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Adv. Department
Phone: +7 (968) 545 78 20
E-mail: adv2@eco-vector.com

EDITORIAL OFFICE:
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E-mail: annaly-nevrologii@neurology.ru
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WEB: https://neurology.ru

ИЗДАТЕЛЬСТВО:
ООО «Эко-Вектор»
Адрес: 191181, Россия, Санкт-Петербург, Аптекарский переулок, д. 3, литера А, помещение 1Н.
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E-mail: podpiska@eco-vector.com

РЕДАКЦИЯ:
Адрес: Россия, 125367, Москва, Волоколамское шоссе, д. 80.
Тел.: +7 (499) 740 80 79
E-mail: annaly-nevrologii@neurology.ru
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РЕЦЕНЗИРУЕМЫЙ НАУЧНЫЙ МЕДИЦИНСКИЙ ЖУРНАЛ

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В номере:

Коллектив ФГБНУ «Российский центр неврологии и нейронаук» поздравляет сотрудников Центра, избранных в 2025 году в Российскую академию наук:

Маринэ Мовсесовна Танашян, заместитель директора РЦНН по научной работе, избрана академиком РАН по специальности «неврология».

Елена Владимировна Гнедовская, заместитель директора РЦНН по научной и научно-организационной работе, избрана членом-корреспондентом РАН по специальности «неврология».

Алла Борисовна Салмина, заместитель директора Института мозга РЦНН, избрана членом-корреспондентом РАН по специальности «общая патология, в том числе молекулярная медицина».

Желаем вновь избранным коллегам активной и плодотворной работы на благо отечественной науки!

К 80-летнему юбилею Российского центра неврологии и нейронаук

М.А. Пирадов, С.Н. Иллариошкин

Российский центр неврологии и нейронаук, Москва, Россия

On the 80th anniversary of the Russian Center for Neurology and Neuroscience

Mikhail A. Piradov, Sergey N. Illarioshkin

Russian Center of Neurology and Neurosciences, Moscow, Russia

Научно-исследовательский институт неврологии Академии медицинских наук СССР был открыт 1 апреля 1945 г., за месяц до окончания Великой Отечественной войны. Базой для его создания явилась Клиника нервных болезней и отдела физиологии и патологии органов чувств Всесоюзного института экспериментальной медицины им. А.М. Горького (ВИЭМ). На основе ВИЭМ в 1944 г. была образована Академия медицинских наук СССР, в число первых институтов которой вошёл НИИ неврологии.

Рис. 1. Первое здание НИИ неврологии АМН СССР на ул. Щипок.

Становление Института (1945–1964)

Институт расположился в двухэтажном здании бывшей Александровской больницы в центре Москвы на улице Щипок. Организатором и первым директором Института стал выдающийся учёный Н.И. Гращенков. В первый состав учёного совета вошли выдающиеся исследователи из других научных учреждений страны: Н.Н. Бурденко, А.В. Вишневский, Е.К. Сепп, З.В. Ермольева и др. Для работы были приглашены великие нейрофизиологи Н.А. Бернштейн и А.Р. Лурия. Немногие учреждения могли бы похвастаться такой концентрацией интеллектуального потенциала.

В первые годы перед Институтом были поставлены две основные задачи, определяемые потребностями военного и послевоенного периодов: изучение травматических поражений нервной системы и исследования в области нейроинфекций. В 1945–1947 гг. был завершён комплекс работ, посвящённый военной травме головного и спинного мозга, включая обобщение опыта лечения в военно-полевых условиях черепно-мозговой травмы сульфанилами-

Рис. 2. Фотографии директоров Института (Центра) неврологии 1945–2014 гг. на Аллее славы.

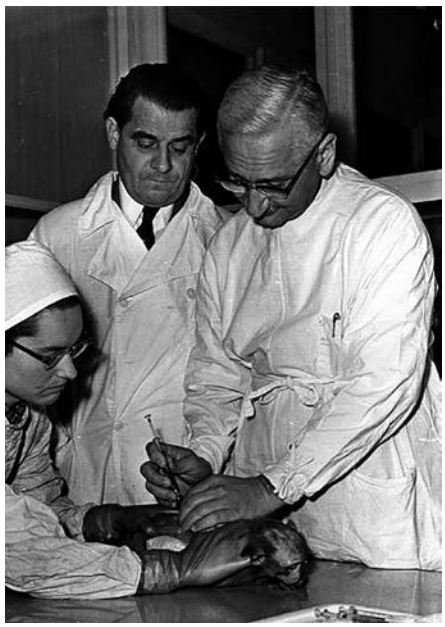

Рис. 3. М.П. Чумаков (в центре) и известный американский вирусолог А. Сейбин (справа) проводят эксперимент по заражению обезьяны по время рабочей поездки советских учёных в США (1956 г.).

дами и антибиотиками, описание анаэробной инфекции мозга, неврозов военного времени, речевых нарушений при нейротравмах.

С середины 1940-х гг. классик мировой вирусологии М.П. Чумаков и его сотрудники проводили в Институте неврологии цикл исследований энцефалитов. На базе Института была создана вирусологическая лаборатория, а ряд экспериментов проводился совместно с Центральным институтом экспериментальной медицины во главе с Л.А. Зильбером. В результате экспедиций в эпидемические очаги были описаны омская и крымская геморрагические лихорадки, джулангарский энцефалит и др.

С 1948 по 1966 г. Институт возглавлял ученик Н.И. Россолимо, крупнейший советский невролог Н.В. Коновалов, вице-президент АМН СССР. Были созданы хорошо оснащённые лаборатории морфологии центральной нервной системы, электрофизиологии, биохимии, психологии, которые возглавили такие крупнейшие учёные, как А.Н. Колтовер, Ф.В. Бассин, Е.А. Жирмунская, Ю.С. Юсевич, А.А. Миттельштедт, Э.С. Бейн и др. Институт взялся за решение проблемы острого эпидемического полиомиелита, который в середине XX в. во всём мире стал настоящим бедствием. Клиническая часть работы осуществлялась под руководством Н.В. Коновалова, а вирусологическая часть, выполнявшаяся М.П. Чумаковым, включала эксперименты на обезьянах и других видах лабораторных животных. В результате ситуацию с полиомиелитом удалось переломить, а созданная в дальнейшем вакцина практически ликвидировала это тяжелейшее заболевание в нашей стране.

Проблема полиомиелита имела прямое отношение к созданию Л.М. Поповой в стенах Института совершенно нового для нашей страны направления – нейрореаниматологии и первого специализированного отделения нейрореанимации (1962 г.). Благодаря этому удалось достигнуть беспрецедентного снижения летальных исходов при тяжёлых формах полиневропатий разного генеза, миастении, ботулизме, энцефаломиелитах, получить пионерские данные по механике дыхания у неврологических больных. К этому же периоду относятся и работы Т.Л. Буниной, открывшей при боковом амиотрофическом склерозе специфические цитоплазматические РНК-содержащие включения в мотонейронах спинного мозга («тельца Буниной»). Л.А. Зильбером и Н.В. Коновалом была выдвинута гипотеза о возможном значении персистирующих вирусов в этиологии отдельных форм бокового амиотрофического склероза, подтверждённая в эксперименте с обезьянами. Это стало одним из наиболее ранних аргументов в пользу широко признанной сегодня концепции церебральных трансмиссивных протеинопатий. Говоря о нейродегенеративных заболеваниях, следует отметить важнейшие исследования оливопонтоцеребеллярной атрофии и гепатолентикулярной дегенерации, которая в нашей стране носит название «болезни Вильсона–Коновалова». Н.В. Коновалову принадлежит и первый в нашей стране систематизированный анализ клинических проявлений рассеянного склероза, который, наряду с другими демиелинизирующими заболеваниями, стал одной из центральных тем для научного коллектива Института.

Рис. 4. Основоположник отечественной нейрореаниматологии Л.М. Попова.

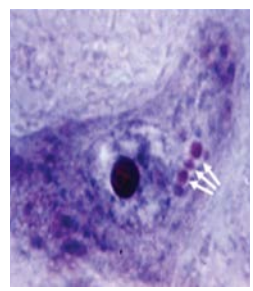

Рис. 5. Тельца Буниной в мотонейронах спинного мозга при боковом амиотрофическом склерозе.

С середины 1950-х гг. в Институте начинается разработка проблемы сосудистых заболеваний мозга, что связано с именем Е.В. Шмидта (возглавлял Институт с 1966 по 1985 г.). Им были начаты совершенно новые для того времени исследования патологии магистральных артерий головы с участием выдающихся клиницистов, морфологов, рентгенологов (Н.В. Верещагин, Л.К. Брагина, Д.К. Лунев, Д.Н. Джибладзе, Л.Г. Людковская и др.). Была продемонстрирована ведущая роль патологии экстракраниальных артерий в генезе атеротромботического и гемодинамического подтипов ишемического инсульта, проведена первая в стране операция каротидной эндартерэктомии (Ю.В. Богатырев). Под руководством профессора А.Н. Колтовер были разработаны принципы системного морфологического исследования целого мозга и его сосудистой системы у пациентов с атеросклерозом и гипертонической болезнью. Проводилось изучение механизмов речевых и двигательных расстройств сосудистого происхождения, разработаны методы кинезотерапии параличей и парезов, создана фундаментальная и прикладная база для восстановления высших корковых функций, в первую очередь нарушений речи, что стало важнейшей вехой в развитии нейрореабилитации.

Новый дом и новые научные направления (1964–1991)

Переезд Института неврологии в здание на Волоколамском шоссе позволил создать новые научные и клинические подразделения. Было открыто специализированное нейрогенетическое отделение, в котором Р.А. Ткачёвым и его продолжателями Е.Д. Марковой и И.А. Ивановой-Смоленской создана уникальная школа изучения дегенеративных и наследственных заболеваний нервной системы, которая сегодня занимает лидирующие позиции в стране. В 1965 г. блестящим нейрохирургом-новатором Э.И. Канделем было создано нейрохирургическое отделение, ставшее на десятилетия флагманом отечественной функциональной и стереотаксической нейрохирургии и неуклонно расширявшее возможности оказания помощи пациентам с паркинсонизмом, дистонией, эссенциальным тремором, болевыми синдромами и др. Э.И. Кандель и его ученик В.В. Переседов разработали не имеющий аналогов в мире метод стереотаксического клипирования аневризм, авторский стереотаксический комплекс — «аппарат Канделя–Переседова», а также предложили новый метод стереотаксического удаления внутримозговых гематом, позволивший более чем вдвое снизить послеоперационную летальность. На рубеже 1960–1970-х гг. Институтом были инициированы масштабные эпидемиологические исследования сосудистых заболеваний мозга, разработаны методические подходы организации регистров инсульта, популяционных скрининговых, проспективных и профилактических программ.

С 1985 по 2003 г. Институт неврологии АМН СССР возглавлял Н.В. Верещагин, с именем которого связан целый ряд ярких свершений в ангионеврологии. В эти годы в Институте были разработаны принципы диагностики и дифференцированной терапии различных подтипов ишемического инсульта, создано специализированное отделение острых нарушений мозгового кровообращения с палатами интенсивной терапии (З.А. Суслина). В отделении нейрореанимации (М.А. Пирадов) была создана система дифференцированной нейрореанимационной помощи при инсультах, применение которой позволило снизить летальность при инфарктах мозга в 1,6 раза, а при кровоизлияниях в мозг — в 1,9 раза.

Рис. 6. Здание Центра на Волоколамском шоссе (вид в 1965 г.).

Рис. 7. Основоположник ведущей школы нейрогенетики в нашей стране Р.А. Ткачев.

Рис. 8. Пионер отечественной функциональной и стереотаксической нейрохирургии Э.И. Кандель.

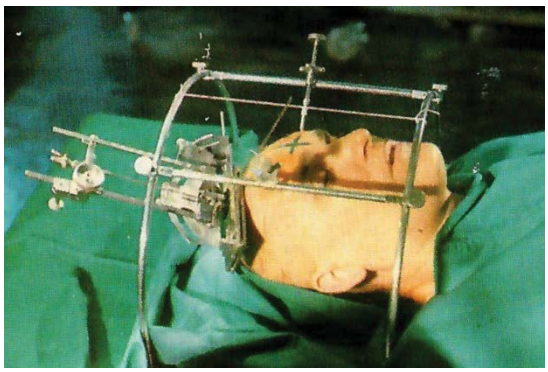

Рис. 9. Аппарат Канделя–Переседова.

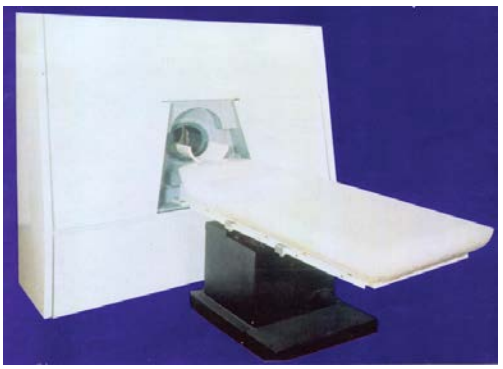

Рис. 10. Отечественный рентгеновский томограф СРТ 1000.

В первом в стране отделении восстановительной неврологии были сформулированы базовые принципы и реализована система этапной нейрореабилитации (Г.Р. Ткачева, Л.Г. Столярова, А.С. Кадыков), создана образцовая афазиолого-логопедическая и нейропсихологическая служба. В нейроинфекционном отделении центральное место заняла проблема рассеянного склероза (включая его атипичные варианты), острого рассеянного энцефаломиелита, болезней мотонейрона (О.А. Хондкариан, И.А. Завалишин).

В 1970-х гг. произошла революция в методах обследования пациентов с патологией головного мозга – началась эпоха компьютерной нейровизуализации. С помощью первого в стране компьютерного томографа в Институте были детально изучены клинико-нейровизуализационные проявления инфарктов мозга и церебральных кровоизлияний, нейродегенеративных заболеваний, рассеянного склероза, объёмных образований мозга. В начале 1980-х гг. сотрудниками НИИ Министерства электротехнической промышленности СССР и учёными Института неврологии во главе с Н.В. Верещагиным был создан отечественный компьютерный томограф – СРТ 1000/1000М. Такие томографы успешно работали во многих учреждениях страны до начала 1990-х гг.

Институт неврологии явился родоначальником ультразвукового исследования сосудов в нашей стране, а также разработчиком функциональных методов нейровизуализации – в конце 1970-х гг. впервые в стране здесь было налажено радиоизотопное (^{133}Xe) исследование мозгового кровотока при окклюзирующих поражениях магистральных артерий головы, изучались механизмы ауторегуляции мозгового кровотока, гемодинамический резерв мозга (И.В. Мусатова, М.А. Пирадов, Т.Н. Шарыпова, В.В. Шведков и др.).

Переходный период (1992–2006)

После организации в начале 1992 г. Российской академии медицинских наук Институт получил новое наименование – НИИ неврологии РАМН. На протяжении 1990-х гг. Институт сумел не просто сохранить свое лицо, но и найти ресурсы для обновления и продвижения вперёд – появлялось новое оборудование, сохранялись высочайшие стандарты клинической работы. На рубеже веков Институт вышел на новый уровень развития. Под руководством М.А. Пирадова были выполнены работы, посвящённые тяжёлым геморрагическим и ишемическим инсультам, демиелинизирующим и воспалительным полинейропатиям, миастеническим и

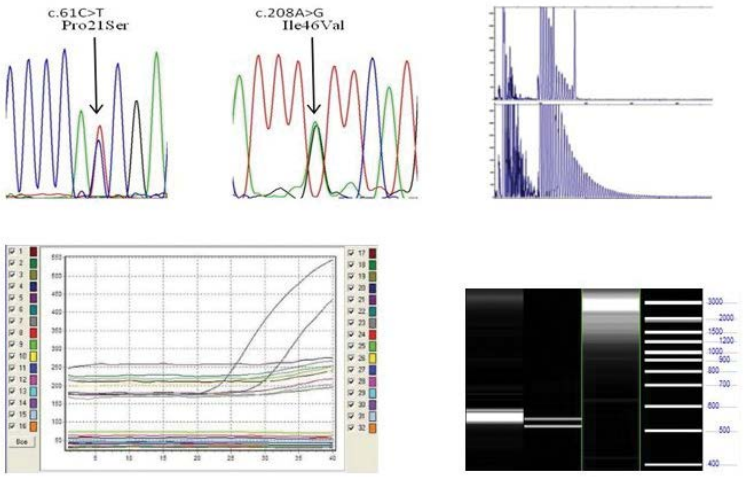

Рис. 11. Различные методы молекулярно-генетического скрининга в ДНК-лаборатории.

холинергическим кризам. Приоритетные исследования по патогенезу и терапии острых воспалительных демиелинизирующих полинейропатий позволили вдвое (до 1–2 мес) сократить сроки восстановления при тяжёлых формах синдрома Гийена–Барре и на порядок снизить летальность при тяжёлых формах дифтерийной полинейропатии.

Ещё с середины 1990-х гг. под руководством З.А. Суслиной, которая являлась директором Института с 2003 по 2014 г., началась фундаментальная разработка проблем кардионеврологии. В Институте появилась первая специализированная лаборатория по изучению гемореологии и гемостаза при неврологических заболеваниях, был внесён значительный вклад в разработку и клиническую апробацию новых антиагрегантов и антикоагулянтов. М.М. Танашян и её сотрудниками была разработана концепция дизрегуляции гемостаза как универсального фактора патогенеза ишемических инсультов. Институт сделал новый шаг в изучении системного тромболизиса: впервые в стране было проведено исследование внутриартериального введения урокиназы при ишемическом инсульте. Новый цикл исследований был посвящён раскрытию причин инсульта в молодом возрасте, проблеме антифосфолипидного синдрома (Л.А. Калашникова). Сотрудники Института внесли большой вклад в организацию оказания помощи больным с инсультом и создание системы такой помощи в Российской Федерации.

Изучению нейродегенеративных и наследственных заболеваний дало новый импульс создание ДНК-лаборатории. Это позволило провести масштабные работы в области мутационного скрининга генов риска и ДНК-диагностики паркинсонизма, дистонии, спиноцеребеллярных дегенераций и других расстройств движений, описать несколько новых наследственных заболеваний нервной системы, создать основанную на молекулярно-генететической диагностике систему медико-генетического консультирования и профилактики при моногенной неврологической патологии (С.Н. Иллариошкин). Исторической заслугой НИИ неврологии РАМН является становление ботулинотерапии как новой области неврологии в нашей стране. В нейроинфекционном отделении выполнены пионерские в стране исследования по прионным заболеваниям. Новым направлением работы стало применение препаратов, изменяющих течение рассеянного склероза.

Сотрудники лаборатории патологической анатомии (В.А. Моргунов, Т.С. Гулевская) описали патологические процессы при артериальной гипертонии и атеросклерозе на всех структурно-функциональных уровнях сосудистой системы головного мозга – от магистральных артерий головы до микроциркуляторного русла. В лаборатории экспериментальной патологии нервной системы (И.В. Ганнушкина) были выполнены приоритетные исследования механизмов индивидуальной предрасположенности мозга к ишемии, роли гематоэнцефалического барьера при нарушениях мозгового кровообращения и черепно-мозговой травме. Лаборатория биохимии (А.А. Болдырев) стала пионером молекулярной нейрохимии и мембранологии в нашей стране и внесла основополагающий вклад в раскрытие молекулярных механизмов окислительного стресса в мозговой ткани.

Современный этап (2006–2025)

В конце 2006 г. решением Президиума РАМН в состав Института неврологии РАМН был включён Институт мозга РАМН – старейшее научно-исследовательское учреждение страны, зародившееся ещё в середине 1920-х гг. как лаборатория по изучению мозга В.И. Ленина. С 1928 г. Институт мозга разрабатывал фундаментальные проблемы анатомии, гистологии, физиологии нервной системы, экспериментальной патологии мозга, к которым со второй половины столетия присоединились исследования в области культур нервной ткани, синаптологии, функциональной морфохимии. В его стенах работали классики отечественной науки о мозге, были созданы первые в нашей стране лаборатории электронной микроскопии, экспериментальной нейроцитологии, нейрокибернетики, а также уникальные объекты, имеющие не только научное, но и большое культурно-историческое значение: Музей эволюции мозга и Пантеон моз-

Рис. 12. Институт мозга (пер. Обуха, дом 5).

Рис. 13. Музей эволюции мозга и Пантеон мозга.

га. В результате произошедшего объединения был создан уникальный научно-исследовательский центр с широчайшим спектром компетенций в различных областях клинических и фундаментальных нейронаук, реализующий на практике передовую модель трансляционной неврологии. Он получил название – Научный центр неврологии, в 2014 г. его возглавил академик М.А. Пирадов. Бурный прогресс в исследовательских и медицинских технологиях, в гуще которого находился Центр, способствовал развитию традиционных направлений его работы и появлению новых областей интереса на стыке с другими дисциплинами.

Активно развиваются в Центре исследования в области нейрореабилитации. Проведено первое в мире исследование эффективности реабилитации пациентов с постинсультными двигательными нарушениями с помощью экзоскелета кисти, управляемого через интерфейс «мозг–компьютер» (ИМК) на основе представления движения. В сотрудничестве с индустриальными партнёрами разработаны прототипы экзоскелета кисти. Продолжаются исследования по использованию в ИМК системы регистрации активности мозга с помощью инфракрасного излучения в ближнем диапазоне. На базе Центра действует лаборатория по созданию нейрореабилитационных высокотехнологичных устройств, и многие разработки уже сегодня находят своё практическое применение у пациентов с различными нарушениями моторных функций.

На мировом уровне проводятся исследования в области неинвазивной нейромодуляции, которая всего за 40 лет прошла путь от экспериментальной методики до способа лечения с очень внушительной доказательной базой, включённого в ряд клинических рекомендаций. Более того, проведённые в Центре исследования показывают фантастические возможности этого метода для изучения самых важных тайн человечества – механизмов сознания и памяти. Достаточно сказать, что сотрудниками Центра уже разработан протокол персонифицированной навигационной транскраниальной магнитной стимуляции, которая способствует улучшению памяти у здоровых людей минимум на 20%, и это только начало пути.

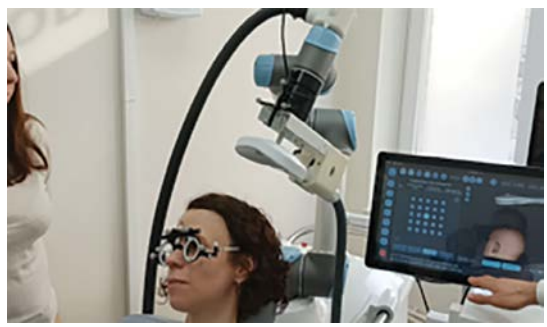

Рис. 14. Робот для навигационной транскраниальной магнитной стимуляции.

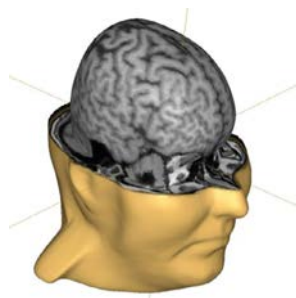

Рис. 15. Индивидуальная 3D-модель головного мозга.

Важнейшим акцентом проводимых сегодня исследований в области нейродегенеративных, сосудистых, демиелинизирующих и других социально значимых заболеваний нервной системы является разработка информативных биомаркеров поражения мозга: молекулярно-генетических, иммунологических, нейровизуализационных и др., что позволяет формировать таргетные группы риска и осуществлять максимально раннюю терапию. Персонализированные методы лечения, применяемые в Центре, включают назначение препаратов моноклональных антител, антисмысловых олигонуклеотидов и других высокоактивных биомолекул, разрабатываются новые подходы генной и генно-клеточной терапии, технологии терапевтической и превентивной нейропротекции.

В Центре успешно реализуются уникальные возможности хирургического лечения заболеваний нервной системы. Так, новым шагом стало применение фокусированного ультразвука под контролем МРТ, позволяющее неизвазивно, без разрезов устранять тяжёлые двигательные симптомы при болезни Паркинсона, эссенциальном треморе и других экстрапирамидных заболеваниях. Оптимизируются подходы к хирургическому лечению фармакорезистентной эпилепсии. Используются методы стимуляции спинного мозга для лечения спастичности и болевого синдрома.

Новым направлением на стыке с пластической хирургией стали реконструктивные хирургические вмешательства на структурах головы и шеи при опухолях, травмах, сосудистых мальформациях, которые выполняются с привлечением в операционную бригаду онкологов и челюстно-лицевых хирургов. Проводятся новаторские операции по восстановлению функции лицевого нерва и мимических мышц, формированию сосудистых анастомозов между интраи экстракраниальными артериями. На высочайшем уровне выполняются вмешательства по поводу аневризм сосудов головного мозга. В хирургии позвоночника приоритет отдаётся разработке и внедрению минимально-инвазивных и эндоскопических вмешательств, что позволяет существенно улучшить неврологические исходы оперативного лечения, в 2 раза уменьшить число осложнений и длительность пребывания больного в стационаре.

В фокусе фундаментальных исследований Центра – разработка новых технологий моделирования ткани головного мозга *in vitro*; создание цифровых двойников клеток и мультиклеточных ансамблей, изучение поведения животных как моделей для оценки влияния внешних факторов на пластичность мозга; создание новых материалов и аппаратно-программных комплексов для трансляционных исследований; молекулярно-генетические исследования когнитивных функций и их нарушений при старении; изучение генетических основ реорганизации нейросетей мозга при различных патологиях; разработка новых фармакотерапевтических и клеточных стратегий в нейронауках. Для решения этих задач активно привлекаются специалисты экспертного уровня в области нейробиологии, нейрофизиологии, нейроморфологии, молекулярной генетики, клеточной биологии, нейрохимии, биоинженерии, биофизики, биоинформатики.

Особенностью исследований, проводимых в Центре, является их междисциплинарный характер, а также кооперация с широким кругом партнёров в Российской Федерации и за рубежом. Стратегическими партнёрами являются МГТУ им. Н.Э. Баумана, МГУ им. М.В. Ломоносова, НИЦ «Курчатовский институт», ИБХ им. акад. М.М. Шемякина и Ю.А. Овчинникова РАН и ещё более 30 крупнейших научных центров страны, а также университеты Москвы, Санкт-Петербурга, Нижнего Новгорода, Казани, Красноярска, Саратова и других городов, более 10 промышленных предприятий и ряд ведущих зарубежных научных центров.

Активное расширение спектра проводимых исследований и появление новых уникальных возможностей в осуществлении клинической деятельности, произошедшие благодаря введению в эксплуатацию нового корпуса и оснащению его самым передовым оборудованием, стали предпосылками для выделения в 2023–2025 гг. в составе Центра 5 институтов: Института клинической и профилактической неврологии, Института нейрореабилитации и восстановительных технологий, Института функциональной нейрохирургии, Института мозга, Института ме-

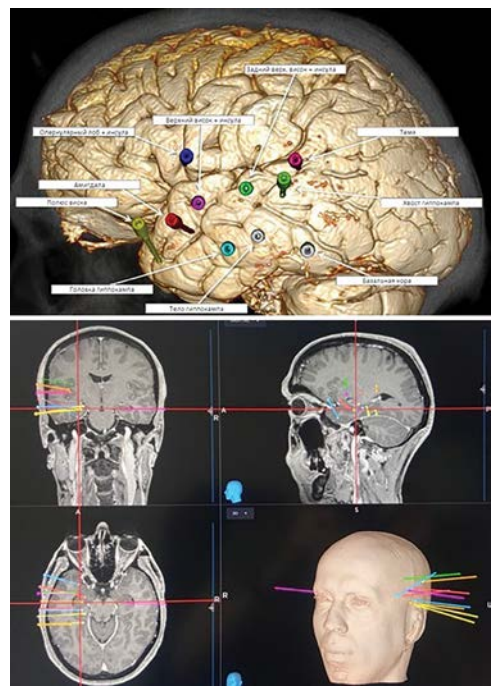

Рис. 16. Стерео-ЭЭГ при предхирургическом обследовании пациента с фармакорезистентной эпилепсией.

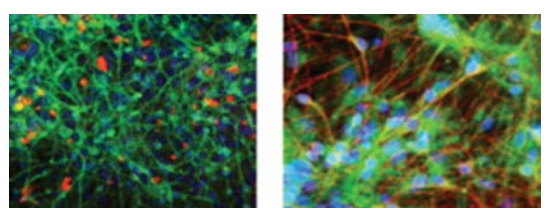

Рис. 17. Персонифицированные клеточные модели заболеваний нервной системы на основе технологии индуцированных плюрипотентных стволовых клеток.

Рис. 18. Сотрудники Центра – члены Российской академии наук.

Рис. 19. Новый корпус Российского центра неврологии и нейронаук.

дицинского образования и профессионального развития. В его структуре созданы Центр эпилепсии, Центр заболеваний периферической нервной системы, Центр боли, Центр когнитивного здоровья, оказывающие все виды высокоспециализированной помощи и реализующие уникальные исследовательские программы.

На базе учреждения реализуются масштабные образовательные программы для студентов (включая обучение свыше 300 студентов из нескольких медицинских университетов Москвы и проведение Национальной олимпиады

«Будущие неврологи XXI века»), клинических ординаторов и аспирантов (свыше 100 обучающихся ежегодно), а также врачей различных специальностей в рамках программ последипломной подготовки (ежегодная аудитория – более 7000 человек).

Ещё несколько впечатляющих цифр:
- в Центре работают 5 академиков и 4 члена-корреспондента Российской академии наук;
- среди представителей научной школы Центра – 2 лауреата Ленинской премии, 9 лауреатов Государственной премии СССР, 8 лауреатов премии Правительства РФ, 8 лауреатов премии Президиума РАМН/АМН СССР, 2 лауреата Золотой медали имени И.П. Павлова АМН СССР, 27 заслуженных деятелей науки;
- сотрудники Центра ежегодно выпускают более 250 научных публикаций, включая статьи в самых влиятельных международных журналах: The Lancet, JAMA Neurology, PNAS и др.;
- за все годы подготовлено более 250 монографий, руководств для врачей, справочников и учебников;
- получено свыше 200 патентов на изобретения, полезные модели, компьютерные программы и базы данных.

Таким образом, в настоящее время Центр перешёл на качественно новый виток своего развития, получив в 2025 г. новое, ёмкое и всеобъемлющее название – **Российский центр неврологии и нейронаук.** Он остаётся флагманом отечественной неврологии и уверенно смотрит в будущее.

Все фотографии – из архива РЦНН.

Biofeedback Training in Rehabilitation of Patients with Neurological Disorders in Post-COVID Syndrome: a Randomized Controlled Trial

Anastasiia N. Cherkasova[1], Ekaterina S. Ikonnikova[1], Roman Kh. Lyukmanov[1], Olga A. Kirichenko[1], Olesya A. Mokienko[1,3], Vladimir A. Konyshev[2], Alexandr A. Zonov[2], Natalia A. Suponeva[1], Mikhail A. Piradov[1]

[1]Russian Center of Neurology and Neurosciences, Moscow, Russia;

[2]Neurobotics, Zelenograd, Russia;

[3]Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences, Moscow, Russia

Abstract

Introduction. *The high prevalence of post-COVID syndrome (PCS), which frequently manifests with emotional disturbances, cognitive impairment, and asthenia, necessitates effective rehabilitation methods. One potential approach is electroencephalography (EEG)-based biofeedback (BFB) therapy, though its use in PCS management has been explored in only a few studies to date.*

The study aimed *to evaluate the effects of EEG α-rhythm BFB training on emotional state and cognitive function recovery, and reduction of asthenia symptoms in PCS patients.*

Materials and methods. *Patients diagnosed with U09. Post-COVID-19 condition were randomly assigned to two groups of 10 participants each. The main group underwent 12–15 sessions of EEG α-rhythm BFB training using the NeuroPlay-6C headset with the Neurocorrection of COVID-19 Psychoemotional Consequences protocol, while the control group received identical training without biofeedback. Assessments performed before and after the intervention included: emotional state evaluation (State-Trait Anxiety Inventory [STAI], Short Health Anxiety Inventory [SHAI], Beck Depression Inventory [BDI], Psychological Stress Measure [PSM-25]), cognitive function assessment (Addenbrooke's Cognitive Examination III [ACE-III], Schulte tables, Stroop test, Tower of London test, N-back test, 10-word memory test), assessment of asthenia (Multidimensional Fatigue Inventory [MFI]), and sleep quality evaluation (Insomnia Severity Index [ISI]).*

Results. *In both groups, the training resulted in a significant reduction of personal anxiety, psychological stress, depression, and asthenia. The main group additionally demonstrated decreased health-related anxiety and improved information retention parameters. Intergroup comparison revealed more pronounced dynamics in the main group: greater reduction of general fatigue manifestations, increased immediate word recall volume, and improved retention of verbal information in working memory. The proportion of patients transitioning to milder symptom severity levels on individual scales was comparable between both groups.*

Conclusion. *EEG α-rhythm biofeedback training can be implemented at the outpatient rehabilitation stage for PCS patients.*

Keywords: *post-COVID syndrome; asthenia; emotional disorders; cognitive impairment; electroencephalographic biofeedback*

Ethics approval. The study was conducted non-invasively in accordance with Helsinki Declaration ethical standards, with patients' voluntary informed written consent. The protocol was approved by the Local Ethics Committee of the Russian Center of Neurology and Neurosciences (Protocol No. 9-5/22 dated October 19, 2022).

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

For correspondence: 80 Volokolamskoye shosse, Moscow, Russia, 125367. Russian Center of Neurology and Neurosciences. E-mail: cherka.sova@mail.ru. A.N. Cherkasova.

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БОС-тренинг в реабилитации пациентов с неврологическими нарушениями при постковидном синдроме: рандомизированное контролируемое исследование

А.Н. Черкасова[1], Е.С. Иконникова[1], Р.Х. Люкманов[1], О.А. Кириченко[1], О.А. Мокиенко[1,3], В.А. Конышев[2], А.А. Зонов[2], Н.А. Супонева[1], М.А. Пирадов[1]

[1]Российский центр неврологии и нейронаук, Москва, Россия;

[2]Нейроботикс, Зеленоград, Россия;

[3]Институт высшей нервной деятельности и нейрофизиологии Российской академии наук, Москва, Россия

Аннотация

Введение. *Распространённость постковидного синдрома (ПКС), среди проявлений которого высока частота встречаемости нарушений эмоциональной сферы, когнитивных функций и проявлений астении, требует разработки методов их преодоления. Одним из таких методов может стать терапия с использованием биологической обратной связи (БОС) по электроэнцефалографии (ЭЭГ), изучение которой в отношении ПКС ограничено единичными работами.*

Цель *исследования – оценить влияние БОС-тренинга по α-ритму ЭЭГ на восстановление эмоционального состояния, когнитивных функций, снижение проявлений астении у пациентов с ПКС.*

Материалы и методы. *Пациентов с диагнозом «U09. Состояние после COVID-19» рандомизировали в 2 группы по 10 человек. Участники основной группы проходили 12–15 тренировок БОС-тренинга по α-ритму ЭЭГ с помощью гарнитуры «NeuroPlay-6C» по программе «Нейрокоррекция психоэмоциональных последствий COVID-19». В контрольной группе применяли те же тренировки, но без обратной связи. До и после тренинга оценивали состояние эмоциональной сферы (Опросник Спилбергера–Ханина, Краткий опросник тревоги о здоровье, Шкала депрессии Бека, Шкала психологического стресса), когнитивных функций (Адденбрукская шкала оценки когнитивных функций III, «Таблицы Шульте», тест Струпа, «Башни Лондона», N-back, «10 слов»), параметры астении (Субъективная шкала оценки астении) и качества сна (Индекс тяжести инсомнии).*

Результаты. *В обеих группах после тренинга произошло значимое снижение личностной тревожности, психологического стресса, депрессии и астении. В основной группе также отмечено снижение тревоги о здоровье и улучшение параметров запоминания информации. При межгрупповом сравнении в основной группе наблюдалась более выраженная динамика снижения проявлений общей астении, увеличения объёма непосредственного воспроизведения слов, удержания вербальной информации в рабочей памяти. Количество пациентов, перешедших на более лёгкий уровень проявления симптомов по отдельным шкалам, в двух группах было сопоставимым.*

Заключение. *БОС-тренинг по α-ритму ЭЭГ может применяться на амбулаторном этапе реабилитации пациентов с ПКС.*

Ключевые слова: *постковидный синдром; астения; нарушения эмоциональной сферы; когнитивные нарушения; биологическая обратная связь по электроэнцефалографии*

Этическое утверждение. Исследование выполнено неинвазивным методом в соответствии с этическими нормами Хельсинкской декларации при добровольном информированном письменном согласии пациентов. Протокол исследования одобрен локальным этическим комитетом Российского центра неврологии и нейронаук (протокол № 9-5/22 от 19.10.2022).

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

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

Адрес для корреспонденции: 125367, Россия, Москва, Волоколамское шоссе, д. 80. Российский центр неврологии и нейронаук. E-mail: cherka.sova@mail.ru. Черкасова А.Н.

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Introduction

COVID-19, which has been spreading worldwide since late 2019, has led to significant medical and social challenges, one of these being the so-called post-COVID-19 condition or post-COVID syndrome (PCS). This condition was first defined by the World Health Organization using the Delphi methodology in October 2021 [1]. According to a large meta-analysis, the prevalence of PCS among patients who recovered from COVID-19 was 41.79% [2].

Neurological and mental disorders are widely represented among PCS symptoms. Meta-analyses indicate that the most frequently reported symptoms include fatigue, sleep disturbances, anxiety, depression, and cognitive impairment. The reported prevalence rates of these symptoms vary but remain consistently high [3–5]. Research is ongoing into the causes of these and other PCS symptoms, with proposed mechanisms including prolonged inflammation, direct neurotoxic and neurotropic effects of the SARS-CoV-2 virus on the central nervous system, pandemic-related stress factors, and others [6, 7].

Given the widespread prevalence of PCS, treatment and rehabilitation methods should be developed, with their effectiveness evaluated. Studies are being conducted on both pharmacological therapies and non-pharmacological interventions [8–10]. One promising approach is electroencephalography (EEG)-based biofeedback (BFB) therapy — neurotraining or neurofeedback. This modality involves regulating various parameters of brain electrical activity through real-time feedback. Numerous studies demonstrate the application of BFB therapy in rehabilitating neurological patients with cognitive and emotional impairments [11]. As many of these impairments are present in PCS, this method may prove effective for managing its symptoms.

In 2022, Russian authors published results from the first controlled study evaluating the efficacy of EEG α-rhythm BFB training in post-COVID patients with emotional disturbances. Participants in the intervention group (n=24) completed 18 sessions using the Neuro V system (Neurobotics) with customized α-rhythm stimulation exercises. The control group (n=16) did not receive BFB therapy. Psychological assessments were performed in both groups before and after the intervention (or without it). At baseline, the groups showed no differences in state anxiety, trait anxiety, depression, or psychological stress levels. Post-intervention comparisons revealed statistically significant improvements across all measured parameters in the intervention group [12].

Czech researchers conducted a pilot study demonstrating reduced anxiety and depression severity lasting at least 1 month after 5 neurofeedback sessions using the Othmer method in a group of 10 PCS patients [13]. A study by Korean researchers showed the effectiveness of EEG α-rhythm and sensorimotor rhythm neurofeedback as part of a comprehensive rehabilitation program for post-COVID cognitive and emotional impairments in older adolescents [14]. Additionally, case reports have been published describing the use of EEG-based biofeedback therapy for COVID-19 sequelae [15, 16].

The study aims to evaluate the effects of EEG α-rhythm biofeedback training on emotional state recovery, cognitive function improvement, and asthenia reduction in PCS patients within a blinded randomized controlled trial with active control.

Materials and methods

Study design

This blind randomized controlled trial was conducted at the Institute of Neurorehabilitation and Recovery Technologies of the Russian Center of Neurology and Neurosciences from June 2022 to June 2024 in an outpatient setting. The study design is shown in **Fig. 1.** A total of 20 patients were enrolled and randomized into two groups using the sealed envelope method. Prior to the BFB-training, all participants underwent neurological examination and qualitative neuropsychological assessment using A.R. Luria's syndromic analysis [17] to identify the structure of higher mental function impairments in PCS (these data will be presented separately). Quantitative assessments of emotional state, cognitive functions, and sleep quality were performed before the first and after the last training session. Participants in the main group underwent EEG α-rhythm BFB-training, while the control group received identical training without BFB. The following measures were implemented to ensure blinding: all patients underwent identical diagnostic and training procedures, including EEG headset placement and use of the same software. Participants were not informed about the principles of the BFB system or their group assignment. All participants received identical instructions and were trained under the same conditions, except for the provision of BFB.

The study duration for participants was 21–27 days according to the following schedule: neurological examination and neuropsychological assessment (1 day), quantitative evaluation of emotional status, cognitive functions, and sleep quality before training sessions (1 day), 12–15 training days on week-

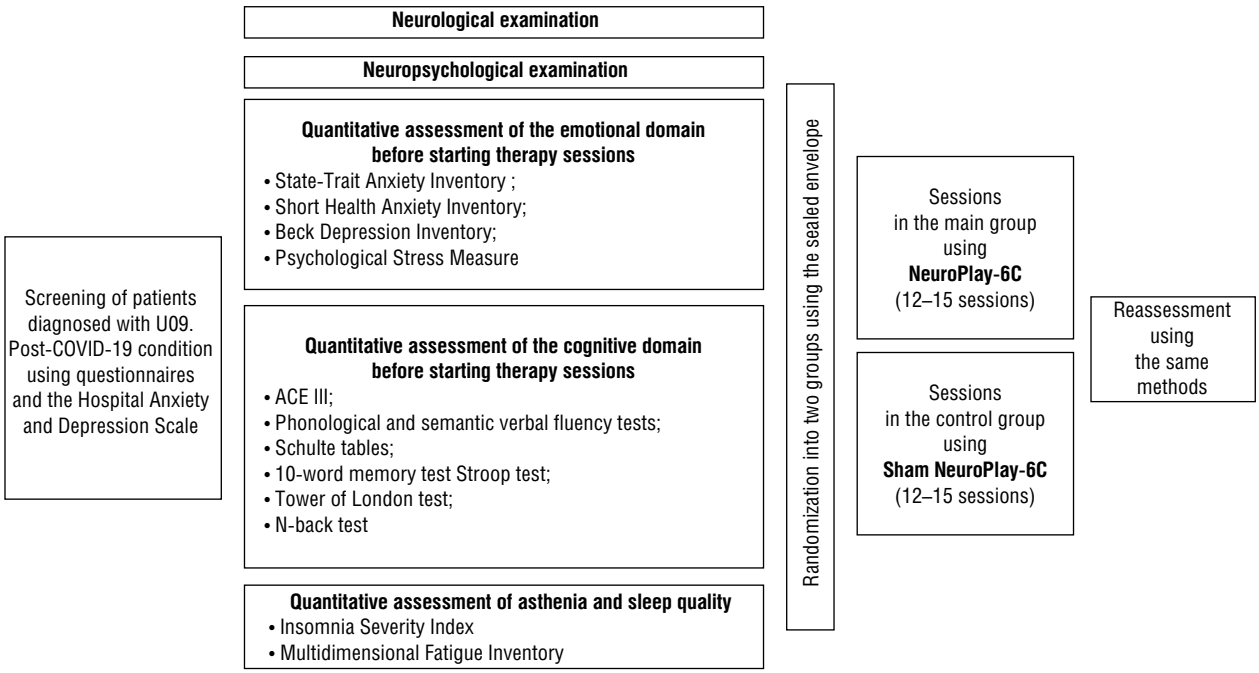

Fig. 1. Study design.

days with weekend breaks (participants were allowed up to 3 non-consecutive missed training sessions during the course, which had to be made up), and quantitative evaluation of emotional status, cognitive functions, and sleep quality after training sessions (1 day). Eighteen patients completed all 15 training sessions, while two patients ended the study at the 14th and 12th training sessions, respectively, due to external circumstances unrelated to the study.

The study protocol was approved by the Local Ethics Committee of the Russian Center of Neurology and Neurosciences (Protocol No. 9-5/22 dated October 19, 2022). Participation was entirely voluntary, with each patient providing written informed consent.

Eligibility criteria

Study participants were recruited through announcements posted on electronic information resources, bulletin boards at the Russian Center of Neurology and Neurosciences, and in special social media groups for PCS patients. A specialized questionnaire was developed for screening, containing questions about COVID-19 history (disease confirmation through medical records, time since infection, severity, current symptoms, chronic conditions, and medications). A separate section of the questionnaire focused on detailed assessment of anxiety, depression, asthenia, cognitive impairments, and sleep disorders – the key symptoms of interest in this study. The questionnaire along with the Hospital Anxiety and Depression Scale (HADS) [18] were sent upon request following telephone conversations with potential participants, during which they received detailed information about study timelines/format and could ask questions. After analyzing questionnaires and HADS results, participants preliminarily meeting inclusion criteria were invited for neurological examination to confirm the diagnosis of U09. Post COVID-19 condition.

Inclusion criteria: Diagnosis of U09. Post COVID-19 condition; subclinical or mild clinical manifestations of anxiety and/or depression (HADS score $\leqslant$ 16); self-reported symptoms from the depression/anxiety group, cognitive impairment group, and/or sleep disturbances/asthenia group associated with COVID-19; age $\geqslant$ 18 years; informed consent.

Exclusion criteria: Presence of other conditions that could explain anxiety, depression, cognitive impairment, sleep disturbances, or asthenia; use of antidepressants, anxiolytics, or other medications affecting studied functions during dose titration or adjustment periods.

Withdrawal criteria: Patient withdrawal of consent; patient-reported escalation of anxiety/depression symptoms to severe clinical manifestations.

During the study period, 87 applications for participation received through various channels were analyzed. Forty-six patients declined participation during the detailed telephone briefing about the outpatient setting, geographical location, and study duration. Nineteen patients were excluded after questionnaire and HADS scale analysis due to meeting various exclusion criteria. Two other patients were excluded after neurological examination (one was referred for psychiatric consultation, the other due to contraindicated medication use).

Consequently, 20 PCS patients were enrolled in the main study. Five patients had confirmed COVID-19 more than once, with disease duration calculated from the episode when PCS symptoms first appeared. According

to questionnaires, 18 patients reported symptoms across all analyzed categories, while 2 reported symptoms in all categories except cognitive impairments. At the time of the study, 2 patients were taking antidepressants in stable doses; other participants were not receiving pharmacological treatment.

EEG α-rhythm biofeedback training

Patients in the main group underwent 12–15 training sessions of 30–50 minutes each using EEG α-rhythm biofeedback technology with the NeuroPlay-6C system ("Neurobotics") via the built-in Neurocorrection of Psychoemotional Consequences of COVID-19 protocol. The headset and software were provided for free use. The headset is a wireless mobile 6-channel EEG recording system (Fp1, Fp2, T3, T4, O1, O2 channels) utilizing dry electrodes mounted on a specialized headband secured around the head. The recorded signals are transmitted to the main device via Bluetooth. The software analyzes EEG spectral characteristics to provide patients with biofeedback about their physiological state.

During training sessions, patients sat at a table in comfortable chair facing a computer monitor. Each session included a theoretical component explaining the upcoming exercises and a practical component for their implementation. During task performance, patients followed voice-guided instructions focusing on breath control, muscle relaxation, mental training, and meditation practices. All training sessions were conducted with closed eyes. Participants received auditory feedback about their physiological state during exercises. Failed task performance triggered increasing noise that masked background music perception. When patients returned to the target state with registered α-rhythm activity, the noise ceased. The main group participants learned to self-regulate their state using BFB during training.

Control group patients completed 12–15 training sessions (30–50 minutes each) using the Sham-NeuroPlay EEG program simulating BFB via the built-in Neurocorrection of COVID-19 Psychoemotional Consequences protocol. This protocol version was specially provided by Neurobotics for the study. Identical to the main group, control participants wore electrode headbands and performed state regulation exercises with the program's voice assistant, but without actual feedback.

Instruments for assessing patients' condition before and after training

To study the impact of training on the emotional state in both groups before and after the intervention, electronically completed questionnaires were used:

- The State-Trait Anxiety Inventory (STAI [19] adapted by Yu.L. Khanin [20]), containing two scales: state (reactive) anxiety and trait anxiety (symptom severity ranges: 0–29 points – low anxiety level, 30–45 – moderate, 46–80 – high);
- The Short Health Anxiety Inventory (SHAI [21] adapted by T.A. Zhelonkina et al. [22]), assessing total scores (maximum 54 points) and three subscales: health anxiety, fear of negative consequences of illness, and vigilance to bodily sensations;
- The Beck Depression Inventory (BDI [23] adapted by N.V. Tarabrina [24]), evaluating total scores (symptom severity: 0–9 – no depressive symptoms, 10–15 – mild depression, 16–19 – moderate, 20–29 – severe, 30–63 – very severe), along with cognitive-affective and somatic subscales;
- The Psychological Stress Measure (PSM-25 [25] adapted by N.E. Vodopyanova [26]), assessing total scores (stress severity: 0–99 – low stress level, 100–155 – moderate, > 155 – high).

To study the effect of training on cognitive functions, both groups of participants underwent quantitative neuropsychological assessment before and after the experimental intervention. The assessment was conducted by a qualified neuropsychologist using methods targeting both general cognitive screening and evaluation of specific cognitive functions that, according to literature data [10], are most susceptible to impairment in PCS.

The following blank assessment tools were used:

- Screening Addenbrooke's Cognitive Examination III (ACE-III) [27], validated by N.A. Varako et al. [28], which assesses total scores (maximum 100 points) across 5 domains: attention (max 18 points), memory (max 26 points), verbal fluency (max 14 points), language (max 26 points), and visuospatial function (max 16 points);
- Phonological and semantic verbal fluency test administered within the ACE-III framework but separately scored based on the total number of correct words generated per minute;
- Schulte tables [29], with calculated parameters including work efficiency (mean time per 5 tables), index of work warming-up (time for first table divided by mean time), and psychological stability index (time for fourth table divided by mean time) according to A.Yu. Kozyreva's method;
- A.R. Luria's 10-word memory test [17], recording parameters of immediate/delayed word recall volume and the number of trials required for complete memorization.

The Stroop test [30], which assessed interference effect parameters under word reading and color naming conditions (automatically calculated by the software), was administered using the Schuhfried hardware-software complex (https://www.schuhfried.com/en/).

Other computerized neuropsychological tests were conducted using Psychology Experiment Building Language Battery software [31]:

- The Tower of London test [32], which measured the total number of moves required to solve all planning subtests and the total time spent completing the entire test;
- The N-back test [33] under dual-task working memory conditions (simultaneous maintenance of letter and spatial stimulus sequences) with a comparison task between current on-screen stimuli and those presented *n* steps earlier ($n = 1, 2, 3$). For analysis, series with $n = 2$ and 3 were considered, recording the number of correct responses and false alarms for both letter and spatial stimuli. After test completion, the d-prime sensitivity index (d') [34] was

calculated for each stimulus type in every series (n = 2 and 3) using the formula:

$$d' = Z(\text{hit rate}) - Z(\text{false alarm rate}),$$

where hit rate = number of patient's correct responses / maximum possible correct responses; false alarm rate = number of patient's false alarms / number of non-target stimuli; these rates were standardized using Z-transformation.

In addition to the techniques targeting emotional and cognitive domains, patients' subjective sleep quality was assessed using the Insomnia Severity Index (ISI [35], adapted by E.I. Rasskazova et al. [36]), which recorded total scores with the following severity categories: 0–7 points — normal, 8–14 points — mild sleep disturbances, 15–21 points — moderate, and 22–28 points — severe. Manifestations of asthenia were evaluated using the Multidimensional Fatigue Inventory (MFI-20 [37], Russian-translated version), with registration of total scores (maximum possible score: 100) and scores across 5 subscales: general fatigue, reduced activity, reduced motivation, physical fatigue, and mental fatigue.

Statistical Analysis

Due to the small sample size and non-normal distribution of data for several variables (according to the Kolmogorov–Smirnov test), non-parametric methods were used for statistical analysis. Intergroup differences in age and all baseline study variables were assessed using the Mann–Whitney U test for two independent samples. Fisher's exact test was used to compare groups based on the nominal variable of participants' sex. The training effect within each group was evaluated using the Wilcoxon signed-rank test (W) for two related samples (comparing preand post-training indicators). For statistical comparison of intervention protocols in each group, delta changes between preand post-training indicators were calculated for all specified variables. These changes were compared using the Mann–Whitney U test for two independent samples. The analysis also included patients who transitioned to milder levels of anxiety, depression, psychological stress, and sleep disturbances in each group (assessed using the State-Trait Anxiety Inventory, Beck Depression Inventory, Psychological Stress Measure, and Insomnia Severity Index). Intergroup comparison of the proportion of such patients was performed using Fisher's exact test. The statistical significance level was set at 0.05. Calculations were performed using IBM SPSS Statistics v.23 software. Data are presented as median [25%, 75% quartile].

Results

Baseline Comparison of Patient Groups

Demographic and baseline clinical characteristics of the main and control groups are presented in Table 1. The groups showed no differences in sex, age, time since COVID-19 infection, or HADS scores used during participant screening.

Both groups underwent quantitative assessments of emotional status, cognitive functions, and sleep disturbances prior to the training. Comparative analysis of all variables revealed significant intergroup differences in Psychological Stress Measure scores. Stress levels in the control group were higher than those in the main group, with median scores in both groups corresponding to moderate stress levels. Differences were also observed in one parameter of the Stroop test (interference effect during word reading condition). All other baseline parameters showed no significant differences between groups (Table 2).

According to the scales assessing the severity of emotional and sleep disturbances, the severity levels in both groups were comparable (when comparing the median values within each scale's score ranges):
- state and trait anxiety scores indicated high levels;
- depression scores corresponded to a mild level;
- stress scores were at a moderate level;
- sleep quality scores suggested mild disturbances.

Cognitive screening using the ACE-III revealed no overt cognitive impairments suggestive of dementia (⩽ 88 points, sensitivity 1.00) in either group (Table 2).

Assessment of intragroup dynamics of study participants' condition

1. Intragroup dynamics of emotional domain

When comparing preand post-training indicators in both the main and control groups, significant improvement was observed across several parameters (hereinafter figures show results for main scale scores; subscale data are described in the text):

Table 1. Demographics and baseline characteristics of two groups

Characteristic	Main group (n = 10)	Control group (n = 10)	Mann–Whitney U test value	p
Sex	4 males, 6 females	1 male, 9 females		0.303
Age	41 [32; 50]	31 [24; 40]	30	0.143
Time since COVID-19 (months)	23 [15; 26]	16 [9; 18]	26	0.075
HADS — anxiety assessment	8 [5; 11]	8 [6; 10]	32	0.190
HADS — depression assessment	9 [8; 10]	7 [5; 11]	45	0.739

Table 2. Comparison of two patient groups across all assessed parameters before intervention

Parameter	Main group (*n* = 10)	Control group (*n* = 10)	Mann–Whitney U test value	*p*
Emotional domain				
STAI, state anxiety	49.5 [37.3; 55.0]	49.5 [37.0; 54.3]	50	1.000
STAI, trait anxiety	56 [42.8; 60.8]	50.5 [43.7; 63.5]	48.5	0.912
SHAI, total score	13 [10; 17]	13 [8.8; 21.0]	48.5	0.912
SHAI, health anxiety	4.5 [3.0; 7.3]	5.5 [2.0; 9.3]	46	0.796
SHAI, fear of negative consequences of illness	5 [3.8; 6.3]	3.5 [3.0; 5.3]	35	0.280
SHAI, vigilance to bodily sensations	3.5 [1.8; 6.0]	4.5 [2.8; 6.5]	39	0.436
BDI, total score	11.5 [8.0; 14.7]	15.5 [9.8; 17.8]	35.5	0.280
BDI, cognitive-affective subscale	6 [5.0; 8.3]	8 [6.0; 11.3]	32.5	0.190
BDI, somatic subscale	5 [3; 7]	5.5 [3.8; 7.5]	44	0.684
PSM-25	102 [87; 115]	115 [99; 120]	**18**	**0.015**
Cognitive domain parameters				
ACE-III, total score	98 [95.5; 99.3]	98 [95.5; 98.3]	41	0.529
ACE-III, attention	18 [18; 18]	18 [17; 18]	39.5	0.436
ACE-III, memory	25.5 [25; 26]	25 [25; 25]	31.5	0.165
ACE-III, verbal fluency	13 [11.8; 14.0]	13 [12.8; 13.3]	45.5	0.739
ACE-III, language	26 [25; 26]	26 [25.8; 26.0]	46.5	0.796
ACE-III, visuospatial function	16 [15; 16]	16 [15.5; 16.0]	47	0.853
Phonological verbal fluency	17.5 [14; 19]	18 [17; 21.5]	40	0.481
Semantic verbal fluency	22.5 [18.5; 25.3]	22.5 [16.5; 26.0]	50	1.000
Schulte tables, efficiency	32.3 [26.1; 41.4]	28.7 [27.1; 39.4]	44	0.684
Schulte tables, work warming-up	0.96 [0.92; 1.01]	0.99 [0.91; 1.05]	41.5	0.529
Schulte tables, psychological stability	0.99 [0.95; 1.08]	1.06 [0.97; 1.13]	37	0.353
10-word memory test, immediate recall volume	6 [5.8; 7.0]	8 [6; 8]	25.5	0.063
10-word memory test, delayed recall volume	9 [7.8; 10.0]	9 [7.8; 10.0]	34	0.247
10-word memory test, number of trials to complete memorization	3.5 [3.0; 5.3]	2.5 [2.0; 4.2]	49	0.971
Stroop test, interference in word reading condition	0.2 [0.17; 0.22]	0.11 [0.09; 0.15]	**22**	**0.035**
Stroop test, interference in color naming condition	0.1 [0.08; 0.17]	0.08 [0.05; 0.10]	28	0.105
Tower of London, total number of moves	150 [136; 162]	158 [151; 166]	34	0.247
Tower of London, completion time	392 [361; 533]	344 [297; 623]	34	0.247
N-back, *n* = 2, letter stimuli, d'	1.2 [0.60; 2.05]	1.47 [0.68; 2.13]	46.5	0.796
N-back, *n* = 2, spatial stimuli, d'	1.8 [0.80; 2.28]	1.63 [0.64; 2.13]	46	0.796
N-back, *n* = 3, letter stimuli, d'	1.07 [0.48; 1.15]	1.11 [0.72; 1.86]	40	0.481
N-back, *n* = 3, spatial stimuli, d'	0.84 [0.16; 1.17]	0.93 [0.64; 1.12]	47	0.853
Sleep quality and asthenia assessment indicators				
ISI	9 [2.8; 17.0]	12.5 [6.0; 17.3]	40.5	0.481
MFI-20, total score	65 [49.5; 70.5]	68.5 [55.0; 76.5]	34	0.247
MFI-20, general fatigue	16 [14.8; 16.3]	14.5 [13.8; 17.0]	41.5	0.529
MFI-20, reduced activity	13.5 [9.8; 16.3]	13.5 [8.7; 17.3]	49	0.971
MFI-20, reduced motivation	9 [6; 12]	11.5 [9; 15]	26	0.075
MFI-20, physical fatigue	11.5 [9.0; 14.3]	13 [11.8; 14.5]	40.5	0.481
MFI-20, mental fatigue	12 [7.5; 17.3]	13 [11.8; 14.5]	44.5	0.684

- reduction in trait anxiety (Fig. 2, *A*);
- reduction in psychological stress (Fig. 2, *B*);
- reduction in overall Beck Depression Inventory scores (Fig. 2, *C*), including scores on the cognitive-affective subscale (main group: W = –2.814; p = 0.005; control group: W = –2.537; p = 0.012) and somatic subscale (main group: W = –1.998; p = 0.046; control group: W = –2.537; p = 0.012);
- reduction in scores on the SHAI vigilance to bodily sensations subscale (main group: W = –2.558; p = 0.011; control group: W = –2.701; p = 0.007).

Additionally, the main group demonstrated reduced overall SHAI health anxiety scores, which was not observed in the control group (Fig. 2, *D*). No changes were observed in other assessed variables.

2. Intragroup dynamics of cognitive domain

When comparing preand post-training indicators in the main group, improvements were observed in the performance of A.R. Luria's 10-words memory test: increased volume of immediate word recall (W = –2.356; p = 0.018) and reduced number of attempts required to memorize all 10 words (W = –2.565; p = 0.010). To illustrate these changes, we present the dynamics of the 10-word learning curve in Patient No. 7 from the main group (Fig. 3). No other significant changes in cognitive domain parameters were identified.

In the control group, cognitive changes showed bidirectional effects: post-training improvements in total completion time for the Tower of London test (W = –2.497; p = 0.013), but reduced efficiency in maintaining letter stimuli in working memory (N-back test, n = 3, letter stimuli, d' – W = –2.293; p = 0.022). No other significant changes were observed.

3. Intragroup dynamics of sleep quality and asthenia manifestations

When comparing preand post-training indicators in both the main and control groups, a significant reduction in asthenia manifestations was observed, both in the total score of the MFI (Fig. 4) and in individual subscales:

- general fatigue (main group: W = –2.670; p = 0.008; control group: W = –2.025; p = 0.043);
- reduced activity (main group: W = –2.677; p = 0.007; control group: W = –2.388; p = 0.017);
- physical fatigue (main group: W = –2.113; p = 0.035; control group: W = –2.120; p = 0.034);
- mental fatigue (main group: W = –2.257; p = 0.024; control group: W = –2.094; p = 0.036).

The control group also showed improvement in the reduced motivation subscale (W = –2.002; p = 0.045).

No significant improvements in sleep quality were demonstrated in either group.

Intergroup comparison of intervention efficacy

When comparing delta changes (degree of improvement across all specified variables), statistically significant intergroup differences were observed for two cognitive measures. The experimental group showed greater improvement compared to the control group in immediate recall scores on A.R. Luria's 10-word memory test (U = 25.5; p = 0.036), as well as higher efficiency in maintaining letter stimuli in working memory (N-back test; n = 3; letter stimuli, d' – U = 23.5; p = 0.034). Intergroup differences were also observed on the general fatigue subscale of the MFI, with more substantial changes in the experimental group compared to controls (U = 19.5; p = 0.019). Changes across all other measured parameters were comparable between groups.

For statistical comparison of the two interventions, we analyzed the number of patients transitioning to milder severity levels of anxiety, depression, psychological stress, and sleep disturbances in both groups. The proportion of such patients on each scale was comparable between experimental and control groups (Table 3).

Discussion

In this blinded randomized controlled trial, both EEG α-rhythm BFB training and various psychological practices without feedback demonstrated positive outcomes, including reductions in trait anxiety, psychological stress, depressive symptoms, and fatigue. The BFB therapy group additionally showed decreased health-related anxiety and improved performance on the 10-word recall memory test. Psychological interventions without feedback exhibited mixed effects on specific cognitive domains.

When comparing intervention protocols, BFB therapy demonstrated superior efficacy in reducing general fatigue, enhancing immediate word recall during learning, and maintaining verbal information in working memory. However, both protocols showed comparable results in the proportion of patients achieving milder symptom severity levels based on emotional state and sleep quality questionnaires.

The obtained results regarding EEG α-rhythm BFB training align with published data on the effective use of biofeedback therapy for anxiety disorders [38], depression [39], stress [40], and asthenia [41] outside the context of PCS. Furthermore, existing evidence demonstrates the influence of EEG α-rhythm BFB training on working and episodic memory in healthy individuals [42]. The cognitive improvements observed in our study may result both from the direct effects of biofeedback therapy on the examined functions and from the more pronounced reduction of asthenia in the main study group, which could enhance neurodynamic aspects of cognitive processing and consequently lead to increased immediate recall capacity and reduced number of trials required for memorization in the 10-word memory test.

The results obtained from various psychological practices indicate that breathing control exercises, muscle relaxation techniques, mental training, and meditation practices exert an independent positive effect on several emotional parameters and manifestations of asthenia, regardless of the feedback. Consequently, the data obtained through BFB therapy may be partially explained by non-specific effects of the applied exercises rather than the feedback mechanism itself.

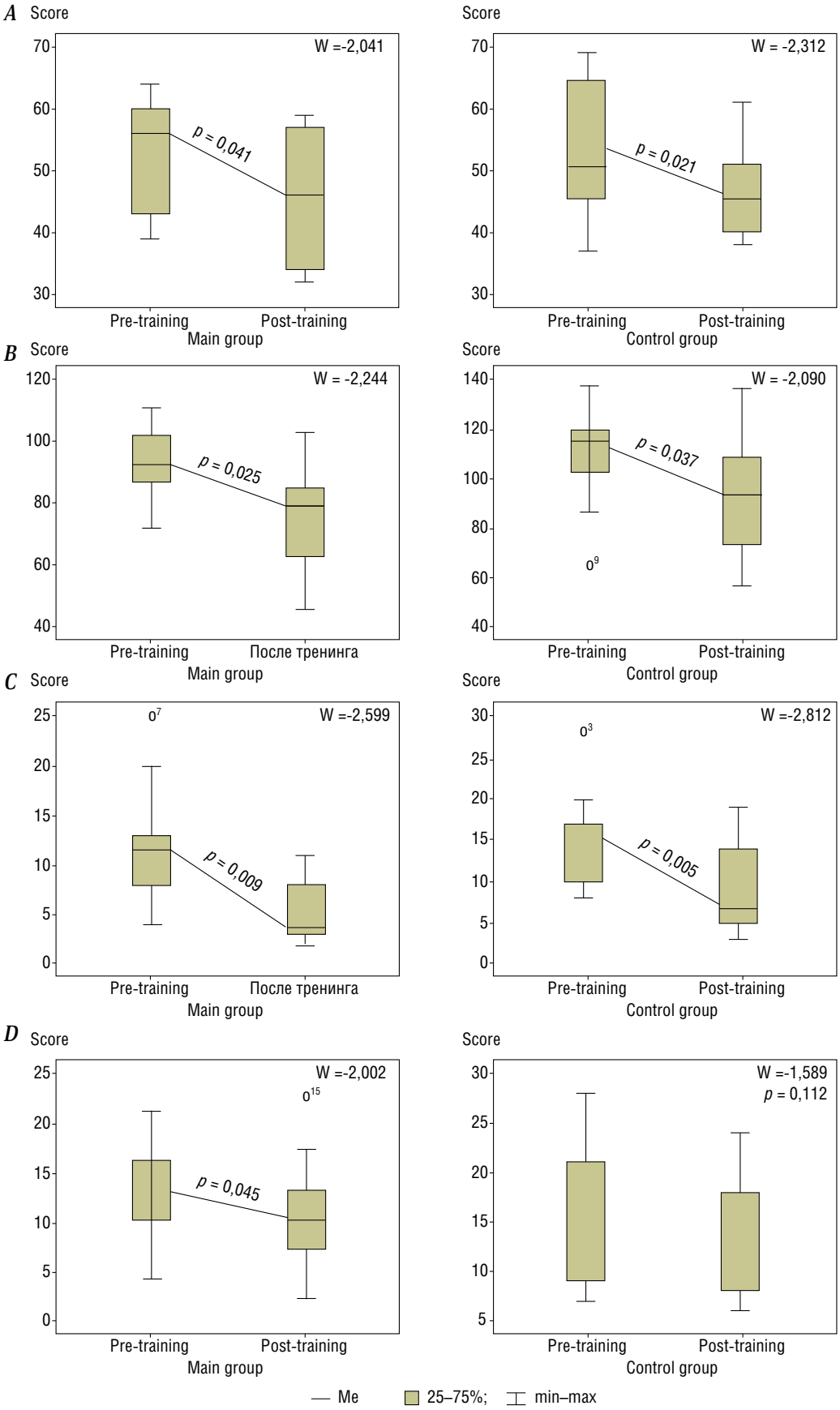

Fig. 2. Intra-group dynamics of trait anxiety scores on the State-Trait Anxiety Inventory (*A*), Psychological Stress Measure (*B*), Beck Depression Inventory (*C*), and Short Health Anxiety Inventory (*D*).

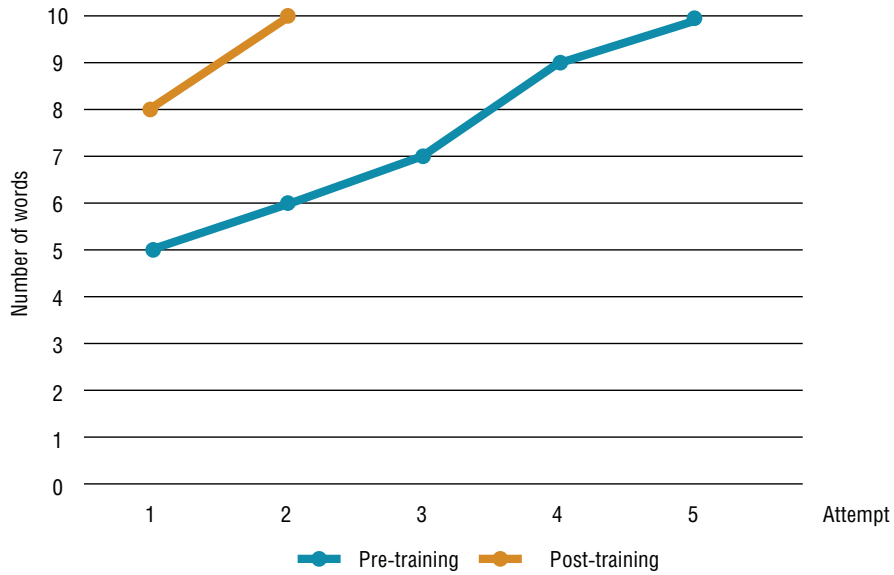

Fig. 3. Learning curves of the 10-word memory test before and after training for patient No. 7 in the main group.

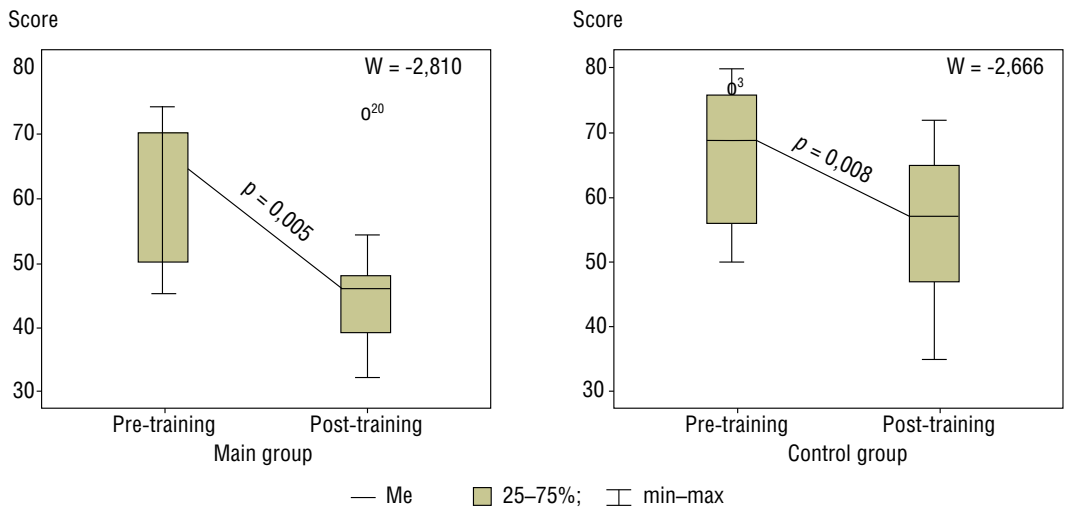

Fig. 4. Intra-group dynamics of Multidimensional Fatigue Inventory total scores in both groups.

Table 3. Comparison of the proportion of patients achieving transition of symptoms to milder severity levels

Proportion	Main group (*n* = 10)	Control group (*n* = 10)	*p*
Achieved improvement on STAI, state anxiety, *n* (%)	5 (50%)	6 (60%)	1.000
Achieved improvement on STAI, trait anxiety, *n* (%)	2 (20%)	1 (10%)	1.000
Achieved improvement on BDI, *n* (%)	6 (60%)	5 (50%)	1.000
Achieved improvement on PSM-25, *n* (%)	2 (20%)	4 (40%)	0.628
Achieved improvement on ISI, *n* (%)	4 (40%)	3 (30%)	1.000

Limitations of this study include small sample sizes (which may account for baseline differences in psychological parameters between groups), lack of preliminary statistical power calculations and sample size estimation, and absence of neurophysiological analysis of EEG parameter changes preand post-training. In this study, the control group received no feedback, potentially raising participants' suspicions about the intervention given that both groups wore headsets and received identical instructions during each session.

In future studies, the use of sham feedback in the control group may help elucidate the specific contribution of feedback mechanisms. Additionally, introducing a no-intervention group could help control for placebo effects associated with study participation. To comprehensively assess the efficacy of BFB therapy, patient evaluations should be conducted at specific intervals (1 month, 6 months, 1 year) post-intervention.

To our knowledge, this study represents the first global comparison of EEG α-rhythm biofeedback training and psychological practices without feedback in addressing PCS symptoms.

Conclusion

While EEG α-rhythm BFB training and feedback-free psychological practices showed comparable efficacy across several emotional parameters, BFB therapy demonstrated advantages in reducing general fatigue, improving immediate word recall during learning, and maintaining verbal information in working memory. These findings suggest that EEG α-rhythm BFB training may be applicable for correcting emotional state, cognitive functions, and asthenia manifestations during outpatient rehabilitation of PCS patients, including home-based settings.

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Information about the authors

Anastasiia N. Cherkasova – junior researcher, Brain-computer interface group, Institute of Neurorehabilitation and Recovery Technologies, Russian Center of Neurology and Neuroscience, Moscow, Russia, https://orcid.org/0000-0002-7831-5833
Ekaterina S. Ikonnikova – junior researcher, Brain-computer interface group, Institute of Neurorehabilitation and Recovery Technologies, Russian Center of Neurology and Neuroscience, Moscow, Russia, https://orcid.org/0000-0001-6836-4386
Roman Kh. Lyukmanov – Cand. Sci. (Med.), senior researcher, Head, Brain-computer interface group, Institute of Neurorehabilitation and Recovery Technologies, Russian Center of Neurology and Neuroscience, Moscow, Russia, https://orcid.org/0000-0002-8671-5861
Olga A. Kirichenko – junior researcher, Head, Department of medical rehabilitation and physiotherapy, Institute of Neurorehabilitation and Recovery Technologies, Russian Center of Neurology and Neuroscience, Moscow, Russia, https://orcid.org/0000-0002-7119-9841
Olesya A. Mokienko – Cand. Sci. (Med.), researcher, Brain-computer interface group, Institute of Neurorehabilitation and Recovery Technologies, Russian Center of Neurology and Neuroscience, Moscow, Russia; senior researcher, Institute of Higher Nervous Activity and Neurophysiology of RAS, Moscow, Russia, https://orcid.org/0000-0002-7826-5135
Vladimir A. Konyshev – Chief Executive Officer, Neurobotics LLC, Zelenograd, Moscow, Russia, https://orcid.org/0009-0004-0576-2626;
Alexandr A. Zonov – product manager, neurophysiologist, Neurobotics LLC, Zelenograd, Moscow, Russia, https://orcid.org/0000-0003-3751-2766
Natalia A. Suponeva – Dr. Sci. (Med.), Corresponding member of RAS, Director, Institute of Neurorehabilitation and Recovery Technologies, Russian Center of Neurology and Neuroscience, Moscow, Russia, https://orcid.org/0000-0003-3956-6362
Mikhail A. Piradov – Dr. Sci. (Med.), Professor, Full member of RAS, Director, Russian Center of Neurology and Neuroscience, Moscow, Russia, https://orcid.org/0000-0002-6338-0392

Authors' contribution: *Cherkasova A.N.* – conceptualization, data curation, formal analysis, investigation, methodology, original draft preparation; *Ikonnikova E.S., Kirichenko O.A.* – data curation, investigation; *Lyukmanov R.Kh.* – conceptualization, methodology, project administration; *Mokienko O.A.* – methodology; *Konyshev V.A., Zonov A.A.* – conceptualization, software; *Suponeva N.A.* – conceptualization, project administration; *Piradov M.A.* – project administration.

Информация об авторах

Черкасова Анастасия Николаевна – м. н. с. группы нейроинтерфейсов Института нейрореабилитации и восстановительных технологий Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0000-0002-7831-5833
Иконникова Екатерина Сергеевна – м. н. с. группы нейроинтерфейсов Института нейрореабилитации и восстановительных технологий Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0000-0001-6836-4386
Люкманов Роман Харисович – канд. мед. наук, с. н. с., рук. группы нейроинтерфейсов Института нейрореабилитации и восстановительных технологий Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0000-0002-8671-5861
Кириченко Ольга Андреевна – м. н. с., зав. отделением медицинской реабилитации и физиотерапии Института нейрореабилитации и восстановительных технологий Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0000-0002-7119-9841
Мокиенко Олеся Александровна – канд. мед. наук, н. с. группы нейроинтерфейсов Института нейрореабилитации и восстановительных технологий Российского центра неврологии и нейронаук, Москва, Россия; с. н. с. Института высшей нервной деятельности и нейрофизиологии РАН, Москва, Россия; https://orcid.org/0000-0002-7826-5135
Конышев Владимир Анатольевич – генеральный директор ООО «Нейроботикс», Зеленоград, Москва, Россия, https://orcid.org/0009-0004-0576-2626;
Зонов Александр Александрович – продакт-менеджер, нейрофизиолог ООО «Нейроботикс», Зеленоград, Москва, Россия, https://orcid.org/0000-0003-3751-2766
Супонева Наталья Александровна – д-р мед. наук, член-корреспондент РАН, директор Института нейрореабилитации и восстановительных технологий Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0000-0003-3956-6362
Пирадов Михаил Александрович – д-р мед. наук, профессор, академик РАН, директор Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0000-0002-6338-0392

Вклад авторов: *Черкасова А.Н.* – создание концепции исследования, курирование данных, анализ данных, проведение исследования, разработка методологии, подготовка текста статьи; *Иконникова Е.С.*, *Кириченко О.А.* – курирование данных, проведение исследования; *Люкманов Р.Х.* – создание концепции исследования, разработка методологии, руководство научно-исследовательской работой; *Мокиенко О.А.* – разработка методологии; *Конышев В.А., Зонов А.А.* – создание концепции исследования, программное обеспечение; *Супонева Н.А.* – создание концепции исследования, руководство научно-исследовательской работой; *Пирадов М.А.* – руководство научно-исследовательской работой.

Predicting the Efficacy of Anti-B-Cell Therapy in Patients with Multiple Sclerosis

Yuliana A. Belova, Yulia Yu. Chuksina, Sergey V. Kotov

M.F. Vladimirsky Moscow Regional Research and Clinical Institute, Moscow, Russia

Abstract

Introduction. *Prognostic markers can be used to evaluate a response to anti-B-cell therapy in patients with multiple sclerosis (MS).*

Aim. *The study aimed to evaluate the characteristics of peripheral blood (PB) lymphocytes and monocytes in patients with aggressive MS during the first 6 months of anti-B-cell therapy.*

Materials and methods. *Twenty-nine patients with aggressive MS were treated with a humanized anti-CD20 monoclonal antibody (anti-CD20 mAb). A panel of MAbs to differentiation antigens of PB lymphocytes was used to assess the parameters of cellular immunity using six-color flow cytometry. The reference values were based on the similar parameters of ten apparently healthy volunteers.*

Results. *At month 6, the initial course of anti-CD20 therapy resulted in low recovery of the PB sub-populations of B cells in 85% of patients. Significant decreases were reported in the absolute counts of T cells, T helper cells, Natural Killer (NK) cells, and relative percentage of natural killer T (NKT) cells. The study also showed low levels of activated T cells and significantly decreased percentage of memory B cells ($CD27^+$) and B cells expressing costimulatory and activation molecules ($CD40^+$, $CD38^+$, and $CD25^+$, respectively). A significant decrease in the mean fluorescence intensity of HLA-DR was observed on PB monocytes compared to normal values and those in patients receiving other disease-modifying therapies. Anti-CD20 therapy may indirectly suppress their antigen-presenting ability. Other immunological criteria for prediction of MS progression and magnetic resonance imaging activity during the first year of anti-B-cell therapy may include the following changes from baseline: increased percentages of $CD3^+$, $CD3^+HLA\text{-}DR^+$, $CD25^+CD3^+$, and $CD95^+CD3^+$ cells; significant expression of the CD40 molecule and B-cell activation markers CD38 and CD25, and decreased expression of CD95.*

Conclusion. *Further research on changes in cellular immunity parameters during anti-CD20 therapy could allow for early adjustment of MS treatment to stabilize the patient's condition.*

Keywords: *multiple sclerosis; T lymphocytes; B lymphocytes; biomarkers*

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

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For correspondence: Bld. 10, 61/2, Shchepkina str., Moscow, Russia, 129110. M.F. Vladimirsky Moscow Region Research Clinical Institute. E-mail: juliannabelova@mail.ru. Yuliana A. Belova.

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Прогнозирование эффективности лечения пациентов с рассеянным склерозом, получающих анти-В-клеточную терапию

Ю.А. Белова, Ю.Ю. Чуксина, С.В. Котов

Московский областной научно-исследовательский клинический институт имени М.Ф. Владимирского, Москва, Россия

Аннотация

Введение. *При назначении анти-В-клеточной терапии больным рассеянным склерозом (РС) оценить ответ на терапию можно по уровню прогностических маркеров.*

Цель: *исследование особенностей популяций лимфоцитов и моноцитов периферической крови (ПК) у пациентов с агрессивным РС в первые 6 мес проведения анти-В-клеточной терапии.*

Материалы и методы. *29 пациентам с агрессивным РС было назначено гуманизированное анти-CD20 моноклональное антитело (анти-CD20-МАТ). Параметры клеточного иммунитета оценивали методом 6-цветной проточной цитометрии с использованием панели МАТ к дифференцировочным антигенам лимфоцитов ПК. В качестве референсных значений использованы аналогичные показатели 10 практически здоровых лиц.*

Результаты. *Проведение 1-го курса анти-CD20-МАТ продемонстрировало низкую степень восстановления количественных параметров популяции В-лимфоцитов ПК у 85% пациентов через 6 мес. Было отмечено выраженное снижение абсолютного количества Т-лимфоцитов, Т-хелперной субпопуляции, NK-лимфоцитов, содержания NKT-субпопуляции и низкий уровень активированных Т-лимфоцитов, существенное снижение содержания В-клеток-памяти ($CD27^+$), а также В-клеток, экспрессирующих костимулирующие и активационные молекулы ($CD40^+$, $CD38^+$, $CD25^+$ соответственно). Обнаружено значительное снижение параметра средней интенсивности флюоресценции HLA-DR на моноцитах ПК по сравнению с нормальными значениями и пациентами, получавшими другие препараты, изменяющие течение РС. Возможно, анти-CD20-МАТ опосредованно подавляет их антигенпрезентирующую способность. Иммунологическими дополнительными критериями прогнозирования обострения РС и активности по МРТ в первый год анти-В-клеточной терапии могут служить изменения по сравнению с исходными следующих параметров: повышение содержания $CD3^+$-, $CD3^+HLA\text{-}DR^+$-, $CD25^+CD3^+$-, $CD95^+CD3^+$-лимфоцитов; выраженная экспрессия костимулирующей молекулы CD40 и маркеров активации В-лимфоцитов CD38, CD25 при снижении экспрессии CD95.*

Заключение. *Дальнейшее изучение динамики изменений показателей клеточного иммунитета под действием анти-CD20-МАТ даст возможность ранней коррекции терапии РС, направленной на стабилизацию состояния пациента.*

Ключевые слова: *рассеянный склероз; Т-лимфоциты; В-лимфоциты; биомаркеры*

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Адрес для корреспонденции: 129110, Россия, Москва, ул. Щепкина, д. 61/2, корп. 10. МОНИКИ им. М.Ф. Владимирского. E-mail: juliannabelova@mail.ru. Белова Ю.А.

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Introduction

Multiple sclerosis (MS) is considered a heterogeneous, multifactorial, immune-mediated disease, with T cells and B cells both playing a key role in its pathogenesis. B cells present antigens to T cells and produce cytokines, which act as inflammatory mediators [1, 2]. B cells also produce autoimmune antibodies to myelin components, thereby affecting the processes of demyelination and axonal damage. In other words, B cells are involved in the humoral immune response at every stage of MS [3].

Treatment strategies for MS are based on its pathogenesis and include reducing the activity of Th1/Th17 cells, activating regulatory T cells, inhibiting the migration of lymphocytes into the nervous system, and targeting

B cells. The mechanisms of autoimmune inflammation, including the role of regulatory B cells, are not fully understood [4, 5].

The research focuses on anti-B-cell therapies, particularly the use of anti-CD20 monoclonal antibodies (mAbs). This protein is expressed on pre-B cells, mature B cells, and memory B cells, but not on early B cell progenitors or plasma cells. Anti-CD20 mAbs deplete B cells via antibody-dependent mechanisms such as phagocytosis, cellular cytotoxicity and apoptosis, resulting in reduced immunopathological inflammation in MS. However, humoral and innate immunity, as well as the ability to recover B cells, are still maintained, and the total T cell count remains almost unchanged [6–9].

Experimental and clinical studies focus on mechanisms by which anti-CD20 therapy depletes and recovers B-cell-rich immunological compartments, such as the bone marrow, peripheral blood (PB), spleen, and lymph nodes, as well as to evaluate B cell function after temporary elimination [10, 11]. The most effective B cell depletion was observed in blood, where anti-CD20 therapy resulted in virtually complete absence of B cells. The lowest depletion of $CD19^+$ B cells was reported in the bone marrow. After treatment, $CD20^+$ B cells repopulated the bone marrow and spleen simultaneously, and then reappeared in the blood [10].

One of the key issues related to prescribing anti-B-cell therapy is to establish personalized criteria, such as prognostic markers for optimal treatment response, as well as treatment dosage and frequency. For some patients, frequency of every six months may be excessive due to a significant decrease the $CD19^+$ B cell count. Therefore, the percentage of memory B cells ($CD19^+CD27^+$) was considered such a prognostic marker [12–14].

In real-world practice, it is particularly relevant to evaluate the effects of anti-CD20 therapy on various parameters of innate and adaptive cellular immunity in patients with MS, especially PB parameters, to assess the systemic effects of therapy.

The study **aimed** to evaluate the characteristics of PB lymphocytes and monocytes in patients with aggressive MS during the first 6 months of anti-B-cell therapy.

Materials and methods

Inclusion criteria:
- informed consent signed by a patient;
- aggressive course of MS;
- anti-CD20 therapy for at least 24 months;
- availability of testing for cellular immunity before the start of therapy and 6 months after the first dose.

Exclusion criteria:
- refusal to sign an informed consent;
- contraindications to anti-CD20 therapy;
- inability to attend follow-up visits.

A control group included 10 apparently healthy volunteers who were matched by sex and age.

The study was conducted in accordance with the Helsinki Declaration of the World Medical Association, the International Council for Harmonization, and local laws. All study participants provided informed written consent after a detailed discussion of the protocol. The study was approved by the Local Ethics Committee at M.F. Vladimirsky Moscow Region Research Clinical Institute (Protocol No. 8 dated June 13, 2019).

Patients with MS (n = 29) were examined according to clinical guidelines[1] to identify contraindications to anti-B-cell therapy with a recombinant humanized mAb that selectively targets B cells expressing CD20 (anti-CD20 mAbs). The first dose of anti-CD20 therapy was administered via a specialized system as two intravenous 300-mg infusions, the second of which was given two weeks after the first dose. This was followed by single 600-mg infusions every six months. PB parameters of cellular immunity parameters were evaluated before the initial course of anti-CD20 therapy and during subsequent courses at 6, 12, 18, and 24 months thereafter, with changes in functional state and neuroimaging assessed.

Six-color flow cytometry was performed to evaluate the cellular immune response in patients with MS, using a panel of mAbs (Becton Dickinson) to differentiate antigens on PB lymphocytes and monocytes.

The percentages and counts of the following cell types were assessed: T-cells ($CD3^+$), B-cells ($CD19^+CD20^+$), Natural Killer (NK) cells ($CD3^-CD16^+CD56^+$), T helper cells ($CD3^+CD4^+$), cytotoxic T cells ($CD3^+CD8^+$), and Natural Killer T (NKT) cells ($CD3^+CD16^+CD56^+$), as well as the percentages of activated T-cells ($CD3^+CD25^+$, $CD3^+$HLA-DR^+, $CD3^+CD95^+$) within the $CD45^+$ lymphocyte population. HLA-DR expression on PB monocytes was evaluated based on the $CD14^+$HLA-DR^+ count. HLA-DR expression intensity on PB monocytes was evaluated using mean fluorescence intensity (MFI), which reflects HLA-DR molecule density on the monocyte membrane and indicates their antigen-presenting function.

The study evaluated the immunophenotypic characteristics and timing of B cell recovery in PB after anti-CD20 therapy. Based on cytometry of the entire lymphocyte population using the $CD45^+$/side scatter gating with no more than 50,000 events to be included, it was assumed that not all patients with MS would have detectable B cells after six months of the initial course of anti-CD20 therapy. Indeed, the majority of patients (85%) had no $CD19^+$ cells. The cell elements were concentrated to collect a large number of B cells, forming a complete cluster. The PB samples were preliminarily divided into several portions of 500–1,000 μL each. The erythrocytes were lysed using PharmLyse solution (Becton Dickinson). After rinsing twice with phosphate-buffered saline, the sediment was concentrated in one test tube. The next step was to perform cytometry on the PB samples that had been incubated with mAbs to specific lymphocyte differentiation antigens (CDs), conjugated with fluorescent dyes. B cells were gated based on side scatter (SSC) and $CD19^+$ expression. The analysis included at least 500,000 events.

[1]Multiple sclerosis. Clinical guidelines, 2025. https://cr.minzdrav.gov.ru/clin-rec (accessed on August 1, 2025).

As a result, the composition of the B cell subpopulations was determined within the $CD19^+$ lymphocyte gate: B1 cells ($CD5^+$), memory B cells ($CD27^+$), and expression of activation and costimulatory molecules (CD40, CD25, CD38, and CD95).

Statistical analysis was performed using SPSS Statistics v. 23 (IBM Corp.). The Kolmogorov–Smirnov test was used to evaluate the data normality. The following tests were used to identify differences between groups: the independent t-test, the Mann–Whitney test, the one-sample t-test with one-way analysis of variance (ANOVA), and the paired t-test with the Wilcoxon test (differences were considered significant at $p < 0.05$). A regression analysis was performed that included the Durbin–Watson pretest and partial correlations to evaluate the strength of dependence between the variables (the effects were considered significant at $p < 0.05$). Discriminant analysis was used to identify the most significant difference factor for nominal variables in independent samples. The analysis included Wilks lambda, one-way ANOVA, the F-test for equality of variances, and stepwise regression. The quantitative data on the HLA-DR expression on PB monocytes are presented as the median and quartiles (Me [Q_1; Q_3]). A Kruskal–Wallis test was used for comparison. Differences between samples with a less than 5% probability of a type I error ($p < 0.05$) were considered significant. In cases of multiple pairwise comparisons, the Bonferroni correction was used.

Results

MS therapy was adjusted with anti-CD20 mAbs in 29 patients in the study group, including 22 women (75.9%) and 7 men (24.1%). The mean age was 36.9 ± 7.7 years. The mean duration of MS was 15.7 years (95% confidence interval [CI]: 6.42, 24.91). The mean Expanded Disability Status Scale (EDSS) score was 3.2 ± 1.5. Since their MS diagnosis, patients had received an average of 3.7 disease-modifying therapies (DMTs) (95% CI: 2.83, 4.59).

Of 29 patients with aggressive MS included in the study, six (23.6%) received interferon beta, 19 (65.2%) received natalizumab, one (3.4%) received teriflunomide, one (3.4%) received glatiramer acetate, and two (6.9%) treatment-naïve patients initiated anti-CD20 therapy.

Of 19 patients who received natalizumab as their last treatment option before treatment adjustment, 14 switched due to a high antibody titer to the John Cunningham virus for more than 24 months of treatment, and high risk for progressive multifocal leukoencephalopathy. Four patients reported a worsening of MS symptoms and progressed to secondary progressive MS. A washout period for natalizumab switch to an anti-CD20 mAb was 7.4 months (95% CI: 4.14, 10.71). Twenty (71.3%) patients included in the study group had experienced a MS exacerbation within the previous 12 months, including patients who were in the washout period after natalizumab discontinuation.

The total PB lymphocyte count before anti-CD20 therapy was significantly higher ($p = 0.001$) than that of healthy volunteers (Table 1). This difference may be due to the previous use of natalizumab, which could be associated with increased PB lymphocyte counts [15].

Compared to normal values, the study group showed a significant increase in the percentage of T helper cells, though not in their absolute counts. There was also a decrease in the percentage of cytotoxic T cells and NKT cells, as well as in absolute counts of NK cells. Levels of T cells and B cells, as determined by CD19 and CD20 markers, as well as their antigen-presenting potential ($CD19^+HLA\text{-}DR^+$), were normal. However, patients demonstrated a significant decrease in activated T cells ($CD3^+HLA\text{-}DR^+$) before the adjustment of anti-CD20 therapy.

Six months after the initial course of anti-CD20 therapy, the total count of PB lymphocytes decreased significantly compared with baseline values and those of the control group (Table 1). However, this decrease did not reach the values determined by the Common Toxicity Criteria (CTC) score.[2] As for the relative parameters, patients showed a significant increase in PB levels of T cells and T helper cells. However, this increase was associated with compensatory mechanisms due to the depletion of B cells, which had not normalized by the start of the study. These parameters showed significantly lower absolute values compared to the control group. The level of the cytotoxic T cells did not differ significantly from that of healthy volunteers, in either relative or absolute terms. There was a significant decrease in the absolute count of NK cells and percentage of NKT cells, as well as low levels of activated T cells. NK cells are considered to play a double role in MS. First, they can demonstrate a cytotoxic effect on autoreactive effector cells. Second, they can promote the damage and lysis of astrocytes and oligodendrocytes, as well as influence the level of regulatory T cells in patients with MS [16].

The percentage of B cells in patients ranged from 0% to 7.5%. Only 15% of patients had normal values within the range of 6.0% to 7.5%. Thirty-eight percent of patients had B cell percentages of 2% to 4%. The remaining 47% had a percentage of up to 1%. Therefore, 85% did not normalize their B cell levels. Similarly, the percentage of B cells that could present antigens ($CD19^+HLA\text{-}DR^+$) decreased dramatically.

Before the start of anti-CD20 therapy, patients with MS did not differ significantly from the control group in terms of the percentage of B cells expressing the costimulatory molecule CD40, the CD95 apoptosis marker, or the B1 cell subpopulation ($CD19^+CD5^+$) associated with the production of autoantibodies (Table 2).

Patients with MS showed a significant ($p < 0,05$) increase in the percentage of memory B cells ($CD19^+CD27^+$) and B cells activated by CD38 and CD25 antigens compared to the control group.

At month 6 after the initial course of anti-CD20 therapy, patients with MS showed a significant increase in the percentage of circulating $CD5^+$ B cells ($p < 0.05$) and a significant decrease in the percentage of memory B cells ($CD27^+$), as well as B cells expressing costimulatory and activation molecules (CD40, CD38, and CD25) ($p < 0.05$).

[2]Multiple sclerosis. Clinical guidelines, 2025. URL: https://cr.minzdrav.gov.ru/clin-rec

Table 1. Cellular immunity parameters in patients with MS ($M \pm SD$)

Parameter		Before B-cell therapy (n = 29)	Six months after the first dose of anti-CD20 therapy (n = 29)	Healthy volunteers (n = 10)	p
		1	2	3	
Total lymphocyte count	× 10^9/L	2,145.6 ± 784.3	1,725.4 ± 648.9	2,070.0 ± 101.3	$p_{1-2} < 0.001$* $p_{1-3} = 0.001$* $p_{2-3} = 0.001$*
$CD3^+$ T cells	%	75.67 ± 6.71	85.03 ± 5.63	74.97 ± 1.53	$p_{1-2} = 0.001$* $p_{1-3} = 0.09$ $p_{2-3} = 0.001$*
	abs.	1520.7 ± 118.2	1,352.9 ± 65.9	1,670.7 ± 131.5	$p_{1-2} = 0.107$ $p_{1-3} = 0.1230$ $p_{2-3} = 0.0173$
T helper cells $CD3^+CD4^+$	%	46.84 ± 7.75	51.54 ± 10.64	40.69 ± 2.27	$p_{1-2} = 0.001$* $p_{1-3} < 0.001$* $p_{2-3} = 0.001$*
	abs.	939.2 ± 71.9	795.8 ± 64.4	1,125.5 ± 103.2	$p_{1-2} = 0.0678$ $p_{1-3} = 0.6870$ $p_{2-3} = 0.0044$*
Cytotoxic T cells $CD3^+CD8^+$, % of cells	%	26.89 ± 7.96	31.43 ± 10.51	33.00 ± 3.08	$p_{1-2} = 0.05$ $p_{1-3} < 0.001$* $p_{2-3} = 0.484$
	abs.	565.7 ± 75.6	477.6 ± 49.7	537.9 ± 56.4	$p_{1-2} = 0.1633$ $p_{1-3} = 0.3820$ $p_{2-3} = 0.2076$
NK cells $CD3^-CD16^+$ $CD56^+$	%	11.50 ± 4.46	12.76 ± 6.09	12.47 ± 1.70	$p_{1-2} = 0.001$* $p_{1-3} = 0.281$ $p_{2-3} = 0.821$
	abs.	189.0 ± 25.2	180.3 ± 17.2	328.7 ± 18.4	$p_{1-2} = 0.3857$ $p_{1-3} < 0.0000$* $p_{2-3} < 0.0000$*
NKT cells $CD3^+CD16^+CD56^+$	%	6.01 ± 4.52	5.7 ± 3.68	10.50 ± 1.73	$p_{1-2} = 0.001$* $p_{1-3} = 0.001$* $p_{2-3} = 0.001$*
B cells $CD19^+$	%	12.78 ± 4.8	1.60 ± 2.25	11.79 ± 1.86	$p_{1-2} = 0.001$* $p_{1-3} = 0.290$ $p_{2-3} < 0.001$*
	abs.	284.7 ± 60.3	25.7 ± 10.0	271.6 ± 29.6	$p_{1-2} < 0.001$* $p_{1-3} = 0.4214$ $p_{2-3} < 0.001$*
B cells $CD20^+$	%	12.25 ± 3.44	0.75 ± 1.37	11.19 ± 1.83	$p_{1-2} < 0.001$* $p_{1-3} = 0.723$ $p_{2-3} < 0.001$*
$CD3^+HLA\text{-}DR^+$	%	7.67 ± 3.08	6.11 ± 2.52	13.30 ± 2.60	$p_{1-2} = 0.001$* $p_{1-3} = 0.001$* $p_{2-3} < 0.001$*
$CD19^+HLA\text{-}DR^+$	%	9.86 ± 5.3	1.30 ± 1.94	10.32 ± 3.41	$p_{1-2} = 0.001$* $p_{1-3} = 0.709$ $p_{2-3} < 0.001$*
$CD3^+CD25^+$	%	19.6 ± 6.64	26.81 ± 23.83	11.16 ± 5.22	$p_{1-2} = 0.06$ $p_{1-3} = 0.056$ $p_{2-3} = 0.35$
$CD3^+CD95^+$	%	10.5 ± 6.85	44.42 ± 25.05	42.14 ± 18.99	$p_{1-2} < 0.001$* $p_{1-3} = 0.69$ $p_{2-3} = 0.96$

Note. The results are presented as the relative percentage (%) and absolute (abs.) count of lymphocytes. The relative value is expressed as a percentage of the total count of $CD45^+$ cells, and the absolute value is expressed as the number of cells in 1 μL of PB. *The difference is statistically significant when adjusted by the Bonferroni correction.

Table 2. Parameters of B cell immunity in patients with MS (% of $CD19^+$ gate cells)

Lymphocyte population	Before B-cell therapy (n = 29)	Six months after the first dose of anti-CD20 therapy (n = 29)	Healthy volunteers (n = 10)	p
	1	2	3	
$CD40^+$	48.32 ± 27.49	17.13 ± 23.12	49.20 ± 4.45	p_{1-2} = 0.001* p_{1-3} = 0.883 p_{2-3} = 0.001*
$CD95^+$	23.02 ± 17.32	25.85 ± 25.05	19.89 ± 2.30	p_{1-2} = 0.004* p_{1-3} = 0.406 p_{2-3} = 0.427
$CD5^+$	14.35 ± 11.10	21.38 ± 20.21	17.29 ± 3.96	p_{1-2} = 0.004* p_{1-3} = 0.228 p_{2-3} = 0.497
$CD27^+$	37.40 ± 15.32 ↑	25.45 ± 18.15	28.30 ± 2.74	p_{1-2} = 0.001* p_{1-3} = 0.01* p_{2-3} = 0.599
$CD38^+$	34.41 ± 20.8 ↑	29.04 ± 23.24 ↑	16,10 ± 2.63	p_{1-2} = 0.001* p_{1-3} = 0.001* p_{2-3} = 0.08
$CD25^+$	23.16 ± 14.59	13.93 ± 12.83	13.93 ± 12.82	p_{1-2} = 0.003* p_{1-3} = 0.007* p_{2-3} = 0.970

Note. *The difference is statistically significant after the Bonferroni correction.

A significant increase in the expression of CD95 and CD5 antigens on B cells from baseline levels ($p < 0.05$) suggests an inadequate response to a single dose of anti-CD20 therapy and high likelihood of a future MS exacerbation.

The study evaluated how different DMTs affect the expression patterns of a HLA-DR molecule on PB monocytes in patients with MS. No significant differences in the percentages of monocytes expressing HLA-DR were found between treatment-naïve patients with aggressive MS, all DMT groups, and healthy volunteers (Table 3). The MFI HLA-DR index in treatment-naïve patients and patients treated with interferon-beta and natalizumab did not differ from that of healthy volunteers. A significant decrease in MFI HLA-DR was only found in patients who received the initial course of anti-CD20 therapy compared to healthy volunteers. This finding suggests that anti-CD20 therapy may indirectly affect PB monocytes by suppressing their ability to present antigens.

The study group (n = 29 patients) continued to be followed up for 24 months, receiving subsequent courses of anti-CD20 therapy at the dose of 600 mg at 6, 12, 18, and 24 months after the initial course.

MRI activity was recorded in 7 patients (24.13%). In 1 patient, gadolinium-enhancing (Gd^+) lesions were detected after 6 and 12 months of therapy. Changes in MRI scans revealed Gd^+ lesions in 2 patients after 6 months, 3 patients after 12 months, and 1 patient after 24 months of therapy. New non-contrast-enhancing lesions were detected in two patients: one after 12 months and the other after 24 months.

Clinical data, disease progression, and cellular immunity parameters in patients before and six months after the start of anti-CD20 therapy revealed changes in PB lymphocyte subpopulations, which can be interpreted as risk factors for MS activity within two years. An increase in the relative percentage of $CD3^+$ T cells in a follow-up test is a significant factor for MRI activity during the first six months of therapy (p = 0.014, predictive accuracy of 68.2%). A decrease in $CD19^+$ and $CD20^+$ counts was not identified as significant factors (p = 0.09).

At month 12, MRI activity with prognostic accuracy of greater than 90% was detected in patients who showed increased levels of $CD25^+CD3^+$ (p = 0.007), $CD95^+CD3^+$ (p = 0.046), $CD40^+CD19^+$ (p = 0.000), $CD5^+CD19^+$ (p = 0.003), and $CD38^+CD19^+$ (p = 0.001) cells, as well as decreased levels of $CD95^+CD19^+$ cells (p = 0.001) after the first course of anti-CD20 therapy. This study revealed no significant biomarkers for MRI activity at month 24, which may be due to PB changes resulting from subsequent courses of anti-B-cell therapy.

An exacerbation was diagnosed in five (17.24%) patients and in one (3.44%) patient after 6 and 12 months of therapy. Increased levels of activated $CD3^+HLA\text{-}DR^+$ cells was a significant risk factor for exacerbations after 6 months of therapy, with a 90.9% probability (p = 0.02).

During 12 months after the start of therapy, the risk of exacerbations increased by more than 90% with increased levels of $CD25^+CD3^+$ (p = 0.01), $CD95^+CD3^+$ (p = 0.05), $CD40^+CD19^+$ (p = 0.000), $CD5^+CD19^+$ (p = 0.003), and

Table 3. HLA-DR expression on PB monocytes, Me [Q_1; Q_3]

Parameter	Healthy volunteers (*n* = 10)	Treatment-naïve patients with aggressive MS (*n* = 2)	Patients receiving interferon beta (*n* = 6)	Patients receiving natalizumab (*n* = 19)	Patients receiving the initial course of anti-CD20 therapy (*n* = 29)	*p*
	1	2	3	4	5	
Monocytes CD14⁺ HLA-DR⁺, % of cells	95.4 [93.1; 100.0]	96.1 [89.7; 97.1]	94.8 [90.4; 96.7]	92.4 [86.9; 96.0]	91.0 [81.4; 94.6]	$p_{1–2}$ = 0.152 $p_{1–3}$ = 0.101 $p_{1–4}$ = 0.123 $p_{1–5}$ = 0.082
MFI HLA-DR	230.4 [198.0; 261.7]	186.1 [115.0; 256.3]	207.3 [83.8; 263.3]	160.2 [126.1; 227.6]	111.6 [100.4; 139.5]	$p_{1–2}$ = 0.148 $p_{1–3}$ = 0.179 $p_{1–4}$ = 0.137 $p_{1–5}$ = 0.008*

Note. *The difference is statistically significant after the Bonferroni correction.

CD38⁺CD19⁺ (p = 0.001) cells. In addition, decreased levels of CD95⁺CD19⁺ cells (p = 0.001) were reported (see Figure). This study did not identify any significant biomarkers of potential exacerbation after 24 months.

Four patients (13.7%) demonstrated MS progression: three (10.3%) during the first year of therapy and one (3.4%) during the second year. No significant changes in immune status parameters were identified as factors for MS progression after the first course of anti-CD20 therapy.

Discussion

Numerous experimental and clinical studies of cellular immunity in patients with MS have shown high variability in all study lymphocyte subpopulations, particularly during DMT compared to untreated patients [14, 15, 18]. The proinflammatory and encephalitogenic effects of CD8⁺ T cells increased upon contact with myelin basic protein molecules [16]. In addition, the percentages of T cells (CD3⁺) and T helper cells (CD4⁺), including activated ones (CD4⁺HLA-DR⁺), decreased, while the percentage of NKT cells (CD3⁺CD16⁺CD56⁺) increased. The increased count of activated CD8⁺ cytotoxic T cells suggests their crucial role in MS progression.

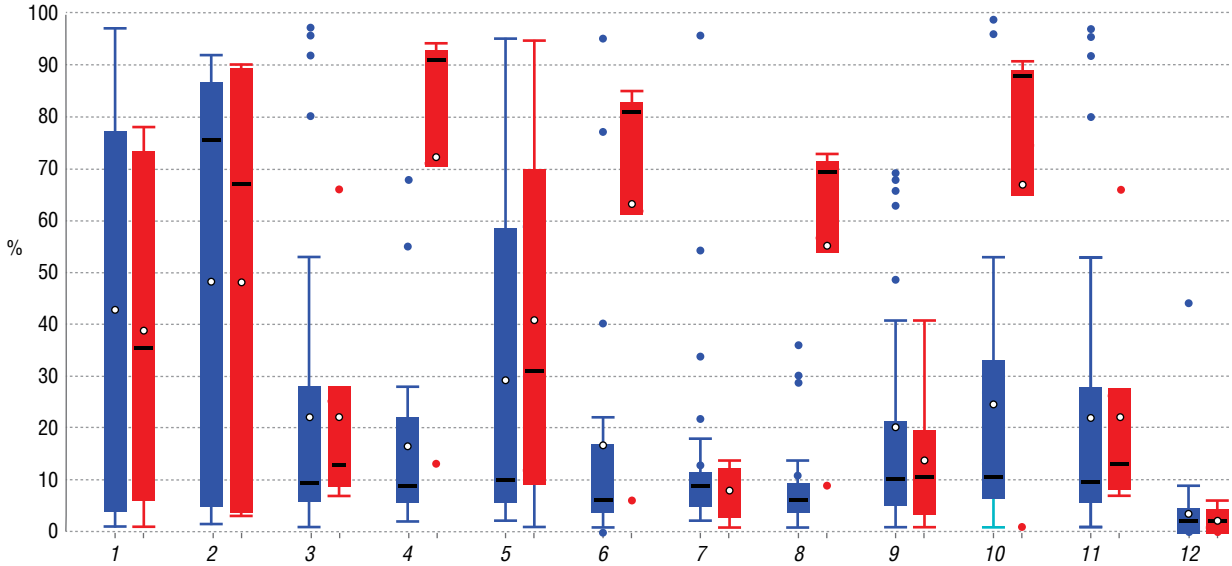
Our study revealed significant changes in baseline cellular immunity parameters in patients with MS compared to healthy volunteers. These changes included the increased percentage of T helper cells (with no change in the absolute count), decreased percentage of cytotoxic T cells and NKT cells, and decreased count of NK cells and activated (CD3⁺HLA-DR⁺) T cells. These patients showed a significant increase in the percentage of memory B cells (CD19⁺CD27⁺), as well as B cells activated by CD38 and CD25 antigens. These changes were correlated with the clinical presentation: at the time of inclusion, 20 (71.3%) patients had experienced an MS exacerbation within the previous 12 months. All examined patients with MS required therapy adjustment.

Patients who received the first course of anti-CD20 therapy showed extremely heterogeneous levels of recovery of quantitative B-cell parameters. By the time of the second dose of anti-CD20 therapy at month 6, 85% of patients had not normalized their B cell counts.

Six months after the first course of anti-B-cell therapy, patients showed a more than tenfold decrease in absolute and relative B-cell parameters, as well as a decrease in total PB lymphocyte counts due to a decrease in the absolute T-cell and T-helper counts, although their percentages increased. In addition, the study reported a significant decrease in the absolute count of NK cells and the percentage of NKT cells, an even lower level of activated T cells (CD3⁺HLA-DR⁺), and a significant decrease in memory B cells (CD27⁺), including the main pool of B cells expressing costimulatory and activation molecules (CD40, CD38, CD25). Therefore, patients with MS demonstrated a significant decrease in the absolute PB counts of key immunocompetent cells, including T cells and NK cells, even after the first course of anti-CD20 therapy. There was also inhibition of the activation potential of T and B cells, including their ability to present antigens.

The interaction between the costimulatory molecule CD40 on B cells and its ligand, CD40L (CD154), on T cells stimulates an immune response and activates B cells to produce antibodies [18]. The presence of CD40 on B cells within inflammatory lesions of the central nervous system in deceased patients with MS suggests that antibody production through interactions between T cells and B cells via CD40 may contribute to the development of the condition [19]. A decrease in CD40⁺ B cells during anti-CD20 therapy may indicate the reduced ability of these cells to trigger an immune response. Therefore, it can be concluded that the anti-CD20 therapy affects mature CD20⁺ B cells directly and indirectly by affecting the costimulatory molecule on these cells and the T-cell component.

In addition, in this group of patients, the expression patterns of HLA-DR on PB monocytes suggest a significant decrease in the density of this molecule, as determined by MFI. This may indicate suppression of the antigen-presenting ability of the monocyte/macrophage component of the immune system. In neuroinflammation and central nervous system lesions in MS,



Parameters of immune status in patients with MS.
1: $CD25^+CD3^+$ at baseline; *2*: $CD25^+CD3^+$ at month 6; *3*: $CD95^+CD3$ baseline; *4*: $CD95^+CD3$ at month 6; *5*: $CD40^+CD19$ at baseline; *6*: $CD40^+CD19$ at month 6; *7*: $CD5^+CD19^+$ at baseline; *8*: $CD5^+CD19^+$ at month 6; *9*: $CD38^+CD19$ at baseline; *10*: $CD38^+CD19$ at month 6; *11*: $CD95^+CD19^+$ at baseline; *12*: $CD95^+CD19^+$ at 6 months. Blue bars: patients with no exacerbation. Red bars: patients who experienced an exacerbation after the first dose of therapy.

macrophages and microglia can act as antigen-presenting cells, promoting the activation of effector lymphocytes and stimulating a specific immune response [20]. Macrophage involvement in the pathogenesis of MS may also influence disease progression. PB monocytes are innate immune cells that differentiate into tissue macrophages when they migrate into tissues and act as specialized antigen-presenting cells because they express class II major histocompatibility complex antigens, which increases when the cells are activated. Antigen presentation is a critical component of the immune response, that links the innate and adaptive immune systems [21]. Therefore, research on the antigen-presenting ability of monocytes can significantly improve our understanding of the MS immunopathogenesis.

Clinical and experimental data suggest that monocytes with low or absent HLA-DR expression cannot properly present antigens and produce inflammatory mediators in response to appropriate stimuli [23].

Some publications report that a decrease in HLA-DR expression on monocytes is associated with a high risk of infectious complications in patients with trauma, burns, pancreatitis, or sepsis, as well as in patients undergoing organ transplantation or heart and vascular surgery [24–28].

Statistical methods were established to determine the association between changes in quantitative parameters of T and B cell subpopulations and significant risk factors for an unfavorable long-term MS prognosis. These parameters included the increased percentage of $CD3^+$ cells, subpopulations of $CD3^+HLA\text{-}DR^+$, $CD25^+CD3^+$, $CD95^+CD3^+$, $CD40^+CD19^+$, $CD5^+CD19^+$, and $CD38^+CD19^+$ cells, as well decreased levels of $CD95^+CD19^+$ cells. Therefore, increased activation of T cells and B cells, as well as decreased B cell apoptosis, are significant risk factors for MS exacerbation and MRI activity in the future.

Conclusion

At month 6, the initial course of anti-CD20 therapy resulted in low recovery of the B cell sub-populations in 85% of patients. A relative increase in the percentage of total T cells was revealed as a result of B cell depletion. In addition, significant decreases were observed in the absolute values of primary parameters of T cells and NK cells, as well as counts of activated T cells and B cells. These results may indicate an insufficient ability of recovering B cells to present antigens and provide the complete immune response.

The ability of monocytes and macrophages to present antigens was suppressed after the first dose of anti-CD20 therapy, but in our study, this effect was not observed in treatment-naïve patients with aggressive MS or during other types of DMTs. These facts may indicate the high efficacy of the first course of anti-CD20 therapy. Further analysis is required to correlate these facts with the clinical characteristics of patients in this group.

Additional immunological criteria for predicting MS exacerbation and MRI activity in the first year of therapy may include changes from baseline in the following immunological parameters: increased percentages of $CD3^+$ cells and subpopulations of $CD3^+HLA\text{-}DR^+$, $CD25^+CD3^+$, $CD95^+CD3^+$, $CD40^+CD19^+$, $CD5^+CD19^+$, and $CD38^+CD19^+$ cells; decreased levels of $CD95^+CD19^+$ cells.

Further research on biomarkers allows for the early adjustment of MS therapy, thereby stabilizing the patient's condition.

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Information about the authors

Yuliana A. Belova – Cand. Sci. (Med.), senior researcher, Neurological department, M.F. Vladimirsky Moscow Regional Research and Clinical Institute, Moscow, Russia, https://orcid.org/0000-0003-1509-9608
Yulia Yu. Chuksina – Cand. Sci. (Med.), senior researcher, Laboratory of biomedical research methods, M.F. Vladimirsky Moscow Regional Research and Clinical Institute, Moscow, Russia, https://orcid.org/0000-0002-4393-1759
Sergey V. Kotov – D. Sci. (Med.), Professor, Head, Department of neurology, Faculty of advanced training for doctors; Head, Neurological department, M.F. Vladimirsky Moscow Regional Research and Clinical Institute, Moscow, Russia, https://orcid.org/0000-0002-8706-7317

Author contribution: *Belova Yu.A.* – collection of material and conducting research, examination and dynamic observation of patients, writing the article; *Chuksina Yu.Yu.* – performing laboratory tests, processing and statistical analysis of data, writing the article; *Kotov S.V.* – research management, data processing, writing and editing of the article.

Информация об авторах

Белова Юлиана Алексеевна – канд. мед. наук, с. н. с. неврологического отделения МОНИКИ им. М.Ф. Владимирского, Москва, Россия, https://orcid.org/0000-0003-1509-9608
Чуксина Юлия Юрьевна – канд. мед. наук, с. н. с. лаб. биомедицинских методов исследования отдела экспериментальных и клинических исследований МОНИКИ им. М.Ф. Владимирского, Москва, Россия, https://orcid.org/0000-0002-4393-1759
Котов Сергей Викторович – д-р мед. наук, профессор, зав. каф. неврологии факультета усовершенствования врачей, руководитель неврологического отделения МОНИКИ им. М.Ф. Владимирского, Москва, Россия, https://orcid.org/0000-0002-8706-7317

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Early Markers of Thrombotic Hazard in Cerebrovascular Diseases

Marine M. Tanashyan[1], Eugene V. Roitman[1,2], Anton A. Raskurazhev[1], Maksim A. Domashenko[3], Alla A. Shabalina[1], Andrey S. Mazur[1]

[1]Russian Center of Neurology and Neurosciences, Moscow, Russia;

[2]Pirogov Russian National Research Medical University, Moscow, Russia;

[3]Lomonosov Moscow State University, Moscow, Russia

Abstract

Introduction. *Cerebrovascular disease (CVD) is a heterogeneous group of difficult-to-diagnose conditions in which hemorheological and hemostatic disorders significantly impact the risk of ischemic stroke (IS), as well as the prognosis and response to reperfusion therapy and preventive treatment. Laboratory thrombotic hazard markers, such as the thrombin-antithrombin III (TAT) complex, the plasmin-α2-antiplasmin (PAP) complex, thrombomodulin (TM), and the tissue plasminogen activator (tPA)/plasminogen activator inhibitor-1 (PAI-1) activity ratio, have not been adequately evaluated as predictors of different IS subtypes. Their potential role in acute IS has also not been determined.*

Aim. *The study aimed to evaluate the diagnostic and predictive value of primary thrombotic hazard markers in patients with CVD.*

Materials and methods. *The retrospective study included 91 patients with acute IS (45% of men; median age: 62 years). At admission, primary clinical parameters were assessed, including a National Institutes of Health Stroke Scale (NIHSS) score. Laboratory parameters and thrombotic hazard markers were also measured using an enzyme-linked immunosorbent assay. Three IS subtypes included large artery atherosclerosis (LAA) related IS (n = 32), lacunar IS (n = 27), and hemorheological (small artery occlusion-related) IS (n = 32). The clinical outcomes were evaluated at day 10 using the NIHSS scale. A comparison group included patients with chronic CVD (n = 29; 34% men; median age: 55 years).*

Results. *The plasma levels of almost all study biomarkers differed significantly between patients with IS and chronic CVD, as well as between patients with different IS subtypes. Four of six markers (PAI-1, PAP, TAT, t-PA/PAI-1) were significantly associated with IS development, with TAT showing the strongest association (odds ratio: 4.78; 95% confidence interval: 2.70, 9.68). Linear regression models were used to evaluate the predictive value of thrombotic hazard biomarkers for IS outcomes, and TAT showed the most significant association in this case ($p < 0.001$). An analysis of the differential value of study biomarkers for different IS subtypes showed that PAI-1 was the most sensitive (0.969) marker for LAA related IS, while t-PA/PAI-1 (0.99) and TAT (0.889) demonstrated high predictive value for lacunar IS.*

Conclusion. *Thrombotic hazard markers are a promising laboratory tool for evaluating IS risk and predicting functional outcomes and response to reperfusion therapy in patients with IS.*

Keywords: *thrombin–antithrombin III complex; plasmin–α2-antiplasmin complex; thrombomodulin; tissue plasminogen activator; plasminogen activator inhibitor-1; cerebrovascular*

Ethics approval. The research protocol was approved by the Ethics Committee of the Russian Center of Neurology and Neurosciences (protocol No. 6-5/17, May 24, 2017). The study was conducted with the informed consent of the patients.

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For correspondence: 80 Volokolamskoye shosse, Moscow, Russia, 125367. Russian Center of Neurology and Neurosciences. E-mail: mazur@neurology.ru. Andrey S. Mazur.

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Ранние маркеры «тромботической опасности» при цереброваскулярной патологии

М.М. Танашян[1], Е.В. Ройтман[1,2], А.А. Раскуражев[1], М.А. Домашенко[3], А.А. Шабалина[1], А.С. Мазур[1]

[1]Российский центр неврологии и нейронаук, Москва, Россия;

[2]Российский национальный исследовательский медицинский университет имени Н.И. Пирогова, Москва, Россия;

[3]Московский государственный университет имени М.В. Ломоносова, Москва, Россия

Аннотация

Введение. *Цереброваскулярные заболевания (ЦВЗ) – патогенетически гетерогенная и сложная для диагностики группа состояний, при которых нарушения в системах гемореологии и гемостаза играют значимую роль, определяя риск ишемического инсульта (ИИ), его прогноз и ответ на реперфузионную и превентивную терапию. Недостаточно изучены лабораторные маркеры «тромботической опасности»: комплекс тромбин–антитромбин III (TAT), комплекс плазмин–α2-антиплазмин (PAP), тромбомодулин (TM) и соотношение активности тканевого активатора плазминогена (tPA) и его антагониста – ингибитора активатора плазминогена 1-го типа (PAI-1) в качестве предикторов различных патогенетических подтипов ИИ. Не уточнён потенциал их значимости у пациентов в остром периоде ИИ.*

Цель *исследования – определение диагностической и прогностической роли основных маркеров «тромботической опасности» у пациентов с ЦВЗ.*

Материалы и методы. *В ретроспективное исследование был включен 91 пациент с ИИ в острейшей стадии (45% – мужчины, медиана возраста – 62 года). В день поступления в стационар были определены базовые клинические (в том числе оценка выраженности неврологических нарушений по шкале NIHSS) и лабораторные показатели, а также вышеперечисленные маркеры «тромботической опасности» с помощью иммуноферментного анализа. ИИ был представлен тремя патогенетическими подтипами: атеротромботическим (n = 32), лакунарным (n = 27) и гемореологическим (n = 32), клинический исход которых оценивали через 10 сут по шкале NIHSS. В качестве группы сравнения были выбраны пациенты с хроническим течением ЦВЗ (n = 29; 34% – мужчины, медиана возраста – 55 лет).*

Результаты. *Плазменная концентрация практически всех исследованных биомаркеров значимо отличалась как при сравнении групп пациентов с ИИ и хроническими ЦВЗ, так и у пациентов с разными патогенетическими подтипами ИИ. С развитием ИИ оказались значимо ассоциированными 4 из 6 маркеров (PAI-1, PAP, TAT и отношение активности t-PA/PAI-1), причём по магнитуде связи наибольший вес имел комплекс TAT – отношение шансов 4,78 (95% ДИ 2,70–9,68). Потенциальную предикторную роль биомаркеров «тромботической опасности» в отношении исхода ИИ оценивали с помощью моделей линейной регрессии: наиболее значимым оказался также уровень комплекса TAT ($p < 0,001$). Уровень PAI-1 является наиболее чувствительным (0,969) в отношении атеротромботического ИИ, в то время как соотношение активности t-PA/PAI-1 (0,99) и уровень TAT (0,889) обладают хорошей предсказательной способностью для лакунарного ИИ.*

Заключение. *Расширение лабораторного арсенала маркерами «тромботической опасности» и использование их в качестве панели у пациентов с ИИ – потенциально перспективный инструмент определения риска ИИ, прогнозирования его функционального исхода и, возможно, ответа на реперфузионную терапию.*

Ключевые слова: *комплекс тромбин–антитромбин III; комплекс плазмин–α2-антиплазмин; тромбомодулин; тканевой активатор плазминогена; ингибитор активатора плазминогена 1-го типа; цереброваскулярные заболевания*

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Адрес для корреспонденции: 125367, Россия, Москва, Волоколамское шоссе, д. 80. Российский центр неврологии и нейронаук. E-mail: mazur@neurology.ru. Мазур А.С.

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Introduction

Cerebrovascular disease (CVD) is a major medical and socioeconomic challenge Epidemiological data indicate rising rates of morbidity, mortality, and disability resulting from acute and chronic cerebrovascular accidents, which also significantly contribute to the increasing prevalence of cognitive dysfunction [1].

After many years of research at the Russian Center of Neurology and Neurosciences (formerly the Research Center of Neurology), the concept of dysregulated hemorheology and hemostasis emerged. This phenomenon has been thoroughly investigated, clinically tested, and proven as one of the primary drivers of cerebrovascular disease (CVD), regardless of its subtype [2]. In addition, laboratory, neuroimaging, and neurological features have been identified for a specific type of ischemic stroke (IS) which is associated with hemorheological occlusion of small arteries. In this subtype, dysregulated hemorheology and hemostasis play a crucial role. The clinical presentation of ischemic cerebrovascular accidents often fails to distinguish between different CVD subtypes (for example, in cases of differential diagnosis of extracranial and intracranial atherosclerotic lesions [3, 4], a combination of brachiocephalic artery atherosclerosis and cardiac disorders with a high risk of cardio-cerebral embolism). This differentiation is crucial for the adequate secondary pathogenetic prevention of IS. This fact highlights the importance of a broader range of neuroimaging, ultrasound, and laboratory parameters for selecting management strategies. However, despite advancements in neurovascular care, including reperfusion techniques such as thrombolytic therapy and mechanical thrombectomy, treatment options for patients with acute IS are often limited and ineffective. One potential reason is the tendency to underestimate and inadequately treat thrombotic hazard factors. These factors include the following potential biomarkers that can be used to better assess the risk of IS and improve the response to antithrombotic and/or reperfusion therapies, as well as provide differential diagnoses of CVD [5]:

- thrombin–antithrombin III complex (TAT), responsible for clotting processes;
- plasmin-α_2-antiplasmin complex (PAP), which is used to evaluate fibrinolysis;
- thrombomodulin (TM), which is used to assess the severity of endothelial dysfunction;
- an activity ratio of tissue plasminogen activator (tPA) and its antagonist, plasminogen activator inhibitor type 1 (PAI-1), which regulates and controls the level of fibrinolytic activation depending on the state of the endothelium.

TAT has been investigated since the 1980s and has been validated as a marker of thrombin generation [6]. A systematic review and meta-analysis have confirmed its role in diagnosing IS [7]. PAP was first described in 1960 [8] as a marker of fibrinolytic activation [9]. Although the primary evidence of its predictive value was obtained for venous thromboembolic conditions [10], higher α_2-antiplasmin levels have been reported as a risk factor for IS [11] and unsuccessful reperfusion (in patients receiving thrombolytic therapy) [12].

TM and soluble TM (sTM) are transmembrane glycoproteins that bind to thrombin and play a dual role in IS: they serve as sensitive markers of acute endothelial injury and modulate restorative and anti-inflammatory processes. For example, an increase in TM levels within the first 24 to 48 hours after IS correlates with IS severity and mortality rates and is associated with risk factors for cardiovascular diseases, such as male sex and dyslipidemia [13]. This highlights the importance of monitoring thrombomodulin levels early after IS to predict clinical outcomes.

PAI-1 is a primary endogenous inhibitor of t-PA. By binding t-PA in a 1 : 1 ratio and forming an inactive t-PA/PAI-1 complex, it significantly reduces plasmin formation and thrombus dissolution [14]. Proinflammatory cytokines, such as interleukin-1 and tumor necrosis factor-alpha, as well as stress factors, such as hypoxia and oxidative stress, increase the expression of PAI-1, leading to endothelial dysfunction and the maintenance of thrombogenesis. High PAI-1 levels prior to thrombolytic therapy is associated with a lower rate of successful recanalization and a higher risk of adverse outcomes within three months [15].

Note that these parameters demonstrate abnormal values long before fibrin formation and, in some cases, thrombosis occur. Therefore, they can potentially serve as early IS biomarkers.

Despite the large number of studies on the diagnostic and predictive value of these markers in various thrombotic conditions (e.g., thromboembolic events and myocardial infarction), the results are not reproducible. This may be due to the fact that changes in the entire pool of biomarkers should be evaluated simultaneously. It should also be noted that studies on ischemic CVD are currently extremely limited.

The study **aimed** to evaluate the diagnostic and predictive value of primary thrombotic hazard markers in patients with CVD.

Materials and methods

The retrospective study included patients who had received inpatient treatment at the Russian Center of Neurology and Neurosciences. A total of 342 patients with acute IS were enrolled based on medical records. Of these patients, 91 had hyperacute IS with available marker testing results (TM, t-PA, PAI-1, TAT, and PAP) on the day of admission, as well as data on changes in these markers to assess severity of neurological deficit using NIHSS[1] at baseline and on day 10 of hospitalization. The control group included 29 patients with chronic CVD (34% of men, median age: 55 years).

Blood samples were obtained via cubital venipuncture in fasting state in the morning using vacuum systems and tubes containing either 3.2% sodium citrate (for citrate plasma) or a coagulation activator and gel (for serum). Blood samples were obtained, transported, stored, and handled during the pre-analytical stage in accordance with the Russian Federation's national standard. Serum/plasma testing for

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t-PA, PAI-1, TAT, and PAP was performed in duplicate using a sandwich enzyme-linked immunosorbent assay (ELISA) with Technoclone and Cloud Clone Corporation reagent kits on a Victor 2 (PerkinElmer) and/or a Real-Best plate readers.

A statistical analysis was performed using the R programming language (v. 4.4.1) in RStudio (v. 2025.05.1) with the following plug-ins: tidyverse, gtsummary, corrplot, pheatmap, ggplot2, and RcppCNPy. In addition, GraphPad Prism 10 (v. 10.4.0) was used. Descriptive statistics were represented by medians, as well as upper and lower quartiles for continuous variables and frequencies for discrete variables. Two unpaired groups were compared using Wilcoxon–Mann–Whitney test for continuous variables or the Pearson χ^2 test for discrete variables. Three or more unpaired groups were compared using the analysis of variance (ANOVA) (Kruskal–Wallis test) with subsequent pairwise comparisons and the *p*-value adjusted using the Dunn multiple comparison test. A heat map showing the relative levels of each variable was created based on preliminary calculations of its percentile in the column. Associations and predictor value were evaluated using regression analysis. In the case of a binomial dependent variable (stroke), univariate and multivariate logistic regression with an odds ratio (OR) and 95% confidence interval (CI) was used. For a continuous variable, linear regression with beta coefficients was used (for a univariate model: changes in the NIHSS score by day 10 according to the formula $\Delta NIHSS = NIHSS_{\text{by day 10}} - NIHSS_{\text{baseline}}$; for a multivariate model: the $NIHSS_{\text{by day 10}}$ score (+ $NIHSS_{\text{baseline}}$ score as a covariate). A correlation analysis was performed using the Spearman's rank correlation coefficient, and the results were visualized using a correlogram. The significance level was set at 0.05, and all tests were two-sided.

Results

Table 1 presents the main clinical data by study subgroups. On average, patients with IS were older than those with chronic CVD. The groups were comparable in terms of sex and anthropometric parameters (weight). As expected, however, the distribution of classical risk factors was shifted toward groups with LAA-related and lacunar IS.

Patients with acute IS were admitted to the Russian Center of Neurology and Neurosciences within 48 hours of a cerebrovascular accident. The clinical presentation included impaired level of consciousness and focal neurological symptoms resulting from injury to one of the cerebral hemispheres. Ischemic injury to the left hemisphere was reported somewhat more frequently (52.7%). A decrease in the level of arousal (obtundation) was recorded in 27 patients (29.7%). Focal symptoms were most often caused by injury to the pyramidal tract fibers on the side of the cerebral hemisphere with the ischemic lesion. In these cases, the most common motor disorders included central hemiparesis (84 patients, 92.3%) and central monoparesis of arm (7 patients, 7.7%). Motor impairment reached the level of hemiplegia in one-third of the patients (29 patients, 31.9%). Central paresis of the facial muscles was observed in 86 patients (94.5%). Speech disorders were also common focal neurological symptoms. For example, aphasia of varying severity occurred in 28 patients (30.8%), and dysarthria occurred in 30 patients (32.9%). Forty-six patients (50.5%) had impaired surface sensation, such as hemihypalgesia and hemianalgesia, and 35 patients (38.5%) had impaired deep sensation and neglect syndrome. Oculomotor disorders such as limited gaze and gaze paresis (either isolated or in combination with forced head turning towards the affected hemisphere) and hemianopsia were reported less frequently, in 12 (13.2%) and 11 (12.1%) patients, respectively.

Reperfusion therapy was not initiated because patients were admitted for more than six hours after the onset of IS.

The group of chronic CVD included patients without a history of acute cerebrovascular accidents. These patients presented with subacute progression of generalized cerebral

Table 1. Main clinical and demographic characteristics of the study groups

Parameter	LAA-related IS (*n* = 32)	Hemorheological IS (*n* = 32)	Lacunar IS (*n* = 27)	Chronic CVD (*n* = 29)	*p* (Kruskal–Wallis test; Pearson χ^2 test)
Age, years, median [Q_1; Q_3]	66 [58; 70]	58 [54; 64]	63 [57; 69]	55 [49; 62]	< 0.001
Male, *n* (%)	16 (50)	11 (34)	14 (52)	10 (34)	0.3
Smokers, *n* (%)	13 (41)	5 (16)	12 (44)	5 (17)	0.019
Weight, kg, median [Q_1; Q_3]	81 [74; 95]	80 [67; 94]	89 [76; 101]	72 [67; 88]	0.081
Type 2 diabetes mellitus, *n* (%)	19 (59)	8 (25)	16 (59)	9 (31)	0.006
The presence and stage of hypertension, *n* (%)					
no	2 (6.3)	0 (0)	0 (0)	2 (6.9)	
stage I	2 (6.3)	14 (44)	2 (7.4)	21 (72)	
stage II	17 (53)	9 (28)	18 (67)	6 (21)	
stage III	11 (34)	9 (28)	7 (26)	0 (0)	

and focal neurological symptoms associated with cerebral atherosclerosis and microangiopathy (as confirmed by neuroimaging results), classified as stage I/II discirculatory encephalopathy. The most common neurological symptoms in this group included cephalgic syndrome (58.6%), vestibulocerebellar symptoms (55.2%), and astheno-neurotic syndrome (55.2%). Patients also had diffuse microsymptoms, including sensation disorders (20.7%), pyramidal symptoms (17.2%), and extrapyramidal symptoms (17.2%).

Levels of study biomarkers differed significantly between the groups (**Fig. 1**), differentially depending on the IS subtype.

Table 2 shows the quantitative values of the markers by study group and changes in neurological deficits by NIHSS scores.

Clinically, patients with lacunar IS initially have less severe neurological deficits. However, by day 10 post-stroke, the median NIHSS score was no lower than 6 (a standard cutoff for a favorable outcome). The further analysis considered these patients based on the progression of their neurological disorders.

A cluster analysis of the relative values was performed to identify a differentiated pattern of changes in thrombogenic markers in patients with various CVD manifestations, and the results were visualized (**Fig. 2**). Almost all patients with lacunar IS demonstrated higher t-PA levels and higher t-PA/PAI-1 ratio, as well as lower TM and TAT levels. Conversely, the reverse pattern was observed in patients with LAA-related IS (to a greater extent) and hemorheological IS (to a lesser extent). Patients with chronic CVD had lower relative TAT and PAI-1 levels and moderate-high t-PA levels.

Regression models were created and characterized in order to further evaluate the potential associations between study

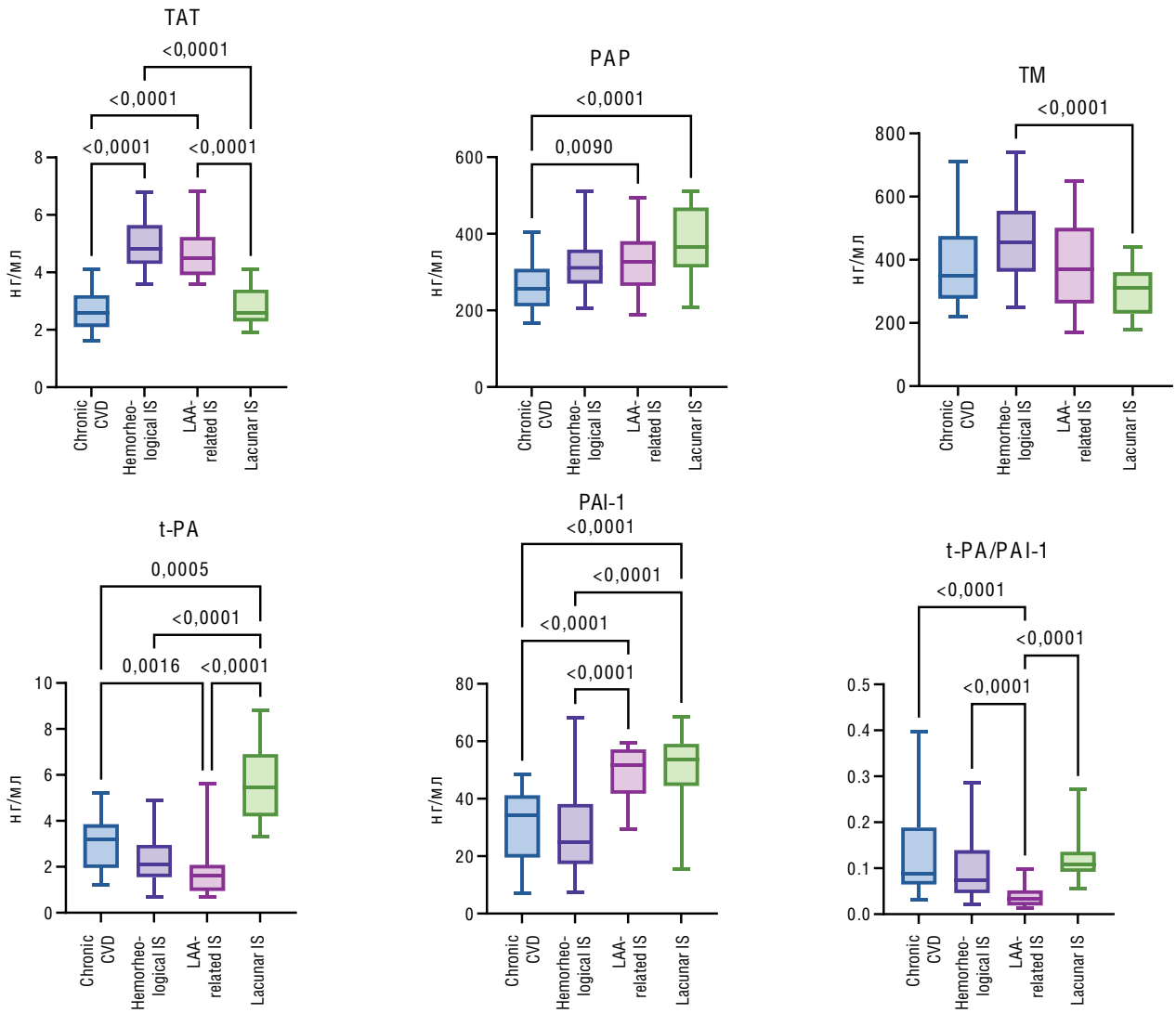

Fig. 1. A box plot of levels of study biomarkers by IS subgroup. Only significant differences in pairwise post hoc comparisons adjusted using the Dunn multiple comparison test are shown. The data are presented as the median, first and third quartiles, and range.
CVD, cerebrovascular disease; IS, ischemic stroke; LAA, large artery atherosclerosis.

Table 2. Thrombotic hazard marker levels and changes in NIHSS scores by IS subtype, median [Q_1; Q_3]

Parameter	LAA-related IS (*n* = 32)	Lacunar IS (*n* = 27)	Hemorheological IS (*n* = 32)	*p* (Kruskal–Wallis test)
NIHSS score				
baseline	13 [11; 16]	10 [9; 12]	14 [9; 16]	0.006
day 10	12 [9; 14]	7 [6; 9]	11 [7; 15]	< 0.001
Thrombomodulin, ng/mL	370 [268; 482]	311 [230; 360]	455 [363; 555]	< 0.001
t-PA, ng/mL	1.60 [0.97; 2.05]	5.45 [4.20; 6.90]	2.10 [1.56; 2.81]	< 0.001
PAI-1, ng/mL	52 [42; 57]	54 [45; 59]	25 [18; 37]	< 0.001
t-PA/PAI-1	0.03 [0.02; 0.05]	0.11 [0.09; 0.14]	0.07 [0.05; 0.14]	< 0.001
TAT, ng/mL	4.51 [3.93; 5.23]	2.60 [2.30; 3.40]	4.82 [4.34; 5.64]	< 0.001
PAP, ng/mL	328 [266; 380]	366 [312; 468]	311 [270; 358]	0.052

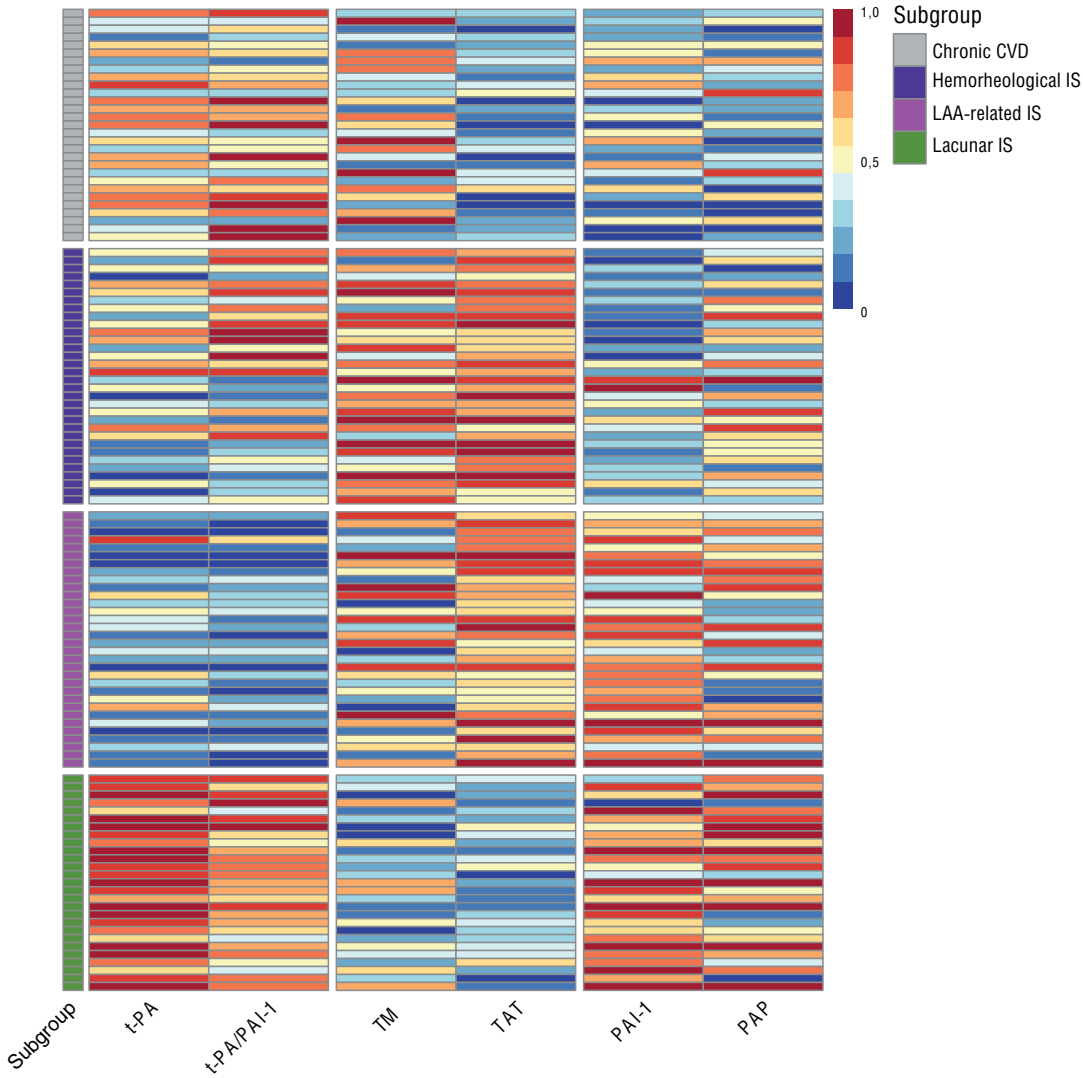

Fig. 2. A heat map of the relative levels of study biomarkers by subgroups.

Table 3. Regression analysis models

Biomarker	Predictors of IS				Adverse outcome predictors			
	univariate model		multivariate model		univariate model		multivariate model	
	OR (95% CI)	*p*	OR (95% CI)	*p*	Beta coefficient (95% CI)	*p*	Beta coefficient (95% CI)	*p*
TM	1.00 (1.00–1.00)	0.8	1.00 (0.99–1.00)	0.2	0.00 (0.00–0.00)	0.009	0.001 (–0.002–0.003)	0.561
t-PA	1.02 (0.83–1.29)	0.8	1.79 (0.80–4.50)	0.2	–0.15 (–0.26–0.03)	0.014	–0.046 (–0.316–0.224)	0.734
PAI-1	1.05 (1.02–1.08)	< 0.001	1.04 (0.96–1.14)	0.4	–0.01 (–0.03–0.01)	0.2	–0.001 (–0.03–0.027)	0.928
PAP	1.01 (1.01–1.02)	< 0.001	1.01 (1.00–1.02)	0.12	00.00 (0.00–0.00)	0.4	0.002 (–0.002–0.005)	0.348
TAT	4.78 (2.70–9.68)	< 0.001	10.9 (4.45–37.4)	< 0.001	0.40 (0.22–0.59)	< 0.001	0.306 (–0.009–0.62)	0.057
tPA/PAI-1	0.00 (0.00–0.10)	0.006	4.11 (0.00–4 × 10^8)	0.9	0.00 (–6.0–2.0)	0.3	1.753 (–6.886–10.393)	0.688

Note. * The baseline NIHSS score was used as a covariate.

Table 4. ROC analysis data for differentiating between IS and chronic CVD

Biomarker	AUC (95% CI)	Cut-off	Sensitivity	Specificity
TM	0.498 (0.376–0.620)	355	0.582	0.517
t-PA	0.56 (0.458–0.663)	1.675	0.319	0.931
PAI-1	0.72 (0.626–0.814)	48.8	0.429	1
t-PA/PAI-1	0.662 (0.555–0.769)	0.061	0.516	0.793
PAP	0.758 (0.66–0.856)	286.95	0.703	0.724
TAT	0.869 (0.806–0.931)	3.55	0.736	0.931

biomarkers and IS development, as well as to determine if the biomarkers could predict short-term IS outcomes (**Table 3**).

Of six markers considered, four (PAI-1, PAP, TAT, and t-PA/PAI-1) were found to be significantly associated with IS development. TAT demonstrated the strongest association (OR = 4.78; 95% CI 2.70–9.68). However, multiple logistic regression analysis revealed that TAT was the only independent significant factor of IS (OR = 10.9; 95% CI 4.45–37.40).

The potential predictive value of thrombotic hazard biomarkers for IS outcomes was evaluated using singleand multivariate linear regression models. TAT was found to be the most significant factor. However, its independent predictive value was not confirmed when considered in combination with other factors.

A ROC analysis was used to assess the sensitivity and specificity of each marker for IS development and determine the cutoff levels of study biomarkers (**Table 4**). TAT showed the strongest association with IS.

A different pattern was observed when the differential value of the study biomarkers was evaluated considering IS subtypes using multinomial logistic regression (**Table 5**). PAI-1 was the most sensitive marker for LAA-related IS, while t-PA/PAI-1 and TAT demonstrated high predictive value for lacunar IS.

A correlation analysis (**Fig. 3**) revealed the multidirectional associations between biomarkers. For example, higher TAT levels were associated with decreased positive changes in NIHSS scores (ΔNIHSS) and decreased tPA levels. At the same time, TAT positively correlated with TM levels.

Discussion

We used a retrospective cohort of patients with CVD of various origins (both acute and chronic) to differentiate patterns of changes in thrombotic hazard markers such as TM, TAT, PAP, and tPA/PAI-1.

The most significant result of the study demonstrated that TAT can serve as an early marker of thrombotic risk in IS. Significant differences in TAT levels were reported across the study groups. The highest levels were found in patients with LAA-related IS (4.51 ng/mL) and hemorheological IS (4.82 ng/mL), while patients with lacunar IS demonstrated significantly lower TAT levels (2.60 ng/mL). These findings were consistent with those of current meta-analyses showing

Table 5. ROC analysis data for differentiating IS subtypes

Biomarker	Subtype	Sensitivity	Specificity	AUC
t-PA	LAA-related IS	0.812	0.729	0.796
	Lacunar IS	1	0.875	0.971
	Hemorheological IS	0.719	0.661	0.710
TM	LAA-related IS	0.375	0.831	0.530
	Lacunar IS	0.704	0.734	0.758
	Hemorheological IS	0.875	0.542	0.755
PAI-1	LAA-related IS	0.969	0.441	0.706
	Lacunar IS	0.815	0.594	0.726
	Hemorheological IS	0.750	0.949	0.893
t-PA/PAI	LAA-related IS	0.969	0.746	0.907
	Lacunar IS	1	0.656	0.821
	Hemorheological IS	0.969	0.237	0.540
PAP	LAA-related IS	0.438	0.593	0.467
	Lacunar IS	0.370	0.938	0.656
	Hemorheological IS	0.719	0.542	0.608
TAT	LAA-related IS	1	0.407	0.721
	Lacunar IS	0.889	1	0.986
	Hemorheological IS	0.781	0.695	0.772

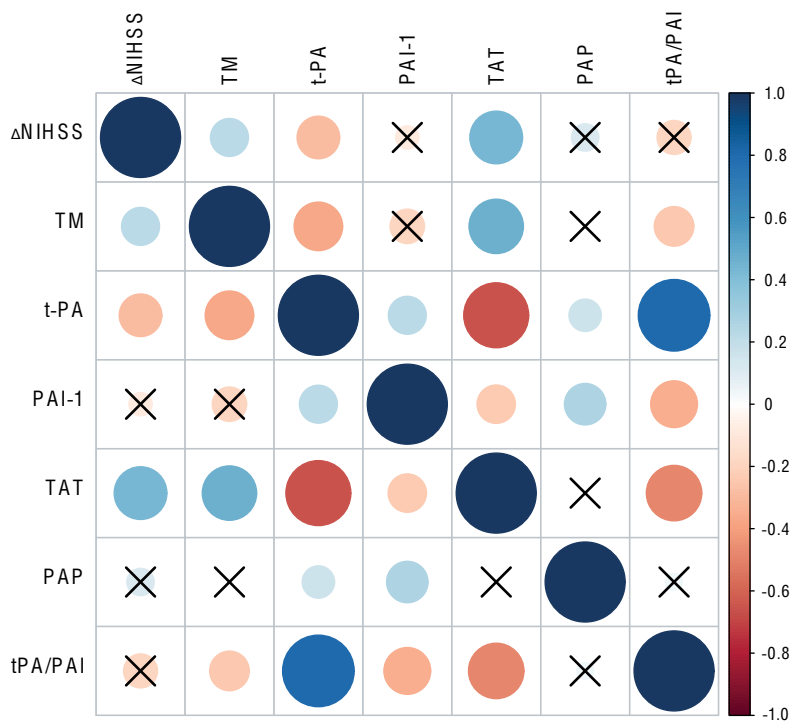

Fig. 3. A correlation analysis of biomarkers and NIHSS changes in a group of patients with IS using Spearman rank-order correlation coefficient. Correlations with $p > 0.05$ were excluded. ΔNIHSS = NIHSS (day 10) – NIHSS (baseline).

that patients with IS had higher TAT levels than controls, with a mean difference of 5.31 (95% CI 4.12–6.51) [7]. Notably, TAT levels were highest during the acute phase of IS and gradually decrease over time. The degree of increase varied depending on IS subtypes.

Importantly, in our analysis, TAT was the only biomarker that maintained predictive value in the multivariate model of association with IS (OR: 10.9; 95% CI 4.45–37.4; $p < 0.001$). Our study found a significant association between TAT and poorer IS outcomes, consistent with other studies. Welsh et al. found higher TAT levels in patients with a modified Rankin score of $\geqslant 3$ in the acute phase of IS [16]. TAT is a sensitive marker of a prothrombotic state. In the context of IS, it may also indicate a systemic inflammatory response [17].

Our study reported significant differences in TM levels between groups. The highest levels were found in patients with hemorheological IS (455 ng/mL), while those with lacunar IS had significantly lower levels (311 ng/mL).

Current publications confirm the important role of TM in the CVD pathogenesis. A large multicenter study in 3,532 patients with IS showed that higher plasma TM levels were associated with a lower risk of adverse clinical outcomes 3 months after IS [18]. This phenomenon can be explained by the dual role of TM in hemostasis. On the one hand, sTM levels indicate endothelial injury, which contributes to thrombogenesis [19]. On the other hand, an increase in TM levels may prevent some patients from developing IS [20]. In our study, TM did not show independent predictive value in the multivariate analysis, which can be explained by the difficulty of interpreting this marker based on vascular history.

Our study revealed significant differences in t-PA and PAI-1 levels between the study groups. Interestingly, patients with lacunar IS had higher tPA levels (5.45 ng/mL) compared to patients with LAA-related IS (1.60 ng/mL) or hemorheological IS (2.10 ng/mL). The latter group showed also lower PAI-1 levels (25 ng/mL) compared to other groups. The tPA/PAI-1 ratio is an important marker of fibrinolytic potential. In our study, patients with lacunar IS had the highest tPA/PAI-1 levels (0.11), which may indicate a compensatory activation of the fibrinolytic system in response to microvascular injury.

Fibrinolytic system disorders are known to play an important role in the pathogenesis of IS. The Northern Sweden MONICA prospective study showed that tPA/PAI-1 is an independent predictor of a new-onset IS (occurring 2.74 times more frequently in patients with upper quartile levels of tPA/PAI-1 compared to lower levels) [21]. PAI-1 may reduce the effectiveness of thrombolytic therapy. The level of active PAI-1 in new thrombi can be thousands of times higher than the normal plasma level, which is sufficient to inhibit the clinical dose of tPA. In addition, PAI-1 produced by astrocytes in the central nervous system can limit excessive tPA activity in the brain parenchyma and prevent injury to the blood-brain barrier, thereby exerting a neuroprotective effect [14].

In recent years, the role of α2-antiplasmin in the pathogenesis of IS has been actively investigated. Epidemiological studies have shown that high levels of α2-antiplasmin are associated with a higher risk of IS [22]. In our study, PAP levels did not show any significant differences between groups ($p = 0.052$), although there was a trend towards higher levels in patients with lacunar IS (366 ng/mL).

Changes in study markers are a topic of active discussion in the literature regarding the effectiveness and safety of reperfusion therapy for patients with IS, particularly intravenous thrombolysis (IVT). The recovery of blood flow during IVT is associated with low levels of sTM [23]. High TAT levels are associated with poorer functional outcomes and higher mortality rates, reflecting a lower percentage of successful revascularization following IVT [7]. Low levels of α2-antiplasmin are associated with poor IVT outcomes and higher rates of intracranial hemorrhagic events [24]. Although higher PAI-1 activity and levels before IVT were associated with adverse progression of cerebral infarction according to neuroimaging 24 hours after IVT, PAI-1 activity was not associated with hemorrhagic events or functional outcomes during IVT. The 5G/5G *PAI-1* polymorphism was shown to be an independent risk factor for intracranial hemorrhage during IVT [25].

Changes in study markers should also be mentioned as important potential predictive markers and predictors of complications during mechanical thrombectomy (MTE), such as hemorrhagic transformation and reocclusion. Even after angiographically successful recanalization, levels of these thrombotic hazard markers may indicate a poorer prognosis for patients. These changes may indicate the patient's initial condition as well as local vascular wall injury during MTE. In addition, current MTE protocols include the systemic administration of thrombolytics prior to endovascular treatment, which can significantly impact the hemostatic response. Xu et al. assessed the levels of sTM, TAT, PAP, and tPA-PAI-1 in arterial blood samples taken from the femoral artery and from an artery located distal to the thrombotic occlusion site [26]. The authors demonstrated that low sTM levels and high TAT, PAP, and tPA-PAI-1 levels were associated with a poor functional outcome following MTE in patients with IS. Moreover, higher TAT and PAP levels in arterial blood samples from the ischemic zone were identified as independent risk factors for symptomatic intracranial hemorrhage after MTE.

Our study also evaluated the predictive value of biomarkers for the short-term outcome of IS. The univariate analysis revealed that t-PA and TAT were the most significantly associated with a poor outcome. However, the multivariate analysis did not confirm the independent predictive value of any biomarkers.

These results are consistent with systematic reviews showing that, despite the associations between many coagulation and inflammatory biomarkers and IS, it is too early to conclude whether these biomarkers can be used therapeutically to predict IS, acute phase severity, or clinical outcome after treatment [27].

The limited predictive value of individual biomarkers can be explained by the complex and multifactorial pathogenesis of IS. Current research shows that combining multiple

biomarkers of different pathophysiological pathways significantly improves risk stratification for poor outcomes [28]. This fully applies to patients who received reperfusion therapy as well as to those who received background and antithrombotic therapy.

In an era when only clinical guidelines should be followed, our study provides unique data on the ability of the study biomarkers to differentiate IS subtypes. Significant differences were particularly evident in t-PA levels between lacunar IS and other subtypes of IS, which may reflect the characteristics of microvascular pathogenesis. These findings are supported by literature indicating that different IS subtypes are characterized by different patterns of hemostatic system activation [7, 29]. All of the above suggest the need for personalized, optimized, and pathogenetically confirmed (for changes in hemorheology and hemostasis) therapy aimed at restoring blood flow properties (hemorheology) and improving vascular wall function. This therapy should be intended to treat existing thrombotic events and prevent new ones.

This study has some important limitations that should be considered when interpreting the results. A relatively small sample size can lead to overfitting of the model and decreased accuracy of parameter estimates in multivariate regression analysis. Therefore, the obtained regression coefficients require careful interpretation. The retrospective design significantly limits the ability to establish causal relationships between the identified factors and disease outcomes because it does not allow for full control of unaccounted confounders. Therefore, our results should be confirmed in larger, prospective studies.

Conclusion

Thrombotic hazard markers (TAT, PAP, TM, and tPA/PAI-1) can potentially be used to determine the risk of IS and predict functional outcomes and response to reperfusion therapy. Our study provided promising data on different expression patterns of hemostatic parameters depending on the IS subtype. This is another step toward personalized treatment strategies for patients with CVD.

The predictive value substantiates the need to investigate and implement this diagnostic approach. It reflects the tendency of the levels of these components of coagulation system to deviate from normal values before fibrin and/or thrombus formation occurs. Early detection of thrombogenic trends could enable personalized prophylaxis with antithrombotic agents for neurological patients. Comprehensive studies of these markers improve our understanding of the mechanisms that determine the effectiveness of pharmacological treatments and endovascular reperfusion for IS, as well as pave the way for personalized antithrombotic therapy for patients undergoing reperfusion interventions.

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Information about the authors

Marine M. Tanashyan – Dr. Sci. (Med.), Professor, Full member of RAS, Deputy Director for Science, Head, 1st Neurological department, Institute of Clinical and Preventive Neurology, Russian Center of Neurology and Neurosciences, Moscow, Russia, https://orcid.org/0000-0002-5883-8119
Eugene V. Roitman – Dr. Sci. (Biol.), leading researcher, Russian Center of Neurology and Neurosciences, Moscow, Russia; Professor, Department of oncology, hematology and radiation therapy, Pirogov Russian National Research Medical University, Moscow, Russia, https://orcid.org/0000-0002-3015-9317
Anton A. Raskurazhev – Cand. Sci. (Med.), senior researcher, 1st Neurological department, Institute of Clinical and Preventive Neurology, Russian Center of Neurology and Neurosciences, Moscow, Russia, https://orcid.org/0000-0003-0522-767X
Maksim A. Domashenko – Cand. Sci. (Med.), Head, Neurology and neurosurgery department, Faculty of fundamental medicine, Lomonosov Moscow State University, Moscow, Russia, https://orcid.org/0009-0000-3630-6130
Alla A. Shabalina – Dr. Sci. (Med.), leading researcher, Head, Laboratory diagnostics department, Russian Center of Neurology and Neurosciences, Moscow, Russia, https://orcid.org/0000-0001-7393-0979
Andrey S. Mazur – postgraduate student, 1st Neurological department, Institute of Clinical and Preventive Neurology, Russian Center of Neurology and Neurosciences, Moscow, Russia, https://orcid.org/0000-0001-8960-721X

Authors' contribution: *Tanashyan M.M., Roitman E.V.* – conceptualization and verification of the research; *Raskurazhev A.A., Domashenko M.A.* – conducting research, collection of clinical, data describing and recording results; *Shabalina A.A.* – verification and actualization of the research; *Mazur A.S.*– conducting research, describing and recording results.

Информация об авторах

Танашян Маринэ Мовсесовна – д-р мед. наук, профессор, академик РАН, зам. директора по научной работе, руководитель 1-го неврологического отделения Института клинической и профилактической неврологии РЦНН, Москва, Россия, https://orcid.org/0000-0002-5883-8119
Ройтман Евгений Витальевич – д-р биол. наук, в. н. с. РЦНН, Москва, Россия; профессор каф. онкологии, гематологии и лучевой терапии РНИМУ им. Н.И. Пирогова, Москва, Россия, https://orcid.org/0000-0002-3015-9317
Раскуражев Антон Алексеевич – канд. мед. наук, с. н. с. 1-го неврологического отделения Института клинической и профилактической неврологии РЦНН, Москва, Россия, https://orcid.org/0000-0003-0522-767X
Домашенко Максим Алексеевич – канд. мед. наук, зав. каф. неврологии и нейрохирургии факультета фундаментальной медицины медицинского научно-образовательного института МГУ им. М.В. Ломоносова, Москва, Россия, https://orcid.org/0009-0000-3630-6130
Шабалина Алла Анатольевна – д-р мед. наук, в. н. с., рук. отд. лабораторной диагностики РЦНН, Москва, Россия, https://orcid.org/0000-0001-7393-0979
Мазур Андрей Сергеевич – аспирант 1-го неврологического отделения Института клинической и профилактической неврологии РЦНН, Москва, Россия, https://orcid.org/0000-0001-8960-721X

Вклад авторов: *Танашян М.М., Ройтман Е.В.* – концептуализация и проверка исследования; *Раскуражев А.А., Домашенко М.А.* – проведение исследования, сбор клинических данных, описание и регистрация результатов; *Шабалина А.А.* – проверка и актуализация исследования; *Мазур А.С.* – проведение исследования, описание и регистрация результатов.

Depression in Amyotrophic Lateral Sclerosis: Screening Using Attention Bias Assessment

Ekaterina V. Pervushina[1], Mansur A. Kutlubaev[1], Adelina E. Bikmetova[1], Yulia I. Murzakova[1], Vladimir D. Mendelevich[2]

[1]Bashkir State Medical University, Ufa, Russia;

[2]Kazan State Medical University, Kazan, Russia

Abstract

Introduction. *Depression is highly prevalent in amyotrophic lateral sclerosis (ALS) [9]. Its detection can be challenging, particularly in advanced disease when many patients develop bulbar dysfunction and upper limb muscle weakness. This necessitates objective methods for diagnosing affective disorders in ALS.*

The study aimed *to evaluate the potential utility of eye-tracking technology for detecting depression in ALS patients using an attention bias assessment.*

Materials and methods. *The study enrolled ALS patients meeting Gold Coast criteria. Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). During eye-tracking sessions, patients viewed a screen displaying pairs of faces – one emotional (sad or happy) and one neutral.*

Results. *Data from 33 participants were analyzed. Comparative analysis of mean gaze fixation duration showed that ALS patients with depressive symptoms had significantly longer fixation times on sad faces compared to non-depressed patients. HADS depression scores correlated with mean fixation duration on sad ($r = 0.421$; $p = 0.018$) and neutral ($r = 0.36$; $p = 0.047$) faces. To analyze the interaction of sensitivity and specificity of mean fixation time on sad faces for detecting depressive disorders, ROC analysis was performed. An area under the curve was 0.722 (acceptable value).*

Conclusion. *Eye tracking-based attention bias screening assessment shows potential utility for depression detection in ALS. This method may be particularly valuable in advanced disease when patients become immobilized and lose capacity for verbal communication or questionnaire completion [9].*

Keywords: *amyotrophic lateral sclerosis; motor neuron disease; depression; diagnosis; eye tracking*

Ethics approval. All patients provided their written informed consent to participate in the study. The study protocol was approved by the Local Ethics Committee of Bashkir State Medical University, Ufa, Russia (protocol No. 6, June 24, 2024).

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For correspondence: 3 Lenin str., Ufa, Russia, 450008. Bashkir State Medical University. E-mail: mansur.kutlubaev@yahoo.com. Mansur A. Kutlubaev.

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Депрессия при боковом амиотрофическом склерозе: скрининг методом оценки предвзятости внимания

Е.В. Первушина[1], М.А. Кутлубаев[1], А.Э. Бикметова[1], Ю.И. Мурзакова[1], В.Д. Менделевич[2]

[1]Башкирский государственный медицинский университет, Уфа, Россия;

[2]Казанский государственный медицинский университет, Казань, Россия

Аннотация

Введение. *Депрессия широко распространена при боковом амиотрофическом склерозе (БАС). Её выявление может представлять сложности, особенно на развёрнутых стадиях болезни, когда у многих пациентов развиваются бульбарные нарушения, слабость в мышцах рук. В связи с этим целесообразна разработка объективных методов диагностики аффективных нарушений при БАС.*

Цель *работы – оценить потенциальную информативность метода трекинга глаз для выявления депрессии у пациентов с БАС на основе парадигмы предвзятости внимания.*

Материал и методы. *В исследование включались пациенты с БАС по критериям Gold Cost. Для оценки депрессивных жалоб использовалась Госпитальная шкала тревоги и депрессии (HADS). При проведении трекинга глаз пациентам показывали экран, на котором демонстрировали изображения пар лиц, одно из которых было эмоциональным (грустным или радостным), второе – нейтральным.*

Результаты. *Проанализированы данные 33 человек. Сравнительный анализ средней длительности фиксации взора на лицах с различными эмоциями показал, что у пациентов с БАС с симптомами депрессии среднее время фиксации на грустных лицах было значимо более длительным, чем у пациентов без депрессии. Выраженность депрессии по HADS коррелировала со средней длительностью фиксации взора на грустных ($r = 0,421$; $p = 0,018$) и нейтральных ($r = 0,36$; $p = 0,047$) лицах. С целью анализа взаимодействия чувствительности и специфичности среднего времени фиксации на грустном лице для выявления депрессивных нарушений был проведён ROC-анализ. Площадь под кривой составила 0,722 (приемлемое значение).*

Заключение. *Скрининг с использованием трекинга глаз, основанный на парадигме предвзятости внимания, потенциально информативен для выявления депрессии у пациентов с БАС. Использование данной методики будет особенно актуально на развёрнутой стадии болезни, когда пациент обездвижен и не может поддерживать речевой контакт или заполнять бумажные бланки опросников.*

Ключевые слова: *боковой амиотрофический склероз; болезнь двигательного нейрона; депрессия; диагностика; трекинг глаз*

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Адрес для корреспонденции: 450008, Россия, Уфа, ул. Ленина, д. 3. Башкирский государственный медицинский университет. E-mail: mansur.kutlubaev@yahoo.com. Кутлубаев М.А.

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Introduction

Depressive disorders are highly prevalent among patients with neurological diseases [1]. These disorders may stem from both organic mechanisms and psychogenic factors related to emotional responses to neurological symptoms. Organic mechanisms are associated with the pathogenesis of the underlying disease and include neurotransmitter imbalances, focal lesions in emotion-related brain regions, aseptic inflammatory responses, and neuroendocrine disturbances [2]. Depression significantly reduces patients' quality of life and worsens the prognosis of the underlying disease [3].

Amyotrophic lateral sclerosis (ALS) is a severe neurological disorder causing motor neuron degeneration and progressive

muscle weakness. Current pathogenetic therapies for ALS are limited to a few agents with minimal therapeutic efficacy [4]. The average life expectancy after symptom onset in ALS is 2–3 years, necessitating improved approaches to palliative care as a key component of medical management [5].

Depression develops in up to 75% of ALS patients, complicating care and potentially reducing life expetancy through mechanisms including low treatment adherence. It is assumed that depression in ALS results from emotional stress associated with the progression of motor deficits and the patient's awareness of the poor disease prognosis. There is also evidence that neurodegeneration in ALS extends beyond the motor centers of the nervous system and involves adjacent structures, such as the prefrontal cortex, which may be considered a predisposing factor for depression [6, 7].

In neurological practice, depressive symptoms are primarily identified using various diagnostic scales. The most widely used scales include the Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI), Montgomery–Asberg Depression Rating Scale (MADRS), among others. Completing them typically takes 10–20 minutes, requiring patient cooperation and demanding specific expertise from the clinician [1].

Speech and motor impairments typical for ALS often compromise communication. In such cases, detecting depressive symptoms becomes particularly challenging, prompting the search for alternative depression biomarkers. One approach for depression detection utilizes the phenomenon of attentional bias. Studies have demonstrated that patients with depression exhibit attentional bias toward images of sad facial expressions [8]. This approach has been previously investigated in psychiatric practice [8], but its applicability in ALS remains unexplored.

Aim: To evaluate the potential utility of attention bias assessment using eye tracking for detecting depression in ALS patients.

Materials and methods

The study enrolled ALS patients meeting Gold Coast criteria [9]. Exclusion criteria were chronic eye diseases, other severe neurological disorders, comorbid ALS with frontotemporal dementia, and use of psychotropic medications.

During eye tracking, patients were positioned in a quiet room with constant illumination in front of a computer screen displaying pairs of facial images: one emotional (sad or happy) and one neutral. The experiment included 20 happy/neutral pairs and 20 sad/neutral pairs (featuring the same actor in each pair). Facial images were selected from a database of professional actors displaying various emotions [10]. Each image measured 506 × 650 pixels, with non-informative elements (e.g., earrings) removed by cropping within an elliptical shape of 280 × 360 pixels. Each pair was displayed twice (80 trials total). The sequence began with a 500 ms black screen, followed by a 1000 ms white fixation cross. Image presentation duration was 3500 ms [11].

Eye tracking was performed using the stationary Gazepoint GP3 device at approximately the same time of day. The study began with a standard calibration procedure of the eye tracker, followed by data recording. Patients were informed that different faces would be displayed on the screen and instructed to continuously look at the screen without further clarification. The following parameters were assessed: direction of the first gaze (toward emotional or neutral faces), mean time to first fixation on faces, mean duration of first fixation, number of revisits to different faces, and mean fixation duration.

Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). A physician read aloud the questions and possible responses, and the patient selected an answer either verbally or by head nod. Scores of 0–7 indicated no depression, 8–10 indicated subclinical depression, and 11 or higher indicated clinically significant depression [12]. Patients scoring 11 points or higher were referred for consultation of a psychiatrist.

The severity of neurological deficit was assessed using the ALS Functional Rating Scale-Revised (ALSFRS-R) [13], and disease staging was performed using the King's College system [14]. Cognitive functions were evaluated with the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) [15], while asthenia was assessed using the Multidimensional Fatigue Inventory (MFI-20) [16].

Statistical analysis was performed using SPSS Statistics v. 26 software (IBM). Non-parametric statistical methods were applied. Data are presented as median and interquartile range (IQR). Comparative analysis was conducted using the χ^2 test and Mann-Whitney U test. Spearman's correlation analysis was used to identify relationships between parameters. ROC analysis evaluated the diagnostic value of the method. A p-value < 0.05 was considered statistically significant.

Results

Data from 33 ALS patients were analyzed. All patients successfully completed the calibration and eye tracking registration procedure. The main characteristics of the study participants are presented in Table 1. Nine patients (27%) showed signs of clinically significant depression (HADS $\geqslant$ 11) and were diagnosed with a depressive episode through clinical interview.

Comparative analysis revealed that ALS patients with depression had longer mean fixation times on all face types compared to non-depressed ALS patients, which may be explained by the cognitive inhibition characteristic of depression [1, 2]. However, these differences reached statistical significance only for sad facial expressions (Table 2). Figure 1 presents heatmaps illustrating the focus of attention on sad and neutral faces in 2 patients with clinically evident depression and without it. Analysis of other eye-tracking parameters did not reveal significant differences between ALS patients with and without depressive symptoms.

Correlation analysis revealed a significant association between depression severity on the HADS [2] and mean fixation duration

Table 1. Social and demographic characteristics of ALS patients

Parameter	Value
Age, years, Me [Q_1; Q_3]	63.0 [52.0; 67.0]
Sex (male/female), *n* (%)	14 (42.4%)/19 (57.6%)
Disease onsetn (bulbar/spinal), *n* (%)	6 (18.2%)/27 (81.8%)
King's College stage, *n* (%)	
I	1 (3.0%)
II	10 (30.3%)
III	10 (30.3%)
IV	12 (36.4%)
Education (higher/secondary), *n* (%)	11(33.3%)/22(66.7%)
Marital status (married/single), *n* (%)	27(81.8%)/6(18.2%)
HADS depression symptoms, Me [Q_1; Q_3]	7 [3; 11]
HADS anxiety symptoms, Me [Q_1; Q_3]	7 [5; 11]
ALSFRS-R disease severity, Me [Q_1; Q_3]	39 [35.0; 43.5]
ECAS cognitive impairment:	
specific Me [Q_1; Q_3]	63 [51.5; 73.5]
non-specific Me [Q_1; Q_3]	25 [20.5; 28.0]
total score Me [Q_1; Q_3]	86 [76.5; 99.0]

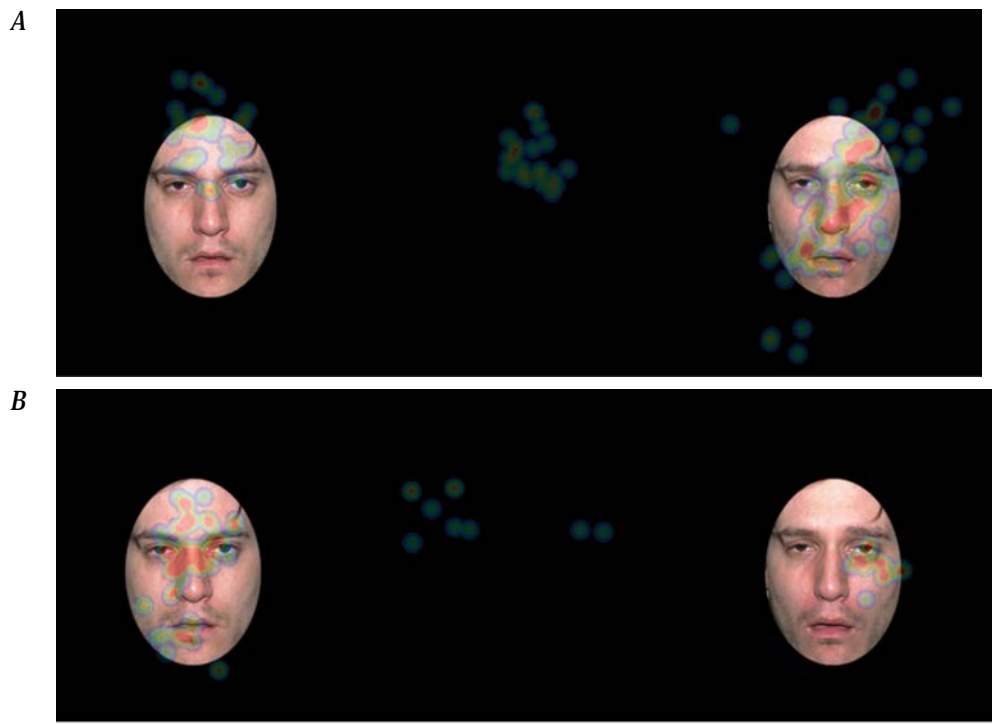

Fig. 1. Heatmaps.
A – patient V. with ALS and clinically significant depression exhibited longer visual fixation on sad faces compared to neutral ones; *B* – patient N. with ALS without depression showed longer fixation on neutral faces than sad ones.

on sad (r = 0.421; p = 0.018) and neutral (r = 0.36; p = 0.047) faces. No significant correlations were found between mean fixation duration on faces with various emotions and HADS anxiety scores, ECAS [3] cognitive decline, MFI-20 asthenia, or ALSFRS-R neurological deficit severity.

To analyze the interaction of sensitivity and specificity of mean fixation time on sad faces for detecting depressive disorders, ROC analysis was performed. The area under the curve (AUC) was 0.72 (95% CI 0.54–0.90 – acceptable value; Fig. 2).

Table 2. Comparative analysis of median gaze fixation duration in patients with and without depressive symptoms, Me [Q_1; Q_3]

Parameter	No depression symptoms (*n* = 26)	Presence of clinically significant depressive symptoms (*n* = 7)	*p*
Mean gaze fixation duration on neutral faces, sec	0.42 [0.08; 1.04]	0.61 [0.32; 1.32]	0.199
Mean gaze fixation duration on happy faces, sec	0.48 [0.05; 0.87]	0.65 [0.32; 1.32]	0.182
Mean gaze fixation duration on sad faces, sec	0.36 [0.12; 0.92]	0.83 [0.44; 1.43]	0.048

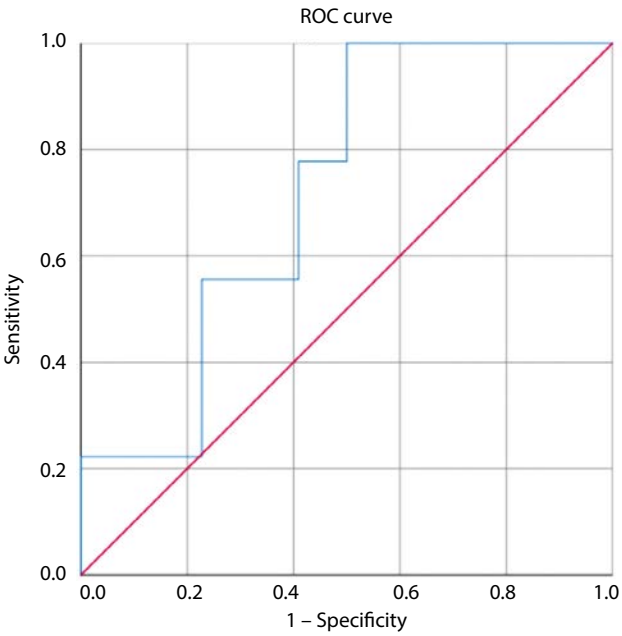

Fig. 2. ROC curve demonstrating the sensitivity and specificity of mean fixation duration on sad faces for detecting depressive symptoms in ALS patients.

The cut-off value for mean fixation duration on sad faces to detect depressive symptoms in ALS patients was determined based on the maximum combined sensitivity and specificity principle. Analysis of the curve coordinates showed that a median average fixation duration on sad face images exceeding 0.37 s indicated depression with 88.8% sensitivity (95% CI 51.75–99.72%) and 50% specificity (95% CI 35.75–82.70%).

Discussion

Analysis of data from a group of 33 ALS patients demonstrated the potential utility of depression symptom screening using eye tracker-based attention bias assessmemt. This approach does not require physician involvement and can be used under the supervision of a trained nurse or technician. No significant correlations between average fixation duration on sad faces and parameters such as severity of asthenia or cognitive impairment suggests that this parameter primarily reflects the presence of depressive disorders. Previous studies have shown that eye-tracking methods can be used in neurological patients with communication deficits, such as post-stroke aphasia [11]. Dysarthria in ALS patients may hinder depression diagnosis through clinical interviews. Paper/electronic questionnaires are also not always feasible due to upper limb muscle weakness progression. Recent studies have revealed that subclinical oculomotor impairments may develop in advanced ALS [17]. However, in this study, the influence of such impairments is unlikely, as the assessment focused on attentional bias rather than visual saccade/antisaccade characteristics.

Digital modalities are increasingly being integrated into the assessment of ALS patients. Most studies in this field focus on evaluating motor deficits. It is hypothesized that technical tools allow for more precise evaluation of neurological impairment severity in ALS and better tracking of disease progression [18]. Significantly fewer studies have explored digital technologies for assessing non-motor manifestations of ALS. Eye-tracking technology is currently successfully employed for alternative communication in advanced ALS, particularly for administering traditional psychometric scales in patients with speech impairment and upper limb paresis [19].

Timely diagnosis of depression remains a critical task in neurological disorders, as depression constitutes an indication for pharmacotherapy. Effective treatment can normalize patients' emotional state, facilitate caregiving, improve compliance, and consequently enhance short-term disease prognosis.

A limitation of this study is the small sample size, the relatively low proportion of patients with symptoms of clinically significant depression, and the absence of patients at the terminal stage of the disease. This research did not perform a detailed evaluation of the diagnostic value of depression screening in ALS using eye tracking.

Future studies should determine the optimal technical parameters of this method and evaluate its sensitivity and specificity compared to standard depression diagnostic tools. The analysis of potential correlations between other parameters and indicators of cognitive and behavioral impairments is also of interest.

Conclusion

Attention bias paradigm-based screening using eye tracking shows potential utility for detecting depression in ALS patients. This method may be particularly valuable in advanced disease when patients become immobilized and lose capacity for verbal communication or questionnaire completion.

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Information about the authors

Ekaterina V. Pervushina — Cand. Sci. (Med.), Assoc. Prof., Department of neurology, Bashkir State Medical University, Ufa, Russia, https://orcid.org/0000-0002-9352-5783
Mansur A. Kutlubaev — Dr. Sci. (Med.), Assoc. Prof., Head, Department of neurology, Bashkir State Medical University, Ufa, Russia, https://orcid.org/0000-0003-1001-2024
Adelina E. Bikmetova — student, Bashkir State Medical University, Ufa, Russia, https://orcid.org/0009-0001-3147-0852
Yulia I. Murzakova — student, Bashkir State Medical University, Ufa, Russia, https://orcid.org/0009-0005-4341-8321
Vladimir D. Mendelevich — Dr. Sci. (Med.), Prof., Head, Department of psychiatry and medical psychology, Bashkir State Medical University, Kazan, Russia, https://orcid.org/0000-0002-8476-6083

Author contribution: *Pervushina E.V.* — conducting research, analyzing data, writing a text; *Kutlubaev M.A.* — creation of a research concept, analyzing data, writing a text; *Bikmetova A.E., Murzakova Yu.I.* — conducting research; *Mendelevich V.D.* — editing of the text.

Информация об авторах

Первушина Екатерина Владимировна — канд. мед. наук, доцент каф. неврологии Башкирского государственного медицинского университета, Уфа, Россия, https://orcid.org/0000-0002-9352-5783
Кутлубаев Мансур Амирович — д-р мед. наук, доцент, зав. каф. неврологии Башкирского государственного медицинского университета, Уфа, Россия, https://orcid.org/0000-0003-1001-2024
Бикметова Аделина Эдуардовна — студентка лечебного факультета Башкирского государственного медицинского университета, Уфа, Россия, https://orcid.org/0009-0001-3147-0852
Мурзакова Юлия Ильинична — студентка лечебного факультета Башкирского государственного медицинского университета, Уфа, Россия, https://orcid.org/0009-0005-4341-8321
Менделевич Владимир Давыдович — д-р мед. наук, профессор, зав. каф. психиатрии и медицинской психологии Казанского государственного медицинского университета, Казань, Россия, https://orcid.org/0000-0002-8476-6083

Вклад авторов: *Первушина Е.В.* — проведение исследования, анализ данных, написание текста, *Кутлубаев М.А.* — создание концепции исследования, анализ данных, написание текста; *Бикметова А.Э., Мурзакова Ю.И.* — проведение исследования; *Менделевич В.Д.* — научное редактирование текста.

Association of *COMT* and *MAO-B* Gene Polymorphic Variants with Sensitivity to Dopaminergic Therapy in Patients with Parkinson's Disease

Yulia I. Khabarova[1], Alexey A. Tappakhov[1,2], Tatiana E. Popova[3], Nadezhda E. Maksimova[4], Aleksandra S. Asekritova[2,4], Olga V. Tatarinova[1,4]

[1]Yakut Scientific Center for Complex Medical Problems, Yakutsk, Russia;

[2]M.K. Ammosov North-Eastern Federal University, Yakutsk, Russia;

[3]Lotus Medical Clinic, Yakutsk, Russia;

[4]Republican Clinical Hospital No. 3, Yakutsk, Russia

Abstract

Introduction. *Levodopa and other dopaminergic agents remain the cornerstone of pharmacotherapy for Parkinson's disease (PD). Two enzymes play key roles in dopamine metabolism: catechol-O-methyltransferase and monoamine oxidase type B, encoded by the COMT and MAO-B genes respectively.*

This study aimed at *analyzing potential association between dopaminergic therapy response and carrier status of COMT (rs4680) and MAO-B (rs1799836) polymorphisms in patients with PD.*

Materials and methods. *The study included 96 PD patients at stages 2–3 on the modified Hoehn and Yahr scale. Most patients (n=64; 66.7%) received levodopa/carbidopa, with 40.6% on combined dopaminergic therapy. All patients underwent assessment of dopaminergic therapy effictiveness using the difference in motor deficit (calculated from part III of the Unified Parkinson's Disease Rating Scale) between the worst and best states (%). COMT and MAO-B polymorhisms were detected by real-time polymerase chain reaction.*

Results. *Allelic analysis demonstrated that carriers of the COMT gene rs4680 G allele responded better to dopaminergic therapy than A allele carriers (p = 0.038) (43.78 ± 18.15% vs 38.53 ± 16.58%; p = 0.038). Among men, we found no significant differences in therapy sensitivity related to MAO-B (rs1799836) variants, while female CC genotype carriers demonstrated better treatment response than TC heterozygotes (35.45 ± 17.78% vs 55.16 ± 11.22%; p=0.019).*

Conclusion. *Our data suggest that in patients with PD, not only drug-induced dyskinesias and motor fluctuations, but also overall sensitivity to dopaminergic therapy may be associated with specific COMT and MAO-B polymorphisms.*

Keywords: *Parkinson's disease; polymorphism; levodopa; dopamine; MAO-B; COMT*

Ethical approval. The study was conducted with the voluntary informed written consent of the patients. The study protocol was approved by the Local committee on biomedical ethics of the Yakut Scientific Center for Complex Medical Problems (protocol No. 51, December 17, 2020).

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For correspondence: 6 Kulakovskogo st., Yakutsk, Russia, 677018. Yakut Scientific Center for Complex Medical Problems. E-mail: september062007@mail.ru. Khabarova Yu.I.

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Ассоциация полиморфных вариантов генов *COMT* и *MAO-B* с чувствительностью к дофаминергической терапии у пациентов с болезнью Паркинсона

Ю.И. Хабарова[1], А.А. Таппахов[1,2], Т.Е. Попова[3], Н.Е. Максимова[4], А.С. Асекритова[2,4], О.В. Татаринова[1,4]

[1]Якутский научный центр комплексных медицинских проблем, Якутск, Россия;

[2]Северо-Восточный федеральный университет имени М.К. Аммосова, Якутск, Россия;

[3]Медицинская клиника «Лотос», Якутск, Россия;

[4]Республиканская клиническая больница № 3, Якутск, Россия

Аннотация

Введение. *Препараты леводопы и другие дофаминергические препараты остаются основой фармакотерапии болезни Паркинсона (БП). В метаболизме дофамина ключевую роль играют два фермента: катехол-О-метилтрансфераза и моноаминоксидаза типа Б, которые кодируются генами COMT и MAO-B соответственно.*

Целью *настоящего исследования явилось изучение возможной взаимосвязи между выраженностью ответа на дофаминергическую терапию и носительством полиморфных вариантов генов COMT (rs4680) и MAO-B (rs1799836) у пациентов с БП.*

Материалы и методы. *В исследовании приняли участие 96 пациентов с БП 2–3-й стадии по модифицированной шкале Hoehn–Yahr. Большинство пациентов (n = 64; 66,7%) принимали препараты леводопы/карбидопы, 40,6% пациентов – комбинированную дофаминергическую терапию. Всем включённым в исследование пациентам проводили тест эффективности принимаемой дофаминергической терапии с расчётом разности двигательного дефицита, оценённого по 3-й части Унифицированной рейтинговой шкалы БП, в фазах наихудшего и наилучшего самочувствия (в %). Определение полиморфных вариантов генов COMT и MAO-B проведено методом полимеразной цепной реакции в реальном времени.*

Результаты. *Аллельный анализ показал, что носители аллеля G гена COMT (rs4680) лучше отвечают на дофаминергическую терапию, чем носители аллеля A (43,78 ± 18,15% против 38,53 ± 16,58%; p = 0,038). Среди мужчин мы не обнаружили значимых различий по чувствительности к дофаминергической терапии в зависимости от носительства полиморфных вариантов гена MAO-B (rs1799836), а женщины – носители генотипа CC характеризовались лучшим ответом на дофаминергическую терапию, чем гетерозиготы TC (35,45 ± 17,78% против 55,16 ± 11,22%; p = 0,019).*

Заключение. *Основываясь на полученных данных, можно предположить, что не только развитие лекарственных дискинезий и моторных флуктуаций, но и чувствительность к дофаминергической терапии в целом у пациентов с БП может быть обусловлена носительством определённых полиморфных вариантов генов COMT и MAO-B.*

Ключевые слова: *болезнь Паркинсона; полиморфные варианты; леводопа; дофамин; MAO-B; COMT*

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

Адрес для корреспонденции: 677018, Россия, Якутск, ул. Кулаковского, д. 6. Якутский научный центр комплексных медицинских проблем. E-mail: september062007@mail.ru. Хабарова Ю.И.

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Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, characterized by progressive degeneration primarily of dopaminergic neurons in the substantia nigra of the brain, leading to severe dopamine deficiency and the emergence of symptoms such as bradykinesia, muscle rigidity, and resting tremor [1, 2]. The prevalence of PD continues to rise annually, which is attributed not only to population aging but also to complex interactions between genetic, epigenetic, and environmental factors that require further investigation [3–5].

The cornerstone of PD pharmacotherapy includes levodopa and other dopaminergic agents [6]. Levodopa, as a dopamine precursor capable of crossing the blood-brain barrier, is converted into dopamine and compensates for the neurotransmitter deficit. Other medications such as dopamine receptor agonists, monoamine oxidase B (MAO-B) inhibitors, and amantadine directly stimulate dopamine receptors or enhance/prolong the effects of levodopa [7, 8].

Individual genetic characteristics may serve as key determinants of therapeutic response to dopaminergic treatment. Dopamine is metabolized by two enzymes: catechol-O-methyltransferase (COMT) and monoamine oxidase type B (MAO-B), encoded by the *COMT* and *MAO-B* genes located on 22q11.21 and Xp11.3 chromosomes, respectively [9].

The *Val158Met* (rs4680) polymorphic variant of the *COMT* gene significantly alters enzyme activity. The G allele (encoding valine) is associated with higher COMT enzyme activity and consequently faster dopamine depletion in the synapse, while the A allele (encoding methionine) is linked to slower COMT activity and prolonged synaptic dopamine retention [10]. The *A644G* (rs1799836) polymorphic variant of the *MAO-B* gene may modify MAO-B enzyme activity. Specifically, *TT (AA)*, *TC* (AG), and *CC* (GG) genotypes correspond to high, intermediate, and low enzyme activity levels, respectively [11].

Most studies have focused on associations between *COMT* and *MAO-B* gene polymorphisms with levodopa-induced dyskinesias and motor fluctuations in PD patients [12–16], but none have investigated the relationship between dopaminergic therapy response intensity and polymorphic variant carrier status. This rationale guided the selection of specific genes and polymorphic variants included in the current study.

Study aim: to analyze the relationship between dopaminergic therapy response and carrier status of *COMT* (rs4680) and *MAO-B* (rs1799836) polymorphisms in patients with PD.

Materials and methods

The study was conducted at the Center for Neurodegenerative Diseases of the Clinic of Yakut Scientific Center for Complex Medical Problems included 96 patients (43 men and 53 women) with PD stages 2–3 according to the modified Hoehn and Yahr scale between January 2021 and December 2022.

Inclusion criteria:
- clinically established diagnosis of PD according to the 2013 criteria of the International Parkinson and Movement Disorder Society;
- continuous use of levodopa or other antiparkinsonian agents for at least the preceding year;
- age 18 years and older.

The non-inclusion criteria:
- patients with secondary parkinsonism or parkinsonism within multisystem neurodegeneration;
- patients with severe medical conditions;
- patients who took anticholinergics, anti-dementia drugs, or antidepressants within the previous 6 months;
- refusal to participate in the study.

All patients provided written informed consent to participate in the study. The study protocol was approved by the Local Biomedical Ethics Committee of Yakut Scientific Center for Complex Medical Problems (Protocol No. 51 dated December 17, 2020).

The mean patient age was 66.58 ± 9.37 years (95% CI 64.68–68.48), with average disease duration of 5.71 ± 3.59 years (95% CI 4.98–6.44). Most patients (66.7%) received levodopa/carbidopa, with a median daily dose of 500.0 [375.0; 750.0] mg. 40.6% of patients received combination dopaminergic therapy. Table 1 shows the complete characteristics of the study participants.

All patients included in the study underwent an efficacy assessment of their dopaminergic therapy. After obtaining consent, all anti-Parkinsonian medications were discontinued until the patient reached their self-assessed worst clinical state (Phase 1), during which motor impairments were evaluated using Part III of the Unified Parkinson's Disease Rating Scale (UPDRS). Following administration of a single dose of their prescribed dopaminergic agents and achievement of the optimal therapeutic effect (Phase 2), motor impairments were reassessed. Scores obtained in the worst clinical state were considered baseline, with percentage change calculated for the best clinical state following dopaminergic agent administration.

The molecular genetic study was conducted at the Laboratory of Molecular Genetics of the Center for Predictive Medicine and Bioinformatics at Republican Clinical Hospital No. 3. Blood samples were collected from patients' cubital veins into Improvacuter vacuum tubes (Guangzhou Improve Medical Instruments, China) containing 0.5 M EDTA solution. Genomic DNA extraction was performed using the AmliSens RIBO-PREP DNA/RNA isolation kit (Central Research Institute of Epidemiology, Rospotrebnadzor, Russia) according to the manufacturer's protocol. The isolated DNA was stored at –20°C. Polymorphic variants of the *COMT* (rs4680) and *MAO-B* (rs1799836) genes were analyzed using real-time polymerase chain reaction on a CFX 96 nucleic acid amplifier (Bio-Rad, USA) with commercial reagent kits (rs4680: Syntol, Russia; rs1799836: TestGen, Russia). For genotyping the *COMT* rs4680 polymorphism, 5'-TCGTGGACGCCGTGATTCAGG-3' and 5'-AGGTCTGACAACGGGTCAGGC-3' primers were used. For genotyping the *MAO-B* rs1799836 polymorphism, 5'-GGAACCTCTTATACCACAGG-3 and 5'-GACTGC-

Table 1. Characteristics of patients

Parameter	Value
Total No. of patients	96
Male, *n* (%)	43 (44.8%)
Mean age, years	66.58 (9.37)
Mean disease duration, years	5.71 (3.59)
Disease subtype, *n* (%):	
complex	65 (67.7%)
akinetic-rigid	18 (18.8%)
tremor-dominant	13 (13.5%)
Use of levodopa/carbidopa, *n* (%)	64 (66.7%)
Median levodopa daily dose, mg	500.0 [375.0; 750.0]
Combined dopaminergic therapy, *n* (%)	39 (40.6%)
Use of dopamine receptor agonists, *n* (%)	45 (46.9%)
Use of amantadine, *n* (%)	31 (32.3%)
Median equivalent levodopa daily dose, mg	500.0 [300.0; 750.0]
Mean Unified Parkinson's Disease Rating Scale (UPDRS) Part III score:	
Phase 1	54.25 (16.57)
Phase 2	32.53 (15.69)
Mean Montreal Cognitive Assessment (MoCA) score:	
Phase 1	19.6 (4.97)
Phase 2	23.43 (4.97)

CAGATTTCATCCTC-3' primers were used. Genotyping results were analyzed using TaqMan allelic discrimination technology with fluorescent probes.

Statistical analysis was performed using SPSS Statistics v. 25.0 software. Quantitative data normality was assessed using Kolmogorov–Smirnov and Shapiro–Wilk tests. For normally distributed data, mean ± standard deviation (M ± SD) with 95% confidence interval (CI) was presented. Non-normally distributed data are shown as median and interquartile range (IQR) (Me [Q_1; Q_3]). One-way ANOVA was used to compare three groups of independent quantitative variables with normal distribution, followed by post-hoc analysis when significant differences were detected. Independent samples t-test was applied for comparing two groups of normally distributed variables. Categorical data are presented as frequencies (%). The level of statistical significance was set at $p \leqslant 0.05$.

Genotype distribution was tested for Hardy–Weinberg equilibrium. Figure 1 shows the frequency distribution of genotypes for the studied gene polymorphisms.

Results

Table 2 compares motor deficit differences in PD patients between the two study phases broken down by the carriage of the *COMT* gene rs4680 polymorphisms. Carriers of the *GG* genotype showed a more pronounced reduction in motor deficit in response to antiparkinsonian therapy compared to *AA* genotype carriers, though the differences were not statistically significant. Allelic analysis demonstrated that carriers of the *COMT* gene rs4680 *G* allele responded better to dopaminergic therapy than *A* allele carriers ($p = 0.038$).

Since the *MAO-B* gene is located on the X chromosome, the analysis was performed both in the overall sample and stratified by gender. In the overall sample, we found no statistically significant difference in the response to antiparkinsonian therapy depending on genotype distribution, though heterozygotes showed a smaller reduction in motor deficit ($p = 0.093$). Among men, no statistically significant differences were observed based on *T* or *C* allele carriage ($p = 0.941$). In women, one-way ANOVA revealed a significant difference ($p = 0.043$) in motor deficit changes depending on

Fig. 1. Distribution of genotype frequencies in the *MAO-B* and *COMT* genes.

Table 2. Association of the *COMT* gene rs4680 polymorphic variant with response to dopaminergic therapy

Genotype/allele	*n*	Difference in UPDRS Part III scores (%)		*p*
		M ± SD	95% CI	
GG	42	45.3 ± 17.8	39.77–50.87	
GA	17	36.15 ± 18.90	26.39–45.91	0.12
AA	37	39.07 ± 16.17	33.68–44.46	
G	101	43.78 ± 18.15	40.2–47.36	**0.038**
A	91	38.53 ± 16.58	35.07–41.97	

rs1799836 polymorphic variant genotypes. Post-hoc testing demonstrated that the difference stemmed from variations between *TC* heterozygotes and *CC* mutant allele homozygotes (35.45 ± 17.78 vs. 55.16 ± 11.22; $p = 0.019$). Consequently, the *CC* genotype in women was associated with a better response to dopaminergic therapy. Meanwhile, allele frequency analysis in both the overall group and gender-stratified subgroups showed no significant differences (Table 3).

Discussion

The polymorphic variants of the *COMT* and *MAO-B* genes included in this study have been extensively investigated across various populations to assess both PD risk and treatment response associations. A meta-analysis of 20 case-control studies involving 2,846 cases and 3,508 controls demonstrated that the *AA* genotype of the *MAO-B A644G* polymorphism is associated with increased PD risk compared to *AG* + *GG* genotypes (OR = 1.32; 95% CI 1.18–1.47) [17]. Conversely, *AG* and *GG* genotypes were linked to earlier onset and higher frequency of drug-induced dyskinesias in patients with PD, potentially due to reduced MAO-B enzyme activity and elevated synaptic dopamine levels [12, 18]. The influence of *COMT* haplotypes (rs6269:*A>G*; rs4633*C>T*; rs4818:*C>G*; rs4680:*A>G*) on levodopa dosing was investigated, revealing that carriers of the *G_C_G_G* haplotype (associated with high COMT enzyme activity) required significantly higher levodopa doses compared to other haplotypes (604.2 ± 261.9 mg vs. 512.2 ± 133.5 mg, $p < 0.05$) [19]. Investigation of *MAO-B* and *COMT* gene effects on PD in the Yakut population remains pending, with planned emphasis on ethnic-specific associations.

Our study assessed whether carrying specific genotypes or alleles of *COMT* and *MAO-B* gene polymorphisms could influence the sensitivity to dopaminergic therapy in patients with PD. By dopaminergic therapy, we meant any treatment capable of enhancing dopaminergic transmission, including levodopa, dopamine receptor agonists, MAO-B inhibitors, and amantadine. We excluded patients taking any other medications that could alter the response to anti-parkinsonian therapy, either by enhancing or suppressing its effects. Our results showed that carriers of the *G* allele of the *COMT* rs4680 polymorphism exhibited more pronounced reduction in motor deficits when receiving anti-parkinsonian medications. However, the *GG* genotype and *G* allele are associated with high COMT enzyme activity and consequent rapid dopamine depletion [15]. Our findings appear partially inconsistent with these data, suggesting the involvement of additional mechanisms modulating treatment response intensity.

According to our data, female carriers of the *CC* genotype of the *MAO-B* gene (rs1799836) demonstrated better response to anti-parkinsonian therapy [17]. The *CC* genotype (designated as *GG* in most studies) is linked to low MAO-B enzyme activity [17]. Consequently, carriers of this genotype may require lower doses of anti-parkinsonian medications or show better response to equivalent drug doses. Conversely, T. Sampaio *et al.* found that male carriers of the *MAO-B G* allele (rs1799836) had a higher relative chance of requiring high-dose levodopa therapy (> 600 mg/day; $p = 0.04$), while no significant differences in genotype/allele frequency or levodopa dosing were observed in women [12].

Table 3. Association of the *MAO-B* gene rs1799836 polymorphic variant with response to dopaminergic therapy

Genotype/allele	*n*	Difference in UPDRS Part III scores, %		*p*
		M ± SD	95% CI	
Overall sample				
TT	56	42.02 ± 18.23	37.13–46.90	0.093
TC	20	35.27 ± 17.3	27.16–43.38	
CC	20	45.26 ± 15.29	38.10–52.42	
T	132	40.99 ± 18.13	37.87–44.12	0.724
C	60	41.93 ± 16.42	37.69–46.17	
Men				
T	30	40.22 ± 17.74	35.71–44.74	0.941
C	13	39.93 ± 14.51	34.07–45.79	
Women				
TT	26	44.09 ± 19.05	36.39–51.78	**0.043** $p_{TT,TC} = 0.1$* $p_{TT,CC} = 0.344$* **$p_{TC,CC} = 0.019$***
TC	20	35.45 ± 17.78	26.89–44.02	
CC	7	55.16 ± 11.22	44.78–65.53	
T	72	41.78 ± 18.86	37.32–46.24	0.604
C	34	43.82 ± 17.97	37.44–50.18	

Our study has several significant limitations. The primary limitation is the lack of stratification of patients by groups of antiparkinsonian medications used. It is likely that carriers of different genotypes will respond differently to levodopa preparations, dopamine receptor agonists, and other agents. Nevertheless, we demonstrated that sensitivity to dopaminergic therapy depends on polymorphic variants of genes whose products are involved in levodopa metabolism. Second, patients received antiparkinsonian agents in varying doses. Therefore, we decided to calculate between-phase differences in the study not in absolute values (points) but in percentage terms. During the study, we did not adjust doses of previously prescribed medications. We temporarily discontinued nighttime antiparkinsonian medications, but most patients did not reach their worst clinical condition by the next morning, necessitating prolongation of the withdrawal period. The third major limitation is the small sample size and lack of ethnic stratification. We hypothesize that representatives of different ethnic groups may also have specific features in sensitivity to antiparkinsonian therapy.

Conclusion

Our data suggest that in patients with PD, not only drug-induced dyskinesias and motor fluctuations, but also overall sensitivity to dopaminergic therapy may be associated with specific *COMT* and *MAO-B* polymorphisms. Larger-scale studies with stratification by antiparkinsonian medications and ethnicity are undoubtedly needed.

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Information about the authors

Yuliya I. Khabarova – junior researcher, neurologist, Head, Neurological department, Center for neurodegenerative diseases, Clinic of the Yakut Scientific Center for Complex Medical Problems, Yakutsk, Russia, https://orcid.org/0000-0002-5674-4426
Alexey A. Tappakhov – Cand. Sci. (Med.), Assoc. Prof., Department of neurology and psychiatry, M.K. Ammosov North-Eastern Federal University, Yakutsk, Russia; senior researcher, Neurodegenerative disorders center, Yakut Scientific Center for Complex Medical Problems, Yakutsk, Russia, https://orcid.org/0000-0002-4159-500X
Tatiana E. Popova – Dr. Sci. (Med.), neurologist, LLC "Lotus Medical Clinic", Yakutsk, Russia, https://orcid.org/0000-0003-1062-1540
Nadezhda E. Maksimova – biologist, Center for predictive medicine and bioinformatics, Republican Clinical Hospital No. 3, Yakutsk, Russia, https://orcid.org/0009-0003-9677-7526
Aleksandra S. Asekritova – Cand. Sci. (Med.), Assoc. Prof., Department of internal medicine and general practice (family medicine), M.K. Ammosov North-Eastern Federal University, Yakutsk, Russia; Head, Center for predictive medicine and bioinformatics, Republican Clinical Hospital No. 3, Yakutsk, Russia, https://orcid.org/0000-0002-5378-2128
Olga V. Tatarinova – Dr. Sci. (Med.), Chief doctor, Republican Clinical Hospital No. 3, Yakutsk, Russia; senior researcher, Yakut Scientific Center for Complex Medical Problems, Yakutsk, Russia, https://orcid.org/0000-0001-5499-9524

Contribution of the authors: *Khabarova Yu.I.* – data collection and research implementation, article design development, data interpretation and analysis, manuscript writing; *Tappakhov A.A.* – conceptualization and article design, coordination of development, manuscript editing and final revision, supervision of the research project, and approval of the final manuscript version; *Popova T.E.* – study design development, final text revision, and manuscript approval; *Asekritova A.S.* – coordination of the study; *Maksimova N.E.* – research implementation; *Tatarinova O.V.* – organization of the study. All authors made significant contributions to the study's conceptualization, execution, and manuscript preparation, and have read and approved the final version for publication.

Информация об авторах

Хабарова Юлия Ильинична – м. н. с., врач-невролог, зав. неврологическим отделением Центра нейродегенеративных заболеваний Клиники Якутского научного центра комплексных медицинских проблем, Якутск, Россия, https://orcid.org/0000-0002-5674-4426
Таппахов Алексей Алексеевич – канд. мед. наук, доцент каф. «Неврология и психиатрия» Медицинского института Северо-Восточного федерального университета им. М.К. Аммосова, Якутск, Россия; с. н. с. Центра нейродегенеративных заболеваний Якутского научного центра комплексных медицинских проблем, Якутск, Россия, https://orcid.org/0000-0002-4159-500X
Попова Татьяна Егоровна – д-р мед. наук, врач-невролог ООО «Медицинская клиника Лотос», Якутск, Россия, https://orcid.org/0000-0003-1062-1540
Максимова Надежда Евгеньевна – биолог Центра предиктивной медицины и биоинформатики Республиканской клинической больницы № 3, Якутск, Россия, https://orcid.org/0009-0003-9677-7526
Асекритова Александра Степановна – канд. мед. наук, доцент каф. «Внутренние болезни и общеврачебная практика (семейная медицина)» Медицинского института Северо-Восточного федерального университета им. М.К. Аммосова, Якутск, Россия; зав. Центром предиктивной медицины и биоинформатики Республиканской клинической больницы № 3, Якутск, Россия, https://orcid.org/0000-0002-5378-2128
Татаринова Ольга Викторовна – д-р мед. наук, главный врач Республиканской клинической больницы № 3, Якутск, Россия; с. н. с. Якутского научного центра комплексных медицинских проблем, Якутск, Россия, https://orcid.org/0000-0001-5499-9524

Вклад авторов: *Хабарова Ю.И.* – сбор и проведение исследования, разработка дизайна статьи, интерпретация данных, анализ данных, написание текста статьи; *Таппахов А.А.* – разработка концепции и дизайна статьи, координация разработки, редактирование и финальная корректировка текста статьи, курирование научно-исследовательской работы, утверждение окончательного варианта текста; *Попова Т.Е.* – разработка проекта исследования, финальная корректировка текста, утверждение окончательного варианта текста; *Асекритова А.С.* – координация разработки исследования; *Максимова Н.Е.* – проведение молекулярно-генетического исследования; *Татаринова О.В.* – организация исследования. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Metabolic Manifestations of Parkinson's Disease in Cell Models Derived from Induced Pluripotent Stem Cells

Nataliya A. Kolotyeva, Regina S. Mudarisova, Natalia A. Rozanova, Arseniy K. Berdnikov, Svetlana V. Novikova, Yulia K. Komleva

Russian Center of Neurology and Neurosciences, Moscow, Russia

Abstract

Induced pluripotent stem cell (iPSC)-based models represent an innovative approach to studying the pathogenesis of inherited Parkinson's disease (PD) at molecular and cellular levels. The ability to derive neurons, astrocytes, and microglia carrying SNCA gene mutations from iPSCs significantly advances our understanding of key metabolic disturbances in PD. Each specific type of SNCA gene mutation (A53T, A30P, triplications, duplications, etc.) exhibits individual effects on functional and biochemical characteristics of differentiated cells. These differences involve synaptogenesis, extramitochondrial oxygen consumption, and protein metabolism. The diversity of effects makes critical the selection of strictly defined iPSC lines depending on research objectives. The **aim** *of this review is to examine metabolic features of brain cells derived from iPSCs with inherited PD associated with SNCA mutations, as well as the potential of using iPSCs to develop personalized in vitro models for understanding disease mechanisms. This approach will facilitate identification of new therapeutic targets and refinement of existing technologies for diagnosis and targeted therapy.*

Keywords: *Parkinson's disease; SNCA gene; metabolic plasticity; induced pluripotent stem cells; astrocytes; neurons; microglia*

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For correspondence: 80 Volokolamskoye shosse, Moscow, Russia, 125367. Research Center of Neurology and Neurosciences. E-mail: kolotyeva.n.a@neurology.ru. Nataliya A. Kolotyeva

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Метаболические проявления болезни Паркинсона в клеточных моделях, полученных из индуцированных плюрипотентных стволовых клеток

Н.А. Колотьева, Р.С. Мударисова, Н.А. Розанова, А.К. Бердников, С.В. Новикова, Ю.К. Комлева

Российский центр неврологии и нейронаук, Москва, Россия

Аннотация

Модели на основе индуцированных плюрипотентных стволовых клеток (ИПСК) являются частью инновационного подхода к изучению патогенеза наследственных форм болезни Паркинсона на молекулярном и клеточном уровнях. Возможность получения из ИПСК нейронов, астроцитов и микроглии, несущих мутации в гене SNCA, позволяет существенно продвинуть понимание ключевых метаболических нарушений, сопровождающих данную патологию. Каждый отдельный тип мутаций в гене SNCA (A53T, A30P, трипликации, дупликации и др.) по-разному влияет на функциональные и биохимические характеристики дифференцированных клеток. Эти различия затрагивают процессы синаптогенеза, внемитохондриального потребления кислорода и белкового обмена. Разнообразие эффектов делает актуальным выбор строго определённых линий ИПСК в зависимости от задач исследования. ***Целью*** *обзора является изучение метаболических особенностей клеток головного мозга, полученных из ИПСК с генетической формой болезни Паркинсона, ассоциированной с мутациями*

в гене SNCA, а также потенциала использования ИПСК для разработки персонализированных моделей in vitro для понимания механизмов заболевания, что будет способствовать выявлению новых мишеней и усовершенствованию существующих технологий для диагностики и таргетной терапии.

Ключевые слова: *болезнь Паркинсона; ген SNCA; метаболическая пластичность; индуцированные плюрипотентные стволовые клетки; астроциты; нейроны; микроглия*

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Адрес для корреспонденции: 125367, Москва, Волоколамское шоссе, д. 80. Российский центр неврологии и нейронаук. E-mail: kolotyeva.n.a@neurology.ru. Колотьева Н.А.

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Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to reduced dopamine levels and diverse motor and non-motor symptoms. The disease is defined by the presence of Lewy body aggregates composed of aberrant α-synuclein. Although PD was first described over 200 years ago, our understanding of its biological basis remains fragmented and insufficiently profound. Hypotheses linking PD to oxidative stress, mitochondrial dysfunction, inflammatory processes, protein metabolism system impairments, and other factors have been proposed [1]. However, none of these theories fully explains all aspects of the disease, underscoring the need for a comprehensive research approach.

In recent decades, significant progress has been made in diagnosing and treating this neurodegenerative disorder, yet many key mechanisms underlying its pathogenesis remain unclear. Genetic studies identifying PD-associated genes, including *SNCA, PRKN, PINK1, GBA*, and *LRRK2*, have played a pivotal role in elucidating PD pathogenesis [2]. The extent of environmental factors, lifestyle changes, and aging effects on disease manifestation in mutation carriers continues to be actively investigated [3].

Current research aims to develop models that most accurately reflect the pathophysiological processes occurring in PD: *in silico* modeling, *in vitro* cellular technologies (including human cells), and *in vivo* experimental organisms, with each system having its own advantages and limitations [4]. Shortly after the groundbreaking discovery that adult human somatic cells can be reprogrammed into an embryonic state through the expression of a specific set of pluripotent transcription factors [5], human disease modeling reached a qualitatively new level. This technology enabled the use of various patient-derived cells, including skin fibroblasts, peripheral blood mononuclear cells, and urine-derived epithelial cells, to generate induced pluripotent stem cells (iPSCs). iPSCs represent a virtually unlimited source of human cells that retain the donor's unique genetic profile and possess the capacity for directed chemical and/or transcriptional differentiation into specific cell types. This breakthrough provides unprecedented opportunities to study molecular and cellular mechanisms of pathogenesis under conditions that closely approximate physiological states. Unlike traditional cell line-based models, iPSCs retain endogenous mechanisms, making them more representative for studying complex hereditary and molecular aspects of PD [6]. Additionally, iPSCs and cells differentiated from them serve as key tools for modeling biological processes in cells and tissues that are difficult to obtain from living donors, particularly those of the neurovascular unit (NVU) and blood-brain barrier.

Most PD studies predominantly focus on iPSCs differentiated into dopaminergic neurons, as the loss of these cells underlies the motor symptoms of the disease. Only a few studies have explored other cell types (astrocytes, oligodendrocytes, microglia, etc.).

This review **aims** to examine the metabolic features of brain cells derived from iPSCs with inherited PD associated with *SNCA* gene mutations, as well as the potential of using iPSCs to develop personalized *in vitro* models for understanding disease mechanisms. Such models could facilitate the identification of new therapeutic targets and the refinement of existing approaches for diagnosis and targeted therapy.

Current Cellular and Molecular Hypotheses of Parkinson's Disease Pathogenesis

The current concept of PD pathogenesis views it not as a single disease, but as a combination of pathological processes characterized by an individual interplay of genetic factors, environmental influences, and comorbid disorders [1]. The contribution of each process varies among patients depending on their predisposition to the disease. Several cellular and

molecular hypotheses describe PD pathogenesis, including the role of mutations in PD-associated *SNCA, PRKN, PINK1, GBA*, and *LRRK2* genes as predisposing risk factors. Biallelic mutations in *PRKN* and *PINK1* genes demonstrate complete penetrance. Mutations in *GBA* and *LRRK2* genes may increase individual risk and are not associated with complete penetrance. Regardless of genetic predisposition, the key processes contributing to PD pathogenesis are mitochondrial dysfunction and pathological α-synuclein accumulation [7].

The mitochondrial damage theory is associated with diverse cellular-molecular mechanisms and bioenergetic disturbances. Mitochondrial dysfunction causes neuronal death in the substantia nigra, promotes oxidative stress, membrane/protein/DNA damage, enhances mitophagy, and depletes autophagy resources. Increased production of reactive oxygen species (ROS) disrupts lysosomal and proteasomal systems, stimulating aggregation of aberrant α-synuclein [8]. Damaged mitochondria release mitochondrial DNA, which amplifies proinflammatory cytokine production and activates cytotoxic T-cells, thereby linking neurodegeneration and neuroinflammation. Under pathogenic stimuli (injury, infection, aging, α-synuclein fibrils, mitochondrial dysfunction), glial cells (astrocytes and microglia) transition from physiological to reactive states, secreting proinflammatory cytokines and activating the complement system. Chronic activation leads to blood-brain barrier permeability disruption, peripheral immune cell infiltration, increased local inflammatory mediator production, and exacerbated oxidative stress [9].

The hypothesis about the role of pathological α-synuclein in PD pathogenesis is based on aberrant protein structures forming toxic fibrillar complexes – Lewy bodies, which can spread between neurons and cause neurodegeneration. α-Synuclein aggregation may result from excessive production of endogenous α-synuclein, particularly in cases of *SNCA* mutations, which can suppress efficient protein clearance pathways; these pathways may also be disrupted by *GBA* gene mutations. α-Synuclein aggregates disrupt membrane integrity, increase intracellular calcium levels, and exacerbate cellular stress. The efficiency of proteasomal degradation and lysosomal clearance decreases, leading to the accumulation of oxidized and aggregated proteins, ROS formation, and worsening cellular damage [10–12]. Chaperones such as GroEL promote the amyloid transformation of α-synuclein, linking microbiota to the pathogenesis of neurodegenerative diseases [13].

Thus, the precise mechanism of dopaminergic neuron loss in PD remains a subject of active research and discussion. Existing hypotheses (α-synuclein toxicity, inflammation, mitochondrial dysfunction, genetic predisposition) describe various critical links in the pathogenesis of neuronal cell degradation. However, each of these research areas highlights the complexity and multifactorial nature of the process, where interactions between different pathophysiological mechanisms create an interconnected network that contributes to disease progression.

Metabolic Plasticity of NVU Brain Cells

The metabolic plasticity of NVU brain cells reflects the ability of various cellular components to adapt their metabolic pathways in response to microenvironmental changes and functional demands. The NVU is a complex multicellular brain structure comprising neurons, astrocytes, cerebrovascular endothelial cells, pericytes, and microglia [14]. 25% of the body's energy expenditure is allocated to the brain. Within NVU cells, there is continuous activation of glycolytic processes (predominant in astrocytes, reactive microglia, and mature oligodendrocytes) as well as oxidative phosphorylation (prevailing in mature neurons, resting microglia, cerebral vascular endothelial cells, and oligodendroglial progenitor cells) [15].

The regulation of energy metabolism and metabolic demands occurs through intercellular interactions. Lactate serves as a crucial energy source for neurons, being synthesized in astrocytes from glucose and transported to neurons via monocarboxylate transporters. After entering neurons, lactate undergoes oxidation in mitochondria providing cellular energy requirements [16]. Mature neurons primarily rely on mitochondrial metabolism to support synaptic activity and can transport mitochondria along dendrites to perisynaptic regions [17]. Activated neurons exhibit increased dependence on lactate of both neuronal and astrocytic origin, which becomes a vital energy substrate during complex cognitive tasks [18]. Glutamate metabolism is tightly regulated through the glutamate-glutamine cycle involving astrocytes. Glutamate and oxaloacetate modulate mitochondrial processes by influencing ROS production [19].

Astrocytes synthesize and utilize fatty acids to support neurons and protect their mitochondria from oxidative stress [20]. Astrocytes possess glutaminolytic enzymes, can synthesize glutamine from glutamate, participate in the glutamate-glutamine cycle essential for neuronal activity [21], and exhibit high pentose phosphate pathway activity to generate NADPH and maintain antioxidant defenses [22]. Furthermore, astrocytes play a key role in regulating local blood circulation by rapidly responding to neuronal demands through the release of vasoactive metabolites [23–25].

During stimulation and polarization, microglia switch from mitochondrial oxidative phosphorylation to glycolysis, associated with lactate-induced histone lactylation and epigenetic changes linked to a pro-inflammatory phenotype [26]. Microglia actively metabolize fatty acids through beta-oxidation, which is crucial for brain plasticity and memory [27]. Under glucose deficiency, microglia utilize glutaminolysis to generate tricarboxylic acid cycle metabolites and energy, maintaining metabolic flexibility for migration and surveillance [28]. Pro-inflammatory factors – interleukin-1 and tumor necrosis factor-α, produced by activated microglia, shift astrocytes into an active phenotype, amplifying inflammatory processes. The close interaction of glial cells within the NVU supports immune functions while maintaining CNS homeostasis [29, 30].

NVU cell metabolism is highly dependent on the local microenvironment and activation states of different cell types, leading to metabolic reprogramming and altered contributions of specific pathways to energy production and biomolecule synthesis, playing a key role in regulating brain plasticity [24]. PD-associated mutations cause mitochondrial dysfunc-

tion and impaired energy metabolism, reducing oxidative phosphorylation efficiency and ATP synthesis. Additionally, these mutations disrupt intercellular interactions, metabolite transport, and the expression and function of relevant transporters, potentially accompanied by vascular changes and other pathophysiological processes. A critical focus is the study of metabolic characteristics in NVU cells derived from iPSCs with *SNCA* gene mutations.

Metabolic features of iPSC-derived neurons with *SNCA* mutations

The *SNCA* gene, first identified as associated with familial PD, encodes α-synuclein protein – a key pathological marker of the disease [31, 32]. Pathogenic *SNCA* variants include point mutations (*A53T*, *A30P*, *E64K*, *H50Q*, *G51D* и *A53E*) and structural variations such as gene duplication and triplication [33]. These mutations or *SNCA* replications induce conformational changes in α-synuclein or increase protein expression, contributing to PD pathogenesis. The association of *A53T* substitution with PD was first identified by M.H. Polymeropoulos et al. [32]. Subsequent studies characterized other substitutions (*A30P*, *E46K*, *G51D*, *A53E*) [34–36] and genotypes with 2 [37, 38], 3 [39], or 4 *SNCA*copies [40]. *SNCA* triplication was first detected in 2003 in an American family with hereditary PD [39]. iPSCs with *SNCA* triplication and differentiated midbrain dopaminergic neurons successfully replicated α-synuclein accumulation phenotypes [41]. Some metabolic alterations in *SNCA*-mutated iPSC-derived brain cells directly contribute to neurodegeneration, while others may represent compensatory mechanisms reflecting cellular adaptation to stress and toxic effects of aberrant protein aggregates.

Morphofunctional Cell Features

In cortical neurons derived from iPSCs with the *SNCA A53T* mutation, significant neurite shortening is observed – their length is 30% less compared to controls, indicating impaired capacity for normal growth and development [42]. These morphological changes reflect disruptions in intracellular transport and cytoskeletal organization, as evidenced by altered gene expression patterns [43]. Dopaminergic neurons derived from iPSCs with heterozygous duplication of exons 2–7 of the *SNCA* gene demonstrate cytoplasmic vacuolization represented by autophagolysosomes of varying density localized in the perinuclear area and processes. Mitochondrial fragments are detected within vacuoles, while axonal swellings contain massive autophagic inclusions that disrupt the parallel arrangement of microtubules [44]. In animals with transplanted iPSC-derived microglia subjected to lipopolysaccharide-induced stimulation, an increased number of amoeboid cells was observed compared to healthy controls [45].

Transcriptomic analysis of dopaminergic neurons with the *SNCA A53T* mutation revealed increased expression of genes responsible for histone modification and chromatin organization, specifically the inhibitor of differentiation *(ID)* family (*ID1–ID4*), which are hypothesized to regulate dopaminergic signaling [43]. In *SNCA* triplication, downregulation of key genes was observed: delta-like homolog 1 (*DLK1*), gamma-aminobutyric acid type B receptor subunit 2 (*GABABR2*), nuclear receptor-related 1 protein (*NURR1*), G protein-coupled inwardly rectifying potassium channels (*GIRK-2*), and tyrosine hydroxylase (*TH*), indicating impaired cellular differentiation [46]. Cortical neurons with the *SNCA A53T* mutation exhibited an increased number of cells with activated caspase 3/7, suggesting enhanced apoptosis [42]. Molecular analysis revealed activation of the ERK1/2 and JNK signaling pathways, which play a central role in regulating cell death [42]. Thus, neurite shortening, cytoplasmic vacuolization with microtubule disorganization, increased caspase-3/7 expression, and ERK1/2-JNK signaling represent direct pathological shifts leading to neuronal dysfunction and activation of apoptotic cascades. The proinflammatory response of microglia further exacerbates neuroinflammation and cellular damage. Autophagolysosome formation serves as a compensatory mechanism for clearing defective organelles and proteins.

Synaptogenesis impairment of is one of the key pathological aspects of PD. Neurons with the *SNCA A53T* mutation exhibit significant alterations in the expression of genes responsible for preand postsynaptic processes. Specifically, dysregulated expression of presynaptic proteins is observed: synaptophysin 3 (SYN3), synaptic vesicle protein 2C (SV2C), rabphilin 3A (RPH3A), and the double C2-like domain-containing beta protein (DOC2B). At the postsynaptic level, reduced expression of SLITRK1, SLITRK2, and SLITRK4 proteins, which regulate dendritic spine morphogenesis and synaptic plasticity, is noted, along with decreased levels of DLG-associated protein 2, GRIN2D, and GRIP2, involved in excitatory synaptic transmission [47]. These findings indicate impairments in synaptogenesis and synapse maturation. Reduced transcription of cadherin family genes (*CDH13* and *CDH15*) suggests defects in intercellular adhesion [47]. A marked decrease in the expression of calcium-binding and calcium-associated proteins (RCN3, HPCA, CCBE1, CACNA2D4, CACNA1D), critical for signal transduction and neurotransmitter release regulation, as well as receptors and ion channels directly involved in synaptic transmission, has been demonstrated. Notably, altered expression of *FABP7* and *ABLIM3* points to issues in axonal guidance [47]. Concurrent downregulation of preand postsynaptic proteins, along with CDH13/15 cadherins, disrupts synaptic morphogenesis and maturity, impairs intercellular adhesion, and compromises proper axonal growth orientation. Reduced GRIN2D expression limits calcium-dependent excitotoxicity but appears insufficient to fully compensate for functional deficits.

Alterations in Protein Homeostasis

Under physiological conditions, α-synuclein is predominantly localized in presynaptic terminals where it regulates the synaptic vesicle cycle by maintaining the reserve pool through interactions with SNARE complex proteins (VAMP2, syntaxin, SNAP-25) and facilitating full neurotransmitter exocytosis. Additionally, in dopaminergic neurons, it modulates tyrosine hydroxylase activity, controlling dopamine synthesis, storage, and metabolism. Recent studies confirm α-synuclein involvement in SNARE-dependent release of postsynaptic endocannabinoids, expanding our understanding of its functions [48].

Neurons differentiated with 3-4 copies of the *SNCA* gene and the *A53T* mutation accumulate higher amounts of α-synuclein [49–51]. Concurrently, reduced expression of the *SNCG*

gene encoding γ-synuclein is observed, potentially reflecting a cellular compensatory mechanism against α-synuclein overabundance. The expression of β-synuclein *SNCB* gene remains stable. Wild-type β-synuclein is known to exert a protective effect by suppressing α-synuclein aggregation [41]. Astrocytes with *SNCA* mutations (*A30P*, *A53T*, duplication, triplication) also demonstrate α-synuclein accumulation. The highest levels of α-synuclein aggregates are observed in astrocytes with *A30P* and *A53T* point mutations and *SNCA* triplication, though their concentrations remain lower than in neurons with triplication [52]. These findings correlate with clinical manifestations: earlier disease onset and greater severity are associated with the *A53T* mutation and *SNCA* triplication, which correspond to increased markers of cell death [39].

Excess α-synuclein in neurons with *SNCA* triplication induces significant endoplasmic reticulum (ER) stress, triggering a cellular response – the unfolded protein response (UPR) to counteract the accumulation of unfolded or misfolded proteins [53,54]. Among the three main stress sensors in the UPR system (PERK, ATF6, and IRE1α), the transcription factor IRE1α demonstrates the highest sensitivity to α-synuclein accumulation. Its activation enhances XBP1 mRNA splicing, generating the active XBP1(S) isoform that translocates to the nucleus to upregulate ER homeostasis genes while simultaneously initiating apoptosis via CHOP and BIM factors, accompanied by reduced levels of the anti-apoptotic protein BCL-2 [53]. However, some studies report insufficient UPR activation during misfolded protein accumulation and ER fragmentation in *SNCA*-triplication neurons, indicating protein quality control system dysfunction [55]. Modeling ER stress in *SNCA*-mutant neurons reveals upregulated expression of genes involved in ubiquitin-proteasomal degradation (*UBB, UBC, RNF187, UCHL1, PSMC4, PSMB1*), heat shock response (*DNAJC4, DNAJB9, HSPA5, PARK7*), and ER stress (*PDIA4, DDIT3*). Concurrently, decreased expression is observed in genes regulating synaptic vesicle transport (*PCLO, RAB3B, RAB3C, ITSN1*) and axonal transport (*KIF2A, KIF1B, KIF3A*), reflecting impaired neuronal communication [43]. *SNCA*-triplication neurons exhibit reduced β-glucocerebrosidase (GCase) activity, with immature enzyme forms accumulating in aggregates, leading to glycosphingolipid deposition and promoting neurodegeneration [55].

Thus, *SNCA* gene mutations (*A30P*, *A53T*, triplication) lead to the accumulation of α-synuclein aggregates, which play a critical role in PD pathogenesis. α-Synuclein fibrils impair presynaptic membrane function by blocking SNARE-dependent exocytosis, resulting in deficient neurotransmitter release and compromised transmembrane transport. These aggregates interfere with clathrin-dependent endocytosis, interact with membrane lipids and cholesterol, and destabilize synaptic membrane structure and function. While the aggregation process is well-documented in literature, the mechanisms underlying α-synuclein dysfunction in *SNCA* mutations and their connection to toxicity remain poorly understood. The *A30P* mutation reduces the protein's ability to associate with lipid vesicles compared to wild-type α-synuclein [56], diminishing synaptic vesicle clustering capacity and adversely affecting neurotransmission [57]. The *A53T* mutation directly accelerates protein nucleation rates, promoting aggregation processes [58, 59]. Elevated α-synuclein levels result from stabilization of mutant forms rather than gene overexpression. *SNCA* triplication drives pathological processes through excessive α-synuclein concentration, though whether this mutation alters individual protein functionality remains unresolved. Pathological changes leading to exocytosis blockade and neurodegeneration arise from combined intracellular and extracellular α-synuclein accumulation, functional alterations, and associated metabolic disturbances. Cells adapt to α-synuclein toxicity by activating the IRE1α-XBP1 unfolded protein response (UPR) pathway, but these protective mechanisms gradually fail, ultimately leading to neuronal death.

Autophagy

In dopaminergic neurons with four copies of *SNCA*, accumulation of the autophagosome marker LC3 is observed [46]. α-Synuclein suppresses autophagy by impairing the fusion of autophagosomes with lysosomes, leading to reduced autolysosome formation [60]. Metabolic disturbances associated with *SNCA* mutations are accompanied by dysfunction in calcium homeostasis regulatory mechanisms [51]. The imbalance between autophagic activity and calcium homeostasis promotes the accumulation of pathological α-synuclein aggregates and increases the susceptibility of dopaminergic neurons to apoptotic death. Altered autophagy activity initially acts as a compensatory mechanism aimed at removing α-synuclein aggregates and damaged organelles. However, prolonged accumulation of autophagic substrates causes autophagosomes to lose their efficiency, transforming into non-functional vacuoles, thereby shifting this process from compensatory to pathological.

Energy Metabolism

In dopaminergic neurons with the *SNCA A53T* mutation and *SNCA* gene triplication, significant metabolic profile alterations are observed, characterized by decreased levels of lactate, N-acetylaspartate, pantothenic acid, and cholesterol, along with increased expression of sirtuin 1 (SIRT1). In response to oxidative stress, neurons carrying this mutation exhibit altered expression profiles of genes associated with glycolysis (*LDHA, ENO1, TPI1, ALDOA*), oxidative phosphorylation (*NDUFA1, COX6A1*), and cholesterol biosynthesis (*SQLE, HMGCS1, MSMO1*) [43]. The metabolic reprogramming, accompanied by reduced levels of lactate, N-acetylaspartate, and cholesterol, as well as suppression of oxidative phosphorylation genes, reflects pathological disruptions in glycolytic flux, mitochondrial functions, and neuronal metabolic activity. Concurrently, elevated SIRT1 levels and induction of glycolytic enzymes LDHA and ENO1 suggest a compensatory shift toward anaerobic ATP production, accompanied by activation of mitophagy and antioxidant pathways.

Neurons with the *SNCA A53T* mutation and *SNCA* triplication exhibit significant mitochondrial dysfunction. Characteristic features include reduced basal respiration and decreased ATP production. These functional changes are accompanied by morphological abnormalities in mitochondria (rounded shape), pronounced fragmentation, and reduced membrane potential, indicating impaired organelle function [49]. Similar impairments were observed in neurons with 4 copies of

the *SNCA* gene, where additional functional reorganization of ATP synthase occurs. The enzyme operates in reverse mode to maintain membrane potential through ATP hydrolysis, accompanied by increased ROS generation, reduced levels of reduced glutathione, and enhanced oxidative stress [51]. Furthermore, increased α-synuclein production due to *SNCA* triplication was shown to cause direct interaction of oligomeric protein forms with mitochondrial ATP synthase complexes. This leads to decreased NADH redox index, exacerbates energy imbalance, and intensifies oxidative stress [61]. In differentiated astrocytes with *SNCA* mutations, cytosolic calcium levels are elevated, with calcium being released at a higher rate in *A30P* and *A53T* mutant lines. *A53T* mutant astrocytes additionally exhibit reduced reserve respiratory capacity, indicating impaired mitochondrial ability to adapt to energy demands [52].

Mitochondrial impairments are a well-documented pathological consequence of *SNCA* gene mutations. Decreased oxygen consumption and ATP production demonstrate that aberrant α-synuclein disrupts efficient oxidative phosphorylation, leading to energy supply deficits. Fragmented depolarized mitochondria are prone to releasing ROS and pro-apoptotic molecules, threatening cell survival. To prevent loss of mitochondrial membrane potential, cells resort to ATP hydrolysis and increased cytosolic calcium levels. Activation of mitophagy serves as a crucial compensatory mechanism that prevents accumulation of damaged mitochondria and suppresses ROS production.

Oxidative Stress

Studies have shown that *SNCA* triplication causes increased α-synuclein mRNA levels in differentiated neurons, overexpression of oxidative stress markers, and heightened susceptibility to H_2O_2-induced oxidative damage [62]. These changes indicate reduced cellular capacity to manage excessive ROS production, leading to impaired mitochondrial function and energy metabolism. Additionally, there is a significant increase in the expression of key genes involved in the oxidative stress response, such as *HMOX2* (heme oxygenase 2). Concurrent activation occurs in genes encoding heat shock proteins (*DNAJA1, HSPB1*) and components of the ubiquitin-proteasome protein degradation system (*UCHL1*) [46, 62], suggesting proteostasis disruption due to increased burden on the degradation system for damaged or misfolded proteins. Differentiated microglia with the *A53T* mutation exhibit elevated oxidative stress levels, increased expression of the *SLC11A1* gene (associated with ROS protection in *in vivo* animal transplantation) [45]. ROS overproduction and heightened sensitivity to redox agents indicate pathological vulnerability of brain cells with *SNCA* gene mutations. The increased expression of these genes likely represents a compensatory mechanism to enhance protective responses under oxidative stress conditions.

The **table** summarizes metabolic alterations observed in human brain cells differentiated from iPSCs carrying mutations associated with inherited PD. These data reveal both shared and distinct metabolic features in *SNCA* mutations, providing insights into pathophysiological mechanisms underlying inherited PD.

Conclusion

There is no consensus regarding the precise understanding of the mechanisms underlying PD. Despite existing hypotheses about PD pathogenesis, including genetic factors, accumulation of aberrant α-synuclein, exposure to mitochondrial toxins, and neuroinflammation, the true cause of PD remains unknown. It is hypothesized that PD etiology is multifactorial, influenced by genetic background variability, environmental conditions, lifestyle factors, and individual manifestations, resulting in each patient having a unique disease form.

By analyzing numerous studies, we identified that mutations in the *SNCA* gene induce complex metabolic alterations in brain cells (neurons, astrocytes, microglia, etc.) differentiated from iPSCs. Research has demonstrated increased secretion and aggregation of pathological α-synuclein, activation of ER stress, heat shock protein response and UPR, oxidative stress, mitochondrial and lysosomal enzyme dysfunction, and disruptions in lipid, protein, and carbohydrate metabolism. These metabolic defects are accompanied by impaired differentiation, reduced neurite outgrowth, and activation of apoptotic signaling pathways. The findings underscore the pivotal role of mitochondrial dysfunction linked to altered mitochondrial gene activity, energy homeostasis disruptions, and impaired intercellular transport in the disease pathogenesis. Despite the abundance of molecular patterns associated with PD, our understanding of its etiology remains merely the tip of the iceberg. Further research should focus on developing personalized *in vitro* cellular models, including iPSC-derived organoids, and implementing omics technologies such as exposomics to identify diverse etiological components and potential lifelong epigenetic changes. From the perspective of clinical practice and therapeutic development, refining personalized approaches, discovering targeted molecular pathways, and identifying novel biomarkers for early diagnosis are critical priorities. Additionally, iPSC-based models provide a platform for high-throughput screening and preclinical testing of new pharmacological agents, enhancing predictive value while reducing costs and timelines for drug development. Thus, despite substantial progress, continued fundamental and clinical research is essential to address these challenges and successfully implement iPSC-driven personalized strategies that could significantly improve early diagnosis, treatment efficacy, and patients' quality of life.

Metabolic features of neurons and astrocytes differentiated from iPSCs with *SNCA* mutations

Cell type	Mutation	Features	Manifestations	Sources
Dopaminergic neurons	*SNCA* (A53T)	· short neurites · synaptic defects · ↑ phosphorylated α-synuclein · ↑ sirtuin 1 · ↓ lactate · ↓ N-acetylaspartic acid · ↓ pantothenic acid · ↓ cholesterol	· mitochondrial dysfunction · dysfunction of protein quality control systems (UPR/ autophagy) · increased basal ROS production · oxidative stress · impaired calcium homeostasis · ↑ α-synuclein	[42, 43, 47, 49, 50, 63]
	SNCA (triplication)	· impaired neuronal differentiation and maturation · ↑ autophagy · ↓ β-glucocerebrosidase activity		[41, 46, 49, 50, 53, 55, 62, 63]
Cortical neurons	*SNCA* (A53T)	· impaired protein translation · ↑ nicastrin · ↑ nitrosative stress	· mitochondrial dysfunction; · ↑ α-synuclein	[53, 54, 64, 65]
	SNCA (triplication)	· reductive stress · abnormal NADH levels · ER stress · ↓ membrane potential		[53, 61]
Astrocytes	*SNCA* (A53T)	· ↑ number of pyknotic nuclei · ↓ rate of extracellular oxidation · ↓ extramitochondrial oxygen consumption	· mitochondrial dysfunction; · ↑ α-synuclein · ↑ cytosolic calcium	[52]
	SNCA (A30P)	· ↓ extramitochondrial oxygen consumption		[52]
	SNCA (triplication)	· ↑ number of pyknotic nuclei · ↓ rate of extracellular oxidation		[52]

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Information about the authors

Nataliya A. Kolotyeva — Dr. Sci. (Med.), Associate Professor, Head, Laboratory of experimental and translational neurochemistry, Brain Institute, Russian Center of Neurology and Neurosciences, Moscow, Russia,
https://orcid.org/0000-0002-7853-6222
Regina S. Mudarisova — postgraduate student, laboratory assistant, Laboratory of experimental and translational neurochemistry, Brain Institute, Russian Center of Neurology and Neurosciences, Moscow, Russia,
https://orcid.org/0009-0008-8522-309X
Natalia A. Rozanova — postgraduate student, researcher, Laboratory of experimental and translational neurochemistry, Brain Institute, Russian Center of Neurology and Neurosciences, Moscow, Russia,
https://orcid.org/0000-0001-9619-4679
Arseniy K. Berdnikov — postgraduate student, laboratory assistant, Laboratory of experimental and translational neurochemistry, Brain Institute, Russian Center of Neurology and Neurosciences, Moscow, Russia,
https://orcid.org/0009-0007-4195-2533
Svetlana V. Novikova — researcher, Laboratory of experimental and translational neurochemistry, Brain Institute, Russian Center of Neurology and Neurosciences, Moscow, Russia,
https://orcid.org/0009-0008-3905-1928
Yulia K. Komleva — Dr. Sci. (Med.), Associate Professor, senior researcher, Laboratory of experimental and translational neurochemistry, Brain Institute, Russian Center of Neurology and Neurosciences, Moscow, Russia,
https://orcid.org/0000-0001-5742-8356

Authors' contribution: *Kolotyeva N.A.* — concept, manuscript editing, approval of the final version of the article for publication; *Mudarisova R.S., Berdnikov A.K.* — literature search and analysis, text writing, figure and table design; *Rozanova N.A., Novikova S.V.* — literature search and analysis, text writing; *Komleva Yu.K.*– concept, manuscript editing.

Информация об авторах

Колотьева Наталия Александровна — д-р мед. наук, доцент, зав. лаб. экспериментальной и трансляционной нейрохимии Института мозга Российского центра неврологии и нейронаук, Москва, Россия,
https://orcid.org/0000-0002-7853-6222
Мударисова Регина Салаватовна — аспирант, лаборант-исследователь лаб. экспериментальной и трансляционной нейрохимии Института мозга Российского центра неврологии и нейронаук, Москва, Россия,
https://orcid.org/0009-0008-8522-309X
Розанова Наталья Александровна — аспирант, н. с. лаб. нейробиологии и тканевой инженерии Института мозга Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0000-0001-9619-4679
Бердников Арсений Константинович — аспирант, лаборант-исследователь лаб. нейробиологии и тканевой инженерии Института мозга Российского центра неврологии и нейронаук, Москва, Россия,
https://orcid.org/0009-0007-4195-2533
Новикова Светлана Викторовна — аспирант, н. с. лаб. нейробиологии и тканевой инженерии Института мозга Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0009-0008-3905-1928
Комлева Юлия Константиновна — д-р мед. наук, доцент, с. н. с. лаб. нейробиологии и тканевой инженерии Института мозга Российского центра неврологии и нейронаук, Москва, Россия,
https://orcid.org/0000-0001-5742-8356

Вклад авторов: *Колотьева Н.А.* — концепция, редактирование рукописи, утверждение окончательного варианта статьи для публикации; *Мударисова Р.С., Бердников А.К.* — поиск и анализ литературы, написание — поиск и анализ литературы, написание текста; *Комлева Ю.К.* — концепция, редактирование рукописи.

Current Approaches to Multiple Sclerosis Management in Pregnancy

Valeriya A. Malko, Ekaterina A. Sadovnichuk, Gennady N. Bisaga

V.A. Almazov National Medical Research Centre, Saint Petersburg, Russia

Abstract

This article reviews literature data on the impact of multiple sclerosis (MS) on fertility and pregnancy outcomes, the specifics of using diseasemodifying therapies (DMTs), and breastfeeding practices. The results demonstrate that fertility rates in women with MS do not differ from the general population, and the frequency of pregnancy complications, including stillbirths, congenital malformations, and spontaneous abortions, does not exceed population-level rates. A reduction in MS activity is observed during the third trimester of pregnancy; however, the risk of relapses increases by 50% within the first three months postpartum, necessitating timely resumption of therapy. Pregnancy management in women with MS should involve interdisciplinary collaboration between neurologists and obstetricians and gynecologists, personalized therapy adjustments, and patient education about safe treatment strategies. Certain DMTs can be safely used during pregnancy and lactation, though careful benefit-risk assessment remains crucial. Women with MS can successfully plan and carry pregnancies to term without significant untoward effects on outcomes. Developing personalized management strategies for these patients will help minimize risks and improve their quality of life.

Keywords: *multiple sclerosis; pregnancy; fertility; breastfeeding; DMTs*

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For correspondence: 2 Akkuratov St., Saint Petersburg, Russia, 197341. V.A. Almazov National Medical Research Centre. E-mail: malko_va@almazovcentre.ru. Valeriya A. Malko

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Современные подходы к ведению рассеянного склероза во время беременности

В.А. Малько, Е.А. Садовничук, Г.Н. Бисага

Национальный медицинский исследовательский центр имени В.А. Алмазова, Санкт-Петербург, Россия

Аннотация

В статье представлен обзор данных литературы о влиянии рассеянного склероза (РС) на фертильность и течение беременности, об особенностях приёма препаратов, изменяющих течение РС (ПИТРС), и грудного вскармливания. Результаты демонстрируют, что у женщин с РС показатели фертильности не отличаются от общей популяции, а частота осложнений беременности, включая мертворождения, врождённые пороки и спонтанные аборты, не превышает популяционные показатели. Установлено снижение активности РС в III триместре беременности, однако в первые 3 мес после родов риск обострений возрастает на 50%, что требует своевременного возобновления терапии. Ведение беременности у женщин с РС должно включать междисциплинарное сотрудничество невролога и акушера-гинеколога, индивидуальную корректировку терапии и повышение осведомлённости пациенток о безопасных тактиках лечения. Некоторые ПИТРС могут безопасно использоваться в период беременности и лактации, при этом важно учитывать соотношение риска и пользы. Женщины с РС могут успешно планировать и вынашивать беременность без значимого влияния на её исходы. Разработка индивидуальных стратегий ведения таких пациенток позволит минимизировать риски и повысить качество их жизни.

Ключевые слова: *рассеянный склероз; беременность; фертильность; грудное вскармливание; препараты, изменяющие течение рассеянного склероза*

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Адрес для корреспонденции: 197341, Россия, Санкт-Петербург, ул. Аккуратова, д. 2. НМИЦ им. В.А. Алмазова. E-mail: malko_va@almazovcentre.ru. Малько В.А.

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Introduction

The global prevalence of multiple sclerosis (MS) is approximately 2.3 million people [1]. In Russia, MS has an incidence rate of 15–55 per 100,000 population. The disease most commonly manifests between the ages of 20 and 50 years. MS is 2.5–3.0 times more common in women than in men, meaning the majority of MS patients are women of reproductive age. Consequently, studying MS effects on fertility, pregnancy, and breastfeeding has become a critical issue [1–4].

Fertility rates among women with MS are lower than in healthy women, likely due not to direct disease effects on the reproductive system, but rather to patients' psychoemotional and physical status, as well as fears surrounding pregnancy and childbirth in the context of chronic illness [5]. Women with MS fear pregnancy both due to risks of disease exacerbations and potential therapy-related fetal effects, highlighting the need for improved patient education about safe pregnancy planning and management strategies [6]. Current approaches to the management of pregnant MS patients requires collaboration between neurologists and gynecologists, with many established concepts having evolved over recent decades. This shift stems from advances in understanding MS pathogenesis, numerous studies on pregnancy outcomes in MS patients, and expanded therapeutic options with disease-modifying therapies (DMTs) [7].

Proper management of women with MS requires understanding the disease's potential impact on preconception counseling, pregnancy, and the postpartum period. Studies confirm no negative effects of multiple sclerosis on fertility, pregnancy, or breastfeeding when proper preparation and pregnancy management are implemented [3, 8]. Compared to the healthy population, MS does not increase the risk of stillbirth, congenital malformations, low Apgar scores, spontaneous abortions, or ectopic pregnancy [9–11]. MS is not a risk factor for complications such as preeclampsia, postpartum hemorrhage, or chorioamnionitis [9, 12]. Additionally, MS does not affect anti-Müllerian hormone levels, follicle-stimulating hormone levels, or ovarian size, although estrogen levels and antral follicle counts are slightly lower, while luteinizing hormone levels are higher compared to the healthy population [6].

Effects of Pregnancy, Delivery, and Breastfeeding on MS

Pregnancy serves as a protective factor against relapses in women with MS: the annualized relapse rate and disease activity gradually decrease by the third trimester, potentially due to elevated hormone levels (17-beta-estradiol, progesterone, prolactin, testosterone) that stimulate anti-inflammatory mediators (interleukin-10) while suppressing pro-inflammatory cytokines (interleukin-6 and -17). This effect may also involve placentaand fetus-derived cytokines that reduce type 1 T-cell immune responses [8, 12–15]. During pregnancy, several myelin repair-promoting factors are produced: the maternal circulating preimplantation factor enhances remyelination, while allopregnanolone (a progesterone metabolite) potentiates gamma-aminobutyric acid (GABA) signaling through oligodendrocyte GABA receptors, thereby stimulating myelin regeneration [14]. Pregnancy does not influence long-term disability accumulation outcomes in MS [6, 14]. However, physiological immunosuppression during gestation may not fully compensate for the withdrawal of DMTs discontinued to mitigate fetal risks, potentially leading to increased MS activity during pregnancy after DMT cessation [13].

MS activity typically increases significantly during the first 3 months postpartum and then gradually decreases over the following year [2, 4, 8, 14, 16]. Risk factors for postpartum relapses include high pre-pregnancy disease activity, relapses during pregnancy, discontinuation of second-line DMTs before or during pregnancy, and delayed resumption of DMTs after delivery [17, 18]. Conversely, early reintroduction of DMTs reduces post-pregnancy relapse risks [13, 16].

Results from retrospective MRI studies during pregnancy and postpartum demonstrated an increased number of T1and T2-weighted lesions during pregnancy without increased gray matter atrophy [14]. Data on gadolinium-enhancing lesions were conflicting: some studies showed no pregnancy-related changes in contrast-enhancing lesions, while others reported increased gadolinium-accumulating lesions postpartum [6, 14]. Studies examining serum neurofilament light chain levels as a biomarker of disease activity and neurodegeneration in MS revealed temporary elevation in untreated postpartum patients. In contrast, patients receiving natalizumab (before and during pregnancy) showed lower neurofilament levels compared to untreated individuals [6].

Data on potential protective role of breastfeeding (BF) in preventing disease exacerbations during the postpartum period were contradictory: while several studies described no effect of BF on MS course, others reported reduced risk and frequency of relapses during BF [4–6, 8, 16–19].

Pregnancy Planning and Management in Patients with MS

Pregnancy planning is a crucial stage of collaboration between the patient, neurologist, and gynecologist, during which healthcare professionals must inform the patient that

pregnancy is not contraindicated in MS provided proper preparation and management are ensured. Therefore, even at the stage of selecting MS therapy, it is essential to clarify with the patient: whether she plans pregnancy (and if so, how long after therapy initiation), her obstetric history, and whether she intends to breastfeed [12] (Table 1).

For women with MS not planning pregnancy, it is important to use effective contraception to prevent unintended pregnancy [6, 14]. Reversible long-acting contraceptive methods (intrauterine device), irreversible permanent methods (tubal ligation), and barrier methods is acceptable, safe, and effective in MS [5, 6]. Long-acting and permanent contraceptive methods may be preferred for patients receiving therapy with proven teratogenic effects [5]. Opinions regarding the use of combined oral contraceptives (COCs) in patients with MS vary [19]. On one hand, earlier studies suggest that COCs may negatively impact the course of multiple sclerosis due to alterations in women's immune status associated with hormonal stimulation; they may also increase the risk of MS by 40% and contribute to a more severe disease course [14, 15]. On the other hand, several authors have demonstrated no association between COCs and the course of multiple sclerosis, even suggesting a possible neuroprotective effect related to changes in hormonal activity during COC use [15, 19]. COCs do not increase the risk of conversion from clinically isolated syndrome to MS [5]. According to the meta-analysis by M. Ghajarzadeh *et al.*, COCs have neither a positive nor negative effect on the course of multiple sclerosis [15]. Progestogen-only contraceptives may have a possible protective effect [14, 15]. Some studies also report that patients taking COCs had lower EDSS scores and reduced annualized relapse rates [2]. To date, there is no definitive understanding of the impact of emergency hormonal contraception on MS course, which underscores the importance of selecting an appropriate long-term contraceptive method [6]. Contraceptive choice should be personalized, considering factors such as drug compatibility, potential contraindications, and reversibility [6]. Interpregnancy contraception reduces the risks of induced abortion, which may trigger MS exacerbations and disease progression due to hormonal stress [6].

When counseling women with MS planning pregnancy, it is crucial to consider their concerns about potential disease exacerbations, MS progression, and challenges of childcare management given their condition [6]. For women planning pregnancy, achieving sustained MS remission prior to conception, adjusting DMTs, and optimizing vitamin/mineral supplementation (e.g., folic acid, vitamin D) are particularly important during pregravid preparation [8, 12]. According to R. Alroughani et al., women who received DMTs for at least two years prior to pregnancy exhibited lower risks of relapses both during gestation and postpartum [20]. Maintaining remission for one year before conception is associated with absence of postpartum MS exacerbations [6]. During pregnancy planning, clinicians should review all medications used for MS symptom management or comorbid conditions (e.g., depression, pain syndrome, anxiety, etc.), as these may impact both hormonal contraceptive efficacy and fetal health [5, 12].

Some medications (particularly cyclophosphamide) used for MS therapy may reduce ovarian reserve and affect

Table 1. Algorithm of managing pregnant women with MS (based on [17])

Before pregnancy	After pregnancy	Postpartum
1. Regular consultations (at least annually) should be conducted to discuss: What type of contraception should be used? Whether the woman is physically capable of pregnancy and how treatment should be adjusted? If pregnancy is not achievable, should assisted reproductive technologies be considered? 2. When preparing for pregnancy, vitamin D and folic acid should be taken in accordance with general recommendations	1. Women with unplanned pregnancies should adjust their DMT regimen and undergo ultrasound examination. Interferon beta and glatiramer acetate may be continued, while other medications should be discontinued as soon as possible: natalizumab may be used until 34 weeks of gestation in cases of high relapse risk. Patients on teriflunomide require an accelerated elimination protocol until plasma drug concentration falls below 0.02 g/L. 2. Maintaining a healthy diet with vitamin D and folic acid supplementation is recommended. 3. Most inactivated vaccines can be administered during pregnancy, whereas live vaccines are generally contraindicated. 4. Relapses may be managed with high-dose methylprednisolone (not dexamethasone) or plasmapheresis. Methylprednisolone can be used starting from the second trimester, and in the first trimester only if maternal benefits outweigh fetal risks of congenital anomalies. 5. Close monitoring is required for urinary tract infections, thromboembolic events, hypothyroxinemia, perinatal depression, and other complications. 6. Multiple sclerosis does not contraindicate any specific delivery method or anesthesia type. The choice should be guided primarily by obstetric indications. 7. MRI necessity should be evaluated case-by-case. A standard 1.5 Tesla protocol is recommended, while gadolinium-based contrast agents should be avoided	1. The woman's wish to breastfeed should be considered. Interferon beta and glatiramer acetate may be continued during BF, while natalizumab and ocrelizumab may be used in select cases. Other DMTs are not recommended. 2. Women at high risk of postpartum relapses should be advised to delay or avoid BF and promptly resume high-efficacy DMTs. 3. The likelihood of relapses increases during the postpartum period. Methylprednisolone and plasma exchange may be used to manage relapses during BF. Breastfeeding may be resumed 4–12 hours after intravenous methylprednisolone administration at the treating physician's discretion. Pharmacological relapse prophylaxis is not recommended. 4. There are no restrictions on MRI use during the postpartum period. Brain MRI is recommended within 2–3 months after delivery, while gadolinium-based contrast agents are not advised during BF

female fertility [14]. Therefore, patients with MS who are not planning pregnancy in the near future may be advised to undergo oocyte cryopreservation or partner sperm preservation before initiating treatment with fertility-affecting agents [8]. The use of fertility-affecting DMTs and the average age of MS onset may necessitate assisted reproductive technologies (ART) [8]. The need for hormonal stimulation of oocyte maturation during ART may lead to increased relapse rates and numbers of active MRI lesions [6, 8, 21]. Studies have shown that the annualized relapse rate may increase following ART using gonadotropin-releasing hormone (GnRH) agonists, which activate autoreactive $CD4^+$ T cells, lead to elevated estrogen levels, and consequently increase proinflammatory factors [5, 14]. However, there is no definitive consensus regarding the association between MS relapse risk and ART. Current evidence suggests that ART protocols using GnRH antagonists may be safer in terms of MS course [6, 19]. When ART is required, it is recommended to achieve stable clinical and radiological remission for at least 12 months before initiating ART and to continue DMTs during ART to reduce relapse risk. When planning pregnancy using ART, patients should be informed about the potential adverse effects of hormonal stimulation [14].

The method of delivery for patients with MS is determined by general obstetric indications; however, obstetricians and gynecologists may unjustifiably opt for cesarean delivery due to excessive caution [13, 14, 22]. Cesarean delivery may be indicated by neurological symptoms that increase the risk of secondary labor dystocia: severe lower paraparesis, weakness of the abdominal muscles, or pelvic organ dysfunction [22–25]. Epidural anesthesia during labor has been shown to have no adverse effects on the course of MS: there is no evidence of increased relapse rates or impact on patient disability [6, 12, 13]. Patients with MS may experience sensory deficits that prevent them from recognizing the onset of labor; therefore, they should be educated about alternative signs indicating the initiation of labor [14].

MRI in Pregnancy

In pregnant patients with MS, routine MRI is not recommended; however, if vital indications are present, the study may be performed at any gestational age. MRI scanners with a magnetic field strength of less than 3 Tesla are permitted [5, 11, 14, 25]. Gadolinium-based contrast agents are not recommended due to their ability to cross the placental barrier, accumulate in the fetal brain, and cause intrauterine fetal demise or developmental abnormalities; their use should therefore be restricted to cases where benefits clearly outweigh risks [5, 12, 14, 25].

Medications Overview and DMT Use Strategy During Pregnancy

Difficulties in prescribing and continuing MS therapy for pregnant women arise from the need to discontinue certain medications due to their teratogenicity [5, 13]. Discontinuation of DMTs increases the risk of MS activity both during pregnancy and postpartum [3, 13, 14]. Currently, the number of patients remaining on DMT therapy during pregnancy decreases by half in the first trimester and sixfold in the second and third trimesters compared to the pre-pregnancy period [26]. Recent studies indicate a significant shift in the perception of DMT safety: continuation of DMT therapy and early resumption of DMTs postpartum are now recommended for all MS patients, as this promotes disease stabilization and reduces the risk of relapses during pregnancy and the postpartum period [4, 5, 7, 16].

According to a retrospective analysis by M. Moccia *et al.* describing data from 2018–2020 in a population of Italian women with MS, continued use of DMTs during pregnancy (glatiramer acetate, interferon beta, and natalizumab) was associated with lower infant birth weight. However, DMT therapy did not affect pregnancy duration, cesarean section rates, congenital malformations, or infant head circumference and length [3]. These data were obtained in comparison with a group that discontinued DMTs after conception. The fetal effects of these agents may be related to their ability to cross the placental barrier: small molecules, predominantly administered orally, penetrate the barrier more easily, unlike large molecules, which are retained due to their size [5].

Interferon Beta and Glatiramer Acetate

For women with MS at high risk of relapses who are planning pregnancy, first-line DMTs such as interferon beta and glatiramer acetate are considered safe due to their large molecular size and limited ability to cross the hematoplacental barrier [14]. Interferon beta and glatiramer acetate were among the first DMTs shown to reduce relapse rates and delay disability progression in MS. According to the study by M. Moccia *et al.*, no cases of congenital malformations were reported in children born to patients who received glatiramer acetate and interferon beta during pregnancy [3]. Interferon beta is not associated with adverse pregnancy outcomes regardless of the timing of administration [7, 27]. However, interferon beta and glatiramer acetate may sometimes be insufficient for disease control, necessitating a switch to second-line DMTs whose safety during pregnancy remains uncertain [28].

Natalizumab

Natalizumab is a monoclonal antibody that can reduce the number and size of active brain lesions while decreasing the frequency of relapses [27]. Although natalizumab can cross the placental barrier, its use during pregnancy is allowed if the potential therapeutic benefits outweigh the risks [12, 14]. Prolonged natalizumab therapy prior to pregnancy significantly improves MS control and reduces the likelihood of relapses during pregnancy and postpartum [28]. Patients who discontinue natalizumab after conception exhibit a higher risk of MS exacerbations and disability progression both during pregnancy and in the postpartum period [4, 5, 12, 29]. Therefore, natalizumab should not be discontinued before pregnancy or during the first trimester, given the elevated risk of severe relapses upon withdrawal (with a ~10% risk of significant disability); instead, therapy should be continued at extended intervals (6–8 weeks) until the third trimester (30–34 weeks gestation), followed by early postpartum resumption to minimize relapse risk [4–6, 12, 30]. Secondand third-trimester natalizumab use is associated with lower

neonatal birth weight and fetal anemia/thrombocytopenia, but does not increase risks of major congenital malformations or spontaneous abortion [3, 5, 12, 28, 30].

Fingolimod

Fingolimod is the first oral agent approved for relapsing MS, effectively reducing relapse rates [27]. Animal studies have demonstrated that fingolimod can cause fetal death and significant congenital anomalies [27]. In a study by M. Moccia *et al.*, 9.1% of women exposed to fingolimod during pregnancy gave birth to children with birth defects [3]. Effective contraception is essential during fingolimod treatment; fingolimod must be discontinued at least 2 months before planned pregnancy, though this carries risks of increased MS exacerbations after discontinuation and severe disability (6%) [4, 5, 12, 27]. The association between fingolimod withdrawal and elevated relapse risk necessitates pregnancy planning with potential transition to alternative fetal-safe therapies capable of controlling MS: first-line DMTs or natalizumab may serve as a therapeutic bridge during fingolimod discontinuation and until conception [31–33]. As fingolimod belongs to agents with a higher risk of withdrawal syndrome, early resumption of therapy during the postpartum period is required.

Siponimod

There is insufficient research on the safety and outcomes of siponimod use during pregnancy [5]. Siponimod is contraindicated during pregnancy and must be discontinued at least 10 days prior to conception [4–6, 8].

Dimethyl fumarate

Data on dimethyl fumarate use during pregnancy are limited, with potential reproductive toxicity in animal studies. Discontinuation is recommended upon pregnancy confirmation, and no washout period is required [6–8, 14, 27]. Use during pregnancy is only permissible if benefits outweigh risks.

Teriflunomide

Teriflunomide has proven teratogenic effects, increasing spontaneous abortion risk by 21–22% [5, 6, 12, 27]. It is contraindicated during pregnancy and requires a washout period until plasma concentrations fall below 0.02 mg/L before conception [4, 7, 12, 27]. Patients must be advised to use contraception during the washout period to prevent unintended pregnancy [12]. Teriflunomide is detectable in semen, necessitating contraceptive measures for males during treatment and washout. Additionally, men should be informed about potential fertility reduction during therapy [34].

Alemtuzumab

The fetal risks associated with alemtuzumab continue to be studied, but it cannot be ruled out that alemtuzumab use later than 4 months before pregnancy may increase the risk of spontaneous abortion and neonatal thyrotoxicosis due to transplacental transfer of thyroid autoantibodies [5, 12, 25, 27, 35]. Studies indicate that the most common pregnancy outcome following alemtuzumab exposure is an uncomplicated pregnancy; however, there is no conclusive evidence regarding the drug's safety [3, 7, 14, 36]. In women with MS receiving alemtuzumab, no increased risk of hypertension, eclampsia, preeclampsia, or postpartum hemorrhage was observed compared to healthy women, though elevated risks of autoimmune thyroid disorders and infectious diseases were noted [14, 27, 35]. Thyroid function should be monitored during treatment and when planning pregnancy. According to prescribing guidelines, the agent must be discontinued at least 4 months prior to conception [3, 4, 6, 14, 27].

Cladribine

The safety of cladribine during pregnancy remains debated: some studies show most infants exposed to cladribine during gestation are born without severe congenital malformations, though animal studies suggest potential reproductive toxicity [3, 5, 6, 14, 37]. Cladribine should be discontinued 6–12 months before planned pregnancy [3–5, 8, 25].

Mitoxantrone

Mitoxantrone is teratogenic and contraindicated for use during pregnancy. Prior to initiating therapy, healthcare providers must confirm the patient is not pregnant, has no pregnancy plans, and is using effective contraception. Discontinuation of mitoxantrone is recommended at least 4–6 months prior to pregnancy [7, 25, 27, 38].

Anti-CD20 Monoclonal Antibodies

The safety of ocrelizumab during pregnancy is under discussion. Use of the agent during pregnancy may lead to toxic effects on the reproductive system [14, 27, 35]. Ocrelizumab should be discontinued 6–12 months before conception [4–6, 12, 35, 39].

Rituximab during pregnancy poses potential risks to the fetus, including preterm birth and congenital malformations [27, 35]. Rituximab must be discontinued 6–12 months prior to pregnancy [35].

Rituximab and ocrelizumab during pregnancy may cause fetal B-cell depletion with gradual recovery over 6 months [5, 12]. This should be considered when administering live vaccines to newborns: vaccination timing should be individualized based on B-cell levels [5].

Limited studies of ofatumumab have not demonstrated fetal toxicity; however, it can cross the transplacental barrier and reduce fetal B-cell counts [5, 35]. Ofatumumab is contraindicated during pregnancy; due to limited safety data, it should be discontinued 6 months before pregnancy [5, 8, 12, 27, 35].

$CD20^+$ B-cell-targeting agents (ocrelizumab, rituximab, and ofatumumab) may serve as preferred options for managing patients in the postpartum period due to their efficacy and safety profile during high relapse-risk phases [6]. They may

also be used as bridging therapy shortly before or immediately after delivery for patients declining natalizumab or fingolimod based on individual indications, to reduce relapse risks [5, 12, 37].

Exacerbation Treatment

Exacerbations of MS during pregnancy should be treated with short courses of methylprednisolone, as unlike dexamethasone, it is metabolized in the maternal body before crossing the placental barrier [14, 28]. Dexamethasone may be associated with lower birth weight and length [5, 14]. In cases of inadequate response to glucocorticosteroids, plasmapheresis is recommended [5, 14, 3].

Therapy During Breastfeeding

An important factor in selecting MS therapy during the postpartum period is the woman's wish to breastfeed. All DMTs, except for interferon beta, are not considered absolutely safe for the child during breastfeeding [4, 8, 12, 14]. This factor raises the question of discontinuing breastfeeding if early resumption of other MS therapies is required. Although interferon beta can penetrate breast milk in small concentrations, no proven association with adverse effects on the child's growth and development has been established [27].

Glatiramer acetate may be used during breastfeeding, but its necessity should be evaluated based on maternal benefit and the agent's ability to pass into breast milk in small concentrations, despite the lack of data on negative effects on the child [4, 8, 12, 27].

Natalizumab is detected in breast milk in small concentrations, with no observed long-term health consequences for the child [12, 27]. However, the European Medicines Agency recommends avoiding natalizumab during breastfeeding [8, 12]. The decision to use natalizumab during BF should be made based on individual indications with a benefit-risk assessment [8, 14].

Breastfeeding can be resumed one week after the last dose of cladribine [8].

Alemtuzumab therapy requires discontinuation of BF during the treatment course and for 4 months after the last administration [8, 14].

Recent evidence suggests that $CD20^+$ cell-targeting drugs may be safe during BF with regular pediatric monitoring [8]. While rituximab demonstrates potential toxicity during BF, no adverse effects have been reported with ocrelizumab [27]. After ocrelizumab administration during ongoing BF, a 4-hour pause before the next feeding is recommended [8].

Mitoxantrone, fingolimod, siponimod, dimethyl fumarate, and teriflunomide are contraindicated during BF due to potential infant toxicity [8, 14, 27].

Prophylactic glucocorticosteroid treatment for postpartum relapses is not recommended [14]. Methylprednisolone is the option of choice for acute relapse management, with minimal breast milk concentration [12, 14]. The prescribing information advises against methylprednisolone use during BF due to milk penetration, though plasma concentrations decrease to undetectable levels within 18 hours (extremely low levels within 12 hours). Research indicates methylprednisolone concentrations in breast milk reach safe levels within 2–4 hours post-administration, allowing clinical discretion in its use [5, 12, 25]. Plasmapheresis may be considered for breastfeeding women with severe methylprednisolone-resistant relapses [25]. Summary of DMT use in MS patients is presented in Table 2.

Conclusion

Management of pregnancy in multiple sclerosis requires a multidisciplinary team approach. It is crucial to evaluate the impact of current therapy on pregnancy and breastfeeding, the need for treatment modification, risks to the mother and fetus, and select appropriate contraception if pregnancy postponement is necessary. Safe contraception should also be selected for patients wishing to avoid pregnancy. Unintended pregnancy and abortion may trigger MS exacerbations. COCs may be used in MS patients, but their safety remains controversial.

MS does not reduce fertility and is not a contraindication to pregnancy or childbirth, but requires careful planning and monitoring. ART may increase relapse risk, necessitating achievement of stable remission prior to ART and use of GnRH antagonist protocols from the perspective of MS exacerbation risk management.

DMT selection depends on both MS type and patient's reproductive plans. While not all therapies are fetal-safe, treatment discontinuation carries risks of relapses and disability progression. The only agents with proven safety during pregnancy are interferon beta and glatiramer acetate. Other agents require individual risk-benefit assessment. When discontinuing therapy, washout periods and required contraceptive coverage must be considered.

Postpartum MS exacerbation risk increases, necessitating prompt DMT resumption with consideration of BF status. Interferon beta and glatiramer acetate are considered safe during BF, while other agents require dose adjustment or BF discontinuation. Postpartum treatment selection should account for maternal breastfeeding preferences and adjust therapy accordingly.

Table 2. Use of disease-modifying therapies for multiple sclerosis before pregnancy, during pregnancy, and during lactation

Drug Product	Contraception before pregnancy	Use during pregnancy	Use during lactation
		Interferon beta	
Interferon beta-1a (Rebif, Teberif) (GRLS)	Not required	Use may be considered following risk assessment by the treating physician Duration of use in the first trimester is undetermined; experience with use in the second and third trimesters is very limited No increased risk of congenital malformations prior to conception and/or during the first trimester of pregnancy	May be used. The amount of drug excreted into breast milk is negligible; no adverse effects on infants are anticipated
Interferon beta-1a (Plegridy) (GRLS)	No information in the label	Available data are insufficient to adequately assess the risk of spontaneous abortion in pregnant women using drugs of the same class; however, they do not indicate an increased risk. Use of the drug may be considered by the treating physician based on clinical necessity	Available data suggest that the amount of drug excreted into breast milk is negligible. No adverse effects on the newborn/breastfed infant are anticipated. Use during breastfeeding is allowed
Interferon beta-1a (Genfaxon, CinnoVex) (GRLS)	Women of reproductive potential should use effective contraceptive methods	Contraindicated	Data on drug excretion into breast milk are unavailable; a choice must be made between discontinuing the drug or ceasing breastfeeding
Interferon beta-1b (Infibeta) (GRLS)	No information in the label	No harmful effects on the newborn/child are anticipated with drug use during pregnancy. In cases of clinical necessity, the treating physician should decide on the possibility of using interferon beta-1b during pregnancy if the expected benefit of the drug outweighs the potential risk of its use	Can be used during breastfeeding. No harmful effects on the breastfed infant are anticipated
Sampeginterferon beta-1a (Tenexia) (GRLS).	No information in the label	Contraindicated	Contraindicated
		Glatiramer acetate	
Axoglatiran FS (GRLS)	No information in the label	Contraindicated	It is unknown whether glatiramer acetate or its metabolites pass into breast milk. The expected therapeutic benefit for the mother should be weighed against potential risks to the child
Timexon, Copaxone Teva, Copaxone 40, Glatirat, Glatsetat (GRLS)	Not required	Not recommended except when maternal benefit outweighs potential fetal risk	May be used. No adverse effects on newborns are anticipated

For continuation of the Table 2, see page 80.

Drug Product	Contraception before pregnancy	Use during pregnancy	Use during lactation
		Teriflunomide	
Femorix, Teriflunomide, Teriflunomide Kanon, Teriflunomide PSK, Teriflunomide-Chemrar, Dissemil (GRLS)	Discontinue 24 months prior to conception Measure drug concentration prior to pregnancy planning; if two measurements 14 days apart show < 0.02 mg/L, no waiting or accelerated elimination is needed. Embryofetal toxicity risk in males is considered low	Contraindicated	Contraindicated
		Dimethyl fumarate	
Eumileo, Fluterio, Dimethyl fumarate (GRLS)	Throughout the entire treatment course	Limited data available. Demonstrated toxic effects on reproductive system. Should only be prescribed in critical cases where maternal benefit outweighs potential fetal risk	Decision should be made after thorough benefit-risk assessment for mother and child
		Fingolimod	
Nescler, Gilenya, Sclimod, Modena, Fingolimod Native, Lifespan, Fingolimod, Fingolimod Medisorb (GRLS)	Throughout treatment and 2 months after discontinuation	Drug discontinuation should be considered, weighing maternal benefits against fetal risks, due to severe relapses after withdrawal. Reproductive toxicity	Contraindicated
		Natalizumab	
Tysabri (GRLS)	No instructions	Should only be used in critical cases. Newborns should be monitored for platelet count and hemoglobin levels	Breastfeeding must be discontinued during drug therapy. Excreted in breast milk
Expert consensus opinion [5, 25]	Not required	Discontinue at 30–34 weeks gestation with extended dosing interval (6–8 weeks), then resume 1–2 weeks postpartum. Alternative approach: Switch to another DMT before pregnancy to reduce relapse risk, particularly in patients with PML risk and JC virus antibodies. Newborn blood parameters (LDH, bilirubin, hemoglobin) require monitoring when used in 2nd/3rd trimester	May be used. No interval required between infusion and subsequent breastfeeding
		Alemtuzumab	
Lemtrada (GRLS)	Throughout treatment and 4 months post-treatment	May be used if maternal benefit outweighs fetal risk. Placental transfer of TSH receptor antibodies causing neonatal Graves' disease has been reported. Untreated hypothyroidism in pregnancy increases miscarriage risk and fetal complications including mental retardation and dwarfism	Breastfeeding benefits should be balanced against maternal clinical need and potential adverse effects of alemtuzumab/maternal disease on infant. Breastfeeding prohibited during treatment and 4 months post-infusion

For continuation of the Table 2, see page 81.

Drug Product	Contraception before pregnancy	Use during pregnancy	Use during lactation
		Ocrelizumab	
Ocrevus (GRLS)	Throughout treatment and 12 months post-treatment	Should be avoided unless benefit outweighs risk Limited data available. Possible B-cell depletion and lymphocytopenia in newborns. Animal studies showed no teratogenic effects but demonstrated reproductive toxicity	Breastfeeding should be discontinued during therapy. Risk cannot be ruled out
Expert consensus opinion [5, 25]	Conservative approach: pregnancy is possible 3 months after the last infusion. Active approach: pregnancy in the next menstrual cycle	In the absence of absolute indications, discontinuation of ocrelizumab during pregnancy is recommended. Decrease in B-cell counts in newborns and a slight increase in the risk of preterm birth and low birth weight were observed in a study involving < 30 pregnancies in women	May be used; a waiting period of ≥ 4 hours after antihistamine administration is required before the next breastfeeding session
		Divozilimab	
Ivlizi (GLRS)	Throughout treatment and 12 months post-treatment	Contraindicated. Should not be used during pregnancy, except in cases where the benefit to the mother outweighs the potential risk to the fetus. Some newborns of mothers treated with anti-CD20 antibodies during pregnancy showed transient depletion of peripheral B-cell pools and lymphocytopenia	Not recommended during treatment with the drug. No data available on potential drug excretion into breast milk
		Ofatumumab	
Bonspri (GLRS)	Throughout treatment and 6 months post-treatment	Contraindicated due to lack of safety data for this therapy. Animal studies showed no reproductive toxicity	Contraindicated due to insufficient safety data
Expert consensus opinion [5, 25]	Either a conservative approach (discontinuing the drug when attempting pregnancy) or an active approach (administering the drug until conception occurs, with injections timed to menstrual periods) is recommended	Limited data (30 pregnancies) show no congenital anomalies. Seventeen live births have been reported	The drug can be safely used 2 weeks postpartum, with no required interval between breastfeeding and infusion
		Cladribine	
Mavenclad (GRLS).	Both men and women must use contraception for 6 months after the last dose	Women who become pregnant during therapy should discontinue the drug. Animal studies demonstrated reproductive toxicity	No data available on drug excretion into breast milk. Breastfeeding should be discontinued during therapy and for 1 week after the last dose
		Siponimod	
Kajendra (GRLS)	Throughout treatment and 10 days post-treatment	Contraindicated. Animal studies demonstrated embryoand fetotoxicity	Contraindicated. Unknown whether it penetrates breast milk

Note. GRLS — the drug prescribing information in Russia is derived from the State Register of Medicinal Products (Russian abbreviation: *GRLS*). Green — safe for use during pregnancy; yellow — use during pregnancy is permissible if maternal benefit outweighs fetal risk; red — contraindicated for use during pregnancy.

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Information about the authors

Valeriya A. Malko – assistant, Department of neurology with the clinic, Medical Education Institute, Almazov National Medical Research Centre, St. Petersburg, Russia, https://orcid.org/0000-0003-2230-3750
Ekaterina A. Sadovnichuk – student, Faculty of medicine, Medical Education Institute, Almazov National Medical Research Centre, St. Petersburg, Russia, https://orcid.org/0009-0007-6275-2725
Gennady N. Bisaga – Dr. Sci. (Med.), Professor, Department of neurology with the clinic, Medical Education Institute, Almazov National Medical Research Centre, St. Petersburg, Russia, https://orcid.org/0000-0002-1848-8775

Author contribution. *Malko V.A.* – formulation and elaboration of the goal, collection and processing of material, writing of the text; *Sadovnichuk E.A.* – collection and processing of material, writing of the text; *Bisaga G.N.* – management and coordination of work, editing of the text.

Информация об авторах

Малько Валерия Алексеевна – ассистент кафедры неврологии с клиникой НМИЦ им. В.А. Алмазова, Санкт-Петербург, Россия,
https://orcid.org/0000-0003-2230-3750
Садовничук Екатерина Александровна – студентка 5-го курса НМИЦ им. В.А. Алмазова, Санкт-Петербург, Россия,
https://orcid.org/0009-0007-6275-2725
Бисага Геннадий Николаевич – д-р мед. наук, профессор кафедры неврологии с клиникой ИМО НМИЦ им. В.А. Алмазова, Санкт-Петербург, Россия, https://orcid.org/0000-0002-1848-8775

Вклад авторов. *Малько В.А.* – формулирование и проработка цели, сбор и обработка материала, написание текста; *Садовничук Е.А.* – сбор и обработка материала, написание текста; *Бисага Г.Н.* – руководство и координация работ, редактирование текста.

Neuroimaging in Huntington's Disease

Georgy A. Anikin, Sergey A. Klyushnikov, Alexey S. Filatov, Alina A. Liaskovik, Sergey N. Illarioshkin

Russian Center of Neurology and Neurosciences, Moscow, Russia

Abstract

Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disorder for which effective disease-modifying treatments have not yet been developed. Current diagnosis of HD relies on clinical criteria and genetic testing. However, neuroimaging plays a crucial role in differentiating HD with similar phenotypes and, most importantly, in objectively monitoring the neurodegenerative process, particularly during the development of disease-modifying therapies. Novel technologies and imaging protocols have significantly advanced neuroimaging capabilities in HD patients in recent years. This review presents a range of promising neuroimaging modalities (magnetic resonance morphometry, functional MRI, diffusion tensor imaging, positron emission tomography, etc.) that assess HD neurodegenerative patterns from multiple perspectives and clarify disease mechanisms and their correlation with clinical manifestations. Further development of these technologies is important not only for neurology but also for neuropharmacology and neurophysiology.

Keywords: *Huntington's disease; neuroimaging; neurodegeneration; biomarkers; magnetic resonance imaging; positron emission tomography; resting-state functional magnetic resonance imaging; diffusion tensor magnetic resonance imaging; magnetic resonance tractography*

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For correspondence: 80 Volokolamskoye shosse, Moscow, Russia, 125367. Russian Center of Neurology and Neurosciences. E-mail: dante3red@mail.ru. Georgy A. Anikin

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Технологии нейровизуализации при болезни Гентингтона

Г.А. Аникин, С.А. Клюшников, А.С. Филатов, А.А. Лясковик, С.Н. Иллариошкин

Российский центр неврологии и нейронаук, Москва, Россия

Аннотация

Болезнь Гентингтона (БГ) – аутосомно-доминантное прогрессирующее нейродегенеративное заболевание, эффективные патогенетические методы лечения которого пока не разработаны. Диагностика БГ в настоящий момент основывается на клинических критериях и данных генетического анализа, но методы нейровизуализации могут иметь большое значение для дифференцирования БГ со сходными фенотипами и главным образом – для объективного мониторинга нейродегенеративного процесса, в том числе на фоне разрабатываемых подходов болезнь-модифицирующей терапии. Возможности нейровизуализации у пациентов с данным заболеванием существенно выросли в последние годы в связи со всё более широким применением ряда новых технологий и режимов исследования. В обзоре представлен спектр наиболее перспективных нейровизуализационных методик (магнитно-резонансная морфометрия, функциональная и диффузионно-тензорная магнитно-резонансная томография, позитронно-эмиссионная томография и др.), которые оценивают нейродегенеративные паттерны БГ с различных сторон и уточняют патогенетические механизмы болезни и их взаимосвязь с клиническими проявлениями. Дальнейшее развитие этих технологий имеет значение не только для неврологии, но также для нейрофармакологии и нейрофизиологии.

Ключевые слова: *болезнь Гентингтона; нейровизуализация; нейродегенерация; биомаркеры; магнитно-резонансная томография; позитронно-эмиссионная томография; функциональная магнитно-резонансная томография покоя; диффузионно-тензорная магнитно-резонансная томография; магнитно-резонансная трактография*

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.

Адрес для корреспонденции: 125367, Россия, Москва, Волоколамское шоссе, д. 80. Российский центр неврологии и нейронаук. E-mail: dante3red@mail.ru. Аникин Г.А.

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Huntington's disease (HD) is a severe progressive neurodegenerative disorder with autosomal dominant inheritance, characterized by multisystem clinical manifestations and degeneration of striatal spiny neurons as the primary target of the pathological process [1]. The classic triad of HD symptoms includes motor disorders (chorea, dystonia, myoclonus, etc.), cognitive decline (progressing to subcortical dementia), and various psychiatric abnormalities (depression, obsessive-compulsive disorder, anxiety, possible psychotic episodes, etc.) [1–3]. Additionally, HD patients often exhibit metabolic abnormalities that may lead to progressive weight loss culminating in cachexia [2, 3].

The genetic basis of HD involves the expansion of tandem polyglutamine-encoding CAG repeats in the *HTT* gene, resulting in elongation of the mutant huntingtin protein, accumulation of aberrant protein molecules in degenerating striatal neurons, and initiation of pathological cascades in brain tissue [1–3]. For over a century, this disease has been a focus of intense global research and is considered a unique genetic model for studying neurodegenerative patterns, mechanisms of brain plasticity, and possibilities of preventive neuroprotection.

Despite some promising studies (e.g., antisense oligonucleotides to suppress expression of mutant polyglutamine-encoding *HTT* alleles), effective evidence-based disease-modifying therapy for Huntington's disease (HD) remains undeveloped, and the disease continues to be largely incurable [3]. Existing therapeutic approaches are purely symptomatic and palliative in nature [2, 3]. The key prerequisite for implementing effective treatment strategies capable of slowing HD progression and preventing symptom onset in asymptomatic mutation carriers is the earliest possible initiation of pathogenetic therapy. This requires detailed investigation of HD's molecular mechanisms and development of methods for timely diagnosis of neurodegenerative processes including the preclinical stage. In this context, the current priority is identifying reliable HD biomarkers applicable in real clinical practice [4], with neuroimaging biomarkers playing a crucial role in detecting subtle structural and functional changes and neural network reorganization across all stages of mutant gene carriage [4, 5]. Numerous studies employing voxel-based morphometry (VBM), resting-state fMRI, diffusion tensor imaging (DTI), MR spectroscopy, and PET demonstrate the significant potential of modern neuroimaging techniques for investigating HD neurobiology, elucidating neuroplasticity mechanisms in this condition, and evaluating novel therapeutics in clinical trials [5–9].

This review synthesizes global research experience with promising HD neuroimaging biomarkers, focusing on relatively accessible structural MRI/fMRI techniques and PET data using different radiotracers. Literature search was conducted in Scopus, Web of Science, PubMed (MedLine), and eLIBRARY.RU databases.

Positron Emission Tomography

Positron emission tomography (PET) is a functional imaging modality based on the ability of radioactive isotopes to accumulate in tissues with high metabolic activity. In HD, PET imaging with various ligands — low-molecular vectors capable of crossing membranes — allows visualization of specific targets [3]. The targets for these ligands include intermediate metabolites, protein complex components, signaling molecules, and nuclear receptors [10], with short-lived radionuclides demonstrating optimal binding properties.

In a study by C. Giampà *et al.*, an early version of a PET ligand for huntingtin — compound CHDI-180R — was presented [11]. It was demonstrated that CHDI-180R molecules exhibit strong binding to toxic huntingtin aggregates *in vitro*. CHDI-180R was successfully used to localize mutant huntingtin aggregates in brain samples of HD mice, with ligand binding to the mutant protein shown to increase with animal aging.

Thus, PET ligands can precisely localize mutant huntingtin and estimate its approximate quantity in the brain, whereas analysis of cerebrospinal fluid and other biological samples in HD does not provide reliable information about disease progression severity, clinical stage, or pathological process dissemination. Unlike PET scanning (which specifically targets the pathological polyglutamine substrate), most existing biochemical methods measure total huntingtin levels, including both mutant and normal forms [5].

Phosphodiesterase 10A (PDE10A), an enzyme expressed in medium spiny neurons of the striatum that regulates their sensitivity to glutamatergic signaling, has been identified as

a promising biomarker for HD [10]. PDE10A inhibition functionally mimics the effects of D1-like receptor agonists and D2-like receptor antagonists while modulating both direct and indirect striato-thalamo-cortical pathways in the central nervous system. To date, research has primarily characterized the effects of PDE10A inhibition, which reproduce the inhibitory effects of D2-like dopamine receptor antagonists.

An international research team from Denmark, the Netherlands, Norway, and Sweden measured PDE10A availability in patients with early-stage HD using the ^{18F}MNI-659 radioligand, revealing significantly reduced binding in the striatal region compared to healthy volunteers [11]. Data from other studies [12–15] suggest that diverse alterations in PDE10A signaling within pathomorphologically intact neural networks of the central nervous system represent the earliest neuroimaging marker detectable before the predicted onset of symptomatic HD. Changes in PDE10A expression also provide valuable information for monitoring cerebral atrophy progression in HD.

Voxel-Based Morphometry

Voxel-based morphometry (VBM) has emerged as a promising MRI biomarker for neurodegeneration, enabling quantitative assessment of atrophy in various brain regions [16, 17]. Russian researchers demonstrated that in HD, VBM not only identifies involvement of specific structures of the central nervous system but also quantifies gray matter changes, reveals subtle process characteristics (such as asymmetry), assesses potential topographic spread of neurodegeneration over time, and establishes correlations between mutation severity, clinical data, and regional brain atrophy [7].

One study in HD patients revealed more pronounced degenerative changes in the dominant hemisphere, along with an inverse correlation between CAG repeat copy number and the severity of atrophy in the caudate nucleus and putamen [18].

Correlation analysis indicates that reduced gray matter volume in the caudate nucleus, putamen, and insula constitutes an early morphometric brain change detectable in preclinical HD mutation carriers [19]. Striatal atrophy in early-stage HD patients is associated not only with motor control impairments but also with executive dysfunction, likely involving cortical regions such as the insular lobe.

A French research group [20] confirmed progressive gray matter volume loss in the basal ganglia, substantia nigra, hypothalamus, amygdala, insular, premotor, and sensorimotor cortices as HD advances to clinical stages. Atrophy was most pronounced in the basal ganglia, subsequently spreading to cortical regions predominantly involved in subcortical-thalamo-cortical pathways.

A recent study in patients with confirmed HD assessed the distribution of atrophic changes across various brain regions using automated volumetry compared to standard clinical measurement methods [21]. Automated caudate nucleus volume measurements were additionally verified using manual segmentation. This study demonstrated that new software developments enable more accurate identification of patients with basal ganglia atrophy and determination of its severity. Prospective studies utilizing state-of-the-art software may facilitate more detailed diagnostics of pathological cerebral processes in HD patients.

It can be concluded that VBM has undeniable advantages, allowing quantitative tracking of progressive brain atrophy during longitudinal monitoring of HD patients.

Functional MRI

Functional MRI (fMRI) indirectly assesses functional activity in various brain regions. It does not measure neuronal electrical activity but instead relies on the neurovascular coupling phenomenon, i.e., regional blood flow changes in response to activation of nearby neurons, as increased neuronal activity requires greater oxygen and nutrient delivery through blood circulation [22].

The literature presents findings on the activation patterns of various brain regions in HD patients during fMRI using diverse paradigms [23]. These results indicate that fMRI is sensitive to neural dysfunction occurring more than 12 years prior to the anticipated onset of HD clinical manifestations [24]. Multiple studies have demonstrated that alterations in spontaneous neuronal activity (resting-state fMRI) within the default mode network in HD correlate with clinical features of the disease and may serve as neuroimaging correlates of visuospatial, affective, memory, executive, and motor control impairments, both at the asymptomatic mutation carrier stage and in patients with manifest HD.

Thus, fMRI is as a valuable neuroimaging tool to objectively assess the progression of neurodegenerative processes and patterns of functional neuroplastic reorganization during longitudinal monitoring of HD patients.

Diffusion tensor MRI and differential tractography

DT-MRI is used for in vivo quantitative and qualitative assessment of water diffusion directionality in the human brain, enabling the study of microscopic structure of white matter pathways in cerebral hemispheres. This technique allows reconstruction of three-dimensional images of commissural, associative, and projection tracts that ensure normal brain function [25].

When assessing white matter integrity in patients with prodromal and clinically manifest stages of HD using DT-MRI, researchers identified white matter disintegration in frontal lobes, preand postcentral gyri, corpus callosum, anterior and posterior limbs of internal capsule, and corticostriatal pathway [26]. Some HD studies also demonstrated altered structural connectivity integrity in white matter – from early manifestations to advanced stages – with most pronounced microstructural changes observed in corpus callosum. Such alterations of commissural fibers in HD patients may lead to cortical disconnection effects [27].

J.V. Barrios-Martinez *et al.* evaluated correlations between changes in white matter pathways in HD and motor, cog-

nitive, and functional assessment scores using a variant of tractography – differential tractography [27]. Unlike conventional tractography, which maps all existing pathways, differential tractography allows quantification of degeneration severity by calculating the volume of affected tract segments based on longitudinal changes in specific pathways within individual patients. Significant differences were observed between manifest and premanifest disease stages. Initial results in manifest HD patients showed substantial involvement of pathways, whereas premanifest mutation carriers exhibited either no or minimal affected pathways. Changes in the volume of affected pathways significantly correlated with disease severity on the Unified Huntington's Disease Rating Scale (UHDRS) ($p < 0.001$), and chronological changes on differential tractography also correlated with worsening scores on this scale ($p < 0.001$). Moreover, one patient demonstrated increased lesion volume prior to symptom onset. A larger volume of involved tracts is considered indicative of reduced structural integrity.

The obtained results confirm that differential tractography can be used as a dynamic neuroimaging biomarker, allowing individualized assessment of HD progression. Importantly, this methodology serves as a quantitative tool for tracking degeneration in presymptomatic patients, with potential applications in clinical trials.

Thus, numerous methodologies have been proposed as neuroimaging biomarkers in HD. These appear to be among the most promising approaches for describing and characterizing patterns of neurodegeneration. New technologies and advances in existing methodologies will enable tracking of therapeutic responses, identification of novel drug targets, and provide deeper insights into disease pathogenesis.

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Information about the authors

Georgy A. Anikin – postgraduate student, 5th Neurological department, Russian Center of Neurology and Neurosciences, Moscow, Russia, https://orcid.org/0009-0005-2447-1418
Sergey A. Klyushnikov – Cand. Sci. (Med.), leading researcher, 5th Neurological department, Russian Center of Neurology and Neurosciences, Moscow, Russia, https://orcid.org/0000-0002-8752-7045
Alexey S. Filatov – Cand. Sci. (Med.), researcher, Department of radiology, Russian Center of Neurology and Neurosciences, Moscow, Russia, https://orcid.org/0000-0002-5706-6997
Alina A. Liaskovik – radiologist, Department of radiology, Russian Center of Neurology and Neurosciences, Moscow, Russia, https://orcid.org/0000-0001-8062-0784
Sergey N. Illarioshkin – Dr. Sci. (Med.), Prof., Full member of the RAS, Director, Brain Institute, Deputy director, Russian Center of Neurology and Neurosciences, Moscow, Russia, https://orcid.org/0000-0002-2704-6282

Authors' contribution: *Anikin G.A.* – writing the article, searching for relevant literature sources, editing the text; *Klyushnikov S.A., Filatov A.S., Liaskovik A.A.* – verification and actualization of the article; *Illarioshkin S.N.* – conceptualization and verification of the article.

Информация об авторах

Аникин Георгий Александрович – аспирант 5-го неврологического отделения Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0009-0005-2447-1418
Клюшников Сергей Анатольевич – канд. мед. наук, в. н. с. 5-го неврологического отделения Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0000-0002-8752-7045
Филатов Алексей Сергеевич – канд. мед. наук, н. с. отдела лучевой диагностики Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0000-0002-5706-6997
Лясковик Алина Анатольевна – врач-рентгенолог отдела лучевой диагностики Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0000-0001-8062-0784
Иллариошкин Сергей Николаевич – д-р мед. наук, проф., академик РАН, директор Института мозга, зам. директора по научной работе Российского центра неврологии и нейронаук, Москва, Россия, https://orcid.org/0000-0002-2704-6282

Вклад авторов: *Аникин Г.А.* – написание статьи, поиск источников литературы, научное редактирование текста; *Клюшников С.А., Филатов А.С., Лясковик А.А.* – проверка и актуализация работы; *Иллариошкин С.Н.* – концептуализация и проверка статьи.

Electrographic Status Epilepticus Following Cardiac Surgery for Congenital Heart Defects in Children

Vadim O. Russkin[1], Alexandra A. Kuznetsova[2,3], Mikhail A. Abramyan[2], Valery A. Sandrikov[1]

[1]Petrovsky National Research Centre of Surgery, Moscow, Russia;

[2]Morozov Children's City Clinical Hospital, Moscow, Russia;

[3]Moscow Research and Clinical Center for Neuropsychiatry, Moscow, Russia

Abstract

Status epilepticus (SE) is a severe complication of cardiac surgery for cyanotic congenital heart defects in children. SE significantly worsens neurological prognosis and increases the likelihood of fatal outcomes. In most cases, epileptic seizures and status epilepticus in intensive care unit patients lack clinical manifestations and are detected exclusively through electroencephalography (EEG). In this study, we present a series of clinical observations demonstrating the transformation of SE from clinical to electrographic manifestations during anticonvulsant therapy in children with cyanotic congenital heart defects during the postoperative period. We emphasize the critical importance of EEG in managing SE in pediatric intensive care settings.

Keywords: *electroencephalography; status epilepticus; congenital heart defect*

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For correspondence: 2 Abrikosovsky lane, Moscow, Russia, 119991. Petrovsky National Research Centre of Surgery. E-mail: russkin.vadim@mail.ru. Vadim O. Russkin

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Электрографический эпилептический статус после кардиохирургических операций, направленных на коррекцию врождённых пороков сердца у детей

В.О. Русскин[1], А.А. Кузнецова[2,3], М.А. Абрамян[2], В.А. Сандриков[1]

[1]Российский научный центр хирургии имени академика Б.В. Петровского, Москва, Россия;

[2]Морозовская детская городская клиническая больница, Москва, Россия;

[3]Научно-практический психоневрологический центр имени З.П. Соловьева, Москва, Россия

Аннотация

Эпилептический статус (ЭС) является тяжёлым осложнением кардиохирургических операций, направленных на коррекцию врождённых пороков сердца цианотического типа у детей. Наличие ЭС значимо ухудшает неврологический прогноз и увеличивает вероятность летального исхода. В большинстве случаев эпилептические приступы и статус у пациентов в отделении реанимации не имеют клинических проявлений и регистрируются исключительно при проведении электроэнцефалограммы. В данной работе мы демонстрируем серию клинических наблюдений трансформации ЭС из клинического в электрографический на фоне противосудорожной терапии у детей с цианотическими врождёнными пороками сердца в постоперационном периоде. Мы акцентируем внимание на важности использовании электроэнцефалографии в купировании ЭС в педиатрической реанимации.

Ключевые слова: *электроэнцефалография; эпилептический статус; врождённый порок сердца*

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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.

Адрес для корреспонденции: 119991, Москва, Абрикосовский пер., д. 2. РНЦХ им. академика Б.В. Петровского. E-mail: russkin.vadim@mail.ru. Русскин В.О.

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Introduction

Congenital heart defects (CHD) are the most common type of congenital defects and the leading cause of childhood mortality in neonatal and infant periods [1, 2]. By the mid-20th century, only one-third of children with CHD reached adulthood. Since the 21st century, due to advances in diagnostic, anesthesiological, and surgical techniques, approximately 90% of children survive into adulthood [3–5]. Having achieved significant reductions in mortality among children with CHD, the medical community is gradually shifting its focus toward improving these patients' quality of life, particularly combating intraand postoperative central nervous system (CNS) complications.

The incidence of epileptic seizures (ES), clinical status epilepticus (SE), and electrographic SE (ESE) following corrective surgery for CHD in children ranges from 8% to 11.5% [6–8]. Most of these cases (up to 85%) lack clinical manifestations. In critically ill children, ESE significantly increases mortality and worsens long-term outcomes, necessitating long-term multi-hour EEG monitoring [9].

In 2013, the Salzburg criteria for diagnosing non-convulsive SE were proposed to standardize critical care EEG assessment and improve the diagnosis of electrographic seizures and ESE, significantly enhancing ESE detection while reducing false-positive results [10–12] (Table 1).

In some patients, electrographic seizures or ESE persist after resolution of clinical SE manifestations. I. Sánchez Fernández *et al.* found that in pediatric intensive care units, transformation of SE into electrographic seizures occurred in 33–52% of cases, and SE into ESE in 12–25% of cases [6, 13],

Table 1. Clinical EEG criteria for diagnosing electrographic seizures and electrographic status epilepticus

Electrographic seizure	Electroclinical seizure
Discharges with a frequency > 2.5 Hz lasting ≥ 10 seconds (≥ 25 discharges over 10 seconds **OR** Any pattern with clear evolution lasting > 10 seconds	Clinical manifestations occur synchronously with EEG discharge patterns **OR** Clinical and electrographic improvement following parenteral antiepileptic drug administration
Electrographic status epilepticus	**Electroclinical SE**
Electrographic seizures lasting > 10 minutes **OR**	Electroclinical seizures lasting > 10 minutes **OR**
> 20% of a 60-minute recording	> 20% of a 60-minute recording **OR**
	> 5 minutes for bilateral tonic-clonic seizures
	Possible SE: electrographic improvement without clinical improvement after parenteral antiepileptic agent administration

which is comparable to adult population data (48% and 14%, respectively) [14].

We present case reports of three pediatric patients who developed SE after cardiac surgery for CHD, which subsequently transitioned into non-convulsive (electrographic) or electroclinical forms.

Clinical case 1

Patient T., 3 months of age. The perinatal history is unremarkable. At three month of age the patient received surgical intervention – radical surgery for tetralogy of Fallot: closure of the ventricular septal defect with a polytetrafluoroethylene patch, infundibulotomy, and transannular patch plasty of the right ventricular outflow tract and pulmonary artery trunk using a xenopericardial patch under cardiopulmonary bypass (CPB) and pharmaco-cold crystalloid cardioplegia. The duration of CPB was 51 minutes.

On postoperative day 2, the child developed focal motor seizures manifesting as clonic twitching in the right arm with impaired awareness progressing to SE. After clinical resolution with 2.5 mg diazepam and 40 mg/kg/day levetiracetam, a follow-up EEG was performed (Fig. 1). Throughout the recording, left-lateralized rhythmic delta activity (LRDA) at 2.5–3.0 Hz was observed, followed by frequency evolution (down to 2 Hz) and transformation into lateralized periodic discharges (LPDs), which according to the Salzburg criteria was interpreted as ESE.

Brain magnetic resonance imaging (MRI) revealed a watershed infarction in the left hemisphere (Fig. 2), while 3D time-of-flight (TOF) MR angiography showed no signal changes in the intracranial arteries.

Given the persistent EEG pattern of SE, midazolam at 0.2 mg/kg/h and sodium thiopental at 5 mg/kg/h were added to the therapy.

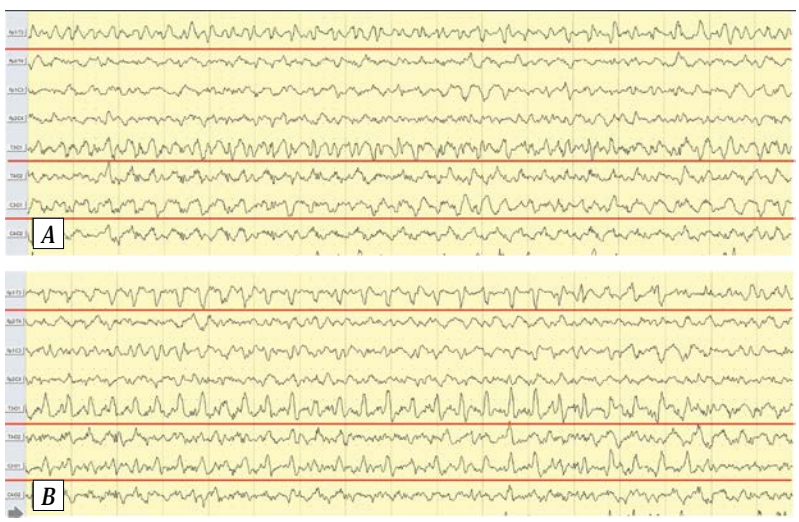

Fig. 1. A fragment of scalp EEG recording from patient T. on day 2 postoperatively.
A – LRDA at 2.5–3.0 Hz recorded under the electrodes over the left hemisphere; B – evolution of frequency characteristics to 2 Hz with transformation into LPDs. The channels where LPDs are recorded are highlighted in color. Longitudinal bipolar montage. Sensitivity – 15 μV/mm.

On day 3, during levetiracetam infusion, continued midazolam sedation, and reduced sodium thiopental dosage, a repeat EEG was performed (Fig. 3). Background activity was represented by diffuse slow waves in the θ and δ ranges. No epileptiform activity or ictal EEG patterns were recorded.

On day 5, midazolam was gradually discontinued. Follow-up brain MRI showed sequelae of acute cerebrovascular accident in the left middle cerebral artery territory and at the watershed zone between the middle and posterior cerebral arteries, without negative changes over time. The neurological status at discharge included moderate right-sided hemiparesis (up to 3 points) and anisoreflexia. Cognitive function was fully restored, and elements of cooing and the animation complex appeared.

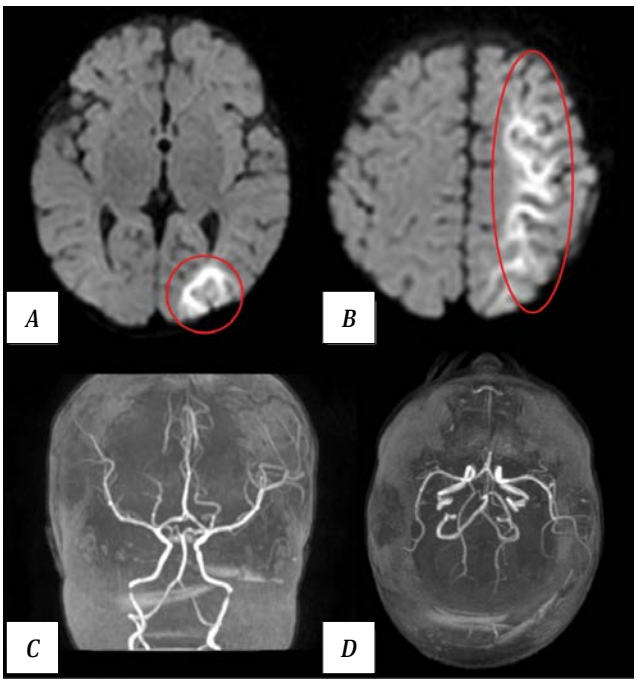

Fig. 2. Results of patient T. MRI on day 2 postoperatively.
A, B – brain MRI. Diffusion-weighted imaging (DWI), axial view. MRI findings of a watershed infarction in the left hemisphere (within the red oval). *C, D* – MR angiography, 3D reconstruction. Blood flow in the intracranial arteries of the head is intact.

In this patient, the combination of an electrographic pattern classified as ictal with the semiology of epileptic seizures (right-sided clonic contractions in the upper limb) led to the suspicion of an acute cerebrovascular accident and prompted an MRI.

Clinical case 2

Patient B., 3 months of age. The perinatal history is unremarkable. At 1 month of age, the diagnosis of CHD was established: subaortic ventricular septal defect measuring 7.5 × 7.9 mm. At 2 months of age, the patient underwent cardiac surgery – closure of the ventricular septal defect with a polytetrafluoroethylene patch under CBP (80 minutes).

On the first postoperative day, focal motor epileptic seizures occurred in the right extremities. To control seizures, valproic acid at 20 mg/kg/h (intravenous microbolus) and midazolam at 0.2 mg/kg/h were administered. Clinical manifestations subsided, but due to the inability to perform nighttime EEG monitoring, the study was conducted 14 hours later.

The first EEG was performed while the patient was already on antiepileptic therapy. The recording showed LRDA up to 4 Hz in the right occipital region with spread to the left occipital region, lasting up to 30 seconds. Independent LPDs as sharp waves at 2–3 Hz were observed under the electrodes of the left hemisphere, lasting up to 60 seconds. Given that LRDA and LPDs were recorded for more than 50% of the tracing, this EEG pattern was interpreted as ESE (Fig. 4). Consequently, sodium thiopental was added to the treatment regimen at 1 mg/kg/h with gradual titration up to 5 mg/kg/h, and the dose of valproic acid was increased to 45 mg/kg/day.

Brain MRI revealed watershed infarctions in both hemispheres (Fig. 5).

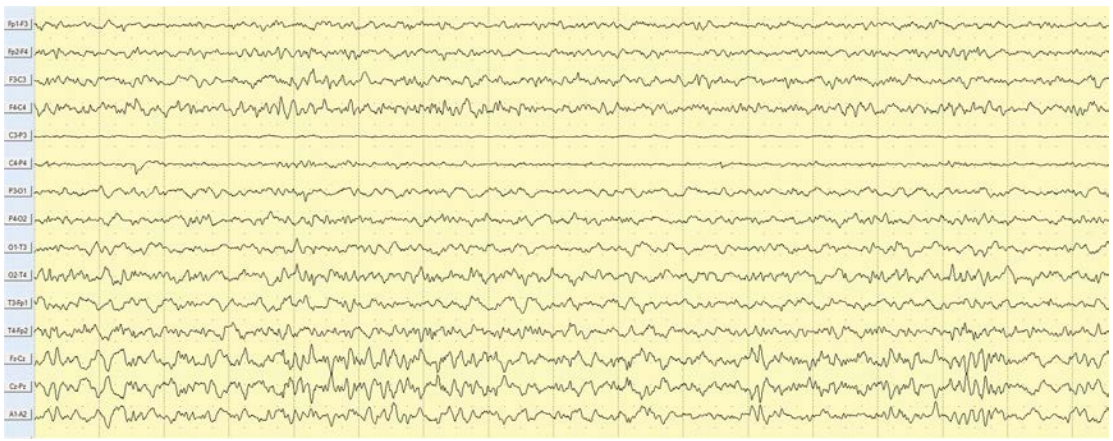

Fig. 3. A fragment of scalp EEG recording from patient T. on day 3 postoperatively.
Background activity is represented by diffuse slow waves. No ictal EEG patterns were recorded. Longitudinal bipolar montage. Sensitivity – 5 μV/mm.

On postoperative day 3, under sodium thiopental and valproic acid therapy, repeat EEG demonstrated bursts of epileptiform activity featuring polyspikes superimposed on diffuse cortical rhythm suppression, consistent with the high epileptiform burst-suppression electrographic pattern (Fig. 6).

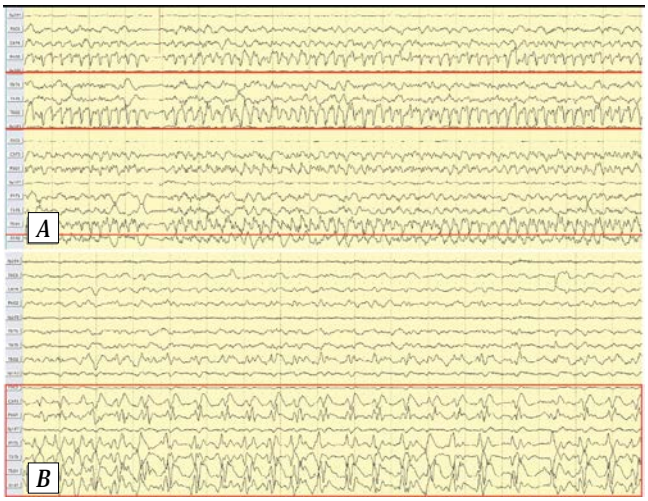

Fig. 4. A fragment of scalp EEG recording from patient B. on day 2 postoperatively.
A – 4 Hz LRDA is recorded in the right occipital region with spread to the left occipital region. *B* – LPDs manifest as 2.0–2.5 Hz sharp waves under left hemisphere electrodes. Red frames highlight electrodes detecting LRDA and LPDs. Longitudinal bipolar montage. Sensitivity – 7 μV/mm.

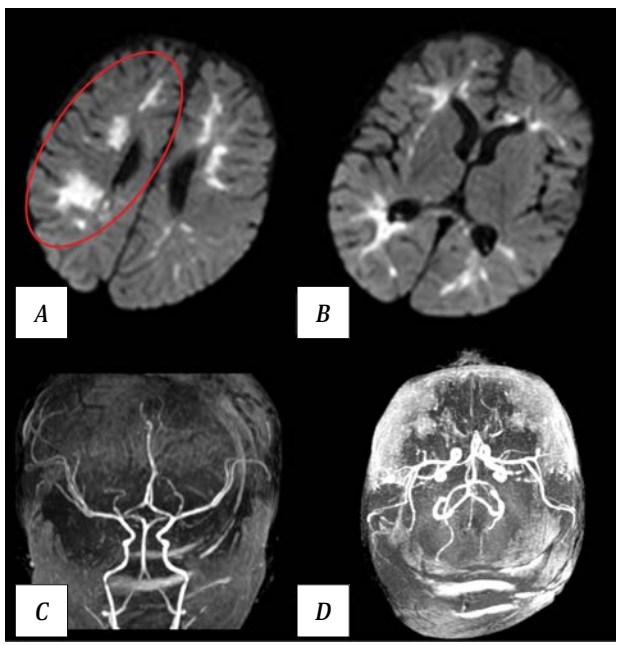

Fig. 5. Results of patient B. MRI on day 2 postoperatively.
A, B – brain MRI. DWI, axial plane. Watershed infarctions in both cerebral hemispheres. Red oval outlines the most extensive area in the right hemisphere; similar regions are observed in the left hemisphere. C, D – MR angiography, 3D reconstruction. Intracranial arterial blood flow remains intact.

This activity was interpreted as reflecting combined effects of sedative therapy and severe cerebral injury.

This morphology of graphoelements in patients with SE has been described as a predictor of seizure recurrence [15, 16], prompting the decision to continue sedative therapy with the addition of a second antiepileptic agent, phenobarbital, with gradual titration up to 3.75 mg/kg/day.

Midazolam was discontinued on postoperative day 5. A follow-up EEG was performed to register a burst-suppression pattern, with diffuse low-amplitude slow waves incorporating a spike component within the burst structure (Fig. 7).

On postoperative day 6, the sodium thiopental dose was reduced to 2 mg/kg/h and discontinued on day 7. Follow-up EEG showed diffuse slow theta waves, regional epileptiform activity in the central regions of the left hemisphere, with no ictal patterns recorded. At discharge on day 20, the neurological examination revealed prolonged disorder of consciousness – unresponsive wakefulness syndrome.

In patient B., the semiology of epileptic seizures was characterized by right-sided hemiclonic jerks, consistent with the localization of the epileptogenic zone in the left hemisphere. Additionally, an independent focus emerged in the right occipital region. Given the multifocal structural lesions on neuroimaging, the initiation zones of epileptic seizures were likely several areas of structural brain changes. Notably, a highly epileptiform burst-suppression pattern was recorded during pharmacological sedation. This EEG pattern, combined with bilateral diffuse MRI changes, carries poor prognostic significance for consciousness recovery, consistent with the functional outcome at the end of observation [17–19].

Clinical case 3

Patient V., 2 months of age. The perinatal history is unremarkable. In the first days of life, the following diagnoses were established: CHD, transposition of the great arteries with left ventricular outflow tract obstruction; muscular ventricular septal defect; mitral valve developmental anomaly; atrial septal aneurysm. At 2 months of age, balloon atrial septostomy (Rashkind procedure) was performed. Cardiopulmonary bypass duration was 40 minutes.

On day 2 postoperatively, focal motor epileptic seizures developed, manifesting as clonic jerking of the upper extremities (D < S), which were managed with midazolam infusion at 0.2 mg/kg/h and intravenous levetiracetam at 25 mg/kg/day. Emergency MRI revealed a watershed infarction zone in the left cerebral hemisphere (Fig. 8).

On postoperative day 2, during continuous midazolam infusion (0.3 mg/kg/h), EEG was performed: diffuse rhythmic theta-range activity (4–5 Hz) was recorded, with left temporo-occipital predominance showing evolution through frequency decrease (to 3 Hz) and morphological changes (appearance of sharp waves), meeting the criteria for electrographic seizure pattern (Fig. 9). The pattern persisted for over 50% of the recording duration, leading to the diagnosis of ESE.

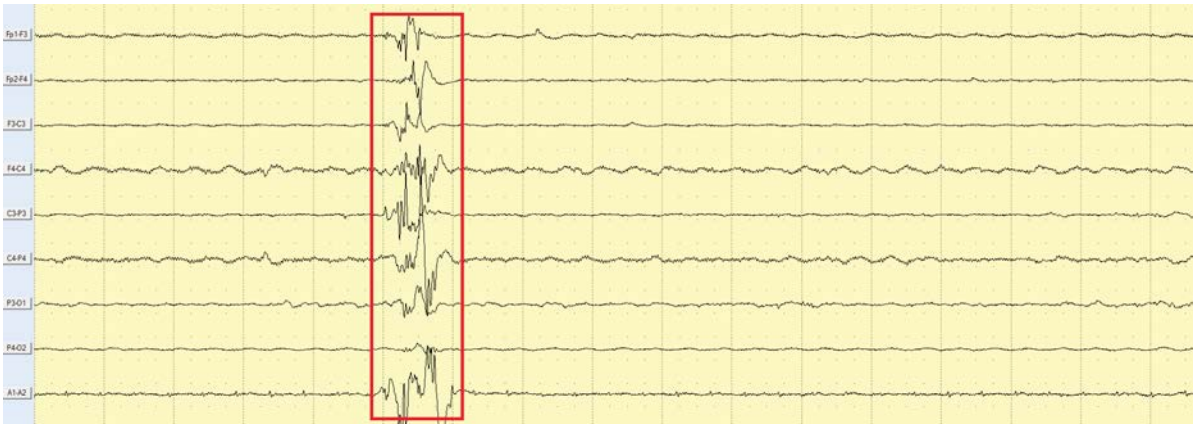

Fig. 6. A fragment of EEG recording from patient B. on day 3 postoperatively.
Epileptiform burst-suppression electrographic pattern. Longitudinal bipolar montage. Sensitivity – 3 μV/mm. The highly epileptiform burst is highlighted with a red frame.

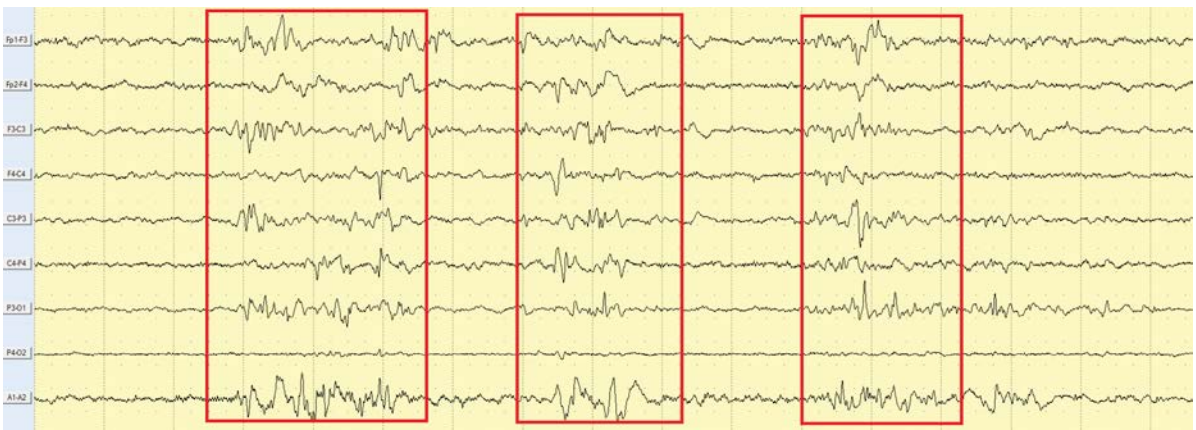

Fig. 7. A fragment of EEG recording from patient B. on day 5 postoperatively.
Epileptiform burst-suppression electrographic pattern. Longitudinal bipolar montage. Sensitivity – 3 μV/mm. Bursts of slow waves incorporating a spike component are highlighted with red frames.

Based on the EEG results, a decision was made to increase the midazolam dose to 0.3 mg/kg/h. On postoperative day 3, a repeat EEG showed diffuse suppression of cortical rhythm with no epileptiform activity (Fig. 10).

On day 5, the midazolam infusion rate was reduced to 0.2 mg/kg/h; on day 7 – to 0.1 mg/kg/h; and on day 8, the agent was discontinued.

After midazolam discontinuation, the EEG showed a dominant occipital rhythm with a frequency of up to 3.5–4.0 Hz (theta and delta range), with no epileptiform activity present.

Neurological examination revealed that the child was conscious, with full and symmetric active and passive limb movements. Cognitive function had recovered by the time of discharge. Follow-up brain MRI prior to the planned discharge (day 26) revealed cystic-glial transformation in the left middle cerebral artery territory.

In this patient, the clinical presentation of epileptic seizures was characterized by clonic jerking of the upper limbs with marked left-sided predominance. On EEG, the seizure pattern was diffuse with emphasis in the posterior regions of the left hemisphere, while MRI visualized an area of cytotoxic edema in the left hemisphere. The discrepancy between the seizure semiology, EEG findings, and neuroimaging data was likely due to the acute paresis in the right limbs, caused by structural changes in the brain parenchyma of the left hemisphere.

Discussion

The most common symptoms of CNS injury following pediatric cardiac surgery are seizures and status epilepticus [19, 20]. Among children undergoing corrective surgery for CHD, their incidence is approximately 10% [7, 8, 21]. In the study by B. Desnous *et al.*, risk factors for seizures included delayed sternotomy wound closure, extracorporeal membrane oxygenation, high RACHS-1 (Risk Adjustment in Congenital Heart Surgery) scores, and prolonged intensive care unit stay [22].

The methodology for EEG interpretation in this patient group significantly differs from that used in outpatient stud-

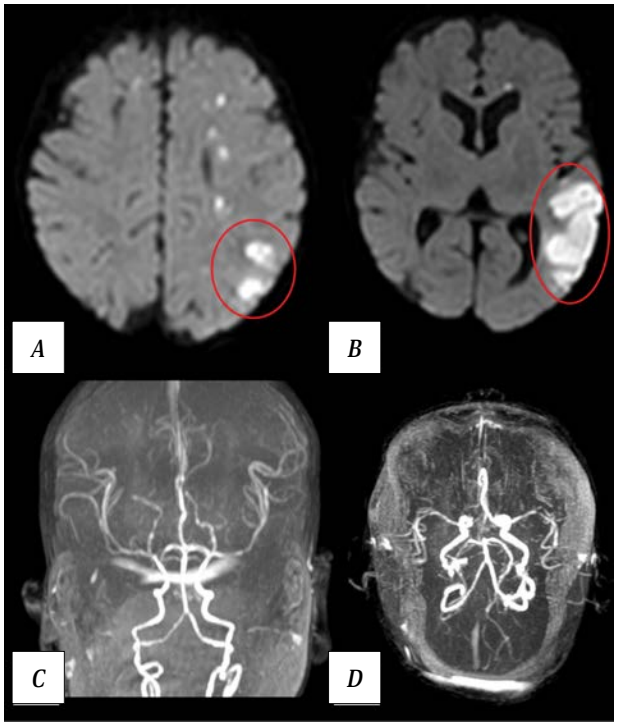

Fig. 8. Results of patient V. MRI on day 2 postoperatively.
A, B – brain MRI. Right DWI, axial plane. Watershed infarction zone in the left cerebral hemisphere (red ovals), multiple small ischemic foci. C, D – MR angiography, 3D reconstruction. Intracranial arterial blood flow remains intact.

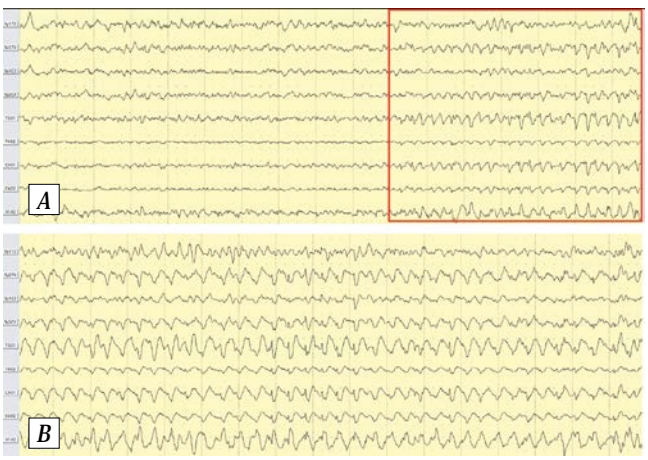

Fig. 9. Fragment of scalp EEG recording from patient V. during midazolam administration on postoperative day 2.
A diffuse ictal pattern is recorded, with emphasis in the left occipital region. A – onset of the ictal pattern; B – evolution of the ictal pattern. The onset of the ictal pattern recording is marked by a red frame. Longitudinal bipolar montage. Sensitivity – 7 μV/mm.

ies. Physicians require specialized terminology for standardized description and interpretation of EEG in patients with severe cerebral injury [23–25]. Furthermore, encephalography equipment is mandated in the operational standards of medical institutions with cardiac surgery departments containing cardiac intensive care units[1].

In a study of 137 patients, K.L. Wagenman *et al.* demonstrated that SE during intensive care unit stay was associated with subsequent deterioration in quality of life and served as a significant risk factor for epilepsy in critically ill children [26]. Therefore, timely diagnosis and treatment of epileptic seizures and management of SE in the intensive care unit are essential to reduce mortality and the risk of new neurological deficits [19, 27].

Several publications confirm that earlier initiation of SE treatment increases the likelihood of successful termination, whereas ESE exerts damaging effects on the CNS and is associated with worse neurological outcomes, similar to SE with prominent motor manifestations [28–31]. Moreover, both electrographic seizures and ESE can develop not only primarily due to acute cerebral injury but also secondary to the management of clinically apparent seizures and SE [6, 13].

In 2011, the American Clinical Neurophysiology Society presented clinical guidelines for the use of prolonged EEG monitoring in the intensive care unit for infants under 1 year of age [32]. These guidelines emphasized that seizures in infants under 1 year of age often occur without clinical manifestations, leading to the recommendation for EEG monitoring in patients at high risk of acute cerebral injury. This high-risk group includes patients with congenital heart defects requiring early surgical intervention with CPB, as well as those on extracorporeal membrane oxygenation.

In the presented clinical case series, all pediatric patients had cyanotic CHD and underwent cardiac surgery using CPB, which increases the risk of cerebral injury. In all cases, the first signs of cerebral injury were seizures, which were managed with a combination of anticonvulsant and sedative agents. Brain MRI in all children revealed areas of cytotoxic edema that localized the cerebral injury and correlated with the electrographic patterns.

Even relatively brief EEG recording after the resolution of overt clinical symptoms revealed electrographic epileptic activity indicative of ESE, and in one case, a pattern specific to unfavorable consciousness recovery prognosis. Standardized EEG terminology for patients with brain injury allowed us to verify nonconvulsive SE and the burst-suppression pattern. We observed the transformation of convulsive SE into nonconvulsive SE under pharmacological sedation, where despite clinical "cessation" of epileptic seizures, its electrographic manifestations persisted, necessitating adjustments to antiseizure therapy.

An unfavorable outcome of cerebral hypoxic-ischemic injury manifested as chronic disorders of consciousness developed only in Patient B. from Clinical case 2 with bilateral brain damage, which was suggested by a "malignant" burst-suppression pattern on EEG. In Patients 1 and 3, the MRI pattern corresponded to a single vascular territory (middle cerebral artery) in the absence of angiographic signs of embolism. Patient B. from Clinical case 2 had a

Appendix 29 to the Procedure for Providing Medical Care to Patients with Cardiovascular Diseases (approved by the Order No. 918n of the Ministry of Healthcare of the Russian Federation dated November 15, 2012).

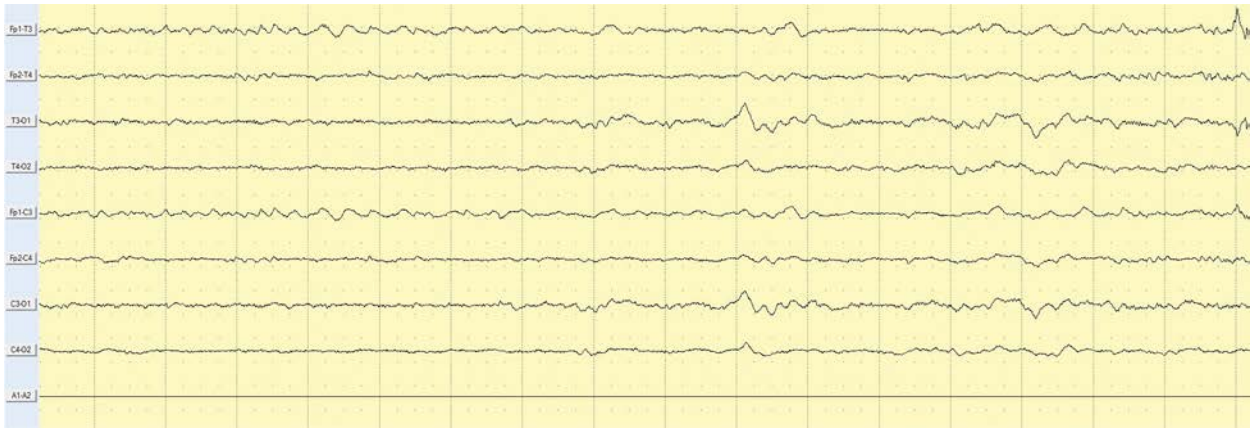

Fig. 10. A segment of scalp EEG recording from patient V. during midazolam infusion at a dose of 0.3 mg/kg/h on postoperative day 3. Diffuse suppression of cortical rhythms is observed. Longitudinal bipolar montage. Sensitivity — 3 μV/mm.

longer cardiopulmonary bypass time during surgery (80 minutes vs. 51 and 40 minutes), consistent with previous publications [33, 34].

Our clinical case series emphasizes the need to expand the use of EEG in intensive care units, not only for patients with impaired consciousness suspected of non-convulsive SE, but also after successful clinical control of seizures using sedative medications. However, in Russia, this method has not yet gained widespread adoption in pediatric intensive care settings. Potential reasons include the need for expensive equipment, the labor-intensive nature of EEG recording, and the challenges of analyzing and interpreting EEGs in patients with altered consciousness levels, which require specialized training for functional diagnostics specialists [24].

Conclusion

Both seizures and SE are common postoperative complications in children following cardiac surgery for CHDs. In some patients, clinical seizure cessation is followed by the transformation of convulsive SE into electrographic SE. EEG in pediatric cardiac intensive care for children at risk of acute brain injury during the intraand postoperative periods enables timely detection and management of electrographic seizures and ESE. This may reduce neurological deficits in CHD patients, accelerate the diagnosis of ischemic brain injury, and allow prompt initiation of antiepileptic therapy. This case series underscores the critical role of EEG in pediatric cardiac intensive care and the need to include electroencephalography in the standard equipment of these units.

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Information about the authors

Vadim O. Russkin – neurologist, junior research assistant, Department of clinical physiology, instrumental diagnostics and radilology, Scientific Clinical Center No. 1, Petrovsky Russian Scientific Center of Surgery, Moscow, Russia, https://orcid.org/0000-0003-4743-5522
Alexandra A. Kuznetsova – neurologist, Morozov Children's Municipal Clinical Hospital; junior research assistant, Head, Pediatric stroke center, Research and Clinical Center for Neuropsychiatry, Moscow, Russia, https://orcid.org/0000-0002-0344-9765
Mikhail A. Abramyan – Dr. Sci. (Med.), cardiac surgeon, Head, Department of emergency cardiac surgery and interventional cardiology, Morozov Children's Municipal Clinical Hospital, Moscow, Russia, https://orcid.org/0000-0003-4018-6287
Valery A. Sandrikov – Dr. Sci. (Med.), Full Member of the Russian Academy of Sciences, Professor, Head, Department of clinical physiology, instrumental diagnostics and radiology, Scientific Clinical Center No. 1, Petrovsky Russian Scientific Center of Surgery, Moscow, Russia, https://orcid.org/0000-0003-1535-5982

Authors' contribution: *Russkin V.O.* – developing a research concept, collecting data for analysis, article writing, editing of the article; *Kuznetsova A.A.* – developing a research concept, editing of the article; *Abramyan M.A., Sandrikov V.A.* – editing of the article.

Информация об авторах

Русскин Вадим Олегович – врач-невролог, м. н. с. отд. клинической физиологии, инструментальной и лучевой диагностики Научно-клинического центра № 1 РНЦХ им. Петровского, Москва, Россия, https://orcid.org/0000-0003-4743-5522
Кузнецова Александра Андреевна – врач-невролог Морозовской ДГКБ; м. н. с., руководитель центра детского инсульта Научно-практического психоневрологического центра им. З.П. Соловьева, Москва, Россия, https://orcid.org/0000-0002-0344-9765
Абрамян Михаил Арамович – д-р мед. наук, врач-кардиохирург, зав. отд. экстренной кардиохирургии и интервенционной кардиологии Морозовской ДГКБ, Москва, Россия, https://orcid.org/0000-0003-4018-6287
Сандриков Валерий Александрович – д-р мед. наук, академик РАН, профессор, зав. отделом клинической физиологии, инструментальной и лучевой диагностики Научно-клинического центра № 1 РНЦХ им. Петровского, Москва, Россия, https://orcid.org/0000-0003-1535-5982

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Combined Spinal Cord and Peripheral Nerve Stimulation in Severe Neuropathic Pain Syndrome

Viktor P. Kondratyev, Emil D. Isagulyan, Alexey A. Tomskiy

N.N. Burdenko National Scientific and Practical Center for Neurosurgery, Moscow, Russia

Abstract

Introduction*. Chronic severe neuropathic pain syndrome (NPS) refractory to conservative and surgical treatments remains a significant clinical challenge. Chronic electrical stimulation of a single neural structure often proves insufficiently effective, highlighting the need for innovative approaches such as combined neuromodulation. This article* ***aims*** *to present a clinical case of combined spinal cord and peripheral nerve stimulation.*

A case report. *A 32-year-old female with iatrogenic injury to the sural nerve following surgical intervention presented with refractory NPS (8 points on VAS). Failed conservative therapy (gabapentin, duloxetine) and surgical management (neuroma excision) led to chronic spinal cord stimulation, achieving 30% pain reduction. Subsequent ultrasound-guided peripheral nerve electrode implantation combined with chronic electrical stimulation resulted in complete pain area coverage and pain intensity reduction to 1–2 points on VAS.*

Conclusion. *Technical challenges associated with combined neuromodulation should not preclude its clinical application. Electrode proximity does not significantly affect system performance. Combined neuromodulation demonstrated synergistic effects in pain management by enhancing analgesia through simultaneous modulation of central and peripheral pain mechanisms. Large-scale studies evaluating the safety and efficacy of this combined approach are required for routine clinical implementation.*

Keywords: *neuropathic pain syndrome; spinal cord stimulation; peripheral nerve stimulation*

Ethics approval. Informed voluntary consent to publication in writing has been received from the patient.

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For correspondence: 16 Tverskaya-Yamskaya str., Moscow, 125047, Russia. N.N. Burdenko National Scientific and Practical Center for Neurosurgery. E-mail: vstenv@gmail.com. Viktor P. Kondratev.

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Комбинированное применение электростимуляции спинного мозга и периферического нерва с целью контроля хронического тяжёлого нейропатического болевого синдрома

В.П. Кондратьев, Э.Д. Исагулян, А.А. Томский

Национальный медицинский исследовательский центр нейрохирургии имени академика Н.Н. Бурденко, Москва, Россия

Аннотация

Введение. *Хронический тяжёлый нейропатический болевой синдром (НБС), резистентный к консервативным и хирургическим методам лечения, остаётся серьёзной клинической проблемой. Хроническая электростимуляция лишь одной нервной структуры не всегда оказывается достаточно эффективной, что подчёркивает необходимость поиска инновационных подходов, одним из которых может являться комбинированная нейромодуляция.*

Целью *данной статьи является представление клинического случая комбинированной электростимуляции спинного мозга и периферических нервов.*

Описание клинического случая. *Пациентка, 32 года, с ятрогенным повреждением икроножного нерва после хирургического вмешательства, страдающая рефрактерным НБС (8 баллов по ВАШ). Неэффективность консервативной терапии (габапентин, дулоксетин) и хирургической коррекции (иссечение невромы) привела к применению хронической электростимуляции спинного мозга, что снизило боль на 30%. Последующая имплантация электрода для периферической стимуляции нерва под УЗ-контролем в сочетании с хронической электростимуляцией позволила достичь полного перекрытия зоны боли и снижения её интенсивности до 1–2 баллов по ВАШ.*

Вывод. *Сложности, связанные с применением комбинированной нейромодуляции, не должны препятствовать её применению. Удалённость электрода не играет значимой роли в функциональности системы. Комбинированная нейромодуляция продемонстрировала синергизм в лечении болевого синдрома, усиливая анальгетический эффект за счёт воздействия на центральные и периферические механизмы боли. Для рутинного использования в клинической практике требуются масштабные исследования, оценивающие безопасность и эффективность комбинированного подхода.*

Ключевые слова: *нейропатический болевой синдром; стимуляция спинного мозга; стимуляция периферических нервов*

Этическое утверждение. Информированное добровольное согласие на публикацию в письменной форме получено от пациента.

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

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

Адрес для корреспонденции: 125047, Россия, Москва, ул. 4-я Тверская-Ямская, д. 16. НМИЦ нейрохирургии им. акад. Н.Н. Бурденко. E-mail: vstenv@gmail.com. Кондратьев В.П.

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Introduction

The prevalence of post-traumatic neuropathy developing as a result of surgical interventions ranges from 3% to 15% [1]. Studies indicate that 6–30% of patients with this condition have chronic neuropathic pain syndrome (NPS) [2]. Several studies evaluating the efficacy of conservative therapy demonstrate that achieving ⩾ 50% pain reduction with monotherapy is possible in only 20–30% of patients, while combined pharmacological approaches show better analgesic effects but are not universally effective [3]. Surgical methods, including neurolysis and neurectomy, demonstrate effectiveness in only 50–70% of cases [4, 5], highlighting the need for innovative treatment approaches. In this context, neuromodulation techniques such as chronic spinal cord stimulation (SCS) and peripheral nerve stimulation (PNS) are gaining

relevance. This article presents a clinical case of combined SCS and PNS in a patient with chronic pharmacoresistant NPS due to sural nerve neuropathy, along with an analysis of current evidence on their efficacy.

Clinical case report

Patient S., a 32-year-old female, underwent surgical removal of a subcutaneous lipoma located on the dorsolateral surface of the left foot posterior to the lateral malleolus. In the early postoperative period, she developed a severe burning pain syndrome radiating along the lateral foot surface, accompanied by paresthesias and hypesthesia of the toes. Pain intensity reached 8 points on the visual analog scale (VAS). Neurological examination and instrumental diagnostics confirmed iatrogenic injury to the sural nerve (*n. suralis*) in the surgical access area. Sequential attempts at surgical management (marginal neurectomy) and conservative therapy (gabapentin 900 mg/day, duloxetine 60 mg/day, venlafaxine 150 mg/day) proved ineffective, showing only short-term analgesic effects with pain recurrence before subsequent dosing. In 2022, the patient underwent implantation of a chronic spinal cord stimulation (SCS) system at Th10-Th12 levels (Fig. 1). Stimulation-induced paresthesias covered 80% of the pain area and reduced pain intensity by 30%.

In 2023, the patient presented to the N.N. Burdenko National Medical Research Center of Neurosurgery, where she underwent a sural nerve block. Complete regression of the pain syndrome was observed during the local anesthetic effect, with complete recurrence of pain occurring on days 2–3 post-block. Consequently, a decision was made to implant an electrode for chronic electrical stimulation of the *n. suralis* under ultrasound guidance. A 3 cm linear incision was made on the posterolateral surface of the calf, through which the *n. suralis* trunk was identified under ultrasound guidance. Using a Tuohy epidural needle (provided with the electrode kit), the electrode was implanted parallel to the *n. suralis* course and secured at the incision site with a thick non-absorbable silk suture (5 metric) (Figs. 2, 3).

The main challenge was advancing the distal end of the electrode to the upper gluteal region, where a subcutaneous pulse generator had previously been implanted. Given the patient's height of 170 cm, the distance from the lateral malleolus to the generator measured approximately 100 cm, necessitating

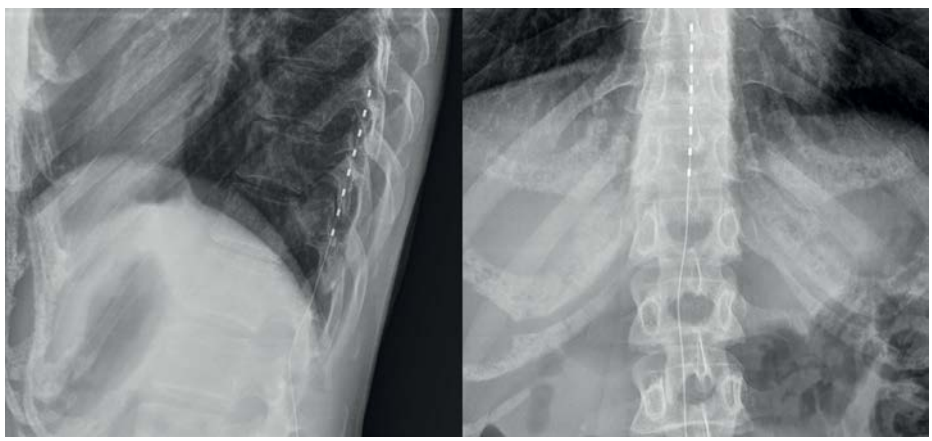

Fig. 1. Radiographic image of the implanted electrode in the posterior epidural space at the T10–T12 vertebral levels.

Fig. 2. Intraoperative photograph. Ultrasound-guided electrode implantation on the sural nerve (*n. suralis*).

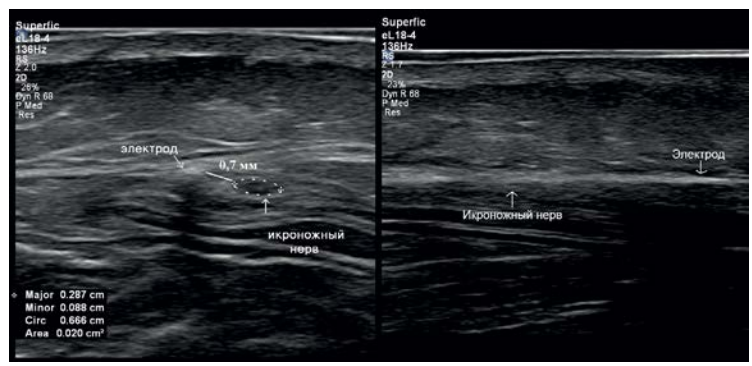

Fig. 3. Ultrasound image of the implanted electrode.
Left: transverse scan. The electrode runs along the trunk of the sural nerve (*n. suralis*) at a distance of less than 1 mm from it. Right: longitudinal scan. Aligning the electrode and *n. suralis* in the same plane is extremely challenging due to their spatial relationship, but the electrode shadow and epineurium of *n. suralis* can be visualized.

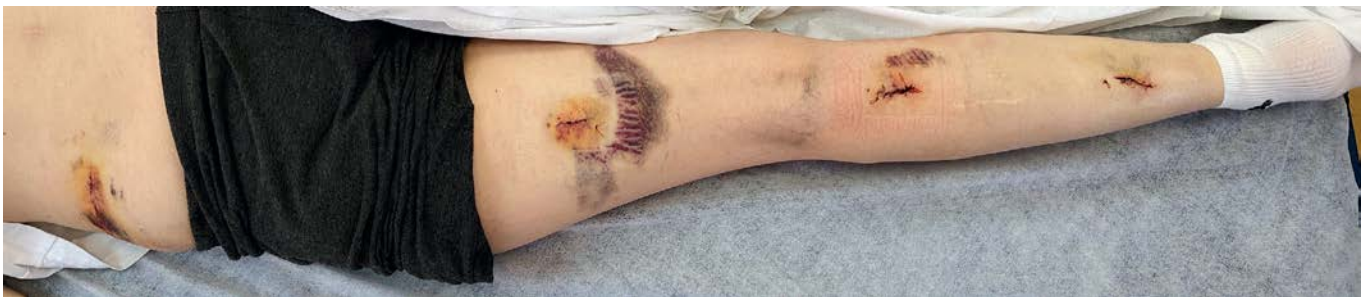

Fig. 4. Photograph of postoperative wounds on day 3 after surgery.
Several hematomas were observed in the loop pocket bed, but they had no clinically significant effect and resolved spontaneously within several weeks.

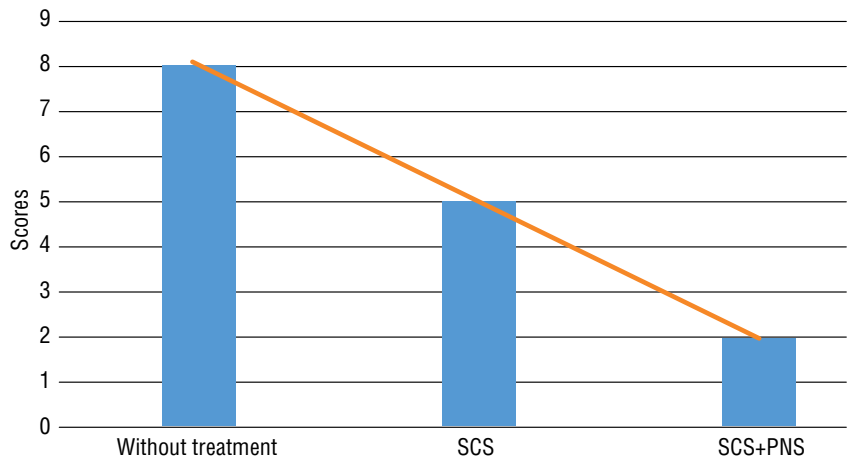

Fig. 5. Changes of pain intensity (VAS scores) over time depending on the treatment method.

a loop system to compensate for joint movements. Additional 2 cm incisions were made in the upper third of the calf and middle third of the thigh; through a subcutaneous tunnel, 55 cm and 35 cm extensions were placed, and two compensatory loops were formed (Fig. 4). This achieved a total system length of 140 cm, eliminating the risk of electrode tension during limb flexion-extension movements. Impedance testing was then performed, which remained within normal limits. The procedure concluded with layered wound closure.

On the following day, neurostimulation programming was adjusted, resulting in complete coverage of the pain area. Combined neurostimulation (SCS + PNS) reduced neuropathic back pain intensity to 1–2 points on the VAS (Fig. 5). At 24-month follow-up, depletion of the implanted pulse generator's battery was noted, requiring its replacement. Pharmacotherapy was maintained at the previous dosage.

Discussion

The presented clinical case demonstrates the potential of combined neuromodulation in managing complex pain syndromes. According to randomized controlled trials, PNS monotherapy achieves ⩾ 50% pain reduction in 38% of patients with posttraumatic neuropathy [6], while a systematic review highlights variability in efficacy (38–78%) depending on injury etiology and location [7]. SCS provides analgesic effects in 50–70% of patients [6, 8]. Several clinical cases describe combined PNS and SCS use with superior analgesic outcomes compared to either modality alone [9–12].

The synergistic mechanism likely involves simultaneous modulation of both spinal and peripheral nociceptive pathways. SCS acts on the dorsal horns of the spinal cord, suppressing central sensitization, while PNS blocks peripheral hyperexcitability of damaged nerves [9]. However, the lack of randomized controlled trials on combined stimulation limits the evidence base, and the increased risk of complications (electrode migration, intraoperative structural damage, infections) necessitates careful patient selection, surgical procedures, and post-operative follow-up.

Another distinctive feature of this clinical case was the remote location of the electrode relative to the generator. When implanting electrodes on the nerves of the lower leg, the generator is typically placed in the lateral thigh area. However, in this case, a generator was already implanted, necessitating the use of multiple extension leads to bridge the distance and minimize the risk of tension on the electrode and extensions, which we successfully achieved. Notably,

there was no significant increase in circuit impedance, which remained around 800 ohms, allowing the use of low stimulation amplitudes and conservation of the generator's battery charge.

Conclusion

The management of NPS refractory to conservative treatments requires a multimodal approach integrating pharmacotherapy, interventional procedures, and neuromodulation techniques. Combined electrical stimulation (SCS + PNS) represents a promising strategy to enhance analgesic effects by targeting multiple pathophysiological components of pain syndromes. The remoteness of the intended stimulation target should not preclude the use of combined modalities. However, the implementation of this strategy in clinical practice must be accompanied by large-scale randomized controlled trials to evaluate long-term efficacy and safety, as well as the development of algorithms for personalized neuromodulation approaches.

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Information about the authors

Viktor P. Kondratyev – postgraduate student, 6th Neurosurgical department (craniofacial neurosurgery) with the group "Functional neurosurgery", N.N. Burdenko National Medical Research Center of Neurosurgery, Moscow, Russia, https://orcid.org/0000-0003-3272-8699
Emil D. Isagulyan – Cand. Sci. (Med.), senior researcher, 6th Neurosurgical department (craniofacial neurosurgery) with the group "Functional neurosurgery", N.N. Burdenko National Medical Research Center of Neurosurgery, Moscow, Russia, https://orcid.org/0000-0003-1191-9357
Alexey A. Tomskiy – Cand. Sci. (Med.), senior researcher, Head, 6th Neurosurgical department (craniofacial neurosurgery) with the group "Functional neurosurgery", N.N. Burdenko National Medical Research Center of Neurosurgery, Moscow, Russia, https://orcid.org/0000-0002-2120-0146

Authors' contribution: *Kondratyev V.P.* – study concept and design, data collection, text writing; *Isagulyan E.D.* – study concept and design, editing; *Tomskiy A.A.* – editing.

Информация об авторах

Кондратьев Виктор Павлович – аспирант 6-го нейрохирургического отделения (краниофациальная нейрохирургия) с группой «Функциональная нейрохирургия» НМИЦ нейрохирургии им. акад. Н.Н. Бурденко, Москва, Россия, https://orcid.org/0000-0003-3272-8699
Исагулян Эмиль Давидович – канд. мед. наук, с. н. с., врач-нейрохирург 6-го нейрохирургического отделения (краниофациальная нейрохирургия) с группой «Функциональная нейрохирургия» НМИЦ нейрохирургии им. акад. Н.Н. Бурденко, Москва, Россия, https://orcid.org/0000-0003-1191-9357
Томский Алексей Алексеевич – канд. мед. наук, с. н. с., руководитель 6-го нейрохирургического отделения (краниофациальная нейрохирургия) с группой «Функциональная нейрохирургия» НМИЦ нейрохирургии им. акад. Н.Н. Бурденко, Москва, Россия, https://orcid.org/0000-0002-2120-0146

Вклад авторов: *Кондратьев В.П.* – концепция и дизайн исследования, сбор и обработка материала, написание текста; *Исагулян Э.Д.* – концепция и дизайн исследования, редактирование; *Томский А.А.* – редактирование.

НЕЙРОФОРУМ-2025

18–19 июня 2025 года в здании Цифрового делового пространства в Москве состоялся юбилейный, 5-й по счёту, НЕЙРОФОРУМ с международным участием. Главным организатором НЕЙРОФОРУМА-2025, уникального мероприятия в области неврологии и нейронаук, выступил Российский центр неврологии и нейронаук, который в 2025 году празднует знаменательную дату – 80 лет со дня своего основания.

Для обеспечения максимальной доступности и привлечения широкого круга специалистов мероприятие было реализовано в гибридном формате. Благодаря такой форме проведения география НЕЙРОФОРУМА-2025 охватила аудиторию из 54 субъектов Российской Федерации и 8 зарубежных стран, включая Азербайджан, Армению, Беларусь, Казахстан, Кыргызстан, Молдову, Таджикистан и др.

В работе НЕЙРОФОРУМА-2025 приняли участие очно 968 человек, онлайн – 1214. Среди них – ведущие эксперты, учёные в области неврологии и нейронаук, а также врачи различных специальностей: неврологи, рентгенологи, нейрохирурги, терапевты, педиатры и многие другие.

В приветственном слове Михаил Александрович Пирадов, академик РАН, вице-президент РАН, директор ФГБНУ «Российский центр неврологии и нейронаук», отметил: «На протяжении многих лет Научный центр неврологии, а ныне – Российский центр неврологии и нейронаук организовывал многочисленные конгрессы, посвящённые различным направлениям в неврологии и смежных дисциплинах. С 2021 года вместо них ежегодно проводится общий консолидирующий форум, который получил название НЕЙРОФОРУМ. Сегодня он объединяет тысячи коллег – очных и онлайн-участников, включая представителей многих стран дальнего и ближнего зарубежья. Пятый форум отличается тем, что совпадает с другим очень важным событием – 80-летним юбилеем нашего Центра».

В выступлении М.А. Пирадова «Путь длиной в 80 лет» был представлен исторический обзор развития Российского центра неврологии и нейронаук, охватывающий период от момента основания Института неврологии Академии медицинских наук СССР в 1945 г. до современности. Особое внимание было акцентировано на ключевых этапах становления РЦНН как ведущего научно-исследовательского и клинического центра в области неврологии и нейронаук. Доклад осветил вклад выдающихся учёных в формирование научных школ и развитие приоритетных направлений исследований, включая изучение патогенеза, диагностики и лечения цереброваскулярных заболеваний, нейродегенеративных и демиелинизирующих процессов и ряда других неврологических расстройств. Подчёркнута эволюция методологической базы исследований – от классических клинических наблюдений до внедрения современных методов изучения патоморфологии, патофизиологии, генетики, ангионейровизуализации. В заключение доклада были обозначены перспективы дальнейшего развития Российского центра неврологии и нейронаук в контексте глобальных тенденций и задач по повышению уровня оказания неврологической помощи пациентам, улучшения качества и продолжительности их жизни.

Научная программа НЕЙРОФОРУМА-2025 отличалась насыщенностью и разнообразием: участники посетили 2 пленарных заседания, посвящённых истории развития неврологии и нейронаук, и 33 тематических симпозиума по вопросам диагностики и лечения неврологических заболеваний, в том числе с освещением последних достижений в области фундаментальных и клинических нейронаук.

В обсуждении ключевых задач, которые стоят перед современной наукой, приняли участие более 100 спикеров, модераторов и докладчиков, российских и иностранных экспертов, в числе которых – лидеры всемирного значения. Так, была представлена лекция иностранного члена РАН, профессора неврологии и эпидемиологии, директора Института инсульта и прикладных нейронаук Оклендского технологического университета в Новой Зеландии В.Л. Фейгина «Цифровая профилактика инсульта: область применения и доказательства эффективности». Докладчик – ведущий специалист в мире по вопросам нейроэпидемиологии, о его высокой результативности можно судить по его индексу Хирша в SCOPUS – 144.

Согласно мнению заместителя директора РЦНН по научной работе, академика РАН С.Н. Иллариошкина, НЕЙРОФОРУМ-2025 задумывался как «мероприятие, которое будет показывать возможности интеграции клинической и фундаментальной неврологии, наши совместные достижения с ведущими университетами и научными институтами страны. Особое внимание мы всегда уделяем поддержке инициатив молодых учёных. Например, на секции фундаментальной науки Конкурса молодых учёных первое место заняла блестящая работа Елены Кондаковой, выполненная по гранту Университета “Сириус”, которая показала новые возможности идентификации функций генов *Spout1* и *CCDC82* в патогенезе врождённых пороков развития нервной системы».

По словам заместителя директора РЦНН по научной работе, академика РАН М.М. Танашян, «опираясь на опыт прошлого, мы стремимся к новым достижениям. В последнее время большой вклад в метаморфозы клинических проявлений различных неврологических заболеваний вносит цереброметаболическое здоровье – предложенный нами новый термин. Необходимо учитывать изменения молекулярно-биохимических, ангиовизуализационных и морфологических биомаркеров при лечении и менять алгоритмы диагностики и лечения, персонифицируя их для каждого пациента».

Участники форума рассмотрели современные возможности нейрохирургии, нейрореабилитации, экспериментальной нейробиологии, цифровых технологий. На симпозиуме по критическим состояниям в неврологии директор Института медицинского образования и профессионального развития РЦНН, член-корреспондент РАН Е.В. Гнедовская рассказала о Всемирном проекте по неврологическим критериям смерти мозга с участием экспертов РЦНН. Отдельное внимание в программе НЕЙРОФОРУМА-2025 было уделено вопросам этики и деонтологии, эффективной коммуникации между врачом и пациентом.

Конкурс молодых учёных, посвящённый фундаментальным нейронаукам и клинической неврологии, высветил и обозначил основные направления «молодёжной» неврологической мысли, а наиболее значимые, на взгляд строгого жюри, работы были отмечены памятными грамотами и ценными призами

В дополнение к научной программе НЕЙРОФОРУМА-2025 был организован шахматный турнир, также показавший тонкую связь неврологической палитры и неврологов с этой древней игрой.

Представленная выставка новейших лекарственных препаратов и технологического оборудования, в том числе отечественного производства, явилась важным дополнением информационного уровня.

Мероприятия НЕЙРОФОРУМА-2025 проходили в тёплой и праздничной атмосфере дружеского общения с коллегами и единомышленниками. Участие в данном событии предоставило возможность прикоснуться к многолетним научным традициям и одновременно ощутить себя частью сплочённого профессионального сообщества. В завершение НЕЙРОФОРУМА-2025 под художественным руководством молодого российского композитора и врача-нейрохирурга РЦНН кандидата медицинских наук Д.В. Петросяна состоялся концерт джазовой музыки, подчеркнувший культурную насыщенность и многогранность мероприятия.