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© Slotina A.E., Ikonnikova E.S., Kotsoev G.A., Egunova A.S., Panina U.V., Fedotova E.Yu., Gnedovskaya E.V., Suponeva N.A., 2025

Strategies for Maintaining Balance in Patients with Parkinson's Disease

Anastasiya E. Slotina, Ekaterina S. Ikonnikova, Georgii A. Kotsoev, Alena S. Egunova, Uliana V. Panina, Ekaterina Yu. Fedotova, Elena V. Gnedovskaya, Natalia A. Suponeva

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Abstract

Introduction. *The relevance of studying balance impairment in patients with Parkinson's disease (PD) lies in the need to prevent falls and injuries while enabling patients to maintain maximum independence and mobility. Promising advances in posture and gait screening using digital image processing require a thorough understanding of fundamental balance maintenance strategies.*

The study was aimed *at investigating balance maintenance strategies during PD "on" and "off" periods using classical and integral stabilometric parameters.*

Materials and methods. *The study included 27 PD patients with the median of 61 years. The mean total daily levodopa equivalent dose was 889.71 mg. All patients underwent clinical balance assessment using the Berg Balance Scale and stabilometric platform testing during "on" and "off" periods.*

Results. *Berg Balance Scale scores revealed mild balance impairments in PD patients, with greater severity during the "off" period ($p < 0.05$). Classical Romberg test parameters during the "on" period demonstrated deteriorated balance function and increased reliance on visual strategies for balance maintenance. Analysis of vector integral parameters during the "off" period showed a significant increase in angular velocity and coefficient of abrupt direction changes ($p < 0.05$). Stabilometry data indicate balance impairments in both PD "on" and "off" states, accompanied by different compensatory strategies.*

Conclusion. *Despite clinical assessments suggesting only mild balance impairments and low fall risk in PD patients, stabilometric parameters revealed more significant static balance disorders contributing to fall risk. Notably, the diagnostic value of classical stabilometric parameters decreases during the "off" period, while vector parameters characterizing balance maintenance strategies gain importance. We propose that these integral parameters can effectively assess balance quality and fundamental compensatory strategies in PD patients undergoing treatment. The findings are valuable for developing digitalized balance analysis technologies incorporating artificial intelligence.*

Keywords: *stabiliometry; Parkinson's disease; balance; postural control; risk of falls*

Ethics approval. All patients provided their voluntary written informed consent to participate in the study. The study protocol was approved by the Local Ethics Committee of the Russian Center of Neurology and Neurosciences (Protocol No. 3-6/22, April 20, 2022).

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Анализ стратегии поддержания равновесия у пациентов с болезнью Паркинсона

А.Е. Слотина, Е.С. Иконникова, Г.А. Коцоев, А.С. Егунова, У.В. Панина, Е.Ю. Федотова, Е.В. Гнедовская, Н.А. Супонева

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Аннотация

Введение. *Актуальность проблемы нарушения равновесия у пациентов с болезнью Паркинсона (БП) обусловлена необходимостью предотвращения падений и травм, а также обеспечения возможности пациентам сохранить максимальную самостоятельность и мобильность. Перспективны разработки в области скрининга позы и походки с помощью цифрового анализа изображений, для которых важно понимание базовых стратегий поддержания равновесия.*

Цель *исследования – изучить стратегии поддержания равновесия в фазах «on» и «off» БП при помощи классических и интегральных показателей стабилометрии.*

Материалы и методы. *В исследование включены 27 пациентов с БП. Медиана возраста – 61 год. Среднее значение суточной эквивалентной дозы леводопы – 889,71 мг. Всем пациентам была проведена клиническая оценка равновесия по шкале баланса Берг и тестирование на стабилометрической платформе в фазах «on» и «off».*

Результаты. *По шкале баланса Берг у пациентов с БП отмечены лёгкие нарушения равновесия, более выраженные в фазе «off» ($p < 0,05$). Данные по классическим показателям теста Ромберга в фазе «on» показали ухудшение функции равновесия и преобладание роли зрения в стратегии её поддержания. При анализе векторных интегральных показателей в фазе «off» отмечено значимое увеличение угловой скорости и коэффициента резкого изменения направления движений ($p < 0,05$). Стабилометрические данные свидетельствуют о наличии нарушений равновесия в обеих фазах при БП, с разными компенсаторными стратегиями.*

Заключение. *Несмотря на наличие у пациентов с БП лёгких нарушений равновесия и низкого риска падения по данным клинической оценки, показатели стабилометрии на самом деле свидетельствуют о более серьёзных нарушениях статического равновесия, способствующих увеличению риска падения. Стоит отметить, что диагностическая значимость классических показателей стабилометрии в фазе «off» снижается, значимую роль приобретают векторные показатели, характеризующие стратегию поддержания равновесия. Мы считаем, что именно данная группа интегральных показателей может эффективно использоваться для оценки качества равновесия и базовых компенсаторных стратегий у пациентов с БП на фоне проводимого лечения. Эти результаты имеют ценность для дальнейших разработок цифровизированных технологий анализа равновесия с применением искусственного интеллекта.*

Ключевые слова: *стабилометрия; болезнь Паркинсона; равновесие; постуральный контроль; риск падения*

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Introduction

Scientific interest in studying balance and postural stability disturbances in Parkinson's disease (PD) is attributed to the fact that postural disorders are most strongly associated with an increased risk of falls, which can lead to serious consequences (fractures, traumatic brain injuries, etc.), including fatal outcomes [1–3]. Epidemiological data show that falls occur at least once in 50% of PD patients, with recurrent episodes observed in 35% of cases [4, 5].

The literature emphasizes the value of computerized stabilometry for studying various balance and vertical posture disorders in neurological diseases [6–8]. This method has long been recognized as an objective assessment of balance function and is actively empoyed in clinical practice [9]. Due

to their widespread availability and potential for objective quantification of postural function data, stabilometric platforms are routinely employed to evaluate the effectiveness of rehabilitation methods and other therapeutic interventions.

Previous recommendations for stabilometric assessments favored simple, reliable parameters like path length, maximum deviations, and peak amplitude [10]. However, most software developers now propose using more complex integral indicators, as their analysis provides a more comprehensive evaluation of balance function and postural control strategies [11]. Integral indicators are mathematically derived parameters that assess various aspects of vertical posture regulation. These indicators lack universal standardization: different devices employ unique mathematical analyses of statokinesiograms. Nevertheless, most integral indicators fundamentally rely on relationships between center of mass displacement areas, path length and area, center of mass position and velocity, and similar vector parameters. These include the Romberg ratio, composite coefficient, displacement asymmetry coefficient, and similar metrics [12]. It is believed that the use of these indicators may reveal new mechanisms of vertical posture regulation in PD patients and enable comprehensive assessment of posturographic profiles. Previous studies have demonstrated the utility of integral indicators for evaluating balance function in PD, including pharmacotherapy monitoring [13–15].

Importantly, the symptoms of PD fluctuate throughout the day during specific therapy, which is associated with the onset ("on" state) and cessation ("off" state) of antiparkinsonian medication effects. The literature review shows that studies investigating postural function in PD typically assess patients exclusively in either the "on" or "off" state [16, 17], though no comparative studies have been conducted. We identified only one study with differentiated evaluation of balance function across both "on" and "off" states [6], which specifically analyzed the effects of apomorphine on postural stability.

Our hypothesis posits that PD patients may employ different compensatory strategies to maintain balance during "on" and "off" periods. Investigation of these state-dependent mechanisms in this patient population could facilitate the development of personalized digital screening programs and fall prevention strategies.

The study aimed to identify balance maintenance strategies in "on" and "off" states using classical and integrated stabilometric parameters.

Materials and methods

Stabilometry data were collected as part of a resarch approved by the Local Ethics Committee of the Scientific Center of Neurology (Protocol No. 3-6/22 dated April 20, 2022).

Inclusion criteria:
- clinical diagnosis of Parkinson's disease (PD) established according to the criteria of the International Parkinson and Movement Disorder Society [18];
- Hoehn–Yahr stage II–III disease;
- age 40–80 years;
- provided consent for personal data processing and signed informed voluntary consent to participate in the study.

The study included 27 patients (14 women and 13 men) with a confirmed PD diagnosis, of whom 13 patients were at Hoehn–Yahr stage II and 14 at stage III. When assessing disease subtype, 4 patients were classified as having the akinetic/rigid PD, and 23 as the mixed PD. The median age was 61.56 [24; 75] years. The median levodopa equivalent daily dose was 889.71 [320; 2073.5] mg.

In accordance with the study objectives, patients underwent stabilometry testing during two daily periods: the "on" state (over 8 hours after levodopa intake) and the "off" state (1.0–1.5 hours after levodopa intake according to the treatment regimen). Additionally, 20 patients were examined twice daily during "on" and "off" periods at 1, 3, and 6 months. Data from repeated stabilometry studies were included in this analysis, resulting in a final total of 58 stabilograms analyzed for the "on" state and 58 for the «off" state.

All patients underwent baseline clinical balance assessment using the Berg Balance Scale [19] during "on" and "off" periods to identify postural stability differences between the both states.

Subsequently, patients underwent instrumental testing using the Stabilan 01-2 computerised stabilometry system (OKB RITM) during both "on" and "off" periods. This system is designed for computerised recording and mathematical processing of human center of pressure (CoP) position and displacement in a two-dimensional coordinate system during clinical diagnostic tests. The following clinical diagnostic tests were selected for patient examination and postural stability assessment:

1. The Romberg test consists of two components – with eyes open and closed – and is designed to assess static postural control while determining the role of vision in maintaining balance. This test serves as the primary and most frequently used assessment tool in various clinical diagnostic studies, essentially representing an instrumental version of the clinical Romberg test performed during routine neurological examinations [20]. The analysis of the findings involves comparing the metrics from eyes-open and eyes-closed trials. Normal values for this parameter range from 100 to 250. A value below 100 indicates that vision negatively affects balance function, with better stability observed eyes closed. A value exceeding 250 suggests that the patient predominantly relies on vision for balance maintenance, with significant deterioration when visual input is eliminated.

2. Limits of stability (LoS) testing evaluates the limits of stability during deliberate leans in one of four directions: forward, backward, right, and left. The normal ratio for forward/backward leans is 1.0–1.5, while the ratio for right/left leans should be 1.

In addition to specific assessments from the aforementioned tests, we analyzed stabilographic signals to evaluate three groups of integral stabilogram parameters:

1. Classical parameters – standardised stabilogram assessment methods applicable to all platform types, including CoP displacement, CoP sway velocity, statokinesiogram area (ellipse area), velocity index, curvature coefficients, CoP trajectory length, length-to-area ratio, and others.

2. Vector parameters characterizing the distribution of CoP velocity and acceleration vectors, including balance function quality, vectorogram area, abrupt direction change coefficient, linear and angular velocity indicators, vectorogram power, and others.

3. Spectral parameters reflecting the frequency spectrum of stabilographic signals in two planes: frontal and sagittal.

The stabilogram spectrum is divided into three main zones:
- High-frequency zone (2–6 Hz) – reflects CoP oscillations associated with physiological processes underlying balance maintenance; predominant amplitudes in this spectrum are often observed in various neurological disorders.
- Low-frequency zone (0.2–2.0 Hz) – indicates CoP oscillations associated with postural regulation through large muscle group contractions during specific balance challenges.
- Very low-frequency zone (0–0.2 Hz) – characterizes CoP oscillations related to fundamental postural adjustments observed during upright stance maintenance in healthy individuals [12].

Spectral parameters include peak amplitudes in statokinesiogram within frontal and sagittal planes, as well as power densities across stabilogram zones.

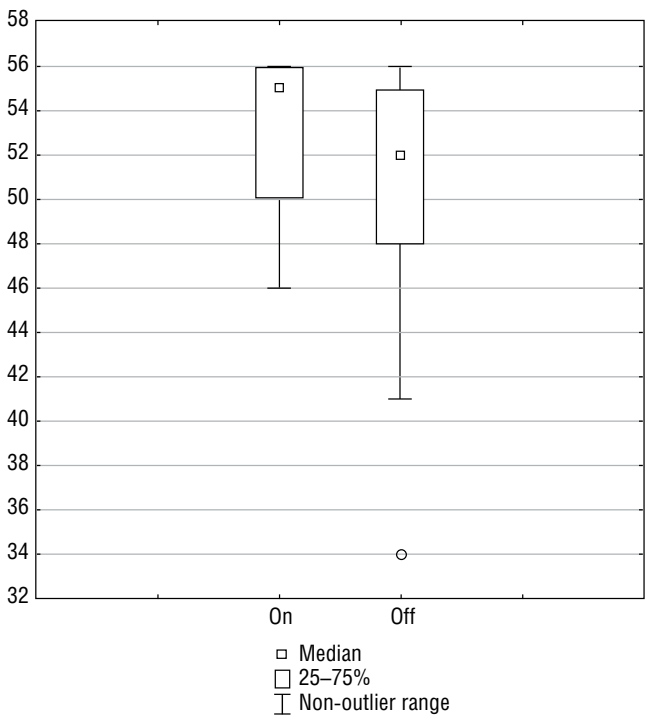

Fig. 1. Changes in the balance function on the Berg Balance Scale during "on" and "off" periods in PD.

Statistical analysis employed the Wilcoxon test (for paired comparisons) and Spearman's correlation coefficient using Statistica v. 13.0 software (Statsoft). Data are presented as median values with interquartile ranges [Q_1; Q_3]. Results were considered statistically significant if $p < 0.05$.

Results

Analysis of clinical data using the Berg Balance Scale revealed that the median scores in PD patients during both "on" and "off" periods corresponded to mild balance impairment and low fall risk: 53.44 [50, 56] and 50.65 [48, 55], respectively. However, balance was significantly worse during the "off" period ($p = 0.001$; Fig. 1).

Following the stabilometric study, we analyzed the general data of the Romberg test (balance maintenance metrics with eyes open and closed) in PD patients during "on" and "off" periods (Table 1). A significant ($p = 0.005$) decrease in the Romberg ratio was observed in the "off" state, with its value normalizing compared to the "on" state. These changes may indicate a predominant reliance on visual input for balance strategy during the "on" periods, as balance function deteriorates sharply when visual input is removed. Analysis of group distribution based on Romberg ratio values in the "off" state revealed a significant shift toward proprioceptive reliance, with vision playing a markedly reduced role in balance maintenance during this period (Fig. 2).

A significant ($p = 0.001$) decrease was observed in the parameter characterizing the correlation between the CoP sagittal plane position relative to the intermalleolar line and CoP sway velocity with eyes closed. Normally, the mean value of this parameter is close to zero. This parameter primarily reflects the degree of CoP displacement during quiet standing posture maintenance (body position with straightened legs, upright trunk, neutral head alignment facing forward, and arms hanging freely at the sides) and, consequently, the intensity of compensatory response (increased gastrocnemius muscle tension) during ankle strategy implementation for balance control. Our data indicated that most patients exhibited CoP position values relative to the intermalleolar line significantly above or below zero during both "on" and "off" periods, reflecting forward or backward CoP displacement, respectively. However, during the "off" periods, patients showed parameter values approaching normal levels (Me = 0.94 [–1.76; 5.61]), suggesting reduced engagement of compensatory mechanisms for balance maintenance and potentially better postural stability during this period. The observed trend toward decreased length-to-area ratio with eyes open during the "on" state ($p = 0.06$) indicates reduced center of mass dispersion over the supporting area during this period. Existing literature associates low length-to-area ratio values with more energy-efficient balance strategies [12]. These changes combined with alterations in the CoP position coefficient relative to the intermalleolar line suggest that despite greater compensatory mechanism engagement, the "on" state demonstrates a more physiologically optimal balance strategy compared to the "off" state.

Subsequent balance function assessment involved analysis of statokinesiograms with eyes open (Table 2) and closed

Table 1. Changes in the general Romberg test parameters in PD patients Me [Q_1; Q_3]

Ratio	"On" state	"Off" state	Significance of differences between the states, *p*
Romberg ratio, %	218 [120; 351]	163 [99; 292]	0.005
CoP position relative to the intermalleolar line, mm^{-1}	2.59 [–0.56; 10.57]	0.91 [–1.76; 5.61]	0.001
Length-to-area ratio, mm^{-1}	0.78 [0.64; 1.12]	1.24 [0.77; 1.67]	0.06 (trend)

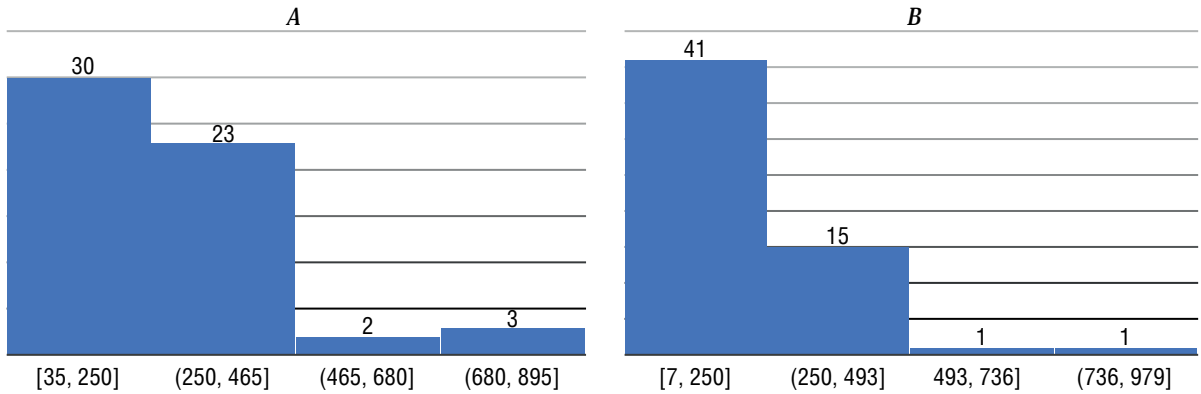

Fig. 2. Romberg ration distribution during "on" (*A*) and "off" (*B*) periods in PD.

(Table 3) using basic integrative parameters: classical, vector, and spectral parameters of postural control.

Statistical analysis yielded significant differences between the "on" and "off" states across all statokinesiogram parameters analyzed for both eyes-open and eyes-closed conditions.

Among classical parameters, special attention should be given to those describing the statokinesiogram ellipse area, i. e. the core portion of the stabilogram's total area (excluding random outliers and loops) which characterizes an individual's working support area. The primary parameter is the ellipse area. Its significant changes were observed in both "on" and "off" states. The ellipse area in the "on" state with open eyes increased by only 50 units (p = 0.049; Table 2), while with closed eyes it doubled (p = 0.001; Table 3). These changes likely result from significantly increased overall rigidity during the "off" period, restricting center of pressure (CoP) oscillations to a smaller plane, whereas transitioning to the "on" state reduces rigidity and expands CoP displacement dispersion. Literature suggests that increased ellipse area indicates impaired balance function, though its changes must be considered alongside other parameters [8, 12]. Additionally, eyes-closed statokinesiograms in the "on" state showed a significant decrease in the ellipse reduction coefficient (p = 0.049; Table 3). This coefficient reflects statokinesiogram "flattening", defined as the ratio of the ellipse's major axis length to its minor axis. Lower reduction coefficient values typically indicate more stable balance maintenance, as the stabilogram assumes an elongated shape. Analysis of statokinesiogram length revealed that "on" state changes primarily involve increased frontal plane displacement (Tables 2, 3). These findings suggest that "on" state transition expands lateral CoP oscillations while reducing anteroposterior sway. Thus, PD patients in the "off" state exhibit hypokinesia and marked muscle rigidity affecting both large intentional movements and automated motor functions – postural synergies. This conclusion is further supported by decreased CoP velocity index values (Tables 2, 3), indicating slower CoP displacement.

In further analysis, we examined the vector parameters of the statokinesiogram. This type of parameter characterizes the distribution of CoP velocity and acceleration vectors. The vector-based approach posits that with timely compensation of body deviations from the vertical, the CoP velocity should remain minimal. Conversely, impairments in the vertical posture regulation system would lead to delays and errors in correcting body deviations from the vertical, resulting in greater CoP displacements, higher velocities, and abrupt directional changes.

In this group of parameters, we observed changes in balance function quality (assessing how minimized the CoP velocity is) in both "on" and "off" states (Tables 2, 3). Normally, this parameter is 100%, where higher values indicate better balance maintenance. We noted a more pronounced decrease in the parameter with eyes closed in both states, with the "on" state showing significantly (p = 0.049) lower values than the "off" state (Table 3), suggesting more pronounced balance impairments in the "on" state. This is further supported by higher values in the "on" state for both mean linear velocity (p = 0.002) and linear velocity variation amplitude (p = 0.001) with eyes open and closed (Tables 2, 3).

However, despite the observed deterioration of balance function in the "on" state, we also obtained interesting data on vector parameters for the "off" state. Significant increases in the abrupt directional change coefficient were observed with both eyes closed and open (p = 0.001; Tables 2, 3), reflecting

Table 2. Changes in statokinesiogram parameters during Romberg test with eyes open in PD patients, Me [Q_1; Q_3]

Ratio	"On" state	"Off" state	Significance of differences between the states, *p*
Classical parameters			
Mean CoP sway velocity	8.64 [6.92; 13.11]	8.43 [6.56; 10.24]	0.049
Velocity of changes in the statokinesiogram area	13.55 [7.60; 14.30]	9.50 [7.60; 14.30]	0.026
Ellipse area	148.35 [89.50; 273.10]	102.80 [77.40; 156.60]	0.049
Velocity index	5.49 [4.41; 8.24]	5.34 [4.12; 6.52]	0.05
Frontal CoP trajectory length	96.50 [73.50; 155.80]	90.20 [63.10; 109.20]	0.012
Vector parameters			
Balance function quality	84.61 [66.54; 89.85]	85.29 [79.45; 90.94]	0.013
Abrupt direction change coefficient	9.08 [4.62; 13.45]	14.26 [9.44; 18.88]	0.001
Mean linear velocity	8.65 [6.92; 13.11]	8.44 [6.55; 10.25]	0.049
Linear velocity variation amplitude	5.12 [4.06; 8.87]	4.60 [3.77; 7.10]	0.003
Mean angular velocity	17.95 [13.10; 23.90]	23.65 [18.50; 28.10]	0.001
Angular velocity variation amplitude	19.80 [16.40; 24.00]	22.10 [18.60; 27.50]	0.003
Spectrum parameters			
2nd peak amplitude, sagittal plane	2.40 [1.51; 3.03]	1.65 [1.20; 2.21]	0.005

the proportion of abrupt velocity vector turns (> 45°) relative to the total vectors. Additionally, significant increases were found in angular velocity variation amplitude ($p = 0.001$) and accumulated displacement angle ($p = 0.026$), corroborating the findings for the abrupt directional change coefficient. The "off" state changes suggest that despite an apparent state of greater stability, stabilometric data reveal persistent alterations in balance maintenance strategies. These conclusions are reinforced by increased statokinesiogram power in the "off" state, indicating larger-amplitude velocity vector oscillations and a coarser (abrupt-movement) balance strategy compared to the "on" state.

Thus, analysis of vector parameters reveals that despite existing balance impairments, patients in the "on" state demonstrate a more physiological and smoother balance maintenance strategy. This is evidenced by altered indicators reflecting the activity of muscles responsible for physiological ankle strategy implementation (triceps surae muscle), along with lower values of vector parameters indicating abrupt changes in CoP direction compared to the "off" state. In the "off" state, despite less pronounced deviations in statokinesiogram area parameters, sharper vector changes with higher velocities are observed, suggesting reduced compensatory potential for maintaining upright posture in the standard stance. These findings are supported by more pronounced balance function impairments on the Berg Balance Scale, which shows significantly worse scores in the "off" state. This scale includes multiple dynamic tests assessing postural instability during task performance. The observed statokinesiogram changes in the "off" state indicate that patients experience greatest difficulties during body position transitions, as physiological smooth balance compensation becomes compromised.

We performed an analysis of spectral parameters as an additional tool to assess changes in stabilographic signals across two planes (frontal and sagittal). The principal differences between patients in "on" and "off" state were observed in the amplitudes of statokinesiogram spectral peaks, though in most cases, these remained within the high-frequency oscillation range associated with physiological processes (Tables 2, 3). However, with eyes closed, patients in the "off" state exhibited amplitude shifts in the 1st, 2nd, and 3rd peaks, which represent the amplitude of the three most prominent CoP oscillations on the stabilogram spectrum below the high-frequency range – indicating a predominance of CoP oscillations required for postural control and balance maintenance.

Analysis of the LoS test revealed significantly fewer differences between "on" and "off" state in PD. The evaluation of lateral displacements (right, left, forward, backward) and classical stabilometric parameters showed no statistically significant changes in balance function during either period. Notably, the main differences in the LoS test were observed in vector parameters and one spectral parameter of the statokinesiogram (Table 4). These statokinesiogram parameters help characterize the velocity of CoP movements in terms of compensatory response.

During the LoS testing, patients with PD in the "off" state showed a significant increase in the coefficient of abrupt directional change, mean angular velocity, and amplitude of angular velocity variation. Additionally, a notable difference was observed in the linear-to-angular velocity ratio, which was significantly lower in the "on" state compared to the "off" one, indicating that the linear CoP displacement velocity during the "on" period exceeds the angular velocity. This parameter, along with vector indicators, confirms that the

Table 3. Changes in statokinesiogram parameters during Romberg test with eyes closed in PD patients, Me [Q_1; Q_3]

Ratio	"On" state	"Off" state	Significance of differences between the states, *p*
Classical parameters			
Mean CoP sway velocity	13.66 [10.90; 27.97]	12.12 [8.93; 18.13]	0.002
Velocity of changes in the statokinesiogram area	26.10 [16.70; 62.10]	18.20 [11.20; 35.20]	0.001
Ellipse area	313.9 [194.0; 474.90]	160.90 [103.0; 306.10]	0.001
Ellipse reduction coefficient	1.64 [1.29; 2.17]	1.79 [1.45; 2.44]	0.049
Velocity index	8.53 [6.82; 17.56]	7.05 [5.58; 11.12]	0.002
Frontal trajectory length	137.05 [88.90; 262.10]	120.50 [79.90; 168.50]	0.001
Sagittal trajectory length	192.9 [134.50; 273.80]	199.80 [156.90; 403.40]	0.049
Vector parameters			
Balance function quality	64.89 [44.97; 76.15]	71.72 [48.69; 83.74]	0.049
Abrupt direction change coefficient	6.93 [5.12; 9.44]	11.65 [7.23; 15.65]	0.001
Mean linear velocity	13.66 [10.88; 27.97]	12.12 [8.93; 18.14]	0.002
Linear velocity variation amplitude	10.19 [6.89; 17.56]	7.64 [6.04; 11.17]	0.001
Mean angular velocity	15.30 [12.90; 19.30]	20.65 [16.20; 25.40]	0.001
Angular velocity variation amplitude	17.95 [16.30; 21.90]	21.85 [19.0; 24.80]	0.001
Accumulated displacement angle	0.22 [-2.40; 4.04]	-0.60 [-4.29; 1.51]	0.026
Linear-to-angular velocity ratio	0.84 [0.58; 1.45]	0.61 [0.45; 0.90]	0.001
Spectrum parameters			
1st peak amplitude, frontal plane	4.67 [3.57; 6.0]	2.99 [2.13; 4.0]	0.001
2nd peak amplitude, frontal plane	3.0 [1.95; 3.95]	1.91 [1.36; 2.55]	0.001
3rd peak amplitude, frontal plane	1.97 [1.38; 2.82]	1.37 [0.91; 1.82]	0.001
3rd zone power	12 [10.0; 15.0]	14 [12.0; 17.0]	0.002
1st peak amplitude, sagittal plane	7.1 [5.32; 8.78]	5.39 [3.34; 7.41]	0.001
2nd peak amplitude, sagittal plane	3.75 [3.01; 5.28]	3.09 [2.42; 3.87]	0.002
3rd peak amplitude, sagittal plane	2.63 [1.93; 3.59]	2.11 [1.54; 2.66]	0.026

balance maintenance strategy during the "on" period is more physiological. The changes observed during testing suggest that, despite unaltered lateral displacement amplitude, the balance maintenance strategy becomes sharper (with more abrupt movements) during both the static-dynamic displacement test and the static Romberg test, where similar "off"-state responses were noted. Despite statistically significant changes in the amplitude of the first sagittal-plane peak on spectral analysis, these changes occurred within the high-frequency spectrum range, reflecting normal compensatory responses during the static-dynamic displacement test in both "on" and "off" states.

Discussion

Studies have shown that although levodopa medications effectively reduce muscle rigidity and stiffness, they may lack an impact on postural function [21]. Therefore, we should identify key parameters of postural instability both during and without antiparkinsonian therapy, which could facilitate the development of screening tools and effective fall risk prevention strategies.

Our study identified key parameters characterizing postural impairments in PD patients and their differences between "on" and "off" state associated with medication effects. Specifically, PD patients during the "on" period demonstrated an increased Romberg ratio, reflecting vision's role in maintaining balance function, i.e., static balance deteriorated when visual control was eliminated. These findings align with research confirming the predominant role of vision in balance maintenance for PD patients [22, 23]. However, visual component significantly diminishes in the "off" state, suggesting a shift in balance control mechanisms toward reliance on pro-

Table 4. Changes in statokinesiogram parameters during LoS test with eyes closed in PD patients, Me [Q_1; Q_3]

Ratio	"On" state	"Off" state	Significance of differences between the state, *p*
Vector parameters			
Abrupt direction change coefficient	6.73 [5.10; 9.26]	8,39 [6,26; 12,20]	0.001
Mean angular velocity	15.30 [12.50; 17.90]	17.10 [14.10; 21.80]	0.001
Angular velocity variation amplitude	18.20 [17.10; 19.70]	19.20 [17.10; 21.40]	0.004
Linear-to-angular velocity ratio	1.84 [1.41; 2.55]	1.58 [1.21; 1.98]	0.003
Spectrum parameters			
1st peak amplitude, sagittal plane	38.55 [31.69; 47.19]	37.65 [28.76; 44.12]	0.049

prioception. Some studies also report similar balance maintenance strategies in PD patients, though researchers typically attribute these changes to disease stage without specifying the assessment period [24]. Thus, balance function impairment persists in both periods, consistent with select study data [25], but compensation strategies differ.

Among classical parameters, the ellipse area (statokinesiogram area) stands out: its value with eyes closed was twice as high as with eyes open during the "off" period, and 1.5 times higher in the "on" one. These changes confirm the aforementioned Romberg ratio alterations and indicate worse balance maintenance in PD patients when visual input is removed. Similar changes have been identified by other researchers [26], confirming impaired balance function in stage 2–3 PD patients with eyes closed, though these studies did not specify the period during stabilometric testing. Our data align with previous studies comparing PD subtypes, which demonstrate comparable statokinesiogram area changes and CoP velocity alterations in patients with akinetic-rigid PD [27].

Comparison between different periods revealed that the value during the "off" period was twice as low as during the "on" period, both with eyes open and closed (accounting for changes in both conditions). These observed changes are most likely associated with increased overall rigidity in patients during the "off" period due to the wearing-off of levodopa, resulting in reduced body displacement during vertical posture maintenance. As previously demonstrated, patients receiving antiparkinsonian therapy show some increase in statokinesigram area with eyes closed compared to untreated patients [28], which generally aligns with our findings. However, the cited study reported less pronounced balance impairments, potentially due to the inclusion of patients with milder PD severity. Thus, this integral parameter (statokinesigram area) may serve as a significant marker of static balance function impairment in PD patients even at early disease stages, particularly during the "on" period. In turn, using this parameter as the primary marker during stabilometric assessment in the "off" state could lead to misinterpretation, especially in mild balance impairments, since its value is statistically significantly lower than that during the "on" period, as demonstrated in our study. The observed smaller statokinesigram area in the "off" state, likely attributable to greater rigidity limiting body sway, is further supported by our findings of reduced overall CoP velocity during both eye-open and eye-closed conditions in this period.

Although our data on classical statokinesiogram parameters reflecting static balance impairments were worse during the "on" period, further analysis of integral parameters revealed mechanisms underlying balance disorders and influencing fall risk elevation in during "off" period. Analysis of vector parameters demonstrated an increase in the coefficient of abrupt direction changes, angular velocity variation amplitude, and accumulated displacement angle during the "off" period. These changes characterize compensatory strategies employed by patients during the "off" period to maintain static balance as fall-risk-prone. During this periods, patients maintain balance predominantly through abrupt changes in CoP sway direction with high angular velocity, which may adversely affect dynamic balance (during body position changes) and lead to falls when movement direction changes or body repositioning is required. Additionally, vector parameters reflecting abrupt CoP sway direction changes may serve as reliable markers of balance impairments in the "off" state, unlike classical stabilometric parameters that show closer alignment with reference values (and sometimes even normal) during "off" periods compared to "on" ones. We consider that this group of integral parameters could be effectively used to assess balance quality and fundamental compensatory strategies in PD patients undergoing treatment. Our literature review revealed no previous analyses of such parameters in PD.

The data we obtained on identified compensatory responses characterizing balance disorders in the "off" state are further supported by an additional analysis of the spectral component of the statokinesiogram. A shift in spectral amplitudes toward low-frequency oscillations was detected, which are utilized by the body as compensatory responses to maintain upright stability. The observed predominance of high-frequency oscillations in the "on" state, characterizing physiological processes in the body, has been linked in the literature to an increased risk of falls in PD patients [13].

On one hand, our findings demonstrate that during the "on" period, patients exhibit more pronounced balance function impairment, particularly with eyes closed, which may be associated with increased fall risk due to reduced overall

rigidity and consequent deterioration of postural functions. On the other hand, despite the seemingly greater stability of patients in the "off" state, pronounced compensatory responses – manifested as more abrupt CoP sways to maintain stability – also contribute to elevated fall risk in PD patients. These very responses may explain the increased frequency of falls in PD patients during morning and nighttime hours when, due to lack of medication effects, patients cannot effectively utilize physiological strategies for maintaining balance function.

Conclusion

Postural instability is a significant PD symptom that can subsequently lead to increased falls and associated severe, often disabling consequences. The findings revealed that despite clinically mild balance impairments according to the Berg Balance Scale, stabilometric assessment demonstrated pronounced static balance disturbances in patients. Analysis of stabilogram integral parameters during "on" and "off" periods allowed us to identify key mechanisms underlying balance maintenance strategies in the upright posture during these periods, as well as to determine core groups of stabilometric parameters reflecting balance impairment: increased statokinesiogram area and velocity indices of CoP displacement, along with their dependence on visual control.

Thus, patients with PD exhibit marked balance impairments while maintaining an upright posture during both "on" and "off" periods; however, the compensatory strategies employed by patients differ between these periods. This underscores the necessity of performing stabilometric assessments in both states when conducting clinical or rehabilitation studies addressing postural impairment correction in this patient population.

The use of integrated stabilometric parameters serves to assess balance function and identify balance maintenance strategies in PD patients. They are also valuable for developing digitalized balance analysis technologies employing artificial intelligence, which could automate and streamline population screening while facilitating implementation of fall prevention measures.

Study limitations This study included patients with drug-induced dyskinesias: severe dyskinesias were observed in 8% of cases, moderate dyskinesias in 15%. During mathematical processing of CoP sway data, software algorithms were used to eliminate extreme outliers occurring during these movements. Calculation of integral parameters excluded abrupt CoP sways.

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Impact of Bobath Based Rehabilitation Program and Conventional Physiotherapy: Children with Hydrocephalus

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Abstract

Introduction. *Hydrocephalus is an abnormal enlargement of the brain ventricles caused by increased amounts of cerebrospinal fluid. The aim of the study was to determine the efficacy of Bobath Based Rehabilitation Program and conventional physiotherapy for improving motor function in children with hydrocephalus and reducing levels of anxiety in parents of children with hydrocephalus.*

Materials and methods. *The study design was quasi experimental in nature. Twenty patients with hydrocephalus, aged below 10 years, both males and females were included as per the eligibility criteria. All parents provided their written informed consent for participations in the study. These subjects were randomly divided into two equal groups using computer generated table: group A (n = 10) and group B (n = 10). All patients were assessed for motor function using GMFM-88 scale, whereas their parents were evaluated for anxiety levels using STAI tool. Group A received Bobath Based Rehabilitation Program whereas group B received conventional physiotherapy. Both groups received interventions for a total of 8 weeks, with 1 60-minute session per week and their parents were taught an individualized program of home exercises and encouraged to practice daily. Then the subjects were re-assessed after completing 8 weeks of interventions. Statistical analysis was performed using paired t-test and unpaired t-test.*

Results. *Our study revealed statistically significant difference in the GMFM-88, STAI-S and STAI-T scores in group A (p = 0.032, 0.0001, 0.0001) and group B (p = 0.0001, 0.001, 0.003), respectively.*

Discussion. *These two interventions have their benefits in improving gross motor function in children with hydrocephalus. These interventions can indeed be customized to address specific needs of children with hydrocephalus, such as muscle weakness, impaired coordination, and balance issues. This personalized approach optimizes the intervention effectiveness directly targeting the areas of difficulty experienced by each child. Moreover, these therapeutic approaches engage mechanisms of neuroplasticity through repetitive and task-specific exercises. Training general physiotherapists to deliver both therapies efficiently could maximize access to rehabilitation services in areas with inadequate healthcare infrastructure.*

Conclusion. *Bobath Based Rehabilitation Program and conventional physiotherapy are effective interventions for improving motor function in children with hydrocephalus and in reducing levels of anxiety in their parents.*

Keywords: *hydrocephalus; motor function; anxiety; Bobath based rehabilitation program*

Ethics approval. The study was conducted with the informed consent of the patients.

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Сравнение эффективности программы реабилитации на основе концепции Бобат и стандартной физической реабилитации у детей с гидроцефалией

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Аннотация

Введение. *Гидроцефалия – это состояние, при котором развивается патологическое увеличение желудочков головного мозга, вызванное избытком спинномозговой жидкости.* **Цель** *исследования – оценить, насколько эффективна реабилитационная программа на основе концепции Бобат и стандартные методы физической реабилитации с точки зрения улучшения двигательной функции у детей с гидроцефалией и снижения уровня тревожности у их родителей.*

Материалы и методы. *Исследование имело квазиэкспериментальный дизайн. В соответствии с критериями включения в исследование были включены 20 пациентов с гидроцефалией, среди которых были представители обоих полов в возрасте до 10 лет. Все родители предоставили письменное добровольное информированное согласие на участие их детей в исследовании. Пациентов рандомизировали в две равные по численности группы с использованием сгенерированной на компьютере таблицы: группу A (n = 10) и группу B (n = 10). У всех пациентов оценили двигательную функцию с помощью шкалы GMFM-88. У их родителей оценивали уровень тревожности с помощью опросника STAI. В группе A пациенты проходили реабилитацию на основе концепции Бобат, а в группе B – стандартную программу физической реабилитации. В обеих группах общая длительность лечения составила 8 нед. Пациентам проводили по одному сеансу длительностью 60 мин 1 раз в неделю, при этом родителей обучали индивидуальному комплексу упражнений и рекомендовали ежедневно выполнять его дома. Через 8 нед пациентов оценивали повторно. Статистический анализ выполнили с использованием t-критерия Стьюдента для зависимых и независимых выборок.*

Результаты. *В рамках настоящего исследования были выявлены статистически значимые различия в оценках GMFM-88, STAI-S и STAI-T между группой A (p = 0,032, 0,0001, 0,0001) и группой B (p = 0,0001, 0,001, 0,003).*

Обсуждение. *Обе программы реабилитации имеют свои преимущества с точки зрения улучшения крупной моторики у детей с гидроцефалией. Рассматриваемые методы можно адаптировать под потребности конкретного пациента с гидроцефалией с учётом степени слабости мышц, нарушения равновесия и координации. Такой индивидуальный подход позволяет максимально повысить эффективность реабилитации и скорректировать нарушения у ребёнка. Кроме того, рассматриваемые методы активируют механизмы нейропластичности благодаря повторению упражнений, направленных на решение конкретных задач. Обучение специалистов обеим программам реабилитации может повысить доступность такой помощи в регионах с недостаточно развитой инфраструктурой здравоохранения.*

Заключение. *Программа реабилитации на основе концепции Бобат и стандартная физическая реабилитация существенно улучшают двигательную функцию у детей с гидроцефалией и снижают уровень тревожности у их родителей.*

Ключевые слова: *гидроцефалия; двигательная функция; тревожность; программа реабилитации на основе концепции Бобат*

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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

Hydrocephalus is a common central nervous system disorder in children and is unique in being caused by widely differing prenatal, perinatal, or postnatal events [1]. It affects patients of any age, with thousands of new cases each year in the United States and many more globally [2]. Hydrocephalus is an abnormal enlargement of the brain ventricles due to increased amounts of cerebrospinal fluid (CSF). Excessive pressure in the ventricles exerted by CSF compresses the nervous tissue, which causes brain damage and may result in disproportionally large head size in new-borns or infants [3].

Paediatric hydrocephalus (namely, congenital, prematurity germinal matrix bleed, postinfectious, and neoplastic) when compared to adult patients of hydrocephalus is more complicated and has significantly more developmental and cognitive morbidities [4]. The incidence of congenital hydrocephalus has been estimated to be about 0.5 cases per 1000 live births and the overall incidence of neonatal hydrocephalus is estimated to be about 3 to 5 cases per 1000 live births [5, 6]. The overall global hydrocephalus prevalence is 85/100,000. When stratified by age groups, the global prevalence of hydrocephalus is 88/100,000 in the paediatric population. The prevalence of hydrocephalus is significantly higher in Africa and South America when compared to other continents [7]. The pooled estimated incidence of congenital hydrocephalus is highest in Africa and Latin America (145 and 316 per 100,000 births, respectively) and lowest in the United States/Canada (68 per 100,000 births) [8]. As far as India (Chhattisgarh) is concerned, male to female ratio for congenital hydrocephalus is 3 : 2. Infective hydrocephalus occurs maximally in children aged 2 to 5 years, while neoplastic hydrocephalus occurs in children aged 5 to 10 years, and congenital hydrocephalus is documented in children aged 1–6 months [9].

The most common cause of acquired hydrocephalus in infants is intraventricular haemorrhage, usually due to premature birth. Older children typically present with a combination of headache, vomiting, cranial nerve signs, loss of developmental milestones, changes in vision, or papilledema. Disabilities associated with hydrocephalus depend on the patient's age. Infants may present with irritability, vomiting, headache, an abnormally increasing head circumference, bulging of the anterior fontanelle, splaying of the cranial sutures, downward deviation of the eyes (sun setting appearance), behavioural changes or decreased interest in feeding [10, 11]. Congenital and early-onset hydrocephalus can be prevented by supplementation with folic acid during pregnancy [12].

Hydrocephalus is the leading indication for paediatric neurosurgical care worldwide [13]. The increased intracranial pressure interferes with the function of the adjacent structures and can cause a range of impairments in brain function. A ventriculoperitoneal shunt is a cerebral shunt that drains extra CSF in hydrocephalus patients [3]. Complications of ventriculoperitoneal shunts include block, infection, shunt chamber migration, shunt tip displacement, shunt tract collection, and seizures [14]. The complications resulting from shunts implanted during infancy can lead to general movement dysfunction and can cause a decreased ability to appropriately interact with peers and understand social cues [15].

Research has shown that complications from shunts for infantile hydrocephalus can lead to lifetime disorders with comorbidities that impair social functioning and mobility. Previous literature suggested application of strengthening exercises for core muscles, upper extremities and lower extremities in a six-year-old boy with lumbar spina bifida with meningocele post resection and hydrocephalus post ventriculoperitoneal shunt placement. A therapeutic program comprising range of motion exercises, trunk control exercises, pelvic stability exercise, and educating parents about positioning and handling and coordination exercises improved the independence of the child [3].

Having a child with hydrocephalus presents significant challenges across various domains, including financial, physical, social, and psychological aspects, profoundly impacting parents. The diagnosis of hydrocephalus elicits feelings of fear, confusion, and helplessness as parents grapple with understanding the condition and its implications for their child's health and future. Uncertainty about the long-term prognosis leads to persistent anxiety, disrupting routines and affecting work and social activities. Neurosurgical treatment adds another layer of stress for both paediatric patients and caregivers [16, 17].

It has been documented that low income, a lack of health insurance, and providing home care for more than one person all contribute significantly to parental worry [18]. Given that the parents of these children are more anxious, a study introducing physiotherapy programmes into the lives of children with hydrocephalus and assessing anxiety as a key variable is needed.

Physical disability is the most common cause of poor quality of life in children with hydrocephalus. There is minimal to scarce literature on physiotherapy interventions especially in such children. Thus, this study is an attempt to investigate the effectiveness of physiotherapeutic interventions on the motor function in children with hydrocephalus, as well as their impact on the levels of anxiety among parents of affected children.

Materials and methods

Twenty-six post operated children with hydrocephalus were screened at the Outpatient Department and Inpatient Department of Paediatric Surgery Division of Department of Surgery, Guru Gobind Singh Medical College and Hospital, Faridkot and Outpatient Department of Physiotherapy, University College of Physiotherapy, Faridkot, Punjab. Twenty-two patients met the eligibility criteria and were enrolled in the study. The selected patients had a diagnosis of hydrocephalus (congenital/acquired, obstructive/non-obstructive) according to CT scan, ultrasound and MRI, confirmed by a paediatric surgeon. The patients were both males and females, aged below 10 years, which had undergone right ventriculoperitoneal shunting. Patients were included minimum 7 days and maximum 3 months post-surgery. Uncooperative patients, patients enrolled in another clinical trial, patients required immediate intensive intervention for safety reasons, patients with other neurological disorders such as spina bifida, cerebral palsy, seizures in combination of hydrocephalus

and patients whose parents did not provide consent to participate were excluded from the study. The ethical approval was granted by the Institutional Ethical Committee, Baba Farid University of Health and Sciences, Faridkot prior to the beginning of the study. The demographic profile and detailed medical history of the patients were taken through their parents' interviews as well as medical records. Written informed consent was obtained from the parents of each enrolled patient, explaining the nature of study thoroughly.

All the patients in both groups were assessed for motor function using Gross Motor Function Measure (GMFM-88), and the parents of all the patients were evaluated for levels of anxiety using State Trait Anxiety Inventory (STAI). The selected patients were randomly divided into two groups using computer generated table: Group A (n = 11) and Group B (n = 11). Group A received Bobath based Rehabilitation Program (BBRP)whereas Group B received Conventional Physiotherapy (CP) for a total of eight weeks, with one supervised session per week lasting for 60 minutes. This study included a rural population and it was challenging for parents and children to come daily for physiotherapeutic program in any setting; therefore, the parents of the children in both groups were taught exercises to perform at home for the rest of the week for a total of eight weeks program. Between therapy sessions, the parents would video call the therapist, and the therapist would also conduct video calls to assess compliance. All the subjects and their parents were re-assessed for the above variables after eight weeks of intervention completion in both the groups.

The motor function was assessed using Gross Motor Function Measure, which consists of 88 items grouped into five dimensions: lying and rolling; sitting; crawling and kneeling; standing; walking, running, and jumping. Items are scored on a four-point ordinal scale. For K-GMFM-88, the intraclass correlation coefficient (ICC) ranged from 0.978 to 0.995, and Spearman's correlation coefficient ranged from 0.916 to 0.997. Parents' levels of anxiety were assessed using State-Trait Anxiety Inventory (STAI), which was developed by Charles Spielberger in 1970. The STAI consists of a 20-item State Anxiety Scale (STAI- S) and a 20-item Trait Anxiety Scale (STAI-T). The STAI-S assesses the temporary anxiety evoked by a situation while the STAI-T assesses general anxiety levels. The STAI was established with the reliability at 0.850. The State Cronbach's alpha was 0.797 and Trait Cronbach alpha was 0.781.

The duration between the surgical intervention and the initiation of rehabilitation ranged from 7 days (minimum) to 3 months (maximum).BBRP comprised exercises for head control, functional reaching exercises, weight shifting in various positions, trunk turning, balance exercises, weight bearing exercises, stepping exercises, quadruped imbalances, and imbalances from the "kneeling" position. The nature of the exercises and the number of repetitions were based on the patient's ability and level of performance. A complete description of BBRP is provided in the Appendix 1. CP comprised exercises for muscle strengthening, postural maintenance, postural changes, bridging, sit to stands, calf raises, standing marches, and step ups. The nature of the exercises and the number of repetitions were also based on the patient's ability and level of performance. A complete description of CP is provided in the Appendix 2.

Two patients voluntarily discontinued the interventional program due to compliance-related issues and were considered dropouts. Thus, a total of 20 patients completed the study: Group A (5 males, 5 females) and Group B (7 males, 3 females).

The data were analysed using SPSS v. 26. The patients were assessed for homogeneity of age, height, weight, and BMI as well as for baseline GMFM-88, STAI-S and STAI-T scores. The differences among all the variables were not significant as illustrated in Table 1.

Table 2 shows the comparison of the mean GMFM-88, STAI-S and STAI-T scores before and after the intervention in two groups. The analysis of the GMFM-88, STAI-S and STAI-T scores using Student's t-test indicated significant difference ($p < 0.05$) at pre- (week 0) and post-intervention (week 8) in both groups.

The analysis of difference between the mean pre- and post-GMFM-88, STAI-S and STAI-T scores in groups A and B is provided in Table 3. A comparison of the GMFM-88, STAI-S and STAI-T scores revealed a statistically non-significant difference ($p > 0.05$) between groups A and B.

Discussion

Our study comprised a rural Indian population of children with hydrocephalus. A total of twenty-two patients with hydrocephalus were initially included in the study. However, two patients were unable to complete the intervention due to compliance-related issues. Thus, a total of twenty patients successfully completed the interventional program. In developed nations, children with hydrocephalus benefit from advanced diagnostics, timely surgical interventions, and structured rehabilitation, ensuring they reach early developmental milestones. In contrast, developing countries like India, especially in rural areas, often lack basic healthcare facilities, leading to delayed diagnosis and surgery for many children.

While urban and affluent families may access comprehensive care, children in remote and lower-income regions face significant barriers to rehabilitation, including insufficient facilities, long travel distances, and unreliable transportation. These challenges limit effective postsurgical rehabilitation and delay developmental progress, despite efforts by programs, NGOs, and government initiatives to improve access. The scarcity of rehabilitation units, compounded by the lower socioeconomic status of these families, restricts the availability of therapy sessions, as travelling to distant centres becomes impractical. Hence, this might be the reason that rehabilitation specialists cannot provide frequent therapy sessions for these children. Thus, the study interventions, which were implemented once a week, included supervised training sessions among rural patients.

Hydrocephalus leads to motor impairments, resulting in delayed developmental milestones such as sitting up, crawling, and walking. The evaluation of motor function in hydroceph-

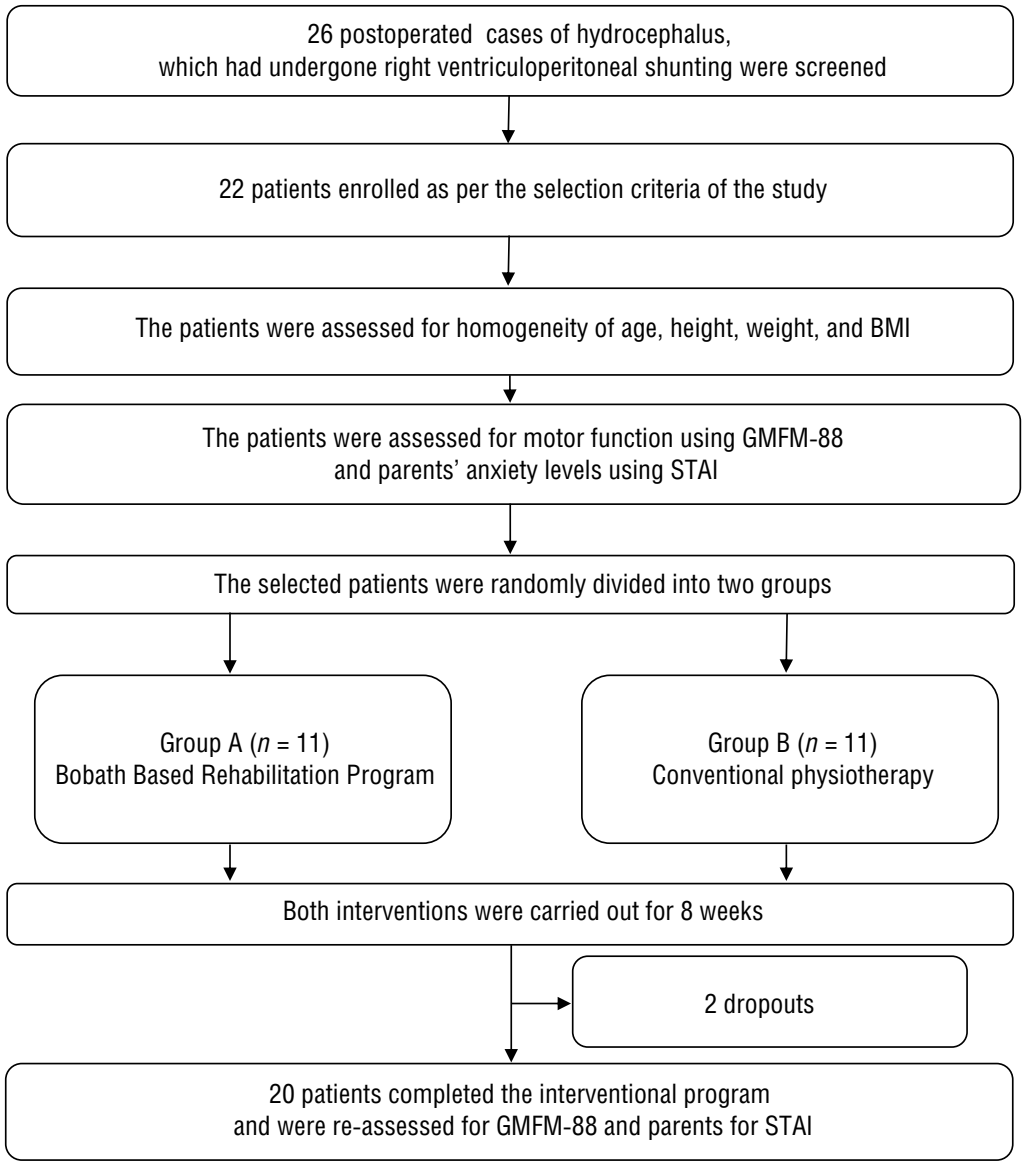

Fig. 1. Study flowchart.

Table 1. Comparison of the mean age, height, weight, and BMI, and baseline GMFM-88, STAI-S and STAI-T scores between groups A and B, *M* ± *SD*

Parameter	Group A (5 males, 5 females)	Group B (7 males, 3 females)	*t*	*p*
Age, months	30.90 ± 31.37	33.4 ± 30.5	–0.181	0.859
Height, cm	77.32 ± 22.9	78.78 ± 23.84	–0.140	0.890
Weight, kg	8.80 ± 2.83	10.00 ± 4.14	–0.757	0.459
BMI, kg/m^2	12.54 ± 2.62	14.07 ± 2.51	–0.985	0.350
GMFM-88, score	25.29 ± 26.70	33.23 ± 33.30	–0.588	0.564
STAI-S, score	57.2 ± 9.8	54.2 ± 10.2	0.67	0.511
STAI-T, score	56.4 ± 8.9	52.6 ± 11.0	0.85	0.406

Table 2. Comparison of the mean GMFM-88, STAI-S and STAI-T scores at pre- and post-intervention in groups A and B, *M* ± *SD*

Parameter	Group A		*t*	*p*	Group B		*t*	*p*
	week 0	week 8			week 0	week 8		
STAI-S, score	57.2 ± 9.84	37.1 ± 4.74	6.339	0.0001	54.2 ± 10.17	38.9 ± 3.63	5.093	0.001
STAI-T, score	56.4 ± 8.86	37.7 ± 3.94	6.121	0.0001	52.6 ± 11.02	38.4 ± 4.59	4.085	0.003
GMFM-88, score	25.3 ± 26.7	38.35 ± 31.07	–2.526	0.032	33.23 ± 33.3	45.18 ± 35.3	–7.827	0.0001

Table 3. Comparison of improvement in the mean GMFM-88, STAI-S and STAI-T scores at pre- and post-intervention in groups A and B, *M* ± *SD*

Parameter	Group A	Group B	*t*	*p*
GMFM-88, score	13.06 ± 16.35	11.95 ± 4.83	0.206	0.839
STAI-S, score	–20.10 ± 10.03	–15.30 ± 9.49	–1.099	0.286
STAI-T, score	–18.70 ± 9.66	–14.20 ± 10.99	–0.972	0.344

alus helps monitor the potential neurological damage caused by increased intracranial pressure. It aids in diagnosing and tracking the progression of the condition, guiding treatment decisions.

In this study, motor function was assessed in both groups using GMFM-88. Although GMFM-88 has not been validated in children with hydrocephalus, it is the most widely used scale in literature. It has been employed to measure motor function in children with cerebral palsy, Down syndrome, and spinal cord diseases [19–21]. D.J. Russell et al. reported that the GMFM-88 might be used to assess functional improvement in individuals other than those with CP [21]. A study performed by K.H. Lee et al. showed that intensive neurodevelopmental treatment was effective not only for managing developmental disabilities without CP but also for addressing them in CP [23].

The GMFM-88 scores improved in groups A and B who received BBRP and CP, respectively. The two interventions have their benefits in improving gross motor function in children with hydrocephalus. They can be customized to address the specific needs of children with hydrocephalus, such as muscle weakness, impaired coordination, and balance issues. This personalized approach optimizes the intervention effectiveness by directly targeting the areas of difficulty experienced by each child. Moreover, these therapeutic approaches engage mechanisms of neuroplasticity through repetitive and task-specific exercises. By consistently challenging the brain with these activities, therapies stimulate the formation of new neural connections, facilitating improvements in motor function over time [24–27].

Furthermore, involving parents or caregivers in the therapy process is crucial for maximizing its benefits. Educating parents about therapeutic techniques and providing them with a home program empowers them to reinforce therapy goals outside the clinical setting. This continuity of care promotes progress in motor function and ensures that the benefits of treatment extend beyond therapy sessions. Additionally, analysis revealed that there was no significant difference in improvement between the two groups, indicating that both interventions are equally effective and that none are superior to one another.

Parents of children with hydrocephalus experience profound anxiety due to uncertainties about the condition's progression, the effectiveness of treatments, and potential complications, as well as with the demanding daily care and lifestyle adjustments needed. Financial concerns about the high costs of treatment add to their stress. They often feel isolated socially and emotionally overwhelmed by their child's health challenges, including fears of developmental delays or disabilities, which can impact the entire family dynamic and further intensify their anxiety.

In a study performed by F.B. Mwiinga et al., parents reported having feelings of anxiety, sadness, stress, and depression as a result of caring for a child with hydrocephalus. In the present study, the level of anxiety in parents of children with hydrocephalus was evaluated using STAI-S and STAI-T, with improvement observed in the STAI-S and STAI-T scores in both groups [28]. A pivotal reason that parents find hope in their child's progress is witnessing them achieving milestones that were previously deemed unattainable, serving as poignant symbols of potential improvement and resilience.

Witnessing tangible growth in their child's motor abilities might help reduce parental worry by instilling hope and providing a sense of relaxation [29].The active involvement of parents in home-based therapy corresponds with recent studies indicating that educating parents about therapeutic strategies develops a sense of control and can lead to improved psychological outcomes [30].

As highlighted in the literature, parents' and therapists' supportive interaction also probably helped lower anxiety. It has been demonstrated that parents who receive effective communication and empathy from healthcare professionals feel less alone, more supported, and validated, all of which considerably reduce anxiety [31]. Engaging parents in a network of shared experiences and offering social support is consistent

with research showing that these components lessen feelings of loneliness and emotional stress [32].

One notable strength of this study is its focus on a rural population, which addresses a gap in the current literature, as no previous studies have specifically explored this demographic. The study was delimited geographically to rural areas around Faridkot. Furthermore, due to compliance and epidemiological issues, the sample size was small. Larger, randomized studies are needed to validate these findings and investigate the long-term effects of both interventions on motor function and level of anxiety in parents. Exploring barriers to rehabilitation access and developing community-based intervention approaches could also help decrease healthcare gaps in remote communities. Training general physiotherapists to deliver both therapies efficiently could maximize access to rehabilitation services in areas with inadequate healthcare infrastructure. Thus, tailored, locally achievable therapies can help children with hydrocephalus in underprivileged areas, reducing the gaps in rehabilitation services that are frequently seen between urban and rural populations [33].

Conclusion

Bobath Based Rehabilitation Program and Conventional Physiotherapy are effective interventions for improving motor function in children with hydrocephalus and in reducing levels of anxiety in their parents

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Appendix 1. Bobath Based Rehabilitation Program

1. Head control by stroking at the middle of the posterior aspect of neck. The child can be seated on the therapist's lap, facing the therapist, and alternately lowered slowly backwards and side-to-side. This action helps stimulate head righting and strengthens the neck and abdominal muscles.
2. Active movements such as reaching to toys in different directions from different developmental positions help stimulate head and trunk control and facilitate trunk elongation.
3. Reaching activities involving sitting (supported or unsupported) to toys in different directions may assist in head control, trunk elongation and rotation, and development of sitting control.
4. Weight shifting in various positions and through therapeutic handling is important to enhance the development of early head and trunk control.
5. Grasping.
6. "Parachute reactions", that is the ability to protect oneself in case of fall.
7. Trunk turning.
8. Equilibrium reaction in case of fall.
9. Equilibrium control during movement.
10. Neck holding exercises on the foam roller.
11. Activities on the foam roller in neurodevelopmental treatment.
12. Vestibular and proprioceptive training on balance board and exercise balls of different sizes, dynamic balance training and proximal stabilization in sitting, kneeling, and standing positions (eyes open and closed).
13. Balance exercises in front of the mirror, standing on one foot to improve the proprioceptive input (eyes open and closed).
14. Weight bearing exercises in the sitting, crawling, kneeling, and standing positions for equal weight transfer on both lower extremities without interfering with postural control.
15. Functional reaching and ball throwing-keeping exercises in various directions.
16. Stepping exercises in different directions and on different grounds.
17. Quadruped imbalances. Execution: a patient is positioned on all fours, a therapist imbalances them by pushing them sideways and backwards from the shoulder and sideways and forwards from the pelvis.
18. Imbalances from the "kneeling". Execution: with the patient supported on their knees, the therapist imbalances them from all directions.
19. The servant knight position. Execution: a patient loads on one knee, the contralateral lower limb performs a triple flexion (flexion at hip level, flexion at knee level and flexion at ankle joint level), the servant knight position.

Appendix 2. Conventional physiotherapy

1. Muscle strengthening:
2. Isotonic contractions of shoulder flexors, extensors, abductors, internal and external rotators.
3. Isotonic contractions of elbow flexors and extensors (with a child in sitting position on a mat or chair).
4. Isotonic contractions of trunk flexors and extensors with a child in a supine or prone position.
5. Postural maintenance (e.g., sitting, crawling, kneeling, standing).
6. Postural changes (e.g., rolling, transition from supine to sitting, from prone to crawling, from crawling to kneeling).
7. Bridging. A patient in a supine position with knees bent to 90 degrees. A patient pushes through feet on flat surface to raise pelvis to neutral position and slowly returns pelvis to the mat.
8. Sit to stands. A patient in a seated position with both feet planted on the floor, hips, and knees in 90 degrees of flexion. A patient stands and slowly descends back to a seated position.
9. Calf raises. A patient standing in parallel bars both feet used to raise heels off floor and back to neutral position.
10. Standing marches. A patient standing in parallel bars, slowly alternates lifting knee to 90 degrees of hip flexion.
11. Step ups. A patient standing in parallel bars, steps up onto raised platform alternating leading leg.
12. Side step-up. A patient standing parallel to one side of parallel bars, steps sideways onto raised platform and off platform on opposite side. A patient sidesteps up and over raised platform, going back and forth.
13. One leg stand. A patient starts by standing facing the wall, with arms outstretched and fingertips touching the wall. A patient lifts one leg, keeping the hips at the level and keeps a slight bend in the opposite leg. Gently place foot back on the floor.

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Young-Onset Amyotrophic Lateral Sclerosis: Genetic Structure and Phenotypic Features

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Abstract

Introduction. *Young-onset amyotrophic lateral sclerosis (yALS) is a rare neurodegenerative disease characterized by the onset of clinical manifestations before the age of 45. The global prevalence, incidence, and genetic structure of yALS remain largely unknown, and the diagnosis is based primarily on clinical presentation, neurophysiologic findings, and molecular genetic analysis.*

Aim. *The aim of this study was to analyze cases of yALS in the Russian Center of Neurology and Neurosciences.*

Materials and methods. *A total of 365 ALS cases were analyzed, of which 47 (12.8%) patients met the criteria for yALS based on the age of onset and were included in this study. All patients underwent the necessary diagnostic procedures to exclude or establish a diagnosis. The coding sequence of the SOD1 gene was analyzed, and the size of the tandem hexanucleotide repeats $(GGGGCC)_n$ in the C9orf72 gene was evaluated. In some cases, massive parallel sequencing was performed.*

Results. *Mutations in causative ALS genes were detected in 15 (32%) patients: in 15% of cases, variants were found in the coding sequence of the SOD1 gene and 3' untranslated region, and in 8.7%, hexanucleotide repeat expansions $(GGGGCC)_n$ were found in the C9orf72 gene. In addition, in 4 (8.5%) yALS cases, mutations in the FUS, UBQLN2, and FIG4 genes were identified using massive parallel sequencing.*

Conclusion. *Early identification of both sporadic and familial forms of yALS and determination of their molecular genetic patterns is critical for timely genetic counseling and identification of potentially treatable etiologies.*

Keywords: *young-onset amyotrophic lateral sclerosis; juvenile amyotrophic lateral sclerosis; SOD1; UBQLN2; FUS*

Ethics approval. Written informed consent was obtained from patients for participation in the study and for the processing and presentation of the data obtained. The study was approved by the Local Ethics Committee of the Russian Center of Neurology and Neurosciences (Protocol No. 2-5/23 dated 15 February 2023).

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Боковой амиотрофический склероз с ранним началом: генетическая структура и фенотипические особенности

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Аннотация

Введение. *Боковой амиотрофический склероз с ранним началом (рнБАС) представляет собой редкое нейродегенеративное заболевание, характеризующееся началом клинических проявлений до 45-летнего возраста. Глобальная распространённость, заболеваемость и генетическая структура рнБАС остаются в значительной степени неизвестными, а диагноз основывается преимущественно на клинической картине, нейрофизиологических исследованиях и молекулярно-генетическом анализе.*

Целью *данного исследования является анализ случаев рнБАС, наблюдавшихся в Российском центре неврологии и нейронаук.*

Материалы и методы. *Проанализировано 365 случаев БАС, по возрасту дебюта критериям рнБАС удовлетворяли 47 (12,8%) пациентов, которые были включены в настоящее исследование. Всем пациентам проводили необходимый объём диагностических вмешательств для исключения/установления диагноза, анализировали кодирующую последовательность гена SOD1 и исследовали размер области тандемных гексануклеотидных повторов $(GGGGCC)_n$ в гене C9orf72, в отдельных случаях проводили массовое параллельное секвенирование.*

Результаты. *У 15 (32%) пациентов обнаружены мутации в каузальных генах БАС: в 15% случаев – варианты в кодирующей последовательности гена SOD1 и 3'UTR-области, в 8,7% – экспансия гексануклеотидных повторов $(GGGGCC)_n$ в гене C9orf72; в 4 (8,5%) случаях рнБАС методом массового параллельного секвенирования выявлены мутации в генах FUS, UBQLN2 и FIG4.*

Заключение. *Ранняя идентификация как спорадических, так и семейных форм рнБАС и установление их молекулярно-генетических основ имеют решающее значение для своевременного генетического консультирования и выявления потенциально поддающихся терапии этиологий.*

Ключевые слова: *боковой амиотрофический склероз с ранним началом; ювенильный БАС; SOD1; UBQLN2; FUS*

Этическое утверждение. Получено письменное информированное согласие пациентов на участие в исследовании, обработку и представление полученных данных. Исследование одобрено Локальным этическим комитетом Российского центра неврологии и нейронаук (протокол № 2-5/23 от 15.02.2023).

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

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Introduction

Amyotrophic lateral sclerosis (ALS) is the main form of both sporadic and hereditary neurodegenerative diseases in adults, collectively known as "motor neuron disease" [1]. ALS is more common in men, with a sex ratio in most populations ranging from 1.2 : 1.0 to 1.7 : 1.0 [2]. Most cases are classified as sporadic ALS, while 10% of patients have a family history of the disease, with two-thirds of them having mutations in ALS-associated genes [3]. Although ALS most commonly manifests between the ages of 50 and 70, in 10% of cases, the disease begins at a younger age, with symptoms appearing before the age of 45, and is classified as "young-onset ALS" (yALS) [4]. This subgroup of the disease is rare, and consequently, studies focusing on this age group are extremely limited [5, 6]. However, yALS is considered a variant of "classic" ALS with combined upper and lower motor neuron involvement and is typically represented by sporadic cases. yALS is characterized by several clinical features, including a less common bulbar onset, a predominance of upper motor neuron involvement, and a longer survival [7, 8]. Clinical cohort studies show that the young-onset phenotype is an independent prognostic factor for longer survival [7].

An extremely rare subgroup, usually included in the cohort of patients with yALS, consists of cases of juvenile ALS (jALS), which is defined as a form with the clinical onset before the age of 25 [7]. The global prevalence and incidence of jALS remain largely unknown. In one of the few multicenter studies, conducted in Europe and evaluating data from 46 specialized ALS centers, the annual prevalence of jALS was estimated to be 0.008 cases per 100,000 population for symptom onset before the age of 18, which accounts for less than 0.1% of all ALS cases [9]. In a Portuguese cohort of patients with yALS, jALS accounted for 14.3% of cases [6]. Since the clinical implementation of massive parallel sequencing, knowledge of the pathophysiological mechanisms of jALS has increased significantly, and the natural history and clinical manifestations of the different monogenic forms of jALS are better understood.

There are several important differences between jALS and adult-onset ALS. First, jALS has a greater genetic contribution: approximately 40% of cases are caused by specific mutations in ALS-specific genes [10, 11] compared to approximately 10% in adult-onset ALS [11]. Mutations in *FUS*, *SETX*, and *ALS2* genes are most commonly associated with jALS. Associations with mutations in *SPG11*, *SOD1*, *SPTLC1*, *UBQNL2*, *SIGMAR1* and other genes have also been reported. Mutations in the *C9orf72* gene, which are the most common in adult-onset ALS, have not been reported in jALS. Second, jALS is characterized by a polysyndromic pattern. In addition to the upper and lower motor neurons, other parts of the central or peripheral nervous system are involved in the pathological process.

In yALS and jALS, the pathological process may involve various neuronal pathways and, less commonly, brain regions responsible for cognition and emotion, and rarely sensory cortical areas. Some genetic subtypes associated with various dysfunctions of neurons and glial cells have been identified [6]. The loss of motor neurons in yALS and jALS is due to multiple pathophysiological mechanisms similar to those in typical forms of sporadic and familial ALS [1]. There is considerable pathophysiological and genetic overlap between jALS and other hereditary neurological disorders, including hereditary spastic paraplegias, axonal forms of hereditary motor and sensory neuropathies, spinal muscular atrophies not associated with the 5q locus, autosomal recessive cerebellar ataxias, and hereditary neurometabolic diseases [12–14].

It is important to systematize the available data and update the current understanding of yALS in light of advances in diagnostic techniques and new therapeutic strategies based on antisense oligonucleotides and viral vectors in gene therapy. This study presents the most important clinical and genetic aspects of patients with yALS and potential directions for developing therapies to treat this severe disease.

The **aim** of this study was to analyze cases of yALS in the Russian Center of Neurology and Neurosciences.

Materials and methods

The study was conducted at Neurology department No. 6 and the Molecular genetic laboratory of Neurology department No. 5 of the Russian Center of Neurology and Neurosciences from 2022 to 2025. A total of 365 ALS cases were analyzed, of which 47 (12.8%) patients met the criteria for yALS based on the age of onset (i.e., before the age of 45) and were included in the study.

Each patient underwent the necessary set of diagnostic procedures to exclude or establish ALS according to the revised El Escorial [15] and Gold Coast 2019 [16] criteria. The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) [17] was used to diagnose cognitive disorders. In addition to the standard clinical, neurophysiological, and neuroimaging examinations, all patients underwent molecular genetic testing, including analysis of the coding sequence of the *SOD1* gene by direct capillary Sanger sequencing and amplified fragment length analysis of the tandem hexanucleotide repeat $(GGGGCC)_n$ in the *C9orf72* gene by polymerase chain reaction with an additional primer for the repeat region. In some cases, patients with yALS and jALS underwent massive parallel sequencing. The whole exome sequencing panel was obtained from patients at other clinics.

Identified pathogenic variants, probable pathogenic variants, and variants of uncertain clinical significance were validated by capillary sequencing on a Nanophore 05 genetic analyzer (NPF Syntol) in the Molecular genetics laboratory of Neurology department No. 5 of the Russian Center of Neurology and Neurosciences.

Written informed consent was obtained from patients for participation in the study and for the processing and presentation of the data obtained. The study was approved by the Local Ethics Committee of the Russian Center of Neurology and Neurosciences (Protocol No. 2-5/23 dated 15 February 2023).

Results

The study included 365 patients with confirmed ALS according to the current criteria. Of these, 47 (12.8%) patients met the age criteria for yALS, including 15 (32%) patients identified as carriers of mutations in ALS-associated genes (Table 1).

Seven (14.8%) *SOD1*gene mutations, including 6 in the coding region and one in the 3' untranslated region (3'UTR), were identified by coding sequence analysis. In addition, 5 (11%) cases were familial forms of *SOD1*-associated ALS, predominantly with an autosomal dominant inheritance, whereas the others were classified as sporadic (4%). The most common mutations in the *SOD1* gene, typical of yALS, included the *p.Asp91Ala* and *p.Asn140Asp* mutations previously described in other populations.

Based on the number of hexanucleotide repeats $(GGGGCC)_n$ in the *C9orf72* gene, an expansion was identified in 4 (8.5%) cases, with the number of repeats exceeding the threshold of 50 copies in all cases. Most studies define a pathological repeat threshold of > 35 [18, 19].

As for jALS, massive parallel sequencing was recommended for all 4 patients because this form of ALS is extremely rare. The results were obtained from the patients for genotype-phenotype correlation analysis and validation of the identified vari-

Table 1. Clinical and genetic profile of patients

No.	Age of onset / sex	Gene / locus	Exon / intron	Genetic variant	Amino acid substitution	Type of inheritance	Form of disease onset
1	38 / male	*c9orf72*/ 9p21.2	1	rs143561967	—	Sporadic	Cervicothoracic
2	36 / female	*c9orf72*/ 9p21.2	1	rs143561967	—	Autosomal dominant	Bulbar
3	44 / male	*c9orf72*/ 9p21.2	1	rs143561967	—	Sporadic	Cervicothoracic
4	33 / female	*c9orf72*/ 9p21.2	1	rs143561967	—	Sporadic	Bulbar
5	43 / male	*SOD1*/ 21q22.11	3'UTR	rs2516661924	—	Sporadic	Lumbosacral
6	35 / female	*SOD1*/ 21q22.11	5	rs1568811471	NP_000445.1: *p.Asn140Asp*	Autosomal dominant	Lumbosacral
7	37 / female	*SOD1*/ 21q22.11	5	rs1568811471	NP_000445.1: *p.Asn140Asp*	Autosomal dominant	Lumbosacral
8	41 / male	*SOD1*/ 21q22.11	4	rs80265967	NP_000445.1: *p.Asp91Ala*	Autosomal dominant	Lumbosacral
9	37 / female	*SOD1*/ 21q22.11	4	rs80265967	NP_000445.1: *p.Asp91Ala*	Sporadic	Lumbosacral
10	41 / female	*SOD1*/ 21q22.11	4	rs80265967	NP_000445.1: *p.Asp91Ala*	Autosomal dominant	Lumbosacral
11	37 / male	*FIG4*/ 6q21	5	rs1455052760	NP_055660.1: *p.Val157Met*	Autosomal dominant / incomplete penetrance	Cervicothoracic
12	24 / female	*SOD1*/ 21q22.11	5	*de novo*	NP_000445.1: *p.Glu134Gly*	Autosomal recessive	Lumbosacral
13	5 / male	*UBQLN2*/ Xp11.21	1	rs764837088	NP_038472.2: *p.Thr134Ile*	Sporadic	Associated with cognitive disorders
14	20 / male	*FUS*/ 16p11.2	14	rs387906627	NP_004951.1: *p.Arg495Ter*	Autosomal dominant	Bulbar
15	18 / male	*FUS*/ 16p11.2	14	rs387906627	NP_004951.1: *p.Arg495Ter*	Sporadic	Bulbar

ants. In 2 cases of jALS, a *p.Arg495Ter* mutation in the *FUS* gene was identified. In one case, the disease was hereditary, in the other it was sporadic with a *de novo* mutation not found in the proband's parents. Variants in the *SOD1* gene (*p.Glu134Gly*) for a familial form and *UBQLN2* (*p.Thr134Ile*) for a *de novo* mutation were also identified as the cause of the ASL.

In the structure of yALS phenotypes with identified mutations, the lumbosacral onset (47%) was predominant, which is typical for *SOD1*-associated cases. In 4 (27%) cases, a bulbar onset of symptoms was observed, which is typical of mutations in the *C9orf72* and *FUS* genes. In 3 (20%) patients, a cervicothoracic yASL was associated with mutations in the *C9orf72* and *FIG4* genes. An extremely rare jALS phenotype with a predominance of upper motor neuron involvement and multimodal cognitive impairment was associated with a mutation in the *UBQLN2* gene.

One patient with a confirmed yALS provided a result of whole exome sequencing that identified a heterozygous *p.Val157Met* mutation in the *FIG4* gene of uncertain clinical significance. Validation of the identified variant revealed that the *p.Val-157Met* mutation was heterozygous in the clinically healthy mother of the proband. A genetic structure of the identified mutations is presented in Figure 1.

Discussion

This study provides the only detailed description of the genetic structure and phenotypic features of a cohort of

patients with yALS in Russia. The predominant form of disease onset in patients with yALS was found to be spinal (67% of patients with identified mutations), affecting the lower limbs (lumbosacral form) and/or upper limbs (cervicothoracic form). Most cases showed a lumbosacral onset of symptoms. The bulbar form was found in 27% of patients with confirmed mutations in causative ALS genes. Large European population studies showed that the percentage of bulbar forms increases with the age of symptom onset, reaching 10–51% in men and 6–72% in women [20, 21]. A low incidence of bulba-onsetr forms in patients with onset before age 41 (mean: 16%) contrasts with a higher incidence in older patients (mean: 43% for onset after age 70) [7]. Our data are consistent with these studies and confirm a higher percentage of spinal-onset forms in the structure of yALS.

Four key causative genes are known to explain approximately 48% of familial ALS cases and approximately 5% of sporadic ALS cases in populations of European origin [11]. These genes are *C9orf72*, *SOD1*, *TARDBP*, and *FUS*. In this study, 15% of yALS cases were associated with mutations in the *SOD1* gene, and the most common mutations were *p.Asp91Ala* and *p.Asn140Asp* previously described in the European population. Lumbosacral ALS was the predominant clinical form. The data obtained are consistent with known studies [22], which report a higher percentage of spinal manifestations, especially with weakness in the lower limbs (lumbosacral form). However, a well-defined phenotype is only known for some mutations in the *SOD1* gene, such as the *D90A* mutation (one of the most common in Europe), which is characterized by a slow progression and lumbosacral onset.

The hexanucleotide $(GGGGCC)_n$ expansion in the non-coding region of the *C9orf72* gene is the most common cause of familial ALS [19]. According to studies conducted [23], the percentage of *C9orf72* mutations responsible for the development of ALS ranges from 7.84% to 41% in patients with a positive family history and is approximately 5% in sporadic cases, depending on the study population. Our study showed that mutations in the *C9orf72* gene were causative in 8.7% of cases, and only one patient had a significant family history, whereas in the other cases were sporadic. Bulbar ALS and cervicothoracic ALS were the most common forms associated with mutations in the *C9orf72* gene. Our data are consistent with one of the large cohort studies on the clinical and genetic features of *C9orf72*-associated ALS, which showed that the first symptoms often affect the bulbar level of the cerebrospinal axis, and the mean age of onset is 58 years, characterizing the hexanucleotide expansion in the *C9orf72* gene as an extremely rare cause of yALS [19].

In 2009, a rare autosomal dominant form of ALS associated with heterozygous pathogenic variants in the *FIG4* gene was first described in patients from North America [24]. *FIG4* encodes a phosphoinositide 5-phosphatase involved in the regulation of phosphatidylinositol-3,5-bisphosphate, which is an intracellular signaling lipid that plays a key role in the transport of endosomal vesicles. Loss of function leads to neurodegenerative processes in the central nervous system, including spinal cord motor neurons, as well as peripheral neuropathy, which has been demonstrated in animal models [25]. To date, at least 14 rare non-synonymous variants

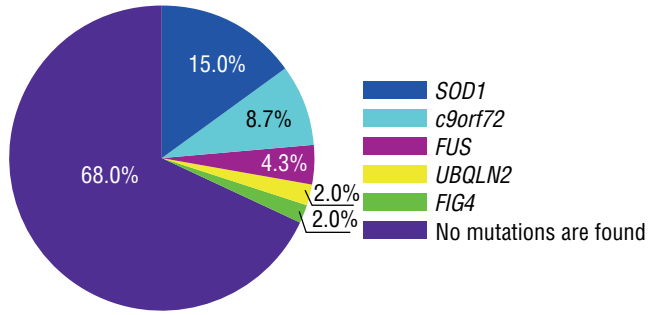

Fig. 1. Distribution of mutations in ALS causative genes in 47 patients with yALS observed at the Neurology Department No. 6 of the Russian Center of Neurology and Neurosciences.

in the *FIG4* gene have been identified, and the contribution of these variants to the pathogenesis of ALS remains controversial, because pathogenic *FIG4* variants were not detected in small patient cohorts, and some carriers of such variants showed incomplete penetrance (absence of clinical manifestations despite the presence of a mutation) [26, 27]. Incomplete penetrance probably explains the absence of clinical manifestations in the proband's mother, who was also a carrier of the heterozygous *p.Val157Met* mutation in the *FIG4* gene. The clinical phenotype in the proband was represented by signs of predominant upper motor neuron involvement, which is also a typical feature of *FIG4*-associated ALS [28], as well as by a cervicothoracic onset. The contribution of environmental factors as ALS risk modifiers is being investigated because even causative mutations may have incomplete penetrance. Potential exogenous factors associated with ALS include toxic factors (such as radiation, pesticides, organic solvents, β-methylamino-L-alanine, methylphenyl tetrahydropyridine, heavy metals, vaccination), infectious factors (such as retroviruses, herpesviruses), and environmental and lifestyle factors (such as dietary habits, low intake of polyunsaturated fatty acids, intense physical activity, sports, repeated traumatic brain injury, occupational exposure to electromagnetic fields, etc.) [1]. These factors can act as potential triggers for yALS in the presence of a genetic predisposition [1, 29].

The most common genetic basis associated with jALS includes mutations in the *FUS*, *ALS2*, *SETX*, and *SPG11* [29]. Autosomal recessive inheritance is more common in consanguineous families and has been described in patients with variants in *ALS2*, *SPG11*, *SIGMAR1*, *ERLIN1*, *VRK1*, *GNE*, *DDHD1*, and *SYNE1* genes. Autosomal dominant inheritance and sporadic cases with *de novo* mutations are more commonly associated with variants in the *FUS* [30], *SETX*, *SOD1*, *SPTLC1* [31], *SPTLC2*, *TRMT2B*, *BICD2*, and *TARDBP* genes. X-linked inheritance is typical of rare pathogenic variants in the *UBQLN2* gene [32], although it has been described in extremely rare cases for mutations in the *TRMT2B* gene [33]. Pathogenic variants in the *FUS* and *SOD1* genes represent the most common monogenic forms of familial jALS with a global prevalence, despite the fact that most cases of jALS are sporadic and are caused by *de novo* mutations [34].

The current literature shows that *SOD1* mutations are associated with three cases of jALS [35–37]. These cases are

characterized by disease onset in the late second or early third decade of life, accompanied by a combination of symptoms of both upper and lower motor neuron involvement. All patients progressed rapidly and developed respiratory failure. Two patients died less than two years after the onset of symptoms. These mutations were considered to be *de novo*, because no clear family history could be identified. Patients with *SOD1*-associated jALS had no signs of sensory or cognitive impairment. Electromyography showed active denervation and chronic neurogenic changes. Sensory conduction parameters remained normal. Neuropathologic examination revealed severe degeneration of the anterior horns of the spinal cord, Bunina bodies, and gliosis in the spinal cord and brain in one patient [37]. Ubiquitin-immunoreactive inclusions and the SOD1 protein were found in the neurons of the anterior horns. An important feature of *SOD1* mutations in jALS is that they are located near zinc-binding sites [35, 37] or in the β-structural domains of the protein [36] and in most cases differ from mutations detected in adult-onset ALS.

In our case of *SOD1*-associated jALS, the onset of symptoms was reported at the age of 24. The clinical presentation was characterized by predominant lower motor neuron involvement and a rapid progression of neurological deficit, leading to almost complete immobilization of the patient within 6 months of progression and death from severe respiratory failure 10 months after the onset of symptoms. The patient was a homozygous carrier of the *p.E134G* variant, whereas the proband's mother (a heterozygous carrier) showed no signs of the disease, which may indicate autosomal recessive inheritance. This clinical case is interesting because *SOD1* mutations most often have an autosomal dominant inheritance type and full penetrance [22], but some studies have shown that *SOD1*-associated ALS can also have a recessive inheritance type [38], and it is also known that incomplete penetrance of *SOD1* mutations is extremely rare [39]. This variant was previously described in one study [40] as a cause of sporadic ALS with a lumbosacral onset at the age of 34 and a slow progression rate.

UBQLN2 is a transport protein involved in the function of the ubiquitin-proteasome system. Disruption of the ubiquitin-proteasome system caused by UBQLN2 mutations is one of the most actively studied mechanisms of the pathogenesis associated with UBQLN2. However, the role of the UBQLN2 protein in disrupting the cytoplasm localization of TDP-43 protein and its aggregation into insoluble inclusions, which is typical of ALS, is well established. Recent studies show that *UBQLN2* mutations associated with ALS also lead to abnormal autophagy, neuroinflammation, and abnormal formation of stress granules [41]. Taken together, these data underscore the key role of UBQLN2 in the pathogenesis of ALS and frontotemporal dementia associated with abnormal metabolism of toxic proteins and failure of their clearance mechanisms.

In one study that included five families with rare cases of jALS, *UBQLN2* mutations were characterized by an X-linked dominant inheritance pattern and also manifested in disease forms combined with dementia [32]. The age of clinical manifestation in *UBQLN2*-associated ALS ranged from 16 years to 71 years. The mean age of onset was 33.9 ± 14.0 years in men and 47.3 ± 10.8 years in women. The mean duration of the disease was about four decades, indicating its slow progression. Frontotemporal dementia is most often associated with *UBQLN2* mutations. Of 40 patients with *UBQLN2* mutations, three had disease onset before the age of 24. One patient had the classic presentation of ALS, another patient had a combination of ALS and frontotemporal dementia, and the third patient had a combination of upper motor neuron signs and dementia. Spinal cord pathomorphology in two patients showed degeneration of anterior horn neurons, atrophy of corticospinal tracts, and severe astrocytosis.

Our case presented a pediatric onset of ALS at the age of 5–6 years with delayed psychomotor development, hand tremor (probably due to muscle weakness) and calf muscle spasms with gradual addition of leg weakness over 10 years. The rate of disease progression in this clinical case can certainly be considered slow, which is consistent with the literature data, and the prognosis can be considered favorable, also due to the absence of respiratory dysfunction. A characteristic feature of our case is the combination of multimodal cognitive impairment, lower motor neuron involvement, which is clinically manifested as mild tongue tremor and marginal hypotrophy, cramps and spontaneous fasciculations in the arms, legs and abdominal muscles, and neurophysiologically manifested as a long-term (for several years) slowly progressive, generalized peripheral motor neuron involvement with a strong predominance of the reinnervation process over denervation, and upper motor neuron involvement manifested as increased deep tendon and periosteal reflexes and mild spastic hypertonia in the legs.

The *FUS* gene is considered one of the most frequent causes of jALS [34]. However, *FUS*-associated cases show considerable phenotypic variability, ranging from classic adult onset to aggressive forms with onset in childhood. Both in juvenile and pediatric populations, the disease with mutations in the *FUS* gene is generally more malignant and rapidly progressive. The pediatric group shows an extremely limited number of genes associated with classic ALS, and this disease is rare and often underestimated in the differential diagnosis of motor neuron diseases in children. However, cases associated with *FUS* mutations are disproportionately represented in this age category.

The reasons why the same gene can cause both an aggressive, early (pediatric) form of ALS and a classic adult-onset form remain unclear. The *FUS* gene is located on chromosome 16 and encodes a protein involved in some important processes related to the regulation of DNA and RNA functions. The literature suggests that the variability of clinical phenotypes may be related to the location of mutations within different functional domains of the *FUS* gene.

Analysis of 38 published cases of *FUS*-associated jALS showed that most of them are caused by *de novo* mutations [42]. The *FUS* mutations associated with jALS differ from *FUS* mutations typical of later-onset ALS, although both are often located in the C-terminal fragment of the protein [43]. The age of disease onset is usually 21 years. The clinical presentation of *FUS*-associated jALS includes signs of both lower and upper motor neuron involvement such as muscle weakness,

hypotrophy combined with spasticity and hyperreflexia. *FUS*-associated jALS is characterized by rapid progression with a fatal outcome due to respiratory failure within 1–2 years from the onset of symptoms. Although bulbar onset is usually associated with faster progression, no significant differences in survival between spinal and bulbar forms of ALS have been identified in young age [43]. In some cases of *FUS*-associated ALS, movement disorders are described, such as myoclonic jerks [44], tremors, and in even rarer cases, oculomotor disorders manifested as diplopia [45].

In two of our cases, a previously described pathogenic *p.Arg495Ter* mutation in the *FUS* gene was found, which leads to the premature appearance of a stop codon, resulting in the truncation of the C-terminal fragment of the FUS protein. The literature shows that this nucleotide variant is associated with an aggressive disease phenotype [46], although the molecular mechanisms of such a malignant clinical presentation currently remain unclear. In the first clinical case, the identified mutation appeared to be inherited from the father, who developed signs of bulbar and respiratory dysfunction at the age of 29, progressing steadily to a fatal outcome at the age of 35. In another clinical case, the identified mutation was not inherited from the parents and, according to the trio analysis, it was a *de novo* variant, which is also consistent with the literature, because most published cases of *FUS*-associated jALS are *de novo* mutations [42].

The main phenotypic difference in our cases of *FUS*-associated jALS is that in the case of the hereditary disease, the onset of symptoms was represented by classic progressive bulbar palsy, which was later accompanied by facial muscle weakness and progressive neurogenic respiratory disorders, whereas in the sporadic *FUS*-associated jALS, the first symptom was facial asymmetry (facial diplegia) with later development of bulbar disorders.

The prognosis for ALS remains largely unpredictable. Although for most patients the course of the disease is similar to classical ALS, with a life expectancy from symptom onset to fatal outcome of 20–48 months [47], more than 10% of patients survive for more than 10 years [48]. Data on the natural history of the various genetic subtypes of jALS are extremely limited, and case series are the most valuable. In general, most young-onset and juvenile forms are characterized by a longer surviva;. However, even with relatively slow progression, patients experience a significant decrease in quality of life, significant loss of functional independence, and often require nutritional support, gastrostomy, and continuous respiratory support and mechanical ventilation [49]. Childhood onset, bulbar onset, and jALS with more complex neurological manifestations usually have a severe course and an unfavorable prognosis [29]. A rapid clinical progression is especially typical of jALS subtypes associated with *FUS* and *SOD1* mutations [29, 50].

Conclusions

Young-onset ALS is a rare neurodegenerative disease with many unmet diagnostic and therapeutic challenges. The diagnosis is based primarily on clinical manifestations, neurophysiological findings, and molecular genetic analysis. However, a definitive diagnosis is not necessarily based on a monogenic cause. Early identification of both sporadic and familial forms of yALS and determination of their molecular genetic patterns is critical for timely genetic counseling and identification of potentially treatable etiologies. Clinical trials are underway for some genetic causes associated with ALS. At the time of this publication, antisense oligonucleotide-based agents for the treatment of *SOD1*- and *FUS*-associated ALS are in phase III clinical trials and are showing promising results.

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Electrophysiological Markers of Chemotherapy-Induced Polyneuropathy

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Abstract

Introduction. *Electrophysiological testing is the gold standard for diagnosing polyneuropathy. However, its use in oncology practice for patients with chemotherapy-induced polyneuropathy (CIPN) remains limited and the value of its findings is not fully understood.*

The study was aimed *at identifying electrophysiological CIPN markers and evaluting their sensitivity and specificity.*

Materials and methods. *The study included patients (n = 71) over 18 years of age with solid tumor presenting with polyneuritic complaints following neurotoxic therapy with platinum-based agents and taxanes. Patients with known risk factors for polyneuropathy were excluded. Electrophysiological and clinical patient data were evaluated no earlier than 3 months following chemotherapy initiation.*

Results. *The study identified electromyographic markers: SRAR index (sural/radial ratio – the ratio between the action potential amplitudes of the sural and radial nerves) and the sural nerve action potential (SNAP), demonstrating equal sensitivity (73.7%) and high specificity (75% and 84.6%, respectively).*

Conclusion. *Electromyographic parameters such as SRAR and SNAP sural nerve can be utilized for the diagnosis and monitoring of CIPN in daily practice.*

Keywords: *electroneuromyography; chemotherapy-induced polyneuropathy; markers; SRAR; cancer*

Ethics approval. All patients provided their voluntary informed consent to participate in the study. The study protocol was approved by the Ethics Committee of the Clinical Research Center at Immanuel Kant Baltic Federal University (Conclusion No. 35 dated October 27, 2022).

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Электрофизиологические маркеры химиоиндуцированной полинейропатии

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Аннотация

Введение. *Электрофизиологическое исследование является стандартом при диагностике полинейропатии. Пока его использование ограничено в онкологической практике у пациентов с химиоиндуцированной полинейропатией (ХИПН), а ценность полученных результатов не до конца понятна.*

Цель *исследования – выявить электрофизиологические маркеры ХИПН и оценить их чувствительность и специфичность.*

Материалы и методы. *В исследование были включены пациенты (n = 71) старше 18 лет с солидными злокачественными новообразованиями, предъявляющие полиневритические жалобы после нейротоксической терапии с использованием препаратов платины и таксанов. Исключались пациенты с известными факторами риска развития полинейропатии. Изучали электрофизиологические, клинические данные пациентов не ранее чем через 3 мес после старта химиотерапии.*

Результаты. *В ходе исследования выявлены электромиографические маркеры: индекс SRAR (sural/radial ratio – соотношение между амплитудой потенциала действия икроножного и лучевого нервов) и потенциал действия икроножного нерва с равной чувствительностью (73,7%) и высокой специфичностью (75 и 84,6% соответственно).*

Заключение. *Для диагностики и мониторинга ХИПН в ежедневной практике могут использоваться электромиографические показатели, такие как SRAR и потенциал действия икроножного нерва.*

Ключевые слова: *электронейромиография; химиоиндуцированная полинейропатия; маркеры; SRAR; рак*

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common neurological complication in patients with malignant neoplasms [1]. CIPN symptoms may be heterogeneous, ranging from mild to severe manifestations that compromise patients' quality of life and require chemotherapy dose reductions or even complete treatment discontinuation, which, in turn, may negatively affect overall survival in cancer patients. CIPN symptoms may build up gradually and not always be overt at early stages, as well as progress after cessation of chemotherapy. CIPN diagnosis is established based on patient complaints and clinical assessment, despite electromyography (EMG), gold standard in diagnosing polyneuropathy (PNP) [2, 3]. Electrophysiological findings are objective markers for monitoring and understanding peripheral nerve disorders. However, most PNP patients with malignancies do not undergo this testing in routine clinical setting. This might be due to the limited availability, lack of CIPN diagnosis algorithms, practical and financial challenges during such testing overburdened oncology settings, and controversial data on the need of neurophysiology studies in this population [4–6]. Therefore, electrophysiological markers should be identified to assess the peripheral nerve status in patients receiving chemotherapy agents and to accumulate sufficient array of reliable data with further implementation in clinical practice.

The study was aimed at identifying electrophysiological CIPN markers and determining their sensitivity and specificity.

Materials and methods

The study included patients (n = 71) with solid tumors of gastrointestinal tract (GIT) (n = 34; 48%), respiratory system (n = 9; 12.6%), and pelvis (n = 28; 39.4%).

Inclusion criteria:
- age > 18 years;
- histologically confirmed solid tumors of GIT, respiratory system, and pelvis;
- polyneuritic complaints;
- first-time chemotherapy.

Exclusion criteria:
- a history of other PNPs and conditions (diabetes, paraproteinemic hemoblastoses, systemic connective tissue disorders, vasculites, hepatitis C, HIV;
- alcohol intake and use of medications (amiodarone, metronidazole, etc.) potentially inducing PNP.

All patients underwent standard neurological examination with assessment of superficial and deep sensation, reflexes, and muscle strength using the MRC scale [7]. PNP severity was assessed using the Neuropathy Dysfunction Score (NDS) [8], and the degree of neurotoxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, 2021 [9]. Nerve conduction studies were performed under temperature-controlled conditions using a Dantec Keypoint electromyograph (Medtronic) [10].

The EMG protocol evaluated long limb nerves, excluding median and ulnar nerves due to susceptibility to entrapment neuropathies. The following sensory nerve action potential (SNAP) parameters were evaluated: amplitude and conduction velocity; compaund muscle action potential (CMAP) included amplitude, distal latency, conduction velocity, F-wave minimal latency, response dispersion, and conduction blocks. The data were compared with normative values [11] and the sural/radial amplitude ratio (SRAR) was calculated, as this marker is reportedly the most senstive to damage of large fibers and independent of age and BMI based on the majority of findings [12–14]. Mean values from bilateral measurements were analyzed.

All participants provided informed consent. The study protocol was approved by the Independent Ethics Committee of the Clinical Research Center at Immanuel Kant Baltic Federal University (Conclusion No. 35 dated October 27, 2022).

Statistical analysis used StatTech v. 4.2.8 (StatTech) and GraphPad Prism v. 8.0.1 (Insightful Science). Quantitative parameters were assessed for normal distribution using Kolmogorov–Smirnov test. Normally distributed quantitative data were described as mean (M) ± SD (SD) with 95% confidence interval (CI); non-normally distributed data – using median (Me) and upper and lower quartiles [Q_1; Q_3]. Categorical variables were described with absolute/percentage values with Clopper–Pearson 95% CIs. Two groups for quantitative variables with normal distribution and equal variances were compared using Student's t-test, while non-normally distributed variables were analyzed with the Mann–Whitney U test.

To assess the diagnostic significance of quantitative predictors for outcome prognosis, ROC analysis was applied with cut-off determination based on the maximum Youden index value. Models with AUC > 0.7 and 95% CI > 0.5 were considered, requiring statistical significance of $p < 0.05$ for the constructed model.

Results

The mean age of the patients (49 women (69%) and 22 men (31%)) was 59.0 ± 10.1 years. Patients were examined 4.50 ± 1.02 months after chemotherapy; the number of chemotherapy courses was 5.2 ± 1.5. Patients predominantly received platinum-based drugs and taxanes (Table 1).

All patients included in the study presented with sensory complaints. During neurological examination with scale-based assessment, convincing changes consistent with CIPN were identified in 52 (73%) patients. Decreased and/or absent brachioradialis and Achilles reflexes of various sensory modalities with lower limb onset were reported. The clinical pattern and electrophysiological data demonstrated a length-dependent predominantly sensory polyneuropathy. Motor function impairment with reduced distal foot extensor strength was observed in only 5 (7%) cases during docetaxel and carboplatin therapy. According to the NDS, neuropathy progression (> 5 points) was seen in 52 (73%) patients, while NCI-CTCAE grade 1–2 neurotoxicity was detected in 62 (87.3%) patients.

The electrophysiology study demonstrated SNAP below normative values in 46 (65%) patients from the superficial peroneal nerve, 29 (41%) from the sural nerve, and 21 (30%) from the radial nerve. The CMAP (distal latency, amplitude, conduction velocity) in peroneal (*n. peroneus*) and tibial (*n. tibialis*) nerves remained within normal limits, thus excluded from further analysis.

Only superficial peroneal nerve SNAP amplitude exceeded normal values at 3.0 μV (Table 2). SRAR of 0.43 ± 0.31 exceeded previously reported parameters. Electromyography revealed no demyelination patterns per EFNS/PNS 2021 criteria [15].

When analyzing the relationship between electrophysiological data and the presence of CIPN and its severity according to the NDS scale, we found significant changes in all parameters ($p < 0.05$). These changes were more pronounced for the superficial peroneal nerve, sural nerve, and SRAR ($p < 0.001$) (Table 3). The data confirm that lower values of the analyzed electrophysiological parameters correlate with greater severity of CIPN.

To evaluate the sensitivity and specificity of sensory nerve action potential (SNAP) parameters in CIPN, ROC analysis was used. All models were statistically significant with acceptable area under the curve (AUC) and 95% CIs, but differed in sensitivity and specificity (Table 4). The most sensitive and specific parameters for assessing CIPN progression were the

Table 1. Treatment regimen

Regimen	Number of patients (%)
CAPOX(XELOX) (oxaliplatin + capecitabine)	17 (23.6)
FLOT (oxaliplatin + docetaxel + calcium folinate + fluorouracil)	6 (8.3)
FOLFOX (oxaliplatin + calcium folinate + fluorouracil)	11 (15.3)
Gemcitabine + cisplatin	1 (1.4)
Doxorubicin + cisplatin/doxorubicin + carboplatin	1 (1.4)
Docetaxel	1 (1.4)
Carboplatin/cisplatin + docetaxel	5 (7.1)
Carboplatin/cisplatin + paclitaxel/etoposide	5 (7.1)
Carboplatin + docetaxel	3 (4.2)
Carboplatin + paclitaxel	17 (23.6)
Carboplatin/cisplatin + paclitaxel	3 (4.2)
Etoposide + cisplatin/docetaxel/paclitaxel + carboplatin/paclitaxel + etoposide/docetaxel	1 (1.4)
Total	71 (100)

SNAP amplitude of the sural nerve and SRAR (Fig. 1), while the SNAP amplitudes of the superficial peroneal and radial nerves demonstrated lower specificity.

Discussion

This study evaluated neurophysiological parameters in patients with malignant neoplasms after chemotherapy, assessing their correlation with clinical manifestations to identify easily reproducible electrophysiological markers for neurophysiologists. Patients with known risk factors for CIPN [16–18] were intentionally excluded from the study.

The enrolled patients with solid tumors primarily received platinum-based agents and taxanes; CIPN was observed in 73% of cases although all patients reported complaints. Therefore, diagnosing CIPN based solely on subjective patient reports is unreliable, as previously indicated in studies [19, 20].

Based on clinical data and electrophysiological findings, we determined that sensory axonal length-dependent peripheral neuropathy predominated in patients, with no signs of demyelination. These results align with prior research [21–24]. According to most literature, CIPN manifests as a length-dependent axonal neuropathy; thus, a reduction amplitude SNAP sural nerve would occur earlier than in the superficial radial nerve. Consequently, changes in the SRAR index may characterize early-stage neuropathy. However, a prospective study by V. Myftiu et al. reported reduced motor nerve conduction velocities alongside axonal damage in platinum- and taxane-induced CIPN [25]. The observed conduction velocity decrease (< 25% of the lower normative limit) in typical axonal patterns might result from rapid loss of large myelinated fibers rather than primary demyelination [3]. Thus, axonal changes may affect conduction velocity without definitive demyelination.

Our mean SRAR values closely matched 1997 data (SRAR = 0.4) [13] but differed from 2005 results (0.21) [11, 12]. When performing ROC analysis and determining the cut-off point adjusted for the Youden index for SRAR, we obtained a value of 0.49, exceeding which was considered a CIPN manifestation, which is also closer to 1997 findings [13] than in the 2005 study. [13] than 2005 ones [11, 12]. This discrepancy

Table 2. Electrophysiological findings

Study nerve	Parameter	M ± SD (95% CI)/Me [Q_1; Q_3]	Normal
Deep peroneal nerve (extensor digitorum brevis muscle)	Distal latency, ms	3.67 [3.37; 4.09]	⩽ 6.5
	Amplitude CMAP, mV	3.41 ± 1.58 (3.03–3.78)	⩾ 2.0
	Conduction velocity, m/s	44.65 [42.75; 46.23]	⩾ 44
Tibial nerve (abductor hallucis muscle)	Distal latency, ms	3.49 ± 0.63 (3.34–3.64)	⩽ 5.8
	Amplitude CMAP, mV	9.07 ± 3.77 (8.17–9.96)	⩾ 4.0
	Conduction velocity, m/s	45.31 ± 3.98 (44.37–46.25)	⩾ 44
	Minimal F-wave latency, m/s	49.40 [46.25; 53.30]	⩽ 56
Superficial peroneal nerve	Amplitude SNAP, μV	3.00 [0.00; 7.15]	⩾ 6
	Conduction velocity, m/s	43.50 [0.00; 47.23]	⩾ 40
Sural nerve	Amplitude SNAP, μV	7.35 [3.67; 12.48]	⩾ 6.0
	Conduction velocity, m/s	46.55 [44.40; 48.42]	⩾ 40
Superficial radial nerve	Amplitude SNAP, μV	19.87 ± 8.39 [17.89–21.86]	⩾ 15
	Conduction velocity, m/s	55.00 [52.95; 57.65]	⩾ 50
SRAR		0.43 ± 0.31 (0.36–0.50)	⩾ 0.21 (0.4)

Table 3. Analysis of correlation between SRAR index/sensory nerve action potential amplitude and CIPN severity using NDS

Parameter	Neuropathy severity (NDS)	M ± SD (95% CI)/Me [Q_1; Q_3]	*p**
SRAR	Normal	0.65 ± 0.36 (0.48–0.83)	< 0.001
	Moderate	0.38 ± 0.25 (0.30–0.46)	
	Severe	0.23 ± 0.18 (0,11–0.35)	
Amplitude SNAP sural nerve, μV	Normal	14.59 ± 6.63 (11.40–17.79)	< 0.001
	Moderate	7.22 ± 5.08 (5.62–8.82)	
	Severe	3.58 ± 3.02 (1.55–5.61)	
Amplitude SNAP radial nerve, μV	Normal	24.15 [20.23; 27.38]	0.004
	Moderate	20.05 [12.20; 24.90]	
	Severe	13.90 [9.12; 16.92]	
Amplitude SNAP superficial peroneal nerve, μV	Normal	7.10 [4.35; 10.00]	< 0.001
	Moderate	2.30 [0.00; 6.45]	
	Severe	0.00 [0.00; 3.22]	

Note. Severity according to the NDS: normal — 0–4 points, moderate — 5–13 points, severe — 14–28 points.

Table 4. ROC analysis of sensory nerve motor potential amplitudes and SRAR index

Parameter	AUC	95% CI	Cut-off, μV	Sensitivity	Specificity
Amplitude SNAP					
superficial peroneal nerve	0.764 ± 0.070	0.628–0.901	4.30	78.9	67.3
sural nerve	0.835 ± 0.061	0.715–0.955	11.65	73.7	84.6
superficial radial nerve	0.705 ± 0.074	0.560–0.851	19.20	84.2	55.8
SRAR	0.778 ± 0.068	0.644–0.911	0.49	73.7	75.0

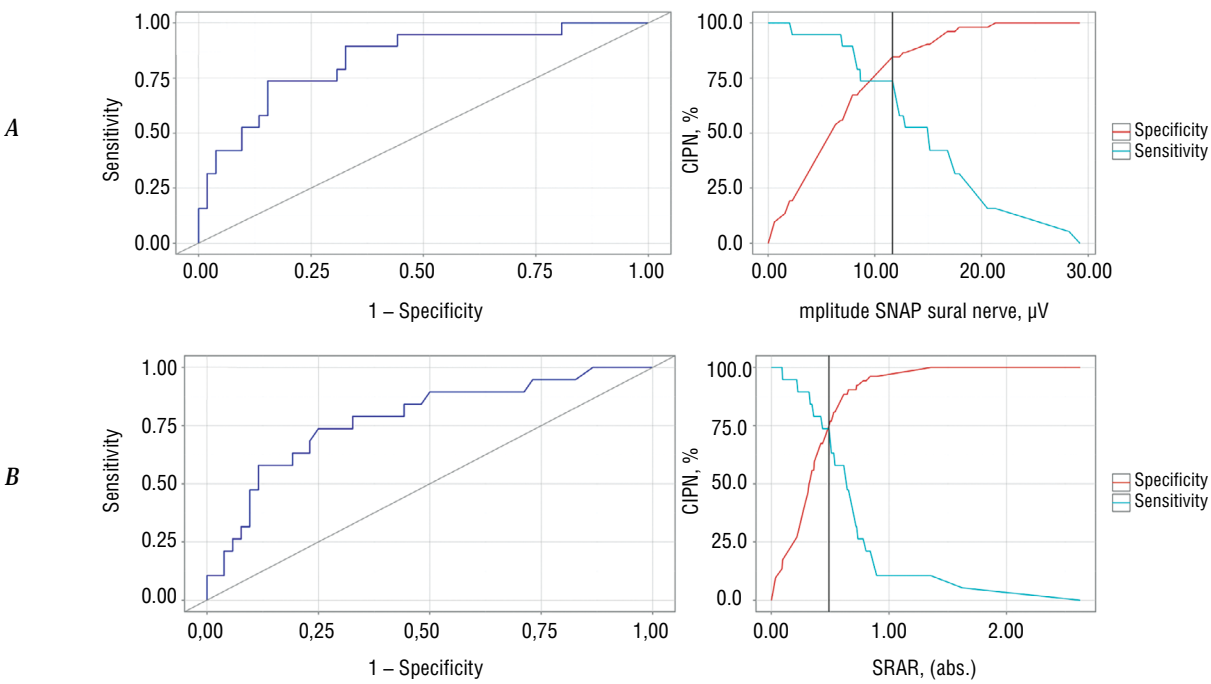

Fig. 1. ROC curve, model specificity and sensitivity, characterizing correlation between CIPN and amplitude SNAP sural nerve (*A*) and SRAR (*B*).

likely stems from study designs and cohorts: the 1997 research evaluated SRAR in patients with polyneuropathy, while the 2005 study involved healthy populations. Earlier studies reported no age-dependent SRAR variability [11–13], but a 2020 Indian study on 146 patients yeilded other normative values and demonstrated age effects [26]. Current literature lacks consensus on SRAR normative values and age influence, highlighting a study limitation requiring further investigation.

Our data show that all models were significant when evaluating sensitivity and specificity of electrophysiological markers for CIPN. SRAR (73.7 and 75.0%, respectively) and sural nerve action potential amplitude (73.7 and 84.6%) had the highest sensitivity and specificity, i.e., the sensitivity of these parameters was equal and specificity was 9.6% higher for the sural nerve. For action potentials of the radial and superficial peroneal nerves, specificity was below 70%, although sensitivity was high. Our findings partially contradict a prior study in patient with malignant neoplasms where SRAR sensitivity/specificity was 56%/77% versus SNAP amplitudes were 64%/70% [27]. That study concluded SRAR was less sensitive than sural SNAP amplitude despite 7% higher specificity, potentially due to unaccounted anamnestic neuropathy risk factors in the cohort.

Conclusion

Clinical CIPN assessment remains limited by patient-reported subjectivity and poor correlation with neurological exams. Electrophysiological markers (SRAR and sural SNAP amplitude) enable objective CIPN evaluation, facilitating early detection of large-fiber neuropathy in cancer patients to optimize treatment strategy and improve their quality of life. The impact of age on SRAR warrants further research in larger cohorts.

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Comparative Analysis of Neurogenesis and Cerebral Angiogenesis in the Hippocampal Neurogenic Niche in Animals with Two Experimental Models of Alzheimer's Disease

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Abstract

Introduction. *Various animal models are employed to uncover the mechanisms of Alzheimer's disease (AD) pathogenesis. Understanding brain damage pathogenesis in animal models of neurodegenerative diseases and identifying common patterns inherent to all relevant models is essential for adequate interpretation of findings, development of new models, as well as prevention and therapy strategies.*

The study *aimed to assess neurogenesis and remodeling of the microvasculature in the subgranular zone (SGZ) of the hippocampal dentate gyrus in mice with two AD models.*

Materials and methods. *The study employed two in vivo Alzheimer's disease models: 1) animals with intrahippocampal administration of amyloid-β protein fragment $A\beta_{25-35}$; 2) 5xFAD transgenic mice. Cognitive functions were evaluated using a passive avoidance test. On days 7 and 28 post-training, we assessed vascular network branching and density in the hippocampus using Evans Blue with subsequent software-based analysis of skeletonized images, analyzed proliferative activity of neuronal and endothelial cells, and their subpopulation composition using BrdU assay and multiparameter immunostaining of brain thin sections.*

Results. *Animals following intrahippocampal $A\beta_{25-35}$ administration demonstrated enhanced neurogenesis and neoangiogenesis over 28 days post-training, unlike 5xFAD mice which showed delayed and less pronounced proliferation of neuronal cells in the SGZ alongside transient increases in proliferating endothelial cells. Both AD models exhibited divergent changes in tip and stalk cell counts within the hippocampal SGZ, indicating non-productive neoangiogenesis confirmed by reduced vascular branching and density in the SGZ of animals from both models.*

Conclusion. *Cognitive deficits associated with experience-induced neurogenesis and cerebral angiogenesis mechanisms in the hippocampal neurogenic niche differ between AD models representing sporadic and familial variants, highlighting the need for fundamentally different approaches to pathogenetic therapy targeting non-productive angiogenesis and aberrant brain plasticity in various Alzheimer's type neurodegeneration scenarios.*

Keywords: *Alzheimer's disease models; neuroplasticity; neurogenesis; neurogenic niche; hippocampus; angiogenesis*

Ethics approval. The study protocol was approved by the Local Ethics Committee of the Russian Center of Neurology and Neurosciences (Protocol No. 5-3/22, 1 June 2022).

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Сравнительный анализ нейрогенеза и церебрального ангиогенеза в нейрогенной нише гиппокампа у животных с двумя моделями экспериментальной болезни Альцгеймера

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Аннотация

Введение. *Механизмы развития болезни Альцгеймера (БА) изучают с использованием разнообразных моделей на животных. Понимание особенностей патогенеза повреждения мозга у животных с разными моделями нейродегенерации и выявление общих закономерностей, присущих всем релевантным моделям, важно для корректной интерпретации полученных данных, разработки новых моделей и способов профилактики и терапии.*

Цель *исследования – оценить изменения нейрогенеза и ремоделирования микрососудов в субгранулярной зоне (СГЗ) гиппокампа головного мозга мышей с двумя моделями БА.*

Материалы и методы. *Для исследования были использованы две модели БА in vivo: 1) животные с интрагиппокампальным введением фрагмента β-амилоидного белка $A\beta_{25-35}$; 2) животные линии 5xFAD. Когнитивные функции оценивали с помощью теста условной реакции пассивного избегания. На 7-е и 28-е сутки после обучения выполняли оценку ветвления и плотности сосудистой сети в гиппокампе с помощью Evans Blue с последующим программным анализом скелетированных изображений, анализ пролиферативной активности нейрональных клеток, эндотелиальных клеток и их субпопуляционного состава – с помощью теста с BrdU и мультипараметрического иммуноокрашивания тонких срезов мозга.*

Результаты. *Животные после интрагиппокампального введения $A\beta_{25-35}$ демонстрировали усиленный нейрогенез и неоангиогенез в течение 28 сут после обучения, в отличие от животных с 5xFAD, у которых пролиферация клеток нейрональной природы в СГЗ носила замедленный и менее выраженный характер на фоне транзиторного увеличения количества пролиферирующих клеток эндотелия. У животных с разными моделями БА изменения количества tip- и stalk-клеток в СГЗ гиппокампа были разнонаправленными, что свидетельствует о несовершенном неоангиогенезе, подтверждаемом снижением ветвления и плотности сосудистой сети в СГЗ животных с обеими моделями БА.*

Заключение. *Формирование когнитивного дефицита на фоне различных по механизмам развития опыт-индуцированного нейрогенеза и церебрального ангиогенеза в нейрогенной нише гиппокампа у животных с моделями БА, характерными для спорадических и семейных вариантов, демонстрирует необходимость в разработке принципиально разных подходов к патогенетической терапии непродуктивного ангиогенеза и аберрантной пластичности мозга при разных вариантах развития нейродегенерации альцгеймеровского типа.*

Ключевые слова: *модели болезни Альцгеймера; нейропластичность; нейрогенез; нейрогенная ниша; гиппокамп; ангиогенез*

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Introduction

Neuroplasticity can be defined as the ability of the brain to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function and connections [1]. This phenomenon plays a crucial role in developing and maintaining neural circuits and cognitive functions. While normal neuroplasticity is essential for brain functioning, its impairments underlie the development of neurodegenerative diseases. Alzheimer's disease (AD) is characterized by accelerated brain aging and aberrant plasticity, associated with progressive neuronal degeneration and the formation of amyloid plaques and neurofibrillary tangles in the brain. Despite extensive researchs, AD pathogenesis remains understudied, and several leading theories of its etiology – including amyloid, calcium, and other hypotheses – remain under debate [2].

Over recent decades, AD pathogenesis research has employed diverse animal models: administration of neurotoxic agents (colchicine, scopolamine, atropine, aluminum salts) or amyloid-β oligomers into brain tissue; transgenic animals carrying mutations in three or five genes encoding proteins associated with Alzheimer'stype neurodegeneration (amyloid precursor protein, presenilin, tau protein); and animals with induced dysmetabolic disorders characteristic of AD (insulin resistance, mitochondrial dysfunction) [3].

Each model has specific strengths and limitations, determining their varying suitability for preclinical and translational research, including pharmacotherapy development [4]. This raises questions about the applicability of specific models for assessing key neurodegeneration mechanisms and the comparability of findings [5].

For instance, 5xFAD mice exhibit significant neuronal loss at 9–12 months of age, while amyloid-β accumulation and neuroinflammation in brain tissue are observed as early as 1.5–2.0 months [6]. Conversely, intracerebral administration (ventricles, hippocampus) of various amyloid-β isoforms (1–40, 1–42, 25–35) induces rapid neuroinflammation (within 3 days), microvascular damage, and cognitive impairment – effects particularly pronounced in aged animals [7].

Suppression of neurogenesis in neurogenic niches is observed in triple transgenic (3xTg) animal model during early stages of postnatal ontogeny (1–2 months after birth) and prior to the onset of cognitive dysfunction [7]. In 5xFAD mice characterized by progressive spread of neuritic dystrophy, gliosis, and amyloid-β accumulation in brain tissue (starting from the *subiculum* and extending to the hippocampus and cortex) [8], neurogenesis suppression becomes evident by 2 months after birth. Paradoxically, some transgenic animals with other Alzheimer's disease (AD) models exhibit intensified neurogenesis at 2–3 months of postnatal ontogeny [9]. As we previously demonstrated, intrahippocampal amyloid-β administration increased Pax6 and Nestin expression in the hippocampal subgranular zone (SGZ) by day 9 [10], followed by a prolonged decline in neurogenesis efficiency [11] accompanied by progressive local neuroinflammation [12].

In this context, studying mechanisms of aberrant plasticity in AD should be grounded in understanding specific features of pathogenetic brain damage mechanisms across different animal neurodegeneration models. However, identifying common patterns inherent to all (or most) relevant models is particularly critical for accurate interpretation of findings.

Neurogenic niches in the brain, particularly the hippocampal SGZ, represent a valuable and informative focus for investigating neuroplasticity, including in progressive neurodegeneration. First, changes in hippocampal neurogenesis are directly linked to cognitive functions, such as through mechanisms regulating engram cell populations or the excitation/inhibition balance in the hippocampus [13]. Second, alterations in hippocampal neurogenesis are clearly detectable during training and memory formation [14]. Third, the hippocampus is one of the most affected brain regions in AD [15]. Fourth, long-term plasticity mechanisms driven by neurogenesis efficiency require support from changes in local microcirculation and remodeling of the microvascular bed in the hippocampus, such as through neoangiogenesis and microvascular regression [16]. Notably, in the hippocampal SGZ – unlike the subventricular zone (SVZ) – angiogenic activity is inherently high, with clusters of proliferating endothelial cells directly contacting neural stem cells and exhibiting high sensitivity to regulatory molecules in the local microenvironment [16]. Thus, alongside neurogenesis mechanisms underlying long-term experience-induced plasticity [17], assessing microcapillary bed remodeling in this neurogenic niche may provide critical insights into thebrain plasticity under normal conditions and during neurodegeneration.

The study **aimed** to compare neurogenesis and remodeling of the microvasculature in the SGZ of the hippocampal dentate gyrus in mice with two AD models: 1) animals intrahippocampal administration of amyloid-β and 5xFAD transgenic mice.

Materials and methods

The study design is shown in Fig. 1.

We employed two *in vivo* models of AD.

The first model involved animals with intrahippocampal administration of the amyloid-β protein fragment $A\beta_{25-35}$. Male C57BL/6 mice aged 6 months and weighing 30–35 g (n = 39) underwent stereotactic surgery. Zoletil 100 (Virbac Sante Animale) and Xyla (Interchemie Werken "de Adelaar" BV) were used for anesthesia. A standard Zoletil 100 solution (500 mg in 5 ml) diluted 1 : 4 with saline was administered intramuscularly at a dose of 1.5 mg active substance per 25 g of mouse weight. Xyla was diluted 1 : 2 with saline and administered intramuscularly at 0.6 mg per 25 g of mouse weight. Under anesthesia, bilateral craniotomies were performed using a manipulator (Stoelting) according to the coordinates from the Mouse Brain Atlas (AP – 2.0; ML – 1.9; DV – 1.3). Then, 2 μL of 1 mM oligomerized $A\beta_{25-35}$ (Sigma-Aldrich Co.) in 0.9% NaCl solution was injected into the hippocampal CA1 region The $A\beta_{25-35}$ solution was prepared according to the manufacturer's instructions: Aβ was dissolved in 1 mL of 0.9% NaCl and incubated at 37°C for 4 days. Sham-operated control group animals (SO; 6 months; n = 34) were injected with 0.9% NaCl in the same volume at matching coordinates.

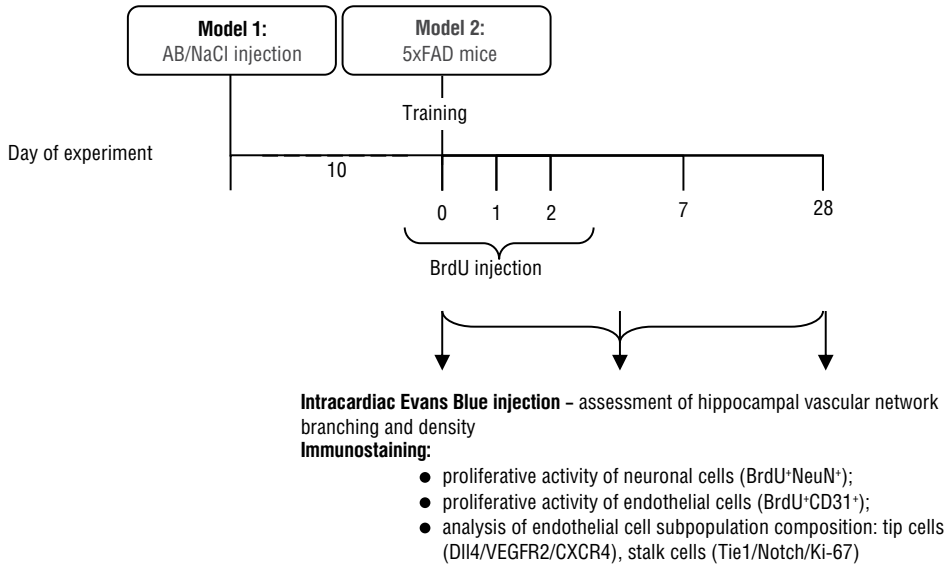

Fig. 1. General design of *in vivo* experiments using two AD models.
Model 1 – animals with intrahippocampal $A\beta_{25-35}$ injection (control – sham-operated animals injected with 0.9% NaCl solution); Model 2 – 5xFAD mice (control – intact C57BL/6 mice).

The second experimental *in vivo* AD model utilized 6-month-old male 5xFAD transgenic mice, strain B6SJL-Tg(APPSWFLon,PSEN1M146L,L286V)6799Vas (n = 21). The control group consisted of intact male C57BL/6 mice (6 months; n = 21).

All experiments complied with humane animal treatment principles and EU Directive 2010/63/EU on animal experimentation. Animals were housed in cages (⩽ 6 per cage) with ad libitum access to food and water under a 12-hour light/dark cycle. The studies were conducted in accordance with approval of the Local Ethical Committee (Protocol No. 5-3/22, June 1, 2022).

The Conditioned Reflex of Passive Avoidance test

Cognitive impairment was assessed using the Passive Avoidance (PA) test according to the standard protocol on day 1 after exposure to an inescapable aversive stimulus (0.2 mA electric current for 3 seconds through a metal floor grid upon entering the dark compartment), as well as on days 7 and 28 post-training. The time taken for the mouse to move from the illuminated compartment to the dark compartment was recorded.

Evaluation of neural and endothelial cell proliferation in the hippocampal neurogenic niche

Mice were intraperitoneally administered BrdU solution (50 mg/kg body weight) 1 hour after the training aversive stimulus, followed by a single BrdU injection every 24 hours for 2 days [18].

Immunostaining

At different time points (days 7 and 28 after PA training), 8 animals from each study group were euthanized by cervical dislocation. Brains were fixed in 4% paraformaldehyde (Wuhan Servicebio Co., Ltd), and 10 μm-thick cryosections were prepared using an FS800A cryostat (RWD). Sagittal sections were prewashed in phosphate-buffered saline (Rosmedbio) for 10 minutes, then in 0.1% Triton X-100 solution (Calbiochem Biochemicals) with 5% bovine serum albumin (BioFroxx) for 1 hour to block non-specific binding, followed by antibody staining. Antibodies were selected based on species specificity and applied according to manufacturer-recommended protocols: primary antibodies – anti-BrdU (Host–Mouse, 1 : 100, A1482, ABClonal); directly conjugated rabbit antibodies – anti-NeuN (1 : 100, FNab05669, FineTest); anti-CXCR4 (1 : 250, AF5279-F555, Affinity); anti-DLL4 (1 : 250, DF13221-F250, Affinity); anti-VEGFR2 (1 : 250, AF6281-F488, Affinity); anti-CD31 (1 : 250, AF6191-F555, Affinity); anti-TIE1 (1 : 250, AF4582-F555, Affinity); anti-Ki-67 (1 : 250, AF0198-F350, Affinity); anti-Notch (1 : 250, AF5307-F488, Affinity); secondary antibodies – anti-Rabbit (1:100, AS011, ABClonal); anti-Mouse (1 : 500, ab150116, Abcam). Sections were covered using fluorescence-preserving mounting medium "Fluoroshield Mounting with DAPI" (Sigma Aldrich).

For assessment of SGZ cell proliferation using BrdU, 26 μm-thick sagittal brain sections were prepared, and-$BrdU^+NeuN^+DAPI^+$- и $BrdU^+CD31^+DAPI^+$ cells were quantified. This method identifies progeny populations of proliferating NSCs/NPCs or endothelial cells activated on day 1 of the experiment (training) [18].

Digital images were acquired using an EVOS M7000 imaging system (Thermo Fisher Scientific) and processed in ImageJ using a plugin for fluorescent label quantification. Expression levels of these markers were characterized by the count of stained cells normalized per 100 $DAPI^+$ cells in the SGZ.

Evaluation of vascular branching and density in the hippocampus

One hour post-PA (day 10 of experiment), mice were intracardially administered 2% Evans Blue solution (6 μl/g body

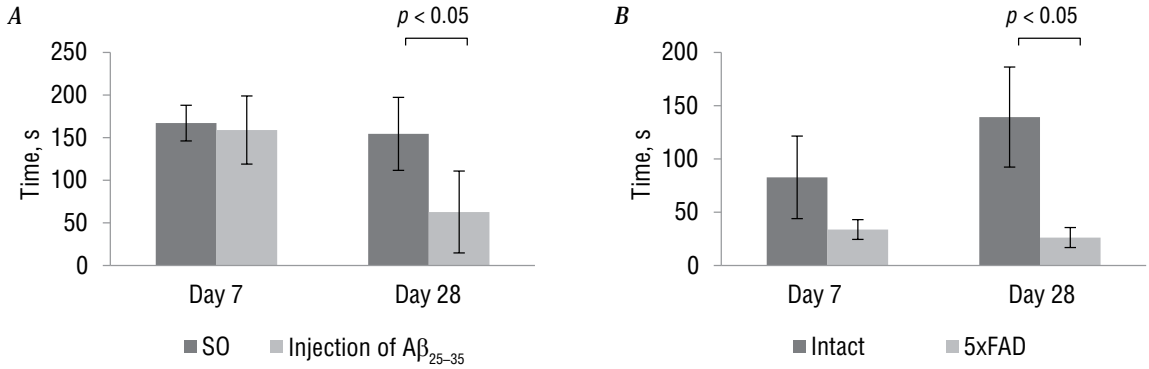

Fig. 2. Results of neurobehavioral PA testing in SO animals and animals with intrahippocampal $A\beta_{25–35}$ injection (*A*), intact animals and transgenic 5xFAD animals (*B*) on days 7 and 28 post-training, $p < 0.05$.

weight) following standard protocol [19]. After 5 minutes, animals were euthanized, and brains were extracted for angiogenesis analysis in thin sections. Microscopic images of sections were analyzed in ImageJ using the following protocol: images were binarized, background-cleared (Threshold), skeletonized (Skeletonize); skeletonized images were quantified using Analyze skeleton option (Shortest branch method) and Vessel Analysis plugin (Vascular Density option). Results were expressed as absolute values for vessel branch point counts in the region of interest, and as vessel length per unit area for vascular density assessment.

Statistical analysis

Statistical data processing utilized Statistica v. 13.3 software (StatSoft). Normality of data distribution was assessed usingthe Kolmogorov–Smirnov and Shapiro–Wilk test. The results were analyzed using the Mann–Whitney U test. The results were considered significant at $p < 0.05$. Data are presented as mean ± standard deviation.

Results

The mechanisms of brain plasticity are closely associated with neurogenesis and cerebral angiogenesis, demonstrating significant alterations during progressive neurodegeneration [19]. Plasticity related to brain development or acquired experience, along with adaptive plasticity inherent to the damaged brain, may influence angiogenesis and neurogenesis processes in different ways [20]. To assess neurogenesis and angiogenesis parameters in experience-induced plasticity within both AD models, we employed an aversive inescapable stimulus as a training stimulus. We found that animals in both models exhibited similar changes in cognitive dysfunction progression by day 28 following the first training session (Fig. 2), consistent with our prior findings using the amyloid-β intrahippocampal administration model [21]. Specifically, a sustained reduction in transition time to the dark compartment was observed in the PA test: $A\beta_{25–35}$-injected mice showed a decrease of 92 s, while 5xFAD mice demonstrated a 113 s reduction compared to control groups ($p = 0.0449$).

As we previously hypothesized [21], cognitive deficits by day 28 after the first training session may correspond to alterations in hippocampal neurogenesis processes, since the complete cycle from neural stem cell recruitment to the formation of a young neuron population takes approximately 4 weeks in mammals [22]. Therefore, we subsequently quantified proliferating neurnal cells whose mitotic entry was initiated during the first training session.

We found that the count of young $BrdU^+$ neurons in animals with intrahippocampal $A\beta_{25–35}$ administration was increased by 52% compared to controls ($p = 0.0449$) on day 7 after aversive stimulus presentation and showed further elevation by day 28 (Fig. 3). Concurrently, the count of $BrdU^+$ neuronal cells in 5xFAD line animals remained significantly lower than in both control groups and Aβ-injected animals at day 7, and subsequently increased without reaching values characteristic of neurodegeneration induced by intrahippocampal amyloid-β administration (Fig. 3). Transgenic animals showed no evidence of enhanced neurogenesis in the SGZ (Fig. 3) on day 7 post-cognitive stimulus presentation, while amplified proliferation of neuronal cells was detected only by day 28 (3.75-fold increase; $p = 0.0450$), potentially due to a mismatch between neurogenic demand and impaired plasticity mechanisms.

Overall, post-training animals with intrahippocampal $A\beta_{25–35}$ administration exhibited enhanced neurogenesis, unlike 5xFAD animals demonstrating delayed and less pronounced neuronal proliferation — likely attributable to neurodegeneration initiated during embryogenesis and depletion of neural stem/neuronal progenitor cell pools.

Cognitive reserve depends on adequate neurovascular coupling, microcirculation in active brain regions, while hippocampal vascularization significantly modulates cognitive performance [23, 24]. We therefore proceeded to analyze changes in local angiogenesis within the brain neurogenic niche. Similar to the assessment of $BrdU^+$ neuronal cells, we analyzed the count of endothelial cells entering mitosis in response to a training (aversive inescapable) stimulus.

We found that the count of proliferating $BrdU^+/CD31^+$ endothelial cells in the SGZ of the brain in animals with intrahippocampal $A\beta_{25–35}$ administration was initially 4.4 times higher than controls ($p = 0.0445$) and remained 95% greater than SO animals by day 28 (Fig. 4), consistent with neurogenic event dynamics. In 5xFAD transgenic animals, angiogenesis

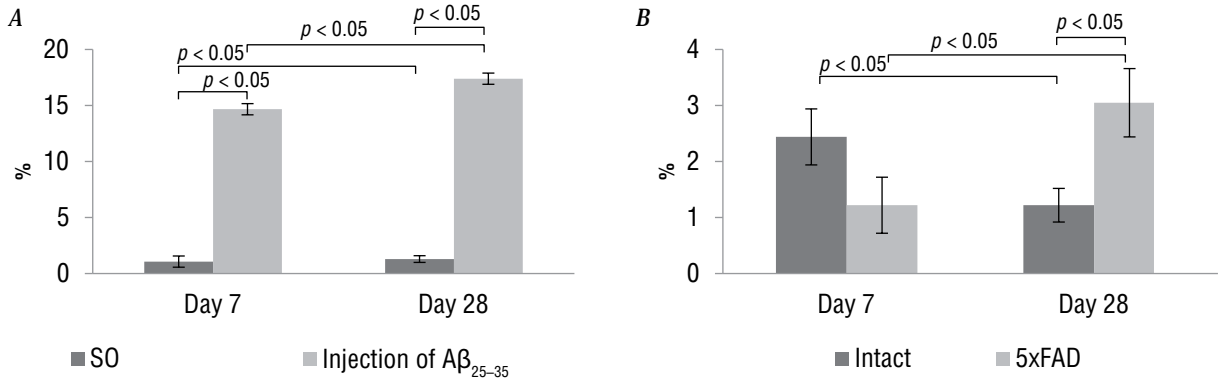

Fig. 3. Changes in the count of BrdU$^+$ neurons (NeuN$^+$) in the SGZ of SO animals and animals with intrahippocampal Aβ$_{25–35}$ injection (*A*), intact and transgenic 5xFAD animals (*B*) on days 7 and 28 post-training.
Data are normalized to 100 DAPI$^+$-cells and are presented as mean and standard deviation, $p < 0.05$.

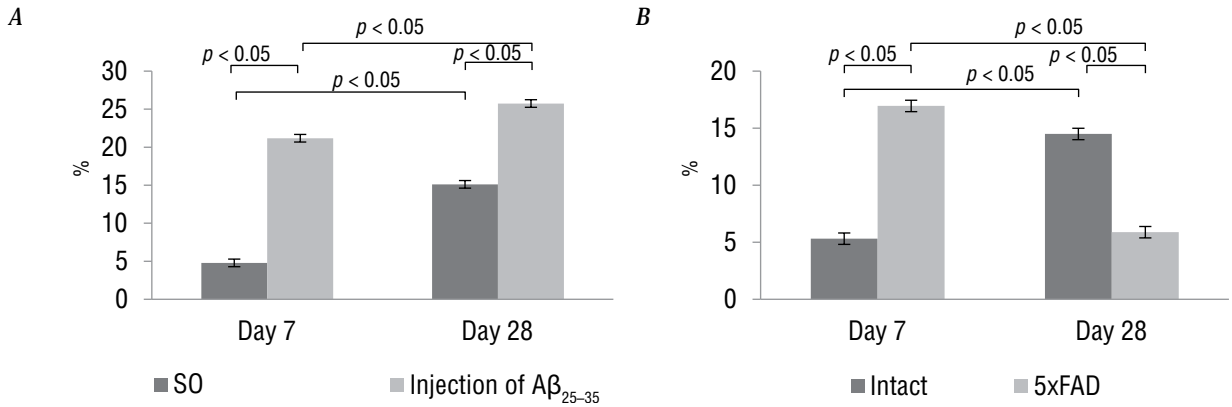

Fig. 4. Changes in the count of BrdU$^+$-endothelial cells (CD31+) in the SGZ of SO and animals with intrahippocampal injection of Aβ$_{25–35}$ (*A*), intact and transgenic 5xFAD animals (*B*) on days 7 and 28 post-training.
Data are normalized to 100 DAPI$^+$-cells and are presented as mean and standard deviation, $p < 0.05$.

in the SGZ showed transient enhancement (BrdU$^+$ endothelial cell count nearly tripled by day 7 post-training). However, by day 28 — corresponding to cognitive dysfunction manifestations — we observed a significant two-fold reduction in proliferating endothelial cells ($p = 0.0445$; Fig. 4).

Thus, in SO animals and those with intrahippocampal β-amyloid injection into the SGZ, a significant increase in the count of proliferating cells of neuronal and endothelial origin — whose mitotic entry was initiated on day 1 of training — was observed post-training. In 5xFAD line animals, the count of BrdU$^+$ neuronal cells increased by day 28, while the count of BrdU$^+$ endothelial cells significantly decreased by this time, indicating a mismatch between the demand for experience-induced angiogenesis and neurogenesis during prolonged progression of Alzheimer's type neurodegeneration.

Stimulation of angiogenesis and remodeling of the microvasculature are accompanied by changes in endothelial subpopulations, with the emergence of phenotypically and metabolically distinct tip and stalk cells that respectively mediate migration and new capillary wall formation [25]. To investigate abnormal angiogenesis features in two AD models, we analyzed the presence of the following endothelial cell types in the SGZ of experimental animals: CXCR4/Dll4/VEGFR2 tip cells and Tie1/Notch/Ki-67 stalk cells, consistent with their documented expression profiles as participants in neoangiogenesis [26].

The SO animals showed no significant changes in endothelial tip and stalk cell counts in the SGZ during post-training follow-up, whereas animals with intrahippocampal β-amyloid injection demonstrated a significant increase in tip-cell count by day 28 (Fig. 5). In intact animals, endothelial tip and stalk cell count increased by day 28, with the stalk cell profile correlating with BrdU$^+$CD31$^+$ cell changes (as stalk cells, unlike tip cells, retain proliferative capacity) [27]. 5xFAD mice exhibited no increase in tip-cell count between days 7 and 28 of follow-up, along with reduced stalk cell counts and significantly lower total endothelial cells of both activated phenotypes compared to controls (Fig. 5).

Thus, animals with different models of AD demonstrate multidirectional changes in the count of tip and stalk cells in the hippocampal SGZ, collectively indicating impaired neoangiogenesis. This conclusion is supported by our observed reduction in vascular network branching and density in the brains of animals with both models of Alzheimer's type neurodegeneration compared to intact controls on days 7 and 28 post-training (Figs. 6, 7).

Discussion

We analyzed the features of proliferative activity in neuronal and endothelial cells within the SGZ, as well as the characteristics of neoangiogenesis and remodeling of the microvasculature in this neurogenic niche of the brain in animals with two models of AD: an intrahippocampal amyloid-β administration model (simulating sporadic AD cases) and a transgenic 5xFAD mouse model characterized by multiple mutations associated with familial AD forms in humans [28].

We found that the development of cognitive dysfunction during the PA test used as an animal training model in 5xFAD mice coincides chronologically with our previous observations in mice receiving intrahippocampal $A\beta_{25–35}$ injections [29]: both experimental groups demonstrated cognitive deficits by day 28 post-initial training in the PA test, aligning with the 4-week cycle of induced neurogenesis in the hippocampal SGZ [22].

However, in both control groups, the implemented training protocol did not induce significant changes in the number of proliferating neuronal cells in the SGZ, whereas experimental modeling of Alzheimer's type neurodegeneration revealed intensified cell proliferation reaching peak levels by day 28. This observation aligns with our and others' experimental evidence that AD may involve not only suppressed neurogenesis in neurogenic niches but also its paradoxical stimulation, typically associated with pro-inflammatory microenvironment formation and amyloid-β oligomer accumulation. These effects have been documented in transgenic animals showing age-dependent multidirectional changes [10, 11, 30–32] and in AD patients [33].

On the other hand, these data indicate that proliferative activity in the SGZ of 5xFAD animals is *a priori* reduced compared to animals with intrahippocampal amyloid-β administration. This suggests that the pool of neural stem cells and neuronal progenitor cells in animals with a familial AD model is significantly impaired, limiting their ability to mount an effective recruitment response during experience-induced neurogenesis stimulation. We propose that this may be attributed to a prolonged period of aberrant neurogenesis starting from the embryonic developmental stage in animals with genetic AD models [34].

One potential reason for the lack of significant neurogenesis intensification during training in 5xFAD animals could be impairments in the local vascular scaffold that maintains the neural stem cell and neuronal progenitor cell pool, as well as their mobilization, proliferation, and differentiation in neurogenic niches [15]. Under conditions of increased neurogenesis demand (e.g., during learning and memory consolidation), suppression of cerebral angiogenesis leads to impaired learning and memory [35]. Indeed, we observed

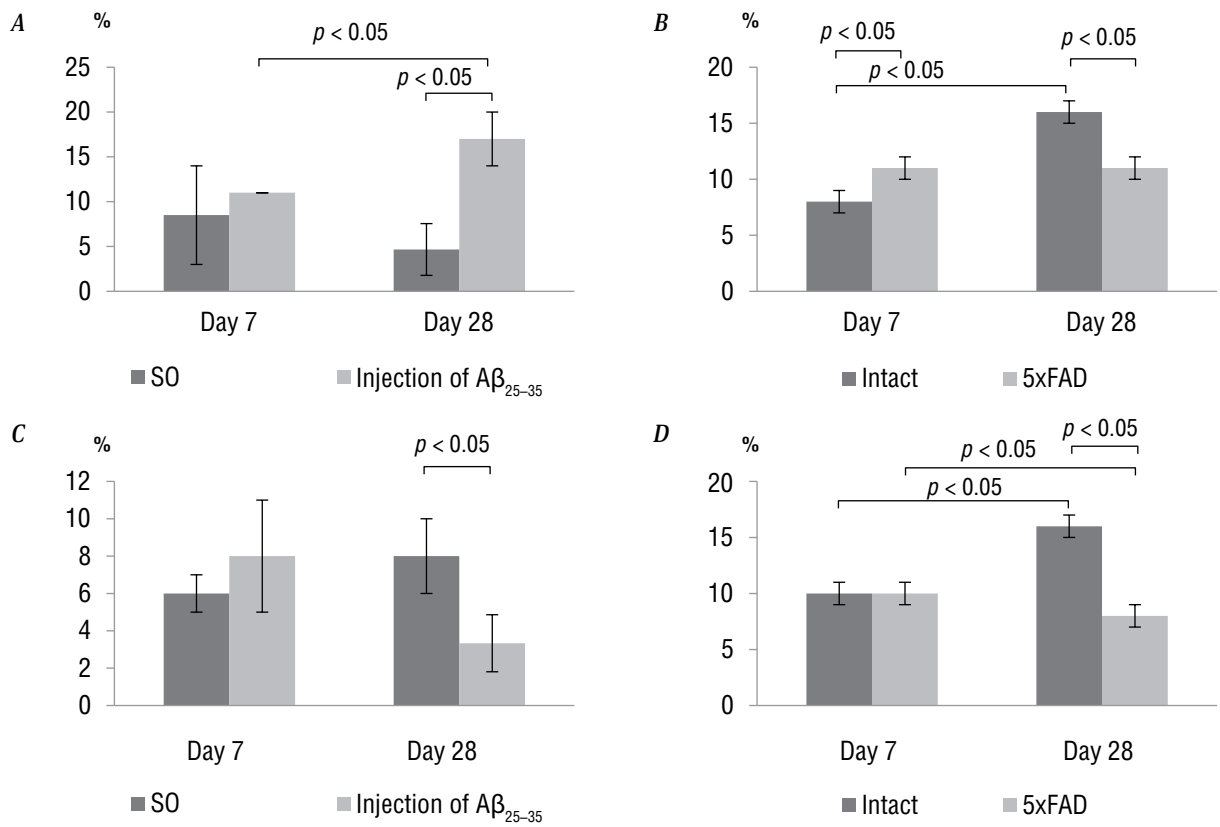

Fig. 5. Changes in the number of CXCR4/DLL4/VEGFR2-immunopositive (tip-) and TIE1/Ki-67/NOTCH-immunopositive (stalk-) endothelial cells in the SGZ of SO animals and animals with intrahippocampal injection of $A\beta_{25–35}$ (*A, C*), intact and transgenic 5xFAD animals (*B, D*) on days 7 and 28 post-training.
Data are normalized to 100 DAPI-positive cells and are presented as mean and standard deviation, $p < 0.05$.

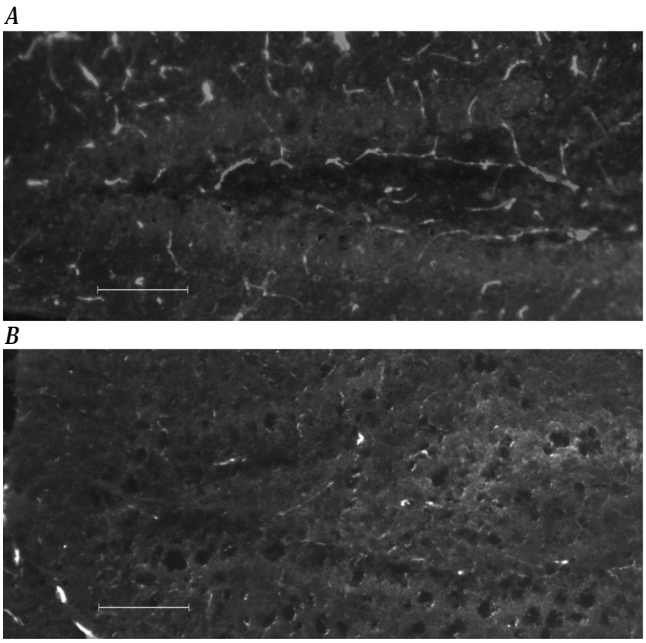

Fig. 6. The vasculature in the SGZ of the hippocampus on day 28 post-training.
A: the SGZ vasculature of an AO animal. *B*: the SGZ vasculature in an animal with intrahippocampal injection of $A\beta_{25-35}$. Scale bar – 65 μm.

reduced proliferative activity of endothelial cells and suppression of phenotypic conversion into tip- and stalk-like phenotypes in 5xFAD animals.

Control group animals demonstrated substantial intensification of neoangiogenesis (increased $BrdU^+CD31^+$ cell count) by days 7 and 28 after the first training session. A similar, and even more pronounced changes in $BrdU^+CD31^+$ endothelial cell counts was observed in animals following intrahippocampal amyloid-β administration. However, 5xFAD transgenic animals initially showed increased counts of endothelial cells entering mitosis after training, followed by a significant reduction in their number in the SGZ, which we associate with intensified cell death (apoptosis) and/or enhanced microvascular regression due to long-term neurodegeneration in transgenic animals, unlike animals primarily exhibiting acute amyloid-β toxicity after intracerebral administration.

Indeed, animals with genetic AD models exhibit all key features of long-term and progressive cerebral amyloid angiopathy with cerebral capillary bed damage, corresponding to AD pathogenesis in humans [36], including the formation of aberrant microvessels with compromised blood-brain barrier integrity [37].

It is noteworthy that in animals with intrahippocampal $A\beta_{25-35}$ administration, proangiogenic activity in the SGZ is high, but

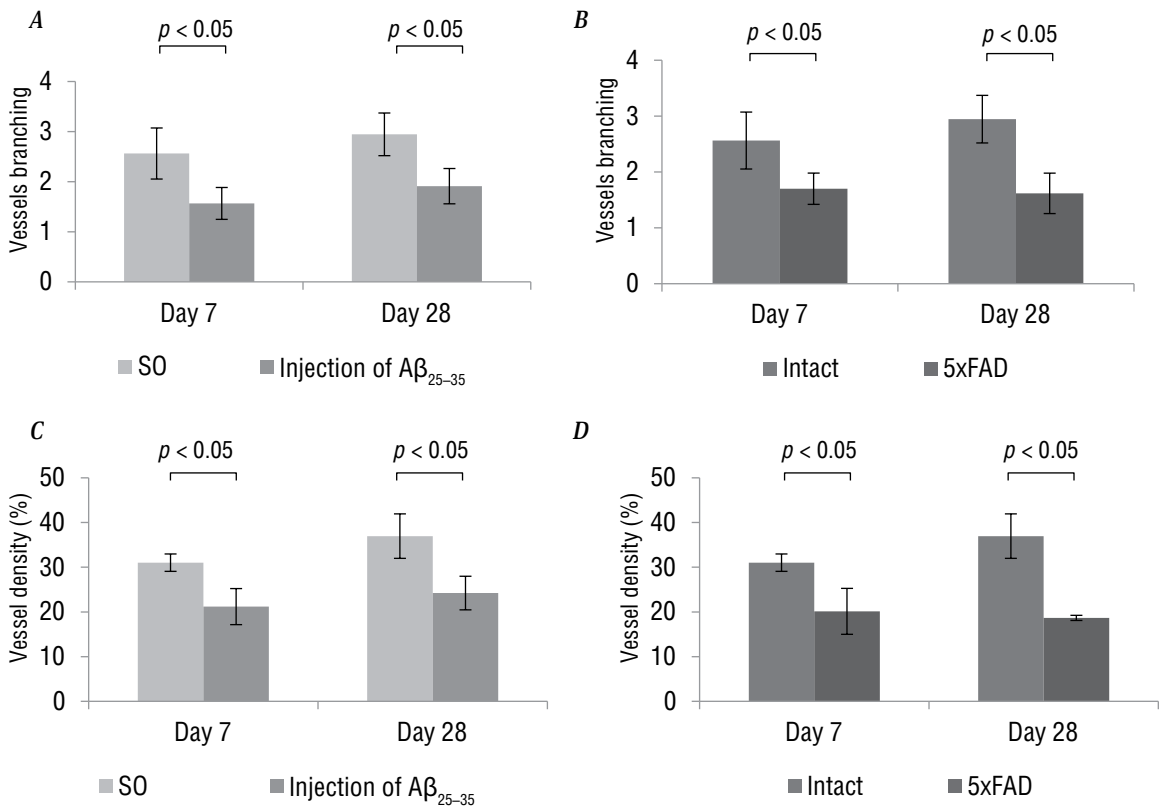

Fig. 7. Branching and density of the vasculature in the SGZ of SO animals and animals with intrahippocampal injection of $A\beta_{25-35}$ (*A, C*), intact and transgenic 5xFAD animals (*B, D*) on days 7 and 28 post-training, $p < 0.05$.

the mechanism of lateral inhibition is likely impaired (the number of tip cells exceeds that of stalk cells throughout the follow-up period). In contrast, transgenic animals exhibit a different dominant mechanism of angiogenesis impairment: proliferative activity of endothelial cells rapidly diminishes (likely due to apoptosis or stimulation of microvessel regression), accompanied by a lack of significant conversion of endothelial cells to the tip phenotype.

The newly obtained data generally align with key changes we previously documented in animals with Alzheimer's type neurodegeneration induced by intrahippocampal amyloid-β administration: imbalanced expression of LC3B, ZO1, VEGFR2, VEGFR3, CD146, ICAM2, Dll4, and Tie2 in the SVZ [38]; impaired mitochondrial dynamics and autophagy of endothelial cells in the SGZ and entorhinal cortex [39]; aberrant maturation of endothelial cells in the SGZ and SVZ, manifested by altered proportions of $CLDN5^+$ cells among total $CD31^+$ cells [40]; dysregulation of tip-, stalk-, and phalanx-type endothelial cells in the prefrontal cortex [41]; increased microvascular permeability and disrupted branching in the CA1, CA2, and CA3 hippocampal regions of 5xFAD mice [42]. Furthermore, in animals with intrahippocampal amyloid-β administration, we previously identified imbalanced neurogenesis and angiogenesis induction at the presymptomatic stage in the SGZ and SVZ [10], as well as differential dynamics of Arg3.1/Arc expression in postmitotic young neurons of the SGZ and SVZ alongside suppressed proliferative activity in the SGZ and elevated activity in the SVZ [29].

Thus, under physiological conditions, training stimulates proliferative activity of endothelial cells in the hippocampal SGZ; however, in the absence of significant neurogenesis changes, this is not associated with phenotypic alterations in SGZ microvascular endothelial cells. In animals subjected to the toxic effects of intrahippocampally administered $A\beta_{25-35}$ oligomers, induction of neurogenic and angiogenic events occurs in the SGZ, but the lateral inhibition mechanism regulating stalk-to-tip cell conversion is disrupted, leading to impaired microarchitecture of the forming hippocampal capillary network. In animals with a genetically determined AD model, the "demand" for enhanced neoangiogenesis during intensified post-training neurogenesis remains unfulfilled. This is accompanied by a lack of significant endothelial subpopulation changes and results in an aberrant microvascular network in the hippocampus.

Conclusion

Non-productive angiogenesis and hypervascularization, extensively studied in recent years within the context of AD pathogenesis [43, 44], manifest through fundamentally distinct mechanisms in the SGZ of animals with two different Alzheimer's type neurodegeneration models. Therefore, although cognitive deficits develop by day 28 post-cognitive "challenge" (training in the PA test) in both AD models regardless of the dominant plasticity impairment mechanism, the identified features of aberrant neurogenesis and angiogenesis implementation in the hippocampus must be considered when developing new therapeutic strategies for sporadic and familial AD.

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Incidence of Facial Palsy Following Microsurgical Removal of Vestibular Schwannoma Using Direct Electrical Stimulation: a Meta-Analysis

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Abstract

Aim. *To determine the incidence of facial palsy (FP) following microsurgical removal of vestibular schwannoma using direct electrical stimulation.*
Materials and methods. *The meta-analysis included 946 publications from PubMed, Google Scholar, Web of Science, and eLIBRARY.RU, of which 9 studies meeting the inclusion and exclusion criteria were selected. The total number of patients was 1875, with 278 having FP after microsurgical removal of vestibular schwannoma. The pooled mean age of patients was 46.9 [44.5; 49.4] years, with a male-to-female ratio of 1 : 1.*
Results. *The pooled incidence rate of early postoperative FP was 16.1% (6.8–25.3%), and delayed FP was 8.7% (0.5–12.4%). At 12 months postoperatively, patients with delayed FP demonstrated better recovery outcomes of facial muscle function.*

Keywords: *vestibular schwannoma; facial palsy; intraoperative neurophysiological monitoring; cerebellopontine angle tumor*

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Оценка частоты развития нейропатии лицевого нерва после микрохирургического удаления вестибулярной шванномы с использованием метода прямой электрической стимуляции

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Аннотация

Цель исследования *– определение частоты возникновения нейропатии лицевого нерва (НЛН) после микрохирургического удаления вестибулярной шванномы с использованием метода прямой электрической стимуляции.*

Материалы и методы. *В метаанализ включены 946 публикаций из баз данных PubMed, Google Scholar, Web of Science и eLIBRARY.RU, из которых отобраны 9 исследований, удовлетворяющих критериям включения и исключения. Общее число пациентов составило 1875 человек, у 278 из них после микрохирургического удаления вестибулярной шванномы развилась НЛН. Обобщённый средний возраст пациентов составил 46,9 [44,5; 49,4] года, соотношение мужчин и женщин 1 : 1.*

Результаты. *Обобщённый показатель частоты развития ранней послеоперационной НЛН составил 16,1% (6,8–25,3%), отсроченной – 8,7% (0,5–12,4%). Через 12 мес после операции у пациентов с отсроченной НЛН наблюдали лучшие результаты восстановления функции мимической мускулатуры.*

Ключевые слова: *вестибулярная шваннома; нейропатия лицевого нерва; интраоперационный нейрофизиологический мониторинг; опухоль мостомозжечкового угла*

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

Vestibular schwannoma (VS; acoustic neurinoma, acoustic neuroma, acoustic schwannoma) is a benign tumor arising from the vestibular division of the VIII cranial nerve, accounting for approximately 8% of all intracranial tumors and 80–90% of cerebellopontine angle (CPA) tumors in adults. VS is rarely observed in children, except in patients with neurofibromatosis type 2. The prevalence of VS varies across populations, ranging from 0.36 to 2.66 per 100,000 individuals. The disease occurs equally in men and women, with a median age at diagnosis of 50 years [1].

Despite the initial description of VS in 1777 [2], the first successful surgical intervention was performed over 100 years later [3]. Since the late 19th century, numerous attempts have been made to optimize surgical approaches to prevent brainstem ischemia caused by the damage of the anterior inferior cerebellar artery. Most CPA tumor surgeries performed at that time were associated with extremely high mortality rates, reaching up to 84% [4].

Another significant intraoperative complication was facial palsy (FP) due to its intraoperative injury. To address this issue, attempts were made to perform single-stage cross-plasty using the accessory and hypoglossal nerves, which were not widely adopted at the time.

In 1898, F. Krause et al. introduced a technique for intraoperative localization of the facial nerve (FN) via its electrical sti-

mulation until visible contractions of facial muscles occurred [5]. The main drawbacks of FN stimulation were the lack of quantitative stimulus control and objective recording of the elicited responses. In 1979, T.E. Delgado et al. proposed intraoperative electromyography (EMG) of facial muscles for more precise monitoring of FN function [6]. Experimental studies established that the FN location coincided with the peak M-wave amplitude obtained at minimal current strength. At the end of surgery, stimulation of the FN root near the brainstem and distally in the auditory canal area was performed. Matching M-wave amplitudes during distal and proximal stimulation served as an indicator of preserved FN conductive function. This technique became widely adopted and remains in use in neurosurgical practice to this day [7].

Despite the close anatomical proximity to the vestibulocochlear nerve in the cerebellopontine angle (CPA) region, facial palsy (FP) as a symptom of vestibular schwannoma (VS) occurs in 5–15% of cases [8]. The incidence of postoperative FP ranges from 2% to 40% [9]. Facial nerve dysfunction occurs immediately after surgery, within 48–72 hours, or may be delayed, developing 5–30 days postoperatively (on average, 10–12 days, after the patient's discharge from the hospital) [10–12].

In patients undergoing VS resection, FP remains a major issue, leading not only to adverse functional outcomes but also to severe psychological consequences [13]. Due to incomplete eyelid closure (lagophthalmos), various corneal injuries may develop, including dryness, erosions, and infection. Patients experience difficulties with speech, food intake, chewing, and emotional expression, which undoubtedly affects their quality of life and provokes anxiety and depressive disorders [14]. The widespread adoption of intraoperative neurophysiological monitoring (IONM) during VS resection since the 1990s has significantly reduced the incidence of FP in the postoperative period [15].

We conducted a systematic literature search and subsequent meta-analysis to determine the incidence of FP following microsurgical resection of VS using direct facial nerve stimulation for its identification and assessment of functional integrity at the end of surgery.

Materials and methods

Paper search and study selection

The literature search and study selection process followed an algorithm developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. We conducted searches in PubMed, Google Scholar, Web of Science, and eLIBRARY.RU using a combination of search queries, keywords, and Boolean operators. To align with the research objectives, conference abstracts, meeting minutes, books, case reports, and case series were excluded. The search strategy utilized the following queries in international databases: "facial palsy", "vestibular schwannoma surgery", "acoustic neuroma surgery"; for Russian-language resources: "нейропатия лицевого нерва" (facial palsy), "вестибулярная шваннома" (vestibular schwannoma), "невринома слухового нерва" (acoustic neuroma). Publication dates were restricted to articles published after 1990 (following the widespread implementation of intraoperative neuromonitoring) and before June 15, 2024.

Inclusion and exclusion criteria

The systematic review included studies where patients had no preoperative impairment of facial nerve function (House–Brackmann [HB] grade I), underwent total or subtotal tumor resection, and where publications specified the surgical approach type and timing of postoperative facial palsy (FP) onset. Postoperative FN function was assessed using the HB scale throughout the follow-up period until hospital discharge and within the first postoperative month during active patient consultations. Delayed facial palsy was defined as a de novo deterioration in its function by >1 point on the House-Brackmann (HB) scale occurring later than 24 hours postoperatively.

Microsurgical VS resection was performed using IONM, which included direct FN stimulation for nerve identification during tumor resection and assessment of its functional integrity at surgery completion via direct stimulation of its root near the brainstem. Favorable surgical outcomes were defined as HB grades I and II.

Studies were excluded from the meta-analysis if patients had preoperative FN deficits, tumor progression (recurrence), or prior VS radiosurgery. Papers involving patients with bilateral tumors associated with neurofibromatosis type 2 were also excluded from the study.

Research Data Extraction and Synthesis

During the initial screening using the aforementioned search queries, 946 publication references were retrieved, of which 33 were duplicates; only unique search results were retained. No Russian-language articles met the inclusion criteria.

Thus, out of the initially identified search results, aggregated quantitative data from 9 (0.95%) articles satisfied the final inclusion criteria for the systematic review and were processed using statistical analysis. All selected publications corresponded to the case-control study type. The selection process is illustrated in Fig. 1.

For each study, the following data were recorded: first author, publication year, study group, number of cases and timing of FP development, surgical approach, degree of FN dysfunction per the House–Brackmann (HB) scale, and potential predictors of unfavorable outcomes.

Bias Risk

The validity and methodological quality assessment of selected non-randomized case-control studies was conducted using the adapted Newcastle-Ottawa Scale (NOS) [17], which accounts for bias risks across 8 domains (D1–D8), divided into 3 categories: patient selection, group comparability, and exposure analysis. For each item, multiple response options are provided. During the assessment, 1 point may be awarded per item within the "patient selection" and "outcome/exposure analysis" domains or 2 points within the "group comparability" domain; the maximum to-

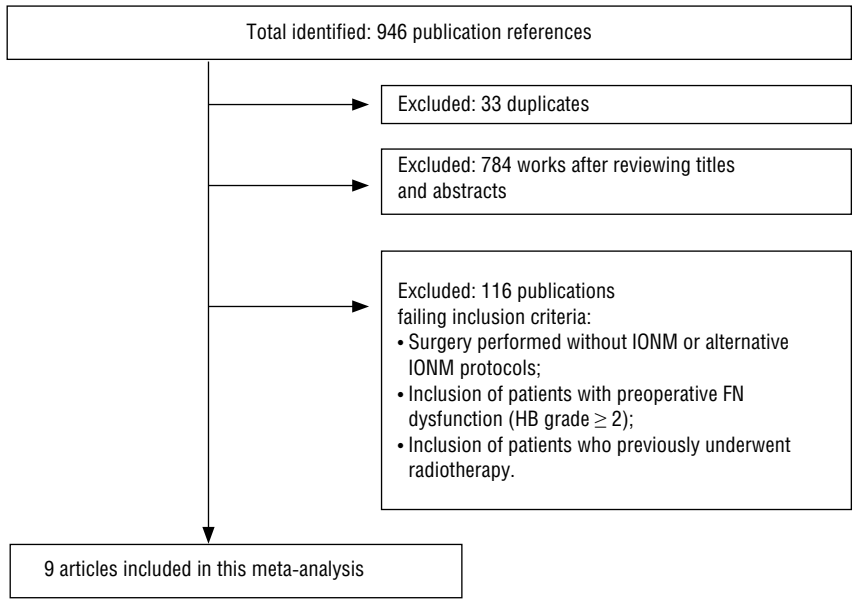


Fig. 1. Flowchart of studies included in the meta-analysis.

Table 1. Validity and Methodological Quality Assessment of Selected Studies, Scores

No.	Study	D1	D2	D3	D4	D5	D6	D7	D8	Total score	Bias risk
1	Arlt, 2022 [18]	1	0	1	0	2	1	1	1	7	Medium
2	Chang, 2020 [11]	1	1	1	1	2	1	1	1	9	Low
3	Gazia, 2023 [19]	1	0	1	1	1	1	1	0	6	Medium
4	Grant, 2002 [20]	1	1	1	0	1	1	1	0	6	Medium
5	Jia, 2023 [12]	1	1	1	1	2	1	1	1	9	Low
6	Karanth, 2024 [21]	1	1	1	1	2	1	1	1	9	Low
7	Morton, 2011 [9]	1	1	1	1	2	1	1	1	9	Low
8	Ren, 2021 [22]	0	1	1	0	1	1	1	1	7	Medium
9	Yawn, 2018 [23]	1	1	1	1	1	1	1	0	7	Medium

tal score is 9 (Table 1). The bias risk assessed using the NOS scale may be categorized as low, moderate, or high. O.Yu. Rebrova et al. [17] propose the following interpretation of bias risk assessment results:

- studies scoring ⩽ 5 points (out of 9) have a high risk of systematic bias;
- studies scoring 6-7 points – moderate risk of systematic bias;
- studies scoring 8-9 points – low risk of systematic bias.

Statistical Analysis

Statistical data processing was performed using Review Manager v. 5.4.1 (The Cochrane Collaboration, 2020) and OpenMeta Analyst software. Study heterogeneity was assessed with the Q-test, while the magnitude of heterogeneity was determined using the I^2 statistic. Statistically significant heterogeneity was considered present at $p < 0.1$. For the latter, a 95% confidence interval (CI) was also calculated. When pooling data from individual studies, given the substantial statistical heterogeneity across most parameters ($I^2 > 40\%$), we used the DerSimonian and Laird random-effects model. Publication bias was assessed using funnel plots and Egger's test; bias was considered significant at $p < 0.05$.

Results

The total number of patients included in the meta-analysis was 1,875, of whom 278 developed FP following microsurgical VS resection. Delayed onset of postoperative FP was observed in 112 patients.

Two publications lacked information on sex distribution in the study samples; among the remaining 1,365 patients, 696 (51%) were female. In the study by R.J. Yawn et al., delayed FP developed in 22 patients, 15 of whom were female [23]; in the study by X.H. Jia et al., 4 out of 15 patients were female [12]. The follow-up period in the majority of publications (67%) was 12 months.

The study samples included in the meta-analysis were heterogeneous in age ($I^2 = 96.55\%$; $p < 0.001$). The youngest

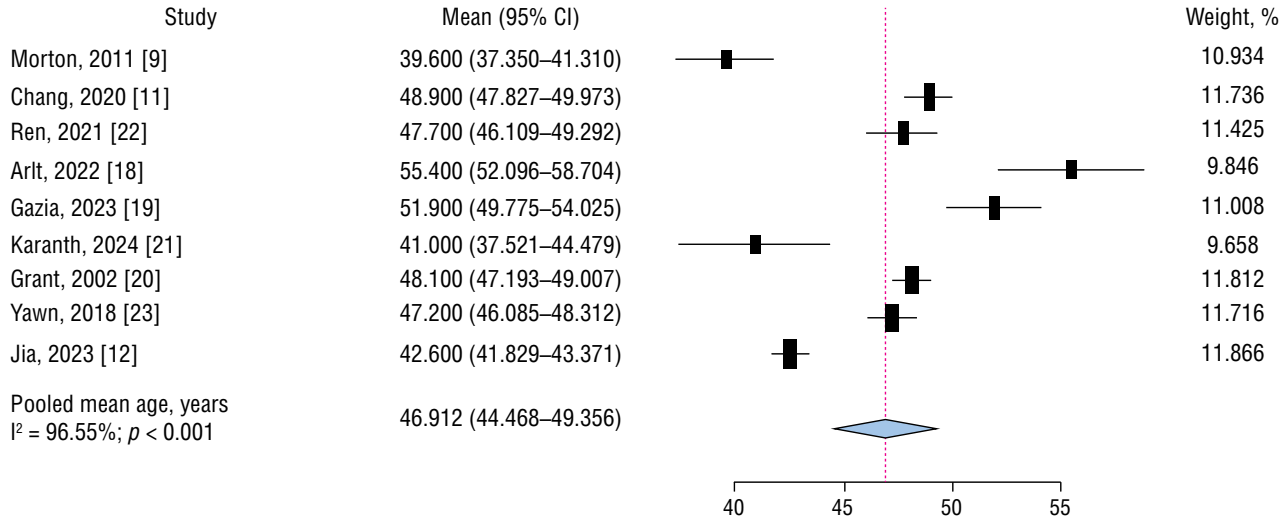


Fig. 2. Results of the meta-analysis of the pooled mean age of patients.
In this figure and in Figs. 3 and 4: squares represent the effect size for each study (square size corresponds to study weight); horizontal lines – 95% CIs; diamond – pooled effect size and its 95% CI.

Table 2. General characteristics of the studies included in the meta-analysis

Study	Country	Surgeon's expertise	Design	*n*	Mean age, years (*M ± SD*)	FP cases	Translabyrinthine approach	Retrosigmoid approach	Middle fossa approach
Early postoperative FP									
Morton, 2011 [9]	US	Neurosurgery, otorhinolaryngology	Retrospective	104*	39.6 ± 11.5	9	43	49	3
Chang, 2020 [11]	Canada	Neurosurgery, otorhinolaryngology	Retrospective	434*	48.9 ± 11.4	25	36	372	17
Ren, 2021 [22]	US	Otorhinolaryngology	Prospective	256	47.7 ± 13.0	71	130	64	62
Arlt, 2022 [18]	Germany	Neurosurgery	Retrospective	75	55.4 ± 14.6	14	0	75	0
Gazia, 2023 [19]	Italy, Spain	Otorhinolaryngology	Retrospective	146	51.9 ± 13.1	45	146	0	0
Karanth, 2024 [21]	India	Neurosurgery	Prospective	35	41.0 ± 10.5	2	0	35	0
Delayed onset of postoperative FP									
Grant, 2002 [20]	US	Neurosurgery, otorhinolaryngology	Retrospective	314	48.1 ± 8.2	15	#	#	0
Morton, 2011 [9]	US	Neurosurgery, otorhinolaryngology	Retrospective	104*	39.6 ± 11.5	26	43	49	3
Yawn, 2018 [23]	US	Neurosurgery, otorhinolaryngology	Retrospective	246	47.2 ± 8.9	22	19**	3**	0
Chang, 2020 [11]	Canada	Neurosurgery, otorhinolaryngology	Retrospective	434*	48.9 ± 11.4	37	36	372	17
Jia, 2023 [12]	China	Otorhinolaryngology	Retrospective	265	42.6 ± 6.4	12	0	265	0

Note. #The surgical approaches used are listed without specifying their quantity. *In the "case" group, we noted the development of immediate and delayed FP. **The study indicates the number of only those approaches where FP was observed.

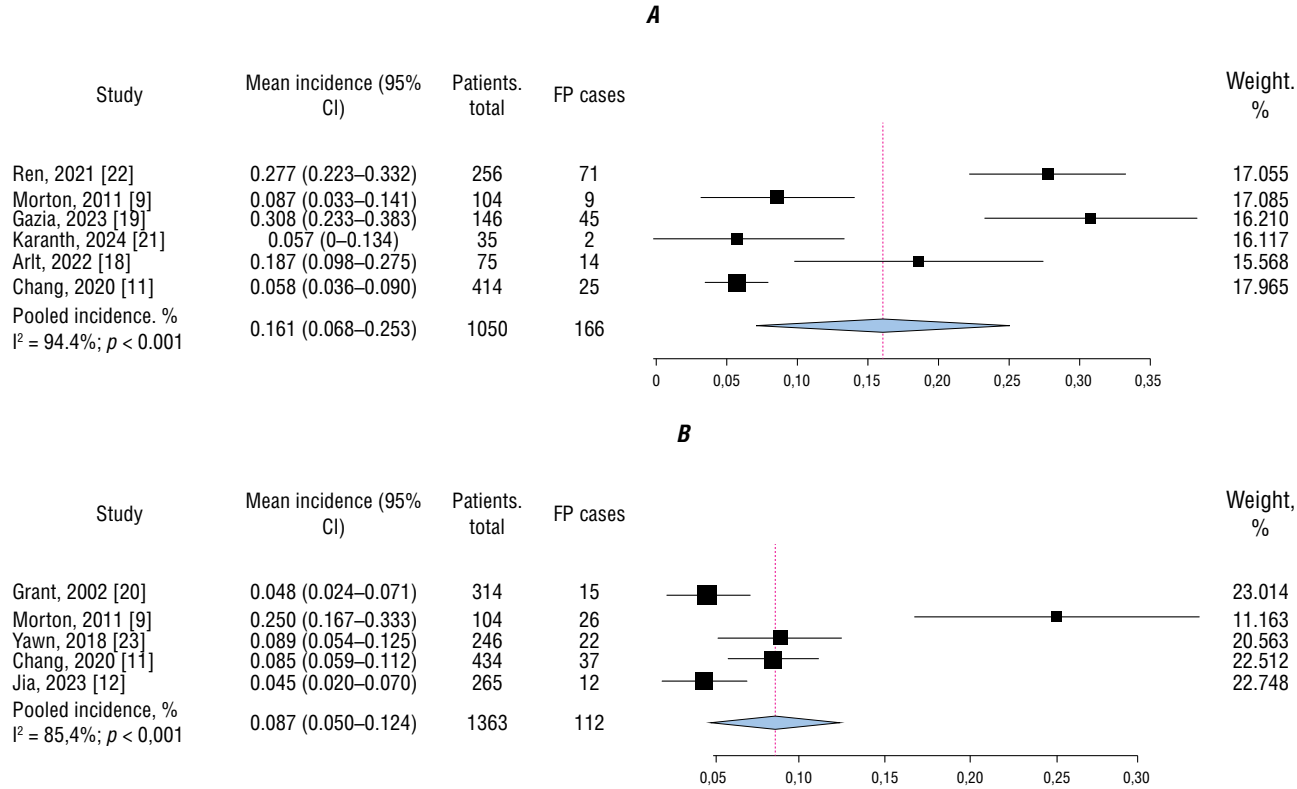


Fig. 3. Results of the meta-analysis of early (*A*) and delayed (*B*) postoperative FP incidence following microsurgical resection of vestibular schwannoma.

patient was 13 years old [9], and the oldest was 87 years old [18]. Three studies included patients under 15 years of age [9, 11, 22]. The pooled mean age of patients was 46.9 (44.5–49.4) years (Fig. 2).

Features of Intraoperative Neurophysiological Monitoring

All selected publications used stimulation at the FN exit zone from the brainstem to predict postoperative FN function. The minimum stimulus intensity required to elicit facial muscle contractions varied across studies. For example, studies by Y. Ren et al. [22] and X.H. Jia et al. [12] used a current intensity of 0.05 mA, while G.A. Grant et al. [20] used 0.1 mA. In the publication by F. Gazia et al., the stimulation protocol started at 0.05 mA, followed by incremental adjustments in 0.01 mA steps until reaching a minimum stimulus of 0.01 mA or a maximum of 5.0 mA [19]. According to V.K.K.S. Karanth et al., a threshold stimulation current of 0.05–0.10 mA during proximal stimulation indicates good functional integrity of the FN, whereas a threshold current of 0.2–1.0 mA may be predictive of its injury and functional impairment [21].

In the study by F. Arlt et al., the reported stimulation intensity was 0.76 (0.70 ± 0.29) V [18].

The majority (80%) of publications were retrospective case-control studies. General characteristics of the studies included in the meta-analysis are presented in Table 2.

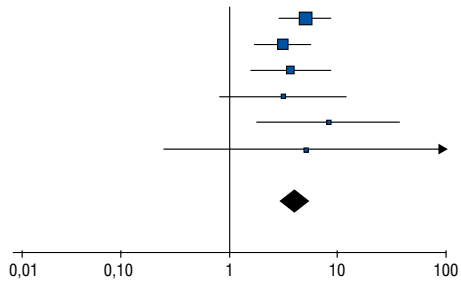
The presented publications lack a unified approach to classifying FP based on the timing of its onset in the postoperative period. Such significant variability complicates the comparison of results. According to R.J. Yawn et al., early postoperative FP develops within the first 24 hours after VS resection. S. Chang et al. consider FP occurring within the first 48 hours postoperatively as immediate [11]. According to G.A. Grant et al., this period is 72 hours, while X.H. Jia et al. report up to 5 days [12].

L.P. Carlstrom et al. defined delayed FP as a deterioration of FN function by at least 2 points on the House-Brackmann scale between the 5th and 30th postoperative days. S. Chang et al. described two subgroups of delayed FP [11]. The early-onset FP group included patients with normal FN function immediately upon awakening in the intensive care unit but developing facial muscle weakness within the first 48 hours after surgery. The late-onset FP group comprised patients if FN dysfunction occurred more than 48 hours postoperatively. These examples highlight the need for consensus on defining assessment timelines for immediate and delayed FP in future clinical studies.

The incidence of immediate FP varied across studies from 5.7% [21] to 27.7% [22], with significant heterogeneity (I^2 = 94.4%; $p < 0.001$). The pooled estimate was 16.1% (6.8–25.3%) (Fig. 3, *A*). The incidence of delayed FP ranged from 4.5% [12] to 25.0% [9], also demonstrating substantial variability (I^2 = 85.4%; $p < 0.001$). The pooled estimate was 8.7% (0.5–12.4%) (Fig. 3, *B*).

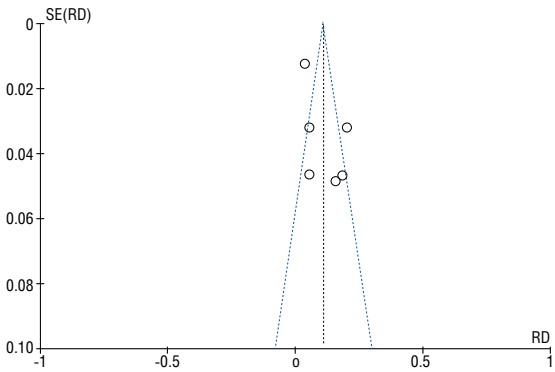
A

Study	Patients. total	FP cases postoperatively	FP cases in 12 months	Weight, %	OR (95% CI)
Ren, 2021 [22]	256	71	18	38.7	5.07 (2.92–8.81)
Gazia, 2023 [19]	146	45	18	32.1	3.17 (1.73–5.81)
Chang, 2020 [11]	434	25	7	16.3	3.73 (1.60–8.72)
Morton, 2011 [9]	104	9	3	6.6	3.19 (0.84–12.14)
Arlt, 2022 [18]	75	14	2	5.1	8.38 (1.83–38.31)
Karanth, 2024 [21]	35	2	0	1.2	5.30 (0.25–114.47)
Total	1050	166	48	100	4.13 (2.93–5.82)



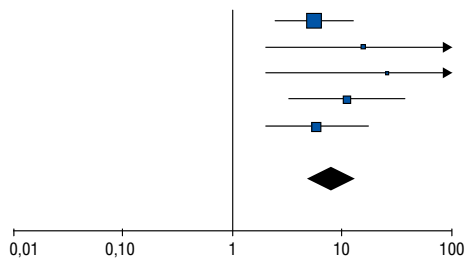
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.34$; df = 5 ($p = 0.80$); $I^2 = 0\%$

Test for total effect: Z = 8.10 ($p < 0.00001$)



B

Study	Patients, total	FP cases postoperatively	FP cases in 12 months	Weight, %	OR (95% CI)
Chang, 2020 [11]	434	37	7	46.7	5.69 (2.51–12.90)
Grant, 2002 [20]	314	15	1	6.9	15.70 (2.06–119.61)
Jia, 2023 [12]	265	12	0	3.5	26.18 (1.54–444.55)
Morton, 2011 [9]	104	26	3	16.4	11.22 (3.28–38.43)
Yawn, 2018 [23]	246	22	4	26.5	8.07 (4.70–13.84)
Total	1363	112	15	100	8.07 (4.70–13.84)



Heterogeneity: $\chi^2 = 2.36$; df = 4 ($p = 0.67$); $I^2 = 0\%$

Test for total effect: Z = 7.58 ($p < 0.00001$)

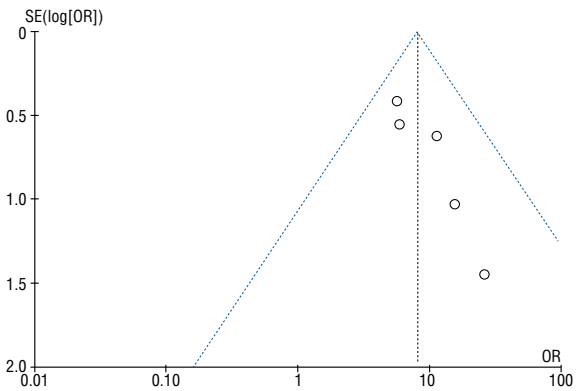


Fig. 4. Results of the meta-analysis assessing FN function 12 months postoperatively in patients with early (*A*) and delayed (*B*) postoperative FP following microsurgical VS resection.

In the study by R.P. Morton et al., patients with a history of herpes infection were prophylactically prescribed the antiviral agent acyclovir during the postoperative period [9]. Four out of nine studies utilized parenteral dexamethasone administration to prevent swelling of the FN [11, 12, 20, 21]. Alongside glucocorticoid therapy, the study by S. Chang et al. also implemented medications to prevent edema and antibiotic therapy [11]. In the study by V.K.K.S. Karanth et al., intraoperative use of papaverine solution as a vasodilator and nimodipine was employed when decreased motor response amplitudes from FN-innervated muscles were observed; the authors suggested nimodipine promoted axonal growth and remyelination processes [21]. Other publications lacked data on pharmacological interventions.

Facial Nerve Function 12 Months After Surgery

A meta-analysis of FN functional recovery outcomes 12 months post-surgery, conducted using a random-effects model, revealed a more favorable disease course in patients with delayed FP (Fig. 4). The odds of mimetic muscle function recovery were twice as low in patients with early postoperative FP (OR = 4.13 [2.03–5.92]) compared to those with FN dysfunction occurring > 48 hours after surgery (OR = 8.07 [4.70–13.84]).

Discussion

The main treatment methods for VS include microsurgical resection, radiotherapy (stereotactic radiosurgery, gamma knife, cyberknife), and observational strategy (typically for asymptomatic cases) [24, 25]. Total or subtotal tumor resection traditionally employs retrosigmoid, translabyrinthine, or middle fossa approaches [26]. Data regarding surgical approach characteristics as risk factors for FP remain controversial [27]. Likely intraoperative damaging factors leading to FN dysfunction include nerve traction, compression, coagulation, or aspiration injury [28].

The gold standard in VS surgery involves IONM to ensure anatomical identification, protect against potential damaging events, and predict postoperative FN function. However, direct nerve stimulation technique cannot be used for continuous FN monitoring, serving rather as a tool for nerve identification at specific operative stages when accessible to the neurosurgeon. In addition to assessing distal and proximal FN stimulation amplitudes, intraoperative evaluation of maximum M-wave amplitude during direct nerve stimulation with 2 mA current at specific tumor resection stages is feasible. An M-wave amplitude < 1200 μV and latency increase > 8 ms prior to VS resection were identified as potential markers of adhesion and FN involvement in the tumor capsule. Conversely, an M-wave amplitude > 3500 μV enabled complete VS resection [29].

In this meta-analysis, we studied the FP incidence following VS microsurgical resection using IONM. According to our data, the incidence of early postoperative FP is 16.1%, while that of delayed FP is 8.7%. These results highlight the high risks of complications associated with surgical treatment of VS and confirm the necessity of using state-of-the-art monitoring methods to reduce their likelihood.

One of the most important findings of the meta-analysis is that patients with delayed neuropathy demonstrated better recovery of FN function at 12 months compared to those with early postoperative FP. We can assume that the later onset of symptoms is likely associated with less traumatic FN injury or the activation of compensatory recovery mechanisms following surgery.

High heterogeneity was observed across the included studies, potentially reflecting differences in surgical approaches, IONM use, and patient follow-up protocols. For instance, the incidence of early postoperative FP ranged from 5.7% to 27.7%, underscoring the need for stricter standardization in defining and classifying FP in clinical practice.

In current VS surgery, multimodal IONM – incorporating resting electromyography, direct nerve stimulation, and transcranial electrical stimulation with recording of motor evoked potentials from facial muscles – is gaining increasing traction. Further studies should evaluate the incidence of postoperative FP with different combinations of these IONM techniques.

Conclusion

This meta-analysis confirms that even with IONM, the incidence of FP following microsurgical VS resection remains 16.1% for early-onset and 8.7% for delayed-onset cases. The findings underscore the importance of IONM use to minimize intraoperative complication risks. Future research should focus on standardizing the classification of postoperative FP by timing of onset and improving IONM protocols in VS surgery.

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Cerebrometabolic Health

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Abstract

The article addresses the global challenge of nervous system damage and cerebral consequences in metabolic disorders. It introduces the concept of impaired cerebral metabolic health as a progredient progression of cerebral dysfunction. Delineating the sequence of changes at all stages underscores the importance of targeted timely interventions to ensure preventive measures and treatment of cerebral vascular diseases.

Keywords: *stroke; cerebrovascular disease; cognitive impairment; obesity; diabetes mellitus; cerebrometabolic health*

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Цереброметаболическое здоровье

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Аннотация

В статье освещена глобальная проблема поражения нервной системы и церебральных последствий при метаболических расстройствах. Представлена концепция нарушения цереброметаболического здоровья как прогредиентное прогрессирование мозговой дисфункции. Выделение последовательности изменений на всех этапах определяет важность и таргетность своевременного вмешательства для обеспечения мер профилактики и лечения сосудистых заболеваний головного мозга.

Ключевые слова: *инсульт; цереброваскулярные заболевания; когнитивные нарушения; ожирение; сахарный диабет; цереброметаболическое здоровье*

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

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Introduction

Preserving the population, strengthening public health, and enhancing people's well-being are strategic national priorities. A key objective is to increase the healthy and active life expectancy of Russia's population. To achieve these critical goals amid rapidly changing modern conditions, it is imperative to promptly implement effective healthcare measures. Advances in medical science, emerging next-generation devices and platforms, and biomedical and cognitive technologies are essential for addressing population preservation challenges in line with contemporary demands.

Combating the global leading cause of death — cardiovascular diseases, among which cerebrovascular disorders (CVD) hold significant and distinct prominence — is a priority task for preserving public health. CVDs are characterized not only by high rates of disability and mortality but also by neurocognitive disorders that can lead to loss of independence. Cognitive impairments and dementia have emerged as public health priorities requiring national-level action.

CVDs represent a group of conditions that constitute not only a major medical but also a socioeconomic issue. Preventive measures for CVD, implemented at both population and individual levels, should target key metabolic risk factors — drivers of vascular disease progression, including acute stroke, chronic CVDs, cerebral microangiopathy, and associated cognitive disorders [1–4].

The link between metabolic and cerebral disorders is well-established; however, the systemic integration of the broad spectrum of brain diseases (primarily vascular) and metabolic disturbances remains unresolved. The high incidence and mortality rates of CVDs, coupled with the burden of stroke and cognitive impairment (CI), raise numerous unresolved questions. The developed ***concept of cerebrometabolic health*** reflects the interplay of metabolic risk factors, vascular system integrity, and the structural and functional state of the brain. In cases of impaired cerebrometabolic health, particularly among individuals with adverse lifestyle factors, there is a pressing need to understand developmental mechanisms and define preventive and therapeutic strategies tailored to the stage of disease progression.

Spectrum of cerebral metabolic disorders

There are a number of factors or underlying causes influencing chronic diseases. These factors reflect the primary driving forces behind social, economic, and cultural changes, primarily globalization, whose effects on human health are mediated through disruptions in homeostasis. Thus, the complex interplay of socioeconomic, demographic, and environmental changes affecting nations underpins the observed syndemia of cerebrometabolic disorders, directly impacting quality and longevity of life.

Global consequences of syndemic cerebral and metabolic disorders

Findings from epidemiological studies and trends in absolute stroke rates over the past three decades underscore the escalating significance of cerebrometabolic health concerns. According to the Global Burden of Diseases, Injuries, and Risk Factors[1] Study (GBD), in 2021, stroke ranked as the third leading cause of death — 7.3 million cases (95% confidence interval 6.6–7.8; 10.7% (9.8–11.3) of all deaths) — after ischemic heart disease and COVID-19, and the fourth leading cause of disability-adjusted life-years (DALYs) (160.5 million (147.8–171.6) DALYs; 5.6% (5.0–6.1) of all DALYs). A substantial rise in DALY values was linked to metabolic factors. Among stroke risk factors, high body mass index (BMI) exhibited the most marked increase — 88.2% (53.4–117.7). Stroke burden correlated with elevated fasting plasma glucose levels — 32.1% (26.7–38.1), diets rich in sugar-sweetened beverages — 23.4% (12.7–35.7), physical inactivity — 11.3% (1.8–34.9), high systolic blood pressure — 6.7% (2.5–11.6), and environmental contributors. Metabolic risk-associated strokes accounted for 68.8% (57.6–77.5) of all stroke cases [1]. These risk factors are modifiable and potentially preventable, highlighting the critical need for their stratification and management to mitigate stroke burden.

Cognitive impairment. The domain of national strategic interests has clearly defined objectives for reducing the burden of age-associated disorders: preventing and treating CI and sensory disorders, advancing preventive medicine, and promoting healthy and active longevity. The primary causes of CI in older age include various neurodegenerative diseases, CVDs, and dysmetabolic disorders. The number of people with dementia is projected to increase globally from 57.4 million (50.4–65.1) cases in 2019 to 152.8 million (130.8–175.9) by 2050. Compelling evidence has been identified supporting the importance of potentially modifiable risk factors for dementia. Characterizing the distribution and magnitude of the projected growth is critical for planning countermeasures. The predicted rise in dementia prevalence (2019–2050) is attributed to three risk factors included in the GBD Study: high body mass index, elevated fasting plasma glucose levels, and smoking. The growing number of people living with dementia underscores the need for public health planning efforts, including multifaceted approaches and scaled-up interventions to address modifiable risk factors.

Elucidating the pivotal role of metabolic disorders in cerebral dysfunction provides a foundation for developing novel approaches to combat neurocognitive disorders associated with impaired cerebrometabolic health.

Metabolic disorders such as diabetes mellitus (DM), arterial hypertension (AH), and obesity represent significant and growing challenges for global healthcare systems [6, 7]. The pathophysiological foundations of these metabolic diseases are interconnected and serve as major risk factors for circulatory system diseases — the leading cause of death worldwide [8, 9]. The global burden of five common metabolic diseases has been revealed [6, 10]: type 2 diabetes mellitus (T2DM), AH, hypercholesterolemia, obesity, and non-alcoholic fatty liver disease (NAFLD) [11–13]. These metabolic disorders often coexist and exert cumulative health impacts [7,13]. In 2021, among the five prevalent metabolic diseases, AH carried the greatest

[1]Global burden of disease, injuries, and risk factors study.
URL: https://www.healthdata.org/research-analysis/about-gbd

burden (226 (259–9190) million DALY), while T2DM (75 (63–90) million DALY) caused substantially greater disability than NAFLD (3.67 (2.90–4.61) million). The significance of these metabolic diseases has increased over the past three decades, with the global consequences of T2DM and obesity predominating, while the burden impact of AH and hypercholesterolemia has diminished. Despite medical treatment and preventive interventions, there has been a sharp rise in fatal outcomes and mortality associated with metabolic diseases, underscoring the need for coordinated measures [5].

Changes in diet and physical activity often result from environmental and social transformations driven by shifts in sectors such as healthcare, agriculture, transportation, urban planning, food production and distribution, marketing, and industrial technologies. Weight gain and obesity driven by these changes lead to global disruptions to public health.

Obesity is a pandemic of the early 21st century. It affects 39–49% of the global population and is associated with CVD. The prevalence of obesity has tripled since 1975, with 30% of the world's population currently having obesity or overweight [1]. Russia follows global trends: the population-average BMI is 27.6 kg/m^2, obesity is more common in women, its prevalence increases with age, and abdominal obesity is becoming more prominent [14]. According to a screening of the working-age population (40–59 years) conducted by the Russian Center of Neurology and Neurosciences, obesity was observed in one-third of participants, reaching 67% when combined with overweight [15].

Overweight and obesity are associated with higher rates of overall acute stroke and ischemic stroke (IS) in particular, in both men and women. In our study group of IS patients, 7% had normal BMI, 40% were overweight (25.0–29.9 kg/m^2), and 53% had obesity: 34% with grade 1 (BMI 30.0–34.9 kg/m^2), 13% with grade 2 (BMI 35.0–39.9 kg/m^2), and 6% with grade 3 (BMI $\geqslant$ 40 kg/m^2). The BMI values in IS patients with T2DM were 32.7 (29–36) kg/m^2 versus 29 (27–31) kg/m^2 in non-diabetic patients.

Furthermore, overweight and obesity are associated with increased risk of hemorrhagic stroke in men [16]. The prevalence of obesity in stroke patients ranges from 18% to 50% [17, 18]. Notably, obese patients who survive their first stroke show lower long-term post-stroke mortality rates — the obesity paradox [19, 20]. However, the obesity paradox effect in stroke outcomes may vary depending on the pathogenetic subtype of IS [21]. This paradox was observed when using BMI as a criterion but not detected with indices such as waist-to-hip ratio and body fat percentage [22], highlighting the importance of considering obesity phenotype in stroke prognosis.

Excess adipose tissue (both general and visceral) is associated with reduced cognitive performance after adjustment for cardiovascular risk factors, education level, and cerebral vascular lesions [23]. In evaluating the impact of adipose tissue on microangiopathy through a cross-sectional study of over 6,000 volunteers, it was found that elevated BMI itself is not associated with a higher burden of cerebral microangiopathy; however, markers of metabolic dysregulation (particularly elevated blood pressure and hyperglycemia) are significant risk factors for microangiopathy [24], confirming the importance of a comprehensive approach to cerebral metabolic health.

It is abdominal obesity, associated with metabolic alterations, that increases the CVD risk. Current research findings suggest that BMI is insufficiently effective in assessing the risk of comorbid conditions, including CVD. Several alternative approaches to evaluating body fat mass in patients have been proposed [25]. The detrimental effects of abdominal obesity are linked to dysfunction of visceral adipose tissue, which correlates with vascular disease risk factors such as insulin resistance, systemic inflammation, dyslipidemia, and AH [18].

Our own study using bioimpedance analysis revealed that patients with CVD differ in body composition from individuals without CVD [26]. In those patients, both anthropometric measurements and instrumental studies demonstrated an increase in markers of visceral fat redistribution. Specifically, increased abdominal fat area (163.4 ± 63.5 *vs.* 136.34 ± 53.4 cm^2; $p = 0.039$), waist circumference (106.7 ± 18.0 *vs.* 98.2 ± 13.3 cm; $p = 0.017$), and waist-to-hip ratio (1.02 ± 0.1 *vs.* 0.95 ± 0.08; $p < 0.001$) were observed, indicating abdominal obesity despite no significant differences in BMI assessment. Visceral fat redistribution, which contributes to metabolic disorders, was associated with a higher prevalence of AH, T2DM, and blood lipid profile abnormalities in CVD patients [26].

The increased prevalence of metabolic disorders elevates the likelihood of cerebrovascular events. A meta-analysis of 87 studies demonstrated an elevated risk of stroke (RR = 2.27 [1.80–2.85]) [27] and stroke recurrence (RR = 1.46 [1.07–1.97]; $p = 0.02$) [28]. Individuals with $\geqslant$ 3 components of metabolic syndrome have an increased overall stroke risk (RR = 1.29 [1.09–1.52]) and ischemic stroke risk (RR = 1.31 [1.05–1.63]) [29]. A heightened risk of cognitive impairment progression — from mild deficits to dementia — has also been noted [30].

Our multiyear research cycle investigating clinical features of both acute and chronic forms of CVD with various metabolic syndrome manifestations revealed their more pronounced and accentuated severity. Furthermore, not only more profound neurological impairments were observed, but also insufficient functional recovery with poorer outcomes in sensory and speech disorders, which may affect patients' rehabilitation potential [31–38].

Diabetes mellitus (DM) is a major global healthcare challenge due to its epidemic growth rates and the associated medical and social burden caused by severe diabetic complications, risks of disability, and premature mortality in patients [39]. According to the International Diabetes Federation[2], DM is one of the fastest-growing global health emergencies of the 21st century. By 2024, the global number of patients with DM aged 20–79 years reached 588.7 million, exceeding earlier projected growth rates, with an anticipated near-doubling to 852.5 million (a 45% increase) by 2050. Russian national statistics report a 74.5% rise in DM cases between 2009 and

[2] IDF Diabetes Atlas 2025. URL: https://diabetesatlas.org/resources/idf-diabetes-atlas-2025/

2023 [40]. Clinical and epidemiological monitoring of DM in Russia revealed that the target glycated hemoglobin (HbA1c < 7%) level is achieved in only 42% patients with T2DM, while effective blood pressure control is attained in 60% [41].

Numerous large-scale epidemiological studies have established DM as a significant independent risk factor for stroke [42]. A multidimensional palette model conceptualizes DM as the cumulative effect of multiple factors and identifies DM subcategories. Within cluster analyses, the risk of circulatory system diseases and stroke is linked to mild, age-related diabetes [45]. Stratification of heterogeneous DM patient groups may help identify high-risk cohorts requiring enhanced monitoring and pharmacological interventions to prevent stroke.

Among patients with IS, those with DM account for up to 33%. These patients are generally younger and have more comorbidities [44, 45]. Even after controlling for all risk factors, DM increases stroke risk by 22% in patients under 55 years; having more risk factors outside target ranges further elevates stroke likelihood, peaking at 6.23-fold in individuals under 55 years. The strongest predictors of stroke include elevated glycated hemoglobin (HbA_{1c}), systolic blood pressure, longer DM duration, low physical activity, and atrial fibrillation. Elevated HbA_{1c} is the most potent predictor of stroke [46]. Post-stroke CI rate is 5.8 times higher in T2DM patients (OR = 5.83 [2.07–16.41]) [47]. Concurrent DM increases the risk of recurrent stroke (OR = 1.50 [1.36–1.65]) [48]. The likelihood of recurrent events is equally high in prediabetes and DM, suggesting vascular involvement even at early stages of carbohydrate metabolism disorders [49].

DM affects not only the risk but also the course and outcome of stroke. Studies conducted at the Russian Center of Neurology and Neurosciences demonstrated significantly worse hospital-stage outcomes in stroke patients with DM compared to those without DM: higher NIH Stroke Scale scores (6 [4–10] *vs.* 4 [1–8]; $p = 0.03$), more frequent lack of improvement or progression of neurological deficits (21.6% *vs.* 7%; $p = 0.02$), and less frequent minor improvement (13.7% *vs.* 4.7%; $p = 0.004$). Functional independence recovery outcomes were also poorer in patients with T2DM, as evidenced by higher modified Rankin Scale scores (3 [1–4] *vs.* 2 [0–3]; $p = 0.02$) and a lower proportion achieving 0–2 points (46% *vs.* 72%), underscoring the social significance of metabolic comorbidity in stroke management [34, 50].

Our data indicate that acute stroke in patients with T2DM is accompanied by hyperglycemia (9.1 [7.1–12.0] mmol/L) and elevated HbA_{1c} levels (7.8% [6.8–9.6]), with 34% of patients showing values ⩾8%, highlighting the role of poor glycemic control in CVD pathogenesis and emphasizing the importance of its correction for prevention [51].

Both hyper- and hypoglycemia, as well as advanced glycation end product (AGE) accumulation, have been shown to negatively affect prognosis and recovery in stroke patients. Parameters such as diabetes duration, HbA_{1c} levels, and glycemia were statistically significant predictors of greater disability. The likelihood of unfavorable stroke outcomes (mRS ⩽ 3) increased with HbA_{1c} ⩾ 7%, confirming the importance of achieving glycemic control targets. An algorithm for assessing carbohydrate metabolism and predicting outcomes in patients during the hyperacute stroke phase has been developed [32, 50].

Metabolic disorders influence CI. Risk factors for CI in DM include the following groups (including genetic ones):
- conventional (advanced age, low education level, depression, sedentary lifestyle, smoking, family history);
- diabetes-associated (hypo- and hyperglycemia, hyperinsulinemia, retinopathy, nephropathy, longer DM duration);

vascular (AH, dyslipidemia, stroke, coronary artery disease, atherosclerotic lower extremity artery disease);
- genetic (ApoE ε4 allele, haptoglobin genotype 1-1, and Gly/Ser genotype of the receptor for advanced glycation end products) [52].

Our study revealed a pattern of changes in CVD and T2DM, characterized by concurrent disturbances in carbohydrate metabolism and neurocognitive dysfunction accompanied by neurophysiological and neuroimaging changes. This comorbidity is associated not only with memory and attention impairments but also with significant executive brain function deficits, while regulatory deficits primarily manifest as mental rigidity and emotional disturbances and volitional disorders. The quality of glycemic control influences cognitive function assessment outcomes. We identified not only an interrelationship between clinical, neurophysiological, and metabolic characteristics but also the potential for diagnosing subclinical manifestations of impaired CNS function in patients with both chronic CVD and DM. The particular importance of early detection and therapy of cognitive impairment in this patient group is underscored by the fact that DM, more than any other disease, requires active patient participation in disease control and treatment [53].

Treatment adherence issues are critical for achieving clinical outcomes, particularly in patients with chronic diseases. Patients with cerebroal metabolic disorders demonstrated incomplete or low adherence across various aspects of therapeutic interventions. Specifically, low treatment adherence was observed in 10.3% of patients without DM and 34.4% of those with T2DM ($p = 0.001$). Obesity parameters, assessed not only by BMI but also by waist circumference, showed significant inverse associations with adherence to lifestyle modifications and overall treatment adherence. According to the developed model for identifying low compliance, the concurrent T2DM and AH are expected to reduce adherence to medical management in over 20% of patients. A multifactorial relationship was identified between treatment adherence aspects, the clinical course of vascular disease, and the presence of metabolic risk markers, forming a vicious cycle: inadequate metabolic control → CVD → CI → low adherence [54].

In the context of age-related brain disorders, it should be emphasized that DM represents a model of accelerated cerebral aging, further increasing the risk of age-related degenerative and vascular diseases of the nervous system. One surrogate biomarker of aging may be the white matter age gap, defined as the difference between instrumentally assessed white

matter age (based on diffusion-weighted MRI) and real age. Among all risk factors, T2DM showed the strongest association with an increased gap (1.39 years; $p < 0.001$), followed by AH and smoking. T2DM may be associated with diffuse brain atrophy, altered functional connectivity, and reduced cerebral perfusion.

Cerebral artery atherosclerosis represents the leading pathological process within the spectrum of CVD subtypes. Findings from a series of studies conducted at the Russian Center of Neurology and Neurosciences confirmed a higher frequency of cerebral atherosclerosis progression in patients with T2DM. Ultrasonographic evaluation of the brachiocephalic arteries demonstrated that the prevalence of multiple vascular territories involvement is significantly higher in patients with combined cerebral metabolic disorders [35]. Progression of atherosclerosis in the internal carotid artery system is further associated with marked changes in vascular wall inflammatory biomarkers and neoangiogenesis – including lipoprotein-associated phospholipase A2, tumor necrosis factor-α, and vascular endothelial growth factor – as well as elevated blood glucose levels. In turn, progression of atherosclerotic lesions in the carotid system was accompanied by new or worsening pre-existing neurological symptoms in 50% of cases [36].

Metabolic disorders correlate with an aggressive atherosclerotic process, evidenced by a predominance of atherothrombotic stroke subtypes and high-grade cerebral artery stenoses. Combined assessment of carbohydrate and lipid metabolism using the triglyceride-glucose index in patients with acute/chronic stroke revealed not only reduced insulin sensitivity in this cohort but also highlighted the role of glucolipotoxicity in hemodynamically significant stenosis formation, CVD progression, and prognosis [35, 37, 50]. A prospective study of CVD patients, focusing on cases with > 50% stenosis in one internal carotid artery, found metabolic syndrome to be more frequently associated with high-grade stenoses (70–99%). Among patients with T2DM and symptomatic stenoses, 87.5% exhibited high-grade stenoses. Ultrasound characteristics in T2DM-comorbid patients predominantly revealed hyperechoic atherosclerotic plaques, including those with calcified areas.

A series of studies on cerebral atherosclerosis has proposeda biomarker-based model for assessing atherogenic potential in patients with ischemic cerebrovascular events and comorbid T2DM. This model incorporates lipid profile markers, endothelial dysfunction indicators, inflammatory markers, hemostasis parameters, and adipokines [55, 56]. Proatherogenic markers include levels of highly sensitive hyperatherogenic small dense low-density lipoprotein (LDL) subfractions, total cholesterol, plasminogen activator inhibitor-1, NO_2-, NO_3-, endothelin-1, monocyte chemoattractant protein-1, vascular endothelial growth factor A, platelet-derived growth factor BB, tumor necrosis factor-α, interleukin (IL)-1β, C-reactive protein, and IL-6. The anti-atherogenic category comprises lipoprotein(a), high-density lipoprotein, nitric oxide, tissue plasminogen activator, and adiponectin. This biomarker-based technology for evaluating cerebral atherosclerosis progression is used to optimize diagnostic approaches and therapeutic strategies in patients with cerebral metabolic disorders [55, 56]. The ongoing search for novel biomarkers amid the epidemic rise of metabolic diseases aims to stratify high-risk patients and holds clinical potential.

Morphological studies of atherosclerotic plaque biopsy specimens obtained during prophylactic carotid endarterectomy provided critical evidence of the adverse effects of comorbid metabolic factors on cerebral atherosclerosis progression. Histopathological analyses frequently reveal critical atherosclerotic stenosis, active atherogenesis, predominant large atheromatous foci with abundant lipophages in plaque composition, and focal fibrosis with calcification in the arterial tunica media [57].

Underlying Mechanisms of Cerebral Metabolic Disorders

The concurrent epidemic increase in the prevalence of metabolic disorders, obesity, and DM inevitably undermines global efforts to combat CVD.

Current evidence suggests that brain is a multifunctional endocrine organ that regulates neuroendocrine processes, coordinating systemic development and maintaining body homeostasis. Obesity represents a continuum of initially adaptive changes that transition to pathological alterations as the disease progresses, triggered by disrupted signaling cascades in the setting of excessive caloric intake. Insulin plays a pivotal role in these processes. Cerebral insulin signaling mediates complex interorgan crosstalk, orchestrating nutrient distribution through regulation of appetite, lipolysis, triglyceride secretion and uptake, amino acid metabolism, thermogenesis, and hepatic glucose production. Ultimately, this system protects against ectopic lipid deposition, lipotoxicity, and hyperglycemia [58–60].

Hypoglycemia prevention is key to survival. Brain insulin resistance can be understood as a physiological adaptation to maintain euglycemia by enhancing lipolysis and increasing hepatic glucose production—a process critical for survival under nutrient-deficient conditions. Overeating rapidly induces brain insulin resistance, which acts as a key driver of metabolic diseases and T2DM [60].

Insulin resistance, chronic hyperglycemia, and dyslipidemia trigger a cascade of changes, including the formation of atherogenic low-density lipoproteins, advanced glycation end products, and activation of proinflammatory signals that affect the arterial wall, initiating and promoting atherosclerotic lesions. Numerous components characterizing metabolic dysfunction lead to a wide range of consequences, including blood-brain barrier disruption, neuroinflammation, vascular pathology, neurodegeneration, and CI [61, 62]. Brain damage is associated with inflammatory processes, including meta-inflammation – a chronic systemic disorder caused by obesity. This pathway serves as the primary pathophysiological mechanism leading to the development, progression, and thrombotic complications of atherosclerosis and vascular disorders [63]. In meta-inflammation, external or endogenous factors may act by stimulating membrane or cytoplasmic receptors of monocytes, macrophages, neutrophils, or dendritic cells. These

factors can induce inflammasome oligomerization and activate the NLRP3 [64]. IL-1β and IL-18, generated through NLRP3-caspase activation, enter a self-amplifying loop and also induce macrophage production of IL-6. IL-6 stimulates hepatocytes to produce C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1, releasing them systemically and mediating thrombotic propensity. IL-6 directly potentiates another prothrombotic pathway mediated by the JAK1/TYK2 membrane receptor, leading to thrombocytosis and procoagulant changes [65].

The primary functional load of the hemostatic system lies in the microvascular bed, including cerebral vessels. The critical role of prothrombotic changes in CVD has been demonstrated in fundamental studies from the Russian Center of Neurology and Neurosciences [66–71]. In patients with acute/chronic CVD accompanied by metabolic syndrome, significant disturbances are observed in platelet and plasma hemostasis components, altered blood microrheological parameters (both baseline and dynamic), elevated blood viscosity, fibrinogen, hematocrit, platelet aggregation activity, and reduced erythrocyte deformability [31, 72].

Hyperglycemia significantly contributes to these hemorheological and hemostatic changes [73, 74]. Increased advanced glycation end product formation activates platelet hemostasis, suppresses fibrinolysis, and promotes prothrombogenic blood potential. AGE levels correlate positively with ADP-induced platelet aggregation (r = 0.4176) and negatively with fibrinolytic activity (r = –0.426117) and fibrinolytic index (r = –0.36) [73].

We confirmed the significance of excessive intra-abdominal fat deposition, which is pathogenetically linked to meta-inflammation, in shaping hemorheological and hemostatic system changes in patients with CVD [26]. Increased visceral fat volume not only negatively impacts metabolic parameters but is also associated with prothrombogenic blood changes. Visceral fat area showed significant correlations with fibrinogen levels (r = 0.83), von Willebrand factor (r = 0.250), factor VIII (r = 0.321), epinephrine-induced platelet aggregation (r = 0.780), and protein S (r = 0.532), while demonstrating inverse correlations with tissue plasminogen activator levels (r = –0.370) and the tissue plasminogen activator/plasminogen activator inhibitor ratio (r = –0.3). The obtained data on hemorheological and hemostatic changes in CVD associated with body composition alterations highlight the role of abdominal obesity in prothrombotic and procoagulant changes in CVD patients [26]. The identified correlations between hemostasis parameters and adipose tissue characteristics reveal mechanisms through which risk factors contribute to the CVD.

Functional and structural cerebral impairments under metabolic load

When damaging stimuli become chronic, as seen in obesity, metabolic syndrome, and T2DM, a persistent reparative process with tissue remodeling occurs. The brain undergoes astrogliosis [61]. Metabolic neuroinflammation is a chronic aseptic inflammatory process characterized by systemic changes involving elevated proinflammatory cytokines (IL-1β and IL-18), microglial activation, and dysregulated NLRP3 inflammasome formation [75]. Hypothalamic neuroinflammation causing gliosis and neuronal death [75] may stem from leptin and insulin effects, as well as factors acting through the pro-opiomelanocortin system [76]. In turn, hypothalamic neuroinflammation modulates satiety regulation, thereby promoting obesity [77], creating a vicious cycle of cerebral and metabolic disturbances. Prolonged neuroinflammation disrupts existing protective barriers, leading to neurodegenerative changes. Individuals with obesity face increased risks of CI, vascular dementia, Alzheimer's disease, as well as Parkinson's and Huntington's diseases [78].

The results of studies conducted at the Russian Center of Neurology and Neurosciences demonstrate the negative impact of chronic hyperglycemia on the white matter of the cerebral hemispheres, mediated through mechanisms of direct damage to brain tissue and microcirculatory vessels [79]. The contribution of insulin resistance and glucolipotoxicity to the clinical manifestation of structural brain changes in chronic CVD has been established, and the concept of an adverse cerebral metabolic profile has been developed, encompassing clinical, neuroimaging, and laboratory characteristics of patients.

Cerebral metabolic health

A series of studies, collectively involving over 5,500 observations of CVD patients, has provided a detailed investigation of its various aspects in the context of metabolic disorders. The study revealed and examined interconnections between obesity, T2DM, metabolic syndrome, and cerebral macro- and microvascular damage, prothrombotic changes, clinical course, and prognosis of acute stroke and chronic CVD, identifying a set of biomarkers for vascular and cerebral injury. Analysis of the current state of neuroscience and the findings of our own research enabled the synthesis of a unified conceptual approach to the issue of cerebral metabolic health.

In cerebral metabolic disorders, the development and progression of brain lesions are associated with the involvement of vessels of various calibers, alterations in hemorheology and hemostasis systems, meta-inflammation and neuroinflammation, and neurodegeneration, which are linked to excessive adipogenesis, dyslipidemia, dysglycemia, and impaired permeability of the blood-brain and blood-nerve barriers, ultimately resulting in the CVDs, cerebral microangiopathy, and CI, with potential involvement of the peripheral nervous system.

A concept of a bidirectional relationship between cerebral and metabolic disorders has been established. Brain functioning is inextricably linked to metabolism; signaling pathways associated with the supply and accumulation of energy substrates influence both the nervous and vascular systems, whereas mechanisms underlying metabolic and neurological disorders are closely intertwined. Therefore, instead of viewing CVD and metabolic diseases as separate processes, it is essential to assess their mutual influence within a unified paradigm. The development of methods for

preventing and treating CVD requires adopting a new strategic concept of cerebral metabolic health, within which the association between metabolic disorders and CVD is examined. The significance of cerebral metabolic health impairment consequences for the healthcare system and society necessitates comprehensive strategies encompassing both population-wide and personalized prevention at different stages of human life.

The concept of cerebral metabolic health defines the interaction of a complex of metabolic risk factors, functional and organic changes in cerebral macro- and microvasculature, and brain structures, which influences the incidence of acute and chronic cerebrovascular events and cognitive disorders, determines worse outcomes and mortality. The implementation of this term reflects the strong interrelationship between the mechanisms of metabolic and cerebral disorders and serves to adjust both population-level and patient-centered treatment strategies for brain diseases, as well as primary and secondary prevention measures.

Disorders of cerebral metabolic health represent a progressive impairment of central nervous system activity, initiated by adverse environmental influences under conditions of genetic predisposition, excessive intake of energy substrates, and disruption of central energy balance regulation, leading to excessive adipose tissue deposition with increased systemic and cerebral insulin resistance, neuroinflammation, and oxidative stress. The synergistic damaging effects of metabolic risk factors (AH, dyslipidemia, and hyperglycemia) have a unidirectional pathway and manifest through combined damage to cerebral arteries of various calibers alongside increased thrombogenic potential. Progression of the process leads to acute and chronic cerebrovascular events, cerebral microangiopathy, neurocognitive disorders, and ultimately to disability and/or death. The concept of staged disturbances in cerebral metabolic health reflects the phasic nature of the pathophysiological process, the progressive advancement of disorders leading to cerebral dysfunction, and underscores the importance of targeted interventions at all stages for CVD prevention and treatment (Fig. 1, Table 1).

The concept of cerebral metabolic health serves to form a comprehensive picture of diverse metabolic processes associated with the nervous system dysfunction. Primarily, this applies to CVDs due to their higher prevalence and severe consequences. At the same time, the methodological advantages of this approach – including integrative strategies, multidisciplinarity, diversification of preventive measures, stepwise diagnostics, and therapy personalization – inevitably extend to other socially significant disorders of the nervous system (i.e., neurodegenerative, demyelinating, autoimmune, etc.).

Conclusion

The syndemia of obesity and DM underlies the progressive rise in CVD, impacting key mechanisms of CVD pathogenesis. The lack of significant success in preventing the spectrum of CVD amid an aggressive increase in metabolic disorders necessitates a revision of approaches to this issue at the national level. Both high-risk strategies and population-wide preventive medicine strategies should complement each other [80].

Promising directions for studying cerebral metabolic health include:
- prevention of CVDs in individuals with disorders of hemostasis, and carbohydrate and lipid metabolism;
- multisystem interrelationships between cerebral metabolic disorders and other endocrine organs: effects of oral contraceptives and menopausal hormone therapy on stroke development, hypogonadism, thyroid diseases, dysregulation of the hypothalamus-pituitary-adrenal axis, etc.;
- development of measures to preserve cognitive health (studies of innovative agents with proposed metabolic and neuroprotective mechanisms of action).

Approaches to overcoming the objective complexity of cerebral metabolic disorders include:
- development of algorithms for multidisciplinary collaboration to preserve cerebral metabolic health in the Russian population;

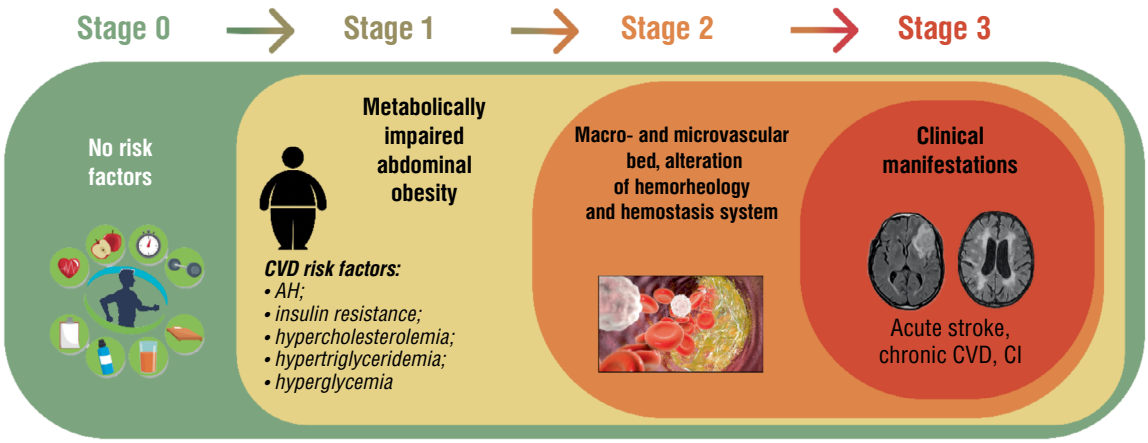

Fig. 1. Sequence of CVD development.

Table 1. Cerebral metabolic disorders

Stage	Description	Characteristic
Stage 0	No metabolic disorders or CVD symptoms	No risk factors: • normal waist circumference (considering race and sex); • BMI < 25 kg/m^2; • no carbohydrate metabolism disturbances (no DM or pre-diabetes) • no dyslipidemia; • no AH
Stage 1	CVD risk factors stage	Stage of metabolically impaired obesity — obesity + risk factors: • abdominal obesity: waist circumference ⩾ 88/102 cm in women/men (for Asians ⩾ 80/90 cm in women/men) plus 2 or more criteria: - AH; - insulin resistance; - hypercholesterolemia; - hypertriglyceridemia; - hyperglycemia: DM or prediabetes (impaired fasting glycemia/impaired glucose tolerance)
Stage 2	Macro- and microangiopathy stage	Brachiocephalic artery atherosclerosis, intracranial atherosclerosis, cerebral microangiopathy, changes in the hemorheology and hemostasis system
Stage 3	Symptomatic CVD	Acute stroke, chronic CVD, CI

- exploration of innovative approaches to cerebroprotection through advancements in brain metabolism research, including artificial intelligence, neuromodulation, and other cutting-edge technologies.

The challenge of preserving cerebral metabolic health and quality of life in society is acquiring a population-wide significance, necessitating the integration of population-based and personalized measures for the prevention and treatment of brain diseases.

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Mitochondrial Dysfunction in the Pathogenesis of Parkinson Disease: Current Concepts and Potential Therapeutic Strategies

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Abstract

Parkinson disease (PD) is a progressive extrapyramidal disorder characterized by the biodegradation of dopaminergic neurons in the substantia nigra. The total number of patients diagnosed with PD worldwide is expected to more than double by 2030, inevitably placing a significant financial burden on healthcare systems. The progression of the disease leads to persistent maladjustment in all aspects of the patient's life, resulting in a loss of human resources. Approximately 85–90% of PD cases are sporadic and multifactorial. The remaining 10–15% are familial forms with conventional inheritance patterns. Current research suggests multiple mechanisms for PD development, but increasing evidence supports a critical role of mitochondrial dysfunction in PD pathogenesis.

*The **aim** of this review was to discuss the key pathogenetic mechanisms of mitochondrial dysfunction in PD pathogenesis. The following keywords and phrases (both in Russian and English) were used to search databases such as eLIBRARY.RU, PubMed, and Web of Science for full-text articles in Russian and English published over the last 20 years: Parkinson disease, neurodegeneration, pathophysiology, mitochondrial dysfunction, bioenergetics, mitophagy, pathogenetic therapy.*

The review describes the factors that cause mitochondrial dysfunction and its impact on PD. Potential therapeutic strategies targeting mitochondrial dysfunction are also described.

Keywords: *Parkinson disease; neurodegeneration; pathophysiology; mitochondrial dysfunction; bioenergetics; mitophagy; pathogenetic therapy*

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Митохондриальная дисфункция в патогенезе болезни Паркинсона: современные представления и потенциальные терапевтические стратегии

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Аннотация

Болезнь Паркинсона (БП) – прогрессирующее экстрапирамидное заболевание, характеризующееся биодеградацией дофаминергических нейронов чёрной субстанции. Прогнозируется, что общее число пациентов с диагнозом БП к 2030 г. в мире увеличится более чем в 2 раза, что неизбежно приведёт к большой материальной нагрузке на систему здравоохранения. Прогрессирование заболевания характеризуется стойкой дезадаптацией пациентов во всех сферах жизни и, как следствие, потерей человеческих ресурсов. Около 85–90% случаев БП являются спорадическими и имеют мультифакториальную природу. Оставшиеся 10–15% являются семейными формами с традиционными формами наследования. Современные исследования доказывают различные механизмы развития заболевания, однако всё больше данных подтверждают решающую роль митохондриальной дисфункции в развитии БП.

Цель *обзора – рассмотреть ключевые патогенетические механизмы митохондриальной дисфункции в контексте патогенеза заболевания. Нами проведён поиск полнотекстовых публикаций на русском и английском языках в базах данных eLIBRARY.RU, PubMed, Web of Science за последнее 20 лет с использованием ключевых слов и словосочетаний: болезнь Паркинсона, нейродегенерация, патофизиология, митохондриальная дисфункция, биоэнергетика, митофагия, патогенетическая терапия.*

В обзоре подробно рассмотрены факторы, индуцирующие митохондриальную дисфункцию, а также влияние митохондриальной дисфункции на развитие БП. Представлены потенциальные терапевтические стратегии, сопряжённые с митохондриальной дисфункцией.

Ключевые слова: *болезнь Паркинсона; нейродегенерация; патофизиология; митохондриальная дисфункция; биоэнергетика; митофагия; патогенетическая терапия*

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

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Introduction

Parkinson disease (PD) is one of the most common neurodegenerative disorders. PD manifests clinically through typical motor and non-motor symptoms. Motor symptoms include resting tremor, bradykinesia, muscular rigidity, hypomimia, and postural instability. Non-motor symptoms, which usually precede motor symptoms during the prodromal period, include cognitive impairment, hyposmia, insomnia, constipation, and depression. The prodromal period lasts for 5–15 years [1]. The clinical symptoms of PD are associated with the death of dopaminergic neurons in the compact region of the substantia nigra in the midbrain. Motor symptoms appear only after 50–80% of these neurons have died. PD is pathologically characterized by the accumulation of Lewy bodies, which are round, eosinophilic intracellular inclusions primarily composed of aberrant alpha-synuclein [2]. The growing elderly population and improved medical care for patients with PD are expected to increase the PD prevalence in the next 20–30 years. It is estimated that the total number of PD patients worldwide will rise from 4.1 million in 2005 to 8.7 million in 2030. This increase will put intense strain on healthcare systems in many countries [2]. The epidemiological parameters of PD prevalence and incidence vary considerably by Russian region. Tomsk has the highest prevalence (238 cases per 100,000 people), whereas Moscow has the lowest prevalence (27 cases per 100,000 people). The incidence rates also vary widely. The lowest incidence rate is reported in Karelia (1.88 cases per 100,000 people per year). The highest rate is reported in the Solnechnogorsky district in the Moscow Oblast (16.3 cases per 100,000 people per year) [3]. In addition, symptomatic therapy becomes less effective as patients' conditions worsen. Currently, there are no treatments that can prevent the onset or progression of PD. Understanding the pathogenesis of PD is critical for the development and clinical implementation of novel, highly effective therapeutic strategies in the near future.

PD is considered a multisystem and multifactorial disease that can be initiated by various etiological factors, including genetic, biological, and environmental factors [3]. From a pathophysiological perspective, familial forms of PD are classified as genetic diseases with Mendelian inheritance patterns. Sporadic forms of PD, which account for 85–90% of cases, belong to multifactorial diseases, meaning that they are genetically predisposed [4]. Sporadic forms have a specific genetic predisposition, but its penetrance depends on environmental factors that induce and potentiate PD development. In recent years, tremendous progress has been made in understanding the molecular basis of PD pathogenesis, leading to various theories. Pathogenetic factors include disturbances in both apoptotic and non-apoptotic programmed neuronal cell death, as well as aberrant autophagy regulation, endoplasmic reticulum dysfunction, and elevated intracellular calcium levels. However, their exact role in neuronal degeneration is still being investigated [5].

Recently, the pathogenetic role of mitochondria in PD has been actively studied. This is because neurons have a complex mitochondrial network extending from the soma to the synaptic terminals. These terminals relay information from one neuron to another. Mitochondria perform many functions, such as adenosine triphosphate (ATP) generation, calcium buffering, and epigenetic neuronal signaling. Unlike many other cell types, neurons have higher bioenergetic needs. For example, ionic homeostasis requires ATP, which is constantly consumed to generate transmembrane ionic fluxes, sequester neurotransmitters into vesicles, facilitate vesicle fusion during synaptic activity, and mediate reuptake during vesicular recycling. ATP is also necessary to maintain and restore a large pool of neurotransmitters. ATP is synthesized

for these processes within the mitochondria. Therefore, mitochondrial dysfunction is considered an essential part of PD pathogenesis [6]. This review focuses on the latest advances in understanding how mitochondrial dysfunction contributes to the development of sporadic and familial forms of PD.

Mitochondrial Dysfunction in the Pathogenesis of Sporadic Parkinson Disease

An electron transport chain (ETC) within mitochondria is the primary source of reactive oxygen species (ROS) in eukaryotic cells. The ETC sequentially reduces molecular oxygen to water. Complexes I and III produce a small amount of superoxide (O_2^-) during this process. Superoxide is formed in the mitochondria and can be converted into hydrogen peroxide by an manganese superoxide dismutase. However, under certain conditions ROS production may exceed the cellular antioxidant capacity. This state, called oxidative stress, can cause irreversible damage to cellular macromolecules and lead to cell death. Markers of oxidative stress, such as oxidized lipids, proteins, and DNA, are found at high concentrations in patients with PD [6]. In addition, patients at risk for PD, including those with frequent constipation, impaired olfactory function, anxiety and depressive thoughts, and sleep behavior disorders, have higher levels of oxidative stress than those at no risk. Increased oxidative stress is one of the effects of complex I deficiency observed in sporadic PD. This is supported by data from a study by Esteves et al., which showed increased oxidative stress and reduced complex I activity in neuronal cells of patients with PD compared to healthy individuals [7].

A major breakthrough in understanding the PD pathogenesis was achieved through the analysis of specific cases of induced parkinsonism in California during the 1980s. Langston et al. (1983) identified individuals with histories of intravenous substance abuse who had inadvertently injected 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a synthetic analog of heroin [6]. They developed parkinsonism within a few days. An autopsy showed significant damage to dopaminergic neurons in the substantia nigra, as well as typical alpha-synuclein inclusions. MPTP easily crosses the blood-brain barrier and is taken up by astrocytes, where it is metabolized into 1-methyl-4-phenylpyridinium (MPP^+) and released into the extracellular space. MPP^+ is a substrate of the dopamine transporter that is selectively taken up by dopaminergic neurons, where it inhibits mitochondrial complex I. After inhibiting complex I, the excess superoxide suppresses the antioxidant capacity of dopaminergic neurons, leading to their death [6]. MPP^+ is toxic to dopaminergic neurons in humans, primates, and rodents. Therefore, MPTP is recommended for use in animal models of parkinsonism by Guidelines for Preclinical Studies of Medicinal Products by the Scientific Center for Expert Evaluation of Medicinal Products.[1] However, MPTP models of PD have some limitations. For example, MPTP experiments rarely result in the formation of Lewy bodies. MPTP induces acute or subacute neurodegeneration, which is differs from the chronic neurodegenerative process in PD. In addition, MPTP-induced parkinsonism models often fail to demonstrate the motor impairments characteristic of PD [8–10]. In experimental settings, other inhibitors of mitochondrial complex I, such as rotenone and annonacin, as well as other pesticides affecting mitochondria (paraquat, maneb, dieldrin, heptachlor, and atrazine), induce pathological, biochemical, and behavioral changes typical of PD [11, 12].

Another molecular hypothesis suggests that the mitochondrial defects in PD result from the accumulation of point mutations in mitochondrial DNA (mtDNA). In eukaryotic cells, mtDNA is organized into nucleoids, which consist of proteins and nucleic acids. Each nucleoid contains an average of 1.4 million copies of mtDNA, and cells can contain up to 2,000 nucleoids [6]. mtDNA is circular and encodes 13 proteins, as well as mitochondrial transfer RNA (tRNA) and ribosomal RNA (rRNA) [6]. The proteins encoded by mtDNA include subunits from all parts of the ETC. Six of these genes encode subunits of complex I [6]. Therefore, point mutations in any of six genes can affect the activity of complex I. Therefore, mitochondria are involved in the pathogenesis of Parkinson-like syndromes. Mitochondrial dysfunction has been reported in the neurons of the substantia nigra, as well as in the myocytes, platelets, lymphocytes, and fibroblasts of patients with PD. These findings support the idea that mitochondrial dysfunction is not limited to neurons alone and is an important feature of PD's multisystem nature.

Alpha-synuclein, a characteristic marker of PD, binds to voltage-dependent anion-selective channel 1 (VDAC1), translocase of the outer membrane (TOM) 40, and TOM20, thereby mediating mitochondrial dysfunction [13, 14]. In sporadic PD, reduced levels of VDAC1 are found in neurons of the substantia nigra due to alpha-synuclein aggregation, which contributes to mitochondrial dysfunction [15]. In addition, alpha-synuclein activates a channel that depolarizes the mitochondrial membrane, leading to mitochondrial fragmentation and degradation. The aggregation of alpha-synuclein disrupts proteostasis, impairing function and transport within the endoplasmic reticulum, the Golgi apparatus, and the autophagolysosomal system. This process destabilizes organelle connections and contributes to mitochondrial dysfunction. Oxidative stress is closely related to mitochondrial dysfunction. Mitochondria produce up to 90% of cellular ROS [16]. Synucleinopathy, oxidative stress, and mitochondrial dysfunction appear to form a vicious cycle in the pathogenesis of sporadic PD [17]. The accumulation of iron in the substantia nigra of patients with sporadic PD can also cause increased ROS production and enhanced alpha-synuclein aggregation [15, 18]. Mitochondria actively exchange iron with the cytoplasm. This exchange is necessary for the synthesis of various enzyme systems that are integral components of mitochondrial complexes I and III [18]. The inhibition of complex I by rotenone, MPTP, and paraquat leads to iron accumulation and induces the development of PD [19]. Inhibition of the ubiquitin-proteasome system also causes an imbalance of iron in cells, further enhancing ROS generation and alpha-synuclein aggregation [20].

[1]Guidelines for Preclinical Studies of Medicinal Products. Part 1. Moscow; 2012. 944 p. URL: https://rsmu.ru/fileadmin/templates/DOC/Zakon_RF/Mironov_Rukovodstvo_po_provedeniju_doklinicheskikh_issledovanii_lekarstvennykh_sredstv.pdf

Mitochondrial Dysfunction in the Pathogenesis of Autosomal Dominant Parkinson Disease

Alpha-synuclein was first associated with PD due to its presence in Lewy bodies. Subsequently, the *SNCA* gene, which encodes alpha-synuclein, was identified as the first gene responsible for autosomal dominant PD [21]. Alpha-synuclein is a small polypeptide consisting of 140 amino acids. It mediates neurotransmitter release in presynaptic terminals and interacts with the membranes of various organelles, including mitochondria. Mullin et al. discovered that alpha-synuclein is present in mitochondrial membranes, where it directly influences the structure and function of organelles [22]. Both *in vitro* and *in vivo* models have demonstrated that *SNCA* gene mutations (*A53T*, *E46K* and *H50Q*) lead to the production of a defective protein, resulting in mitochondrial fragmentation and excessive ROS production [23]. Alpha-synuclein is normally located in a specialized structure called the mitochondria-associated endoplasmic reticulum membrane (MAM). The MAM acts as a barrier between the endoplasmic reticulum and the mitochondria and plays a critical role in regulating calcium signaling and apoptosis. Negative mutations in the *SNCA* gene decrease alpha-synuclein binding to MAM and increase mitochondrial fragmentation. These findings suggest that alpha-synuclein is involved in the regulation of mitochondrial morphology [14, 24]. Overexpression of mutant alpha-synuclein causes the dissociation of mitochondria from MAM, disrupting calcium exchange and reducing mitochondrial energy production [25]. Ryan et al. discovered that alpha-synuclein directly influences mitochondrial morphology and biogenesis by regulating the PGC1α receptor [26].

Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene, which encodes a protein called dardarin, are a frequent cause of autosomal dominant and familial forms of PD [27]. LRRK2 is a multifunctional protein kinase, where PD-associated mutations lead to increased kinase activity. Increased mitochondrial sensitivity to toxins, defects in mitochondrial homeostasis, and increased ROS production have been demonstrated in experimental animal models with mutant *LRRK2* associated with PD [23]. Studies have shown that the *G2019S* mutation in the *LRRK2* gene is associated with mitochondrial abnormalities in dopaminergic neurons of the substantia nigra in patients with PD [26], as well as in PD mouse models [27].

Several proteins interact with LRRK2, mediating pathological effects on mitochondria. For example, the mitochondrial fission protein, dynamin-related protein 1 (DRP1), acts as an effector of mitochondrial fragmentation through LRRK2-mediated phosphorylation [28]. In addition, LRRK2 appears to interact with other mitochondrial fission proteins, including mitofusin and the dynamin-like protein [29]. Excessive activity of uncoupling proteins 2 and 4 may cause increased proton leakage and LRRK2-mediated loss of mitochondrial membrane potential [30]. The *G2019S* mutation in the *LRRK2* gene impairs the proteasomal degradation of an outer mitochondrial membrane protein, which connects mitochondria to microtubule motor proteins, contributing to defective mitophagy [31].

Recently, a link was discovered between PD and the vacuolar protein sorting 35 (*VPS35*) gene in European patient cohorts with a family history of PD, suggesting autosomal dominant transmission [27, 32]. VPS35 is an essential component of a complex that mediates the retrograde delivery of substances from endosomes to the Golgi apparatus and the recycling of substances from endosomes to the cell surface (33). Early studies showed that PD-associated mutations in the *VPS35* gene made cells more vulnerable to the mitochondrial toxin MPP^+ *in vitro* [34]. The primary function of *VPS35* in mitochondria appears to be the regulation of mitochondrial dynamics through interaction with fission and fusion proteins. Recent studies have demonstrated that the mutant *VPS35* protein may cause mitochondrial fragmentation and lead to neurodegeneration [14]. This may occur through decreased degradation of the E3 ubiquitin ligase-1 protein, which increases mitofusin degradation [35], or by enhancing DRP1 complex turnover through vesicle-mediated transport from mitochondria to lysosomes [36]. In addition, the *D620N* mutation in the *VPS35* gene is shown to increase mitochondrial fragmentation, disrupting the assembly and activity of complex I [37].

Another gene, *CHCHD2* (*coiled-coil-helix-coiled-coil-helix domain-containing 2)*, has mutations that have been identified as a potential cause of late-onset, autosomal dominant PD in three Japanese families [38]. This gene produces a protein containing a coiled-coil-helix-coiled-coil-helix domain, which is found in the intermembrane space of mitochondria and the cell nucleus. CHCHD2 is usually found in mitochondria and associated with complex IV. The under-expression of CHCHD2 suppresses the activity of complex IV, which leads to increased ROS production and mitochondrial fragmentation [39]. It should be noted that CHCHD2 translocates into the nucleus and acts as a transcription factor under stress conditions, thereby regulating the expression of subunit 4 isoforms of mitochondrial complex IV [40]. In addition, Drosophila with low CHCHD2 [41] expression or PD-linked *CHCHD* gene mutations exhibit mitochondrial structural and biochemical abnormalities resulting in dopaminergic neurodegeneration in the substantia nigra and motor dysfunction. These findings strongly suggest that the *CHCHD2* gene mutation leads to nigrostriatal neurodegeneration and the development of PD specifically due to mitochondrial dysfunction.

Mitochondrial Dysfunction in the Pathogenesis of Autosomal Recessive Parkinson Disease

The most common cause of autosomal recessive PD is mutations (>120) in the *Parkin*gene, which encodes the Parkin protein. The Parkin protein is a cytosolic E3 ubiquitin ligase that attaches ubiquitin to target proteins for signaling or proteasomal degradation. Parkin primarily functions in association with mitochondria. Parkin-deficient models show severe defects in mitochondrial morphology and function [43]. The E3 ubiquitin ligase plays different functions in maintaining mitochondrial homeostasis and regulating mitochondrial biogenesis and mitophagy. Mitophagy is the process by which dysfunctional mitochondria are removed from a healthy mitochondrial pool and degraded using the autophagolysosomal pathway [44]. During the early stages of mitochondrial degradation, Parkin is recruited to damaged or dysfunctional mitochondria and activated by kinase 1, leading to ubiquitylation of proteins and subsequent proteasomal degrada-

tion [14]. Pickrell et al. demonstrated a defect in Parkin-mediated mitophagy in distal neuronal axons in a rodent model of age-related dopaminergic neurodegeneration accompanied by PD symptoms [45]. These findings further highlight the pathophysiological importance of Parkin-mediated mitophagy in PD, as opposed to data from *in vitro* studies. Apart from its role in mitophagy, Parkin maintains a functional mitochondrial pool by regulating biogenesis [43]. Parkin normally mediates the degradation of peroxisome proliferator-activated receptor gamma coactivator (PGC1α), which leads to its translocation to the nucleus and the activation of transcription of mitochondrial-related genes [46]. Therefore, Parkin dysfunction suppresses mitochondrial biogenesis, resulting in a decrease in the number and function of mitochondria [47]. These results also highlight a key role of Parkin in maintaining the balance between mitochondrial biosynthesis and biodegradation.

Mutations in the *PINK1* gene are the second most common cause of early-onset, autosomal recessive PD [48]. PINK1 (PTEN-induced putative kinase 1) is a serine-threonine kinase associated with mitochondria and plays a critical role in maintaining mitochondrial homeostasis. PINK1 is shown to enhance mitochondrial fission by increasing the activation of protein kinase A [49] and to modulate mitochondrial biogenesis by regulating Parkin-dependent degradation [50]. A defective *PINK1* gene impairs mitochondrial function, resulting in the destruction of mitochondria. Mitophagy is the most widely studied function of PINK1 [45, 51]. PINK1 activates Parkin through two mechanisms: direct phosphorylation [52] and transactivation via the phosphorylation of ubiquitin, followed by Parkin binding [51, 53, 54]. In addition, PINK1 can mediate mitophagy independently of Parkin by recruiting nuclear dot protein and optineurin [55]. Like LRRK2, PINK1 promotes mitophagy by arresting mitochondrial transport through phosphorylation, followed by proteasomal degradation [56]. Experiments on Drosophila and mice have shown that partially inhibiting PINK1 results in various mitochondrial dysfunctions. This is primarily due to the loss of PINK1/Parkin-mediated mitophagy. However, PINK1 regulates mitochondrial homeostasis through another mechanism [43]: a PINK1 deficiency leads to mitochondrial calcium overload [57] and a decrease in mitochondrial complexes I and III [58].

A rare form of autosomal recessive juvenile PD, Kufor–Rakeb syndrome, is caused by mutations in the *ATP13A2* gene [59]. This gene encodes a P5B-type ATPase that mainly localizes to the endolysosomal compartment. Although ATP13A2 is believed to transport cations across organelle membranes [59], its transport activity is not fully defined. However, a loss of ATP13A2 in cells in patients with PD reveals increased sensitivity to Zn^{2+} and Mn^{+}, suggesting a critical role for ATP13A2 in maintaining the balance of these trace elements [14, 59]. The association between the *ATP13A2* gene and mitochondrial dysfunction was first identified in skin fibroblasts from patients with mutations in this gene [14, 60]. Grünewald et al. [60] and Ramonet et al. [61] demonstrated mitochondrial dysfunction, characterized by reduced ATP production, increased mitochondrial fragmentation, and elevated ROS production, in a model of ATP13A2-deficient cells [60, 61]. Park et al. proposed that ATP13A2 has a broader impact on cellular bioenergetics. They found that loss of ATP13A2 worsens glycolysis and causes more severe mitochondrial dysfunction [62]. In addition, the literature describes ATP13A2 mutations that cause Zn^{2+} homeostasis disruption due to an imbalance in vesicular sequestration, resulting in mitochondrial dysfunction [61]. Disruption in Zn^{2+} metabolism can also cause lysosomal dysfunction [63] and contribute to defective mitophagy. This highlights the complex relationship between interconnected intracellular processes in PD pathogenesis.

Potential Therapeutic Strategies

Since mitochondrial dysfunction plays a significant role in the development of PD, novel pathogenetic approaches are needed to treat PD. Various strategies are being developed to improve mitochondrial function in both familial and sporadic forms of PD. An effective approach to treating PD appears to involve targeting the mitophagy process in defective mitochondria. Increasing the activity of the cytosolic ubiquitin ligase E3 (Parkin) by nilotinib, which inhibits phosphorylation, is shown to provide a neuroprotective effect [64]. Inhibition of the deubiquitinating enzymes increases Parkin-mediated mitophagy because a ubiquitin-specific peptidase counteracts Parkin's effects, whereas inhibition of the ubiquitin-specific peptidase increases mitochondrial degradation [14, 65]. In addition, activation of mitophagy in PD may create alternative conditions that restore mitochondrial function. Hamacher-Brady et al. demonstrated that the proteins FUNDC1 (FUN14 domain containing 1) and Ambra1 (autophagy and Beclin 1 regulator 1) are able to modulate mitophagy independently of PINK1 or Parkin activity [66]. However, it has been discovered that Nip3-like protein-mediated mitophagy [14, 67] restores mitochondrial function and prevents neurodegeneration in case of Parkin or PINK1 deficiency, which justifies this mechanism as a new potential target for PD treatment [14].

Another neuroprotection strategy involves increasing mitochondrial biogenesis. Hayashi et al. demonstrated in animal experiments and human subjects that dimethyl fumarate (BG-12) increases mitochondrial biogenesis through the transcription factor NRF2 (nuclear factor erythroid 2-related factor 2) [68]. Phase III clinical trials demonstrated the efficacy of BG-12 in treating relapsing multiple sclerosis [69], and the agent was approved for patient use. These findings highlight the potential use of BG-12 in PD treatment. Other activators of the NRF2-mediated pathway include synthetic triterpenoids, which have demonstrated protective effects on dopaminergic neurons against MPTP [70]. Johri et al. reported that PGC-1α, a powerful inducer of mitochondrial biogenesis, might be another candidate for a target in PD treatment [71]. Other studies on animal models of neurodegeneration have demonstrated that bezafibrate [71] and quercetin [72] increase mitochondrial numbers. These findings open up opportunities for developing new PD treatment strategies.

Conclusion

A literature review has revealed the significant role of mitochondrial dysfunction in PD development. Both exogenous environmental factors and endogenous factors, such as genetic aberrations characteristic of familial forms of PD, can

lead to mitochondrial dysfunction. Mitochondria are affected by these etiological factors directly and indirectly, through the activation or inhibition of secondary messenger systems. Pathogenetically, mitochondrial dysfunction can arise from either defective mitophagy or disrupted mitochondrial biogenesis. Therefore, new treatment strategies for PD should aim to enhance mitophagy of defective mitochondria or increase the biogenesis of new mitochondria.

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Cerebrospinal Fluid Biomarkers of Alzheimer Disease

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Abstract

Alzheimer disease (AD) is a chronic neurodegenerative disorder and the most common cause of dementia in the elderly. Current international guidelines for the clinical diagnosis of AD consider the diagnosis to be both clinical and biological. It requires a specific clinical phenotype and a confirmed biological origin based on biomarkers of amyloid and tau pathology. In Russia, only a few research centers perform laboratory diagnosis of AD using cerebrospinal fluid (CSF) biomarkers. Better access to laboratory diagnosis of AD and wider use of CSF biomarkers in clinical practice will help to assess the true prevalence of AD in the Russian population and to select patients for targeted pathogenic therapies based on the use of monoclonal antibodies against abnormal brain proteins, which have been actively developed in recent years. This review summarizes information on the main CSF biomarkers of AD and their diagnostic and prognostic value.

Keywords: *Alzheimer's disease; dementia; biomarkers for Alzheimer disease; cerebrospinal fluid biomarkers*

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Диагностические ликворные биомаркеры при болезни Альцгеймера

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Аннотация

Болезнь Альцгеймера (БА) – хроническое нейродегенеративное заболевание и самая распространённая причина деменции в пожилом возрасте. Согласно последним международным рекомендациям по клинической диагностике БА, данный диагноз является клинико-биологическим: он требует наличия специфического клинического фенотипа и подтверждения биологической природы заболевания на основании исследования биомаркеров амилоидной и тау-патологии. В России методы лабораторной диагностики БА с исследованием ликворных биомаркеров проводятся лишь в отдельных научно-исследовательских центрах. Расширение доступности лабораторной диагностики БА и более широкое использование ликворных биомаркеров в клинической практике позволит оценить реальную распространённость БА в российской популяции, а также в ближайшем будущем отбирать пациентов для активно разрабатываемой в последние годы таргетной патогенетической терапии заболевания, основанной на применении моноклональных антител против патологических церебральных белков. В данном обзоре обобщена информация об основных биомаркерах БА в цереброспинальной жидкости и их диагностической и прогностической значимости.

Ключевые слова: *болезнь Альцгеймера; деменция; биомаркеры болезни Альцгеймера; ликворные биомаркеры*

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Introduction

Alzheimer disease (AD) is a chronic neurodegenerative disorder and the most common cause of dementia in the elderly [1]. Neuropathologically, AD is characterized by the deposition of beta-amyloid (Aβ) in the brain as extracellular plaques and the formation of intracellular neurofibrillary tangles of phosphorylated tau protein [2].

In Russia, there are approximately 9,000 registered patients with AD [3]. However, it is estimated that more than 90% of AD cases in Russia remain undiagnosed [4]. This is mainly due to a lack of awareness among primary care physicians about the early signs of AD (when symptoms are interpreted as part of normal aging or cerebrovascular disease), a reluctance to make the diagnosis at more advanced stages because of the potential social consequences, or the presence of an atypical clinical phenotype that makes it difficult to identify the nature of the neurodegenerative process without additional diagnostic tools.

Until recently, the diagnosis of AD was based primarily on clinical data, namely on the development of a typical cognitive deficit [5]. However, according to the latest guidelines from the International Working Group for the Clinical Diagnosis of Alzheimer Disease (2021), diagnosis of AD should be based on both clinical and biological features and requires a specific clinical phenotype and confirmation of biological origin based on amyloid and tau pathology biomarkers [6]. Amyloid pathology can be confirmed by low levels of $A\beta_{1-42}$ in the cerebrospinal fluid (CSF) or the detection of abnormal amyloid deposition in the brain using positron emission tomography (PET). Tau pathology can be diagnosed by high CSF levels of phosphorylated tau protein or abnormal deposition of tau protein identified by brain PET with an appropriate ligand.

In Russia, only a few research centers are able to perform laboratory diagnosis of AD based on CSF biomarkers, whereas it remains inaccessible for most Russian clinics [7–10]. PET scans with ligands for Aβ and tau proteins are not available in every clinic in Russia. However, the need to verify the diagnosis for targeted therapy will soon require a sharp increase in the availability of laboratory diagnostic tools for AD as well as a wider clinical use of CSF biomarkers (as a more accessible method compared to PET).

The **aim** of this review was to summarize data on the key CSF biomarkers of AD and their diagnostic and predictive value.

Main Pathogenic Mechanisms of Alzheimer Disease

In 1906, Alois Alzheimer first described a clinical case of dementia in a young woman with progressive memory loss, speech, movement and behavioral disorders, and hallucinations. Postmortem brain pathomorphology revealed macroscopic signs of extensive brain atrophy. Using a novel silver impregnation technique for brain histology, Alzheimer identified typical neuropathologic changes namely extracellular amyloid plaques and intracellular neurofibrillary tangles [11]. n 1987, the gene *APP* (amyloid precursor protein), which encodes the amyloid precursor protein located on chromosome 21, was identified [12]. In 1992, the official amyloid hypothesis of AD was proposed [13].

APP is a transmembrane protein found in many tissues of the body. However, its physiological functions are not fully understood. This protein may be involved in learning, memory and neuroplasticity, including synaptogenesis, which may be a key element of neuroprotection [14]. Proteolytic cleavage of APP can involve two pathways: a non-amyloidogenic pathway that results in the production of soluble α-amyloid and an amyloidogenic pathway that results in the formation of insoluble and aggregation-prone Aβ fragments [15]. According to the amyloid theory, a critical role in AD is attributed to the altered cleavage pattern of the APP protein, leading to excessive production of Aβ peptides. Aβ is formed by the sequential cleavage of APP by specific enzymes such as β-secretase and γ-secretase (identified as a presenilin complex) [16]. γ-Secretase-mediated APP cleavage results in the production of amyloid peptides consisting of 36–43 amino acids [17]: a peptide consisting of 40 amino acids ($A\beta_{40}$) is produced in larger quantities and a peptide consisting of 42 amino acids ($A\beta_{42}$) is produced in smaller quantities [18]. Although different isoforms of Aβ can be detected in AD patients, the levels of $A\beta_{42}$ and $A\beta_{40}$ and their ratio are considered the most reliable biomarkers for AD [19].

Historically, hyperproduction of Aβ was thought to be the main cause of AD [20, 21]. In recent years, however, a defect in Aβ clearance mechanisms has been suggested to play a major role [22, 23]. Yoon *et al.* identified four main mechanisms of Aβ clearance, divided into non-enzymatic and enzymatic pathways [24]. The non-enzymatic pathway includes three mechanisms:

1) Drainage of interstitial fluid into the blood through periarterial Virchow–Robin spaces [22];
2) Phagocytosis by microglia or astrocytes [25];
3) Transport across blood vessel walls, mediated by some clearance receptors (low density lipoprotein receptor-related protein 1 (LRP1); very-low-density-low-density lipoprotein receptor (VLDLR); P-glycoprotein) [26].

The enzymatic pathway involves the cleavage of Aβ by proteases, including neprilysin [27], insulin-degrading

enzyme [28], matrix metalloproteinase-9 [29], and glutamyl carboxypeptidase II [30]. The imbalance between Aβ peptide production and clearance initiates a cascade of pathological reactions that are the main cause of AD development [15].

Intracellular accumulation of soluble amyloidogenic Aβ oligomers has a neurotoxic effect even before the formation of extracellular plaques, leading to synaptic dysfunction, postsynaptic hyperexcitability, disruption of homeostasis, and increased production of reactive oxygen species in neuronal mitochondria [31, 32]. The extracellular aggregates of insoluble fibrils containing Aβ peptides (amyloid plaques) also have a neurotoxic effect. Simultaneous dysfunction of astrocytes and microglia, the brain's immune cells, develops. Overproduction of inflammatory cytokines occurs and phagocytosis of Aβ is impaired. These processes activate cell signaling pathways associated with apoptosis and neuronal death [33].

Tau protein is associated with microtubules, is expressed primarily in neurons and is encoded by the *MAPT* (microtubule-associated protein tau) gene located on chromosome 17. Neuroimaging studies show that the onset and location of tau pathology correspond to both the onset and type of cognitive deficit [34, 35]. The main functions of this protein include stimulation of tubulin polymerization, stabilization of microtubules, and transport of intracellular organelles [36]. Tau aggregation is a multi-step process that likely begins with the hyperphosphorylation of tau protein and its detachment from microtubules. During aggregation, tau protein moves into the somatodendritic regions of neurons where further phosphorylation and structural changes occur. Misfolded proteins begin to aggregate, forming freely spreading pathogenic oligomers, which leads to further disease development, affecting healthy cells and causing neuronal death [37].

Several mechanisms leading to tau hyperphosphorylation and conformational changes and formation of neurofibrillary tangles are described:
1) activation by Aβ proteins of specific enzymes that catalyze hyperphosphorylation;
2) neuroinflammation triggered by Aβ deposition and promoting the activation of pro-inflammatory cytokines;
3) decreased ability to degrade hyperphosphorylated tau proteins;
4) axonal transport defect [38].

Aβ oligomers first induce phosphorylation of tau protein at specific epitopes and then cause cytoskeleton collapse and neuronal degeneration [39].

Cerebrospinal Fluid Biomarkers of Alzheimer Disease

Lumbar puncture is a routine medical procedure used for diagnostic and therapeutic purposes. The CSF is in direct contact with the extracellular space of the brain and spinal cord, and its biochemical changes may reflect the characteristics of neurodegenerative diseases. CSF is the main biological fluid used for the diagnosis of AD [40]. $Aβ_{1-42}$ and $Aβ_{1-40}$, total tau (t-tau), and phosphorylated tau (p-tau) are the best-known CSF biomarkers for AD [41].

$Aβ_{1-42}$

The $Aβ_{1-42}$ protein in CSF is recognized as a key biomarker for AD. Reduced levels of $Aβ_{1-42}$ have been shown in several international studies to be highly accurate in diagnosing dementia and mild cognitive impairment in AD. This biomarker has high sensitivity and specificity in diagnosing AD at all stages [42–45]. Reduced levels of $Aβ_{1-42}$ in CSF are found to be the earliest pathological change in AD, preceding Aβ ligand PET imaging [46]. The concentration of $Aβ_{1-42}$ declines long before the onset of clinical symptoms [47], making this biomarker particularly suitable for early diagnosis [48].

The mechanisms leading to decreased CSF levels of $Aβ_{1-42}$ in patients with AD are still unclear. Some authors suggest that this may be due to excessive deposition of $Aβ_{42}$ in amyloid plaques, as the aggregated state impedes transport of $Aβ_{1-42}$ from the interstitial fluid into the CSF [49]. Other hypotheses include decreased production rates of $Aβ_{42}$ [23], increased $Aβ_{42}$ degradation due to proteolytic breakdown [50] or microglial phagocytosis [51], as well as increased clearance of $Aβ_{1-42}$ into the blood [52], although these are considered less likely [53].

One limitation of isolated $Aβ_{1-42}$ studies in CSF is the frequent finding of decreased levels of this biomarker in other neurodegenerative diseases, such as cerebral microangiopathy [54], dementia with Lewy bodies [55], Creutzfeldt–Jakob disease [56], and frontotemporal dementia (FTD) [57]. Although the levels of $Aβ_{1-42}$ in AD are usually significantly lower than in these diseases, this overlap limits the differential diagnosis.

Aβ1-40

While $Aβ_{1-42}$ constitutes approximately 10% of the total Aβ peptide population, the protein $Aβ_{1-40}$ is the dominant form in the brain, CSF, and plasma [58]. The total concentration of Aβ varies little between diseases, and the concentration of $Aβ_{1-40}$ does not differ significantly between patients with AD, healthy individuals, and patients with dementia of other origin [59]. Therefore, CSF levels of $Aβ_{1-40}$ may be considered the most accurate reflection of total brain Aβ burden, although the value of this test in isolation remains controversial. $Aβ_{1-40}$ levels are primarily used to evaluate the $Aβ_{1-42}/Aβ_{1-40}$ ratio.

The $Aβ_{1-42}/Aβ_{1-40}$ Ratio

The $Aβ_{1-42}/Aβ_{1-40}$ ratio was proposed in the late 1990s to improve the differential diagnosis of AD [60]. This ratio is important and accounts for constitutive interindividual differences in total CSF burden of Aβ between high and low amyloid production [61]. Studies have found a high correlation between a lower $Aβ_{1-42}/Aβ_{1-40}$ ratio and higher levels of total and phosphorylated tau protein [62]. Patients with a lower $Aβ1_{-42}/Aβ_{1-40}$ ratio show a faster cognitive and functional decline and a more rapid decline in episodic memory [63]. These data demonstrate the advantage of using the $Aβ_{1-42}/Aβ_{1-40}$ ratio over isolated CSF levels of $Aβ_{1-42}$ for predicting the progression of cognitive impairment.

Total Tau Protein

The first study that successfully evaluated total t-tau in CSF was published in 1995 and showed that t-tau levels were significantly higher in patients with AD compared to patients with other neurodegenerative diseases and controls [64]. Similar results have been found in hundreds of other studies [65]. However, elevated CSF levels of t-tau were later found in some acute conditions (such as stroke [66], traumatic brain injury [67], Wernicke encephalopathy [68]), as well as in rapidly progressive neurodegenerative diseases (such as Creutzfeldt–Jakob disease [69]). Based on the data obtained, the level of t-tau is proposed to be used as a marker of the activity of the neurodegenerative process or the severity of acute neuronal damage in the brain [70]. In patients with AD, higher levels of t-tau may predict faster clinical progression of the disease [71].

Phosphorylated Tau Protein

Tau protein undergoes multiple post-translational modifications, such as glycosylation [72], glycation (non-enzymatic glycosylation) [73], phosphorylation, etc. Phosphorylation is the most important modification and level phosphorylation regulates the biological activity of the tau protein [74]. Normally, more than 30 different sites of the protein at serine, threonine, or proline positions are phosphorylated [75]. These modifications can control normal biological functions of tau, such as regulating the stability of microtubules, and lead to the development of pathological processes associated with the protein's ability to self-assemble into neuronal filaments found in neurodegenerative diseases [76].

Tau protein phosphorylated at threonine 181 (p-tau181) in CSF is the best understood form of p-tau as an AD biomarker used in current disease diagnosis [77]. This biomarker (in combination with $A\beta_{42}$) accurately discriminates between patients with AD and healthy individuals and can also predict cognitive decline in preclinical and prodromal stages of the disease [78]. Levels of p-tau181 are significantly higher in AD than in other tauopathies, including FTD, progressive supranuclear palsy, and corticobasal degeneration. Therefore, this parameter can be used in the differential diagnosis of dementia in these conditions [57, 79, 80].

The levels of tau phosphorylated at positions 217 (p-tau217) and 231 (p-tau231) have received considerable attention in recent years. For example, elevated levels of p-tau217 in CSF have been shown to be the most specific parameter for detecting both preclinical and advanced stages of AD [81]. CSF p-tau217 levels in patients with prodromal stage and AD dementia were several times higher than p-tau181 levels in the same patients [82]. The superiority of p-tau217 over p-tau181 has also been demonstrated in studies showing stronger correlations of p-tau217 with amyloid PET results [83].

For p-tau231, there is evidence that it is most sensitive to the earliest manifestations of amyloid pathology in the medial orbitofrontal cortex, precuneus, and posterior cingulate cortex, before the threshold of pathological amyloid ligand accumulation is reached on PET scans [84]. This biomarker is thought to reach diagnostically significant abnormal levels only at disease onset [85] and may be key to identifying the recently described pre-amyloid phase of AD [86], which occurs before the abnormal accumulation of Aβ is detectable by PET. Stronger correlations between CSF p-tau231 levels and amyloid PET burden in individuals without clinically evident cognitive impairment suggest that increases in CSF p-tau231 levels occur during the lag phase of Aβ protein aggregation in the brain [84].

Markers of Neurodegeneration and Microglial Activation

Although a hallmark of AD is the formation of Aβ and tau protein aggregates in the brain, there are also typical neuroinflammatory responses that occur in the affected brain areas, leading to neuronal dysfunction, neuronal death, and synapse loss [87]. Further research into the diverse pathogenetic mechanisms of AD is needed to identify alternative therapeutic approaches.

Accumulating data in recent years suggest an association between synaptic loss in AD and neurogranin (Ng). Neurogranin is a neuron-specific postsynaptic protein that is abundantly expressed in the brain, particularly in the dendrites of hippocampal and cortical neurons [88]. It binds to calmodulin at low calcium ion concentrations and regulates synaptic plasticity of neurons by modulating Ca^{2+}/calmodulin-dependent pathways. It is also involved in long-term potentiation, which is important for learning and memory processes [89]. Another hallmark of AD is an increase in CSF levels of Ng, which gradually increases with cognitive decline and negatively correlates with Mini Mental State Examination scores, likely reflecting synaptic damage due to Aβ aggregation with plaque accumulation [90, 91]. Some authors report a significant increase in CSF Ng levels in AD compared to Lewy body dementia, FTD, and amyotrophic lateral sclerosis [92], while others report only a high correlation between CSF Ng levels and CSF t-tau and p-tau181 levels [93]. Therefore, the value of CSF Ng level assessment is still controversial.

Neurofilament light chain (NfL) is a scaffold protein of the neuronal cytoskeleton that plays an important role in axon and dendrite branching and growth. Following axonal injury, CSF NfL levels increase and serve as a biomarker for axonal injury and neurodegeneration [94]. In recent years, the use of this biomarker to assess the progression of various neurological diseases, including AD, has increased significantly [95]. Higher CSF levels of NfL are also found in cognitively healthy individuals with hippocampal atrophy on neuroimaging [96] and in preclinical stages of AD [97, 98]. Longitudinal studies in patients with AD have shown that an increase in CSF NfL level is associated with a more intense progression of brain atrophy and cognitive decline. Therefore, higher NfL levels in early clinical stages of AD appear to predict faster conversion to dementia [99]. However, the specificity of this biomarker for AD is low since the highest levels are found in other neurodegenerative disorders such as amyotrophic lateral sclerosis, FTD, corticobasal degeneration, and progressive supranuclear palsy [100].

The pathogenesis of AD is also accompanied by reactive astrogliosis, which is characterized by morphological, molecular, and functional remodeling of astrocytes [101]. Glial fibrillary acidic protein (GFAP) is a type III intermediate filament protein that is predominantly expressed by astrocytes in the CNS [102]. In animal models, high levels of GFAP expression are found in astrocytes of the hippocampus, the corpus callosum and the cerebral peduncles [103]. Its expression is significantly increased in neurodegenerative diseases, including AD, reflecting neuroinflammatory processes and astrocyte activation [104]. In AD, elevated CSF levels of GFAP are a potential marker of progressive cognitive impairment; these levels have been shown to increase as cognitive deficits progress [105]. However, these changes are not specific to AD, because an increase in GFAP levels with progressive cognitive impairment has also been described in patients with Parkinson's disease, FTD, multiple sclerosis, and other neurological disorders [106].

These biomarkers are being studied for research purposes, but are not yet used in clinical practice due to insufficient specificity for diagnosing AD.

Clinical Use of CSF Biomarkers for AD in Neurology

As mentioned above, according to the International Working Group Recommendations for the Clinical Diagnosis of Alzheimer's Disease (2021), a diagnosis of AD requires the presence of a specific clinical phenotype and confirmation of the biological origin of the disease based on biomarker testing [6]. These guidelines distinguish between common and rare AD phenotypes. The main clinical phenotypes of AD include the classic amnestic (hippocampal) variant, posterior cortical atrophy, and the logopenic variant primary progressive aphasia. Rare phenotypes include frontal (behavioral/dysregulation) variant, corticobasal syndrome, and semantic and agrammatic variants of primary progressive aphasia. It is proposed to establish probability levels for AD as the primary diagnosis based on the combination of the clinical phenotype and the results of key biomarker testing (in CSF or by PET). The diagnosis of AD is categorized as definite, probable, and possible, with additional categories of unlikely and excluded. For controversial cases, recommendations for further patient evaluation are provided (Table 1).

Conclusion

According to international guidelines, the key CSF biomarkers for the clinical diagnosis of AD (gold standard) include $A\beta_{1-42}$, $A\beta_{1-42}/A\beta_{1-40}$ ratio, and p-tau181. CSF t-tau levels can be used to assess the activity of the neurodegenerative process and predict the clinical progression of the disease. Novel biomarkers of tau pathology (including CSF p-tau217 and p-tau231 levels) could also be used to diagnose AD, because they are both highly sensitive and specific even in the preclinical stages of the disease. The clinical applicability of markers of neurodegeneration and astrocyte activation (Ng, NfL, GFAP) requires further discussion, so their use is currently warranted only in research settings.

The wider availability of CSF biomarkers in Russian clinical practice will allow for the assessment of the true prevalence of AD in the Russian population, as well as the selection of patients for targeted therapy, which has been actively developed in recent years.

Table 1. International Working Group Recommendations for the Clinical Diagnosis of Alzheimer's Disease (2021)

Phenotype	Likelihood of AD as a primary diagnosis	Further investigation
Common clinical phenotypes in AD (amnestic variant, posterior cortical atrophy, logopenic variant primary progressive aphasia)		
Amyloid positive; tau positive	Highly probable – established	None required
Amyloid positive; tau unknown	Probable	Consider a tau measure (PET, CSF)
Amyloid positive; tau negative	Probable	Consider an additional tau measure (PET, CSF)
Tau positive; amyloid unknown	Possible	Consider an amyloid measure (PET, CSF)
Tau positive; amyloid negative	Possible	Consider an additional amyloid measure (PET, CSF)
Amyloid negative; tau unknown	Unlikely	Full investigation of cause and consider a tau measure (PET, CSF)*
Amyloid unknown; tau negative	Unlikely	Full investigation of cause and consider an amyloid measure (PET, CSF)*
Amyloid unknown; tau negative	Highly unlikely – excluded	Full investigation of cause*▽
Amyloid unknown; tau unknown	Non-assessable	Consider tau and amyloid and measure (PET, CSF)
Uncommon clinical phenotypes in AD (frontal variant, corticobasal syndrome, semantic and agrammatic variants of primary progressive aphasia)		
Amyloid positive; tau positive	Probable	None required; careful follow-up needed: an incongruent clinical phenotype and neurodegeneration pattern should trigger a new investigation*
Amyloid positive; tau unknown	Possible	Consider a tau measure (PET, CSF)
Amyloid positive; tau negative	Possible	Consider an additional tau measure (PET, CSF)
Tau positive; amyloid unknown	Unlikely	Full investigation of cause and consider an amyloid measure (PET, CSF)*
Tau positive; amyloid negative	Unlikely	Full investigation of cause*
Amyloid negative; tau unknown	Highly unlikely – excluded	Full investigation of cause*▽
Amyloid negative; tau negative	Highly unlikely – excluded	Full investigation of cause*▽
Amyloid unknown; tau negative	Highly unlikely – excluded	Full investigation of cause*▽
Amyloid unknown; tau unknown	Non-assessable	Full investigation of cause and consider tau and amyloid measure (PET, CSF)*

Note. *Full investigation of cause depends on the specific clinical phenotype and can imply, for example, ^{18}F-fluorodeoxyglucose PET (FDG-PET), dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT), serum progranulin assay, genetic analysis, oculomotor recordings, or electromyoneurography. ▽Consider a new Alzheimer's disease biomarker investigation only if there is a reasonable doubt about the validity of the biomarker results.

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Ischemic Stroke in MCA Dissection with the Formation of the Double Lumen: Diagnostic Challenges

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Abstract

We describe a patient who experienced a right middle cerebral artery (MCA) stroke at the age of 12. Its clinical manifestations (acute onset of left-sided hemiparesis and headache during swimming) and signs of connective tissue weakness (joint hyperflexibility, increased skin elasticity) suggested right MCA dissection as the stroke cause. However, 1.5T MRI/MRA did not confirm the clinical suspicion: blood flow in the right MCA was preserved, and no intramural hematoma was detected. Only an irregular MCA contour was noted. High-resolution 3T MRI performed seven years later revealed a double lumen in the right MCA – a characteristic dissection sign – confirming the initial clinical hypothesis. This case demonstrates that when MCA dissection is clinically suspected as the cause of ischemic stroke, high-resolution MRI is necessary to verify neuroimaging signs of dissection.

Keywords: *dissection; middle cerebral artery; double lumen; ischemic stroke; children; young stroke*

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Ишемический инсульт вследствие диссекции средней мозговой артерии с развитием двойного просвета. Трудности диагностики

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Аннотация

Описан пациент, который в возрасте 12 лет перенёс ишемический инсульт в бассейне правой средней мозговой артерии (СМА). Его клинические проявления (острое развитие левостороннего гемипареза и головной боли во время плавания) и наличие признаков слабости соединительной ткани (гиперфлексия суставов, повышенная растяжимость кожи) предполагали диссекцию правой СМА как причину инсульта. Однако МРТ/МРА (1,5 Т) не подтвердили клиническое предположение: кровоток по правой СМА был сохранён, интрамуральная гематома не обнаружена. Отмечен только неровный контур СМА. При высокоразрешающей МРТ (3 Т) через 7 лет обнаружен двойной просвет в правой СМА – характерный признак диссекции, что подтвердило первичное клиническое предположение. Представленное наблюдение показало, что при клиническом подозрении на диссекцию СМА как причину ишемического инсульта необходимо проведение высокоразрешающей МРТ для верификации нейровизуализационных признаков диссекции.

Ключевые слова: *диссекция; средняя мозговая артерия; двойной просвет; ишемический инсульт; дети; молодой возраст*

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Introduction

Spontaneous intracranial artery dissection (ICAD) is an uncommon, understudied, and underdiagnosed cause of ischemic stroke (IS) [1–3]. Compared to extracranial artery dissection, it is less common. ICAD accounts for 12.5–15.8% of dissections in arteries supplying the brain [4], while among all IS cases caused by dissection, the frequency of ICAD is 33.5–48.8% [3]. Among isolated dissections of the anterior, middle (MCA), posterior cerebral, and basilar arteries, the MCA is most frequently affected. Patients with ICAD are younger than those with cervical artery involvement, and ICAD represents one of the causes of IS in children, who rarely experience extracranial artery dissection [1, 5, 6].

Risk factors for dissection include head trauma, physical exertion, straining, recent infection within the month preceding IS, and oral contraceptive use in women [1]. Migraine in the past history is frequently reported by patients with ICAD [3]. The underlying cause of dissection is vascular wall weakness due to dysplasia. Pathomorphological studies reveal dysplastic changes not only in intracranial but also extracranial arteries [7, 8]. Moreover, in patients with dissection, these changes are widespread, including the musculoskeletal system involvement [9].

IS caused by MCA dissection typically manifests acutely with ipsilateral headache. Headache appears simultaneously with focal neurological symptoms, less often it precedes it by several hours or days. Decreased level of consciousness is uncommon and occurs in rapidly progressing dissection leading to MCA occlusion and large cerebral infarction. Transient ischemic attacks preceding IS by several days may be the first sign of developing ICAD [1].

The mechanisms of IS in ICAD include hemodynamic disturbances due to narrowing/occlusion of the arterial lumen by an intramural hematoma (IMH), artery-to-artery embolism from the site of intimal rupture, and block the place of the M1 MCA segment where the penetrating arteries branch off. Brain infarcts are located in the territory of the perforating branches of the MCA (posterior limb of the internal capsule, head and body of the caudate nucleus, globus pallidus; 45%), less frequently in the cortex and subjacent white matter of the cerebral hemispheres [1, 2].

Radiologic diagnosis of MCA dissection is challenging due to MCA small size and the nonspecificity of many imaging signs. Magnetic resonance angiography (MRA) reveals stenosis or occlusion, sometimes combined with aneurysmal dilation of the MCA. A characteristic feature distinguishing MCA stenosis/occlusion due to ICAD from atherosclerotic plaque or inflammation is the gradual restoration of arterial patency over 1.5–2.0 months in many cases.

The pathognomonic MRI sign of ICAD on vessel wall imaging is the IMH. Its detection, considering the small artery diameter, is facilitated by specialized MRI sequences (T1-weighted fat-suppressed, T1fs) with thin slices on high-field MRI scanners (3T) [1–3, 6, 10, 11]. Seven Tesla MRI scanners have higher resolution, enabling IMH detection not only in the M1 segment but also in the M2 segment [12]. IMH becomes visible 48–72 hours after disease onset. An additional significant feature is the expansion of the artery's external diameter due to IMH within the vessel wall. A rare neuroimaging sign of MCA dissection is the double lumen, which also requires high-resolution MRI for identification – a technique not universally available, that creates diagnostic challenges. In the literature, we found only one such case description verified by MRA and subtraction angiography.

The limited coverage of ICAD in the literature and the inevitable diagnostic and differential diagnostic difficulties determined the preparation of this publication.

Clinical case report

Patient S., 19 years old, was undergoing examination in the 3rd Neurological Department of the Russian Center of Neurology and Neurosciences from August 23, 2023, to September 1, 2023 with the aim to clarify the cause of IS in the right MCA dated January 19, 2017.

On admission, the patient complained of slight clumsiness in the left hand, pulsating headaches predominantly in the occipital region worsening with movement and accompanied by phonophobia, and dizziness.

Medical history: Since the age of 8 (2012), he has experienced headaches accompanied by phonophobia that intensify with movement. At the age of 10 (2015), brain MRI revealed significant ventricular system dilation. On January 19, 2017, during swimming, he suddenly developed severe short-lasting headache, left-sided limb weakness, and required assistance to exit the pool. He remained conscious but lethargic, provided incorrect parental phone numbers, and had poor recollection

of the acute events. He was hospitalized at Morozov Children's City Clinical Hospital.

Brain MRI demonstrated an ischemic area in the right MCA territory and hydrocephalus (Fig. 1). MRA performed on January 27, 2017 and analyzed at the Radiology Department of the Russian Center of Neurology and Neurosciences, revealed irregular contours of the M1 segment of the right MCA (Fig. 2, *A*) and hypoplasia of the A1 segment of the right anterior cerebral artery. No intramural hematoma in the right MCA or pathological vessel wall contrast enhancement was detected. These findings were interpreted as arteriopathy. Echocardiography showed no abnormalities. Routine blood tests, biochemical analysis, and coagulation tests were unremarkable. Antiphospholipid antibodies were negative. Tests for antinuclear factor, anti-DNA, and C-reactive protein were within normal limits. Treatment included heparin followed by acetylsalicylic acid 50 mg and neurotrophic agents. His condition improved, with only mild left arm weakness remaining at discharge. Discharge diagnosis: acute ischemic stroke in the right MCA territory. Arteriopathy.

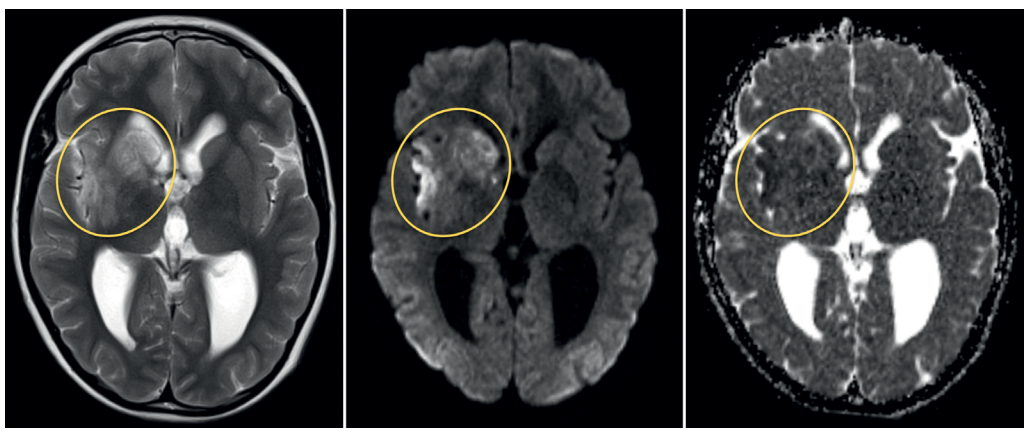
Following IS, blood pressure began to rise, recently reaching up to 180 mm Hg at times. The patient is currently taking amlodipine and fosinopril. Six months after the ischemic stroke, headaches recurred, now localized in the occipital region rather than the frontotemporal area as before; their character changed from pressing to pulsating and became accompanied by blurred vision, visual field narrowing, and dizziness.

At the age of 15 (2019), the patient was evaluated at the Neurosurgical Department of the Morozov Children's City Clinical Hospital. A lumbar puncture was performed, and CSF analysis showed protein of 0.416 g/L and no cytosis. In 2022 (at the age of 18), a follow-up MRA (1.5 T) revealed reduced blood flow signal in the right MCA (when viewing an MRI at the RCNN - double lumen in the right MCA). Ventricular enlargement of the brain was observed. On June 23, 2023, high-resolution MRA (3 T) performed at the Russian Center of Neurology and Neurosciences demonstrated a double lumen of the MCA – a sign of arterial dissection (Fig. 2, *B*, *C*). On examination general condition was satisfactory. Joint hypermobility (Fig. 3) and increased skin extensibility were noted. Neurological examination revealed slowed movement speed in the left hand. No sensory or coordination deficits were detected. The patient studies at university.

Discussion

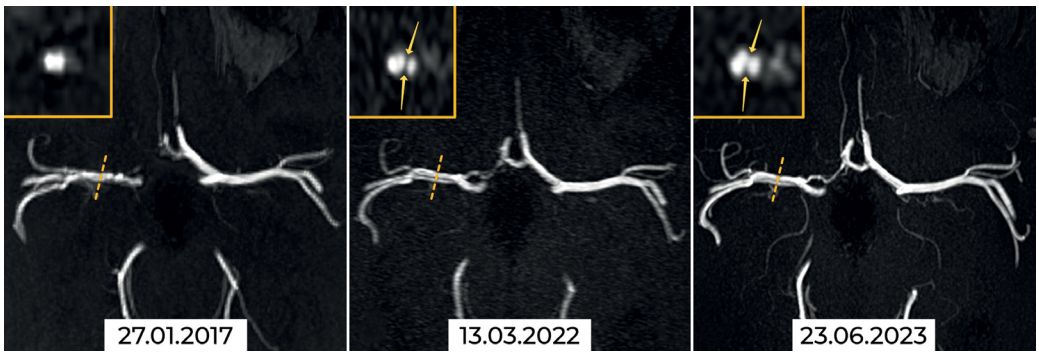
This paper presents a case of a patient who had an ischemic stroke at the age of 12 due to ICAD of the right MCA. The diagnosis was confirmed only 7 years later using high-resolution MRI, which revealed a double lumen in the right MCA – a pathognomonic neuroimaging sign of dissection. The limited understanding and diagnostic challenges of ICAD are also highlighted in the literature [2, 3]. ICAD most commonly leads to intramural hematomas, which narrow or occlude the arterial lumen, thereby causing IS. In such cases, MCA occlusion is often misattributed to thrombosis. Accurate diagnosis is facilitated by brain MRI with T1-weighted imaging with fat suppression (T1fs) using thin slices, given the small diameter of the MCA. IMH in this imaging modality is detectable from 5–7 days of stroke and persists for 1.5–2.0 months. During this period, IMH gradually diminishes with restored arterial patency, though occlusion may persist in some cases.

In our patient despite clinical manifestations characteristic of MCA dissection, T1-weighted fat-saturated MRI did not detect an IMH. The reason was that the IMG did not form, since the blood penetrated the arterial wall through the intimal rupture and made a new lumen in it, which connected distally with the main lumen as a result of secondary intimal rupture. Both lumens were functionally significant, resulting in the absence of hematoma within the vessel wall. The imaging study at acute stroke stage was performed using 1.5 T MRI, which could not visualize the double lumen. In such cases, a comprehensive analysis of clinical and instrumental data helps clarify the cause of IS and determine indications for high-resolution MRI. The IS during swimming



A *B* *C*

Fig. 1. MRI of patient S. dated 27.01.2017, axial plane.
A – T2-weighted imaging; *B* – DWI (b-1000); *C* – ADC map. Heterogeneous areas of increased intensity of MR signal in T2 and DWI (b-1000) sequences, with heterogeneous reduction of MR signal on ADC map ("acute" infarction), are observed in the head of the caudate nucleus, putamen, anterior limb of the internal capsule, and gray/white matter of the insular lobe in the right cerebral hemisphere.



A *B* *C*

Fig. 2. MRA of patient S., MIP reconstruction, axial plane.
A – 27.01.2017: irregular contours of the M1 segment of the right MCA. MR signal from the A1 segment of the right anterior cerebral artery appears fragmented (hypoplasia?); *B*, *C* – 23.06.2023: restoration of normal contour configuration of the right MCA, with visualization of a double lumen in the M1 segment (arrows).

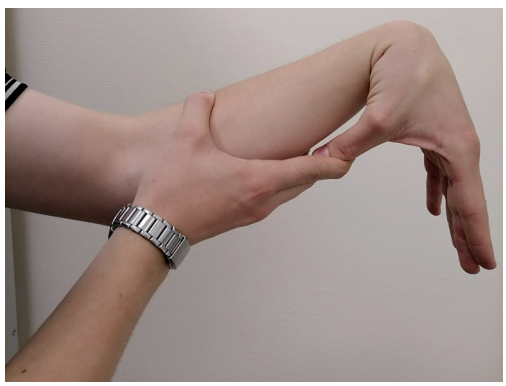


Fig. 3. Hypermobility of the wrist joint.

involving head rotations and physical exertion, along with the simultaneous onset of headache and focal neurological symptoms, is pathognomonic for ICAD [1]. Additionally, the patient exhibited signs of connective tissue dysplasia (joint hypermobility, increased skin elasticity), commonly found in patients with dissections of brain-supplying arteries [9]. According to morphological studies, connective tissue dysplasia underlies the vascular wall weakness leading to dissection [7, 8]. These features allowed clinical suspicion of dissection, which was not confirmed by neuroimaging during the acute phase and subsequently justified by high-resolution MRI that revealed a double lumen in the MCA.

Differential diagnosis of MCA dissection as a cause of ischemic stroke was carried out with cardiogenic embolism, taking into account the acute development of ischemic stroke. The absence of cardiac pathology on echocardiography, as well as the deep (rather than superficial) location of the cerebral infarction – a typical feature of cardioembolism – ruled out this etiology of IS. Thrombophilia, one of the causes of IS in childhood and adolescence, was excluded due to the absence of systemic venous or arterial thromboses and laboratory markers of thrombophilia.

Treatment of IS caused by ICAD in the acute phase includes antithrombotic therapy to prevent thrombotic complications at the site of intimal rupture. Comparative studies of antiplatelets versus anticoagulants in ICAD have not been conducted. Due to the thin MCA arterial wall, which may predispose to aneurysm formation, high-dose anticoagulants are not safe. In the development of extensive cerebral infarction due to intracranial dissection, the use of anticoagulants is contraindicated due to the risk of increasing IMG. Antiplatelet therapy is preferred in such situation [14, 15].

In conclusion, the diagnosis of MCA dissection relies on a comprehensive evaluation of clinical and instrumental data. Negative MRI findings for IMH in patients with typical clinical manifestations of MCA dissection warrant high-resolution MRI to exclude a double lumen – another pathognomonic neuroimaging feature of ICAD.

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Withdrawal of Antiepileptic Drugs Following Surgical Treatment of Drug-Resistant Epilepsy

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Abstract

The number of patients with successful outcomes following surgical treatment of drug-resistant epilepsy has been rapidly increasing. This trend has heightened the relevance of addressing the appropriateness of postoperative withdrawal of antiepileptic drugs (AED). There are no unified guidelines regarding the optimal timing and rates for discontinuing pharmacological therapy. This article reviews the timing, rate, and specifics of AED withdrawal following surgical treatment of drug-resistant epilepsy using two exemplary clinical cases. The decision to discontinue pharmacotherapy depends on multiple factors, including patient preferences. In cases of favorable outcomes following epilepsy surgery, AED withdrawal one year into remission is considered safe and does not affect long-term seizure outcomes in adult patients who have undergone anterior temporal lobectomy, remain completely seizure- and aura-free, and show no epileptiform activity on electroencephalography. Patients with multiple epileptogenic zones, epileptiform EEG activity, or persistent seizures/auras have less favorable prognoses regarding AED withdrawal.

Keywords: *epileptic seizures; structural epilepsy; drug resistance; epilepsy pharmacotherapy; antiepileptic drug withdrawal; epilepsy surgery*

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Отмена противоэпилептических препаратов после хирургического лечения фармакорезистентной эпилепсии

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Аннотация

Количество пациентов с успешным исходом после хирургического лечения фармакорезистентной эпилепсии стремительно увеличивается. На этом фоне возрастает актуальность вопроса о целесообразности послеоперационной отмены противоэпилептических препаратов (ПЭП). Единые рекомендации относительно оптимальных сроков и скорости отмены лекарственной терапии отсутствуют. В статье проанализированы сроки, скорость и особенности отмены ПЭП после хирургического лечения фармакорезистентной эпилепсии на примере двух клинических случаев. Решение об отмене фармакотерапии складывается из множества факторов, в том числе с учётом настроя пациента. В случае благоприятного исхода после хирургического лечения эпилепсии отмена ПЭП после 1 года ремиссии считается безопасной и не влияет на долгосрочный исход приступов у взрослых пациентов после передневисочной лобэктомии, полностью свободных от приступов и их предчувствий, не имеющих эпилептиформной активности на электроэнцефалограмме. Менее благоприятный прогноз при отмене ПЭП имеют пациенты с несколькими эпилептогенными зонами, эпилептиформной активностью на электроэнцефалограмме, с сохраняющимися приступами или аурами.

Ключевые слова: *эпилептические приступы; структурная эпилепсия; фармакорезистентность; фармакотерапия эпилепсии; отмена противоэпилептических препаратов; хирургия эпилепсии*

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Introduction

Surgical treatment of epilepsy allows many patients to achieve complete seizure freedom [1]. Remission of epileptic seizures is the goal of surgical intervention for drug-resistant epilepsy. However, patients typically consider themselves healthy only after complete withdrawal of antiepileptic drugs (AEDs) [2].

The data on AED use following successful epilepsy surgery are limited. Clinical guidelines for managing patients and discontinuing pharmacotherapy after epilepsy surgery are lacking. The issue of postoperative drug therapy is relevant both for patients and neurologists due to reduced quality of life, cognitive impairment, and/or adverse drug reactions in patients [3]. Therefore, understanding patient motivation and potential concerns regarding AED withdrawal is crucial [4]. Practices for AED discontinuation vary across centers and countries. Physicians have significant disagreements regarding management strategies and timing of medication withdrawal after surgical treatment [5].

Some studies have shown that AEDs can be successfully discontinued in 30–50% of patients after anterior temporal lobectomy [6, 7]. However, the optimal timing for initiating withdrawal and long-term outcomes in patients undergoing pharmacotherapy discontinuation remain undefined. The likelihood of seizure recurrence with early AED withdrawal compared to late discontinuation or continued therapy has not been sufficiently studied [8].

We present care reports of patients who achieved seizure freedom following surgical treatment and discontinued AEDs.

Case report 1

Patient S., 40 years old. Epilepsy began at the age of 14 with focal motor seizures accompanied by oropharyngeal automatisms and automatism-related seizures. Magnetic resonance imaging (MRI) revealed right hippocampal sclerosis. Video-EEG monitoring demonstrated interictal regional epileptiform activity in the right temporal region. The patient's history included an episode of febrile seizures at the age of 3.

Over several years, continuous modification of antiseizure treatment was made using both monotherapy and various combination regimens, yet epileptic seizures persisted. During AED therapy, the patient experienced adverse reactions including diffuse alopecia, thrombocytopenia, menstrual cycle irregularities, and Landolt's syndrome. Despite therapeutic adjustments, the frequency of epileptic seizures progressively increased. In 2013, due to pharmacoresistant disease, a neurosurgical consultation was conducted to evaluate potential surgical intervention. In 2014, a right temporal lobectomy was performed. The postoperative course was uneventful. Histological examination of resected tissue revealed morphological pattern consistent with hippocampal sclerosis.

At the time of surgery, the patient was receiving AED polytherapy with valproic acid, oxcarbazepine, and lacosamide at moderate therapeutic doses. Two and a half months postoperatively, a single focal motor seizure was observed. EEG revealed periodic slowing of cortical rhythms in the right frontotemporal region near the surgical site. One and a half years postoperatively during the first trimester of pregnancy, the patient self-discontinued lacosamide due to medication access challenges, which coincided with a single nocturnal bilateral tonic-clonic seizure. No further epileptic seizures occurred thereafter. Two and a half years after epilepsy surgery, a decision was made for gradual sequential AED withdrawal. The patient has now maintained complete clinical and electroencephalographic remission of epileptic seizures for 10 years.

Case report 2

Patient K., 35 years old. Epilepsy began at the age of 16, presenting with focal non-motor (cognitive, sensory) and motor seizures accompanied by oroalimentary and hand automatisms, occurring with both preserved and impaired

consciousness, and periodic evolution into bilateral tonic seizures. Over several years, the most effective AED combination was gradually selected, with epileptic seizures of varying frequency documented. Neuroimaging revealed an encephalocele in the basal surface of the left temporal lobe. EEG findings showed focal epileptiform activity in the left temporal region.

In 2017, the patient underwent microsurgical resection of the epileptogenic focus in the left temporal lobe and left temporal pole resection under neurophysiological monitoring. At the time of surgery, the patient was on dual therapy with two medications: valproic acid and oxcarbazepine at adequate daily doses. On the first day postoperatively, two seizures with impaired awareness were recorded. Over the next six months, the patient reported sporadic brief déjà vu episodes. Subsequently, epileptic seizures were absent, and EEG demonstrated regional cortical slowing in the left temporal lobe at the encephalocele resection site, with no epileptiform activity registered. Consequently, gradual dose reduction of valproic acid and oxcarbazepine was recommended 2.5 years after surgery. To date, both clinical and electroencephalographic remission of epileptic seizures has been maintained for over seven years.

Discussion

In 2017, the International League Against Epilepsy introduced the concept of "resolution of epilepsy" [9]. Epilepsy is considered resolved in patients with age-dependent epileptic syndromes who have reached a specific age, or in patients who have been free of epileptic seizures for 10 years, including those who have been off AEDs for the last 5 years. There are no specific guidelines for declaring epilepsy resolution in patients following surgery, although surgical treatment is considered the only potential cure for the disease [2]. Additionally, there is no clear definition of «remission of epilepsy,» which creates challenges for both patients and practicing neurologists[1].

According to M.T. Foged et al., complete cure following resective epilepsy surgery is defined by the absence of both seizures and AED use [10]. Significant reduction observed both in the number and daily maintenance dosages of AED following each year of treatment may be an indirect measure of the effectiveness of epilepsy surgery. [11].

There are no unified guidelines to assist in deciding the timing of AED withdrawal or management strategies for patients after successful epilepsy surgery. Various neurosurgical centers employ different approaches to discontinuing AEDs postoperatively [8]. Most commonly, pharmacotherapy continues for at least 2 years following epilepsy surgery due to the potential risk of seizure recurrence and the possibility of failing to achieve remission even after AED resumption [12].

So, M.T. Foged et al. demonstrated that 62% of patients who achieved 3-year seizure remission after successful epilepsy surgery still continued AED therapy. Of those, 20% maintained the same AED dose, while 50% were unwilling to adjust treatment voluntarily. Seven years post-surgery, 18% of patients continued AED use despite sustained seizure remission [10].

Approaches to determining the rate of AED withdrawal require individualized decision-making. Specifically, there is insufficient evidence regarding whether and when to discontinue AEDs, the patient profile suitable for medication withdrawal, or the relapse risks associated with discontinuation [10, 13].

According to C. Rathore et al., many centers discontinue AEDs early in the postoperative period following epilepsy surgery, while others extend pharmacotherapy indefinitely [8].

Some studies report that patients with early gradual AED dose reduction achieved complete seizure remission at rates comparable to those continuing AED therapy [2, 14, 15]. Conversely, an earlier study by D. Ladino et al. found that 1 in 5 surgically treated patients experienced seizure recurrence after medication withdrawal [6].

Several studies indicate that the average time to initiate AED withdrawal ranged from 1.0 to 3.6 years post-surgery, with relapses occurring in only 15% of patients who discontinued therapy [14, 16].

A 1-year seizure-free period following anterior temporal lobectomy is generally considered the minimum standard before attempting AED withdrawal, as over 80% of recurrences occur within the first postoperative year. A single seizure during the first postoperative year increases the likelihood of subsequent seizures sixfold [7, 17]. C. Rathore et al. demonstrated that early complete AED withdrawal starting 1 year after anterior temporal lobectomy is associated with a higher risk of early seizure recurrence compared to continued AED therapy. However, delaying withdrawal until 3 years post-surgery does not protect against potential recurrences, with similar relapse rates and long-term outcomes observed between early and delayed withdrawal groups. Thus, early AED withdrawal starting 1 year after anterior temporal lobectomy appears safe and does not affect long-term seizure outcomes in adult patients [8].

Nevertheless, many clinicians hesitate to discontinue AEDs due to one or more factors: occurrence of seizures in the early postoperative period, epileptiform activity on EEG, age at epilepsy onset and seizure characteristics, and fear of relapse.

In the first clinical case presented, the patient experienced a single focal motor seizure 2.5 months after surgical treatment for drug-resistant epilepsy, and a single nocturnal bilateral tonic-clonic seizure 1.5 years postoperatively during pregnancy and following self-discontinuation of one of AEDs. Subsequently, no epileptic seizures were observed, with an Engel Class Ic outcome. Gradual discontinuation of the second AED was recommended 2.5 years after surgery.

In the second case, two seizures with fluctuating consciousness levels were recorded in the first 24 hours postopera-

[1]Ayvazyan SO, Akzhigitov RG, Alferova VV, et al. Epilepsy and status epilepticus in adults and children. Clinical recommendations, 2022. URL: https://cr.minzdrav.gov.ru/recomend/741_1 (Accessed: February 14, 2025).

tively, followed by isolated brief aura episodes over the next six months, resulting in an Engel Class Ib outcome. This necessitated prolonged AED use, with gradual discontinuation initiated only 2.5 years postoperatively.

Multiple studies indicate that preoperative and postoperative generalized tonic-clonic seizures influenced the decision to continue therapy in approximately half of cases. Post-discharge seizure recurrence, persistent auras, and postoperative epileptiform EEG abnormalities were generally decisive factors against AED discontinuation [18, 19].

In our cases, both patients exhibited regional slowing in the resected epileptogenic zone. Similar patterns may occur in patients with structural brain damage. Additionally, postoperative patients may demonstrate breach rhythm – an artifact associated with skull defects [20]. This artifact superimposed on slow waves can mimic epileptiform activity and, if misinterpreted, may influence clinical decision-making regarding patient management [21].

In the survey by A.T. Berg et al., 9 out of 10 respondents considered epileptiform EEG activity a critical concern against AED withdrawal [18]. A quarter of respondents viewed it as the sole or predominant factor. Conversely, focal slowing and nonspecific findings had no impact on approximately 80% of respondents.

Neuroimaging in our first case revealed right hippocampal sclerosis, while the second case showed encephalocele at the basal surface of the left temporal lobe, both histologically confirmed. Both cases shared well-defined focal pathology concordant with the epileptogenic zone and resection area, likely contributing to favorable surgical outcomes and eventual AED withdrawal despite postoperative seizures.

In A.T. Berg et al. study, MRI-detected unilateral medial hippocampal sclerosis favored AED discontinuation for nearly 75% of respondents, whereas multifocal or bilateral MRI findings were contraindications [18]. Physician responses regarding other brain pathologies varied significantly, though nearly 90% agreed that malignant tumors contraindicated AED discontinuation.

According to a number of authors, maintenance of seizure remission after AED withdrawal can be expected in carefully selected patients. Most commonly, these are patients with mesial temporal sclerosis and a history of febrile seizures [7, 22]. Notably, in the first clinical case described, the patient had a single documented episode of febrile seizures at 3 years of age.

The absence of febrile seizures in the medical history is associated with a higher risk of relapse after epilepsy surgery following AED discontinuation. J. Janszky et al. report that a history of febrile seizures and relatively late age of epilepsy onset are useful diagnostic indicators for clinicians [23]. These patients demonstrate better outcomes following temporal lobectomy compared to those with hippocampal sclerosis but no history of febrile seizures.

Women of childbearing age often express concerns about potential AED teratogenicity, which may motivate attempts to reduce medication doses, ideally long before actual pregnancy planning [24]. In our case, self-discontinuation of one of three AEDs coincided with pregnancy onset, followed by a single seizure occurring 1.5 years post-surgery. Approximately 19–50% of pregnant women with epilepsy do not adhere to prescribed AED therapy, with seizure exacerbation during gestation observed in 90% of these cases compared to 9.8% in treatment-compliant women [25, 26].

Furthermore, a correlation has been demonstrated between seizure frequency during pregnancy and sex steroid hormone levels [27]. Seizure frequency increased with elevated estrogen and reduced progesterone levels, attributable to the pro-epileptogenic effects of estradiol. A similar hormonal effect was observed in the first clinical case.

Other reasons for AED discontinuation may include treatment costs and patients' desire to perceive themselves as «cured» while avoiding the inconvenience and stigma of daily medication use [4]. Up to 88% of patients experience AED-related adverse effects, including dizziness, lethargy, cognitive impairment, and neuropsychiatric symptoms that may negatively impact quality of life [28, 29].

The concepts of early and late seizure relapses following epilepsy surgery remain undefined in clinical guidelines. A.M. McIntosh et al. defined late seizure recurrence was defined as a first postoperative seizure > 2 years after surgery [30]. In cases of late recurrence following AED withdrawal, 71% of respondents reported typically resuming their last used AED, 13% initiated a different AED, and 16% did not resume pharmacological treatment. When seizures recur, most patients regain seizure control after treatment re-initiation, though up to 20% fail to achieve immediate remission [14]. Some authors report that patients experiencing seizure relapse due to AED dose reduction are more likely to regain epilepsy control than those with relapses from other causes [31].

According to K.I. Park et al., post-AED withdrawal seizure relapse can be readily controlled in most patients; however, therapy discontinuation carries a risk of future development of drug-resistant epilepsy [32]. Some patients may not maintain seizure freedom achieved during the first several postoperative years. Several studies have reported late seizure relapses, though these remain underinvestigated due to limited availability of large cohorts with extended follow-up periods [33, 34].

Additional risk factors for postoperative seizure relapse following AED withdrawal include: age >30 years at surgery, long disease duration, residual gliotic changes on postoperative MRI, focal cortical dysplasia as epilepsy etiology, and neurological deficits [19].

Conclusion

The decision to continue or discontinue AED treatment requires an individualized assessment of risks and benefits for the patient. One of the primary concerns is the recurrence of epileptic seizures following treatment discontinuation. It is crucial to engage patients in discussing whether this risk outweighs the potential benefits of AED withdrawal. Patients'

concerns and motivations for discontinuing AEDs must be thoroughly explored. The decision should be personalized, incorporating clinical and electroencephalographic data.

Thus, discontinuing AED therapy requires consideration of numerous factors. Further large-scale studies are needed to establish management strategies for patients after successful epilepsy surgery, including identifying the optimal timing for initiating AED withdrawal. Additionally, identifying early predictors of outcomes in surgical treatment for drug-resistant epilepsy remains an important objective.

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