptic, postsynaptic or glial kainate receptors, include "reactive" plasticity of DG granular neurons, pro-inflammatory glial responses, and changes in the release of neurotrophic factors and gliotransmitters (signaling molecules that ensure communication between glial cells and control the excitability of neurons) [11].

Astrocytes are involved in regulation of glutamatergic neurotransmission; they control levels of extracellular glutamate using EAAT1 (GLAST) and EAAT2 (GLT-1) transporters and participate in the metabolism and detoxification of glutamate using a gliospecific enzyme called glutamine synthetase (GS) [12]. Astrocytes form so-called "tripartite synapses" by encompassing with their processes the area of the synaptic contact between neurons, which allows astrocytes to modulate neurotransmission. Astrocytes also release gliotransmitters, such as purines, D-serine, and various glutamate receptor ligands, which affect neuronal excitability [6]. Neuronal group activity is regulated by interastrocytic networks formed with gap junction proteins connexins (Cx30, Cx43), which are involved in the transport of small molecules and organization of the glial network, regulation of glutamate transport, and diffusion of energy metabolites and gliotransmitters [6, 13]. Factors that cause neuron hyperexcitability include disturbed water balance in the nervous tissue, which is regulated by a water channel protein called aquaporin-4 (AQP4) [12, 14]. Localized in the distal parts of astrocyte processes, AQP4, as well as Cx43, is associated with redistribution of ions and water in the intercellular area; it affects levels of neurotransmitters and regulates the volume of astrocytic perisynaptic sheaths. AQP4 and Cx43 are also involved in migration of astrocytes and regulation of the motility of their processes [13], which suggests their importance in gliosis and tissue remodeling.

Structural and functional characteristics of neuro-glio-vascular interactions in brain structures are determined by regional characteristics of astroglia [12]. The glioarchitecture of the hippocampus, as well as other brain structures, is closely related to its synaptic organization. Astrocytes of different hippocampus regions and layers have morphological, neurochemical, and functional heterogeneity [15, 16]. Region-specific characteristics are likely to be associated with normal functioning of the structures and determine astrocyte response to pathological processes; reactive astroglia maintains a regional profile of homeostatic gene expression [17]. Genes that determine regional specificity of hippocampal astroglia include *slc1a2* (EAAT2), *slc1a3* (EAAT1), *Gja1* (Cx43), *Glul* (GS), and *Aqp4* [16, 18]. Dysregulation of several groups of genes can affect specific astroglial subpopulations [19]. Relationship between AQP4, Cx43, and EAAT1/EAAT2, taken together with macromolecular complexes they form on astrocyte membranes [20], require a joint assessment of changes in these functional proteins in HS.

Therefore, data from modern experimental studies showed a significant contribution of astroglia to epileptogenesis; however, the role of astroglia in the pathogenesis of HS has not been sufficiently studied yet.

Aim. This study aimed at evaluating region-specific changes in the distribution of functional astroglial proteins in reactive astrocytes in kainate-induced HS.

Materials and methods

The study was performed in 10 male Wistar rats aged 3.5 to 5.0 months weighing 300 to 350 g, which were obtained from Stolbovaya Laboratory Animals Breeding Facility of Biomedical Technology Research Center. The animals were kept in a vivarium with constant access to

water and food. The experiment was carried out in compliance with bioethics standards for experiments with laboratory animals according to the European Convention for the Protection of Vertebral Animals Used for Experimental and Other Scientific Purposes (CETS No. 170). The study was approved by the Ethics Committee of Research Center of Neurology (Protocol No. 5-3/22, dated 06/01/2022).

Stereotactic injections

Zoletyl-xylazine anesthesia was used for anesthesia after premedication with atropine (Dalkhimfarm JSC) 0.04 mg/kg s.c. for 10–15 minutes. Then, a mixture of zolazepam hydrochloride and tiletamine hydrochloride (0.3 mg/kg, Zoletil-100, Virbac) was administered i.m. followed by xylazine hydrochloride (3 mg/kg, Xyla, De Adelaar) i.m.

KA solution (Sigma) 0.5 μg in 3 μL of normal saline was injected using an RWD stereotaxic manipulator into the CA1 region of the rostral hippocampus on the right (n = 5) according to the coordinates (AP = –3.0; ML = 2.0; DV = 2.8) in the rat brain atlas[1]. The same volume of normal saline was injected on the left. Sham-operated (control) rats (n = 5) were administered bilaterally with 3 μL of normal saline.

Immunofluorescence staining

Twenty-eight days after KA injection, the animals were decapitated using a guillotine; their brain was removed, dissected in the frontal plane, and fixed for 24 hours in 4% neutral formalin. After soaking in a 30% sucrose solution, samples were placed in O.C.T. (Tissue-Tek), and a series of frozen frontal sections (12 μm thick) was prepared at the level of the frontal third of the hippocampus. The sections were heated in a steamer in citrate buffer pH 6.0 (Leica) for 15 min. Staining was performed according to the recommendations of the primary antibody manufacturers. The following antibodies were used: antibodies to NeuN (Abcam, ab104224) and synaptophysin (SF, Sigma, S5768) neuronal proteins; antibodies to astrocyte proteins, i.e. EAAT1 (GLAST, Abcam, ab181036) and EAAT2 (GLT1, Abcam, ab203130) glutamate transporters, GS (Sigma, G2781), Cx43 (Abcam, ab11370), AQP4 (Sigma, HPA014734), vimentin (Vim, Abcam, ab92547), and gliofibrillar protein (GFAP; Abcam, ab207165). Microglia was detected using anti-IBA1 antibody (GeneTex, GTX635399). Primary antibodies were incubated with the sections in a humidified chamber for 18 hours at room temperature. Corresponding anti-murine or rabbit Ig antibodies (Invitrogen) labeled with Alexa Fluor 488 or Alexa Fluor 555 fluorochromes were used to detect binding. Sections were mounted in Fluoroshield medium (Abcam) containing 4',6-diamidino-2-phenylindole (DAPI) to stain cell nuclei.

[1] Paxinos G., Watson Ch. The Rat Brain in Stereotaxic Coordinates. Amsterdam; Boston, 2005.

Morphometry

From each animal, 6–12 sections were examined at the level of the rostral third of the hippocampus, which were taken at equal intervals along the rostrocaudal axis. Sections were documented using a Nikon Eclipse Ni-U microscope (×20), and average tissue fluorescence intensity (adjusted for background staining) in gradations of brightness of the 8-bit image was evaluated using ImageJ software.

Besides regions (sectors) of the hippocampus (CA1, CA2, CA3, DG), staining for neuronal and glial proteins allowed differentiating the layers of the CA3 region: *stratum lacunosum-moleculare*, *stratum radiatum*, *stratum lucidum*, *stratum pyramidale*, *stratum oriens*. The granular cell layer (*str. granulare*) and the polymorphic layer (*hilus*, *stratum polymorphe*) were detected in the DG [21].

Measurements were performed in the CA3 region as a whole and in the *stratum lucidum* separately, as well as in the polymorphic layer of the DG of the right (ipsilateral to the damage) and left (contralateral) hippocampus for the animals administered with KA and on the right (on the side of administration of 0.9% NaCl) for control animals. Areas of interest were manually segmented in the images. To estimate the area of $AQP4^+$ vessels using local threshold segmentation in ImageJ, the area of the vessels was isolated in relation to the area of the visual field. Gray level co-occurence matrix (GLCM) image texture analysis was used to assess Cx43 distribution in the tissue. GLCM contrast is inverse to changes in the homogeneity of marker distribution. The use of GLCM for histological images was reported earlier [22].

Statistical analysis

Mean values were calculated for each animal. Statistical analysis was carried out using GraphPad Prism 7.0. Two-way analysis of variance (ANOVA) with Tukey's post-hoc test was used to identify between-group differences. Data were presented as $M \pm SD$, where M is mean and SD is mean-square deviation. If results of Shapiro–Wilk test deviated from normal distribution (data for SF), Wilcoxon test was used to compare the hemispheres. Data for SF were presented as median (Me) and interquartile range [Q_1; Q_3]. Differences were considered significant at $p < 0.05$.

Results

Neuronal damage in CA3 was seen in all animals that received KA (Fig. 1, *A*). Assessment of staining intensity for NeuN neuronal marker showed a significant ($p < 0.001$) decrease (to 60.63% ± 22.11% vs. control) in the pyramidal layer of the CA3 region on the side where the toxin was injected but not on the opposite side (to 89.8% ± 16.8% vs. control). Neuronal damage was also detected in the CA1

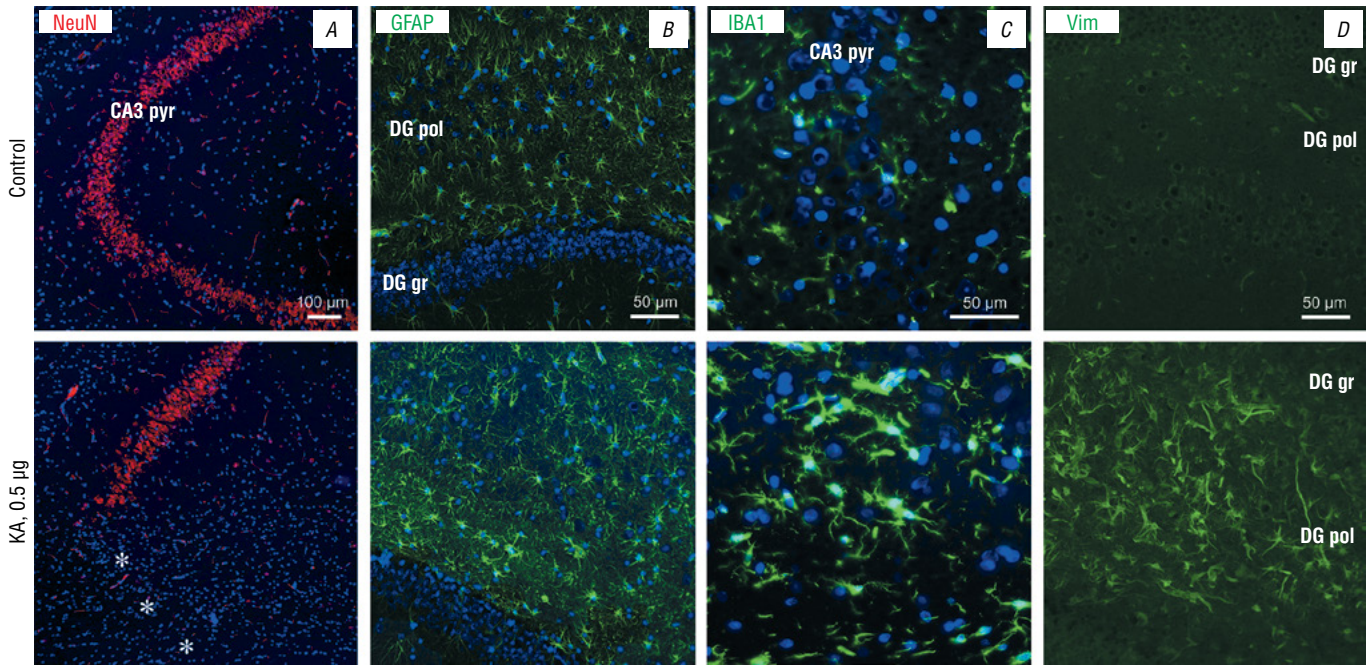

Fig. 1. Administration of KA into the hyppocampus resulted in neuronal damage in the CA3 region and glia activation in the DG.
A, detection of NeuN neuronal marker (stained with red), CA3, × 10;
B, astrocyte activation, GFAP (stained with green), DG, × 20;
C, microglia hypertrophy, IBA1 (stained with green), CA3, × 40;
D, expression of vimentin (stained with green) by reactive astrocytes of the polymorphic layer of the hippocampus, × 20.
CA3 pyr, pyramidal layer of CA3; DG pol, polymorphic layer, DG gr, granular layer, * damage area. Nuclei stained with DAPI (blue).

region; however, due to the proximity of the needle track and glial activation caused by mechanical damage, this region of the hippocampus was excluded from the analysis in our study. No significant staining for NeuN was seen in the DG. Staining intensity for SF in the *stratum lucidum* on the side where the toxin was injected (Me = 73.44 [67.76, 87.15]) was significantly ($p < 0.05$, Wilcoxon test) higher compared with the contralateral hippocampus (Me = 68.12 [56.67; 77.81]).

In both CA3 and DG of the hippocampus, pronounced gliosis, increased staining for GFAP, hypertrophy and deformation of astrocyte processes were seen (Fig. 1, *B*), as well as activation of microglia (Fig. 1, *C*). Some astrocytes in both CA3 and DG expressed Vim, which is typical for immature and reactive astrocytes, with the highest staining intensity for Vim seen in the DG. It is of note that Vim^+-astrocyte bodies were changed to the highest extent (Fig. 1, *D*).

Therefore, KA caused activation of astrocytes both directly in the area of maximum neuronal damage (in the CA3 region) and in the polymorphic layer of the DG, without neuronal loss in the latter.

The boundaries of the *stratum lucidum*, which is formed predominantly by the axons of DG granular neurons, were detected by both SF staining and glial marker identification (Fig. 2), with the exception of relatively uniform staining for AQP4. The greatest differences in staining between CA3 layers were visually noted for EAAT1 and Cx43, with the stratum lucidum having their lowest content.

Besides a dramatic increase in immunofluorescence intensity for GFAP ($p < 0.001$) in the CA3 region (without considering layers, compared with the sham-operated control), the side of KA administration demonstrated increased levels of Cx43 ($p < 0.001$) and GS ($p < 0.001$) and significantly decreased staining for AQP4 ($p < 0.001$) (Fig. 2, 3).

Together with a decrease in immunofluorescence intensity for AQP4 in the CA3 region, the bodies of glial cells were more clearly identified and a decrease in staining intensity of blood vessels were seen, which indicates AQP4 redistribution in the cells and a decrease in its content in the astrocyte endfeet. This was confirmed by percentage area of stained vessels in the CA3 in the visual field: it was significantly ($p = 0.022$) reduced from 0.99% ± 0.48% in the control group to 0.55% ± 0.15% on the side of KA administration. Similar changes were found in the DG.

The increase in total fluorescence intensity (Fig. 3) for Cx43 in CA3 was predominantly due to glial cells in the *stratum oriens* and *stratum lacunosum molecularis*. Changes in the distribution of Cx43 in the tissue was confirmed by assessing the "contrast" of the image, i.e. a parameter inverse to homogeneity of marker distribution

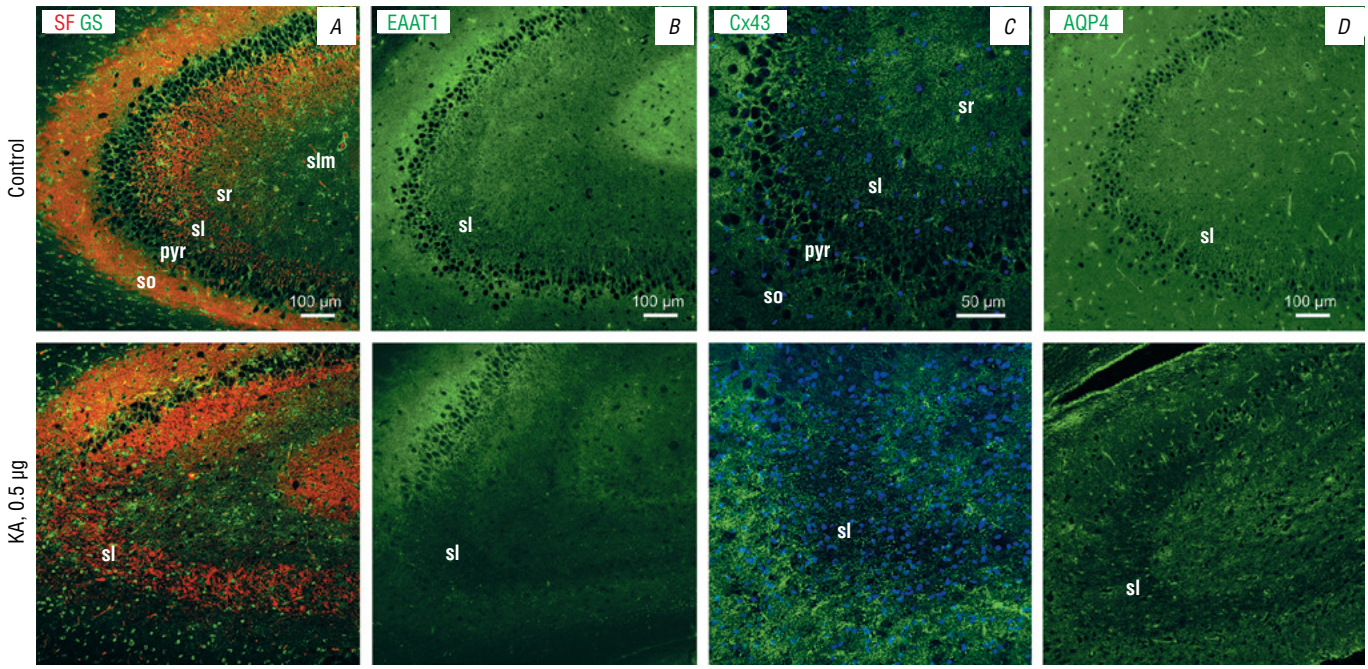

Fig. 2. Changes in expression and localization of astrocyte functional proteins in hippocampal CA3 layers after administration of KA.
A, identification of GS localization (stained with green) and SF (stained with red) in hippocampus layers, × 10;
B, EAAT1 detected, × 10;
C, Cx43 detected (stained with green), nuclei further stained with DAPI (stained with blue), × 20;
D, AQP4 detected, × 10.
so, *stratum oriens;* **pyr**, *stratum pyramidalis;* **sl**, *stratum lucidum;* **sr**, *stratum radiatum;* **slm**, *stratum lacunosum moleculare.*

in the sample. This parameter significantly (p = 0.021) increased threefold (214.49 ± 116.51) in CA3 compared with control (70.97 ± 2.41) on the side where KA was injected. Demonstrated decrease in the uniformity of Cx43 distribution appeared to reflect Cx43 redistribution in astrocyte processes. It is of note that large $Cx43^+$ staining clusters around vessels were seen in animals treated with KA, which may be due to increased expression of Cx43 by endothelial cells or impaired distribution of Cx43 in the astrocyte endfeet.

GS distribution also changed differently across hippocampal layers. On the side where KA was injected in the CA3 region, a large number of ovoid GS^+-glial cells with intense staining of the cytoplasm were detected, which were likely to be oligodendroglia. These cells were rare in control animals. Decreased GS staining was observed in astrocyte processes in the *stratum lucidum* (Fig. 3, 4). At the same time, GS+-reactive astrocytes with hypertrophied processes and intensely stained cytoplasm were detected in the stratum oriens, *startum radiatum*, and *stratum lacunosum moleculare*.

For EAAT1 glutamate transporter, the average intensity in the CA3 region (without considering the layers) increased significantly (p = 0.0149) under the influence of KA on the damaged side, and areas with both increased and decreased EAAT1 expression were visually noted, which may be related to varying degrees of damage to neurons in the CA3 region.

Immunofluorescence in the *stratum lucidum* on the side of KA administration (Fig. 3) demonstrated a significant decrease in levels of functional astrocyte proteins vs. sham-operated control (i.e. EAAT1, EAAT2, GS and AQP4 but not Cx43, for which a trend to increased staining was detected; p = 0.053). In the *stratum lucidum* of the hippocampus of the contralateral hemisphere, immunofluorescence was also decreased with this effect being the greatest for GS and AQP4.

Similar to the changes in the *stratum lucidum*, a less pronounced decrease in levels of evaluated proteins (i.e. EAAT1, GS, and AQP4) was also seen in the polymorphic layer of the DG in the hippocampus (Fig. 3), which is probably related to the general direction of changes in astroglia in the areas of synaptic contacts of mossy fibers with neurons. It is noteworthy that opposite changes (increased immunostaining) were detected only for EAAT2 in the DG compared with the *stratum lucidum.* Increased staining intensity for EAAT2 was likely to be related to intense staining of reactive astrocyte soma (Fig. 4).

Therefore, KA administration led to unilateral damage to pyramidal neurons of hippocampus CA3 and gliosis; these reactive changes in astroglia were accompanied with

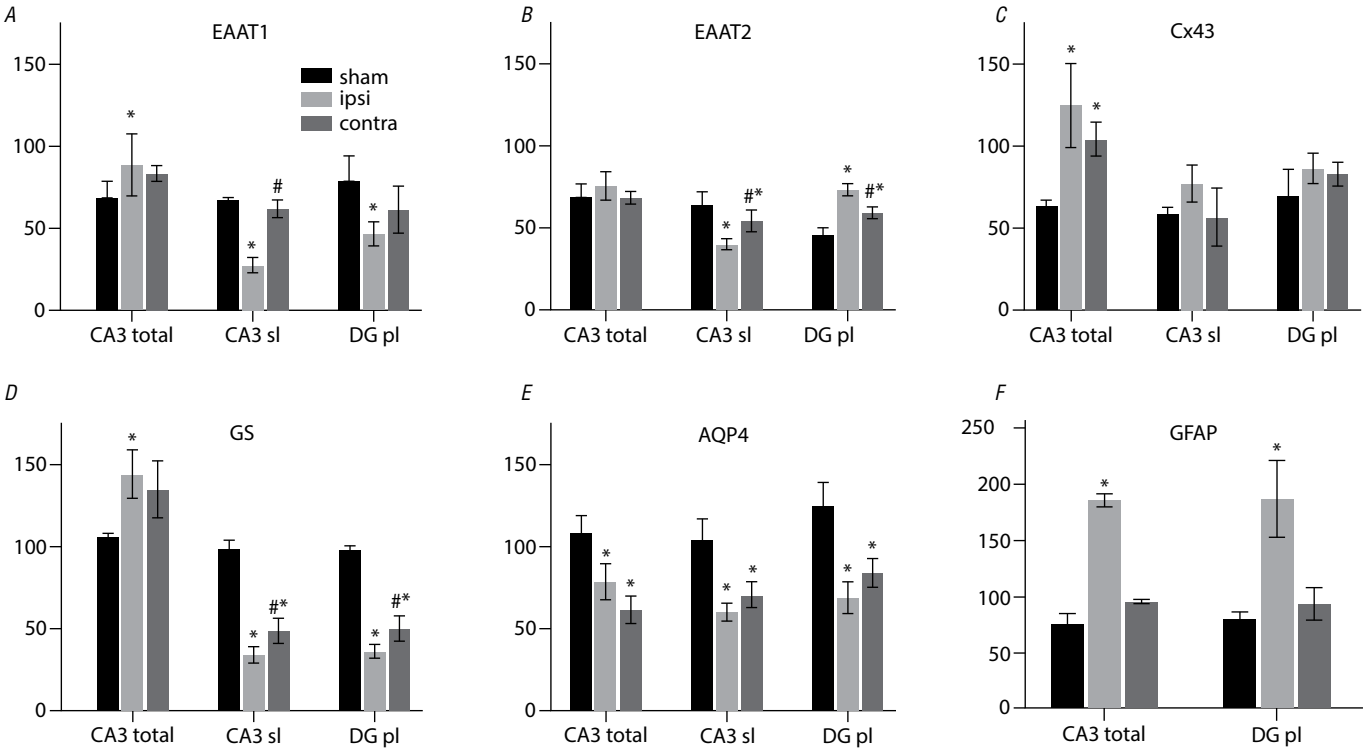

Fig. 3. Changes in immunofluorescent staining intensity for functional astrocyte proteins in CA3 of the hippocampus (CA3 total), *stratum lucidum* (CA3 sl), and the polymorphic layer of DG (DG pl) after administration of KA.
A, EAAT1 glutamate transporter (GLAST); *B*, EAAT2 glutamate transporter (GLT-1); *C*, Cx43; *D*, GS; *E*, AQP4; *F*, GFAP.
sham, sham-operated animals; ipsi, on damage side; contra, contralateral to damage side; *$p < 0.05$ compared with sham-operated animals; #$p < 0.05$ compared with damage side (ANOVA, Tukey's post-hoc test).

decreased expression of its functional homeostatic proteins in the *stratum lucidum*, namely in a layer of mossy fibers both on the side where the toxin was injected and in the contralateral hemisphere. In the CA3 region, KA-induced damage resulted in increased expression of GFAP, Vim, GS and Cx43, together with AQP4 redistribution with a moderate decrease in immunostaining intensity. At the same time, reactive changes in astroglia of the *stratum lucidum* differed from the total CA3 region and were associated with a significant decrease in glutamate metabolism proteins (GS, EAAT1/2) and AQP4, while levels of Cx43 did not change significantly although tended to increase. Besides changes in Cx43, AQP4, GS and EAAT2 levels, changes in their cellular localization and distribution in the tissue were also found, including those associated with disruption of glio-vascular contacts.

Discussion

Intrahippocampal administration of KA caused gliosis in the CA3 and DG regions and pronounced changes in the regional expression of functional astrocyte proteins to varying degrees in the CA3 region as a whole and in the *stratum lucidum layer* in particular. Neuronal damage was detected in CA1 and CA3 on the side where the toxin was injected, corresponding to type 1 HS [4]. The changes detected in astroglia were also seen in the contralateral hemisphere, where no statistically significant neuronal damage was recorded.

The *stratum lucidum* of the hippocampus CA3 region is represented by mossy fibers, i.e. axons of granular cells of the DG, which form many glutamatergic "detonator" synapses on the pyramidal neurons of the CA3 region. Their functional significance in epileptogenesis and mossy fiber rearrangements observed in epilepsy determine interest in changes in glial cells in this area [10]. Our data on increased immunostaining for SF in the *stratum lucidum* are consistent with literature data [23] that showed increases SF levels 30 days after KA administration and may indicate "reactive" plasticity.

Astrocytes of different regions of the hippocampus differ in their characteristics, which depend, among others, on the synapses they "serve" [15]. The hilus and stratum lucidum of the hippocampus have relatively high astrocyte density [24]. Astrocytes in the stratum lucidum change their intracellular $Ca2^{+}$ levels only in response to burst activity of neurons and significant increases in glutamate levels, in contrast to DG astrocytes, which provide fine regulation of synaptic transmission [25]. Compared with synapses in other areas of the hippocampus, contacts of

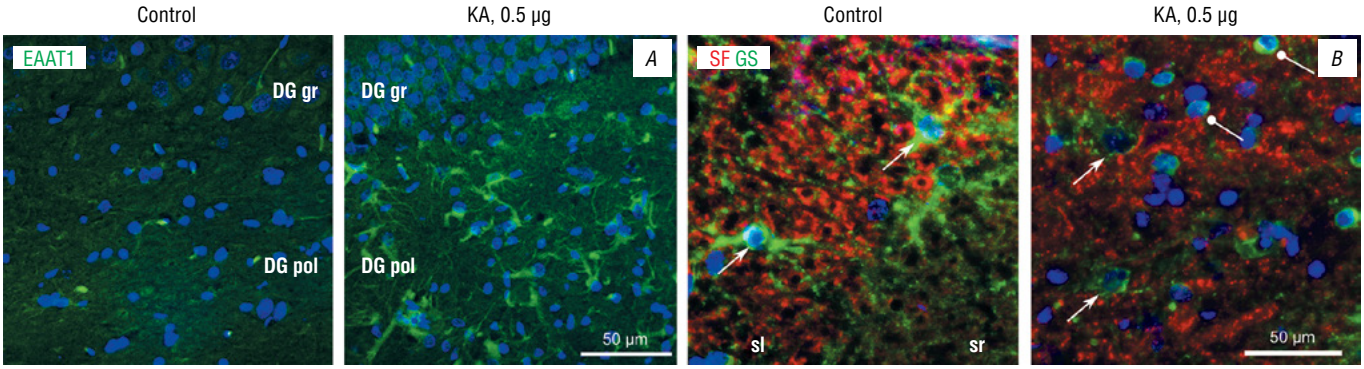

Fig. 4. Changes in intracellular EAAT2 and GS location in astrocytes after KA administration.
A, intense staining for EAAT2 glutamate transporter (green) in reactive astrocyte bodies of the polymorphic layer, × 40;
B, GS detected (stained with green) and SF (stained with red) in the processes and bodies of reactive astrocytes (arrows) in *stratum lucidum and* cells without processes identified (line segments with a dot at the end), × 40.
DG gr, granular layer; DG pol, polymorphic layer; sl, *stratum lucidum*; sr, *stratum radiatum*.

astrocytes with synaptic buttons on mossy fibers are less close [25]. It is of note that the *stratum lucidum* was shown to have extremely high levels of brain-derived neurotrophic factor [26], which is involved in neuroinflammation and regulation of astroglial morphogenesis [27, 28].

Changes in the levels and localization of AQP4, glial glutamate transporters (EAAT1/EAAT2), GS, and Cx43 in our study were associated with increased neuronal excitability, as well as initiation and maintenance of epileptic activity [7]. Inconsistent changes in the levels of these proteins in publications of various authors were associated with differences in measurement methods, evaluated areas, and timing of KA administration. For example, AQP4 levels in rat hippocampus were decreased one day but increased one month post KA-induced status epilepticus [29]. On the other hand, total content of AQP4 was increased but its immunostaining in the perivascular endfeet was decreased in patients with lobe epilepsy and HS [30]. Our study showed redistribution of AQP4 in astrocytes and decreased area of $AQP4^+$ perivascular staining, consistent with other authors, and an overall decrease in APQ4 levels. Previously, the kainate model in CA1 and CA3 showed decreased AQP4 levels in the perivascular compartment both in the latent and late periods of epileptogenesis [31]. Subcellular redistribution of AQP4 in the neuropil but not in the astrocyte endfeet was also shown in a model of posttraumatic epilepsy [32].

A macromolecular complex of AQP4 with EAAT2 and Kir4 determines possible AQP4 participation in the exchange of K^+ and glutamate [29, 33]. Disrupted association of AQP4 and EAAT2 glutamate transporter in astrocytes was suggested to lead to neuronal dysfunction [34, 35]. Evaluation AQP4 and EAAT2 levels in a KA model of epilepsy showed a decrease in their expression in the early period of epileptogenesis [29], which is consistent with our results for the *stratum lucidum*. Changes in the distribution of these proteins in astroglial processes, which were also shown in our study, indicated disturbances in the organization of gliovascular and glioneuronal contacts in the astrocyte endfeet. According to publications, EAAT2 (but not EAAT1) glial glutamate transporter was directly inhibited by KA [36], and an increase in their levels in the DG that we found may reflect a compensatory increase in their expression. Heterogeneous changes in EAAT2 in the *stratum lucidum* and DG may be related to astrocyte heterogeneity in these areas of the hippocampus or different intensity of their reaction.

Several studies showed an increase in EAAT1 expression after KA administration, which was considered by the authors as a compensatory reaction [36]. We detected an increase in EAAT1 levels in CA3, which, however, was not due to the astrocytes of the *stratum lucidum*, where, on the contrary, staining was reduced for both transporters. Overall, dysfunction of EAAT1/2 transporters in epileptic foci led to impaired utilization of extracellular glutamate [37]; however, the changes in the expression of these proteins in patients with temporal lobe epilepsy were often inconsistent and demonstrated different directions of changes [38, 39].

GS, an astroglia-specific enzyme of glutamine-glutamate metabolism, also plays a key role in preventing the accumulation of toxic glutamate. In patients with mesial temporal lobe epilepsy, the intensity of GS staining was reduced in the CA1, CA3, and DG regions of the hippocampus, demonstrating an association with seizure patterns [40]. We found decreased GS staining intensity in astrocyte processes in the *stratum lucidum* but not in other layers where GS^+-reactive astrocytes had hypertrophied processes. Previously, GS redistribution in astrocyte processes in CA1 and CA3 of the hippocampus was shown in models of temporal lobe epilepsy [40, 41].

Neuronal excitability and synchronization are also largely regulated by coordinated activity of the astrocytic network

together with connexins. Cx43 gene knockout led to seizures and motor disorders in animals [42]. Disruption of connections between astrocytes promotes epileptogenesis by reducing buffering of K^+ and Na^+ followed by inhibition of glutamate clearance from the synaptic space. The experiment showed disruption of communication between astrocytes via Cx43 already at the early stages of epileptogenesis [43]. On the other hand, functioning of the astrocytic network is required for delivery of energy substrates [44], and, therefore, reduced astrocyte communication may inhibit seizure activity and be protective in the later stages of epileptogenesis [45].

Evaluation of Cx43 levels in hyppocampus specimens from HS patients showed increased expression of Cx43, which, however, did not form functional channels [46]. This was related to subcellular Cx43 redistribution in the perivascular endfeet together with post-translational protein modifications that affected channel permeability. We observed similar changes in our study: total content of Cx43 in CA3 increased, and although changes in staining intensity in the *stratum lucidum* were not statistically significant, Cx43 redistribution and formation of Cx43 clusters around the vessels were seen in this layer. Changes in AQP4 and Cx43 expression and localization was previously shown to disrupt BBB permeability [20] and result in negative effects. It is of note that AQP4 and Cx43 changed their localization in different directions, while Cx43 was accumulated around the vessels with AQP4 immunoreactivity decreased. These results demonstrated disturbed organization of water channels and connexins in reactive astrocytes, which, in its turn, may cause disturbances in ionic and water homeostasis [32] and contribute to epileptogenesis.

Conclusion

1. Astrocyte reaction in kainate-induced HS was heterogeneous and had regional differences, with *stratum lucidum* astrocytes associated with mossy fibers demonstrating the greatest vulnerability.
2. Changes in the expression of homeostatic proteins in hippocampal astrocytes were observed in both hemispheres (i.e. ipsilateral and contralateral to the damage), which aggravated epileptogenesis in the intact hippocampus.
3. Changes in astrocytic glutamate metabolism proteins in KA-induced HS enhanced neurotransmission disturbances and may induce secondary excitotoxic damage to neurons during epileptogenesis.
4. Disturbances in the localization and expression of AQP4 and glial glutamate transporters were unidirectional, indicating their common regulatory mechanisms and local dysregulation of water and ion homeostasis by astrocytes in HS.
5. Disturbances in the perivascular localization of Cx43 and AQP4 showed that the two classes of membrane proteins were interdependent with glio-vascular interactions reconfigured in HS.

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Changes in Contractile Characteristics of Rat Skeletal Muscles Associated with P2-Receptor Activation After Spinal Cord Transection

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Abstract

Introduction. *Traumatic spinal cord and peripheral-nerve injury is associated with release of proinflammatory cytokines and chemokines, which may stimulate neuronal activity. Adenosine triphosphoric acid (ATP) is an important pain mediator involved in the acute and chronic neuropathic pain development. Its excessive release from primary injured tissue leads to activation of P2-receptors, which may further start secondary injury mechanisms. Although the effects of ATP on the peripheral nervous system are relatively well studied, the pathophysiological role of purinergic signaling after spinalization remains unclear.*

The study was ***aimed*** *at assessing the post-spinalization effects of P2-receptors on the contractile characteristics of rat skeleton muscles.*

Materials and methods. *The objects of the study were the soleus muscle, the extensor digitorum longus (EDL) muscle, and diaphragm in intact rats and spinalized rats. Seven days after laminectomy followed by spinal cord transection, animals were anesthetized, exsanguinated, and their muscles with nerve stumps were isolated. Contractile response parameters were recorded using mechanomyography (MMG). To study effects of ATP on ligand binding, ATP was added to a bath and mechanical responses in the rat muscles were assessed 7 min after. After washing with Krebs–Henseleit solution, the preparations were incubated with suramin solution for 20 min with subsequent ATP application. Then the mechanical responses in the muscles were again recorded. Statistical significance was assessed using Student's t-test for independent (unpaired) and paired samples.*

Results. *We found a significant ($p < 0.05$) decrease in the modulating activity of ATP, as the main endogenous signaling agent, in the cholinergic synapse of the soleus muscle from 32.4 to 5.8% and from 13.7 to 5.6% for the EDL muscle after the spinalization (spinal cord injury at the Th6–Th7 level) compared with intact animals. No such dramatic changes were observed in the diaphragm.*

Conclusions. *Abnormal ATP-mediated modulation of neuromuscular transmission demonstrated in this study supports the involvement of purinergic signaling in the neurotrophic control and functioning of various motor units.*

Keywords: *spinalization; ATP; P2-receptors; skeletal muscles; post-traumatic movement disorders; synapse; suramin*

Ethics approval. The research protocol was approved by the Ethics Committee of the Kazan Federal University (protocol No. 30, June 28, 2021).

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Динамика сокращений скелетных мышц крысы при активации P2-рецепторов после перерезки спинного мозга

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Аннотация

Введение. *Травма спинного мозга, периферических нервов сопровождается выделением провоспалительных цитокинов и хемокинов, которые могут усиливать активность нейронов. Среди медиаторов повреждения особо можно выделить аденозинтрифосфорную кислоту (АТФ), которая вовлечена в процессы формирования острой и хронической нейропатической боли, и чрезмерное её высвобождение травмированной тканью вызывает активацию P2-рецепторов, что может повлиять на механизмы вторичного повреждения тканей. При общей изученности эффектов АТФ на периферическую нервную систему патофизиологическая роль пуринергического сигнального звена при спинализации не раскрыта.*

Цель *исследования – оценка динамики сокращений скелетных мышц крысы при воздействии на P2-рецепторы после спинализации.*

Материалы и методы. *Объектом исследования выступали камбаловидная мышца, длинный разгибатель большого пальца и диафрагма интактных крыс и животных после спинализации. Через 7 сут после ламинэктомии с последующей перерезкой спинного мозга животных наркотизировали, обескровливали и выделяли мышцы с культями нервов. Параметры сократительных ответов регистрировали механомиографическим методом. Для оценки эффектов лигандов в ванночку добавляли АТФ и через 7 мин оценивали механические ответы мышц. После отмывки раствором Кребса инкубировали с раствором сурамина в течение 20 мин с последующим добавлением АТФ и вновь регистрировали механические ответы мышц. Статистическую значимость оценивали с помощью критерия Стьюдента для независимых и попарно сопряжённых выборок.*

Результаты. *Выявлено значимое ($p < 0,05$) снижение модулирующей активности основного эндогенного агента – АТФ в холинергическом синапсе камбаловидной мышцы с 32,4 до 5,8% и с 13,7 до 5,6% для длинного разгибателя большого пальца вследствие спинализации (повреждения спинного мозга на уровне Th6–Th7) в сравнении с интактными животными. На диафрагме столь драматических изменений не наблюдалось.*

Заключение. *Продемонстрированная нами аномальная модуляция АТФ нервно-мышечного перехода предоставляет доказательства вовлечённости пуринергического звена в нейротрофический контроль и функционирование различных двигательных единиц.*

Ключевые слова: *спинализация; АТФ; P2-рецепторы; скелетные мышцы; травматический двигательный синдром; синапс; сурамин*

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Introduction

Traumatic spinal cord and peripheral nerve injuries are not unusual among people of working age and can be accompanied by severe and often irreversible motor disorders. Traumatic spinal cord injury (SCI) is characterized by immediate and irreversible tissue loss at the injury site followed by the secondary injury in adjacent tissues over time. Traumatic peripheral nerve injury is known to cause various changes in the expression of intracellular signaling molecules in the spinal cord [1], primarily in response to increased release of various mediators in activated spinal cord microglia [2], which may play an important role in the neuropathic pain development and maintenance [3].

Microglia activated by a trauma produces and releases pro-inflammatory cytokines and chemokines [4], which can stimulate neuronal activity. Adenosine triphosphoric acid (ATP) is an important pain mediator involved in the development of acute and chronic neuropathic pain after an injury [5]. Its excessive release by injured tissue activates high-affinity purinergic receptors in microglial cells, which may further affect the mechanisms of additional tissue damage, known as secondary injury [3].

Although the effects of ATP on the peripheral nervous system are relatively well understood, the pathophysiological role of purinergic signaling associated with spinalization remains unclear. So, the objective of the study is to evaluate the changes in contractile characteristics of rat skeletal muscles associated with P2-receptor activity after spinalization.

Materials and methods

Male Wistar rats aged 9–12 months, weighing 160–240 g, were used for the experiments. The objects of the study were the pelvic girdle and lower limb muscles, which are fundamentally important for motor activity (slow-twitch muscles [soleus muscle, *m. soleus*], fast-twitch muscles [*extensor digitorum longus muscle, m. extensor digitorum longus, EDL*], and functionally distinct respiratory muscle [*diaphragm, m. diaphragma*] with their corresponding neuromuscular synapses) isolated from intact rats and spinalized animals.

One week prior to and during the experiments, rats were housed in individual cages at room temperature of 22ºC with a 12 h/12 h light/dark cycle, access to water and food *ad libitum*. All manipulations were performed at the same time of a day. Rats were divided into 2 groups of 12 animals each: the control group included intact animals and the spinalization group included animals after spinal cord transection.

The surgery was performed under aseptic conditions and combined intramuscular analgesia using zoletil (Zoletil 50, Virbac) at a dose of 0.5 mg/kg and xylavet (XylaVET, Pharmamagist Ltd.) at a dose of 0.5 ml/kg. After dissection of Th6–Th7 vertebrae, a laminectomy was performed to expose the spinal canal with subsequent transection of the spinal cord at this level (Fig. 1).

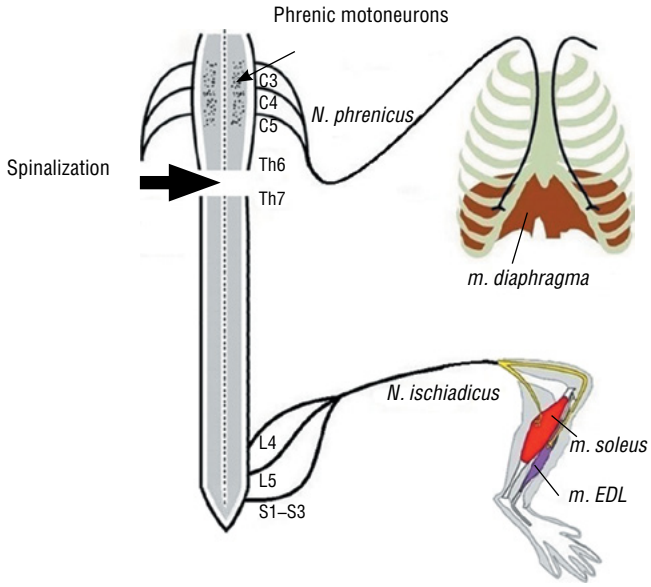

Fig. 1. Schematic diagram of spinalization at Th6–Th7.

Seven days after the surgery, the animals were anesthetized with sodium ethaminal (40 mg/kg intraperitoneally) and exsanguinated. *M. soleus, m. EDL, m. diaphragma* were isolated with nerve stumps fixed by both tendon ends, immersed in 10 ml beakers filled with Krebs–Henseleit solution [6].

The nerve stump of the isolated muscle was placed in a special nerve stump suction electrode for electrical stimulation [7]. Rectangular pulses of 10 V amplitude and 0.5 ms duration at a frequency of 0.1 Hz were applied for 2 min using D330 MultiStim System. Contractile force was recorded with a force displacement transducer (Linton FSG-01), the analog signal was digitized and processed using a Biopack MP100WSW data acquisition system.

The initial load on the myoneural preparations was 1 g on *m. soleus* and *m. diaphragma* and 0.5 g on *m. EDL*. The muscle preparations were kept in the solution for half an hour for adaptation, then the stability of the contractile responses was assessed twice at 5-minute intervals [8].

To study the effects of purinergic agonists and antagonists, 100 μM ATP was added to the bath and the muscle mechanical responses were assessed 10 minutes after. Further, after 20-minute washout of muscle preparations with Krebs–Henseleit solution, the electrical stimulation was repeated. To confirm the ATP effects on synaptic transmission, the muscles preparations were maintained in 100 μM suramin

(non-selective P2-receptor antagonist) for 20 min, followed by the addition of 100 μM ATP (P2-receptor agonist), and mechanical muscle responses were again recorded. In control experiments, contractile responses to indirect electrical stimulation were recorded after 20-minute neuromuscular tissue incubation with 100 μM suramin [9].

The responses recorded within 2 min (12 contractions) were averaged and processed as a single value in % of the baseline results obtained at the beginning of the experiment. Statistical data analysis was performed with SPSS Statistics software. Conformity to normal distribution was checked using the Kolmogorov criterion. Statistical significance was assessed using multivariate analysis of variance (MANOVA) for independent and paired samples. The differences were considered significant at $p < 0.05$.

Results and discussion

After the spinalization, contractile responses in *m. soleus* and *m. EDL* changed divergently in contractile force and in time parameters (Fig. 2; Table 1). In contrast, amplitude-time parameter values in *m. diaphragma* remain stable, perhaps due to a higher position of phrenic motor neurons, which were less affected by spinalization.

Application of 100 μM ATP to muscle preparations of intact rodents modulates the contractility parameters: a 10-min exposure to ATP decreased the contractile force of locomotor *m. soleus* and *m. EDL* and increased the contractility of respiratory *m. diaphragma*. ATP had virtually no effect on the neuromuscular preparations from the spinalized animals. Only *m. diaphragma* remained sensitive to the study nucleotide (see Table).

Suramin (100 μM) as a non-competitive inhibitor of P2-receptors showed no significant effects. In the presence of suramin (100 μM), exogenous ATP (100 μM) activity was completely inhibited in all study objects (see Table).

Our findings demonstrate a significant suppression of the peripheral nervous system activity in the SCI animal model. Changes in synaptic signaling indicate axon degeneration after the injury of the spinal cord at its upper levels.

Understanding mechanisms underlying suppression of the peripheral nervous system is important to prevent functional decline and maintain a high potential for motor function recovery, especially with cellular therapies aimed at SCI repair.

Disorders of muscle function caused by SCI can result from a mechanical injury and from secondary injury caused by pathophysiological response to the initial trauma. For example, there are studies demonstrating abnormally high and persistent ATP release levels in peritraumatic tissues in SCI rat models, indicating P2-signaling involvement in the cascade of degenerative events, known as secondary injury, and neurodegeneration after the initial injury [10].

This cascade of injury-associated events include extensive hemorrhage, necrosis of cellular components of the central and peripheral nervous systems. The subsequent activation of astrocytes and other cells located in close proximity to the injury site results in extremely unfavorable conditions for axon repair. The concurrent activation of the immune system leads to additional tissue damage at the injury site by attracting immune inflammatory cells, such as neutrophils and macrophages. On the other hand, macrophages and T-helpers provide trophic support to damaged components of the CNS. All of the above processes lead to axon degeneration and the loss of communication between neurons, which primarily results in various functional muscle disorders [11].

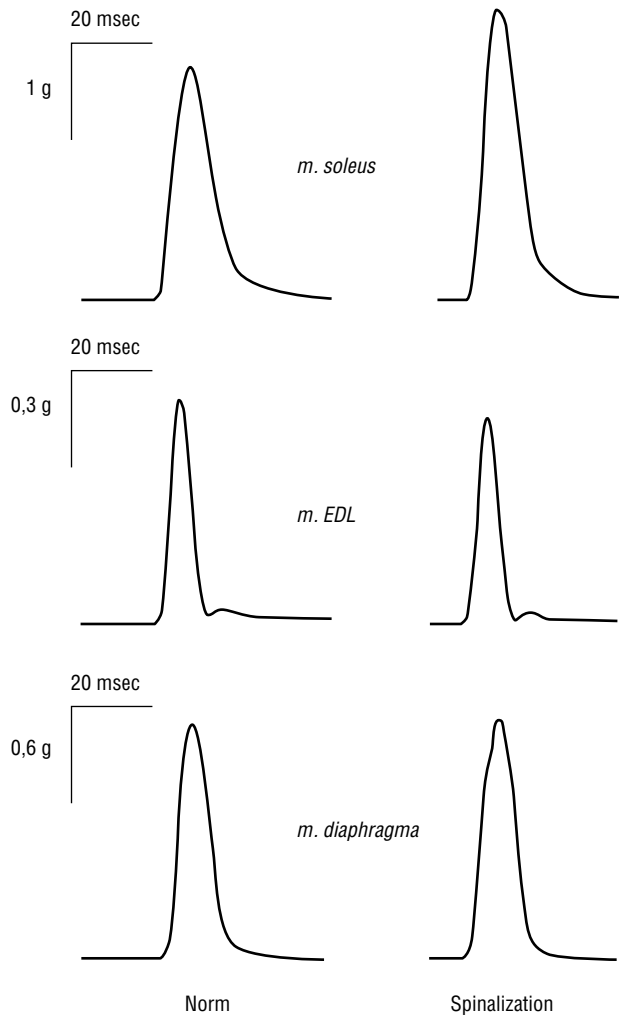

Fig. 2. Traces of single contractile responses of the isolated rat *m. soleus*, *m. EDL* and *m. diaphragma* evoked by electrical stimulation in controls and in spinalized rats (selected representative traces are presented).

Table 1. Parameters of rat muscle contractility evoked by electrical stimulation in different experimental conditions, n = 10–12

Experimental conditions	*n*	Parameter	Control	ATP, 100 μM	Suramin, 100 μM	Suramin, 100 μM + ATP, 100 μM
M. soleus						
Normal value	10	CF	100,0 ± 4,2	67,6 ± 5,2*	104,3 ± 3,9	98,5 ± 7,1
		CT	0,081 ± 0,004	0,083 ± 0,006	0,080 ± 0,004	0,079 ± 0,005
		RT/2	0,092 ± 0,007	0,105 ± 0,011	0,090 ± 0,006	0,093 ± 0,010
Spinalization	10	CF	119,8 ± 5,1#	114,0 ± 6,1#	120,2 ± 4,3#	121,8 ± 6,4#
		CT	0,073 ± 0,005	0,076 ± 0,007	0,071 ± 0,006	0,074 ± 0,004
		RT/2	0,101 ± 0,009	0,116 ± 0,010	0,098 ± 0,008	0,105 ± 0,010
M. EDL						
Normal value	10	CF	100,0 ± 4,5	86,2 ± 3,9*	102,0 ± 6,1	98,7 ± 5,3
		CT	0,057 ± 0,003	0,056 ± 0,005	0,059 ± 0,004	0,058 ± 0,006
		RT/2	0,067 ± 0,005	0,069 ± 0,004	0,065 ± 0,007	0,068 ± 0,005
Spinalization	10	CF	88,7 ± 3,8#	83,1 ± 5,4	85,9 ± 4,8#	83,1 ± 6,7#
		CT	0,068 ± 0,005	0,069 ± 0,006	0,068 ± 0,006	0,067 ± 0,005
		RT/2	0,071 ± 0,006	0,073 ± 0,007	0,070 ± 0,005	0,073 ± 0,004
M. diaphragma						
Normal value	12	CF	100,0 ± 3,7	114,6 ± 5,2*	98,3 ± 4,7	102,9 ± 6,2
		CT	0,065 ± 0,004	0,066 ± 0,003	0,064 ± 0,006	0,064 ± 0,004
		RT/2	0,075 ± 0,006	0,075 ± 0,005	0,074 ± 0,006	0,076 ± 0,004
Spinalization	12	CF	103,2 ± 4,1	112,7 ± 3,9*	102,0 ± 4,9	103,8 ± 7,5
		CT	0,071 ± 0,005	0,070 ± 0,003	0,069 ± 0,004	0,072 ± 0,004
		RT/2	0,074 ± 0,003	0,076 ± 0,006	0,074 ± 0,005	0,075 ± 0,006

Note. *p < 0.05 compared with the control group; #p < 0.05 compared with normal value. CF — contractile force (% from the level in the control group); CT — contractile time, s; RT/2 — half-relaxation time, sec.

The obtained data demonstrate significant differences in the mechanisms of contractility control in fast-twitch and slow-twitch skeletal muscles of warm-blooded animals, which is consistent with our earlier observations in spinal shock models [12]. The suppression of P2-receptors affecting muscle contraction associated with such a striking response to spinalization demonstrates the involvement of the purinergic signaling in the neurotrophic control and functioning of various motor units.

Activation of spinal microglia caused by trauma leads to an increased expression of P2-receptors. For example, P2X4R levels have been shown to increase in association with SCI, while P2X4R inhibition has been shown to reduce neuropathic pain [13]. Another ATP-sensitive purinergic receptor, P2X7, can form a macromolecular pore under repeated or prolonged exposure to high concentrations of ATP [14], which is of paramount importance taking into consideration that ATP release in peritraumatic regions rises massively. The role of this receptor is particularly important in understanding SCI pathophysiology due to its extensive expression in CNS neurons [10]. There are data indicating potential involvement of other receptor subtypes, namely, P2Y6, P2Y13 and P2Y14, in the physiological responses of microglia [15, 16].

Despite the severity of the damage, even with extensive SCI at the level of the thoracic segments, electrical stimulation applied slightly below the level of the injury allows to register stable rhythmic motor activity in the lower limbs, which was demonstrated in a number of animal models [17, 18].

Inhibiting purinergic receptors can improve outcomes in SCI patients. For example, intraspinal injection of a P2X7-receptor antagonist into the peritraumatic region reduced the damage caused by SCI [10]. P2X7R inhibition also reduced motor neuron loss and promoted subsequent functional recovery in injured animals.

On the other hand, axon membrane damage caused by an injury is associated with rapid changes in intracellular ion concentrations. The effects of ATP on spinal cord neurons cause their excitation leading to a persistent irreversible increase in Ca^{2+} levels resulting in a cell death [10].

Moreover, a number of fundamental animal model studies demonstrated pathological changes in skeletal muscles associated with SCI: the massive ATP release from damaged tissues provokes local and generalized inflammatory process with the release of proinflammatory cytokines (in particular, interleukins-1 and -6), which mediates muscle disorders, similar to muscle denervation atrophy [14]. ATP activates ionotropic P2XRs, particularly P2X7, which

mainly leads to an increase in intracellular Ca^{2+} levels and induces cytoskeletal reorganization, inflammation, apoptosis/necrosis, and proliferation, usually in a long-term perspective [19].

Conclusion

Thus, all the data available by now only outline the ways to study the mechanisms of the effects we have described. Further studies of P2-signaling role in post-spinalization processes are required.

Abnormal ATP-mediated modulation of neuromuscular transmission demonstrated in this study indicates axon degeneration and suggests that transsynaptic degeneration of motor neurons may occur below the level of spinal cord injury after the traumas similar to the ones described in the study.

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Dysphagia in Neurological Disorders

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Abstract

Neurogenic dysphagia is a disorder with impaired swallowing, which is caused by various disorders of the central and peripheral nervous systems, neuromuscular transmission, or muscles. Dysphagia is one of the most common and at the same time the most dangerous symptoms of many neurological disorders. Patients with dysphagia often have severe disability, a higher risk of aspiration pneumonia, and significantly increased mortality rate. Despite the availability of many diagnostic screening methods, clinical scales, questionnaires, and instrumental diagnostic methods, the issue of neurogenic dysphagia is underestimated, especially in the early stages. As a result, patients do not receive timely treatment and prevention of dysphagia and associated complications. Validation of available diagnostic scales, development of international protocols and standards for the diagnosis, treatment, and prevention of dysphagia and associated complications are important to establish a unified and evidence-based approach for patients with dysphagia.

Keywords: *neurogenic dysphagia; oropharyngeal dysphagia; aspiration pneumonia; cachexia*

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Проблема дисфагии в неврологии

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Аннотация

Нейрогенная дисфагия – это расстройство, характеризующееся нарушением акта глотания, вызванным различными заболеваниями центральной и периферической нервной системы, нервно-мышечной передачи или мышц. Дисфагия является одним из наиболее частых и в то же время наиболее опасных симптомов многих неврологических заболеваний. Пациенты, страдающие дисфагией, получают зачастую тяжёлую степень инвалидности, у них выше риск развития аспирационной пневмонии и значительно повышена смертность. Несмотря на большое количество разработанных скрининговых методов диагностики, клинических шкал, опросников и инструментальных методов диагностики проблеме нейрогенной дисфагии, особенно на ранних стадиях, уделяется недостаточное внимание, в результате чего пациенты не получают своевременное лечение и профилактику дисфагии и сопутствующих осложнений. Валидация имеющихся диагностических шкал, разработка международных протоколов и стандартов диагностики, лечения и профилактики дисфагии и ассоциированных осложнений актуальны и важны для создания унифицированного и научно-обоснованного подхода к пациентам, сталкивающимся с дисфагией.

***Ключевые слова**: нейрогенная дисфагия; орофарингеальная дисфагия; аспирационная пневмония; кахексия*

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Introduction

According to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), dysphagia is a disorder characterized by difficulty in swallowing, i.e. disturbed transfer of food and/or liquid from the oral cavity through the pharynx and esophagus into the stomach. Over 30% of hospitalized patients were estimated to have one or another type of dysphagia [2]. A total of 400,000 to 800,000 new cases of dysphagia secondary to neurological disorders are diagnosed annually, and the incidence of neurogenic dysphagia among patients over 60 years of age is 46% [3–5]. Dysphagia is more prevalent in patients with stroke (in 8.1–80% of cases), Parkinson's disease (11–81%), or traumatic brain injury (27–30%) [6]. Dysphagia also occurs in patients with dementia (in up to 85.9% of cases), Huntington's disease (90.5%), multiple sclerosis (25.4%), and in children with neuromuscular disease (47.3%) [7–10]. Chronic dysphagia leads to malnutrition, dehydration, and aspiration pneumonia; it is associated with longer hospital stay, increased anxiety, and risk of death [1]. An informed decision about treatment, rehabilitation, prevention, and improving the quality of life of patients with neurogenic dysphagia involves understanding the physiology and pathophysiology of the act of swallowing, the etiology and clinical features of dysphagia, development of international approaches to diagnosis, and patient's management by an interdisciplinary team of specialists.

Physiology of normal swallowing

International Classification of Functioning, Disability and Health describes swallowing as "functions of clearing substances, such as food, drink and saliva, through the oral cavity, pharynx and oesophagus into the stomach at an appropriate rate and speed" . Current understanding of the swallowing mechanism has been established on the basis of numerous scientific studies that were performed mainly in mammals. Owing to these studies, we know that the act of swallowing is a complex process that consists of three successive phases and involves the organized functioning of approximately 50 pairs of skeletal muscles and 5 pairs of cranial nerves (V, VII, IX, X, XII), which is mediated by the cerebral cortex and the nuclei of the brain stem [3, 11, 12].

The first (i.e. oral transit) phase is a preparatory voluntary step of swallowing, which consists of two stages. First, food is crushed and mixed with saliva due to contraction of the muscles of the tongue, orbicularis oris, masticatory and cheek muscles. This is followed by the stage of holding food or liquid over the lower part of the mouth by stimulating receptors around the soft palate, palatine arches, and root of the tongue. The back of the tongue and the velum palatinum are raised to prevent the bolus from entering the pharynx prematurely. During the second stage, the distal part of the tongue elevates, while its proximal part descends, pushing the bolus along the hard palate toward the oropharynx.

The second (i.e. pharyngeal) phase is a reflex phase, during which the food bolus moves from the oropharynx into the esophagus. When the food bolus reaches the pharynx, the velum palatinum rises, which seals off the nasopharynx and prevents nasal regurgitation, and the tongue rises to the back wall of the pharynx to prevent regurgitation of the bolus into the oral cavity. The oral and nasal cavities are closed, thus creating the pressure to move the bolus through the pharynx. At the same time, the pharyngeal constrictor muscles contract to push the bolus into the esophagus. As the velum palatinum rises, the hypoglossal-laryngeal complex moves upward and forward due to the contraction of the larynx muscles, ensuring closure of the larynx lumen with the help of the epiglottis. The vocal cords close once the adductor muscles of the larynx are activated. With this mechanism, the larynx and lower respiratory tract are protected from aspiration of the bolus passing through the pharynx. The total duration of the oral and pharyngeal swallowing phases is 0.6 to 1.0 seconds.

The muscles of the upper esophageal sphincter (UES) finally relax (their tonic activity is normally constantly maintained outside swallowing), and the third (esophageal) phase of swallowing begins. It is longer (from 10 seconds or longer), is controlled by both the somatic and autonomic nervous systems, and involves transit of the food bolus through the esophagus toward the stomach due to the peristaltic wave caused by contraction of the striated and smooth muscles of the esophagus [3, 12, 13].

Key centers involved in the act of swallowing include the anterior part of the insular cortex and the frontoparietal operculum, including the lower part of the primary motor, somatosensory, and premotor cortex [3, 11]. The primary motor and somatosensory cortex was shown by functional magnetic resonance imaging to be simultaneously activat-

ed during swallowing or oral sensory stimulation, likely functioning synchronically. The primary motor cortex is assumed to initiate and execute swallowing because electrical stimulation of this area causes rhythmic swallowing movements. There are efferent projections from the primary motor cortex to the muscles involved in swallowing, including the mylohyoid, pharyngeal, and esophageal muscles. The somatosensory cortex is activated when various types of sensory information enter the oral cavity, larynx, pharynx, or esophagus [11].

In adults, functional magnetic resonance imaging that was performed during swallowing showed cortical activation of the insula, cingulate cortex, supplementary motor area, premotor cortex, auditory cortex, inferior frontal gyrus, parieto-occipital and prefrontal cortex, tegmentum, putamen, thalamus, globus pallidus, cerebellum, corpus callosum, basal ganglia, caudate nucleus, and inferior parietal lobe [11, 14]. These structures are considered to be interconnected through two main functional circuits, i.e. cerebellar and insular loops. The cerebellar loop includes functional connections between the inferior frontal gyrus, secondary sensory cortex, corpus callosum, basal ganglia, thalamus, and between the sensorimotor cortex and cingulate cortex and cerebellum. The cerebellar loop modulates swallowing movements and coordinates swallowing-related events such as respiration. The insular loop includes connections between the premotor cortex and posterior parietal cortex, the sensorimotor cortex and the cingulate gyrus and insula. The insular loop synchronizes swallowing movements and integrates sensorimotor information in the cerebral cortex. The insula, known as the primary gustatory cortex, is activated during painful and non-painful stimulation of the esophagus and may be involved in the processing of mechanical sensory information. The insula is the primary integrative region for voluntary swallowing, which coordinates visceral sensory and motor information and may play a key role in the initiation of swallowing. The cingulate cortex is a part of the lymbic system, which is involved in the initiation and motivation of goal-directed behaviors, attention, and cognition. The cingulate cortex is involved in higher order cognitive processing of swallowing [11].

The cortical masticatory area plays an important role in swallowing; its repeated stimulation induced rhythmic chewing movements of the jaw in primates [15]. The cortical masticatory area includes the principal part, which is located in the precentral gyrus anterolateral to the primary motor cortex, and the deep part, which is located in the inner face of frontal operculum [11]. This region of the cortex receives projections from the sensory and motor nuclei of the thalamus, intracortical projections from the frontal, parietal, and orbital parts of the cerebral hemispheres, and communicates with the swallowing central pattern generator (SCPG) in the brainstem directly or indirectly through the basal ganglia. While being modulated by sensory feedback, this complex network allows performing a sequence of chewing movements. Located in the medulla oblongata around the solitary tract nucleus, the SCPG consists of two blocks of interneurons of the reticular formation on each side of the medulla oblongata, which regulate the final stage of swallowing, and modulates the swallowing process depending on the size, texture, and temperature of the bolus. The SCPG is connected through the nucleus ambiguus to the muscular complex that is involved in swallowing and to the receptors of the oral mucosa, pharynx and larynx through the trigeminal, glossopharyngeal, and vagus nerves and the solitary tract nucleus [3]. Information about the texture, temperature, taste, and movement of the food bolus is transmitted through transient receptor potential (TRP) receptors, which lead to depolarization of the sensory neurons due to the entry of calcium ions: transient receptor potential vanilloid 1 (TRPV1), which is activated by high temperature (more than 43ºC) and capsaicin, transient receptor potential ankyrin 1 (TRPA1), which is activated by low temperature (less than 17ºC), and transient receptor potential melastatin 8 (TRPM8), which is activated by the temperature of 25 to 28ºC and menthol [16].

Etiology of dysphagia

Dysphagia can occur in any of the three swallowing phases; however, considering that the pathogenesis of oral and pharyngeal dysphagia is similar, dysphagia is most often classified to oropharyngeal and esophageal [17].

The etiology of oropharyngeal dysphagia includes structural, toxic, and neurological disorders. Neurogenic dysphagia is associated with damage to various brain regions (including primary and secondary somatosensory and motor cortex, supplementary motor area, inferior frontal gyrus, anterior cingulate cortex, orbitofrontal cortex, supramarginal gyrus, insula, basal ganglia, corona radiata, thalamus, internal capsule, periventricular white matter and brain stem), damage to the peripheral nervous system, neuromuscular junction, and primary muscle damage [11]. Neurogenic dysphagia occurs mainly in patients with acute stroke, Parkinson's disease, head injury, dementia, amyotrophic lateral sclerosis, myositis, or myasthenia gravis [6, 18, 19]. The swallowing function is also affected by dental disease and decreased saliva production (see Table) [20]. A meta-analysis by F. Rajati et al. showed that the global prevalence of oropharyngeal dysphagia in different populations is 43.8% with a trend toward increasing with age [21]. Oropharyngeal dysphagia may be associated with odynophagia, hypersalivation, heartburn, oral or nasal regurgitation, weight loss, cough or nausea when swallowing [17]. A meta-analysis by KJ. Banda et al. based on 39 studies with 31,488 participants showed that in patients aged 60 years and older, oropharyngeal dysphagia

Etiology of oropharyngeal dysphagia [3, 20]

Nervous system disease	Structural causes	Other causes
• Multiple sclerosis • Spinocerebellar ataxia • Head injury • Brain tumors • Neurodegenerative disease: - Parkinson's disease - progressive; supranuclear palsy - multiple system atrophy - Alzheimer's disease - corticobasal degeneration - frontotemporal dementia - dementia with Lewy bodies - vascular dementia - Huntington's disease - Wilson's disease • Motor neuron disease: - amyotrophic lateral sclerosis - primary lateral sclerosis - spinal muscular atrophy • Neuromuscular disease: - nemaline myopathy - mitochondrial myopathy - inclusion body myositis - dermato-/polymyositis - myasthenia gravis • Peripheral neuropathies: - Guillain–Barre syndrome - polyneuropathy in systemic disease - diabetic neuropathy • Vascular disease: - acute stroke - vascular dementia - congenital cerebral palsy • Iatrogenic causes: - tardive dyskinesia with choreiform movements of the tongue during the treatment with antipsychotics	• Mass lesions of the head and neck • Surgery or radiation for malignant tumors of the head and neck • Chemoradiation mucositis and edema • Zenker's diverticulum • Cervical osteophytes • Lymphadenopathy • Goiter • Cricopharyngeal bar	• Dental disease • Hyposalivation with xerostomia, e.g. of toxic origin (treatment with α- and β-blockers, angiotensin-converting enzyme inhibitors, anticholinergics, antihistamines, anxiolytics, calcium channel blockers, diuretics, muscle relaxants, or tricyclic antidepressants)

is a risk factor for pneumonia, cachexia, and mortality and associated with urinary and fecal incontinence, immobility syndrome, pressure ulcers, sarcopenia, delirium, and frequent falls [4].

Esophageal dysphagia is associated with structural damage to the esophagus and surrounding structures (such as esophagitis of various origin, mass lesions, scleroderma, cardiomegaly, etc.) and with primary and secondary motility disorders of the smooth muscles in the esophagus and esophageal sphincter (such as hyperactive esophageal sphincter syndrome and achalasia). Unlike patients with oropharyngeal dysphagia, who are more likely to report difficulty in food swallowing early in the act of swallowing, patients with esophageal dysphagia typically experience the feeling of "food sticks in the throat or chest" a few seconds after swallowing. Dysphagia for solids is associated with structural abnormalities of the esophagus or oropharynx, while dysphagia for liquid food or liquids is associated with neurogenic causes [17]. Structural or esophageal dysphagia requires gastroenterological examination, which should include qualified examination of the oropharynx, pharyngolaryngoscopy, esophagogastroscopy, and manometry [22]. Esophageal and structural dysphagia is usually managed by gastroenterologists and otolaryngologists, so this review will consider mainly oropharyngeal dysphagia, which is associated with neurological disorders.

Diagnosis of neurogenic dysphagia

Clinical diagnosis

According to the Guidelines of the German Society of Neurology, a survey of the patient or their relatives if neurogenic dysphagia is suspected should include special

questions about changes in eating and drinking behavior; avoidance of certain foods and consistencies; difficulty in taking medications; time needed for a meal; posture during eating; difficulties in chewing; food residues after swallowing in the oral cavity or throat; feeling of "food sticks in the throat" [22].

The clinical assessment of swallow quality includes the following examination protocol [22]:
1) Examining the movement of the jaw and the elevation of the larynx during swallowing. It is recommended to palpate the masticatory muscles and the area above the thyroid cartilage during swallowing.
2) Examination of the soft palate and oral cavity, tongue and lips at rest using a spatula and mirrors with assessment of the pharyngeal and palatal reflexes and the presence of salivary disorders before or after swallowing.
3) Examination of the soft palate, oral cavity, and tongue during phonation, assessment of sound characteristics of the patient's voice.
4) Screening testing for swallowing disorders.

Screening testing should allow quick identification of patients at risk of aspiration to start preventive measures and further diagnosis. Most published testing protocols were evaluated only in stroke patients and have relatively high sensitivity (> 80%) but moderate specificity (up to 60%). However, the optimal testing paradigm have not been defined yet [22]. Three procedures are used as screening methods for diagnosing dysphagia:
1) Water swallow test, which assesses the volume of liquid that the patient can drink without experiencing symptoms of dysphagia [23];
2) Multi-consistency test, which assesses the degree of impairment in swallowing liquids and foods of various consistencies [22];
3) Swallow provocation test, which assesses the involuntary pharyngeal reflex, i.e. only the pharyngeal phase of swallowing [22, 23].

Various clinical scales and questionnaires are used to assess the severity of dysphagia at baseline diagnosis and during follow-up:
- Swallowing Disturbance Questionnaire, which consists of 15 questions on swallowing disturbance to be filled in by the patient [24];
- Swallowing Quality-of-Life Questionnaire, which consists of 10 subscales and a dysphagia symptom battery (14 items assessing symptom severity) to be filled in by the patient [25];
- Eating Assessment Tool, which assesses the severity of dysphagia and its impact on quality of life, with each question rated with a 5-point scale, to be filled in by the patient. Total score of 3 or more is considered abnormality [26];
- Munich Swallowing Score to assess dysfunction of swallowing saliva, food, and liquids [27];
- Gugging Swallowing Screen, a dysphagia screening tool developed for acute stroke patients, which consists of 2 parts: direct and indirect swallow test [28];
- The Functional Oral Intake Scale (FOIS), a 7-point scale used to describe a patient's functional oral intake level with scores ranging from "1" (Nothing by mouth) to "7" (Total oral diet with no restrictions) [26].

Fiberoptic endoscopic evaluation of swallowing

Fiberoptic endoscopic evaluation of swallowing is performed with a fiberoptic flexible endoscope, which is passed transnasally through the middle or lower nasal passages above the velum palatinum into the pharyngeal region. This method allows evaluating the entire pharyngeal phase of swallowing, partially the oral and esophageal phases, including the activity of the velopharyngeal sphincter, pharyngeal and laryngeal reflexes. A colored solution or solid bolus is used to diagnose swallowing disorders and aspiration during swallowing [22, 29].

This method can be used for an objective initial assessment of dysphagia severity, selection of nutrition strategies and food consistency, and assessment of the condition over time during rehabilitation [3, 22]. To assess changes of the condition over time and diagnose latent dysphagia, the following instrumental scales are used: Penetration-Aspiration Scale, Yale Pharyngeal Residue Severity Rating Scale, Murray Secretion Scale, etc. [30–32].

Fiberoptic endoscopy can be used in differential diagnosis of neurological disease or diagnosis of the underlying cause of oropharyngeal dysphagia. A study of T. Warnecke et al. showed that seven dysphagia phenotypes can be identified based on fiberoptic endoscopy findings [18]:
1) "Premature bolus spillage" before the swallowing reflex is triggered: a non-specific phenotype observed in many neurological disorders;
2) "Delayed swallowing reflex": no pharyngeal reflex for more than 3 seconds after the food has reached the valleculae (recesses in the epiglottis), which occurs mainly in stroke patients;
3) "Predominance of residue in the valleculae", which occurs mainly in patients with Parkinson's disease;
4) "Predominance of residue in the piriform sinus", which occurs mainly in patients with myositis, motoneuron disease, or brainstem stroke;
5) "Pharyngolaryngeal movement disorder" (i.e. oropharyngeal "freezing", pharyngeal bradykinesia and pharyngolaryngeal tremor), which occurs mainly in patients with atypical Parkinsonian syndromes or stroke;
6) "Fatigable swallowing weakness", when repeated swallowing attempts result in food residue in the larynx or

increased food residue, which occurs mainly in myasthenia gravis;
7) "Complex disorder" with a heterogeneous dysphagia pattern (i.e. with at least 2 of the mechanisms listed above, another mechanism or with its mechanism that cannot be determined), which occurs mainly in patients with amyotrophic lateral sclerosis.

Videofluoroscopic swallow study

Videofluoroscopic swallow study is an X-ray study of the entire swallowing process, including its oral, pharyngeal, and esophageal phases. The patient swallows a bolus of varying consistency (from solid to liquid) mixed with radiopaque contrast agent. The swallowing process from the formation of a bolus in the oral cavity to the entrance through the UES into the stomach is assessed through the monitor screen in the lateral and anteroposterior projections. This study allows measuring the time needed for the bolus transit in the oral, pharyngeal, and esophageal phases of swallowing, the duration and width of the closure/opening of the velopharyngeal valve and the esophageal sphincter [22, 29]. The following specific scales were developed for this study: Modified Barium Swallow Impairment Profile Scoring, Dynamic Imaging Grade of Swallowing Toxicity, Video Fluoroscopic Swallowing Study for patients with Parkinson's disease, Dysphagia Outcome and Severity Scale [33–36]. The advantage of videofluoroscopic swallow study over fiberoptic endoscopy is that the latter can assess hypertonicity and strictures of the upper esophagus. Videofluoroscopic swallow study is also used to assess the severity of dysphagia and choose a diet in patients after acute stroke or head injury, patients with Parkinson's disease, amyotrophic lateral sclerosis, spinal muscular atrophy, multiple sclerosis or Alzheimer's disease. However, it requires interaction with the patient for correct positioning during the study [17, 22].

High-resolution pharyngeal manometry

Manometry allows measuring pressure in the pharyngeal region and esophagus during the act of swallowing. This method is commonly and most often used for gastroenterological causes of dysphagia to confirm impaired relaxation of the esophageal sphincter and impaired motility of the esophagus with achalasia or diffuse esophagospasm. This method allows evaluating resting pressure, the function of the upper and lower esophageal sphincters, esophageal peristalsis, peak pressure, contraction time of the palatopharyngeal arch and base of the tongue, occlusion pressure in the lumen of the pharynx, hypopharyngeal intrabolus pressure, total swallowing time, wave speed of pharyngeal contraction, and length of active pharyngeal segment [22]. Recently, this method has been used to assess esophageal motility in patients with neurological disease, which is associated with impaired function of the esophageal sphincter and decreased pressure in the lumen of the pharynx, such as Parkinson's disease and atypical parkinsonism, myopathies of various origin, Huntington's disease, and brainstem infarction [17].

Other instrumental methods for diagnosing neurogenic dysphagia

Stimulation electroneuromyography allows evaluating the activation pattern of most muscles involved in the act of swallowing. It is used to assess the orbicularis oris and masseter muscles involved in the oral phase of swallowing, and the suprahyoid and infrahyoid muscles involved in the pharyngeal phase. Needle electrodes are used to record the activation of the cricopharyngeal muscle, which is part of the UES. This method is used in research studies to assess the degree of activation of muscles involved in the oropharyngeal phase of swallowing and to identify target muscles for the administration of botulinum toxin in the treatment of dysphagia [3, 22].

Ultrasound examination is another promising modality for diagnosing and assessing the severity of dysphagia; it allows evaluation of the morphometry of the oropharyngeal muscles and real-time visualization of oral bolus movement, the motor activity of the tongue, larynx movement, and activity of the supraglottic and sublingual muscles. Ultrasound can be used to diagnose structural changes caused by dystrophy or denervation of the muscles involved in swallowing, as well as to detect involuntary movements such as fasciculations and tremor. Advantages of the ultrasound diagnostic method include its non-invasiveness and low cost; however, study protocols and standards should be developed for its use in clinical practice [22, 37].

Dynamic magnetic resonance imaging adopting "Turbo Fast Low Angle Shot (turbo-FLASH) Sequences" at higher field strengths ($\geqslant$ 3 Tesla) provides a series of anatomical images in rapidly acquired consecutive slices. It allows a direct view on the deeper oropharyngeal muscles and soft tissue and tracking of the bolus transit during the swallowing act. Key limitations of this technique in diagnosing dysphagia include the horizontal position of the patient's body during the examination, which is usually not physiological for swallowing and can aggravate the swallowing disorder, and a limited ability to assist during the examination of patients with a high risk of aspiration. Potentially possible methods for diagnosing swallowing disorders include multi-slice computed tomography with high temporal resolution, which can be performed in a semi-sitting position [22, 38].

Treatment and rehabilitation of patients with neurogenic dysphagia

Treatment of patients with neurogenic dysphagia is primarily symptomatic and aims at improving swallowing

safety and efficiency. Treatment of neurogenic dysphagia should be personalized based on a thorough clinical and instrumental diagnosis of the patient, taking into account specific pathophysiological mechanisms of dysphagia. Treatment should be chosen by a multidisciplinary team, which includes a neurologist, speech therapist, physiotherapist, physical therapy instructor, dentist, and gastroenterologist [39].

Three therapy principles have been identified:
- restitution, which is aimed at restoring lost muscle functions;
- compensation, i.e. use of compensatory strategies to replace lost functions;
- adaptation, i.e. use of dietary modifications and other options to ensure safe swallowing [40].

Adaptation measures

Methods aimed at adapting the patient to live with dysphagia include modification of diet and posture during meals [16]. Most common dietary modification strategies include the use of liquid food thickeners and the selection of food bolus size and food consistency based on instrumental findings. It is recommended to calculate the patient's nutritional status, food caloric value, and fluid intake to prevent dehydration and cachexia, and maintain oral hygiene to prevent aspiration pneumonia [22, 38, 41, 42].

Physical methods of compensation and restitution

Physical exercise for patients with dysphagia are chosen individually, taking into account the course of the neurological disorder and the cause of dysphagia. Most common restitution methods include a set of shaker head lift exercises, which is intended for patients with weakness of the suprahyoid muscles and impaired opening of the UES; exercises for training the muscles of the tongue (Masako maneuver); and exercises to strengthen the expiratory and mental muscles. Methods aimed at compensating for impaired swallowing function and preventing complications include various modifications of the head position when swallowing, the "swallowing with effort" technique, which is used in patients with ineffective swallowing, i.e. predominance of food residue in the valleculae and pharynx. The following methods are also used: supraglottic swallowing, which is used as a compensatory maneuver for patients with reduced airway closure, Mendelsohn maneuver (i.e. keeping the larynx in an elevated position while swallowing), and swallowing with blocking the flow of the air to block the access to the glottis and prevent aspiration etc. In many cases, a combination of various adaptive, compensatory, and restorative physical methods is required to improve the quality of swallowing in patients with dysphagia [12, 22].

Medication treatment

Available medications aim at either stimulating the neural pathways in the peripheral or central nervous system that control swallowing or activating the muscles involved in swallowing. Medications that were shown to be effective in improving the swallowing reflex and reducing the incidence of aspiration pneumonia include TRPV1 agonists, TRPA1 agonists, TRPM8 agonists, levodopa and other dopaminergic agents, calcium blockers, dopamine D2 receptor antagonists, angiotensin-converting enzyme inhibitors (ACEIs), β-blockers, nitric oxide donors, and acetylcholinesterase inhibitors [16].

The mechanism of action of TRPV1, TRPA1 and TRPM8 receptor agonists includes stimulation of afferent pathways through the corresponding receptors located in the oropharynx, the activation of which leads to neuroplastic changes in the cerebral cortex. TRPV1 agonists may modulate swallowing through releasing substance P, which enhances cough reflex [16]. The relationship between substance P and swallowing function is not fully understood; however, in patients with Parkinson's disease and dysphagia, increased levels of substance P were shown to be associated with improved swallowing performance and a reduced risk of aspiration pneumonia [43]. A meta-analysis by I. Cheng et al. based on 14 studies including 2186 patients showed that TRPV1, TRPA1, and TRPM8 agonists were significantly superior to placebo in reducing swallowing time and severity of dysphagia [16].

As for other medications, a limited number of randomized clinical trials have been conducted to confirm their efficacy. However, calcium channel blockers (e.g. nifedipine) and dopamine D2 receptor antagonists (e.g. metoclopramide) were shown to be more effective than ACE inhibitors (e.g. lisinopril) and acetylcholinesterase inhibitors (e.g. physostigmine) [16]. The mechanism of action of capsaicin, ACE inhibitors, and β-blockers is thought to be related to increased levels of substance P, while levodopa and dopaminergic agents may improve swallowing efficiency by improving dopamine metabolism. Finally, acetylcholinesterase inhibitors (e.g. physostigmine) may improve swallowing function through cholinergic stimulation [16, 44–46].

Neurostimulation methods

Recently, peripheral neurostimulation methods, such as neuromuscular electrical stimulation (NMES) and pharyngeal electrical stimulation (PES), and central neurostimulation methods, such as rhythmic transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (TES), have been actively developed for the treatment of neurogenic dysphagia [22].

NMES is electrical transcutaneous stimulation of sensory and motor nerve fibers that are involved in swallowing; it is performed in order to restore and enhance the motor function of weakened muscles and prevent their atrophy. Stimulation is performed using surface electrodes applied to the skin of the chin and/or anterior neck [22, 40]. A meta-analysis by S. Miller et al. based on 14 studies showed that NMES is an effective method for the treatment of dysphagia, especially in combination with conventional rehabilitation options. However, further studies are needed as available stimulation protocols are very heterogeneous, and the effectiveness of the method was studied mainly in stroke patients [40].

PES is based on electrical stimulation of the bottom of the tongue and the posterior wall of the pharynx using a transnasal catheter with bipolar ring electrodes. Unlike NMES, PES is aimed at inducing neuroplasticity of the motor and sensory cortex and restoring sensorimotor integration [22]. PES showed its efficacy in patients with multiple sclerosis or stroke [47–49] but not in patients with amyotrophic lateral sclerosis [50]. Results of meta-analyses by R. Speyer et al., I. Cheng et al. were also controversial, and, therefore, the efficacy of PES requires further confirmation [51, 52].

rTMS and direct current TES are used to modulate cortical activity and cause long-lasting changes in synaptic plasticity [22, 51, 53–55]. In 2018 clinical guidelines, the effect of rTMS in stroke patients is considered unknown due to the heterogeneity of results and treatment protocols [53]. However, a meta-analysis by X. Wen et al. showed that low-frequency and high-frequency rTMS can improve swallowing function in stroke patients. Cortical representations of the muscles involved in swallowing (including the mylohyoid muscle) and the cerebellum were used as targets. The analysis of the studies demonstrated that stimulation of the cerebral cortex was effective in both affected and unaffected sides in comparison with standard physical treatments and placebo [54]. Similar results were shown by a meta-analysis by N. Zhao et al. for direct current TES; a significant positive effect of TES on reducing post-stroke dysphagia was demonstrated [55]. Limited data are available for other neurological disorders, so new randomized clinical studies are needed to confirm rTMS and TES efficacy.

Surgical methods

Minimally invasive surgical procedures are offered for patients with UES hyperactivity or other disorders of its opening. Such methods include open or endoscopic cricopharyngeal myotomy and dilatation of the UES using a balloon. Chemical cricopharyngeal myotomy using endoscopic or percutaneous injection of botulinum toxin is a safer and less invasive option. These methods have been used in patients with inclusion body myositis, muscular dystrophy, multiple sclerosis, amyotrophic lateral sclerosis, stroke, or Parkinson's disease. Surgical interventions may be associated with side effects such as supraglottic edema, mediastinitis, retropharyngeal hematoma, esophageal damage, laryngospasm and bleeding, so they should be administered after the comprehensive diagnosis is established and if conservative treatment is ineffective [22].

If severe dysphagia develops, i.e. if there is a high risk of cachexia and dehydration, insertion of a nasogastric tube or percutaneous endoscopic gastrostomy should be considered. Insertion of a nasogastric tube is indicated for patients with acute conditions, such as acute stroke or head injury, in which dysphagia may resolve within weeks or months. Percutaneous endoscopic gastrostomy is more suitable for patients with chronic progressive disorders such as Parkinson's disease, dementia or amyotrophic lateral sclerosis [3].

Conclusion

Neurogenic dysphagia is a common symptom of many neurological disorders. It significantly impairs patients' quality of life and leads to serious complications such as aspiration pneumonia, cachexia, and death. Despite the availability of relatively simple screening and highly informative instrumental diagnostic methods, treatment and prevention of swallowing disorders in neurological patients, as well as rehabilitation of patients with neurogenic dysphagia, remain insufficiently studied and require the development of unified treatment protocols based on large-scale multicenter clinical studies for medications and high-tech rehabilitation options.

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Rapid Eye Movement Sleep Behavior Disorder: Modern Concept and Parkinson's Disease Correlation

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Abstract

This review describes the association between rapid eye movement (REM) sleep behavior disorder (RBD) and synucleinopathies, primarily Parkinson's disease. This article reviews the diagnostic criteria, the epidemiology of RBDs, their pathogenesis, and their association with early non-motor symptoms. The data are presented to assess the risk of phenoconversion of RBDs to Parkinson's disease or other synucleinopathies such as Lewy body dementia and multiple system atrophy. A prodromal period of RBDs may precede synucleinopathies years or decades before potential manifestation of motor, cognitive, or autonomic disorders, and this may be important for initiating the neuroprotective therapy. Other causes of RBDs are also reviewed.

Keywords: *Parkinson's disease; early stages; REM sleep behavior disorders; non-motor disorders; rapid eye movement sleep; alpha-synuclein; synucleinopathies*

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Нарушения поведения в REM-фазе сна: современная концепция и взаимосвязь с болезнью Паркинсона

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Аннотация

Обзор посвящён взаимосвязи нарушения поведения в фазе быстрого сна (фаза с быстрым движением глаз, Rapid eye movement, REM-фаза) и синуклеопатий, преимущественно болезни Паркинсона. Обсуждаются критерии постановки диагноза, эпидемиология нарушений поведения в REM-фазе сна, взаимосвязь с ранними немоторными симптомами заболевания, патогенетические причины развития нарушения поведения во сне. Представлены данные об оценке риска феноконверсии нарушений поведения в REM-фазе сна в болезнь Паркинсона или другие синуклеопатии: деменцию с тельцами Леви, мультисистемную атрофию. Продромальный период с нарушениями в REM-фазе сна может предвосхищать синуклеинопатии за годы или десятилетия до возможных явных двигательных, когнитивных или вегетативных нарушений, что может иметь важное значение для начала нейропротекторной терапии. Рассмотрены также другие причины появления нарушений в REM-фазе сна.

Ключевые слова: *болезнь Паркинсона; начальные стадии; нарушения поведения в REM-фазе сна; немоторные нарушения; фаза сна с быстрым движением глаз; альфа-синуклеин; синуклеинопатии*

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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Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by dreaming, complex motor behavior, and loss of physiological muscle atonia. This behavior disorder is confused with REM sleep without atonia (RSWA), which is often detected by a sleep study. However, RSWA provides a neurophysiological substrate for full progression of RBD in the future [1]. When RBD is not associated with other apparent neurological disorders, it is called idiopathic RBD (iRBD). When accompanied by other neurological symptoms such as akinetic rigid syndrome, cognitive decline, metabolic disorders, etc., RBD is considered to be symptomatic and may be associated with neurodegenerative, autoimmune, and structural brain disorders and medications [2–16]. RBD most commonly begins in the 5th or 6th decade of life. However, in some cases, symptoms of iRBD (most notably, sleep-related motor activity) may manifest at a younger age [8, 11]. The frequency of motor events during the REM sleep can vary widely, from several episodes per night to one episode per month [8]. In each patient, the severity and frequency of RBD varies from night to night [11]. The mechanisms of such fluctuation remain unknown.

RBD was first described by S.N. Schenck et al. in 1986 [17]. No generally accepted criteria for diagnosing RBD exist to date. Questionnaires have been developed to identify RBD patients. However, they are not very specific. Patients with RBD are unaware of motor activity during sleep in 44% of cases and report good quality of sleep in 70% of cases [18]. The diagnosis of RBD usually requires an accurate observation history from a bed partner of the patient. In cases of doubt, or for patients who do not have a bed partner, a polysomnography can be performed.

According to the American Academy of Sleep Medicine's International Classification of Sleep Disorders, a sleep pattern must meet four criteria to diagnose an RBD:

1) Repeated episodes of bed activity during the dream phase corresponding to the dream content,
2) Episodes of motor activity during REM sleep, confirmed by polysomnography,
3) No REM sleep atonia confirmed by polysomnography,
4) No association with known adverse drug effects or substance abuse [19].

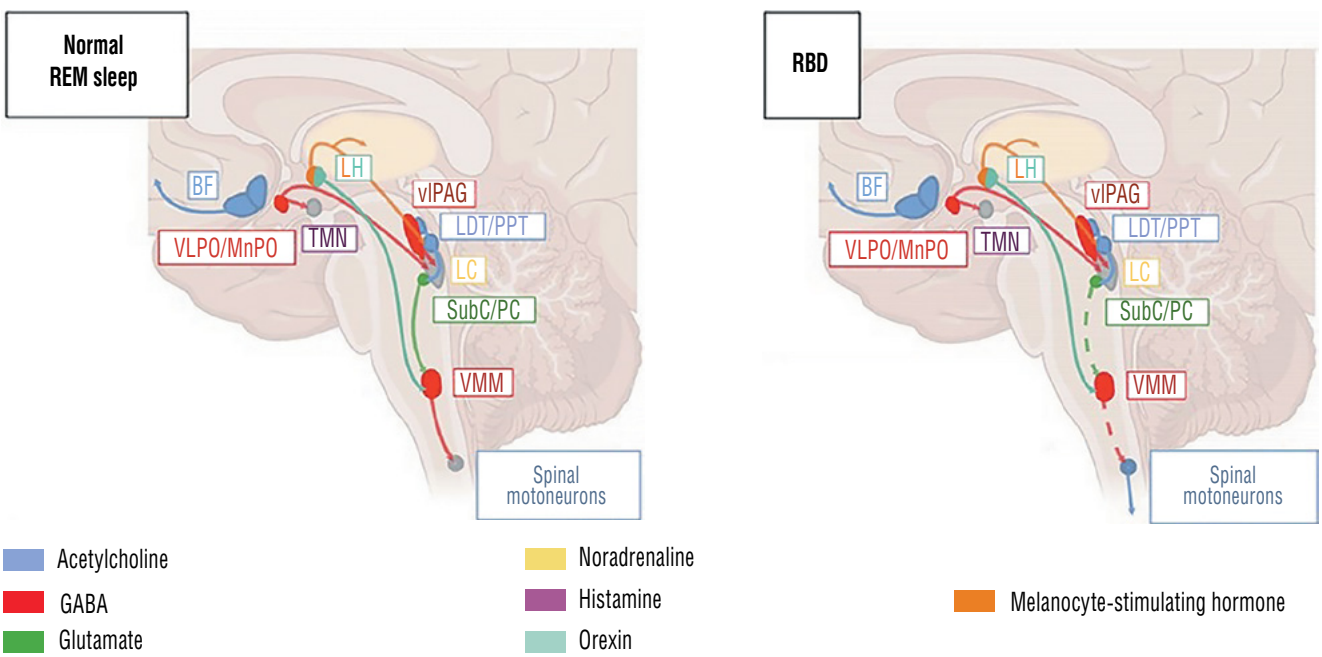
All of these factors complicate the determination of the exact RBT incidence. A large phone survey estimated the prevalence of iRBD to be 0.38% to 0.50% in the general population [20]. However, up to 4.8% of sleep clinic patients have RBD [21]. In 2013, a population-based study by S.H. Kang et al. showed that in Korea, the overall age- and sex-adjusted prevalence of RBD was 2.01% (1.15% for iRBD), and another 4.95% of the general population had isolated polysomnographically confirmed RSWA [22]. J. Haba-Rubio et al. estimated the incidence of RBD to be 1.06% in the middle-aged and elderly population in Switzerland [23]. Other population-based studies show that suspected RBD (without confirmatory polysomnography) is even more common, occurring in 5% to 6.8% of the elderly population over the age of 60–70 years [24, 25]. Although prevalence studies without confirmatory polysomnography may overestimate the incidence of RBD, their data suggest that burden of RBD has been significantly underestimated [26]. Some large studies have reported that RBD is more common in men than in women, but in patients under 50 years of age (with non-neurodegenerative RBD appearing to be more common) the incidence does not differ by sex [4, 6, 16, 18, 27–31]. The risk of RBD is 5 and 9–10 times higher in patients taking antidepressants and in those with a psychiatric diagnosis, respectively [4].

Cohort studies suggest that RBD (including iRBD) is closely associated with α-synucleinopathies, particularly Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [2–11, 13–15, 32–38]. In the largest multicenter study of RBD, B.F. Boeve et al. found that 94% of patients had abnormal accumulation of

α-synuclein at autopsy, in some cases with accumulation of β-amyloid, τ-protein, or iron [5]. At the same time, the risk of phenoconversion of RBD to PD is approximately 15–35% over the 2–5-year period and increases to 91.9% when the observation period is extended to 12–25 years, making RBD by far the most specific clinical prodromal marker for PD [10, 39]. Investigating the validity of criteria for assessing the likelihood of prodromal PD and determining the independence of prodromal markers for predicting PD or DLB, S.M. Fereshtehnejad et al. found that diagnostic accuracy of International Parkinson and Movement Disorder Society criteria was highest in people with RBD [40, 41].

The mechanism of RBD development remains unclear. The states of wake and sleep are initiated and maintained by complex interplay between multiple brainstem and diencephalic nuclei. Dysregulation, structural damage, or degeneration of these nuclei can result in various circadian rhythm disorders. RBD is thought to cause an excitation/inhibition imbalance in the brainstem nuclei controlling REM muscle tone (Figure) [42].

Movement during REM sleep is controlled by two systems: the extrapyramidal system controls the input to spinal cord motor neurons to generate muscle atonia, and the pyramidal system controls motorcortex activation to suppress locomotor activity. The main generator of REM sleep is the glutamatergic Subcoeruleus/Pre-Locus Coeruleus complex (SubC/PC), which is anatomically situated just below the noradrenergic *locus coeruleus* in the pons [43] and analogous to the rat/mouse sublaterodorsal nucleus. In addition to projecting to many subcortical brain regions to promote and maintain REM sleep, the SubC/PC projects caudally to control the REM atonia [44]. Before and during REM sleep, the REM-active SubC/PC excites the inhibitory ventromedial medulla (VMM) and glycinergic neurons of the spinal ventral horn, which in turn tonically hyperpolarize spinal motor neurons [44, 45]. This results in a temporary paralysis of skeletal muscles and thus significantly reduced REM muscle tone (atonia) during REM sleep. It is not definitively known whether RBD is caused by an imbalance originating in the glutamatergic SubC/PC or downstream in the GABA/Glycinergic VMM, though animal studies suggest the latter is more likely [46]. This brainstem function disorder does not exist in isolation. Since RBD is characterized not just by an increase in small sleep twitches but also complex movements and dream enactment, it is likely that abnormal disinhibition occurs in the pyramidal motor tract during REM sleep, leading to execution of the complex movements "imagined" by the motor cortex. Neuroimaging studies have shown that RBD can also be accompanied with changes in multiple neurotransmitter systems, including the cholinergic, noradrenergic, and dopaminergic circuits [47]. Therefore, one of the key challenges in treating RBD derives from uncertainty about the underlying pathology and the extent of dysfunction throughout the brain.



Key brain regions and neurotransmitters involved in regulating and maintaining REM sleep in healthy people and RBD patients. In RBD, dysfunction within the SubC → VMM → Spinal Motor Neuron pathway results in a lack of REM sleep atonia (depicted by the dotted line). BF, basal forebrain; LC, locus coeruleus; LDT/PPT, laterodorsal tegmentum/pedunculopontine tegmentum; LH, lateral hypothalamus; Subc/PC, subcoeruleus/pre-locus coeruleus; TMN, tuberomammillary nucleus; vlPAG, ventrolateral periaqueductal gray matter; VLPO/MnPO, ventrolateral preoptic nucleus/median preoptic nucleus; VMM, ventromedial medulla.

It should be mentioned that the development of RBD in the prodromal phase of PD corresponds to the neurodegeneration concept proposed by H. Braak et al [48], according to which Lewy bodies begin to appear in the dorsal motor nucleus of the medulla (Braak stage I). Subsequently, deposits appear more rostrally, in the reticular formation and in the SubC/PC nucleus region (Braak stage II) [15, 49–52]. Therefore, patients with RBD may formally be in Braak stage II of the neurodegenerative process or in the so-called prodromal phase of PD. This was confirmed in several studies by the presence of non-specific signs of PD in the form of hyposmia and sympathetic denervation of the myocardium in these patients [4, 14, 15]. In the third and subsequent Braak stages of the neurodegenerative process, α-synuclein accumulation progresses, involving the substantia nigra, the pedunculopontine nucleus, and the amygdala. At Braak stage IV, degeneration of the substantia nigra reaches a qualitative threshold when akinetic rigid syndrome manifests clinically [48].

However, RBD may not be observed in all patients with α-synucleinopathy, and this is likely to reflect variability in the topographic onset and progression of neurodegeneration in patients. Considering this, an alternative concept of disease progression has been proposed. This unified staging system classifies Lewy body diseases by the distribution of the abnormal protein. Stage I denotes the presence of abnormal α-synuclein in the olfactory bulbs only. Then α-synuclein accumulates predominantly in the brainstem (stage IIA), in the limbic system (stage IIb), in the brainstem and limbic system (stage III), and in the neocortex (stage IV). Progression through these neurodegenerative stages correlated with increased α-synuclein density in certain regions and clinical deterioration of cognitive impairment and motor dysfunction [53]. J. Horsager et al. recently hypothesized that PD comprises two subtypes based on progression patterns: brain-first PD and body-first PD [54]. According to the "brain-first" hypothesis, abnormal α-synuclein first affects the brain and then spreads in a caudal gradient to the peripheral autonomic nervous system [54, 55]. According to the "body-first" hypothesis, abnormal α-synuclein is first formed in the peripheral autonomic nervous system and spreads rostrally into the brain along the autonomic nerves, primarily along the *n. vagus* [54, 55]. This hypothesis is consistent with the fact of intercellular transmission of abnormal α-synuclein in cellular and animal models of PD [56]. However, it remains controversial because no cases have been reported showing that abnormal α-synuclein exists only in the peripheral nervous system and not in the brain [57–59]. It should be noted that these newly proposed concepts can explain that PD is often preceded and accompanied by prodromal and progressive non-motor symptoms and signs [60, 61].

Another unsolved issue is that some patients with RBD and PD do not fit the Braak model of neurodegeneration progression. In some patients, RBD may manifest at the same time or significantly later than the development of cognitive, motor, or autonomic symptoms of PD or DLB, and these RBDs are in fact secondary/symptomatic to a neurodegenerative process [6, 62]. However, RBD has the same features as iRBD.

Some evidence suggests that PD associated with RBD is phenotypically different from PD without RBD. Patients with RBD-associated PD have more severe and diffuse neurodegeneration, which is associated with a greater deterioration in quality of life, cognitive impairment, psychiatric complications, and slowing of the awake background electroencephalogram, more severe autonomic dysfunction, akinetic rigid syndrome, and longer disease duration [63–67]. Recent studies confirm that the motor phenotype of RBD-associated PD is more severe than in PD without RBD, with a greater tendency toward akinetic rigid syndrome, poor response to levodopa, lack of tremor, earlier and more severe gait disturbances, and longer disease duration [68, 69]. Motor decline also appears to be faster in patients with PD and RBD than in patients without RBD [70]. Study results on the effect of RBD on cognitive impairment are controversial [71–73].

Other synucleinopathies are also associated with RBD. For example, in DLB, which is characterized by the presence of dementia in combination with parkinsonism, visual hallucinations, and fluctuations in cognitive status and sleep/wake state, 80% of patients develop RBD several years before the appearance of other clinical signs [74, 75]. RBD is diagnosed in more than 88% of patients with multiple system atrophy [76]. RBD has been reported to be associated with clinically diagnosed Alzheimer's disease [77]. However, a concomitant Lewy body disorder should still be suspected in RBD, as the largest autopsy study of RBD patients to date found synucleinopathies in 94% of patients [5]. RBD has also been reported in association with progressive supranuclear palsy, although in contrast to synucleinopathies, RBD symptoms accompany rather than precede motor dysfunction in progressive supranuclear palsy [78]. In other primary tauopathies, RBD is very rare [79]. There are few reports on its association with Guadelupian parkinsonism (tauopathy) and the autoimmune anti-IgLON5 disease. In the latter, deposition of τ protein in the brain and hypothalamus has been demonstrated in deceased patients [80, 81].

It should be noted that iRBD occurring at a younger age, i.e. before the age of 50, is more often associated with non-neurodegenerative processes such as narcolepsy, autoimmune disorders, antidepressant use, or structural brain lesions. Almost half of patients with type 1 narcolepsy (narcolepsy with cataplexy) are reported to have

RSWA with or without RBD [82–85]. The RBD associated with narcolepsy typically develops much earlier, between the 2nd and 4th decades of life, likely due to the pathophysiology of type 1 narcolepsy with the unstable REM sleep phase in narcolepsy with hypocretin deficiency [82]. In young and elderly patients, RBD may be a manifestation of paraneoplastic and autoimmune neurological disorders such as Morvan syndrome (caused by antibodies to voltage-gated calcium channels) or autoimmune brain disorders (anti-IgLON5 disease and brainstem lesions associated with inflammatory, neoplastic, or cerebrovascular disorders) [7, 86–91]. In addition, the use of selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and tricyclic antidepressants was associated with symptoms of RBD and RSWA without RBD. It remains unclear whether the RBD/RSWA association with antidepressants is mediated by either reversible pharmacological effects, or whether antidepressants lead to RSWA and RBD detection in predisposed individuals with latent synucleinopathy [11, 14, 16, 30].

Therefore, RBDs, whether idiopathic or symptomatic, are closely associated with neurodegeneration, particularly with synucleinopathies such as PD, DLB, and MSA [92–94]. A prodromal period of RBDs may precede synucleinopathies years or decades before potential manifestation of motor, cognitive, or autonomic disorders, and this may be important for initiating the neuroprotective therapy in order to prevent RBD phenoconversion to PD, DLB, or MSA. More data is required to understand RBDs, how they progress clinically, and how to treat them.

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Вклад авторов. *Залялова З.А., Хасанова Д.М.* – постановка проблемы, разработка концепции статьи, критический анализ литературы, написание статьи, формирование выводов; *Ильина Г.Р.* – анализ литературы, редактирование; *Багданова Н.И.* – анализ литературы. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Monoclonal Antibodies as Analgesia of Chronic Low Back Pain: a Systematic Review and Meta-analysis of Efficacy and Safety

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Abstract

Introduction. *Monoclonal antibodies (mAb) emerged as a possible option in addressing the partial response to current treatment modalities in chronic low back pain (CLBP).*

Objective: *to evaluate the efficacy and safety of mAb for CLBP.*

Materials and Methods*. Randomized controlled trials on adult patients with CLBP who received mAb-therapy compared to those who did not as a control group. The result was the changes in Low Back Pain Intensity (LBPI) Numeric Rating Score and Roland–Morris Disability Questionnaire (RMDQ) indicating improved pain, disability, and the risk of adverse events. Meta-analysis, risk of bias, and confidence in the evidence for each analysis were assessed. We* ***aimed*** *at reviewing current treatment methods for degenerative lumbosacral spinal stenosis with an emphasis on surgical treatment methods.*

Results*. Six studies were included, with a total of 3851 participants. mAb significantly reduce LBPI and RMDQ score (weighted mean difference –1.48; 95% CI –2.63 to –0.33; p = 0.01). Tanezumab and fasinumab were significantly reduced both LBPI (weighted mean difference of –4.11; 95% CI –6.27 to –1.95; p = 0.0002 and weighted mean difference –0.24; 95% CI –0.47 to –0.02; p = 0.04 respectively) and RMDQ scores (weighted mean difference –3.72; 95% –5.48 to –1.97 and weighted mean difference –0.50; 95% –0.73 to –0.26 respectively, both p < 0.0001). The mAb have significantly greater odds of any adverse events (OR 1.23; 95% 1.06 to 1.43; p = 0.007) but no greater odds regarding serious adverse events (OR 1.00; 95% 0.69 to 1.46; p = 0.98).*

Conclusion*. Depending on the types of drugs used, mAb had a favorable outcome and were relatively safe in reducing LBPI and RMDQ scores.*

Keywords: *monoclonal antibody; tanezumab; fasinumab; fulranumab; denosumab; chronic low back pain; LBPI; RMDQ*

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Применение моноклональных антител в качестве анальгетиков при хроническом болевом синдроме в нижней части спины: систематический обзор и метаанализ эффективности и безопасности

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Аннотация

Введение. *Моноклональные антитела (мАТ) всё чаще рассматриваются как возможное средство для достижения частичного ответа при хроническом болевом синдроме (ХБС) в нижней части спины.*

Цель: *изучить эффективность и безопасность мАТ при ХБС в нижней части спины.*

Материалы и методы*. Проведены рандомизированные контролируемые исследования с участием взрослых пациентов, страдающих ХБС в нижней части спины и получавших мАТ, и контрольной группы, не получавшей мАТ. Выявляли изменение оценки по числовой оценочной шкале выраженности боли в нижней части спины (LBPI) и опроснику Роланда–Морриса для определения уровня инвалидизации (RMDQ), отражающие уменьшение боли, сопутствующей инвалидизации, а также риск нежелательных явлений. Нами подготовлен метаанализ и проанализированы риск систематических ошибок и доказательная сила каждого отдельного анализа.*

Результаты*. В обзор вошли 6 исследований, в которых участвовал в общей сложности 3851 пациент. Применение мАТ привело к значимому снижению оценки по LBPI и RMDQ: средневзвешенная разница –1,48; 95% доверительный интервал (ДИ) (–2,63; –0,33), p = 0,01. На фоне применения танезумаба и фасинумаба отмечалось значимое снижение балла по LBPI (танезумаб – средневзвешенная разница –4,11; 95% ДИ (–6,27)–(–1,95), p = 0,0002; фасинумаб – средневзвешенная разница –0,24; 95% ДИ (–0,47)–(–0,02); p = 0,04) и RMDQ (танезумаб – средневзвешенная разница –3,72; 95% ДИ (–5,48)–(–1,97); p < 0,0001; фасинумаб – средневзвешенная разница –0,50; 95% ДИ (–0,73)–(–0,26); p < 0,0001). На фоне применения мАТ значимо увеличивался риск развития любых нежелательных явлений (отношение шансов 1,23; 95% ДИ 1,06–1,43; p = 0,007), однако риск развития серьёзных нежелательных явлений не повышался (отношение шансов 1,00; 95% ДИ 0,69–1,46; p = 0,98).*

Заключение*. В зависимости от препарата применение мАТ приводило к благоприятному исходу с уменьшением оценки по LBPI и RMDQ и было относительно безопасным.*

Ключевые слова*: моноклональное антитело; танезумаб; фасинумаб; фулранумаб; деносумаб; хроническая боль в нижней части спины; LBPI; RMDQ*

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

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage[1]. Pain is responsible for informing the body of the danger, while chronic pain becomes a disease, losing its function of signaling a danger and producing suffering for the patient. Low back pain is a common reason for presentation to emergency departments, general practice and rehabilitation services worldwide [1]. Even after treatment, many patients report persistent pain and severe disability ⩾ 3 months after the first episode. Many patients with chronic pain, especially chronic low back pain (CLBP), remain challenging to treat and respond only partially to currently available treatment options [2]. Monoclonal antibodies (mAb) may address an unmet need for patients with CLBP that is unresponsive or poorly tolerant to conventional forms of treatment. In this setting, mAb have emerged as a possible option [3].

mAb are artificially produced antibodies for therapeutic purposes developed from single animal or human cell lines. They consist of large B-cell-derived glycoproteins made up of two heavy and two light chains held together by disulfide bonds to form a Y-shaped protein. They are typically derived from the Y-immunoglobulin (or IgG) isotype [4]. The hypervariable regions of each heavy and light chain combine to form the antigen binding site, referred to as the fragment antigen binding domain. In contrast, the crystallisable or constant fragment domain responsible for the effector function comprises two regular domains [4, 5]. Advances in preclinical and clinical research have led to the development of biological agents targeting specific cytokines in the potentiation and transmission of pain in CLBP where inflammatory processes occur; these targets are mainly nerve growth factor (NGF) and tumour necrosis factor (TNF) [5, 6]. The efficacy and safety of mAb for CLBP still faces challenges because of the lack of research. This systematic review and meta-analysis aims to evaluate the efficacy and safety of mAb in patients with CLBP.

Materials and methods

Protocol and registration

This systematic review and meta-analysis reported the literature findings according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2021 [7]. The protocol of this review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database with the registration number CRD42023449999.

Search Strategy

A literature search was conducted across published studies from January 2011 to July 2023 and was not limited to any language. We searched the literature on 16 July 2023 across the Pubmed, NCBI, Google Scholar, Science Direct, Europe PMC and Cochrane Central Register of Controlled Trials (CENTRAL) databases. The keywords used in each database are presented in the Table 1.

Inclusion and exclusion criteria

This systematic review included randomised controlled trial reports in adult patients (over 18 years) with CLBP who received mAb-therapy compared to those who did not receive mAb as a control group. In this case, the control group can be placebo or other treatments other than mAb plus placebo. This study includes patients with CLBP defined as more than 12 weeks or more than 3 months, not limited to any severity grade. The primary results are changes in the Low Back Pain Intensity (LBPI) Numeric Rating Score, indicating pain improvement and changes in the Roland–Morris Disability Questionnaire (RMDQ) indicating improvement in pain-related disability. The secondary outcome is the risk of adverse events in patients receiving mAb and controls. The exclusion criteria are research on animals, non-randomised controlled trials, studies without full-text reports, studies with using only active substance as control (non-placebo control) and studies in participants with a history or evidence of spinal disease (e.g. malignancy, fracture, trauma, spondyloarthritis, infection, former low back surgery, autoimmune disease, and mental disorders). Literature reviews were screened for references that could be used before they were excluded.

Data extraction

Data were collected in a standard format, including study citations, demographic characteristics of the participants (age, sex), number of patients, daily dose intervention, regimen, mAb classification, mAb target, comparison, outcome, and safety data (adverse events). The adverse events in this study were analysed based on the number of participants who reported any adverse event during treatment.

Assessment of quality and risk of bias in the included studies

The authors performed a preliminary search and quality assessment of each included analysis using the Jadad

[1] International Association for the Study of Pain. IASP Taxonomy. URL: http://www.iasp-pain.org/Taxonomy

Table 1. Keywords (MeSH) that have been used in every database

Database	Medical subject heading	Number of studies found
PubMed	(«monoclonal antibody»[All Fields] AND «chronic low back pain»[All Fields]) AND ("treatment"[All Fields])	47
NCBI	((((«antibodies, monoclonal»[Supplementary Concept] OR «antibodies, monoclonal»[All Fields] OR «monoclonal antibodies»[All Fields] OR «antibodies, monoclonal»[MeSH Terms] OR («antibodies»[All Fields] AND «monoclonal»[All Fields]) OR («monoclonal»[All Fields] AND «antibodies»[All Fields])) AND (chronic[All Fields] AND («low back pain»[MeSH Terms] OR («low»[All Fields] AND «back»[All Fields] AND «pain»[All Fields]) OR «low back pain»[All Fields]))) AND («therapy»[Subheading] OR «therapy»[All Fields] OR «treatment»[All Fields] OR «therapeutics»[MeSH Terms] OR «therapeutics»[All Fields])) AND («randomized controlled trial»[All Fields] OR «randomized controlled trials as topic»[MeSH Terms] OR «randomized controlled trial»[All Fields] OR «randomised controlled trial»[All Fields]) AND («2010/01/01»[PubDate] : «2023/12/31»[PubDate])	2017
Google Scholar	"monoclonal antibody" AND "chronic low back pain" AND "treatment" AND "randomized controlled trial"	399
Science Direct	«monoclonal antibody» AND «chronic low back pain» AND «treatment» AND «randomized controlled trial»	48
Europe PMC	«monoclonal antibody» AND «chronic low back pain» AND «treatment» AND Randomized Controlled Trial AND (((SRC:MED OR SRC:PMC OR SRC:AGR OR SRC:CBA) NOT (PUB_TYPE:»Review»)))	86
Cochrane Central Register of Controlled Trials (CENTRAL)	"monoclonal antibody" AND "chronic low back pain" AND "treatment" AND "randomized controlled trial"	18

Scale Assessment for randomised controlled trials, where a score of 3 to 4 is deemed moderate high-quality studies. In contrast, a score of higher than 4 indicated high-quality studies [8].

Review team members assessed the risk of bias using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions [9] The evaluation items included the following seven domains:

- random sequence generation;
- allocation concealment;
- blinding (participants and personnel);
- blinding (outcome assessment);
- incomplete outcome data;
- selective outcome reporting;
- 'other bias' (comparability of treatment and control group at entry, and post-randomisation recruitment bias in studies with cluster allocation).

According to the extracted information, each item of the included studies was classified into three levels: "low risk of bias", "unclear risk of bias", or "high risk of bias". Where necessary, we contacted the study authors for clarification. Disagreements were resolved by discussion between the review authors and where necessary. The confidence in the evidence for each analysis using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [9].

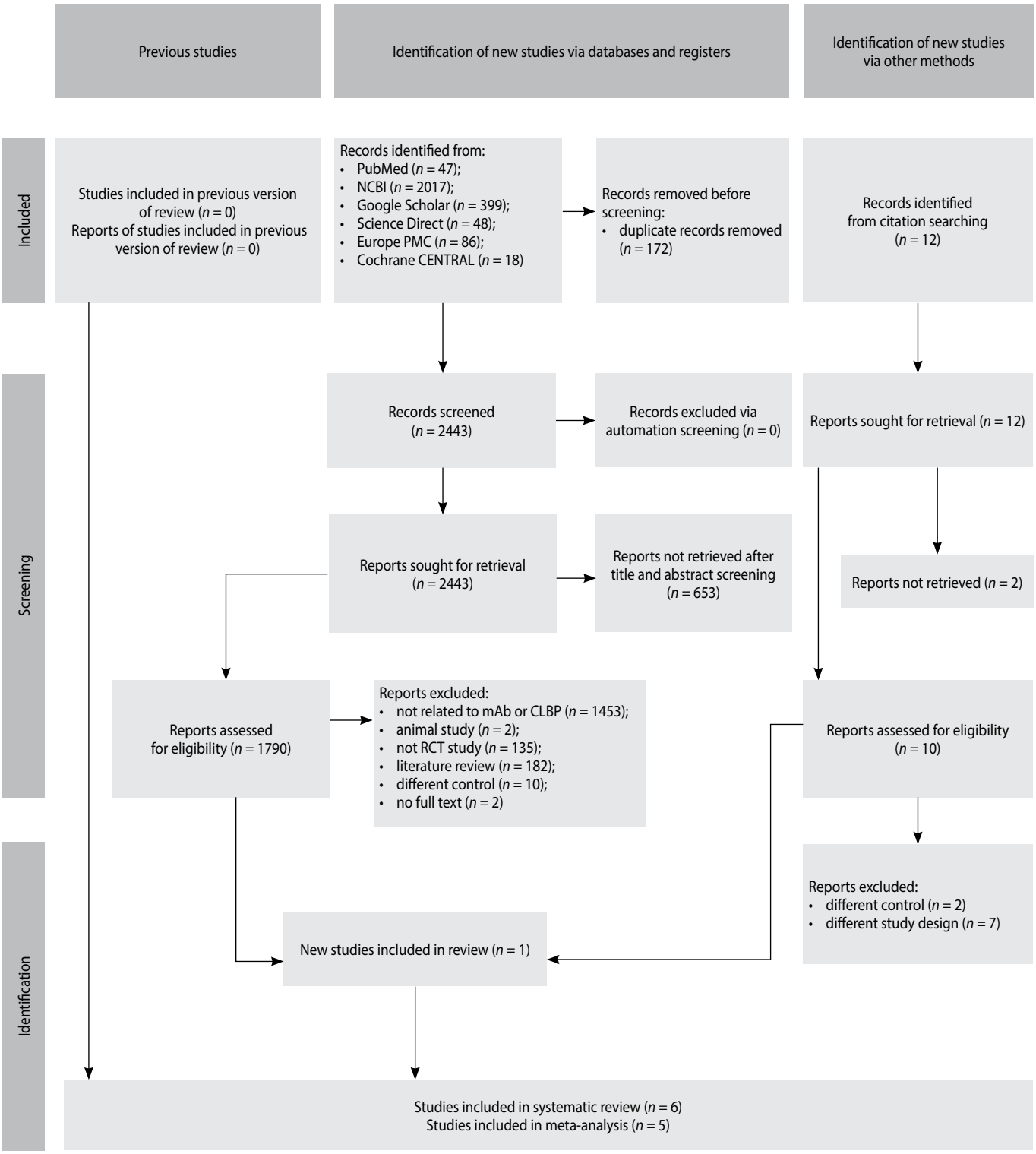

Fig. 1. PRISMA flow diagram for the included study.

Table 2. Risk of bias in included studies based on Cochrane Risk of Bias Tool

Study	Random sequence generation)	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete data (high < 80%)	Selective reporting	Other bias
Markman J.D. et al. (2020)	Low	Low	Low	Low	High	Low	Low
Katz N. et al. (2011)	Unclear	Unclear	Low	Low	Low	Low	Unclear
Kivitz A.J. et al. (2013)	Unclear	Unclear	Low	Low	Low	Low	Unclear
Dakin P. et al. (2021)	Low	Low	Low	Unclear	Low	Low	Unclear
Sanga P. et al. (2016)	High	Unclear	Low	Low	High	Low	Unclear
Cai G. et al. (2018)	Low	Low	Low	Low	Low	Low	Low

Table 3. LBPI and RMDQ score changes from baseline to endpoint ($M \pm m$)

Author (year)	Changes in LBPI score from baseline		Changes in RDMQ score from baseline		Duration of treatment
	monoclonal antibody group	control group	monoclonal antibody group	control group	
Markman J.D. et al. (2020)	NA	NA	NA	NA	16
Katz N. et al. (2011)	–3,17 ± 0,24	–2,41 ± 0,34	NA	NA	6
Kivitz A.J. et al. (2013)	–1,97 ± 0,29	–1,25 ± 0,16	–2,82 ± 0,42	–1,75 ± 0,29	16
Dakin P. et al. (2021)	–2,41 ± 2,04	–1,9 ± 2,1	–6,28 ± 5,30	–3,8 ± 4,5	16
Sanga P. et al. (2016)	–2,05 ± 1,98)	–2,0 ± 2,17)	NA	NA	12
Cai G. et al. (2018)	–6,0 ± 2,0	–3,0 ± 1,9	–1,6 ± 1,4	–1,8 ± 1,3	26

Note. NA — not accessed.

Statistical analysis

Review Manager 5.4 software was used to perform this meta-analysis. The primary outcome of this study is the difference in LBPI and RMDQ scores. We calculated the weighted mean difference and 95% confidence intervals (CI) for changes from the baseline level in the mAb-group *vs* the control group. We calculated the odds ratio (OR) and 95% confidence intervals (CI) for the risk of adverse events in both groups. A random-effects model was used when $I^2 > 50\%$ or $p < 0.1$; when $I^2 \leqslant 50\%$ and $p > 0.1$, a fixed-effect model was used to merge the data. The degree of heterogenicity was assessed based on the I^2 statistics A value of $I^2 < 25\%$ was deemed low heterogenicity, 26–50% moderate heterogenicity, and > 50% high heterogenicity. Subgroup analyses were done based on each drug used (denosumab, fasinumab, tanezumab, fulnarumab).

Agent; study	Dose, route of administration	Monoclonal antibody			Placebo			Weight, %	Std. mean difference; IV, fixed; 95% CI
		M	*m*	total	*M*	*m*	total		
Denosumab; Cai G. et al. (2018)	60 mg SC	–6	5.4525	31	–3	5.6986	37	2.5	–0.53; (–1.02)–(–0.04)
	Subtotal			31			37	2,5	–0.53; (–1.02)–0.04
	Heterogeneity: not applicable								
	Test for overall effect: Z = 2.14; *p* = 0.03								
Tanezumab; Katz N. et al. (2011)	20 µg/kg IV once	–3.17	2.2514	88	–241	2.1771	41	4.3	–0.34; (–0.71–0.03
Tanezumab; Kivitz A.J. et al. (2013)	10 mg/kg IV every 8 weeks	–2.06	2.4046	295	–125	2.4265	230	19.8	–0.34; 0.51–(–0.16)
	20 mg/kg IV every 8 weeks	–2.18	2.4046	295	–125	2.4265	230	19.8	–0.38; –(–0.56)–(–0.21)
	5 mg/kg IV every 8 weeks	–1.58	2.437	232	–1.25	2.4265	230	17.9	–0.14; (–0.32)–0.05
	Subtotal			910			731	61.8	–0.29; (–0.39)–(–0.19)
	Heterogeneity: $\chi^2 = 4.21$; df = 3 (*p* = 0.24); $I^2 = 29\%$								
	Test for overall effect: Z = 2.14 (*p* < 0.00001)								
Fulranumab; Sanga P. et al. (2016)	10 mg SC every 4 weeks	–2.1	2.18	77	–2	2.17	76	6.0	–0.05; (–0.36)–0.27
	1 mg SC every 4 weeks	–1.9	2.14	77	–2	2.17	76	6.0	–0.05; (–0.27)–0.36
	3 mg SC every 4 weeks	–2.2	1.89	77	–2	2.17	76	5.9	–0.10; (–0.41)–022
	6 mg LD + 3 mg SC every 4 weeks	–2	1.72	78	–2	2.17	76	6.0	0.00; (–0.32)–0.32
	Subtotal			309			304	23.8	–0.02; (–0.18)–0.13
	Heterogeneity: $\chi^2 = 0.44$; df = 3; *p* = 0.93; $I^2 = 0\%$								
	Test for overall effect: Z = 0.30; *p* = 0.76								
Fasinumab; Dakin P. et al. (2021)	6 mg SC every 4 weeks	–2.1	1.9	48	–1.9	2.1	49	3.8	–0.10; 0.50–0.30
	9 mg SC every 4 weeks	–2.6	2	55	–1.9	2.1	49	4.0	–0.34; (–0.73)–0.05
	9 mg SC every 8 weeks	–2.5	2.2	56	–1.9	2.1	49	4.0	–0.28; (–0.66)–0.11
	Subtotal			159			147	11.8	–0.24; (–0.47)–(–0.02)
	Heterogeneity: $\chi^2 = 0.77$, df = 2; *p* = 0.68; $I^2 = 0\%$								
	Test for overall effect: Z = 2.09; *p* = 0.04								
Total				**1409**			**1219**	**100.0**	**–0.23; (–0.31)–(–0.15)**
Heterogeneity: $\chi^2 = 14.96$; df = 11; *p* = 0.18; $I^2 = 26\%$									
Test for overall effect: Z = 5.80; *p* < 0.00001									
Test for subgroup differences: $\chi^2 = 9.55$; df = 3; *p* = 0.02; $I^2 = 68.6\%$									

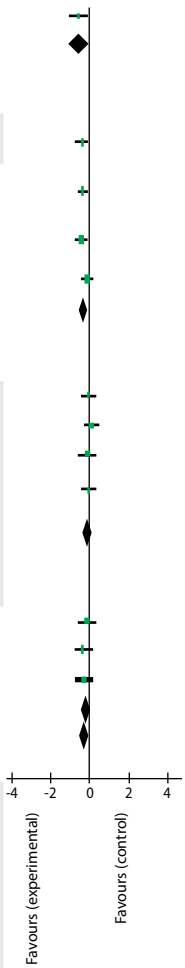

Fig. 2. Effect of monoclonal antibodies divided by each type of drug compared with placebo by LBPI score changes from baseline.
Here and in Figs. 3–5: (▪) this square represents the individual studies effect. The square size varies to reflect the weight a particular study has in the overall analysis; (–) the black line represents the CIs of a study; (♦) the diamond represents the overall or summary effect. The outer edges of the diamond represent the CIs. IV — intravenously; SC — subcutaneously.

Results

Search results

We screened 2,443 records, and after removing duplicate studies, studies that are not related to mAb or CLBP, animal studies, non-randomised controlled trials, literature reviews, ineligible control, and reports without the full text, we screened article meeting inclusion criteria. Six clinical trials were included in this review study based on PRISMA algorithm (Fig. 1).

The studies included in this review were assessed according to the Jadad Scale, and all studies were deemed as high-quality studies (Table 2); thus, all studies were fit to be included in the review.

A total of six trials were included in the review, with 2223 participants in the mAb-group and 1628 in the control group. All included studies used a parallel-group double-blind design . All studies, except one, analysed the changes in LBPI and RMDQ scores as their primary outcome. Five out of six trials used nerve growth factor (NGF)-type mAb, and one study used receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL).

Six trials evaluated the efficacy of mAb for CLBP using the decrease in LBPI score as its outcome. The summary of included studies is presented in Table 3, Appendicies 1 and 2. Of these, five trials were included in the meta-analysis comparing the efficacy of mAb to placebo in reducing LBPI score. Meta-analysis showed a result favouring the mAb-group in decreasing the LBPI score compared to placebo,

Agent; study	Dose, route of administration	Monoclonal antibody			Placebo			Weight, %	Std. mean difference; IV, fixed; 95% CI
		M	*m*	total	*M*	*m*	total		
Denosumab; Cai G. et al. (2018)	60 mg SC	–1.6	3.8168	31	–1.8	3.899	37	3.7	0.05; (–0.43)–0.53
	Subtotal			31			37	3.7	0.05; (–0.43)–0.53
	Heterogeneity: not applicable								
	Test for overall effect: Z = 0.21; $p = 0.83$								
Фасинумаб Fasinumab; Dakin P. et al. (2021)	6 mg SC every 4 weeks	–6	5.7	46	–3.8	4.5	46	4.9	–0.42; (–0.84)–(–0.01)
	9 mg SC every 4 weeks	–6.2	4.7	55	–3.8	4.5	46	5.3	–0.52; (–0.91)–(–0.12)
	9 mg SC every 8 weeks	–6.6	5.6	55	–3.8	4.5	46	5.3	–0.54; (–0.94)–(–0.14)
	Subtotal			156			138	15.4	–0.50; (–0.73)–(–0.26)
	Heterogeneity: $\chi^2 = 0.17$; df = 2 ($p = 0.92$); $I^2 = 0\%$								
	Test for overall effect: Z = 0.21 ($p = 0.83$)								
Tanezumab; Kivitz A.J. et al. (2013)	10 mg/kg IV every 8 weeks	–3.18	4.4656	295	–1.75	4.3981	230	27.8	–0.32; (–0.50)–(–0.15)
	20 mg/kg IV every 8 weeks	–2.8	4.4656	295	–1.75	4.3981	230	28.0	–0.24; (–0.41)–(–0.06)
	5 mg/kg IV every 8 weeks	–2.37	4.4171	232	–1.75	4.3981	230	25.1	–0.14; (–0.32)–(0.04)
	Subtotal			822			690	80.9	–0.24; (–0.34)–(–0.13)
	Heterogeneity: $\chi^2 = 1.99$; df = 2 ($p = 0.37$); $I^2 = 0\%$								
	Test for overall effect: Z = 4.55 ($p < 0.00001$)								
Total				**1009**			**856**	**100**	**–0.27; (–0.36)–(–0.17)**
Heterogeneity: $\chi^2 = 7.95$; df = 6 ($p = 0.24$); $I^2 = 25\%$									
Test for overall effect: Z = 5.69 ($p < 0.00001$)									
Test for subgroup differences: $\chi^2 = 5.78$; df = 2 ($p = 0.06$); $I^2 = 65.4\%$									

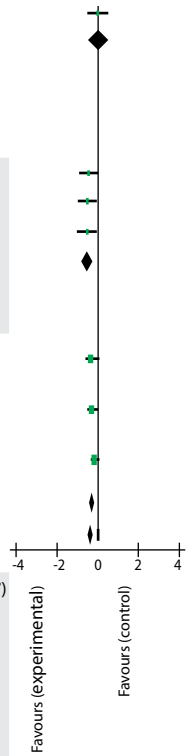

Fig. 3. Effect of monoclonal antibodies divided by each type of drug compared with placebo by RMDQ score changes from baseline.

with a statistically significant difference (weighted mean difference –0.23; 95% CI –0.31 to –0.15; $p \leqslant 0.001$), high certainty. However, the analysis revealed moderate heterogenicity (I^2 = 26%; fixed effects modelling). Subgroup analysis was done for each drug, and tanezumab showed a significant effect in lowering LBPI score (weighted mean difference of –0.29; 95% CI –0.39 to –0.19; $p \leqslant 0.001$) as well as fasinumab (weighted mean difference –0.24; 95% CI –0.47 to –0.02, p = 0.04). However, fulranumab showed a nonsignificant difference in lowering LBPI score, compared to placebo (weighted mean difference –0.02; 95% CI –0.18 to 0.13; p = 0.76; Fig. 2).

The meta-analysis included three trials to compare mAb efficacy using RMDQ scores. The analysis showed a result favouring the mAb-group in decreasing RMDQ score compared to placebo with significant difference (weighted mean difference –0.27; 95% CI –0.36 to –0.17; $p \leqslant 0.001$), high certainty. Nonetheless, low heterogeneity was found in the analysis with I2 25%. Subgroup analysis showed that fasinumab and tanezumab are significant in reducing RMDQ score (weighted mean difference –0.50; 95% CI –0.73 to –0.26 and weighted mean difference –0.24; 95% CI –0.34 to –0.13 respectively, both $p < 0.0001$; Fig. 3).

The most common adverse events reported in tanezumab group are arthralgia (128), nausea (108), and headache (90). However, in fasinumab group, arthralgia (52), headache (27), and nasopharyngitis (27) are the most frequent adverse events. In fulranumab group, back pain (47), arthralgia (46), and upper respiratory tract infection (45) are the most common adverse events. Unlike other mAb, denosumab only has a few adverse events. The most common adverse events are headache (10) and psychological effects (10), which we did not find in other drugs [10] (Table 4). Some studies defined serious adverse events as a condition requiring non-elective hospital admission and leading to deaths. The most common serious adverse events are musculoskeletal and connective tissue disorders requiring surgical management (femur fracture, patella fracture, intervertebral disc protrusion, and meniscus injury) [11, 12]. Other serious adverse events, although very rare, are represented by one case of haemorrhagic stroke in fasinumab 9 mg subcutaneously [12], lumbar radiculopathy (fulranumab 6 mg loading dose + 3 mg), peripheral neuropathy (fulranumab 10 mg) [13]. Other adverse events that occurred but the dose of tanezumab was not mentioned are headache, pneumonia, deep vein thrombosis and pulmonary embolism, with no deaths in that study [11].

Table 4. Adverse events with each agent

Agent (total patients with adverse events, *n*)*	Most common adverse events, *n* (%)	Least common adverse events
Tanezumab (954)	Headache 90 (9.43%); arthralgia 128 (13.41%); nausea 108 (11.32%); dizziness 55 (5.76%); parasthesia 93 (9.74%)	Back pain (4.08%); nasopharyngitis (4.50%); constipation (5.87%); upper respiratory tract infection (4.82%); neuralgia (0.1%); hyperesthesia (2.83%); hypoesthesia (2.51%); pain in extremity (4.71%); peripheral edema (2.20%)
Fasinumab (160)	Arthralgia, 52 (32.5%); headache, 27 (16.88%); nasopharyngitis, 27 (16.88%); paresthesia, 24 (15%); nausea, 12 (7.5%)	Dizziness (8.75%); hypoesthesia (8.75%); diarrhea (7.5%); pain in extremity (7.5%); urinary tract infection (6.88%); upper respiratory tract infection (5.63%); back pain (5.63%)
Fulranumab (259)	Back pain, 47 (18.15%); arthralgia, 46 (17.76%); upper respiratory tract infection, 45 (17.37%); paresthesia, 43 (16.60%); diarrhea 37 (14.29%); headache, 36 (13.9%); hypoesthesia, 34 (13.13%)	Pain in extremity (12.74%); sinusitis, (11.97%); nasopharyngitis (11.58%); edema peripheral (10.42%)
Denosumab (27)	Headache 10 (37%); phycological effects (malaise, insomnia, and depression), 10 (37%); musculoskeletal pain and stiffness (spasm), 9 (33.33%)	Flu-like (18.52%)

Note. *Each patient may have more than one adverse event.

Meta-analysis of six trials indicates that mAb have significantly greater odds of adverse events, favouring the placebo group (OR 1.23; 95% CI 1.06 to 1.43; $p = 0.007$). Moderate heterogenicity was found in the analysis with I^2 29% (Fig. 4). However, meta-analysis demonstrated no greater risk regarding the serious adverse events in mAb vs. placebo with OR 1.00 (95% CI 0.69 to 1.46; $p = 0.98$; Fig. 5).

Risk of bias of the included studies

The risk of bias assessment was low in a few trials: random sequence generation ($n = 3$; 50%), allocation concealment ($n = 3$; 50%), blinding of participants and personnel ($n = 6$; 100%), blinding of outcome assessment ($n = 5$; 83%), incomplete data ($n = 4$; 67%), selective reporting ($n = 6$; 100%), other bias ($n = 2$; 33%; Table 5).

DISCUSSION

Efficacy

This systematic review and meta-analysis evaluated the efficacy and safety of mAb for CLBP. mAb significantly improve the intensity of pain scale and disability as shown by the LBPI and RMDQ scores, compared to placebo.

Agent; study	Dose, route of administration	Monoclonal antibody		Placebo		Weight, %	Odds ratio (M–H, random); 95% CI
		events	total	events	total		
Denosumab; Cai G. et al. (2018)	60 mg SC	27	31	25	37	1.4	3.24; 0.92–11.37
Fasinumab; Dakin P. et al. (2021)	6 mg SC every 4 weeks	41	139	52	140	6.8	0.71; 0.43–1.17
	9 mg SC every 4 weeks	63	139	52	140	7.3	1.40; 0.87–2.26
	9 mg SC every 8 weeks	56	140	52	140	7.2	1.13; 0.70–1.83
Tanezumab; Katz N. et al. (2011)	20 µg/kg IV once	50	88	27	41	3.4	0.68; 0.32–1.48
Tanezumab; Kivitz A.J. et al. (2013)	10 mg/kg IV every 8 weeks	171	295	120	230	11.1	1.26; 0.89–1.79
	20 mg/kg IV every 8 weeks	190	295	120	230	11.0	1.66; 1.17–2.36
	5 mg/kg IV every 8 weeks	141	232	120	230	10.3	1.42; 0.98–2.05
Tanezumab; Markman J.D. et al. (2020)	10 mg	211	407	189	409	14.3	1.25; 0.95–1.65
	5 mg	191	407	189	409	14.2	1.03; 0.78–1.38
Fulranumab; Sanga P. et al. (2016)	10 mg SC every 4 weeks	66	86	58	76	3.7	1.02; 0.49–2.12
	1 mg SC every 4 weeks	59	77	58	76	3.6	1.02; 0.48–2.15
	3 mg SC every 4 weeks	64	77	58	76	3.2	1.53; 0.69–3.39
	6 mg LD + 3 mg SC every 4 weeks	70	78	58	76	2.5	2.72; 1.10–6.70
Total			**2491**		**2310**	**100.0**	**1.23; 1.06–1.43**
Total events		1400		1178			
Heterogeneity: $Tau^2 = 0.02$; $\chi^2 = 18.37$; df = 13 ($p = 0.14$); $I^2 = 29\%$							
Test for subgroup differences: Z = 2.69 ($p = 0.007$)							

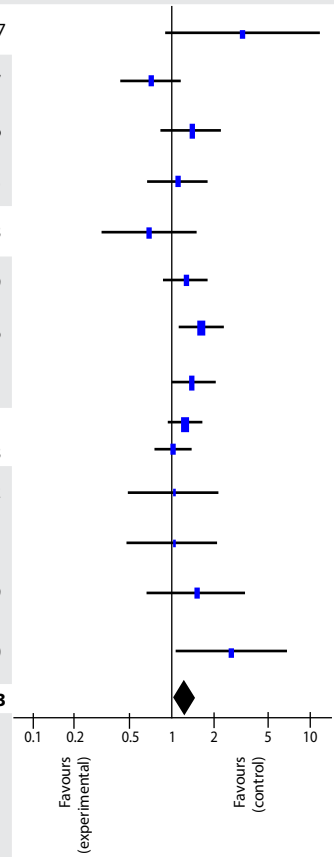

Fig. 4. Adverse events (safety) of monoclonal antibody compared to placebo for CLBP.

Tanezumab is a humanised IgG2-mAb that inhibits NGF by activating trkA receptors on nociceptive neurons. This inhibition of NGF affects both acute and chronic painful states, thereby acting as a novel mechanism of action, unlike opioids and nonsteroidal anti-inflammatory drugs. Tanezumab interferes with pain signals produced by skin, muscles, and organs precluding them from reaching the central nervous system. In our study tanezumab showed a significant effect in lowering LBPI and RMDQ scores. Tanezumab was first indicated for treating moderate to severe chronic osteoarthritic pain of the hip and knee joint and CLBP. One study by Brown et al. found that tanezumab is superior in providing pain relief and improved physical function and patient's global assessment compared to placebo in painful hip arthritis [14]. Other clinical trials investigate the role of NGF inhibition in neuropathic conditions. The study by C. Bramson et al. found that tanezumab provided effective pain relief in patients with diabetic peripheral neuropathy. It is also found to cause pain reduction in postherpetic neuralgia patients but at higher doses, although the results were insignificant [15]. Common adverse events observed in previous tanezumab studies were peripheral sensations such as paresthesia and hypoesthesia followed by headache, arthralgia, extremity pain, urinary tract infection, and upper respiratory tract infection. The list of adverse events was consistent with the result of this study.

Fasinumab 6 mg subcutaneously, 9 mg subcutaneously, and 9 mg intravenously significantly improved pain intensity and disability, as shown by the LBPI and RMDQ scores. Fasinumab has also been used in other diseases to decrease joint pain and improve physical function in hip or knee osteoarthritis patients [16]. Our study found that fasinumab is generally well tolerated, similar to the previous research [16].

Our study found that all doses of fulranumab did not significantly improve LBPI scores. A study by A.J. Mayorga et al. compared fulranumab, placebo, and oxycodone

Agent; study	Dose, route of administration	Monoclonal antibody events	Monoclonal antibody total	Placebo events	Placebo total	Weight, %	Odds ratio (M–H, random); 95% CI
Denosumab; Cai G. et al. (2018)	60 mg SC	0	31	2	37	1.5	0.23; 0.01–4.88
Fasinumab; Dakin P. et al. (2021)	Combined	10	418	4	140	10.1	0.83; 0.26–2.70
Tanezumab; Katz N. et al. (2011)	20 µg/kg IV once	0	88	0	41		Not accessed
Tanezumab; Kivitz A.J. et al. (2013)	10 mg/kg IV every 8 weeks	3	295	5	230	6.7	0.46; 0.11–1.96
	20 mg/kg IV every 8 weeks	3	295	5	230	6.7	0.46; 0.11–1.96
	5 mg/kg IV every 8 weeks	4	232	5	230	7.9	0.79; 0.21–2.98
Tanezumab; Markman J.D. et al. (2020)	10 mg	7	407	4	409	9.2	1.77; 0.51–6.10
	5 mg	6	407	4	409	8.7	1.51; 0.42–5.41
Fulranumab; Sanga P. et al. (2016)	10 mg SC every 4 weeks	7	77	7	76	11.6	0.99; 0.33–2.96
	1 mg SC every 4 weeks	9	77	7	76	12.9	1.30; 0.46–3.70
	3 mg SC every 4 weeks	6	77	7	76	10.8	0.83; 0.27–2.60
	6 mg LD + 3 mg SC every 4 weeks	11	78	7	76	13.9	1.62; 0.59–4.42
Total			**2482**		**2330**	**100.0**	**1.00; 0.69–1.46**
Total events		66		57			
Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 5.78$; df = 10 ($p = 0.83$); $I^2 = 0\%$							
Test for overall effect: Z = 0.02 ($p = 0.98$)							

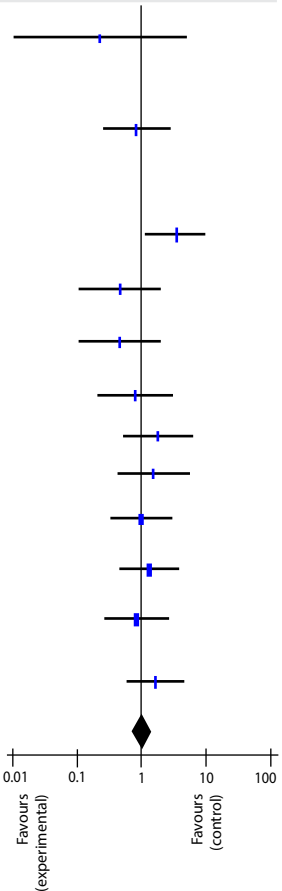

Fig. 5. Serious adverse events (safety) of monoclonal antibody compared to placebo for CLBP.

to find that responder rates were significantly greater in the fulranumab groups compared with the oxycodone group, but no significant differences in responder rates were observed between the two fulranumab groups and placebo groups [18]. However, at that time, the FDA held all anti-NGF trials [17, 18]. Nonetheless, data from patients who did not withdraw show that the oxycodone group had a greater discontinuation rate because of treatment-emergent adverse events compared to fulranumab and placebo groups. Fulranumab at all doses showed minimal adverse events and was mainly well tolerated, which parallels other studies [17, 18].

The humanised mAb is one for which both chain types are humanised due to antibody engineering. A humanised chain is typically one in which the complementarity determining regions of the variable domains are foreign, originating from one species other than human or synthetic. In contrast, the remainder of the chain is of human origin. Humanisation assessment is based on the resulting amino acid sequence and not on the methodology that allows protocols other than grafting. The variable domain of a humanised chain has a V region amino acid sequence, which, analysed as a whole, is closer to humans than other species [19]. Humanized mAb are created by grafting the murine hypervariable regions of the light and heavy chains onto a human antibody framework. This results in molecules that are approximately 95% human [20]. Human mAb (fulranumab and fasinumab) are mAb created using animals carrying human Ig genes. These transgenes include parts of the variable regions, which enable the recombination of the human antibodies and inactivated endogenous Ig genes in animals, thus generating fully human mAb.

MAb focusing on particular cytokines involved in the amplification and transmission of pain sensation in chronic low back pain (CLBP) have primarily targeted inflammatory processes associated with NGF and TNF cytokines [6]. Tanezumab, fasinumab and fulranumab are mAb that target NGF, a pleiotropic neurotrophin that plays significant role in generation and maintaining both nociceptive and neuropathic pain. NGF also contribute to chronic pain [3]. Expression of NGF has been found to occur early in

Table 5. GRADE Assessment

No. of studies	Certainty assessment: study design	risk of bias	inconsistency	indirectness	imprecision	considerations	No. of patients: antibody	placebo	Effect, absolute (95% CI)	Certainty
LBPI changes										
12	Randomised trials	Not serious	Serious	Not serious	Not serious	—	1409	1219	< **1.48**; (< 2.63)–(< 0.33)	⊕⊕⊕◯ High
RMDQ changes										
7	Randomised trials	Not serious	Serious	Not serious	Not serious	—	1009	865	< **1.81** (< 3.2)–(< 0.41)	⊕⊕⊕◯ High

response to inflammatory mediators such as interleukin one and TNFα involved in neurogenic pain transmission [21]. Moreover, NGF is involved in peripheral sensitisation and then sensitises nociceptive neurons to painful stimuli through upregulation of ion channels and receptors present on primary afferent nerve fibres and increases the release of pain mediators that potentiate the pain response such as substance P [3, 22]. Currently, studies on the effect of infliximab that targets TNF on CLBP are in progress [23]. Future results may add more information regarding the best mAb to address chronic back pain.

One study used denosumab targeting RANKL as the choice of mAb. Denosumab showed a significant improvement in reducing LBPI score but not substantial for RDMQ score. Another prospective cohort study assessing denosumab's effectiveness for back pain in post-menopausal women showed a significant effect [24]. None of the fatal or life-threatening adverse events were shown in this study and the previous one [25].

Denosumab is the most potent anti-resorptive agent and a fully human igG2-mAb that neutralises RANKL, blocking the interaction between the cytokine and its receptor (RANK), with consequent inhibition of osteoclast-mediated bone resorption [26]. Denosumab can reduce bone pain through several mechanisms. Denosumab lowers osteoclast-mediated acidification by negatively modulating the NF-κB by inhibiting the RANK/RANKL pathway and delaying the pain catastrophising response [27].

Safety

The safety profile of mAb is parallel with previous studies [15–18, 25]. Although the mAb group reported more adverse events, none were life-threatening or led to death. mAb had no greater risk regarding serious adverse events than placebo. Dakin et al. reported one patient from fasinumab 6 mg group with a history of smoking who died of small cell lung cancer during the post-treatment follow-up period. The event was considered unrelated to the study drug [12]. P. Sanga et al. also reported one patient from fulranumab 10 mg group who died due to streptococcal pneumonia and malignant lung neoplasm [13] J.D. Markman et al. reported 7 deaths during the study (56-week treatment period and 24-week follow-up period) [28]. However, none of those deaths (cardiac failure, road traffic accident, myocardial infarction and aneurysmal rupture, influenza and toxicity to multiple agents, i.e. cocaine, heroin, and fentanyl) was considered to be treatment-related by investigators.

Application

The potential of mAb agents in this study, like tanezumab, fulranumab, fasinumab, and denosumab, to inhibit or block crucial steps in the generation and exaggera-

tion of pain and inflammation suggests that these drugs could have a adjunctive role in the management of CLBP where traditional therapy and interventions have failed to provide improvement and adequate relief for patients. In studies that we included, mAb therapy can be prescribed in moderate-to-severe axial predominant CLBP (primary location between the 12th thoracic vertebra and lower gluteal folds, with or without radiation into the posterior thigh) of ⩾ 3 months in adult patients ⩾ 18 years, average LBPI score ⩾ 5 (on an 11-point numeric rating scale, NRS) and history of inadequate response to ⩾ 3 different categories of standard of care analgesics [13, 28]. Other conditions that we found that can be treated with mAb are non-radiculopathy CLBP, with the primary pain location between the 12th thoracic vertebra and lower gluteal folds, use of analgesic medications for > 4 days per week over the month, average LBPI score of ⩾ 4 using an 11-point NRS over the previous 24 hours at screening while on current treatment [10–11, 29].

Strength and weakness

To our knowledge, this study is the first to analyse the efficacy of mAb regardless of their mechanism of action in CLBP. This meta-analysis has low to moderate heterogeneity based on the I2 value, which can be the strength of this study. Nonetheless, this result should be seen in the light of a few limitations. Data regarding the efficacy of each drug, especially denosumab, were minimal due to limited studies. The definition of serious adverse events in this study may vary as we defined it based on each trial. Nonetheless, CLBP is a diverse condition arising from various factors, including degenerative spinal changes and central brain structure dysfunction. A significant portion of the participants have likely experienced primary CLBP due to central sensitization. Unfortunately, this aspect could not be explored in greater depth in this review, representing one of its limitations. Despite these limitations, our study included more than 2,000 patients receiving mAb; thus, it is considered an extensive analysis to compare the mAb efficacy.

Conclusion

This systematic review and meta-analysis found that mAb had a favourable effect in reducing LBPI and RMDQ scores compared to the placebo group, with relatively safe adverse events profile under short-term surveillance. This effect may depend on the types of drugs used, with tanezumab and fasinumab as drugs that reduced both LBPI and RMDQ scores significantly.

Additionals to the article:

Appendix 1. Summary of the studies included.

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Appendix 2. Summary of primary and secondary end-points of the studies included.

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Optimization of Laboratory Diagnostics of Neuromyelitis Optica Spectrum Disorders: Indications and Algorithms

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Abstract

Neuromyelitis optica spectrum disorders are a group of autoimmune demyelinating diseases of the central nervous system characterized by severe exacerbations with development of residual neurological deficit. Anti-aquaporin-4 antibody is a key factor in diagnosing, differentiating, and prescribing pathogenetic therapy. The paper discusses indications for tests and methods of detecting anti-aquaporin-4 antibodies.

***Keywords**: neuromyelitis optica spectrum disorders; laboratory diagnostics; anti-aquaporin-4 antibodies.*

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Оптимизация лабораторной диагностики заболеваний спектра оптиконевромиелита: показания и алгоритмы

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Аннотация
Заболевания спектра оптиконевромиелита – группа аутоиммунных демиелинизирующих заболеваний центральной нервной системы, которые характеризуются тяжёлыми обострениями с формированием остаточного неврологического дефицита. Определение антител к аквапорину-4 является ключевым фактором диагностики, дифференциальной диагностики и назначения патогенетической терапии. В статье обсуждаются вопросы показаний к назначению исследования и методик определения антител к аквапорину-4.

Ключевые слова: *заболевания спектра оптиконевромиелита; лабораторная диагностика; антитела к аквапорину-4*

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

Neuromyelitis optica spectrum disorders (NMOSD) are a group of severe autoimmune demyelinating diseases of the central nervous system (CNS) that share a common pathogenic mechanism of complement-dependent astrocytopathy induced by the production of antibodies to aquaporin-4 (AQP4-IgG) [1]. This term expands the long-used diagnosis of neuromyelitis optica (Devic's disease) because NMOSD can be identified in the early stages of the disease, allowing timely initiation of pathogenetic therapy to prevent exacerbations, which are a significant contributor to the persistent disability of patients [2]. Differential diagnosis of NMOSD with other immune-mediated CNS disorders, especially multiple sclerosis (MS), is necessary because many disease-modifying treatments can cause severe exacerbations of NMOSD [3–8]. According to diagnostic criteria proposed in 2015, the diagnosis of NMOSD should be established not only using the clinical and radiological picture, but also considering such a key aspect as AQP4-IgG based on cell antigen presentation [9].

In Russia, three agents are approved for the prevention of exacerbations of NMOSD, including satralizumab, eculizumab, and ravulizumab. They proved to be effective in seropositive forms of NMOSD in which AQP4-IgG was detected [10–12]. AQP4-IgG detection is therefore a critical test required for both the diagnosis of NMOSD and the selection of pathogenetic treatment. However, the AQP4-IgG assay has some challenging aspects, such as the limited

availability of laboratory kits in Russia [13], the influence of treatment on test results [14], as well as the use of other methods that are not based on antigen cell presentation, such as enzyme-linked immunosorbent assay (ELISA) [15]. Therefore, it is necessary to clarify the indications for primary and repeat testing for AQP4-IgG and to develop an algorithm for the laboratory diagnosis of NMOSD. The authors analyzed and discussed the scientific literature on the laboratory diagnosis of NMOSD, particularly the determination of AQP4-IgG, and proposed recommendations for initial and repeat testing of patients for AQP4-IgG.

Methods for Determination of Autoantibodies

The source of the antigen is a critical component of all autoantibody detection methods. Anti-neuronal antibody assays often use neuronal antigens from laboratory animals. Tissue sections are used as the so-called tissue substrates for antibody binding which is assessed by indirect immunofluorescence or immunohistochemistry for autoantibodies. In neuroimmunology, such tissue substrates traditionally include cryosections of the cerebellum, hippocampus, optic nerve, and smooth muscle neural plexi from laboratory rodents or primates (macaques). Since many antigens are present in the tissue, the obvious advantage of this approach is the possibility of multiple detection of different autoantibodies by determining different staining types of the tissue [16]. However, accurate identification of detected antibodies requires verification assays using a predetermined autoantigen. In addition, this method may have low sensitivity due to the low tissue expression of most proteins [17]. The Mayo Clinic laboratories first discovered AQP4-IgG using this tissue assay. This was done using indirect immunofluorescence on cryosections of rodent cerebellum, stomach, and kidney, confirmed by immunoprecipitation [18, 19].

ELISA or immunoblotting methods using protein molecules, most of which are genetically engineered, are commonly used to characterize autoantibody serum spectra. The solid phase is polystyrene plastic materials of ELISA plates or different types of nitrocellulose membranes [20]. Such methods are suitable for identifying a wide range of antineuronal antibodies directed against structural proteins localized in the nucleus and cytoplasm of neurons (e.g. Hu, Ri, Yo-1, etc.). In addition, the ELISA is traditionally used to detect antibodies against gangliosides or other myelin components (anti-MAG).

The antigenic epitopes of most neural tissue proteins expressed on the cell membrane have a complex lipid bilayer-bound conformation which is irreversibly destroyed when the proteins are released from the cell and attempt to adhere to the solid phase. Complex methods were used to address this issue. For this reason, radiolabelled α-bungarotoxin was used to detect antibodies to the acetylcholine receptor, allowing the autoantibody detection in solution. However, the limited range of high-affinity receptor antagonists made it difficult to study autoantibodies to transmembrane channels and nervous tissue receptors. Other methods using labelled recombinant proteins include fluorescence immunoprecipitation or radioimmunoprecipitation, which ensure antibody-antigen interaction in solution, but their sensitivity for detecting antineuronal antibodies is low [21].

Assays with cell expression of antigens and genetically modified cells are based on transfection of eukaryotic cell lines (most commonly the embryonic kidney line HEK293) with plasmids containing a nucleotide sequence that encodes the target protein. When expressed, significant amounts of protein either accumulate in the cell cytoplasm or become exposed on cell membranes [22].

Transfection can be classified as transient and stable. Transient transfection is a relatively rapid and simple technique, but stable transfection provides a higher level of sensitivity. Flow cytometry, confocal microscopy, and indirect immunofluorescence are used to detect autoantibody and protein binding, with non-transfected cells used as a negative control [23]. In addition, some commercially available substrates contain a pre-optimized mixture of transfected and non-transfected cells of the same line to facilitate visual assessment of reaction results.

Flow cytometry and confocal microscopy are suitable for live cell assays and are considered by some authors to be the most sensitive methods for the detection of antineuronal antibodies to membrane antigens [24]. Their clinical use is limited by the need for cell line maintenance in the laboratory and difficult standardization.

Recently, indirect immunofluorescence using fixed adhesion cell lines has become widespread. The method of fixation depends on the cellular localization of the protein. For membrane localization of the target protein, special fixatives such as glutaraldehyde, paraformaldehyde, or formalin are used, and for cytoplasmic localization, additional fixation is used to increase the permeability of cell membranes. Since the HEK293 cell line is an embryonic kidney line that normally synthesizes aquaporins, the expression and processing of the AQP4 protein result in the appearance of AQP4 on the cell membrane [25].

The ability to use ready fixed cell preparations ensures the standardization of the cell substrate of autoantibody detection methods between laboratories, making them accessible to the majority of clinical laboratories. The result of antibody detection on fixed cells is expressed as a final titer, which is inversely proportional to the last dilution of serum that gives a positive signal (Figure 1). Using flow cytometry and confocal microscopy, the intensity of

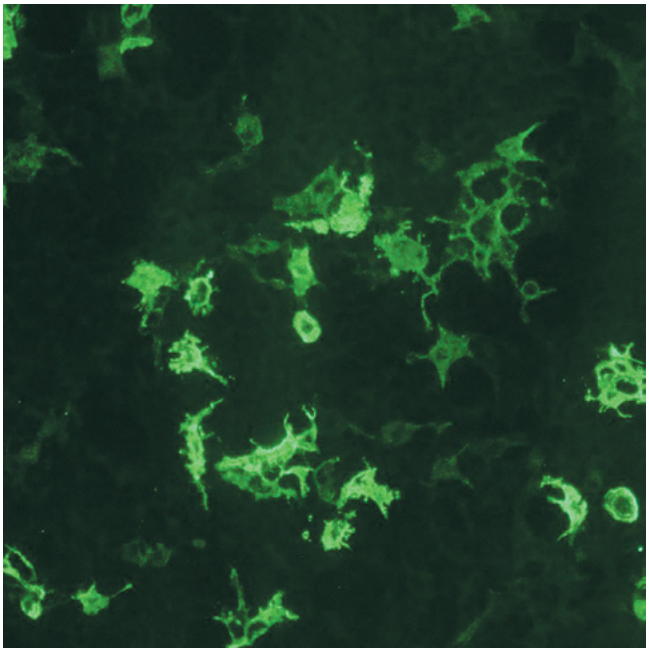

Fig. 1. Positive test result for anti-AQP4 antibodies. Indirect immunofluorescence with antigen cell presentation, 1 : 1000 titer, fluorescence intensity +++.

the fluorescent signal can be quantified. Due to their high sensitivity, cell-based antigen expression assays have become the recognized gold standard for the detection of many types of antineuronal antibodies, including anti-AQP4-IgG and anti-myelin oligodendrocyte glycoprotein (MOG) IgG [9].

Aquaporin-4 as an Autoantibody Target

AQP4 is a member of a family of 13 transmembrane water channels consisting of 6 alpha-helical domains spanning the cell membrane within which the water channel is located. Two types of AQP4, the longer (AQP4-M1) and the shorter (AQP4-M23), are expressed in the body. The shorter AQP4-M23 can form orthogonal arrays of particles with higher affinity for AQP4-IgG in the membrane, making the M23 isoform a preferred target of autoantibodies [21]. In the CNS, AQP4 protein is found as orthogonal clusters predominantly on astrocytes around small brain vessels, which are the primary target of the immune response in NMOSD.

In multicenter studies, the average sensitivity for the detection of AQP4-IgG using cellular antigen expression methods is 76.7% [21]. Some respected researchers reported high sensitivity of in-house flow cytometry or confocal microscopy methods using live transfected cells compared to commercially available kits [26]. This is especially helpful with borderline confounding results where nonspecific membrane staining can make a specific reaction difficult to detect. For example, some laboratories, including the Mayo Clinic laboratory, use flow cytometry with live transfected cells, which has an 80% sensitivity and a 100% specificity [27]. However, in-house assays are challenging due to the significant variability in transfection quality. Fixation of transfected cells to membranes prevents nonspecific reactions caused by other common autoantibodies, such as antibodies to mitochondria or antinuclear factor. AQP4-IgG is a highly specific indicator of NMOSD, as the false positive rate for AQP4-IgG in patients with classic MS using the autoantigen expression in cells assay is only 0.1% [28]. By contrast, autoantibody detection by recombinant-antigen enzyme immunoassay has a low sensitivity (63–64%) and a relatively high incidence of false positive reactions (0.5–1.3%) [21].

In comparison to many other antineuronal antibodies, synthesis of AQP4-IgG is predominantly systemic. Studies of large collections of paired blood serum and cerebrospinal fluid samples show that in all cases, autoantibodies are more frequently detected in the blood and the titers are higher [29]. Asymptomatic carriage of AQP4-IgG has been described [30], while some seronegative patients may seroconvert at diagnosis [31], and some patients have seroreversion during successful immunosuppressive therapy [14].

Clinical Phenotypes Requiring Anti-Aquaporin-4 Antibody Testing

The classic phenotypes of NMOSD have 6 clinical manifestations: the most common ones include optic neuritis (ON), acute myelitis, *area postrema* syndrome (the chemoregulatory center at the floor of the fourth ventricle) characterized by uncontrollable nausea, vomiting, and hiccups. Less common manifestations include acute brainstem lesion, acute diencephalic syndrome (with symptomatic narcolepsy and/or endocrine disorders), and hemisphere injury. The latter two manifestations are always associated with symptomatic lesions on magnetic resonance imaging (MRI) [9].

According to the scientific literature, serum testing for the presence of AQP4-IgG is recommended for all patients with suspected NMOSD [9, 32]. The term "suspected NMOSD" is interpreted differently by different authors, and there are no precise guidelines for prescribing the test that would be absolutely clear to clinicians. The first proposed indications included longitudinal extensive transverse myelitis (LETM); acute idiopathic transverse myelitis (TM) with signs that are not typical for MS; severe ON with poor recovery, simultaneous bilateral ON, extensive optic nerve injury or chiasmal involvement on MRI; intractable (difficult to control) nausea, vomiting, or hiccups in the absence of gastrointestinal disorders; MRI lesions of the dorsal medulla oblongata; clinically significant diencephalic disorders (hypersomnia, narcolepsy, endocrine disor-

ders characteristic of hypothalamic pituitary dysfunction); cryptogenic leukoencephalopathy; and suspected MS with unexplained severe exacerbations on treatment with disease-modifying agents for MS [33, 34].

Other guidelines recommend AQP4-IgG testing in patients with LETM without focal MRI brain changes or with brain lesions not characteristic of MS; with frequent recurrent ON; with diencephalic syndrome with unspecified focal changes, and with encephalopathy of unknown nature [35–37]. In 2020, V.S. Krasnov et al. recommended expanding the proposed indications to include newly developed partial TM or ON, regardless of severity of neurological dysfunction and recovery level [38]. This recommendation is supported by the data from routine clinical practice. In 8 (28.6%) of 27 NMOSD patients with AQP4-IgG, the first exacerbation manifested as partial TM or unilateral ON with subsequent regression of symptoms, so the test was not performed, resulting in a longer delay in diagnosis. The relevance of this recommendation is confirmed by the fact that 5 (62.5%) of these 8 patients were subsequently misdiagnosed with MS and treated with MS-modifying agents, which can worsen the course of NMOSD [2–5].

Back in 2007, NMOSD experts recommended that optic nerve or spinal cord injury in a patient with systemic lupus erythematosus or Sjögren's syndrome should be considered a manifestation of concomitant NMOSD rather than a neurologic complication of rheumatic disease due to vasculitis [39]. This recommendation was re-confirmed in 2015 [9]. Later, Latin American experts concluded that patients with a known systemic autoimmune disease with clinically apparent ON, acute TM, or *area postrema* syndrome should be tested for blood AQP4-IgG [40]. In 2023, Russian neurologists proposed some new indications for this test including a neuroimaging sign such as extensive ($\geqslant$ 3 vertebral segments) spinal cord atrophy on MRI, as well as cases not inconsistent with the diagnosis of MS but without oligoclonal antibodies detected in cerebrospinal fluid [41].

In 2023, the Neuromyelitis Optica Study Group (NEMOS) published a consensus paper recommending testing for AQP4-IgG in all patients with clinical or radiologic findings (both current and historical) that suggest a diagnosis of NMOSD. This includes all patients with one of the main clinical syndromes of NMOSD, including ON, acute myelitis, *area postrema* syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic syndrome with typical diencephalic MRI lesions, cerebral syndrome with typical hemispheric MRI lesions. Experts also recommend testing in all cases where the patient is diagnosed with NMOSD according to the 2015 diagnostic criteria without AQP4-IgG or an unknown status for antibodies to AQP4. In all other cases, the decision to test or not to test should be made on a case-by-case basis. It has also been suggested that AQP4-IgG screening in MS patients who do not meet the above criteria, especially in regions where NMOSD represents only a small percentage of idiopathic inflammatory demyelinating diseases, may increase false positive results and is not recommended [42]. The above guidelines require clarification of the type of brainstem manifestations for which the test should be performed. It is recommended to limit them to the most common oculomotor disorders, facial paresis, facial numbness, and ataxia, which are the most common in brainstem syndrome [42, 43].

Similar recommendations have been proposed for children, as the main clinical manifestations of NMOSD and the diagnostic criteria are similar to those for adults [44]. 50–75% of pediatric patients have ON at onset, with 50% having bilateral ON [45, 46]; 30–50% of patients with NMOSD have TM, although LETM is less common in children with NMOSD compared to that in adults and may be present in acute disseminated encephalomyelitis. In contrast, acute diencephalic syndrome, especially endocrinopathies, and symptomatic cerebral syndrome are more common in the pediatric population with NMOSD than in adults: up to 60% and up to 16–32%, respectively [47, 48]. Neuroimaging in pediatric patients shows large confluent lesions with vasogenic edema (a phenotype similar to acute disseminated encephalomyelitis). Lesions often involve the corticospinal tract and periventricular region, and nonspecific hemispheric white matter lesions are also visualized [49]. The frequency of AQP4-IgG seropositivity in children with NMOSD is significantly lower than in adults. A study of pediatric NMOSD in the United States showed that only 65% of children were seropositive for AQP4-IgG, and in some cases, antibodies were not detected until 3 years after disease onset [50]. Moreover, MOG-IgG is much more prevalent in the pediatric NMOSD population than in adults [51].

Special attention should be paid to situations where routine testing is not recommended. AQP4-IgG testing was considered inappropriate for patients with ON if it did not meet strictly defined criteria as mentioned above, or in the presence of clinical, MRI, and laboratory signs typical of MS, so as not to increase the number of false positive results [33, 34]. However, this position is contradicted by data demonstrating the possibility of a mild ON at the onset of NMOSD [38], as well as information that the detection of oligoclonal IgG in CSF does not exclude the diagnosis of NMOSD, which occurs in 20–43% of patients with NMOSD, especially at the time of exacerbation, but may be transient and not detected in subsequent samples [9, 40]. Since AQP4-IgG is a highly specific test and the reported incidence of initial MS misdiagnosis in NMOSD patients is 33.0–42.5% [27, 32], clinicians often use the test beyond the above indications in an attempt to avoid misdiagnosis.

Possible Causes of False Positive and False Negative Results

Causes of false laboratory results for AQP4-IgG testing can occur at both the pre-laboratory and laboratory stages. False negative results are most often caused by pre-laboratory factors. These include noncompliance with patient preparation rules, including general conditions (test to be done in the morning and in fasting state, no fatty food or alcohol the day before, limited physical activity, no hypothermia/hyperthermia, no smoking 1 hour before testing) and special conditions such as sampling after or during pathogenetic therapy (corticosteroids, plasmapheresis, immunosuppressive agents, monoclonal antibodies, that prevent NMOSD exacerbations) [52].

Observations of antibody status in patients undergoing repeat AQP4 IgG testing are of particular interest. In China, 400 NMOSD patients with AQP4-IgG who were receiving immunosuppressive therapy were evaluated. At a median follow-up of 3.7 years, 32% of patients had seroreverted to seronegative status and no AQP4-IgG was detected. These patients had a lower incidence of exacerbations, and a direct relationship was found between time to seronegative status and exacerbations [14].

The Mayo Clinic (USA) followed patients who were tested at least twice for AQP4-IgG. Out of 986 NMOSD patients with AQP4-IgG, 53 patients had a negative result at baseline, i.e. they experienced a seroconversion to seropositive status (more than 9,000 patients were tested with a baseline negative result), and 6 patients were tested during treatment (corticosteroids, plasmapheresis, azathioprine, natalizumab). Of 933 NMOSD patients initially positive for AQP4-IgG, 11% demonstrated seroreversion at a mean of 1.2 years. This was observed mainly in young patients (up to 20 years of age) and in patients with initially low titer of AQP4-IgG. Seroreversion has been reported with anti-B-cell therapy, azathioprine, mycophenolate mofetil, plasmapheresis, and autologous stem cell transplantation. Half of the patients with seroreversion experienced subsequent seroconversion [53].

A seronegative window has also been proposed when AQP4-IgG is either completely bound to the antigen, making detection impossible, or present at a concentration insufficient for detection but sufficient to cause clinical manifestations, as it was demonstrated for *area postrema* syndrome [54].

Causes of false positive results are much less common and may be related to the presence of tuberculosis. Aquaporins of *Mycobacterium tuberculosis* and human AQP4 may have homologous epitopes, which can lead to cross-reactivity, whereas AQP4-IgG titers are usually higher in tuberculosis than in NMOSD. Natalizumab enhances the membrane surface presentation of AQP4, so patients treated with this drug may also have false positive AQP4-IgG assay results [55].

False AQP4-IgG assay results may be due to errors in the pre-analytical and analytical laboratory phases. The most common pre-analytical errors include non-compliance with sample collection, transportation, and storage (repeated freezing/thawing), significant hemolysis or milky white serum. False negative errors in the laboratory include the hook effect which is an immunological phenomenon of decreased affinity of antibodies to form immune complexes when the concentration of antibodies is very high. This phenomenon is important for clinical practice because it interferes with the analysis and can lead to false negative results [56]. There are some other reasons for false negative results, such as a defect in the microslide or non-compliance with a test procedure (overdrying of the microslide during the staining, burning out of the microslide after long exposure to microscope light) [57].

Due to the high complexity of this assay, many skills are needed, both in indirect immunofluorescence and in this specific assay. Therefore, insufficient operator experience may lead to false positive results (interpretation of non-specific fluorescence as specific for AQP4-IgG) [58]. However, the antibodies can be present at the borderline level (⩽1:10), which can be referred to as non-specific fluorescence (Figures 2–5).

The prognosis of NMOSD can be based on factors such as the age of onset, the number of exacerbations during the first 2 years, the severity of the first exacerbation, the association with other autoimmune diseases, and the serologic status of AQP-IgG [59]. Many studies have shown a lower rate of recovery of visual impairment after exacerbation in patients with AQP4-IgG compared to seronegative patients [60]. A prospective study of 29 patients with isolated LETM found that only 55% of AQP4-IgG seropositive patients had no exacerbations at 1 year, while none of seronegative patients had exacerbations [61]. Given the significant risk of new exacerbation in the first year after disease onset, it is recommended to perform 2-3 repeat tests within 6-12 months after the initial negative result [62]. Since repeat assay in repeatedly seronegative patients increases the risk of false positive results, AQP4-IgG "seroconversion" of previously seronegative patients should ideally be confirmed by further assay [34].

Recommendations for AQP4-IgG Testing

The following are the basic principles of how and for which clinical and radiologic phenotypes the AQP4-IgG assay should be performed for the first time, as well as at what time point the assay should be repeated.

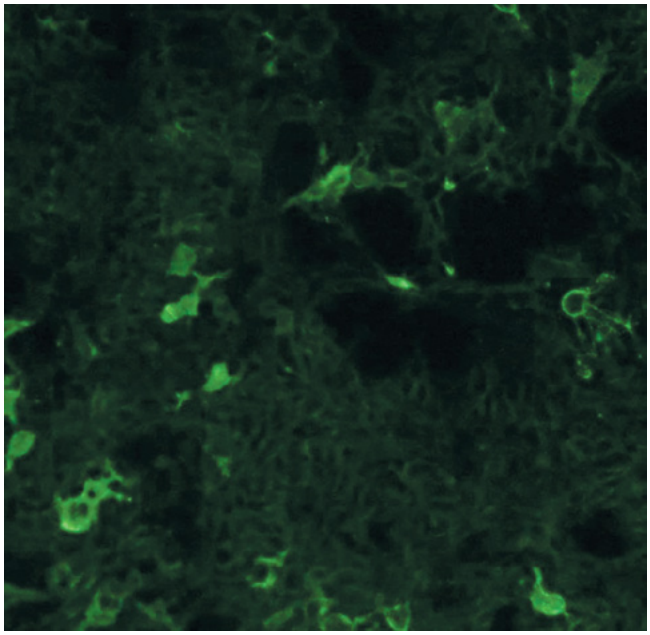

Fig. 2. Positive test result for anti-AQP4 antibodies.
Indirect immunofluorescence with antigen cell presentation, 1 : 10 titer, fluorescence intensity ++.

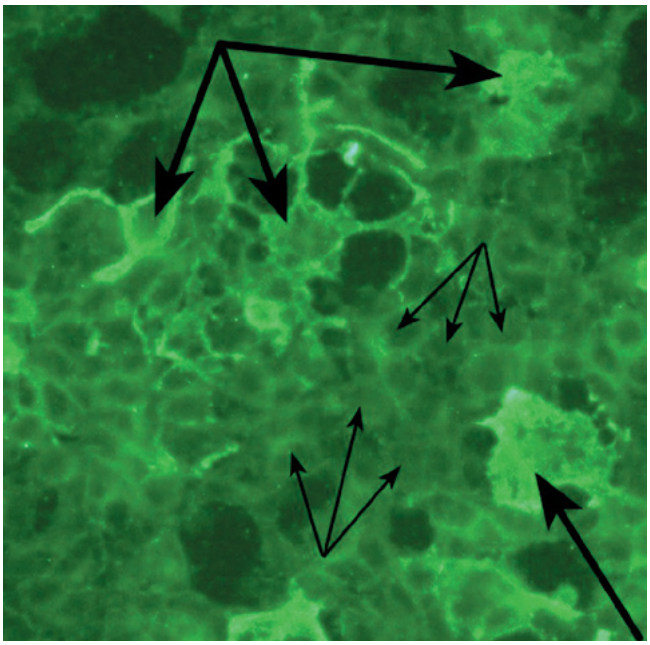

Fig. 3. Positive test result for anti-AQP4 antibodies.
Indirect immunofluorescence with antigen cell presentation, 1 : 320 titer, fluorescence intensity ++ (thick arrow) with areas of nonspecific fluorescence (thin **arrows).**

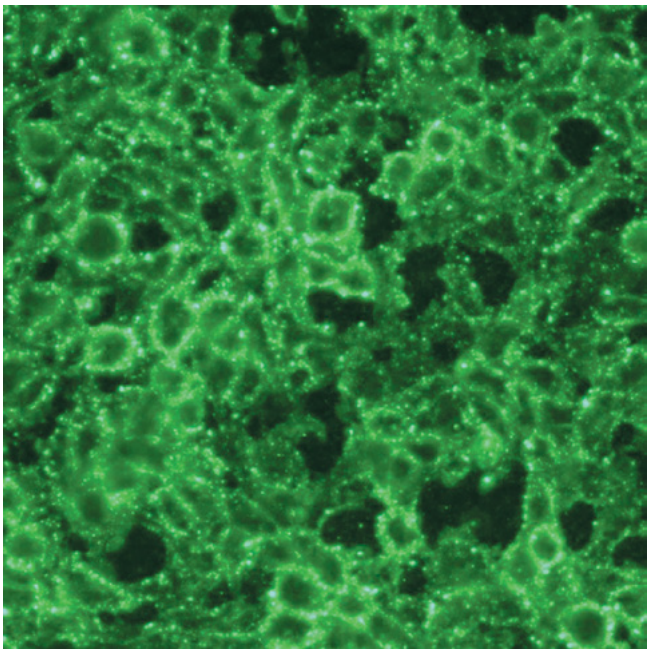

Fig. 4. Negative test result for anti-AQP4 antibodies to be confirmed by repeat test.
Indirect immunofluorescence with antigen cell presentation, nonspecific fluorescence (+/–).

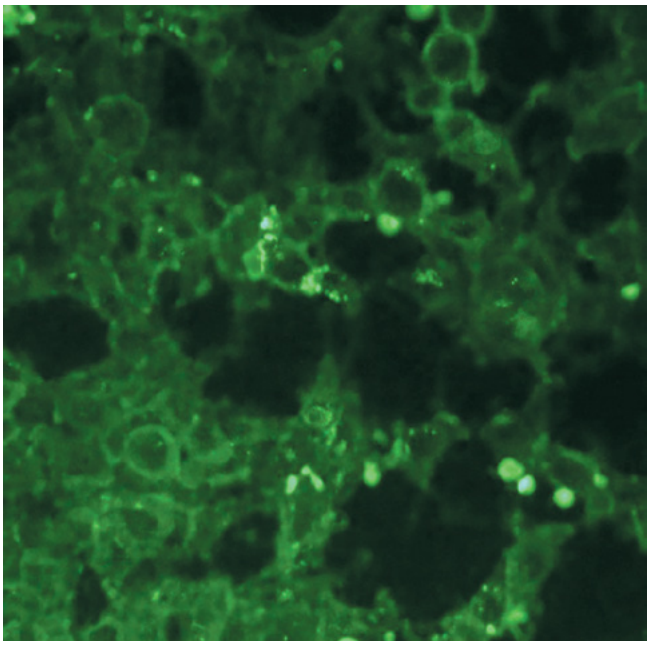

Fig. 5. Negative test result for anti-AQP4 antibodies to be confirmed by repeat test.
Indirect immunofluorescence with antigen cell presentation, nonspecific fluorescence (+/–).

1. Serum testing for anti-AQP4 antibodies should be performed in all patients with suspected NMOSD by indirect immunofluorescence with antigen cell presentation (enzyme immunoassay is not recommended).
2. NMOSD is suspected when a patient has:
   1) 1 of 6 main acute/subacute clinical syndromes (both current and historical):
      a) ON (severe ON with poor recovery; bilateral ON; extensive optic nerve injury or chiasmal involvement on MRI; frequent recurrent ON; ON as the first disease manifestation regardless of its severity; ON in a patient with systemic autoimmune disease),
      b) acute myelitis (LETM, acute idiopathic TM with signs that are not typical for MS; TM as the first disease manifestation regardless of its severity; TM in a patient with a systemic autoimmune disease; extensive (⩾ 3 vertebral segments) spinal cord atrophy on MRI indicating history of acute/subacute myelopathy),
      c) *area postrema* syndrome (in the absence of gastrointestinal disorders and other causes such as vestibular disorders, infectious diseases, intoxication, drug therapy, endocrine disorders, stroke, neoplasms), including a known systemic autoimmune disease,
      d) isolated acute brainstem syndrome (oculomotor dysfunction, facial paresis, facial numbness, ataxia, symptomatic brainstem injury involving periepidermal areas),
      e) symptomatic narcolepsy or acute diencephalic syndrome (hypersomnolence, syndrome of inappropriate antidiuretic hormone release) with typical diencephalic MRI lesions not clearly explained by other causes,
      f) acute cerebral syndrome (hemiparesis or tetraparesis, visual field loss, varying degrees of consciousness disorders, epileptic seizures) with typical unspecified hemispheric MRI lesions (cryptogenic leukoencephalopathy with characteristic MRI brain changes),
   2) suspected MS with unexplained severe relapses on treatment with MS-modifying agents,
   3) suspected MS with clinical manifestations of at least one of the main NMOSD syndromes, atypical clinical manifestations, and the absence of oligoclonal IgG in the CSF (the presence of oligoclonal IgG in the CSF does not exclude NMOSD). However, a reliable diagnosis of MS based on clinical and radiologic features (McDonald criteria 2017) in the absence of the above signs does not suggest NMOSD.
3. When submitting biomaterial for anti-AQP4 testing, the stage of disease (exacerbation or remission), the sampling time (before, during, or after corticosteroid and plasma exchange/immunoadsorption therapy), and the name of the drug if treated with drugs to prevent exacerbations should be provided.
4. To reduce the risk of a false negative result, serum samples for serum anti-AQP4 testing should be collected prior to initiation of corticosteroid pulse therapy, plasmapheresis/plasma exchange therapy, or treatment with drugs to prevent exacerbations.
5. AQP4-IgG test results should include information on the antibody titer, the technique used, and the presence or absence of non-specific fluorescence for AQP4-IgG.
6. If an initial negative result (< 1 : 10) is obtained and NMOSD is still suspected, repeat the AQP4-IgG test after 3-6 months and/or in case of repeated exacerbations.
7. If an initial positive result is 1 : 10 or there are clinical, neuroimaging, or laboratory changes that require clarification of NMOSD diagnosis (red flags), or there is nonspecific fluorescence for AQP4-IgG, repeat the assay after 1 month.
8. Two or three repeat assays may be performed within 6–12 months of an initial negative result, as well as after 12 months, depending on the clinical situation. The upper limit of 12 months is due to the significant risk of re-exacerbation of NMOSD in the first year.
9. Patients diagnosed with NMOSD with AQP4-IgG who are receiving therapy to prevent exacerbations may experience seroreversion (reversion to a seronegative status), which does not require repeat testing and is not a reason to discontinue or change therapy.

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A Man Who Changed Six Spectacles: a Case of Heidenhain Variant of the Creutzfeldt–Jakob Disease

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Abstract

Creutzfeldt–Jakob Disease (CJD) is a rare and rapidly progressive condition. A 54-year-old professor initially presented with insidious, progressive visual symptoms. Imaging suggested post-infectious encephalitis, but symptoms progressed to ataxia, coordination difficulties, and cognitive decline. Repeat MRI revealed findings consistent with CJD, supported by clinical and electrophysiological evidence. Though 14-3-3 protein in CSF was inconclusive, Heidenhain variant CJD was strongly suspected. Isolated visual symptoms progressing rapidly alongside ataxia and dementia prompt suspicion of this variant. Clinical examination, neuroimaging, and EEG play crucial roles in the diagnosis.

Keywords: *Creutzfeldt–Jacob disease; Heidenhain variant*

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Человек, который шесть раз менял очки. Описание клинического случая пациента с болезнью Крейтцфельдта–Якоба (вариант Хайденхайна)

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Аннотация

Болезнь Крейтцфельдта–Якоба (БКЯ) представляет собой редкое и быстро прогрессирующее заболевание. Пациент 54 лет, профессор, впервые обратился за медицинской помощью по поводу постепенно прогрессирующего ухудшения зрения. Данные визуализации позволили предположить наличие постинфекционного энцефалита, однако симптомы усиливались, появились нарушения координации, атаксия и снижение когнитивных функций. При повторной МРТ были выявлены признаки БКЯ, что также подтверждали данные клинического и электрофизиологического обследований. Несмотря на то что определение уровня белков 14-3-3 в спинномозговой жидкости не позволило прийти к однозначным выводам, возникло серьёзное подозрение на наличие у пациента БКЯ, вариант Хайденхайна. Быстро прогрессирующие изолированные зрительные симптомы, атаксия и деменция подкрепляют это предположение. В установлении такого диагноза важнейшую роль играют результаты клинического обследования, нейровизуализации и электроэнцефалографии.

Ключевые слова: *болезнь Крейтцфельдта–Якоба; вариант Хайденхайна*

Этическое утверждение. Исследование проводилось при наличии информированного согласия законных представителей пациента.

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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Introduction

Creutzfeldt–Jakob disease (CJD) is a fatal neurodegenerative disorder typically characterized by rapidly progressive dementia associated with other neurological or ophthalmologic symptoms [1]. The Heidenhain variant defines a peculiar clinical presentation of sporadic CJD, characterized by isolated visual disturbances at disease onset and reflecting the early damage to the occipital cortex by prions. These isolated visual symptoms can progress for weeks challenging the diagnosis [1]. We report a 54-year male who presented with progressive visual symptoms, followed by neurological symptoms, and after the evaluation was diagnosed with Heidenhain variant of CJD (HVCJD).

Clinical case

A 54-year-old male professor developed insidious onset visual disturbances 4 months prior to presentation. The visual symptoms were noted when he complained of difficulty setting and correcting question papers. They included a blurring of the entire visual field, with no field restriction, blank spots, flashes of light, headache or ocular pain or difficulty recognizing shapes and objects. He had no diplopia, visual hallucinations, visual distortion, altered depth perception, or perception of movement/persistence of images. He had an initial ophthalmological consultation and was prescribed glasses. However, the visual symptoms had been persistent and mildly progressive over the next two months for which his glasses were changed repeatedly at least 6 times. Subsequently, a month prior to presentation, following dengue infection, his symptoms had worsened. One week prior to the presentation, the patient developed a slowing of his gait with unsteadiness when using his right hand. No history of fever at that point, seizures, vomiting, nuchal rigidity, sensory, or autonomic symptoms had been reported.

On examination, he appeared as an attentive, well-groomed, mildly anxious man, with a normal Montreal Cognitive Assessment score (MoCA) score of 29 points. Visual examination revealed a best-corrected visual acuity of 20/60 bilaterally, with inconsistent right hemianopia. His eye movements, pupil and fundus were normal. During the examination, macropsia was also observed. Spino-motor examination revealed asymmetrical (right > left) cerebellar signs, mild bradykinesia, and impaired tandem walk, with normal muscle power. The other neurological and systemic examination was unremarkable.

The patient's routine lab evaluation including CBC, renal, hepatic, thyroid tests, glycemia and electrolytes was normal. Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain revealed T2/FLAIR gyriform hyperintensities with corresponding restricted diffusion in the left parafalcine parieto-occipital cortex with no evidence of abnormal contrast enhancement with MR angiogram was unremarkable (Fig. 1, *A–C*). The gyriform lesion pattern along with insidious symptoms were suggestive of encephalitis and CSF analysis showed an acellular tap with normal protein levels. Infections and immune workups in both CSF and serum were normal. Considering the recent dengue infection, possible post-infectious encephalitis was considered and the patient was pulsed with high-dose steroids.

The patient continued to progress, with the development of new visual symptoms of macropsia and agnosia with worsening discoordination. He had developed memory loss to the extent that he couldn't recall his wife's name or his education. A neurological examination revealed a MoCA score of 8/30 with a significant increase in his cerebellar signs and bradykinesia. The duration between the two MoCA assessments were less than 3 weeks. A repeat gadolinium-enhanced MRI brain showed an increase in the gyriform diffusion restriction with corresponding T2 FLAIR hyperintensities noted in bilateral temporal and

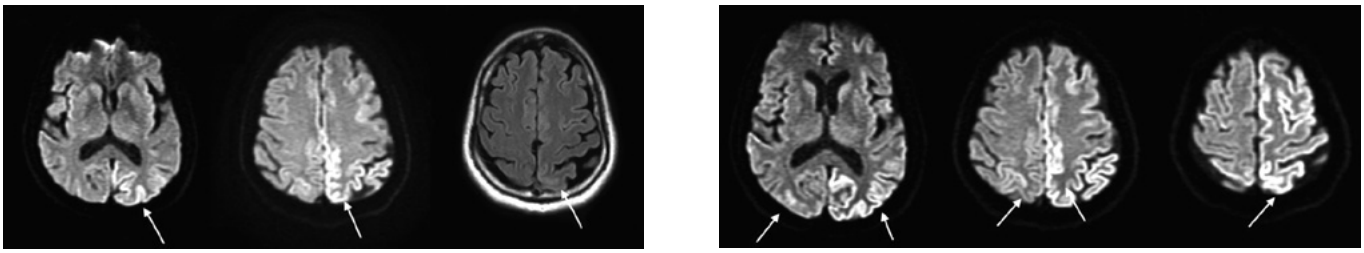

Fig. 1. Brain MRI (axial section, diffusion-weighted images; *A, B*) performed during the initial admission shows left occipito-parietal and parafalcine gyri form diffusion restriction (arrows).
C – T2 FLAIR hyperintensity in the corresponding areas; *D–F* – subsequent brain MRI (diffusion-weighted sequences, axial section) done during the next admission show an increase of the gyriform diffusion restriction to involve the contralateral hemisphere and high frontoparietal region, sparing the perirolandic cortex.

left parieto-occipital lobes with sparing of the perirolandic region with no contrast enhancement (Fig. 1, *D–F*). Considering the rapidly progressive cognitive decline, onset with visual symptoms, and cerebellar signs, with imaging features, the Heidenhain variant of CJD (HVCJD) was suspected. Electroencephalography showed repeated cycles of short interval periodic discharges of triphasic morphology with background slowing (Fig. 2). For confirmation of CJD, RT-QuIC and 14-3-3 protein were available. The results of 14-3-3 protein test were in high normal range which was attributed to very early measurement in the course of disease. Moreover, 14-3-3 protein is relatively nonspecific and its levels can be high in a variety of neurological diseases. RT-QuIC test was not done due to logistical reasons. Patient attendees were counselled regarding the disease, and the supportive care was initiated. The patient was later followed up via telephone communication, a month after discharge. By that time, he had become completely bed bound and mute.

Discussion

CJD is a rare prion (proteinaceous infectious particles)-associated neurodegenerative disorder resulting in a spongiform encephalopathy with an estimated incidence of 1 case per 1 million people annually [1]. The HVCJD is a form of sporadic CJD associated with visual signs and symptoms at onset. The majority of reports detailing

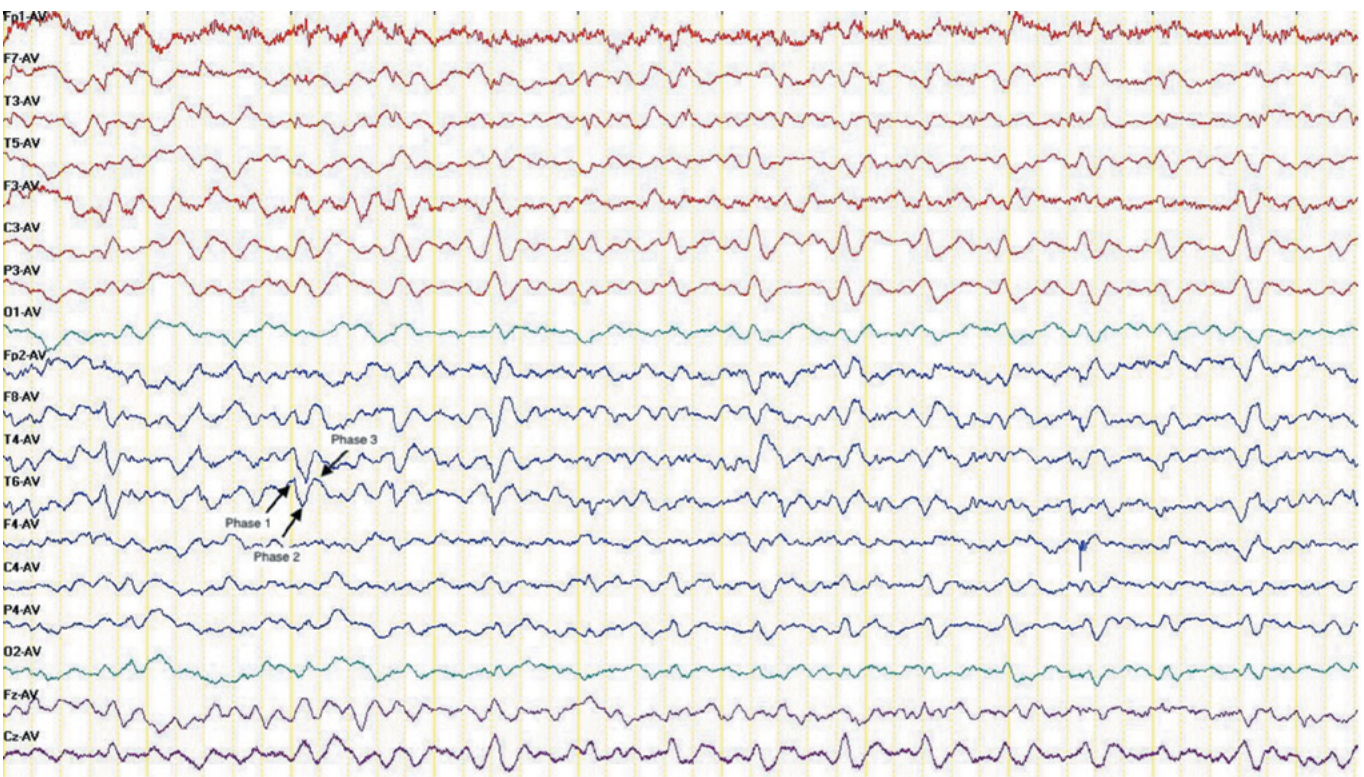

Fig. 2. Electroencephalogram recording of the patient in the average montage shows intermittent runs of short interval periodic triphasic discharges (arrows).

HVCJD are epidemiological studies, reviews, and case reports given the low incidence of the disease and lack of controlled clinical studies [2]. Ophthalmic manifestations of HVCJD may occur weeks or months before the onset of other symptoms, with a retrospective case series detailing that blurred vision and diplopia were the most common initial symptoms. The ophthalmologic manifestations of HVCJD include [2, 3]:

1. Eye signs:
   - decreased visual acuity;
   - sluggish pupils;
   - absent optokinetic reflex;
   - no response to visual threat;
   - spasm of fixation;
   - optic disc pallor;
   - normal opthalmoscopy and biomicroscopy;
   - poor colour vision;
   - visual field constriction;
   - nystagmus;
   - supranuclear palsy;
   - ocular dipping;
   - saccadic abnormalities;
   - impaired convergence;
   - eyelid abnormalities;
   - homonymous hemianopia with and without macular involvement.

2. Eye symptoms:
   - worsened visual acuity;
   - cortical blindness;
   - blurry vision;
   - palinopsia;
   - oscillopsia;
   - diplopia;
   - visual hallucinations;
   - vision distortion;
   - altered depth perception;
   - simultagnosia;
   - optic anosognosia;
   - environmental agnosia;
   - complete loss of vision;
   - tunnel vision.

Diagnosis of HVCJD in its early stages can be difficult as it may not entirely satisfy the clinical criteria which required presence of dementia, and include cerebellar signs, and parkinsonism. But the visual symptoms actually denote occipital lobe involvement and represent the visuospatial domain. So, the diagnosis is usually made based on ancillary testing such as EEG and brain MRI. In a series of HVCJD, EEG was found to be the most sensitive, with periodic triphasic waves, which were spread both generally or with posterior predominance [4]. Other diagnostic modalities include the CSF 14-3-3 test or the RT-QuIC. Human 14-3-3 proteins are normal neuronal and nonneuronal proteins that participate in the modulation of signal transduction pathways and are released into the CSF when there is nonspecific, rapid, and extensive destruction of brain tissue. The sensitivity of 14-3-3 protein gamma isoform has most commonly been reported as between 85% and 95% with a specificity anywhere from 40% to 100% for diagnosing CJD. In addition, the 14-3-3 protein test is not sensitive to other types of prion diseases [5]. The moderate sensitivity, but poor specificity is likely due to its elevation in a number of different neurologic diseases [5]. There are no effective treatment strategies at present for prion diseases.

Conclusion

This case report demonstrates the importance of considering this rare condition in patients with rapidly progressive visual disturbances. Prompt recognition of this condition prevents the patient and caregivers from additional evaluation and for early institution of end-of-life support services.

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Postoperative Hemorrhages in Vestibular Schwannoma Surgery Pontine Hemorrhage. Clinical Case Report

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Abstract

Vestibular schwannoma (acoustic neuroma) is a benign tumor that develops from Schwann cells and can be life-threatening. Nowadays, surgical treatment is the method of choice in the management of patients with this type of tumor.

We present a clinical case report of 71 y.o. patient with vestibular schwannoma (Koos grade IV, Samii grade 4B) with severe compression of the pons and the left cerebellar hemisphere. Microsurgical removal of the tumor was performed via the retrosigmoid approach. Starting from postoperative day 1, signs of respiratory distress developed. Control multislice spiral computed tomography (MSCT) of the brain revealed the area of hemorrhage in the left regions of the pons. On postoperative day 24 the patient's condition rapidly worsened progressing to coma with pronounced arterial hypotonia and cardiac arrest.

Hemorrhage in the brain stem structures is a rare and life-threatening postoperative complication in vestibular schwannoma surgery. The incidence of postoperative hemorrhage is 2–11% of cases. Vascular complications are the leading cause of mortality. The key predisposing factors are older age, large and giant size of the tumor, tumor invasion into the pia mater of the brainstem, and vascularization of the tumor stroma. Comprehensive assessment of the tumor blood supply status, the state of the brainstem, intra- and postoperative clinical and neurophysiological monitoring, careful and thorough dissection of the tumor capsule and strict control of blood pressure in the postoperative period are the basis for the prevention of these complications.

***Keywords**: vestibular schwannoma; postoperative hemorrhage; posterior cranial fossa*

Ethics approval. The article is a part of the study approved by the Local Ethics Committee of Professor V.F. Voyno-Yasenetsky Krasnoyarsk State Medical University (protocol No. 116, dated 12 December, 2022). The study, including publication of the clinical case, was conducted with the patient's informed consent.

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Послеоперационные кровоизлияния в хирургии вестибулярных шванном. Клинический случай кровоизлияния в мост

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Аннотация

Вестибулярная шваннома – это доброкачественная опухоль, растущая из шванновских клеток и представляющая реальную угрозу для жизни пациента. В настоящее время хирургическое лечение является методом выбора в лечении пациентов с этими новообразованиями.

Представлен клинический случай пациента 71 года с вестибулярной шванномой (Koos 4, Samii 4B) с грубой компрессией моста и левого полушария мозжечка. Выполнено микрохирургическое удаление опухоли ретросигмовидным доступом. С 1-х суток послеоперационного периода у пациента отмечались дыхательные нарушения. По данным контрольной мультиспиральной компьютерной томографии головного мозга визуализирован участок кровоизлияния в левых отделах моста. На 24-е сутки после операции состояние пациента резко ухудшилось с нарушениями уровня бодрствования до комы, появлением выраженной артериальной гипотонии и остановкой сердечной деятельности.

Кровоизлияния в стволовые структуры являются редким и грозным осложнением в хирургии вестибулярных шванном. Частота геморрагических осложнений в послеоперационном периоде составляет 2–11% случаев. Именно сосудистые осложнения являются основными причинами летальных исходов. Ключевые предрасполагающие факторы: пожилой возраст, большие и гигантские размеры новообразования, прорастание опухолью пиальной оболочки стволовых структур и вовлечение сосудов в её строму. Всесторонняя оценка кровоснабжения опухоли и состояния стволовых структур, интра- и послеоперационный клинический и нейрофизиогический мониторинг, бережная и тщательная диссекция капсулы опухоли и максимальный контроль артериального давления в послеоперационном периоде являются основой профилактики этих осложнений.

***Ключевые слова**: вестибулярные шванномы; послеоперационные кровоизлияния; задняя черепная ямка*

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Introduction

Despite the great advances in the treatment of patients with vestibular schwannomas (VS), this type of tumors remains one of the most challenging in neurosurgery due to the proximity of the brainstem, cranial nerves, and vessels of the vertebrobasilar system [1–4]. While mortality associated with small VS resections is close to zero, in large and giant tumors it reaches 2.5–7.7% [5–8]. The vast majority of hospital patients have large and giant VS [3, 9–11].

Many studies on complications of the VS resection are focused on cranial nerve dysfunction and CSF leak, while publications on vascular complications are scarce. However, many authors consider hemorrhage and ischemia to be the leading causes of postoperative mortality [1, 2, 5, 8, 9, 11–13].

There are various types of intracranial hemorrhage: tumor bed hematoma, with or without rupture into the brain's ventricular system, intracerebral hemorrhage in the cerebellum or the brainstem with or without bleeding into the ventricular system, subarachnoid hemorrhage, subdural and epidural hematoma [11]. Pontine hemorrhage is a relatively rare condition.

Clinical case report

Patient M., 71 years old, was admitted to the neurosurgical department of the Krasnoyarsk Regional Clinical Hospital in February 2018 with complaints of moderate occipital headache, unsteady gait, dizziness, left-sided deafness, and facial asymmetry.

The patient has been experiencing a gradual decrease in hearing in the left ear for 2 years. In 2018, the patient's condition worsened: headache, unsteady gait, dizziness, lacrimation from the left eye, and complete deafness in the left ear developed. Magnetic resonance imaging (MRI scan) of the brain revealed the following: a VS up to 4.6 cm on the left (Fig. 1); severe compression of the pons and the left cerebellar hemisphere; compression and displacement of the fourth cerebellar ventricle; and communicating triventricular hydrocephalus without periventricular edema or girus flattening.

Comorbidities: stage 2 hypertension, grade 3. No coronary heart disease or cardiac arrhythmias. The patient took no anticoagulants or antiaggregants.

Karnofsky score 60 at hospital admission. Clear consciousness. Spontaneous horizontal left-beating nystagmus with rotary component and upbeat nystagmus. No corneal reflex on the left. Non-severe left-sided numbness of the face and tongue. Left-sided facial nerve palsy (House–Brackmann grade II–III) [14]. Left anacusia. No decline in caudal cranial nerve function. Muscle strength is normal (score of 5). Moderately active symmetrical tendon reflexes (D = S). Coordination tests: left-sided dysmetria and intention tremor. Romberg test is positive. Hypermetria, left-sided dysdiadochokinesia.

Diagnosis: left VS with gross compression of the pons and left cerebellar hemisphere (Koos 4, Samii 4B). Communicating triventricular hydrocephalus.

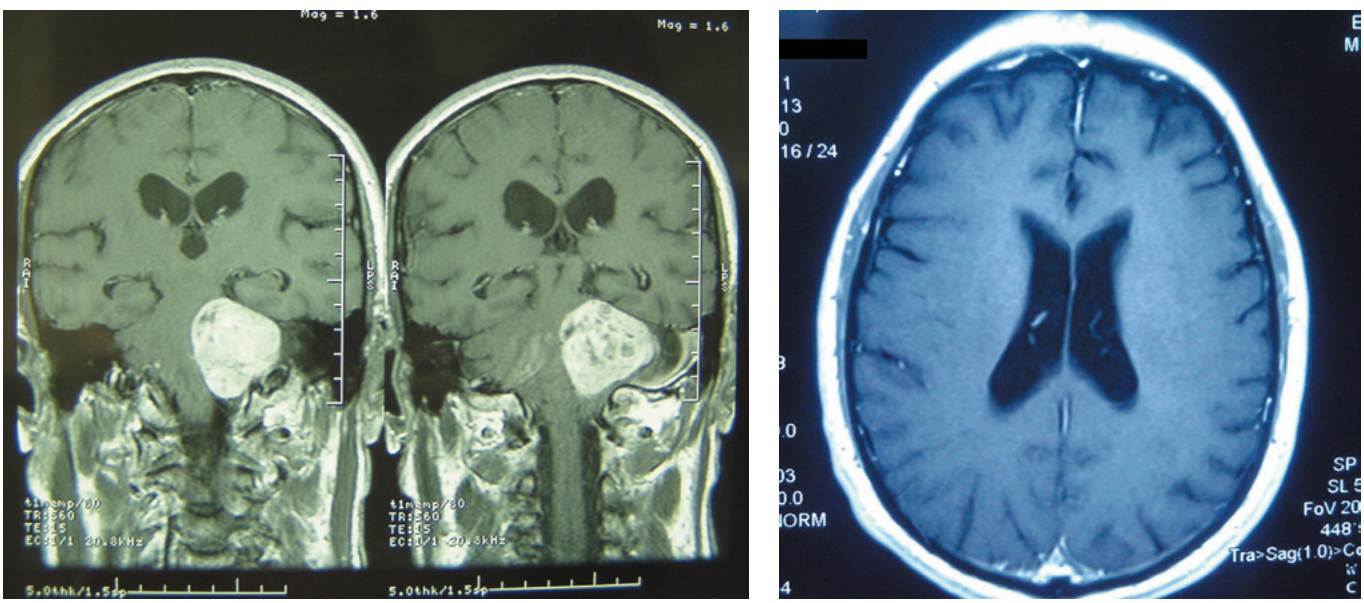

Fig. 1. Preoperative brain MRI of the patient revealed a left cerebellopontine angle tumor with intense inhomogeneous accumulation of paramagnetic contrast agent. Lateral ventricles are dilated.
Preoperative coronal and axial contrast-enhanced T1-weighted MR images.

Given the size of the tumor, severe compression of the brainstem and the cerebellar hemisphere, progressing symptoms of the cerebellum, the brainstem, and the cranial nerve damage, surgical treatment was indicated.

Microsurgical removal of the VS was performed in the patient's sitting position using a standard left-sided retrosigmoid approach with 1 burr hole craniotomy. The bone flap was additionally resected with burr to expose the medial parts of the transverse-sigmoid sinus junction, and the borders of the sigmoid sinus. The dura mater (DM) was tense, did not transmit pulsation, and was dissected with an arcuate incision. Left cerebellar hemisphere was edematous. After cerebrospinal fluid (CSF) evacuation from the large occipital cistern, the tension in the cerebellar hemisphere decreased. The access to the left cerebellopontine angle was performed after a slight retraction of the cerebellar hemisphere, where the tumor rising from the internal auditory canal (IAC) and clearly separated from the cerebellar tissue was detected and visualized. The tumor capsule was opened. The tumor stroma looked yellow, friable, moderately vascularized, and difficult to vacuum aspirate. Internal decompression of the tumor and removal of its stroma up to the capsule was performed with microsurgical instruments and vacuum aspirator under microscope control. The capsule was bluntly and sharply separated from the caudal cranial nerves and the posterior inferior cerebellar artery. The next step was to separate the tumor capsule from the vein of Dandy and the trigeminal nerve. The DM covering the petrous part of the temporal bone adjacent to IAC was coagulated and dissected. The bony plate of IAC was resected up to 5 mm wide peripherally using a microbore. The tumor capsule was separated from the facial nerve in the IAC area using microsurgical instruments. Next, the tumor capsule was sharply dissected from the facial nerve and the anterior inferior cerebellar artery, up to the cerebellopontine angle. The biggest challenge was to separate the tumor capsule from the distal parts of the facial nerve and the pons. The anatomical vestibulocochlear nerve integrity could not be preserved. During dissection of the tumor capsule from the pons, the patient had episodes of arterial hypertension without cardiac arrhythmias clearly related to surgical manipulations (type 1 centrogenic reactions, systemic hemodynamic responses) and required a brief interruption of the surgery until the BP stabilized. Surgicel® Fibrillar™ hemostatic agent was used to achieve hemostasis. The DM was sutured tightly and additionally sealed by the Tachocomb plates. The bone flap was replaced and secured to the skull with two CranioFix®2 fixation systems. The soft tissues were sutured layer by layer. No cardiac arrhythmias were observed during surgery.

After waking up from sedation, the patient regained clear consciousness. However, it was not possible to wean him from the mechanical ventilation due to rapid exhaustion and blood gas disturbance during independent breathing, so respiratory support in SIMV mode was provided. Systolic BP was fairly stable ranged from 140 to 160 mm Hg with an increase during independent breathing. Facial palsy progressed up to House–Brackmann grade V–VI [14], left-side facial numbness and fine horizontal left-beating nystagmus developed. There were no motor symptoms or any damage to other cranial nerves. Control MSCT (Fig. 2) revealed an area of hemorrhage up to 1.5–2.0 ml in the left regions of the pons. There was no hemorrhage in the tumor bed. The ventricular system was moderately dilated, but, compared to preoperative levels, no increase in volume was observed.

Over the next few days, the patient varied from being clearly conscious to mild obtundation. Respiratory sup-

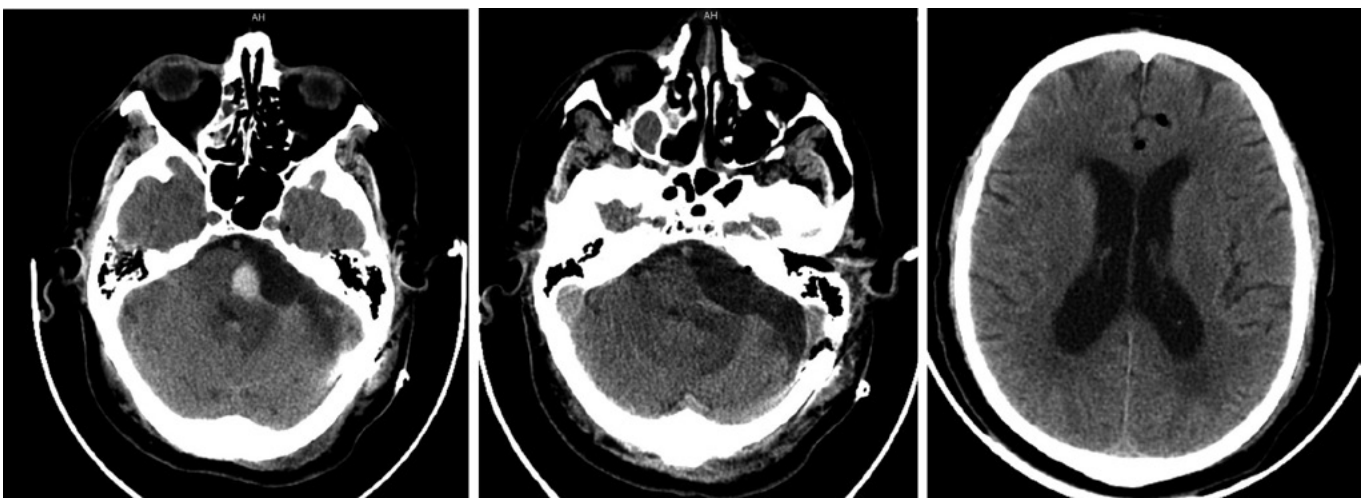

Fig. 2. Contrast-enhanced head MSCT on postoperative day 1. No contrast-enhancing areas observed. Hemorrhage site is detected in the left regions of the pons.

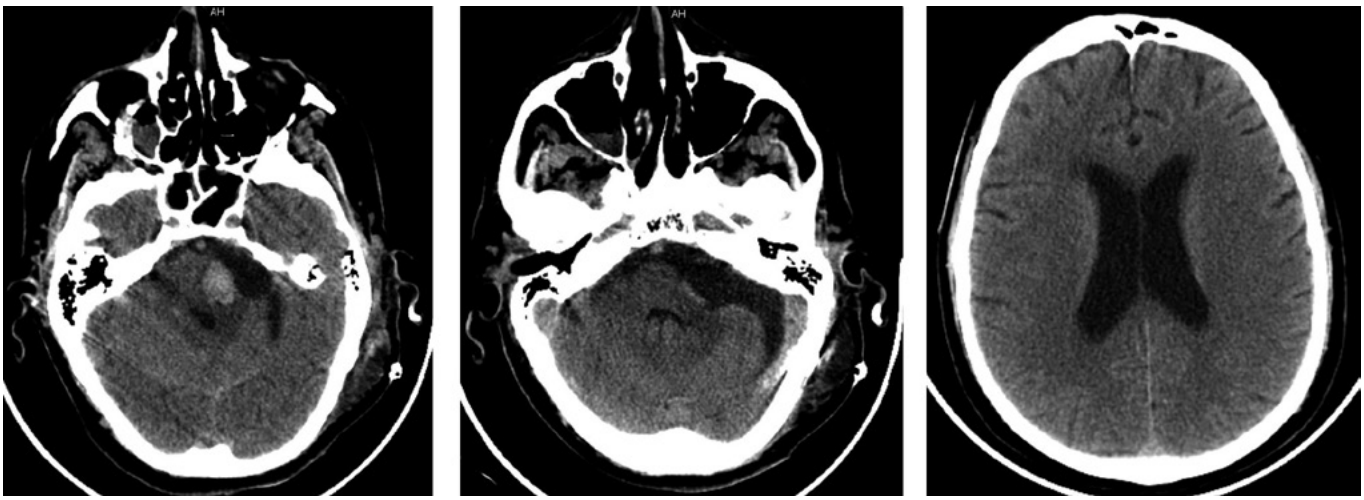

Fig. 3. Head MSCT on postoperative day 5.

port in SIMV mode was continued. Repeated attempts to wean the patient from the MV failed due to the rapid increase in respiratory failure. There were episodes of BP increasing up to 150 mm Hg. No cardiac arrhythmias were observed. Based on MSCT data (Fig. 3), neither progression of hydrocephalus, nor increase of hemorrhage area in the pons region, nor brainstem involvement were detected.

A tracheostomy tube was placed on postoperative day 5. From postoperative day 14, periods of psychomotor agitation and episodes of atrial fibrillation were noted. The patient was placed on fully controlled mechanical ventilation. From day 20, febrile hyperthermia and neutrophilic leukocytosis developed, and bilateral pneumonia was diagnosed. Based on the results of sputum cultures, antibacterial therapy was prescribed. On postoperative day 24, the patient's condition acutely worsened with development of coma accompanied by arterial hypotension and cardiac arrest. Resuscitation was unsuccessful.

Post-mortem examination stated that the patient died from cerebral edema with cerebellar tonsillar herniatio in the foramen magnum and brainstem dislocation.

Discussion

Prevalence of complications

There are controversial data in the literature regarding the incidence of postoperative hemorrhages after VS removal. A number of studies report only on isolated clinical cases with this type of complications [15–18]. V.N. Shimansky et al. (the authors of clinical guidelines on VS surgical treatment) indicate a 2% complication rate after VS removal.[1]

Other authors estimate VS surgery hemorrhage incidence at 2.4–5.0% [2, 8, 13, 19–24]. J. Betka et al. reported that tumor bed hematoma was the most common complication and required reoperation (2.4%), while cerebellar hemorrhages (1.2%) and epidural hematoma (1%) were less common.[2]

M. Samii et al. based on their extensive experience in VS surgery reported hemorrhagic complications in 2.2% of 962 operated patients, which required reoperation in 15 (1.5%) cases [25]. In another article, the same authors noted that tumor bed and cerebellar hemisphere hemorrhages did not require reoperation in 8% of cases after giant VS removal and only in 1.2% of cases after small-sized tumor removal [26].

One of the most recent studies on VS surgery was published by X. Guo et al. [4]. In a series of 452 tumors resected via the retrosigmoid approach, the authors registered 8.2% of hemorrhages, and 3.1% of them required reoperation. In most cases, hematoma was localized in the tumor bed. One of the patients died, and the other went into a prolonged coma.

The largest number of postoperative hemorrhages is reported by R. Philip et al., F.S. Kazim et al. These authors registered hematomas in 11.0–11.5% of patients after resection of VS > 4 cm [7, 27].

In general, hemorrhages after resection of intracranial tumors are associated with high mortality. T. Kageji et al. reported that in 2.09% of patients, who underwent intracranial tumor resection, 30-day mortality was 12.5% [28]. In the study conducted by S. Wang et al., postoperative hemorrhages requiring reoperation were registered in 1.8% of cases with 20% mortality [29].

The data on the hemorrhages developing after VS removal and requiring reoperation also differ. In a series of tumor resections performed by I. Yamakami et al., there were no

cases requiring reoperation [20]. B. Sade et al., on the contrary, noted that these complications required reoperation in at least 50% of cases [24].

Noteworthy, S. Rahimpour et al. believe that the incidence of postoperative complications in VS surgery has recently increased. The authors explain it by a decrease in surgical experience due to the wide introduction of radiosurgical methods of treatment, by the growing number of tumors requiring resection, and by a certain percentage of irradiated VS, as their dissection during surgery is quite challenging [30].

Causes and risk factors

The literature describes the following preoperative risk factors for hemorrhage complications after removal of intracranial tumors, including VS: age over 65 years, high international normalized ratio (INR), factor XIII deficiency, ischemic heart disease, atrial fibrillation and anticoagulant use, tumor > 4 cm, peritumoral edema, cystic VS and VS without capsule [4, 22].

Older age as a risk factor for postoperative hemorrhage is determined by a number of subfactors: higher incidence of arterial hypertension, age-related brain atrophy, frequent intake of anticoagulants and antiaggregants due to multiple comorbidities.

According to S. Wang et al., the age of patients and large tumor size are statistically significantly associated with the development of postoperative intracerebral hemorrhages [29]. The authors explain this by a large surgical area of exposure, retraction injuries and a significant decrease in intracranial pressure after the tumor resection.

R. Gerlach et al. analyzed such complications after neurosurgical interventions [31]. They found factor XIII deficiency (a fibrin-stabilizing factor involved in a dense clot formation and influencing platelet adhesion and aggregation) in 40% of patients. The authors proved that this condition is statistically significantly associated with the development of hemorrhage.

Of the preoperative risk factors in our patient, age over 65 years and a giant tumor were identified. There were neither coagulation disorders nor significant arterial hypertension.

M. Samii et al. emphasize that peritumoral edema in patients with VS indicates tumor hypervascularity and a tendency to form tumor bed hemorrhage in the postoperative period [32]. According to preoperative MRI findings, our patient had no peritumoral edema. However, MSCT data (Fig. 4) indicated hypodense changes in the region of the pons and in the adjacent regions of the cerebellum.

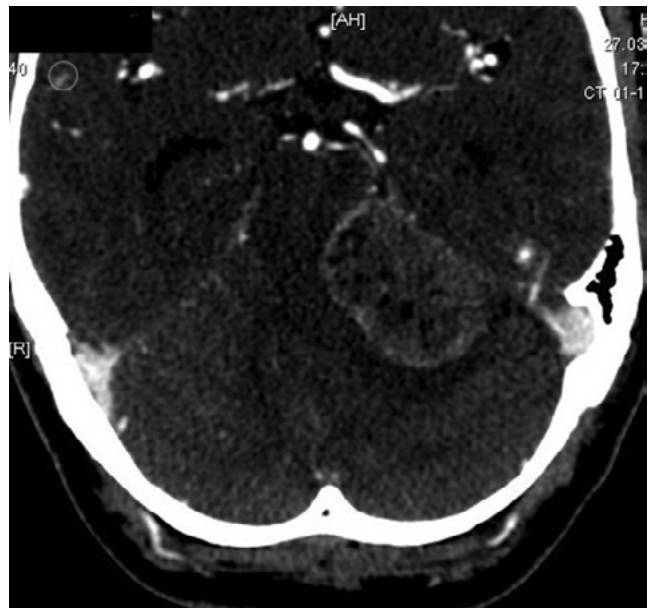

Fig. 4. Preoperative axial contrast-enhanced head MSCT scan with a peritumoral hypodensity area.

V.E. Kocharyan et al. performed a systematic review and detailed analysis of intraoperative causes of hemorrhagic complications in VS surgery [11]. According to the authors, the main surgical causes of cerebellopontine angle hematomas are the ineffective hemostasis in the branches of the anterior inferior cerebellar artery, rupture of the veins of the cisterna pontis lateralis and middle cerebellar peduncle (brachium pontis), as well as damage to the superior jugular bulb during drilling the IAC. The leading causes of cerebellar hemorrhages and subdural hematomas are the bleeding surface of the tumor bed and the cerebellar tissue during its lateral resection, and cerebral venous infarction with secondary hemorrhagic transformation. Epidural hematomas are caused by bleeding from muscular branches of the posterior auricular and occipital arteries with secondary spread into the epidural space, or by damage to walls of sinuses or mastoid emissary veins. The authors consider the tumor bed hematoma to be the most frequent hemorrhagic complication with the worst prognosis [11].

According to H. Mahboudi et al., the incidence of iatrogenic large vessel injuries in posterior cranial fossa surgery is 0.8% [6]. J. Betka et al. believe that damage to the cerebellar arteries is unlikely due to their large size, so they can be easier identified during surgery, unlike smaller vessels [2].

A number of studies indicate a higher risk of hemorrhage in case of incomplete tumor removal. J. Bartek et al. found a clear correlation between subtotal resection of the VS and the development of postoperative hematoma [22]. M.M. Tastanbekov et al. also consider incomplete tumor

removal and cerebellar hemisphere resection to be the risk factors for complication development [13].

K. Mattok et al. associate hemorrhagic complications with coagulopathy caused by excess thromboplastin due to tumor destruction during its removal, and ischemia that may develop in the lateral parts of the pons. The authors consider the giant size of the tumor to be a risk factor for the development of intraoperative coagulopathy [33].

According to G.I. Moisak et al., the risk factors for the development of circulatory disorders in the brainstem are the brainstem pronounced displacement based on preoperative MRI data, rapidly progressing neurological symptoms, signs of decompensation during hospital admission, and hypertension syndrome [9].

Noteworthy, A. Harders et al. suggest that intracerebral arterial blood flow causing cerebral ischemia becomes lower in a sitting position. When the patient is repositioned after surgery, there is hyperperfusion of brain tissue that may cause intracerebral hemorrhages in the ischemic area [34].

The theory of centrogenic reactions (CR; i.e., systemic hemodynamic responses) developed by A.N. Kondratyev [35] is important for understanding the development of vascular disorders in the brainstem. The author believes that CR are caused by a direct multifactorial impact on cerebral structures during the removal of an intracranial tumor. The damaging effect of CR is produced by disturbances of cerebral blood flow autoregulation leading to inadequate compensation of central hemodynamic fluctuations. Thus, arterial hypertension resulting from CR may be accompanied by an increase in blood flow into the brain parts without autoregulation, followed by the edema development and the risk of hemorrhage in these areas. During surgery, type 1 CR is characterized by fluctuations in BP, heart rate and heart rhythm, and type 2 is defined by a steady, gradual increase in BP, multidirectional changes in heart rate and heart rhythm.

M. Zetterling et al. assume that major intraoperative blood loss is also significantly associated with the development of hemorrhagic complications [36]. However, in the study by T. Kageji et al. no such correlation was found [28].

In our clinical case, the tumor was radically removed, cerebellar hemisphere was not resected, and no intraoperative blood loss was observed.

A. Basali et al. consider intra- and postoperative arterial hypertension up to 160–90 mm Hg and higher to be an important risk factor for the development of postoperative hemorrhage in neurosurgery. They report on BP elevation within 12 h after the intervention in 62% of patients with these complications [37]. Similar data are presented by K. Lillemae et al.: hemorrhages requiring reoperation developed in 84.6% of patients with BP > 160 mm Hg episodes in the early postoperative period [38].

In our patient, episodes of arterial hypertension up to 160 mm Hg were observed on postoperative day 1, which, apparently, caused the development of a rare local hemorrhage in the pons.

Timing of complications

There are different views regarding the timing of these complications. Some researchers observed hemorrhages during urgent MSCT due to patients' condition worsening, the others detected them during routine MSCT/MRI on the next day after surgery.

Most often hemorrhages manifest on postoperative day 1 [19]. A. Basali et al. analyzed the results of 11 214 craniotomies. On average, postoperative intracranial hemorrhages developed 21 h after surgery [37].

S.E. Heman-Ackah et al. report that hemorrhages can be observed not only in the early postoperative period, but also on postoperative days 10–14 [39].

Data obtained by M. Zetterling et al. indicate that 80% of hemorrhage complications develop on day 1 after tumor removal, and > 50% of them develop within the first 6 hours. The authors note that hematomas developed on day 1 were more life-threatening than those developed later [36].

V.E. Kocharyan et al. presented 3 interesting clinical case reports of the hematomas developed in the cerebellopontine angle with clinical manifestation 16–28 h after VS removal [11].

Clinical presentation

In the postoperative period, clinical manifestations of vascular complications may vary from mild neurological disorders to symptoms of dislocation and herniation of the brain structures.

Small hemorrhages in the cerebellar hemisphere manifest only by ataxia symptoms [20]. Larger ischemia and hemorrhage areas may often cause deterioration of consciousness of varying severity, arterial hypertension, bradycardia, pupil dilation, and hemiparesis [2].

M. Sanna et al. emphasize the key role of progressive deterioration of consciousness in the diagnosis of hemorrhagic complications [17].

In our clinical case report, hemorrhage developed on postoperative day 1 and manifested with respiratory distress.

Intraoperative diagnosis

According to intraoperative analysis of brainstem auditory evoked potentials (BAEP), type 1 CR is manifested by longer interpeak intervals I–III and III–V and altered amplitude of III and V peaks on the side of the removed tumor. Data presented by M.M. Tastanbekov et al. demonstrate that these reactions develop more often when the tumor capsule is separated from the pons Varolii, trigeminal nerve, and caudal cranial nerves. These authors emphasize that peak amplitude and duration of interpeak intervals typically return to normal after brief interruption of the surgery [13].

Type 2 CR is associated with an increased and/or decreased peak III and V height, especially on the side of the removed tumor, and with bilateral prolongation of interpeak intervals III–V and I–V. It was found that with type 2 CR, the BAEP parameters significantly outpaced the systemic hemodynamic changes by 10 min on average [13].

Patient management strategies

The choice of appropriate management for patients with these complications depends on the type, localization and size of hemorrhage, the patient's consciousness level and neurological disorders. The management can be both conservative (infusions of mannitol, diuretics, correction of coagulation disorders) and surgical.

The type of reoperation varies from hemorrhage removal to decompressive trepanation and external ventricular drainage [4, 11].

J. Betka et al. note that if the patient with postoperative hemorrhage develops hypertension, its immediate removal is indicated [2]. M. Sanna et al. believe that after removal of VS, the patient should be brought out of sedation as quickly as possible and extubated to assess the neurological status [17], The authors believe that in case of progressive worsening of the patient's condition, revision of the postoperative wound with hematoma removal, decompression and ventricular drainage should be performed in the ICU prior to MSCT scanning [17].

Taking into account the small volume of hemorrhage, its localization in the region of the pons, and no progression of hydrocephalus, we did not perform any active surgical actions in our case.

Intra- and postoperative prophylaxis

The postoperative hemorrhage prevention measures include thorough hemostasis with modern local hemostatics and BP control during the wound closure [1].

M. Samii et al. emphasizes the importance of meticulous arachnoid dissection when removing the VS and preserving all the vessels located on its capsule [25].

G. Iacob et al. use no coagulation when separating tumor fragments tightly adhered to the pons [40].

There is still more attention in the literature to the physiological feasibility of surgical interventions, which generally determines acceptable extent of the tumor resection. It is emphasized that changes in clinical and BAEP parameters allow early diagnosis of the brainstem involvement and enable the surgeon to respond to the threatening situation in a timely manner. The development of type 2 or type 1 CR transiting to type 2 CR during surgery is a poor prognostic risk factor and justifies brief interruption and sometimes even termination of surgery [9, 13, 35].

In case of large and giant VS, two-stage tumor removal can be considered [41, 42].

V.E. Kocharyan et al. recommend continuous 24–48 h postoperative neurological monitoring after tumor removal [11].

V.N. Shimansky et al. emphasize the importance of detection and timely correction of arterial hypertension in the postoperative period as significant intracranial hemorrhage preventive measures [1].

Thus, postoperative hemorrhage complications in VS surgery are rare but dangerous, being the leading cause of unfavorable treatment outcomes. The key predisposing factors are older age, large and giant size of the tumor, tumor invasion into the pia mater of the brainstem, and vascularization of the tumor stroma. Comprehensive assessment of tumor blood supply and the state of the brainstem, intra- and postoperative clinical and neurophysiological monitoring, careful and thorough dissection of tumor capsule and strict BP control in the postoperative period are the basic preventive measures for these complications. Progressive deterioration of consciousness in patients with postoperative hemorrhage may require decompressive trepanation of the posterior fossa, hematoma evacuation, and ventricular drainage.

The presented clinical case report demonstrates that hemorrhage into the brainstem can be caused by minor arterial hypertension in the early postoperative period and even with a small hemorrhage volume can lead to fatal outcomes.

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