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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

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Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

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In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

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1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

НАУКА

ЭНДОМЕТРИОЗ: НОВЫЙ ПОДХОД К ЭТИОПАТОГЕНЕЗУ (ОБЗОР)

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Эндометриоз является одной из наиболее актуальных проблем не только гинекологии, но и медицины в целом, так как эндометриоидная ткань может обнаруживаться практически во всех органах и сопровождаться выраженным болевым синдромом. Кроме того данная проблема крайне актуальна ввиду ее социальной и экономической значимости, обусловленной широкой распространенностью среди женщин репродуктивного возраста, высоким процентом нарушения фертильности и склонностью к инвалидизации среди пациенток.

Эндометриоз – одно из наиболее распространенных гинекологических заболеваний. Согласно статистике, эндометриоз обнаруживается у 45-82% женщин с хронической тазовой болью, у 2,1-78% женщин с бесплодием, а 25-50% женщин с эндометриозом бесплодны [11]. Оценить в полной мере распространенность эндометриоза достаточно трудно ввиду сложности диагностирования и отсутствия централизованной статистики по заболеванию.

Ежегодно большое количество исследований посвящается вопросам этиологии, патогенеза, диагностики и выбора оптимального метода лечения эндометриоза, однако многие из них по сей день остаются без ответа, а подходы к этиопатогенезу, а следовательно, и к профилактике и терапии этого заболевания продолжают меняться.

На сегодняшний день известно, что эндометриоз – это дисгормональное, иммунозависимое, генетически детерминированное заболевание. Морфологически эндометриоз представляет собой доброкачественно разрастающуюся вне полости матки ткань, подобную ткани нормального эндометрия, проявляющую признаки клеточной активности. Однако эта ткань имеет некоторые особенности, позволяющие дифференцировать ее.

Ранее эндометриоз было принято разделять на генитальный и экстрагенитальный, а генитальный – на внутренний, т.е. эндометриоз тела матки, и наружный, локализующийся в шейке матки, влагалище, промежности, ретроцервикальной области, яичниках, маточных трубах, брюшине или в прямокишечно-маточном углублении. В настоящее время данная классификация утратила свою актуальность, так как эндометриоидное поражение тела матки на сегодняшний день рассматривается как отдельное заболевание – аденомиоз. В настоящее время множество работ посвящено разработке универсальной и лаконичной международной классификации [8].

Выделяют следующие клинические формы эндометриоза:
- перитонеальный эндометриоз
- эндометриомы
- ректовагинальные эндометриоидные узлы.

Эти формы, несмотря на свои различия, имеют схожие гистологические признаки, такие как наличие в очагах эндометриальных стромальных и эпителиальных клеток, персистирующих кровоизлияний и воспаления.

Эндометриоз – полиэтиологичное мультифакторное заболевание, на его развитие влияют факторы окружающей среды, образ жизни и наследственность. Патогенез эндометриоза связан с множеством процессов, образующих сложную систему, в которой все компоненты потенцируют действие друг друга. Они включают в себя: воспаление, ангиогенез, экспрессию цитокинов и хемокинов, а также эндокринные нарушения, такие как нарушения экспрессии стероидных гормонов и рецепторов к ним. При этом основная роль в развитии эндометриоза принадлежит генетическим и эпигенетическим факторам.

Процессы деметилирования приводят к изменению экспрессии генов ключевых факторов патогенеза эндометриоза: усиливается экспрессия ароматазы, тероидогенного фактора 1 (SF1) и эстрогеновых рецепторов (ЭР).

Основным регулятором транскрипции, имеющим отношение к развитию эндометриоза, является SF1 [3]. Он связывается с промоторами стероидогенных генов при стимулирующем воздействии простагландина Е2 (ПГЕ2). В норме в эндометрии SF1 метилируется и репрессируется, однако в эндометриоидных клетках этого не происходит.

Другим важным аспектом является изменение работы рецепторов к эстрогену. Известны две изоформы эстрогеновых рецепторов: ЭР-α и ЭР-β, чье функционирование определяется наличием лиганда и корегуляторов. Показано, что экспрессия ЭР-β при эндометриозе выше в 140 раз по сравнению с нормальной тканью эндометрия [21]. Причем за счет активации

ЭР-α в основном стимулируется пролиферация клеток, а при взаимодействии эстрогена с ЭР-β наблюдается локальное повышение синтеза эстрогенов и опосредованное снижение экспрессии прогестерона (Р4), а впоследствии и развитие резистентности к нему [18].

ЭР-α и ЭР-β экспрессируются на рецепторных и симпатических нейронах, доказывая влияние эстрогена на аксоны афферентных нейронов, а значит, и его участие в возникновении болевого синдрома при эндометриозе [10]. Кроме того болевые импульсы могут возникать за счет стимуляции ноцицепторов нерегулярными сокращениями эндометриоидной ткани, вызванными действием местных провоспалительных агентов (ПГF2α). Вместе с этим важная роль отводится индуцированному эстрогенами усилению экспрессии фактора роста нервов (NGF) в перитонеальной жидкости, который стимулирует аксоны афферентных нейронов, усиливая иннервацию в эндометриоидных очагах. Более того, предшественник NGF (proNGF), может связываться с рецептором p57, оказывая нейротоксичное действие на восприимчивые к NGF симпатические нейроны [10].

Помимо этого в развитии эндометриоза участвуют и изоформы рецепторов к Р4 –PGR-A и PGR–B. Обе формы PGR присутствуют в эндометрии, но их соотношение меняется с течением менструального цикла. На ранней стадии пролиферации уровни PGR-A относительно выше, чем PGR-B. В периовуляторной фазе цикла уровень PGR-B повышается до уровня PGR-A, а к поздней секреторной фазе экспрессия обоих рецепторов понижается, в результате чего их уровень возвращается к исходным значениям, наблюдавшимся на ранней пролиферативной фазе. В одном из недавних исследований было обнаружено, что при эндометриозе PGR-A преобладают независимо от фазы цикла, причем не только в эктопическом, но и в эутопическом эндометрии, что отрицательно влияет на репродуктивную функцию [7].

В отличие от нормального эндометрия, в эндометриоидной ткани содержится меньше рецепторов к Р4. В связи с этим в очагах эндометриоза преобладает его ингибиторная форма, в результате чего развивается резистентность к данному гормону. Резистентность к Р4 приводит к снижению антипролиферативной активности, апоптоза и активности противовоспалительных агентов, а также к повышению секреции ПГ и усилению активности металлопротеиназ и факторов гипоксии (HIF1A). Это способствует инвазии эндометриоидных гетеротопий и неоангиогенезу, что в сочетании со всем вышеперечисленным является ключевыми звеньями патогенеза эндометриоза [2].

Кроме того имеются данные, согласно которым эндометриодная ткань может самостоятельно потенцировать системные и локальные иммунные нарушения, что связано в основном с повышением активности цитокинов (TNFα, IL-4, IL-8), а также с развитием особых механизмов, таких как изменение экспрессии белков теплового шока и антигенных свойств клеток, с помощью которых эндометриоидные клетки способны избегать иммунного надзора [14]. В итоге происходит формирование порочного круга, так как в результате перечисленных выше процессов повышается концентрация медиаторов воспаления, что приводит к локальной гиперпродукции эстрогенов, что, в свою очередь, стимулирует ЦОГ-2, участвующую в синтезе ПГЕ2, который затем потенцирует продукцию ароматазы [16]. Далее ароматаза катализирует превращение андростендиона и тестостерона в эстрон и эстрадиол (Е2). Важно отметить, что изоформа 2 фермента 17β-гидростероид-дегидрогеназы (17β-HSD2), катализирующая превращение Е2 в эстрон, отсутствует в эндометриоидных очагах, а изоформа 1 (17β-HSD1), преобразующая эстрон в Е2, в них присутствует. Это способствует локальной кумуляции эстрогенов за счет увеличения производства Е2 и снижения его инактивации [6] и потенцирует местные изменения, вызванные действием эстрогена.

Другим важным вопросом в проблеме эндометриоза является возможность его малигнизации. Несмотря на то, что это заболевание считается доброкачественным, эндометриоидная ткань обладает свойствами, присущими опухолевым клеткам. К ним относятся: инвазивный и автономный рост, неоангиогенез, преобладание процессов пролиферации над апоптозом, а также эпителиально-мезенхимальная трансформация. На сегодняшний день эндометриоз считается самостоятельным фактором риска развития злокачественных новообразований не только органов репродуктивной системы, но и толстого кишечника, мочевого пузыря, молочных желез [9]. Однако согласно исследованиям, эндометриоз яичников в большей степени склонен перерождаться в злокачественные новообразования (эндометриоз-ассоциированный рак яичников), хотя сам процесс малигнизации и связанные с ним процессы требуют дальнейшего изучения [4].

На сегодняшний день известны два непосредственных пути возможного злокачественного перерождения гетеротопий. Первый путь – гормональный, связанный с избыточной продукцией эстрогена очагами эндометриоидной ткани, которые способствуют развитию гормон-зависимых опухолей. Второй путь – воспалительный. Рак в этом случае индуцируется оксидативным стрессом, медиаторами хронического воспаления и свободным железом, присутствующим в большом количестве в эндометриоидной ткани.

Существуют две основные теории, объясняющие возникновение первоначальных изменений по тому или другому пути и, как следствие, развитие ассоциированных с эндометриозом злокачественных новообразований. Первая теория – теория развития раковых опухолей из так называемого атипичного эндометриоза. Атипичный эндометриоз характеризуется гиперплазией эндометриальных желез, выраженной клеточной атипией и, в некоторых случаях, наличи-

ем клеток типа «обойного гвоздя», характерных для светлоклеточного рака яичников [5]. То, что атипичный эндометриоз может быть предраковым состоянием, подтверждается предыдущими исследованиями, в которых при гистологическом обследовании пациенток с эндометриозассоциированным раком яичников (ЭАРЯ) он обнаруживался в 80% случаев [20].

В этом случае важным фактором развития злокачественного новообразования является накопление мутаций в онкогенах и антионкогенах, причем многие из этих мутаций встречаются как при злокачественных патологиях, так и при эндометриозе [13]. В одном из исследований был проведен молекулярный анализ генетических нарушений у пациенток с наличием как эндометриоза, так и рака яичников. При этом было обнаружено большое количество перекрестных мутаций, таких как потеря гетерозиготности, мутации генов PTEN, p53 и ARID1A, в связи с чем можно сделать вывод, что эндометриоз может быть предшественником подтипа рака яичников [15]. Ген ARID1A представляет собой антионкоген, который кодирует BAF250a - белок, связанный с ремоделированием комплекса SWI/SNF. Данный комплекс отвечает за регулирование многих процессов, таких как пролиферация, дифференцировка, репарация ДНК и супрессия опухолевого роста. Полученные результаты подтверждают, что инактивация ARID1A часто предшествует развитию светлоклеточного и эндометриозассоциированного рака яичников [12]. В рамках другого исследования проводилось сравнение уровней метилирования длинных диспергированных повторов (LINE-1) в нормальном эндометрии, эндометриоидных кистах яичника, ЭАРЯ и светлоклеточном раке яичников. Результаты показали, что гипометилирование LINE-1 является молекулярным событием, инициирующим злокачественную трансформацию и может быть показателем малигнизации эндометриоидных гетеротопий [17].

Согласно второй теории, эндометриоз сам по себе не является предраковым состоянием, однако ассоциированные с ним нарушения способствуют развитию онкологических заболеваний. Исследования показали, что микроокружение при ЭАРЯ и эндометриозе имеет сходный состав медиаторов и цитокинов [11].

Важным механизмом, способным потенцировать малигнизацию, является оксидативный стресс. Периодические кровоизлияния и накопление железа в гетеротопиях, а также недостаточная активность антиоксидантной системы приводит к образованию реактивных форм кислорода, которые повреждают эндотелиальные клетки и нарушают их функционирование. Роль оксидативного стресса в патогенезе эндометриоза была доказана измерением уровней тиола, каталазы и церулоплазмина в сыворотке [19]. Также было показано, что концентрация свободного железа в эндометриотических кистах выше в 100 раз по сравнению с нормальным эндометрием [22]. Это приводит к экспрессии молекул адгезии и генетическим изменениям, а также индуцирует воспалительный процесс [1].

Подводя итог можно сказать, что взгляд на эндометриоз продолжает меняться. Для своевременной диагностики, эффективной профилактики и назначения патогенетически обоснованного лечения необходимо учитывать актуальные на сегодняшний день модели патогенеза. Знание специфики этого заболевания важно и в отношении возможности присоединения злокачественного процесса. Врачи должны быть осведомлены о повышенном риске развития определенных подтипов рака яичников и предупреждать об этом пациентов. Кроме того важно продолжать изучение вопросов эндометриоза, так как более глубокие знания в этой области необходимы для разработки новых стандартов ведения пациенток с этой патологией и своевременной постановки диагноза.

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SUMMARY

ENDOMETRIOSIS: A NEW APPROACH TO ETIOLOGY AND PATHOGENESIS (REVIEW)

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Endometriosis is a dyshormonal immune-dependent genetically determined disease, which appears as an endometrioid tissue that grows outside the uterine. Endometriosis is one of the most urgent problems of medicine.

To date, new concepts of the endometriosis etiology and pathogenesis have been developed, but, despite their abundance, there is no unified theory. Genetic and epigenetic factors result in changes in an expression of aromatase, steroidogenic factor 1, and estrogen receptors are suggested to be the main cause of endometriosis. These changes lead to an active synthesis of various pro-inflammatory agents and a nerve growth factor, that are important in the development of pain syndrome. Also, changes in the progesterone receptor functioning and the local progesterone resistance development decrease the antiproliferative activity, apoptosis, and the anti-inflammatory substances level, as well as increase the prostaglandin, metalloproteinase activity, and level of hypoxia factors.

In addition, there are shreds of evidence that endometriosis is associated with the risk of malignant tumors development, so new concepts for understanding these mechanisms are actively developing. Some of these mechanisms are discussed in this review.

Keywords: endometriosis, etiology, pathogenesis, malignancy, endometriosis-associated ovarian cancer.

РЕЗЮМЕ

ЭНДОМЕТРИОЗ: НОВЫЙ ПОДХОД К ЭТИОПАТОГЕНЕЗУ (ОБЗОР)

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В настоящее время разрабатываются новые концепции этиологии и патогенеза эндометриоза, но, несмотря на их многочисленность, ни одна из них не признана универсальной. Основная роль в патогенезе эндометриоза отводится генетическим и эпигенетическим факторам, приводящим к изменению экспрессии ароматазы, стероидогенного фактора 1 и эстрогеновых рецепторов, приводящих к активному синтезу различных провоспалительных агентов и фактору роста нервов, имеющих важное значение в развитии болевого синдрома. Немаловажно также изменение функционирования рецепторов к прогестерону и развитие локальной резистентности к данному гормону, что приводит к снижению антипролиферативной активности, апоптоза и активности противовоспалительных агентов, а также к повышению секреции простагландинов и усилению активности металлопротеиназ и факторов гипоксии.

Кроме того, существуют доказательства риска развития злокачественных новообразований, связанных с эндометриозом, благодаря чему активно разрабатываются новые концепции понимания данных механизмов, некоторые из которых рассматриваются в данном обзоре.

რეზიუმე

ენდომეტრიოზი: ახალი მიდგომები ეტიოპათოგენეზთან დაკავშირებით (მიმოხილვა)

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ფედერალური სახელმწიფო ავტონომიური უმაღლესი საგანმანათლებლო დაწესებულება "რუსეთის ფედერაციის ჯანდაცვის სამინისტროს ი. სეჩენოვის სახ. მოსკოვის პირველი სახელმწიფო სამედიცინო უნივერსიტეტი (სეჩენოვის უნივერსიტეტი), სამედიცინო-პროფილაქტიკური ფაკულტეტი, მეანობა-გინეკოლოგიის კათედრა, რუსეთი

დღეს მკვლევარები ავითარებენ ახალ კონცეფციებს ენდომეტრიოზის ეტიოლოგიისა და პათოგენეზის შესახებ, მაგრამ, მათი სიმრავლის მიუხედავად, არც ერთი მათგანი არ ითვლება უნივერსალურად. თუმცა, ძირითადი როლი ენდომეტრიოზის ეტიოპათოგენეზში იმ გენეტიკურ და ეპიგენეტიკურ ფაქტორებს ენიჭება, რომლებიც იწვევენ არომატაზას, სტეროიდული ფაქტორი 1-ის და ესტროგენების რეცეპტორების ექსპრესიის შეცვლას, ასევე, განაპირობებენ სხვადასხვა პროანთებითი აგენტის და ნერვის ზრდის ფაქტორის აქტიურ სინთეზს, რასაც მნიშვნელოვანი გავლენა აქვს ტკივილის სინდრომის განვითარებაში. ამასთან, არც თუ უმნიშვნელოა პროგესტერონის მიმართ მგრძნობიარე რეცეპტორების ცვლილებები და ამ ჰორმონისადმი ლოკალური რეზისტენტობის განვითარება, რაც განაპირობებს ანტიპროლიფერაციული აქტივობის, აპოპტოზის და ანთების საწინააღმდეგო აგენტების აქტივობის შემცირებას, ასევე, პროსტაგლანდინების სეკრეციის ზრდას და მეტალოპროტეინაზას და ჰიპოქსიის ფაქტორების აქტივაციას.

ამას გარდა, არსებობს მტკიცებულებანი ენდომეტრიოზთან დაკავშირებული ავთვისებიანი ახალწარმონაქმნების განვითარების რისკის შესახებ, რის გამოც აქტიურად მუშავდება კონცეფციები ამ მექანიზმების გაგებისათვის, რომელთა ნაწილიც განხილულია წარმოდგენილ მიმოხილვაში.

FEATURES OF FORMATION OF COLLATERAL CIRCULATION IN PATIENTS WITH SUBCLAVIAN STEAL SYNDROME

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Patients with combined carotid, subclavian and vertebral artery lesions constitute the most difficult group among extracranial artery pathology. The difficulty is due to the fact that the compensation of cerebrovascular disturbances in occlusive lesions of the major arteries of the head and neck is complex and diverse and depends on various factors [5,6].

Subclavianstealsyndromeis a complex of morphological and hemodynamic changes which develops due to an occlusion or stenosis reducing more than 50% diameter of brachiocephalic trunkor proximal portion of the first segment of the subclavian artery to the level of entry of the ipsilateral vertebral artery [7,8].

Subclavianstealsyndrome affects the left side more frequently; however it may be bilateral [12]. Hypoperfusion abnormalities in blood flow of the ipsilateral vertebral artery and compensatory steal of blood from the contralateral vertebral artery and vertebrobasilar arteries form a characteristic symptom complex (dizziness, vertigo, visual deterioration, hemianopia, ataxia) [6,12]. Reduced vertebral arterial perfusion pressure on the affected side is the main mechanism of hemodynamic changes and compensatory reallocations [3]. It leads to the occurrence of pressure gradient for the contralateral vertebral artery resulting in blood flow reallocations within its basin [1]. In occlusive lesions of the subclavian arteries the compensation of blood flow in the ipsilateral vertebral artery is often formed due to changes in the blood flow direction in the major and posterior cerebral arteries creating vertebrobasilar steal [4,6].

Diagnostic ultrasound and radiological methods play a leading role in determination of indications for surgical treatment of atherosclerotic lesions of the major arteries of the head and neck [3]. They determine the nature and degree of occlusive lesions, state of compensatory mechanisms, and functional state of cerebral hemodynamics.

Nowadays three stages of subclavian-vertebral steal syndrome and four stages of chronic upper extremity ischemia are known [11]. However, both classifications do not consider hemodynamic course of subclavian steal syndrome and the degree of collateral compensation. Considering the importance of compensatory mechanisms of cerebral blood supply in atherosclerotic lesions of the extracranial arteries the study of the features of formation of collateral circulation is relevant.

The objective of the research was to study the features of formation of collateral circulation in patients with subclavian steal syndrome.

Material and methods. The paper presents the results of examination of 42 patients with subclavian steal syndrome. The average age of patients was 63.5 (±2.5) years. Diagnostic algorithm included bilateral duplex ultrasonography (DUS) of the extracranial and intracranial arteries andneurological examination.

The results of neurologic manifestations are presented in Table 1.

To assess the results of the examination all patients were divided into 3 groups depending on the clinical course of subclavian steal syndrome (Table 2).

Group I included 11 (26.2%) patients with latent subclavian steal syndrome, Group II consisted of 23 (54.8%) patients with transient subclavian steal syndrome, and Group III comprised 8 (19.0%) patients with a persistent course of the disease.

The 3 groups did not differ significantly in age and gender.

In addition, the stage of chronic upper extremity ischemia (CUEI) was determined using the standard classification:

Stage I – stable compensation of blood flow;

Stage II - relative compensation of blood flow (signs of extremity ischemia manifest themselves during physical activity);

Stage III - exhaustion of compensation (signs of extremity ischemia are present at rest);

Stage IV – decompensation or stage of necrotic ulcerative changes.

Compensatory hemodynamic mechanisms which provided collateral circulation in subclavian steal syndrome were studied using DUS of the extracranial and intracranial arteries. There were considered the peak systolic velocity (PSV), functional parameters of blood flow – resistance index (RI) and pulsatility index (PI), and integrated hemodynamic parameter –volumetric blood flow (VBF).

Using DUS there were determined two intracranial and three extracranial routes of collateral circulation (Tables 3, 4).

Results and their discussion. Latent subclavian steal syndrome was detected in 11 (26.2%) patients, transient subclavian steal syndrome was found in 23 (54.8%) patients, and a persistent course of the disease was observed in 8 (19.9%) patients. Stage I CUEI was detected in 20 (47.6%) patients; stage IICUEI was found in 8 (19.0%) patients; stage III CUEI was observed in 9 (21.4%) pa-

Table 1. Clinical symptoms of vertebrobasilar insufficiency in patients

Symptoms	Incidence, %
Headache	71.4%
Amnesia	45.2%
Rotatory vertigo	54.8%
Tinnitus	52.4%
Loss of consciousness	42.9%
Bulbar symptoms (dysarthria, dysphagia)	9.5%
Coordination disorders	21.4%
Signs of visual impairment (temporary blindness, greyout)	26.2%

Table 2. Distribution of patients according to the course of subclavian steal syndrome and stages of CUEI

Stages of CUEI	Course of SSS			Total
	Latent	Transient	Persistent	
I	9 (21.4%)	11 (26.2%)	-	**20 (47.6%)**
II	2 (4.8%)	5 (11.9%)	1 (2.4%)	**8 (19.0%)**
III	-	7 (16.7%)	2 (4.8%)	**9 (21,4%)**
IV	-	-	5 (11.9%)	**5 (11.9%)**
Total	**11 (26.2%)**	**23 (54.8%)**	**8(19.0%)**	**42**

CUEI - chronic upper extremity ischemia

Table 3. Hemodynamic mechanisms of collateral compensation

Extracranial compensation, n= 27 (64.3%)			**Intracranial compensation,** n=15 (35.7%)	
Occipito-vertebral mechanism	Thyroid mechanism	Brain stem-occipital mechanism	Vertebro-vertebral mechanism	Cerebrobasilar mechanism
n=16 (38.1%)	n=7 (16.7%)	n=4 (9.5%)	n=9 (21.4%)	n=6 (14.3%)

Table 4. Distribution of patients according to compensatory mechanisms and the course of subclavian steal syndrome

Compensatory mechanisms	**Course of subclavian steal syndrome**			**Total**
	Latent	**Transient**	**Persistent**	
Extracranial	**8 (19.0%)**	**14 (33.3%)**	**5 (11.9%)**	**27 (64.7%)**
Occipito-vertebral	5 (11.9%)	8 (19.0%)	3 (7.1%)	16 (38.1%)
Thyroid	2 (4.8%)	4 (9.5%)	1 (2.4%)	7 (16.7%)
Brain stem-occipital	1 (2.4%)	2 (4.8%)	1 (2.4%)	4 (9.5%)
Intracranial	**3 (7.1%)**	**9 (21.4%)**	**3 (7.1%)**	**15 (35.7%)**
Vertebro-vetebral	2 (4.8%)	5 (11.9%)	2 (4.8%)	9 (21.4%)
Cerebrobasilar	1 (2.4%)	4 (9.5%)	1 (2.4%)	6 (14.3%)
Total	**11 (26.2%)**	**23 (54.8%)**	**8 (19.0%)**	**42 (100%)**

tients; stage IV CUEI was diagnosed in 5 (11.9%) patients.

Symptoms of vertebrobasilar insufficiency were detected in 26.6% of patients, and combination of CUEI of different stage and vertebrobasilar insufficiency was diagnosed in 73.8% of patients.

When analyzing the mechanisms of collateral compensation of inadequate blood flow the extracranial mechanism was observed in 27 (64.3%) patients, and it was provided by three main groups of collateral hemodynamic reallocation:

•the occipito-vertebral hemodynamic mechanism of compensation was detected in 16 (38.1%) patients;

•the thyroid compensatory mechanism was found in 7 (16.7%) patients;

•the brain stem-occipital compensatory mechanism was observed in 4 (9.5%) patients.

The intracranial compensatory mechanism was observed in 15 (35.7%) patients, and it was provided by two main groups of collateral hemodynamic reallocation:

•the vertebro-vertebral compensatory mechanism was found in 9 (21.4%) patients;

•the cerebrobasilar compensatory mechanism was detected in 6 (14.3%) patients.

When evaluating the extracranial compensatory mechanisms, the occipito-vertebral hemodynamic mechanism was the most common (38.1%). It was formed due to increased blood flow in the carotid artery with hemodynamic reallocationto the occipital artery. The occipital artery anastomoses with muscular branches of the vertebral artery via its own branches. It is the main anatomical basis of collateral circulation [9,11].

Next important route of collateral circulation was the thyroid mechanism (16.7%) which was formed due to significantly increased blood flow in the common and external carotid arteries with hemodynamic reallocation to the superior thyroid artery. This mechanism of collateral circulation is mainly responsible for hemodynamics of the ipsilateral upper extremity; vertebral artery blood flow is supported by the amount of blood passing through the stenotic segment of the subclavian artery [1].

The brain stem-occipital mechanism was formed due to increased blood flow in the external carotid artery (ECA) with hemodynamic reallocation to the occipital artery. This mechanism of collateral circulation is also responsible for hemodynamics of the ipsilateral upper extremity; vertebral artery blood flow is supported by hemodynamic function of the stenotic segment of the subclavian artery.

The intracranial compensatory mechanism was observed in 12 (35.7%) patients, and it was provided by two main groups of collateral hemodynamic reallocation:

-the vertebro-vertebral compensatory mechanism (21.4%) was formed due to increased blood flow in the contralateral vertebral artery with hemodynamic reallocation to the ipsilateral vertebral artery and partial steal of blood from the main carotid artery and the ipsilateral posterior cerebral artery;

-the cerebrobasilar compensatory mechanism (14.3%) was formed due to hemodynamic reallocation to the ipsilateral vertebral artery by blood flowing from the ipsilateral middle cerebral artery (with its distal steal) through the ipsilateral posterior communicating artery to the vertebrobasilar basin with steal of blood from it and further reallocationof blood supply to the vertebral artery on the affected side.

The above-mentioned data indicate a significant role of the ECA basin in the formation of hemodynamic compensatory mechanisms due to collateralization and hemodynamic reallocation of blood flow to the large collateral arteries (occipital and superior thyroid arteries).

Each of compensatory mechanisms has its own hemo-

dynamic peculiarities. There is usually no direct correlation between changes in the parameters of blood blow in the carotid and vertebral arteries [4,9,10].The occipito-vertebral compensatory mechanism has the most positive influence on the compensation of hemodynamic failure of the vertebrobasilar basin. Ambiguously expressed hemodynamic parameters are registered in the brain stem-occipital compensatory mechanism that is caused by many variants of collateral reallocation.

The stage of subclavian steal syndrome is generally not decisive for hemodynamic changes dynamics of which is not always proportional depending on the course of the disease [2,6,8]. To determine the hemodynamic characteristics of collateral compensationmore accurately hemodynamic changes in distal segment of the subclavian artery should be considered. In addition, cerebral hemodynamics should be studied in detail and the intracranial compensatory mechanisms should be taken into account. Blood flow parameters in the contralateral vertebral artery should also be considered [3,4].

Therefore, treatment tactics for patients with subclavian steal syndrome should depend not only on the patency of homo- and contralateral vessels supplying the brain with blood, concomitant atherosclerotic lesions but on the level of development of compensatory mechanisms.

Consideration of the features of collateral circulation in patients with subclavian steal syndrome may serve as a prognostic criterion for selecting an optimal treatment tactics. Each of compensatory mechanisms has its own hemodynamic peculiarities. The occipito-vertebral compensatory mechanism has the most positive influence on the compensationof hemodynamic failure of the vertebrobasilar basin.

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SUMMARY

FEATURES OF FORMATION OF COLLATERAL CIRCULATION IN PATIENTS WITH SUBCLAVIAN STEAL SYNDROME

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To date in patients with subclavian steal syndrome diagnosis is only grade of stenosis or localization of occlusion described. Authors recommend to take into account also type of a collateral compensation of cerebral circulation for selection of an optimal treatment

The objective of the research was to study the features of formation of collateral circulation in patients with subclavian steal syndrome.

The authors described changes in the direction of blood flow in the extracranial vessels of 42 patients with subclavian steal syndrome. Latent subclavian steal syndrome was detected in 26.2% of patients, transient subclavian steal syndrome was found in 54.8% of patients, and a persistent course of the disease was observed in 19.9% of patients. Symptoms of vertebrobasilar insufficiency were detected in 26.6% of patients, and combination of chronic upper extremity ischemia and vertebrobasilar insufficiency was diagnosed in 73.8% of patients.

When analyzing the features of collateral circulation in 64.3% of patients the extracranial compensatory mechanism was observed being provided by three main groups of collateral hemodynamic reallocation: the occipito-vertebral hemodynamic mechanism of compensation was detected in 38.1% of cases, the thyroid compensatory mechanism was found in 16.7% of cases, and the brain stem-occipital compensatory mechanism was observed in 9.5% of cases. In 35.7% of patients the intracranial compensatory mechanism was observed being provided by two main groups of collateral hemodynamic reallocation: the vertebro-vertebral compensatory mechanism was found in 21.4% of cases and cerebrobasilar compensatory mechanism was detected in 14.3% of cases.

Consideration of the features of collateral circulation in patients with subclavian steal syndrome may serve as a prognostic criterion for selecting an optimal treatment tactics.Each of compensatory mechanisms has its own hemodynamic peculiarities. The occipito- vertebral compensatory mechanism has the most positive influence on the compensationof hemodynamic failure of the vertebrobasilar basin.

Keywords: subclavian artery stenosis, subclavian steal syndrome, vertebrobasilar insufficiency, atherosclerosis.

РЕЗЮМЕ

ОСОБЕННОСТИ ФОРМИРОВАНИЯ КОЛЛАТЕРАЛЬНОГО КРОВООБРАЩЕНИЯ У БОЛЬНЫХ С SUBCLAVIAN STEAL-СИНДРОМОМ

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Цель исследования - изучить особенности формирования коллатерального кровообращения у больных с subclavian steal-синдромом.

Описаны изменения направления кровотока в экстракраниальных артериях 42 больных при subclavian steal-синдроме. Латентное течение steal-синдрома обнаружено у 26,2% больных, переходное течение - 54,8% и постоянное - у 19,0%. Проявления вертебро-базилярной недостаточности обнаружены в 26,2% случаев, а сочетание явлений хронической ишемии верхней конечности и вертебро-базилярной недостаточности диагностированы у 73,8% пациентов, позвоночно-позвоночный механизм – у 21,4%; церебро-базилярный механизм – у 14,3%.

Учет особенностей коллатерального кровообращения у больных с subclavian steal-синдромом может быть прогностическим критерием в выборе тактики лечения этой группы пациентов. Каждый механизм компенсации имеет свои гемодинамические особенности. Наиболее положительное влияние на компенсацию гемодинамической недостаточности вертебро-базилярного бассейна имеет затылочно-позвоночный механизм компенсации.

რეზიუმე

კოლატერალური სისხლის მიმოქცევის ფორმირების თავისებურებანი subclavian steal-სინდრომის მქონე პაციენტებში

[1,2]ი. კოპოლოვეცი, [2]პ. შტეფანიჩი, [1]ვ. რუსინი, [3]შ. ტოტი, [1]ვ. მაშურა, [1]პ. ბერეკი

[1]უჟგოროდის ეროვნული უნივერსიტეტი, მედიცინის ფაკულტეტი, უკრაინა; [2]სისხლძარღვთა ქირურგიის კლინიკა, აღმოსავლეთ სლოვაკეთის გულ-სისხლძარღვთა დაავადებების ინსტიტუტი, პ. შაფარიკის უნივერსიტეტი, მედიცინის ფაკულტეტი, კოშიცე; [3]შინაგანი მედიცინის კლინიკა, ლ.პასტერის საუნივერსიტეტო კლინიკა, მედიცინის ფაკულტეტი, კოშიცე, სლოვაკეთის რესპუბლიკა

კვლევის მიზანს შეადგენდა კოლატერალური სისხლის მიმოქცევის ფორმირების თავისებურებების შესწავლა subclavian steal-სინდრომის მქონე პაციენტებში.

42 ავადმყოფში subclavian steal-სინდრომით აღწერილია სისხლის ნაკადის ცვლილებები ექსტრაკრანიულ არტერიებში. steal-სინდრომის ლატენტური მიმდინარეობა აღენიშნა პაციენტთა 26,2%-ს, გარდამავალი მიმდინარეობა - 54,8% -ს, მუდმივი - 19,0%-ს. ვერტებრობაზილარული უკმარისობა გამოვლინდა 26,2%-ში, ზედა კიდურების ქრონიკული იშემიის და ვერტებრობაზილარული უკმარისობის შერწყმა დიაგნოსტირებული იყო პაციენტების 73,8%-ში.

კოლატერალური სისხლის მიმოქცევის თავისებურებების გათვალისწინება subclavian steal-სინდრომის დროს შესაძლოა აღმოჩნდეს პროგნოზული კრიტერიუმი ამ ჯგუფის პაციენტების მკურნალობის ტაქტიკის შერჩევისას. თითოეულ საკომპენსაციო მექანიზმს აქვს ჰემოდინამიკური თავისებურებები. ვერტებრობაზილარული აუზის ჰემოდინამიკური უკმარისობის კომპენსაციისათვის ყველაზე დადებითი გავლენა აქვს კომპენსაციის თხემ-ხერხემლის მექანიზმს.

ENDOMETRIAL POLYPS IN WOMEN OF REPRODUCTIVE AGE: CLINICAL AND PATHOGENETIC VARIATIONS

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Endometrial polyps (EP) are the most common structural abnormalities of endometrium with the prevalence ranging from 10% in asymptomatic women to 26% in women with unexplained subfertility [13] and up to 47% in women with endometriosis-associated subfertility [7]. In a large prospective trial including 1000 infertile women scheduled for in vitro fertilization, the prevalence of endometrial polyps was found to be 32% [5].

Despite the development of new diagnostic techniques, general agreement on the causes of EP does not exist. Today one thing is clear, it is a multifactorial disease, which involves a variety of complex mechanisms in order to occur [6]. Three central causes of endometrial polyps have been suggested:

- polyps are local outgrowths of the basalis endometrium;
- polyps form in response to an imbalance of estrogen and progesterone receptors;
- polyps are a product of genetic mutations that increase mitosis and decrease apoptosis [2].

However, the steadily growing number of publications on the inflammatory genesis of endometrial hyperplasia, as well as the accumulation of a large amount of experimental data on the activation of stem cells overgrowth by local inflammatory microenvironment, proves undisputedly the alternative inflammatory mechanism for polyps occurance [3, 10, 12].

EP are benign protrusions occasionally found on transvaginal ultrasound tomography, hysterosalpingography and sonohysterogram [1].

The concept of endometrial micropolyp (MP) was introduced as a small lesion typically 1-2 mm in length [4]. In contrast to classical EP being often predictable with ultrasound screening, endometrial MP are generally undetectable with diagnostic imaging techniques other than hysteroscopy. Endometrial MP co-exist at a high rate with chronic endometritis (CE), which is an unusual plasmacytes infiltration within the endometrial stromal compartment [11]. CE, which is fraught with the potential of hyperplastic and neoplastic growth, contributes not only to the pathogenesis of benign endometrial changes, but also to the formation of infertility. According to different authors, CE rate in infertile women ranges from 12 to 60%, and in patients with multiple failed IVF attempts exceeds 60% [8, 9]. Highest frequency indices of CE were observed in patients with recurrent miscarriage, where the disease rate was from 33% to 70% or more [8,10].

EP and CE are two most common causes of unexplained infertility in women of reproductive age. Given that CE is always identified with the existence of MP, the idea that EP and MP are phases of the same disease is the subject of the most heated scientific debates to date.

The aim of our study was to study the relationship between the morphofunctional characteristics of the endometrium, hormonal homeostasis and microbiocenosis of the reproductive system in patients with EP.

Material and methods. The study conducted by the authors of this article was based on the patients aged 18 to 35 who consulted for pregnancy planning. After studying the anamnesis and the ultrasound results, 30 healthy women were selected and made up the control group (group III).

All the patients with abnormalities of the reproductive function (infertility, miscarriage, EP) based on the echographic data received hysteroscopy. After the hysteroscopic characteristics analysis and the study of the pathological study results, the patients were divided into two groups. Group I consisted of 70 women who had shown (and confirmed histologically) EP during hysteroscopy. The second group included 30 women with MP recorded during hysteroscopy. Given that the specificity of detection of MP with CE is 99%, group II included women whose accuracy of morphological verification of CE was increased due to mandatory detection of plasma cells using the CD138 marker. Comparative analysis of clinical-anamnestic, sonographic, hysteroscopic, morphological data and results of microbiological research constituted the result of the first stage of the study.

After the morphological and immunohistochemical confirmation of the CE diagnosis, to further study the pathogenic processes of the patients in detail, the patients from group I were divided into two subgroups. The subgroup Ia included women with isolated EP, the subgroup Ib included patients with EP and MP all together. The second stage studies were carried out in groups Ia, Ib, II, III and included: immunohistochemical study of immunoreactive cells (CD138, CD56, CD16, CD45, CD68), proliferation marker (Ki-67), estrogen (ER) and progesterone receptors (PR) in the glands and stroma of the endometrium, as well as the evaluation of the hormonal status (determination of the level of FSH, LH, prolactin, estradiol and progesterone).

Clinical evaluation of the health status of the women studied was carried out according to anamnestic data on the menstrual cycle violations, the age of menarche, periodicity, duration, pain, intensity of menstruation. Features

of sexual life, genital function, gynecological diseases and surgical interventions in the past were assessed in detail. A sonographic study in conjunction with Doppler mapping was carried out on Nemio XG ("Toshiba", Japan), Voluson E8 ("General Electric", Austria) using abdominal and vaginal transducers on the 5th-9th day of the MC.

Assessment of the state of vaginal microbiocenosis: pH test, study of normobiota (Lactobacillus spp.), aerobic, anaerobic flora, yeast-like fungi used the "Femoflor" test system. For microflora of the cervical canal and the endometrium study PCR was used to detect specific DNA fragments of *Chlamydia trachomatis*, *Mycoplasma hominis*, *genitalium*, *Ureaplasma urealiticum*, *parvum*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, Herpes simplex virus (HSV) 1, 2 and 6 type, Cytomegalovirus, Enterovirus, Human papilloma virus (HPV) with genotyping and culture methods for the detection of facultative anaerobic bacteria and fungi. Microbiological examination and PCR-diagnostics were performed before the operative intervention.

Immunochemical method with electro chemiluminescent detection (ECL) was used to study the level of hormones. Basal levels of FSH, LH, estradiol and prolactin were determined on the 3-5th day of the MC. The progesterone content was determined in the second phase of the menstrual cycle, on the 21st day.

Hysteroscopic examination was performed on the 7th-10th day of the menstrual cycle with the help of equipment from Karl Storz (Germany) and Stryker (USA) with 7.5 mm optics and viewing angle of 30 ° according to the generally accepted procedure.

The control group patients received the endometrial biopsy using the aspiration curette Pipelle de Cornie on the 7-10th day of the MC.

For the histological study, serial paraffin sections stained with hematoxylin-eosin and picrofuxin were used according to the Van Gieson method. For the endometrial immunohistochemical study the indirect streptavidin-peroxidase method was used based on the detection of the expression of the relevant factor with the help of primary and secondary Kit-monoclonal antibodies to ER and PR antigens, Ki67, CD138, CD16, CD56, CD45, CD68.

Statistical data processing was carried out by the standard software package "Statistica for Windows" (V. 13.0, StatSoft Inc., USA).

Results and their discussion, The groups were represented by age (the mean age of patients of group I was 30,2±4,11 years, group II – 32,4±2,57 years, control group – 31,0±2,77 years) and body mass index: its mean value in the first group was 23,0±4,1 kg/m^2, in group II – 20,9±2,26 kg/m^2, in group III – 21,0±1,52 kg/m^2.

The mean age of menarche, the average duration of the menstrual cycle and the duration of menstruation also did not have statistically significant differences in all three groups.

The clinical picture of the presence of EP was characterized primarily by the presence of pain syndrome (39%), abnormal uterine bleeding (64%) and dysmenorrhea (49%). Proportion of the patients with infertility was 67% in this cohort.

There were no statistically significant differences in the quantitative composition of the vaginal microflora in women of all study groups. The representatives of the conditionally pathogenic flora (CPF) most often showed *Gardnerella vaginalis*, *Eubacterium spp*. and *Ureaplasma spp*. As a percentage, the distribution of these microorganisms in patients with EP looked as follows: 34, 36 and 36, respectively, in women with MP – 30, 17 and 17, respectively, in healthy participants – 53, 30 and 30, respectively. It must be noted that only healthy women demonstrated high titers of CPF (>10^4 CFU/ml) balanced out by the normal content of lactobacilli. Changes in the microbiocenosis of the vagina, which consisted in decrease in the level of lactobacilli (<10^7 CFU/ml), were found in patients of both groups and were more pronounced in the presence of MP than in the case of EP.

Analysis of the contamination of the cervical canal showed a relatively high percentage of its sterility in all groups (up to 30%). The spectrum of the isolated pathogenic agents was significantly narrower, compared with that in the vagina and was mainly represented by ureaplasma and mycoplasma. The frequency of their detection among the representatives of groups I, II and III was 29, 20, 30% and 6, 7, 13%, respectively. Highly oncogenic HPV strains had the highest prevalence among viruses in the cervical canal. And although the revealed differences in the frequency of occurrence were not statistically significant, it is necessary to note a significantly higher infectious load in patients with EP in comparison with the representatives of the control group and group II (31% vs. 13 and 20%).

The frequency of detection of the microbial agent in the endometrium was high enough and was 83% in patients with EP, 73% with MP and 77% in healthy women. The endometrial microbiocenosis in patients with MP did not differ significantly from that in the control group and was mainly represented by *Ureaplasma spp.* (27 and 30%, respectively), *Streptococcus spp.* (10 and 13%, respectively) and *Enterococcus faecalis*. The latter was detected in the endometrium of the control group patients considerably more often than in patients from group I and II (43% vs. 11% and 17%, respectively, p_{I-III}=0,001, p_{II-III}=0,049). It is important to note that in 17% of women with EP endometrium was colonized with HSV 1, 2, 6th type, in 21% had fungi of the *Candida* genus, while healthy participants of the study demonstrated none of HSV and *Candida* in neither case (p_{I-III}=0,016 and p_{I-III}=0,012, respectively).

According to the immunohistochemical study of the endometrium it was established that isolated EP (Ia group) is characterized by a significant decrease in the number of CD56 and CD16 – 17 (15-20) and

Table 1. Endometrial mononuclear cell subsets and level of Ki67 in the groups

Indicators, %	Ia group (n=34)	Iб group (n=36)	II group (n=30)	III group (n=30)
CD138	0[c, d]	14±9,01[a, b]	10,1±2,41[a, b]	0
CD56	17 (15–20)[a, c, d]	35 (34–35)[b]	45 (35–45)[a, b]	24,57±3,6
CD16	19,67±3,43[a, d]	15 (12–15)[a, d]	35 (30–35)[b, c]	32,57±5,13
CD45	38,89±6,97[d]	54 (50–55)[a]	54,14±3,44[a, b]	30 (30–35)
CD68	11,56±6,37[d]	13,44±4,45	30 (30–32)[a, c]	6,71±1,25
Ki 67 glands	28,78±7,73[a, c, d]	42,89±10,61[a, b]	44,29±8,86[a, b]	5,43±1,13
Ki 67 stroma	6,67±1,0[c, d]	18 (15–20)[b]	14 (12–15)[b]	12,0±1,53

Depending on the distribution of the indicator, data are presented as:
M ± SD (Shapiro-Wilk test, p>0,05) or Me (IQR) (Shapiro-Wilk test, p<0,05)
a- reliable difference with respect to group III (p<0,05);
b- reliable difference with respect to the group Ia (p<0,05);
c- reliable difference with respect to the group Ia (p<0,05);
d- reliable difference with respect to group II (p<0,05)

19,67±3,43%, respectively. EP in combination with micropolyps (Ib group) were characterized by an imbalance in the subpopulations of lymphocytes with a decrease in the number of CD16 (15 (12-15) %), normal CD56 level (35 (34-35) %), presence of CD138 (14±9,01 %) and high content of CD45 (54 (50-55) %). MPs were characterized by a high density of CD56 (45(35-45) %), a significant increase in the amount of CD45 (54,14±3,44 %), an increase of more than 4,5 times in CD68 (30 (30-32) %) and expression of CD138 (10,1± 2,4 %) (Table 1). A significant correlation between the percentage content of each subspecies of mononuclear cells in the endometrium and the amount of EP and MP is not detected (rs in the range from -0,39 to +0,26 (p=0,582) and -0,19 to 0,26 (p=0,492), respectively).

The level of cell proliferation in the endometrium was assessed through the immunohistochemical study with the expression of the Ki67 marker. The highest level of expression of Ki67 in cells of glandular epithelium was recorded in that with MP. In groups Ib and II its value was almost identical and amounted to 42,89±10,61 and 44,29±8,86%, respectively, which was 8 times higher than in the control group (5,43±1,13%; p_{Ib-III}=0,000, p_{II-III}=0,000) and 1,5 times than in EP group (p_{Ia-Ib}=0,000, p_{Ia-II}=0,000). In patients with EP, even in the absence of CE, there was also an increase in the mitotic activity of glandular epithelial cells, the expression level of Ki67 was 28,78±7,73% and was significantly higher than in healthy women (p_{Ia-III}=0,000).

The average basal levels of FSH, LH, estradiol and prolactin in women of all the examined groups were within the normal range. All women with EP, irrespective of the presence or absence of concomitant CE, were characterized by absolute hypoesthesia in the II phase of the menstrual cycle. The average content of progesterone in serum of the patients of group I was 5,25±4,43 ng/ml, which is 4 times lower than in the control group (20,96±1,06 ng/ml, p=0,000), and 3 times lower than in women from group II (15,6±2,44 ng/ml, p=0,017). A similar phenomenon was observed in patients from group Ib – the average progesterone content in their blood was 9,32±5,65 ng/ml (p=0,004).

The endometrium of women with isolated EP was characterized by the inverse correlation between an increased expression of Ki67 and a reduced amount of CD16 (r=0,81, p=0,007) and CD56 (rs=0,63; p=0,016) (Fig. 1). This reduction in NK cells indicated the presence of immune hyporeactivity and hypofunction and a possible role of a reduced antiviral and antitumor protection in polyp formation. In those patients in whom EP existed against the background of MP, similar changes were detected for CD16 (rs=0,84, p=0,003 in the glands and rs=0,76, p=0,017 in the stroma), CD138 (r=0, 66, p=0,046 in the glands and rs=0,75, p=0,019 in the stroma) and CD68 (rs=0,62, p=0,014 in the glands and rs=0,82, p=0,006 in the stroma). Proliferative activity of the endometrium in these patients proved to be dependent both on the severity of immunodeficiency and on the intensity of the inflammatory process. MPs demonstrated the presence of a direct correlation relationship between the value of Ki67 and the number of macrophages (CD68) (rs=0,91; p=0,043) and plasma cells (CD138) (r=0,84; p=0,001 in the glands and rs=0,51; p=0,042 in the stroma).

Thus, on the basis of the studied clinical and anamnestic data, the results of sonographic, microbiological, hormonal research and immunohistochemical characteristics of the morphofunctional state of the endometrium, separate clinical and pathogenic variants of EP were highlighted: MP; EP in combination with MP; isolated EP (Table 2).

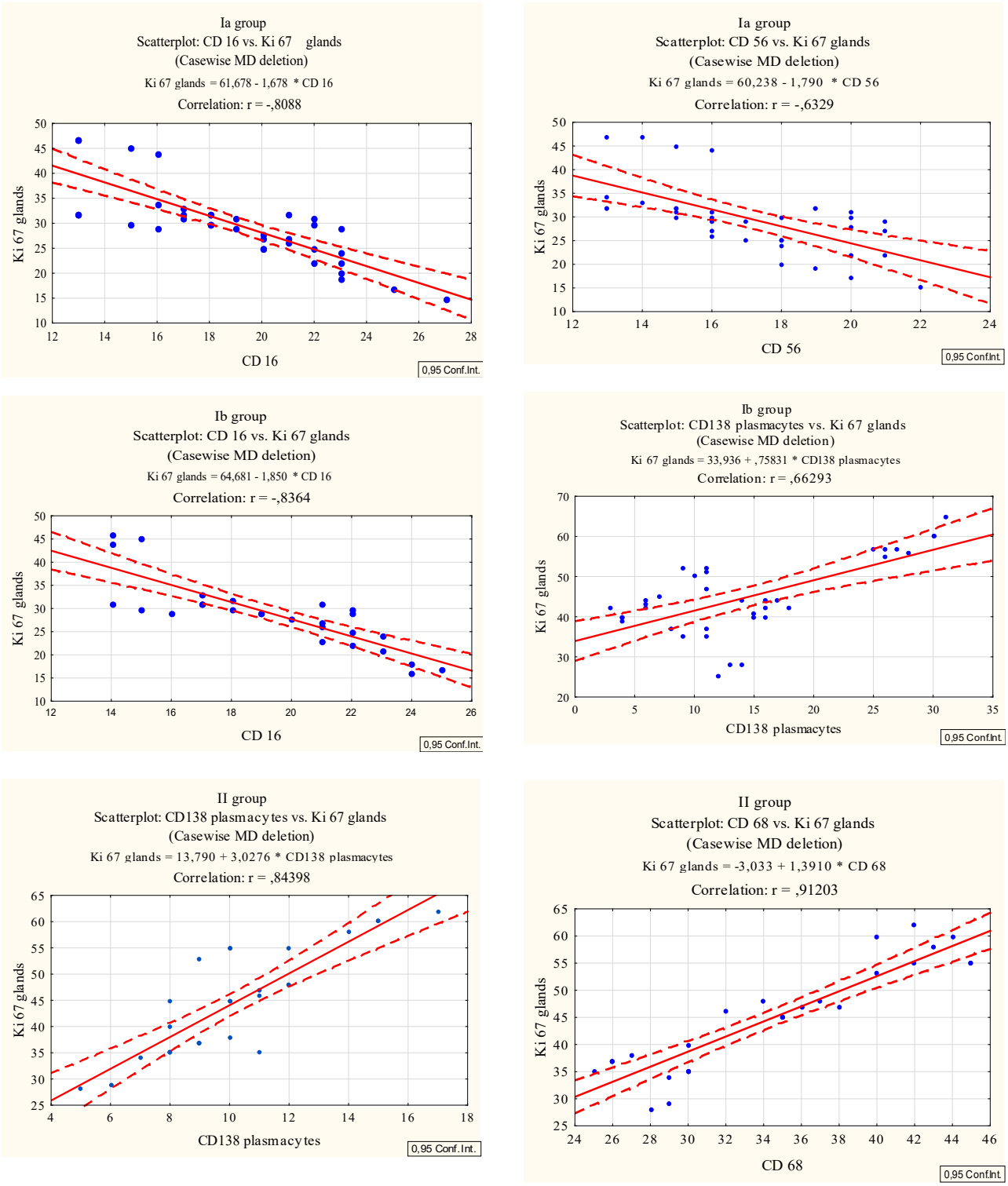

Fig. 1. Correlation between Ki67 *and CD16, CD56, CD138, CD68 in the endometrium of patients*

In the mechanism of a development of an isolated EP, a large role is played by progesterone deficiency and local immune imbalance with a pronounced hypofunction of NK-cell link, which, against the background of viral and fungal infestation, is proven to lead to an excessive proliferation of endometrial cells. In the case of a combination of EP with MP, all of the above mechanisms potentiate an active inflammatory process by an additional initiation of the proliferation. MP, as a macroscopic manifestation of an active inflammatory process in CE, is characterized by focal cellular infiltrates, more often represented by plasma cells, macrophages and NK cells, whose activity leads to an excessive pathological proliferation of the endometrium, even in the absence of hormone-receptor disorders.

Table 2.Clinical and pathogenetic variants of endometrial polyps

Indicators		Isolated EP	EP in combination with micropolyps	Micropolyps
Infectious agent: • Vagina • Endometrium		*Lactobacillus* 10^6–10^7 CFU/ml		*Lactobacillus* <10^6 CFU/ml
		Candida, *Herpes Simplex Virus* 1, 2, 6 type	CPF did not differ significantly from that in the control group	
Hormonal status		↓↓ progesterone	↓ progesterone	Norm progesterone
ER		Norm	Norm	Norm
PR		Norm	Norm	Norm
	↓	CD56, CD16	CD16	-
	↑	-	CD138, CD45	CD138, CD45, CD56, CD68
Proliferation (Ki67)		↑	↑↑	↑↑
Correlation		Proliferation/ Immunodeficiency	Proliferation/ Immunodeficiency / Inflammation	Proliferation/ Inflammation

Conclusion

The above results of the research showed that during the formation of EP there are two key factors: a viral and a fungal infection, and on the other hand - hypoprogestheronemia, which, even in the absence of pathological changes in the receptor apparatus, initiates a cascade of inflammatory reactions.

Of course, to date, surgical methods of treatment continue to occupy the leading position in the treatment of EP. However, the fact remains: in general, the frequency of repeated episodes of EP occurrence after a surgical treatment is 26-78%; therefore, limiting the treatment to a mere removal of the polyp, given the proven role of the inflammatory microenvironment, local immune disorders and imbalance in the proliferation/apoptosis system would be very imprudent. Therefore, a complex ancillary etiopathogenetic therapy directed not only at eliminating hormonal disorders, but also at correcting inflammatory changes and immune disorders deserves much more attention that it draws today.

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SUMMARY

ENDOMETRIAL POLYPS IN WOMEN OF REPRODUCTIVE AGE: CLINICAL AND PATHOGENETIC VARIATIONS

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The aim of the study was to study the relationship between the morphofunctional characteristics of the endometrium, hormonal homeostasis and microbiocenosis of the reproductive system in patients with endometrial polyps.

The study involved 130 patients aged 18-35 years: 34 patients with endometrial polyps, 30 patients with micropolyps, 36 patients with endometrial polyps and micropolyps, 30 healthy women of the control group.

Hysteroscopy was performed for women who had been suspected for endometrial polyps and who had infertility or repeated recurrent miscarriages. Endometrial samples from healthy women were obtained by aspiration biopsy. The endometrial sections were immunostained with monoclonal antibodies against the specific markers of plasmacytes (CD138), NK cells (CD56, CD16), pan-leukocytes (CD45), macrophages (CD68), cellular marker for proliferation (Ki-67), ER, PR. Bacteriological examination of the endometrium was performed by PCR and by cultivating aerobic and anaerobic microorganisms on special growth media. In all groups of women the content in blood serum for 3-5 day of a menstrual cycle of gonadotropic hormones (FSH, LH) and sex steroid hormones (estradiol, prolactin) was studied, for 21 days of a cycle estimated the content of progesterone. Level of an expression of receptors of progesterone and estrogen estimated in endometrium and at EP, also in I a cycle phase.

Highlighted are separate clinical and pathogenetic variations of endometrial polyps: isolated polyps, micropolyps, polyps in conjunction with micropolyps. In the course of study, it was found that progesterone deficiency and local immune imbalance with severe hypofunctional NK cells against viral and fungal infestations result in excessive endometrial cell proliferation and development of an isolated polyp. The case of a polyp merging with micropolyps potentiates an active inflammatory process alongside all of the mechanisms mentioned above. Micropolyps as a macroscopic manifestation of an active inflammatory process in chronic endometritis are characterized by focal infiltrates of leukocytes (CD45), macrophages (CD68), plasmacells (CD138) and NK (CD56) cells, whose activity leads to excess abnormal proliferation of endometrium, even in the absence of hormone receptor disorders.

Keywords: endometrial polyps, endometrial micropolyps, chronic endometritis.

РЕЗЮМЕ

ПОЛИПЫ ЭНДОМЕТРИЯ У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА: КЛИНИКО-ПАТОГЕНЕТИЧЕСКИЕ ВАРИАНТЫ

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Цель исследования изучить взаимосвязи между морфофункциональными характеристиками эндометрия, гормональным гомеостазом и микробиоценозом органов репродуктивной системы у пациенток с полипами эндометрия.

В исследовании участвовали 130 пациенток в возрасте 18-35 лет: 34 пациентки с ПЭ, 30 пациенток с МП, 36 пациентов с ПЭ и МП, 30 здоровых женщин контрольной группы.

У женщин с подозрением на наличие ПЭ, бесплодием или повторными выкидышами в анамнезе была выполнена гистероскопия. Образцы эндометрия у здоровых женщин были получены путем аспирационной биопсии. Серийные срезы эндометрия были иммунизированы моноклональными антителами к антигенам плазмозитов (CD138), NK-клеток (CD56, CD16), пан-лейкоцитов (CD45), макрофагов (CD68), клеточного маркера пролиферации (Ki-67), ER, PR. Бактериологическое исследование эндометрия проводили с помощью ПЦР и культивирования аэробных и анаэробных микроорганизмов на специальных средах. Во всех группах женщин было изучено содержание в сыворотке крови на 3-5 день менструального цикла гонадотропных гормонов (ФСГ, ЛГ) и половых стероидных гормонов (эстрадиол, пролактин), на 21 день цикла оценивали содержание прогестерона. Уровень экспрессии рецепторов прогестерона и эстрогена оценивали в эндометрии и в ПЭ, также в I фазу цикла.

Выделены отдельные клинико-патогенетические варианты полипов эндометрия: изолированные полипы, микрополипы, полипы в сочетании с микрополипами. Установлено, что дефицит прогестерона и локальный иммунный дисбаланс с выраженной гипофункцией NK-клеточного звена на фоне вирусной и грибковой инвазии эндометрия приводят к избыточной пролиферации клеток и развитию изолированного полипа. В случае сочетания

полипа с микрополипом все перечисленные выше механизмы потенцирует активный воспалительный процесс. Микрополипы, как макроскопическое проявление активного воспалительного процесса при хроническом эндометрите, характеризуются очаговыми инфильтратами из лейкоцитов (CD45), макрофагов (CD68), плазматических (CD138) и NK (CD56) клеток, активность которых приводит к избыточной пролиферации эндометрия даже при отсутствии гормонально-рецепторных нарушений.

რეზიუმე

ენდომეტრიუმის პოლიპები რეპროდუქციული ასაკის ქალებში: კლინიკური და პათოგენური ვარიანტები

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კვლევის მიზანს წარმოადგენდა მორფოფუნქციურ დახასიათებას, ჰორმონალურ ჰომეოსტაზსა და რეპროდუქციული სისტემის ორგანოების ბიოცენოზს შორის ურთიერთკავშირის გამოვლენა.

კვლევაში მონაწილეობდა 18-35 წწ. 130 პაციენტი, მათ შორის 34 პაციენტი ენდომეტრიუმის პოლიპით (ეპ), 30 - მიკროპოლიპით (მპ) და 36 - ეპ და მპ ერთდროულად. საკონტროლო ჯგუფი შეადგინა 30 ჯანმრთელმა პირმა. ქალებს ენდომეტრიუმში პოლიპზე საეჭვო დიაგნოზით, უნაყოფობით და ანამნეზში ნაყოფის განმეორებით მოშლით ჩაუტარდა ჰისტეროსკოპია. ჯანმრთელი ქალებისაგან ენდომეტრიუმის ნიმუშები მიღებული იყო ასპირაციული ბიოფსიის მეშვეობით. ენდომეტრიუმის სერიული ანათლები იმუნიზებული იყო მონოკლონური ანტისხეულებით ქვემოჩამოთვლილი ანტიგენების მიმართ: (CD138) პლაზმოლიტების, NK უჯრედების (CD56, CD16), პან-ლეიკოციტების (CD45), მაკროფაგების (CD68), პროლიფერაციის უჯრედული მარკერის (Ki-67), ER, PR. ენდომეტრიუმის ბაქტერიოლოგიური გამოკვლევა ჩატარდა PCR მეთოდით და აერობული და ანაერობული მიკროორგანიზმების კულტივირებით სპეციალურ ნიადაგზე. ყველა ჯგუფის ქალების სისხლის შრატში მენსტრუალური ციკლის მე-3-5 დღეს შესწავლილი იყო გონადოტროპული ჰორმონების (FSH, LH) და სტეროიდული სასქესო ჰორმონების (ესტრადიოლი, პროლაქტინი) შემცველობა; ციკლის 21-ე დღეს განსაზღვრული იყო პროგესტერონის შემცველობა. პროგესტერონის და ესტროგენის რეცეპტორების დონე შეფასებული იყო ენდომეტრიუმში და ენდომეტრიუმის პოლიპში აგრეთვე I ფაზაში.

გამოყოფილი იქნა ენდომეტრიუმის პოლიპების კლინიკურ-პათოგენური ვარიანტები: იზოლირებული პოლიპები, მიკროპოლიპები და პოლიპები თანდართული მიკროპოლიპებით. დადგენილია, რომ პროგესტერონის დეფიციტი და ლოკალური იმუნური დისბალანსი, NK -უჯრედული რგოლის გამოხატული ჰიპოფუნქციით, ენდომეტრიუმის ვირუსული და სოკოვანი ინვაზიის ფონზე იწვევს უჯრედების ჭარბ პროლიფერაციას და იზოლირებული პოლიპის განვითარებას. პოლიპის და თანდაყოლილი მიკროპოლიპის შემთხვევაში ზემოჩამოთვლილი მექანიზმები ააქტიურებენ ანთებით პროცესს. მიკროპოლიპები, როგორც აქტიური ანთებითი პროცესის მიკროსკოპული გამოხატულება ქრონიკული ენდომეტრიტის პირობებში ხასიათდება პან-ლეიკოციტების (CD45), მაკროფაგების (CD68), პლაზმური (CD138) და NK(CD56) უჯრედების კეროვანი ინფილტრატებით, რომელთა აქტივობა განაპირობებს ენდომეტრიუმის ჭარბ პროლიფერაციას ჰორმონალურ-რეცეპტორული დარღვევების არსებობის პირობებშიც კი.

THE PECULIARITIES OF THE STATE OF THE AUTONOMIC NERVOUS SYSTEM ESTIMATED BY THE METHOD OF HEART RATE VARIABILITY IN PATIENTS WITH CIRRHOSIS AND SYNTROPIC DAMAGES OF CARDIOVASCULAR SYSTEM

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All organs and systems of human's organism are under the constant neural-humoral control. The close symbiosis of sympathetic and parasympathetic parts of autonomic nervous system with humoral factors provides the optimal adaptation of organism to the changeable circumstances of external and internal environment and they rapidly react in case of pathological process formation [1,8]. If there are any chronic diseases, the organism attempt to provide the optimal homeostasis followed by the change of neurohumoral autonomic regulation that can be noted with the help of heart rate variability because heart rate is a reliable detector of autonomic nervous system deviation [2,5,7,9].

Cirrhosis occupies a highly important place in the structure of digestive system diseases, is an essential socioeconomic and clinical-epidemiologic healthcare problem [6]. Numerous researches have proved that autonomic dysfunction which increases parallel to augmenting disease severity is one of the pathogenic chains in patients with cirrhosis [1,2], and also that cirrhosis is accompanied by involving other organs and systems in pathologic process, particularly the circulatory system organs [3].

However there is no available information about the researches dedicated to the participation of autonomic nervous system in formation of syntropic comorbid damages of cardiovascular system in patients with cirrhosis – cardiomyopathy and arterial hypotension which are dangerous because of the congestive heart failure formation and imbalance of microcirculation of all organs and tissues, and sometimes cause the patients' death [1].

So the aim of our research is to investigate the peculiarities of the condition of autonomic nervous system, estimated by the method of heart rate variability in patients with cirrhosis with syntropic damages of cardiovascular system.

Material and methods. After receiving the consent on conduction the complex examination due to the principles of Declaration of Human Rights of Helsinki, Council of Europe Convention of Human Rights and Biomedicine and relevant Laws of Ukraine, randomly with the previous stratification due to the presence of cirrhosis there were 603 patients (445 men (73.8%) and 158 women (26.2%) at the age of 19-80 (average age 49.2±10.6) who were treated in the Lviv Regional Hepatological Centre. The complex of clinical-laboratorial and instrumental research of all organs and systems before treatment due to the orders of the Ministry of Healthcare of Ukraine № 271 from 13.06.2005, № 436 from 03.07.2006 was held to them.

Using the results of examination of 603 patients with cirrhosis, we have separate 490 (81.3%) cirrhotic patients with extrahepatic damages of cardiovascular system (investigational group (IG) which is stratified into: a) those who have only syntropic cardiomyopathy (103 patients; 21.0%) - IG A; b) only syntropic hypotension (89 patients; 18.2%) - IG B; c) those who gave other comorbid damages of cardiovascular system (298 patients; 60.8%)), and also those who do not have the damages of cardiovascular system (113 patients; 18.7%) - the comparison group comparison (CG)). Randomly, to achieve the aim, the autonomic nervous system condition of 50 patients of IG A, 54 patients of IG B and 45 patients of CG using heart rate variability was evaluated.

Estimation of the state of autonomic nervous system was conducted by using the heart rate variability registering on the basis of assessment the R-R interval duration of sequential heartbeat cycles on the electrocardiogram during definitive amount of time (in our case we estimated the change of R-R interval period during 5 minutes in prone position – test before the activity, and additionally during 6 minutes in the upright position - test before the activity). Records were made using the computerized electrocardiograph 'Poly-Spectrum' ('Neurosoft' corporation, Ivanovo, Russia).

Among the methods of time analysis we used the definition of heart rate and statistic quantities that come from it, it gave us an opportunity to estimate heart rate variability in terms of amount during certain period of time. We analyzed the following time indexes of heart rate variability: maximum duration NN intervals (NN max), minimal duration NN intervals (NN min), average duration NN intervals (MNN), standard deviation NN intervals (SDNN), the square root of arithmetic average from squares of differences of gradual NN intervals (RMSSD), percentage adjoining cardiocycles which differ more than by 50 milliseconds (pNN50%), coefficient of variation (CV) and coefficient K30:15. The last one shows 'the transition period' of heart rate – the change of heart rate during the moving from horizontal position into vertical one and is a correlation of R-R interval minimal meaning, which equals 15th beat, to the longest R-R interval , which usually equals 30th beat (normal K30:15 varies from 1,20 to 1,69). Frequency analysis supposes the estimation of wave force structure with determination of general spectral power and its structure: quotient of high frequency fluctuation (HF%), quotient of low frequency fluctuation (LF%) and quotient of fluctuation with very low frequency (VLF%).

The achievement of the aim which we set we divided into 3 steps, 1st – to study the time indexes of heart rate variability in patients of both IG and CG, 2nd – partial indexes, 3rd – to conduct the test with loading and study the coefficient K30:15 due to the amount of which we additionally estimate the lack of parasympathetic chain autonomic nervous system, then we compare the received results of the patients with cirrhosis with comorbid syntropic damages of cardiovascular system IG to the results of the patients without cirrhosis with comorbid syntropic damages of cardiovascular system CG and also IGA and IGB.

Current material was processed on the personal computer in the program EViews (Quantitative Micro Software) using descriptive statistic and ANOVA analysis of variance. The deviation when $p<0.05$ is consider to be statistically significant. The results are presented by the way of M±m, where M - arithmetic average, m – standard deviation of arithmetic average. n means the number of patients.

Results and their discussion. The received results of the 1st step of the research are at the chart 1 and 2. The heart rate , which is the most variable factor and straightforwardly depends on the activity of autonomic nervous system, accurately differs between the group of patients we study (Table 1). In patients of IG A with cirrhosis and syntropic cardiomyopathy the heart rate equals 88.50 beats per minute, in patients of IG B with cirrhosis and syntropic arterial hypotension heart rate equals 88.09 beats per minute. Both results are the highest among the samplings , there is no essential differences (Anova F-statistic=0.03; p=0.87). In patients of CG with cirrhosis but without comorbid syntropic damages of cardiovascular system heart rate equals 69.44 beats per minute, that is lower than in both IG. It is confirmed statistically.

Statistically significant difference is between heart rate between samplings CG and IG A (Anova F-statistic = 75.41; p=0.00) and between samplings CG and IG B (Anova F-statistic = 66.47; p=0.00).

We calculated the confidence intervals of heart rate in both samplings by method of analysis of variance. Confidential material gives us an opportunity to define the limit points or boundaries, between which with the prescribed confidential possibility we can expect the quantity of estimated index. In patients of IG A the boundaries of confidential material equals 86.11-91.89 beats per minute, which is the highest result, in patients of IG B – 84.58-91.61 beats per minute, and in patients of CG – 66.71-71.18 beats per minute, which is the lowest result.

The learnt time indexes of heart rate variability are at Table 2. NN min in patients of IG A equals 645.08 milliseconds that almost does not differ from the quantity in IG B (652.28 мs; Anova F-statistic = 0.16; p = 0.69), but is exactly lower than in patients of CG (771.71 мs; Anova F-statistic = 30.86; p = 0.00). Consequently, in pair CG and IG B is statistically significant difference (Anova F-statistic = 27.86; p = 0.00). Low and high boundaries of confidence interval NN min in patients of IG A equals 620.03 and 670.13 milliseconds, consequently, in patients of IG B – 626.97 and 677.59 milliseconds, consequently, and in patients of CG – 732.31 and 811.29 milliseconds which equals the highest quantities.

NN max in patients of IG A equals 747.98 milliseconds, and in patients of IG B – 729.15 milliseconds which are the lowest results among all the samplings, between which is no essential difference (Anova F-statistic = 0.70; p=0.40). In patients of CG arithmetic average NN max equals 989.60 milliseconds. Statistically significant difference was discovered during the comparison of the samplings CG and IG A (Anova F-statistic = 103.18; p=0.00) and CG and IG B (Anova F-statistic = 106.80; p=0.00). With the 95% probability NN max indexes in IG A and IG B are almost at the same boundaries, i.e. in IG A – between 718.31 and 777.65, and in IG B – between 695.61 and 762.69 milliseconds. In patients of CG confidence boundaries are significantly lower from IG and equals 947.66 milliseconds and 1073.11 milliseconds.

MNN is reversible quantity to heart rate and shows the ultimate result of numerous regulatory influences of sympathetic and parasympathetic parts of autonomic nervous system on sinus rhythm. MNN in patients of IG A and IG B almost does not differ from each other (Anova F-statistic = 0.01; p = 0.93) and equals 694.64 milliseconds and 692.81 milliseconds, consequently. In patients of CG there was significantly higher the index of MNN – 888.58 milliseconds. Statistically significant difference was be-

Table 1. Heart rate recorded with the help of heart rate variability in patients of examined groups with cirrhosis and syntropic damages of cardiovascular system

Heart rate, BPM	**Examined group**		**CG**
	IG A	**IG B**	
	n=50	**n=54**	**n=45**
Arithmetic average, M±m	88,50±1,68 #	88,09±1,75 #	69,44±1,36
Low boundary of 95% confidential interval of the average meaning	85,11	84,58	66,71
High boundary of 95% confidential interval of the average meaning	91,89	91,61	72,18

 # - statistically significant difference in comparison with CG (p<0,05)

Table 2. The indexes of time analysis of heart rate variability in patients of examined groups with cirrhosis and syntropic damages of cardiovascular system

The indexes of heart rate variability IG A n=50		Examined groups IG B n=54	IG B n=54	CG n=45
NN min, ms	Arithmetic average, M±m	645,08±12,47 #	652,28±12,62 #	771,71±19,64
	Low boundary of 95% confidential interval of the average meaning	620,03	626,97	732,14
	High boundary of 95% confidential interval of the average meaning	670,13	677,59	811,29
NN max, ms	Arithmetic average, M±m	747,98±14,76 #	729,15±16,72 #	989,60±18,96
	Low boundary of 95% confidential interval of the average meaning	718,31	695,61	951,38
	High boundary of 95% confidential interval of the average meaning	777,65	762,69	1027,82
MNN, ms	Arithmetic average, M±m	694,64±3,66 #	692,81±13,76	888,58±18,79
	Low boundary of 95% confidential interval of the average meaning	667,19	665,22	850,70
	High boundary of 95% confidential interval of the average meaning	722,09	720,41	926,45
SDNN, мс	Arithmetic average, M±m	15,98±0,80 #	14,54±1,07 #	35,18±1,21
	Low boundary of 95% confidential interval of the average meaning	14,36	12,39	32,73
	High boundary of 95% confidential interval of the average meaning	17,60	16,69	37,63
RMSSD, мс	Arithmetic average, M±m	9,16±1,09 #	6,98±0,63 #	24,64±1,49
	Low boundary of 95% confidential interval of the average meaning	6,96	5,72	21,63
	High boundary of 95% confidential interval of the average meaning	11,36	8,25	27,66
pNN50%%	Arithmetic average, M±m	0,48±0,30 #	0,15±0,06 #	5,43±1,06 *
	Low boundary of 95% confidential interval of the average meaning	0,00	0,02	3,30
	High boundary of 95% confidential interval of the average meaning	1,09	0,28	7,56
CV%	Arithmetic average, M±m	2,30±0,11 #	2,23±0,13 #	4,02±0,15
	Low boundary of 95% confidential interval of the average meaning	2,09	1,96	3,70
	High boundary of 95% confidential interval of the average meaning	2,51	2,49	4,26

 # - statistically significant difference in comparison with CG (p<0,05)

tween the groups of quantities in patients of CG and IG A (Anova F-statistic = 71.64; p = 0.00) and in patients of CG and IG B (Anova F-statistic = 73.52; p = 0.00). 95% confidence interval in patients of IG A is between 667.19 and 722.09 milliseconds, in patients of IG B – between 665.22 and 720.41 millisecondsm and in patients of CG – between 850.70 and 926.45 milliseconds.

SDNN – an integral index that describes heart rate variability in general, indicates the infrequency heart rate and depends on the balance between sympathetic and parasympathetic parts of autonomic nervous system. Due to the received results the quantities SDNN in patients of IG A and IG B equal 15.98 milliseconds and 14.54, consequently, and do not differ statistically significant between each other (Anova F-statistic = 1.31; p = 0.29), but are twice times lower than in patients of CG (35.18 milliseconds). The difference between the group is confirmed statistically: between CG and IG A (Anova F-statistic = 180.10; p = 0.00) and between CG and IG B (Anova F-statistic = 163.29; p = 0.00). 95% confidence interval SDNN in patients of IG A is between 14.36 and 17.60 milliseconds, in patients of IG B – between 12.39 and 16.69 milliseconds which are the lowest boundaries among the examined groups, and in patients of CG – between 32.73 and 37.63 milliseconds which are the highest and the widest boundaries.

Usually RMSSD changes parallel to SDNN and also shows the influence of parasympathetic part of autonomic nervous system on the heart rhythm. There was the lowest RMSSD in patients of IG B (6.98 milliseconds), and RMSSD in patients of IG A is by one third higher (9.16 milliseconds). In patients of CG RMSSD equals 24.64 milliseconds and is the highest result. Statistically significant difference is between pairs of quantities in patients of CG and IG A (Anova F-statistic = 71.86; p = 0.00) and in patients of CG and IG B (Anova F-statistic = 133.61; p = 0.00). There is no statistic difference between the patients of IG A and IG B (Anova F-statistic = 3.09; p = 0.08).

Confidence boundaries in patients of IG A and IG B are the lowest ones and equal 6.96 and 11.36 milliseconds, and 5.72 and 8.25 milliseconds consequently, and in patients of CG – higher (from 21.63 to 27.66 milliseconds).

Also, the balance between the parasympathetic and sympathetic autonomic nervous system show pNN 50.0%. In patients of IG A and IG B quantities pNN50% are the lowest ones which we recorded, equal 0.48% and 0.15% consequently, and statistically do not differ from each other (Anova F-statistic = 1.24; p = 0.27). In patients of CG the index is higher and equal 5.43%. There is an essential difference between pNN50% in CG and IG A (Anova F-statistic = 22.20; p = 0.00), and also between CG and IG B (Anova F-statistic = 29.92; p = 0.00). With the 95% probability quantities pNN50% in patients of IG A are between 0.00 and 1.09%, in patients of IG B – between 0.02 and 0.28%, and in patients of CG – between 3.30 and 7.56%.

CV is estimated as the quotient SDNN from MNN and shows SDNN with an additional heart rate influence. CV index in patients of IG A equals 2.30% and there is no statistic difference from CV index in patients of IG B (2.23%; Anova F-statistic = 1.82; p = 0.18). CV in patients of CG is almost twice higher than in IG and equals 4.02%. Statistically essential difference is between: CG and IG A (Anova F-statistic = 89.50; p = 0.00) and CG and IG B (Anova F-statistic = 94.49; p = 0.00). 95% high and low confidential boundaries of the average meanings in patients of IG A equals 2.09-2.51%, in patients of IG B – 1.96-2.49%, and in patients of CG – 3.70-4.26%.

The received results of time analysis of heart rate variability shows the existence of autonomic imbalance in patients with cirrhosis and syntropic damages of circulatory system. Heart rate in patients with cirrhosis and syntropic cardiomyopathy, and patients with cirrhosis and arterial hypotension is significantly higher, and consequently the average, minimal and maximum R-R interval duration is significantly lower which shows the parasympathetic lack in patients of IG. And also, significantly higher indexes of SDNN, RMSSDM, pNN50% in patients with cirrhosis without syntropic damage of circulatory system in comparison with the indexes in group of patients with cirrhosis and syntropic cardiovascular damages point out the variable heart rhythm of the last ones. The high heart rate and irregular heart rhythm are the elements of rigid rhythm in the patients of both IG that is also the demonstration of the activity reduction of parasympathetic part of autonomic nervous system. There is no significant difference between time indexes of heart rate variability in patients with cirrhosis and cardiomyopathy, and with cirrhosis and arterial hypotension.

During the 2nd step of research we studied the frequency analysis of heart rate variability (Table 3). In patients of IG A with cirrhosis and syntropic cardiomyopathy and IG B with cirrhosis and syntropic arterial hypotension of TP are almost the same (Anova F-statistic = 0.04; p = 0.85) and equal 345.72 and 334.60 ms^2/Hz, consequently. TR indexes in patients of CG an with cirrhosis, but without syntropic damage of circulatory system, are more than in five times higher in comparison with IG and equal 1696.64 ms^2/Hz. The difference between the groups is confirmed statistically: between IG A and CG (Anova F-statistic = 99.09; p = 0.00) and between IG B and CG (Anova F-statistic = 94.04; p=0.00). 95% confidence boundaries of TR in patients of IG A equal 295.04-396.41 ms^2/Hz, in patients of IG B – 295.04-396.41 ms^2/Hz, and CG – 1413.76-1979.53 ms^2/Hz.

We estimated the indexes of the structure of spectral power with the aim of detailed analysis. HF% in patients of IG A equals 13.15%, in IG B – 8.30% which is the lowest result among the samplings. In patients of CG HF% it is twice higher and equals 22.93%. Statistically significant difference is between the samplings IG A and CG (Anova F-statistic = 12.00; p = 0.00), IG B and CG

Table 3. The quantities of the spectral analysis of heart rate variability in patients of examined groups with cirrhosis and syntropic damages of cardiovascular system

The indexes of heart rate variability IG A n=50		Examined groups		CG n=45
		IG B n =54	IG B n=54	
TP, ms2/Hz	Arithmetic average, M±m	345,72 ± 25,22 #	334,60 ± 52,79 #	1696,64 ± 140,36
	Low boundary of 95% confidential interval of the average meaning	295,04	228,48	1413,76
	High boundary of 95% confidential interval of the average meaning	396,41	440,24	1979,53
VLF, ms2/Hz	Arithmetic average, M±m	214,74 ± 18,18 #	237,41 ± 36,44 #	720,57 ± 52,56
	Low boundary of 95% confidential interval of the average meaning	178,20	164,32	614,65
	High boundary of 95% confidential interval of the average meaning	251,28	310,50	826,49
LF, ms2/Hz	Arithmetic average, M±m	82,76 ± 7,13 #	66,45 ± 12,12 #	510,73 ± 46,37
	Low boundary of 95% confidential interval of the average meaning	68,43	42,14	417,28
	High boundary of 95% confidential interval of the average meaning	97,08	90,77	604,18
HF, ms2/Hz	Arithmetic average, M±m	44,49 ± 7,21 #	30,44 ± 7,98 #	464,92 ± 83,50
	Low boundary of 95% confidential interval of the average meaning	30,00	14,44	296,63
	High boundary of 95% confidential interval of the average meaning	59,99	46,45	633,21
VLF%	Arithmetic average, M±m	63,26 ± 1,96 #	73,43 ± 1,34 #^	46,78 ± 2,34
	Low boundary of 95% confidential interval of the average meaning	59,33	70,73	42,04
	High boundary of 95% confidential interval of the average meaning	67,20	76,12	51,49
LF%	Arithmetic average, M±m	23,18 ± 1,03 #	18,27 ± 1,04 #^	30,32 ± 1,27
	Low boundary of 95% confidential interval of the average meaning	21,12	16,19	27,76
	High boundary of 95% confidential interval of the average meaning	25,25	20,35	32,87
HF%	Arithmetic average, M ± m	13,15 ± 1,77 #	8,30 ± 0,79 #^	22,93 ± 2,24
	Low boundary of 95% confidential interval of the average meaning	9,60	6,72	18,42
	High boundary of 95% confidential interval of the average meaning	16,69	9,89	27,44

 # - statistically significant difference in comparison with CG (p<0,05);
^ - statistically significant difference in comparison with IG A (p<0,05)

Table 4. The coefficient K30:15 which was examined during the test with loading in patients of examined groups with cirrhosis and syntropic damages of cardiovascular system

Coefficient K30:15	Examined groups		CH n=45
	IG A n=50	IG B n=53	
Arithmetic average, M±m	1,04±0,01 #	1,03±0,01 #	1,19±0,01
Low boundary of 95% confidential interval of the average meaning	1,03	1,02	1,16
High boundary of 95% confidential interval of the average meaning	1,06	1,05	1,22

Annotation : # - statistically significant difference in comparison with CG (p<0,05)

(Anova F-statistic = 43.47; p = 0.00) and IG A and IG B (Anova F-statistic = 6.60; p = 0.01). With 95% probability quantities HF, are shown in percentage terms, in patients of IG A are between 9.60 and 16.69%, in patients of IG B – between 6.72 and 9.89% which is equal to the smallest boundaries, and in patients of CG - between 18.42 and 27.44% which are the highest boundaries.

Quotient LF% is the lowest in patients of IG B (18.27%), higher – in patients of IG A (23.18%), and in patients of CG LF% - the highest one (30.21%). There is a significant difference between the quantities LF% in patients of CG and IG B (Anova F-statistic = 55.24; p = 0.00), CG and IG A (Anova F-statistic = 19.46; p = 0.00) and in patients of IG A and IG B (Anova F-statistic = 11.32; p = 0.00). In patients of IG B confidence interval LF% is the lowest between 16.19 and 20.35%. In patients of IG A confidence boundaries are higher (21.12% and 25.25%), and in patients of CG – the highest and equal 27.76 and 32.87%.

The highest quotient VLF% was in patients of IG B (73.43%), smaller – in patients of IG A (63.26%). In patients of CG is the lowest quantity of VLF% (48.04%). Comparing the groups we studied the statistically significant difference between CG and IG A (Anova F-statistic = 29.56; p = 0.00), CG and IG B (Anova F-statistic = 105.56; p = 0.00) and IG A and IG B (Anova F-statistic = 18.77; p = 0.00). The low and high boundaries of 95% confidence interval VLF% in patients of IG B equals 70.73% and 76.12%, in patients of IG A – 59.33% and 67.20%, and in patients of CG – 42.04% and 51.49%.

Due to the received results, in patients of IG A with cirrhosis and syntropic cardiomyopathy and patients of IG B with cirrhosis and syntropic arterial hypotension the general spectral power is significantly lower in comparison with quantities in patients of CG, it means the decrease of the summarized autonomic influence on the heart rhythm in patients of the groups. The estimation of the spectrogram structure means the significant prevalence in patients of both IG fluctuation with very low frequency, the power and quotient of which point out the activity of humoral-metabolic regulating mechanism, and in patients of CG – low frequent fluctuation with combined origin and show primarily the influence sympathetic part of autonomic nervous system. And also, in patients of IG A with cirrhosis and syntropic cardiomyopathy is higher quotient of low frequent fluctuation in comparison with the patients of IG B with cirrhosis and syntropic arterial hypotension, it points out the additional activation of sympathetic part of autonomic nervous system in connection with humoral-metabolic regulating, that was not noted in patients of IG B with cirrhosis and syntropic arterial hypotension.

The last 3rd step of our research - the conduction of the test with loading and studying the coefficient K30:15 which is a simple, accessible and highly efficient method for characteristic of vagal nerve function, and the patient's speed of rising during the test and his age do not affect the result. According to the Table 4, coefficient K30:15 is the lowest in patients of IG A and IG B – 1.04 and 1.03 consequently, there is no significant difference between them (Anova F-statistic = 0.70; p = 0.40). In patients of CG the arithmetic average K30:15 is also lower than its normal quantity and equals 1.19. Statistically significant difference is between the values in following pairs of samples: between CG and IG A (Anova F-statistic = 92.38; p = 0.00) and between CG and IG B (Anova F-statistic = 106.15; p = 0.00). 95% boundaries of confidence interval equals 1.03 and 1.06 in patients of IG A, in patients of IG B – 1.02 and 1.05, and in patients of CG – 1.16 and 1.22.

The received coefficients K30:15 in patients of both IG are lower than normal ones and confirm the reduction of parasympathetic activity of autonomic nervous system.

Conclusions. Studying the condition of autonomic nervous system by the method of heart rate variability in patients with cirrhosis with syntropic damages of cardiovascular system, we can confirm that:

1) they have the peculiarities of autonomic imbalance the characteristics of which are the low summarized activity of vegetative influence on heart rhythm and special dynamics of indexes of percentage structure of general spectral power;

2) they depend on the clinical variant of this damage – in patients with cirrhosis and syntropic cardiomyopathy the regulating of internal processes involve the humoral-metabolic influence, i.e. local vasoactive conjunctions, catecholamine, renin-angiotensin-aldosterone system, with a simultaneous influence of sympa-

thetic system and activity reduction of parasympathetic vegetative nervous system, and in patients with cirrhosis and syntropic arterial hypotension – the internal regulation involves the local humoral-metabolic factors with the lack of both sympathetic and parasympathetic parts of vegetative nervous system.

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SUMMARY

THE PECULIARITIES OF THE STATE OF THE AUTONOMIC NERVOUS SYSTEM ESTIMATED BY THE METHOD OF HEART RATE VARIABILITY IN PATIENTS WITH CIRRHOSIS AND SYNTROPIC DAMAGES OF CARDIOVASCULAR SYSTEM

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In the article the features of the autonomic nervous system state were estimated by the method of heart rate variability in patients with cirrhosis with syntropic damages of cardiovascular system - cardiomyopathy and arterial hypotension. As a result of an examination of 50 patients with liver cirrhosis and cardiomyopathy (investigational group A), 54 patients with liver cirrhosis and arterial hypotension (investigational group B), and 45 patients with liver cirrhosis also those who don't have the damages of cardiovascular system (group of comparison) it was established that: 1) they have the peculiarities of vegetative imbalance the characteristics of which are the low summarized activity of vegetative influence on heart rhythm and special dynamics of indexes of percentage structure of general spectral power; 2) they depend on the clinical variant of this damage – in patients with cirrhosis and syntropic cardiomyopathy the regulating of internal processes involve the humoral-metabolic influence, i.e. local vasoactive conjunctions, catecholamines, renin-angiotensin-aldosterone system, with a simultaneous influence of sympathetic system and activity reduction of parasympathetic vegetative nervous system, and in patients with cirrhosis and syntropic arterial hypotension – the internal regulation involves the local humoral-metabolic factors with the lack of both sympathetic and parasympathetic parts of vegetative nervous system.

Keywords: cirrhosis, syntropic damages of cardiovascular system, autonomic nervous system.

РЕЗЮМЕ

ОСОБЕННОСТИ СОСТОЯНИЯ ВЕГЕТАТИВНОЙ НЕРВНОЙ СИСТЕМЫ, ОЦЕНЕННОЙ МЕТОДОМ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА, У БОЛЬНЫХ ЦИРРОЗОМ ПЕЧЕНИ И СИНТРОПИЧЕСКИМИ ПОРАЖЕНИЯМИ СИСТЕМЫ КРОВООБРАЩЕНИЯ

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В статье исследуются особенности состояния вегетативной нервной системы по результатам оценки вариабельности сердечного ритма у больных циррозом печени и синтропическими поражениями системы

кровообращения - кардиомиопатией и артериальной гипотонией. В результате обследования 50 больных циррозом печени и кардиомиопатией (опытная группа А), 54 больных циррозом печени и артериальной гипотонией (опытная группа Б) и 45 больных циррозом печени, которые не имели поражений органов системы кровообращения (группа сравнения) установлено, что: 1) у пациентов с циррозом печени и синтропическими коморбидными поражениями системы кровообращения зафиксирован вегетативный дисбаланс, который характеризуется низкой суммарной активностью вегетативного влияния на сердечный ритм и особой динамикой показателей структуры общей спектральной мощности; 2) указанные особенности зависят от клинического варианта поражения - у пациентов с циррозом печени и синтропической кардиомиопатией регулирование внутренних процессов происходит за счет гуморально-метаболических влияний, таких как местные вазоактивные соединения, катехоламины, ренин-анґиотензин-альдостероновая система, с одновременным воздействием симпатической и снижением активности парасимпатической вегетативной нервной системы, а у пациентов с циррозом печени и синтропической артериальной гипотонией внутренняя регуляция осуществляется путем включения местных гуморально-метаболических факторов с недостаточностью как симпатического, так и парасимпатического отделов вегетативной нервной системы.

რეზიუმე

გულის რითმის ვარიაბელობის მეთოდით შეფასებული ვეგეტატიური ნერვული სისტემის მდგომარეობის თავისებურებანი ღვიძლის ციროზით დაავადებულ სისხლძარღვთა სისტემის სინტროპული დაზიანების მქონე პაციენტებში

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ნაშრომში წარმოდგენილია ვეგეტატიური ნერვული სისტემის მდგომარეობის თავისებურებანი, შეფასებული გულის რითმის ვარიაბელობის მეთოდით ღვიძლის ციროზით და სისხლძარღვთა სისტემის სინტროპული დაზიანებით პაციენტებში.

გამოკვლეულია 50 პაციენტი ღვიძლის ციროზით და კარდიომიოპათიით (ექსპერიმენტული „A“ ჯგუფი), 54 პაციენტი ღვიძლის ციროზით და არტერიული ჰიპოტონიით (ექსპერიმენტული „B“ ჯგუფი) და 45 პაციენტი ღვიძლის ციროზით სისხლძარღვთა სისტემის დაზიანების გარეშე (შედარებითი ჯგუფი). დადგენილია: 1) ღვიძლის ციროზის და სინტროპული კომორბიდული დაზიანებების მქონე პაციენტებში დაფიქსირდა ვეგეტატიური დისბალანსი, რომლისთვისაც დამახასიათებელია გულის რითმზე ვეგეტატიური გავლენის დაბალი ჯამური აქტივობა და სპექტრალური სიმძლავრის მაჩვენებლების თავისებური დინამიკა; 2) აღნიშნული თავისებურებანი დამოკიდებულია დაზიანების კლინიკურ ვარიანტზე - ღვიძლის ციროზით და სინტროპული კარდიომიოპათით პაციენტებში შინაგანი პროცესების რეგულირება მიმდინარეობს ჰუმორალურ-მეტაბოლური ფაქტორების გავლენის ხარჯზე (ადგილობრივი ვაზოაქტიური ნაერთები, კატეხოლამინები, რენინ-ანგიოტენზინ-ალდოსტერონის სისტემა, ერთდროული სიმპათიკური სისტემის ზემოქმედებით და პარასიმპათიკური ნერვული სისტემის აქტივობის დაქვეითებით). ციროზის და სინტროპული არტერიული ჰიპოტონიის მქონე პაციენტებში შინაგანი რეგულირება ხორციელდება ადგილობრივი ჰუმორალურ -მეტაბოლური ფაქტორების ჩართვით, როგორც სიმპათიკური, ასევე პარასიმპათიკური ვეგეტატიური ნერვული სისტემის უკმარისობით.

CLINICAL EFFICACY OF S-ADENOSYLMETHIONINE IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS AND CHRONIC KIDNEY DISEASE I-II STAGE

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The comorbid flow of non-alcoholic steatohepatitis (NASH) and chronic kidney disease (CKD) has often recently attracted the attention of both practitioners and researchers [4,9]. Without correction of clinical and biochemical syndromes of liver and kidney damage by interrupting the cascade of interactions, the cessation of the progression of their inflammation, the fibrosing of both organs and the restoration of their functional state can not be corrected [1,7-9]. An important place in the pathogenesis of both diseases is the disturbance of carbohydrate and lipid homeostasis, oxidative and nitrosatitistic stress, endogenous intoxication that helps to accelerate apoptosis of hepatocytes, endothelium, and further their cytolysis on the background of autoimmunic cytokine mechanisms activation of inflammation progression and fibrosing reactions, which leads to progressive functional lack of organs [4,9]. One of these drugs is S-adenosylmethionine (SAM), which, according to the literature, has detoxification, antioxidant, membrane-stabilizing properties (promoting the synthesis of glutathione), the ability to eliminate intrahepatic cholestasis (by activating enzymes that provide transport of bile micelles on the cholangiolar polypeptide of hepatocyte), and administrating antidepressant and regenerative effects [1-3,5,10]. At the same time, in Ukraine, the study of the effectiveness of SAM in patients with NASH on the background of obesity is isolated [1-3,5], and on comorbidity with the CKD, in particular, with regard to the probable effect on the functional state of the kidneys - not conducted at all, which determines the relevance of conducting this research.

The objective of the article was to determine the likely effect of S-adenosylmethionine and Meldonium on the clinical course of non-alcoholic steatohepatitis (NASH) and chronic kidney disease (CKD) of the I-II stages.

Material and methods. We examined 75 patients with NASH with comorbid obesity I degree and CKD I and II dgrees. To determine the efficacy of the treatment, 3 groups of patients were randomized according to age, sex, degree of obesity, activity of the cytolytic syndrome of NASH and the stage of the CKD (chronic uncomplicated pyelonephritis with latent course in the phase of subsiding acute exacerbation). Control group (1) (24 persons) received a hypocaloric diet, metformin 500 mg twice daily, Essentiale H as a hepatoprotective drug (1 capsule 3 times a day), canephron (50 mg 3 times a day) for 90 days The second group (2) (26 people) received a hypocaloric diet, metformin 500 mg twice daily, canephron (50 mg 3 times a day), adenosylmethionine (Ahepta) (SAM) as a hepatoprotective drug (200 mg 3 times on a sublingual day) for 90 days. The third group (3) (25 people) received a hypocaloric diet, metformin 500 mg twice daily, canephron (50 mg 3 times daily), SAM (200 mg 3 times daily sublingual), and Meldonium (vazonate) (V) (250 mg 2 times a day) as an energy, lipid, and carbohydrate metabolism stabilizer for 90 days. The average age of patients was (45.8±3.81) years. During the study of cases of side effects of drugs has not been established.

The statistical analysis of the results was carried out in accordance with the type of research carried out and the types of numerical data that were obtained. Distribution normality was verified using Liliefors, Shapiro-Uilka tests and the direct visual evaluation of eigenvalues distribution histograms. Quantitative indices having a normal distribution are represented as mean (M) ± standard deviation (S). Discrete values are presented in the form of absolute and relative frequencies (percentage of observations to the total number of subjects surveyed). For comparisons of data that had a normal distribution pattern, parametric tests were used to estimate the Student's t-criterion, Fisher's F-criterion. In the case of abnormal distribution, the median test, Mann-Whitney Rank U-Score, and Wilcox's T-criterion (in the case of dependent groups) were used for multiple comparison. Statistica for Windows version 8.0 (Stat Soft inc., USA), Microsoft Excel 2007 (Microsoft, USA) software packages were used for statistical and graphical analysis of the obtained results.

Results and their discussion. The analysis of the effects of SAM and SAM with (V) in course of therapy of patients with NASH and CKD (group 2 and 3) on the course of the disease compared to the control group (group 1) showed the following results (Table 1).

Improvement of well-being, reduction of signs of astheno-vegetative, intoxication syndrome and dyspeptic manifestations in patients of groups 2nd and 3rd were observed 3-4 days after treatment, whereas in patients with 1st group only 10 days. 4 weeks after the start of therapy, the manifestation of astheno-vegetative syndrome in patients 2nd and 3rd groups was significantly less than in 1stgroup: respectively, in 1,3 and 1,8 times ($p<0,05$). After a month of treatment, patients in groups 2 and 3 marked a significant increase in physical and mental working capacity, which exceeded the rate in patients in group 1, respectively, in 1.6 and 1.9 times ($p<0.05$).

The existing manifestations of depression in patients 2nd and 3rd groups significantly decreased and in most patients disappeared, which exceeded the effectiveness of the influence of traditional therapy in patients 1st group -

Table 1. Intensity of clinical symptoms of non-alcoholic steatohepatitis (in points) in patients with obesity and CKd I-II st. in the dynamics of treatment

Clinical symptom	The group surveyed patients		
	Group 1, n=24	Group 2, n=26	Group 3, n=25
General weakness (asthenia)	2,6±0,17	3,5±0,19 *	4,7±0,12*/**
Capacity (physical, mental)	2,4±0,11	3,9±0,12 *	4,6±0,15*/**
Depression	1,1±0,13	4,0±0,08 *	4,7±0,09 */**
Bitterness in the mouth	1,5±0,22	4,3±0,08 *	4,8±0,12*/**
Dryness in the mouth	1,7±0,12	4,1±0,16 *	4,7±0,15*/**
Nausea	1,5±0,17	4,0±0,05 *	4,6±0,10*/**
Bloating	1,9±0,12	4,5±0,15 *	4,6±0,17 *
Itchy skin	1,6±0,08	4,6±0,07	4,9±0,02*/**
Heaviness in the right subcostal area	2,4±0,12	4,4±0,11*	4,9±0,09*/**
Hepatomegaly	3,2±0,13	4,1±0,10 *	4,7±0,09*/**

notes: Scale of assessment: 1 point - negative effect; 2 points - no effect; 3 points-satisfactory; 4 points - good; 5 points - very good.

** - differences are probable compared to the group of patients treated with Essentsial H (p<0,05);*

*** - the differences are likely compared with the group of patients treated with adenosylmethionine (p<0.05)*

respectively, in 3,6 and 4,3 times (p<0,05) (Table 1). The comparative dynamics of the intensity of the main clinical syndromes on the 30th day of treatment was as follows: the general manifestations of the dyspeptic syndrome decreased in comparison with the indicator after treatment in patients 1st group, respectively, in 2nd group - in 2,4-2,9 times (p<0, 05), in 3rd group - in 2,8 - 3,2 times, clinical manifestations of cholestasis - respectively, in 2,9 and 3,1 times (p<0,05), of the basic discomfort (severity, pain) - 1,8 and 2.0 times (p<0,05), hepatomegaly - 1,3 and 1,5 times respectively (p<0,05).

Indicators of biochemical markers of the functional state of the liver and kidneys in the dynamics of treatment are illustrated in Table. 2. Within 30 days of the initiation of treatment, a probable decrease in the total bilirubin content in the blood was recorded only in patients with 2nd and 3rd groups: 1.4 and 1.8 times respectively (p<0.05) with the achievement of standard limits (p>0,05), while in patients in 1st group there was only a tendency to decrease (p>0,05). After 90 days of treatment, the reduction was more significant: 1.8 and 2.1 times respectively (p<0.05) with unlikely changes in 1stt group. Only after 3 months. After treatment in 1st group, the total bilirubin content decreased significantly, however, the normative indicators did not reach (p>0.05), whereas in the 2nd and 3rd groups the indicators remained within the normative (p>0.05) throughout the entire observation period.

The content of conjugated bilirubin at 30 days of treatment in patients 2nd and 3rd group was decreased by 1.8 and 2.0 times with normalization (p<0.05), while changes in 1stgroup were unlikely (p>0.05), which indicates the powerful membrane-protective properties of the sublingual form of SAM and its ability to eliminate the hepatocyte cytolysis syndrome and the cholestatic component of NASH (Table 2). At the same time, the combination and SAM and V had a more effective effect on pigment exchange correction, as evidenced by the likely difference between the indicator 30 days after treatment in patients 2nd and 3rd groups (p<0.05). A similar trend towards the content of total bilirubin was observed in relation to its direct fraction after 90 days of treatment, as well as in 3 months after treatment with stable normalization of indicators only in patients in 2nd and 3rd groups (p> 0.05).

Integrated therapy involving SAM and SAM with V has also significantly accelerated the conjugation processes of the free fraction of bilirubin with a decrease in its content in the blood for 30 days of treatment - respectively, in 1,3 and 1,6 times (p<0,05), at 90 Day of treatment - in 1,6 and 1,9 times (p<0,05) and continued to decrease for 3 months after treatment (p<0,05), in contrast to traditional therapy, where the reduction of unconjugated bilirubin in the month of treatment was 1,2 times, after 3 months of treatment - the rate decreased by 1,3 times, however, the normative values were not reached (p<0,05). In patients of 2nd and 3rd groups, the normalization of pigmentary metabolism rates was stable and stable both before the end of the course of treatment and in the long term (3 months).

Another confirmation of the possibility of eliminating the manifestation of the cytolytic syndrome in patients with NASH during one month of treatment is a possible decrease in the activity of AST in the blood: 11.2%, 48.4% and 60.0% respectively (p<0.05), moreover, with a significantly higher efficiency of complex therapy with SAM with V (p<0,05). After 90 days of follow-up, the decrease in the activity of AST was more significant than in the first observation period: 1.6 times, 3.1 and 4.2 times (p<0.05), with stable normalization of the indicator only in patients 2nd- and 3rd- groups (p> 0.05). We also found a decrease in the activity of ALT on the 30th day of treat-

Table 2. Biochemical parameters of the functional state of the liver and kidneys in patients with non-alcoholic steatohepatitis and chronic kidney disease I-II st. in the dynamics of treatment (M±m)

Indicator	Practically healthy person, n=20	Group	Before treatment	After 30 days	After 90 days	After 3 months of treatment
Total bilirubin, μmol/l	19,2±1,12	1	35,2±1,03 *	30,9±4,1*	28,9±3,8 *	25,2±3,7 */**
		2	35,6±1,08 *	24,8±1,01 **/#	20,2±0,76 **/#	19,1±0,73 **/#
		3	35,3±1,16 *	20,2±1,05 **/#/***	16,9±0,83 **/#/***	16,2±0,48 **/#/***
Direct bilirubin, μmol/l	4,5±0,25	1	10,2±0,35 *	9,5±0,97 *	8,9±1,10 *	7,4±0,73 */**
		2	10,1±0,37 *	5,7±0,21 **/#	4,7±0,05 **/#	4,6±0,05 **/#
		3	10,1±0,31 *	5,0±0,13 **/#/***	4,4±0,03 **/#/***	4,4±0,04 **/#/***
Indirect bilirubin, μmol/l	14,7±0,43	1	25,0±1,13 *	21,4±0,27 */**	20,0±0,45 */**	17,8±1,23 **
		2	25,5±1,08 *	19,1±0,35 */**/#	15,5±0,35 **/#	14,5±0,64 **/#
		3	25,1±1,16 *	15,2±0,21 **/#/***	13,5±0,37 **/#/***	11,8±0,52 */**/#/***
AST, μmol/hour×l	0,39±0,01	1	1,25±0,02*	1,11±0,02 */**	0,8±0,02 */**	0,6±0,03 */**
		2	1,24±0,01 *	0,6±0,01 */**/#	0,4±0,01 **/#	0,4±0,03 **/#
		3	1,25±0,01 *	0,5±0,01 */**/#/***	0,3±0,01 **/#/***	0,4±0,02 **/#
ALT, μmol/hour×l	0,38± 0,014	1	1,4±0,02 *	1,2±0,08 *	0,8±0,03 */**	0,7±0,05 */**
		2	1,4±0,02 *	0,6±0,02 */**/#	0,5±0,02 */**/#	0,4±0,02 **/#
		3	1,4±0,01 *	0,5±0,02 */**/#/***	0,4±0,01 **/#/***	0,4±0,01 **/#
Total protein, g/l	76,13±2,12	1	60,30±2,11*	65,26±2,25 *	66,5±2,39 *	70,3±2,53 **
		2	60,31±1,92*	75,8±2,31**	78,2±2,04 **/#	81,2±2,31 **/#
		3	60,28±1,84*	80,2±2,37 **/#	82,3±2,13 **/#	82,6±2,12 **/#
Albumìn, %	59,37± 2,23	1	43,63±2,33*	45,32±1,97 *	50,42±1,79 *	51,0±1,92 *
		2	43,62±2,34 *	54,83±1,35**/#	59,27±1,25 **/#	59,8±1,18 **/#
		3	43,63±2,35 *	57,15±1,42 **/#	60,42±1,34 **/#	60,1±1,24 **/#
Bile acid, mmol/l	1,27±0,01	1	2,83±0,06 *	2,74±0,35 *	2,72±0,53 *	2,60±0,17 *
		2	2,81±0,08 *	2,12±0,03 */**/#	1,57±0,05 **/#	1,39±0,04 **/#
		3	2,82±0,07 *	1,94±0,05 */**/#/***	1,36±0,02 **/#/***	1,20±0,05 **/#/***
Thymol test, conditional units	2,82±0,13	1	4,30±0,15*	4,24±0,21*	4,13±0,13*	4,01±0,21 *
		2	4,33±0,13*	3,53±0,17 */**/#	3,21±0,07 */**/#	3,09±0,08 **/#
		3	4,32±0,12*	3,41±0,10 */**/#	2,90±0,06 */**/#/***	2,76±0,07 **/#/***
Glomerular filtration rate, ml/min	117,0±3,37	1	78,5±3,26*	80,2±3,75*	82,7±3,14*	87,3±3,79*
		2	78,3±3,25*	96,5±2,43 */**/#	100,2±2,64 **/#	105,8±2,28 **/#
		3	78,6±3,28*	106,8±2,27 */**/#/***	112,5±2,51 **/#/***	116,1±2,39 **/#/***

*notes: * the difference is probable compared to the indicator for practically healthy persons (p<0,05);*
*** the difference is probable compared with the indicator before treatment (p<0,05);*
 # - the difference is probable compared to the indicator after treatment in patients in group 1 (p<0.05);
**** - the difference is probable compared to the indicator after treatment in patients in group 2 (p<0,05)*

ment in patients 2nd and 3rd groups: respectively, 2.3 and 2.8 times (p<0.05), compared with only the tendency to decrease (p>0.05) in group 1 , with a probable intergroup difference (p<0,05). It should be noted that the activity of AST and ALT in patients with NASH 1 group in the treatment dynamics remained significantly elevated during the entire observation period, which required the appointment of an additional course of treatment. The use of SAM and SAM with V also produced a powerful anti-inflammatory effect. Thus, in patients with 2nd- and 3rd- groups in the dynamics of treatment, the thyme test decreased by 1.2 and 1.3 times (p<0.05) with unlikely changes in group 1 (p> 0.05); The albumin / globulin ratio increased by 1.3 and 1.4 times (p<0.05) versus the growth trend in group 1 (p> 0.05). The highest anti-inflammatory effect of SAM therapy with V versus the appointment of SAM alone is evidenced by the results of the study of the thyme sample after 90 days of treatment: a decrease of 1.3 and 1.5 times *(p<0.05*) and 3 months later after treatment with a stable normalization of the indicator (p>0.05).

In the dynamics of treatment with SAM and SAM with V, a significant increase in the liver protein function was found (albumin content in the 2nd and 3rd groups increased 1.3 times (p<0.05) versus 7.7% (p> 0.05) in group 1) and a probable increase in the content of total protein in the blood, respectively, in 1,3 and 1,4 times (p<0,05) versus 1,2 times in group 1, 3 months after treatment (p<0,05). Thus, SAM possesses powerful membrane-stabilizing properties, stably eliminates the manifestations of cytolysis, cholestasis, mesenchymal-inflammatory syndrome, increases the albumin-synthesizing function of the liver in patients with NASH and prevents the loss of albumins in the conditions of CKD I-II st. At the same time, complex therapy SAM with V is superior to the effectiveness of correction of these syndromes due to the implementation of powerful metabolic, antioxidant, antihypoxant, energy-specific properties of Meldonium [6-8] and may be recommended for the introduction into the practice of internal medicine and gastroenterology for treatment NASH on the background of obesity and CKD I and II stages.

Analyzing the functional status of the kidneys in the examined patients in the dynamics of treatment, it should be noted that the proposed therapy of SAM and SAM with V contributed to the correction of a significantly reduced GFR (Table 2) after 30 days treatment with an increase of 1.2 and 1.4 times, respectively (p<0.05). In the distant term, a stable normalization of the indicators in patients with 2nd and 3rd groups was observed, with an increase of 1.3 and 1.5 times, respectively (p<0.05).

The established nephroprotective properties of SAM that are potentially Meldonium are probably due to the ability of these drugs to eliminate endothelial dysfunction, improve microcirculation, and prevent the progression of kidney fibrosis.

Conclusion. S-adenosylmethionine (ahepta) in a dose of 600 mg sublingually in patients with non-alcoholic steatohepatitis on the background of obesity and chronic kidney disease of the 1st and 2nd st. produces powerful membrane-stabilizing effects on the affected hepatocytes, stably eliminates the clinical manifestations of the disease, the intensity of cytolysis, cholestasis, mesenchymal-inflammatory syndrome, inhibits the progression of hepatic and renal dysfunction (increases the albumin-synthesizing function of the liver, the velocity of glomerular filtration) by optimizing the control of fibrosis of the liver and kidneys. Complex therapy with S-adenosylmethionine (ahape) and Meldonium (500 mg / day vasonate) is superior to the correction of these syndromes NASH and CKD, since the vasonate potentially potentiates the action of S-adenosylmethionine in acute and distant observation periods.

Promising further research in this area. is the establishment of probable mechanisms of the influence of S-adenosylmethionine and Meldonium on the course of chronic kidney disease and non-alcoholic steatohepatitis on the background of obesity, the intensity of oxidative and nitrosatitistic stress, functional state of the endothelium and the intensity of fibrous reactions in the liver and kidneys.

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SUMMARY

CLINICAL EFFICACY OF S-ADENOSYLMETHIONINE IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS AND CHRONIC KIDNEY DISEASE I-II STAGE

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The article presents a theoretical generalization of the results of the clinical efficacy of S-adenosylmethionine in patients with non-alcoholic steatohepatitis (NASH) in comorbidity with obesity and chronic kidney disease (CKD) of the 1st-2nd stages.

The objective of the article was to determine the likely effect of S-adenosylmethionine and Meldonium on the clinical course of non-alcoholic steatohepatitis (NASH) and chronic kidney disease (CKD) of the I-II stages.

We examined 75 patients with NASH with comorbid obesity I degree and CKD I and II dgrees. To determine the efficacy of the treatment, 3 groups of patients were randomized according to age, sex, degree of obesity, activity of the cytolytic syndrome of NASH and the stage of the CKD.

SAM possesses powerful membrane-stabilizing properties, stably eliminates the manifestations of cytolysis, cholestasis, mesenchymal-inflammatory syndrome, increases the albumin-synthesizing function of the liver in patients with NASH and prevents the loss of albumins in the conditions of CKD I-II st. At the same time, complex therapy of SAM and vazonate is superior to the effectiveness of correction of these syndromes due to the implementation of powerful metabolic, antioxidant, antihypoxant, energy-specific properties of Meldonium and may be recommended for the introduction into the practice of internal medicine and gastroenterology for treatment NASH on the background of obesity and CKD I and II stages.

The established nephroprotective properties of SAM that are potentiated by Meldonium are probably due to the ability of these drugs to eliminate endothelial dysfunction, improve microcirculation, and prevent the progression of kidney fibrosis.

S-adenosylmethionine (ahepta) in a dose of 600 mg sublingually in patients with non-alcoholic steatohepatitis on the background of obesity and chronic kidney disease of the 1st and 2nd st. produces powerful membrane-stabilizing effects on the affected hepatocytes, stably eliminates the clinical manifestations of the disease, the intensity of cytolysis, cholestasis, mesenchymal-inflammatory syndrome, inhibits the progression of hepatic and renal dysfunction (increases the albumin-synthesizing function of the liver, the velocity of glomerular filtration) by optimizing the control of fibrosis of the liver and kidneys. Complex therapy with S-adenosylmethionine (ahape) and Meldonium (500 mg /day)(vasonate) is superior to the correction of these syndromes NASH and CKD, since the vasonate potentially potentiates the action of S-adenosylmethionine in acute and distant observation periods.

Keywords: non-alcoholic steatohepatitis, chronic kidney disease, clinical syndromes, S-adenosylmethionine.

РЕЗЮМЕ

КЛИНИЧЕСКАЯ ЭФФЕКТИВНОСТЬ S-АДЕНОЗИЛМЕТИОНИНА У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНЫМ СТЕАТОГЕПАТИТОМ И ХРОНИЧЕСКИМ ЗАБОЛЕВАНИЕМ ПОЧЕК I-II СТАДИИ

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Целью данного исследования явилось определение вероятного эффекта S-аденозилметионина и мельдония на клинический курс неалкогольного стеатогепатита и хронического заболевания почек I-II стадии.

Исследованы 75 пациентов с неалкогольным стеатогепатитом, сопутствующим ожирением I степени, хроническим заболиванием почек I и II стадии. Для определения эффективности лечения были рандомизированы, в зависимости от возраста, пола, степени ожирения, активности цитолитического синдрома безалкогольного стеатогепатита и стадии хронического заболивания почек, три группы пациентов.

Установленные нефропротекторные свойства S-аденозилметионина, потенциированые мелдонием, вероятно, связаны с способностью этих препаратов устранять эндотелиальную дисфункцию, улучшать микроциркуляцию и предотвращать прогрессирование фиброза почек.

S-аденозилметионин (Агепта) в дозе 600 мг сублингвально у пациентов с неалкогольным стеатогепатитом на фоне ожирения и хронического заболевания почек I-II стадий оказывает сильное мембрано-стабилизирующее действие на пораженные гепатоциты, стабильно устраняет клинические проявления заболевания, интенсивность цитолиза, холестаза, мезенхимально-воспалительного синдрома, ингибирует прогрессирование печеночной и почечной дисфункции путем оптимизации контроля фиброза печени и почек. Комплексная терапия с S-аденозилметионином (Агепта) и мельдонием (Вазонат) 500 мг/день превосходит коррекцию синдромов неалкогольного стеатогепатита и хронического заболевания почек, поскольку Вазонат потенциально потенцирует действие S-аденозилметионина в острые и отдаленные периоды наблюдения.

რეზიუმე

S-ადენოზილმეთიონინის კლინიკური ეფექტურობა პაციენტებში არაალკოჰოლური სტეატოჰეპატიტით და თირკმლების დაავადების I-II ქრონიკული სტადიით

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ბუკოვინის სახელმწიფო სამედიცინო უნივერსიტეტი, ჩერნოვცი, იკრაინა

კვლევის მიზანს შეადგენდა S-ადენოზილმეთიონინის და მელდონიუმის შესაძლო ეფექტის განსაზღვრა არაალკოჰოლური სტეატოჰეპატიტის და თირკმლების დაავადების I-II ქრონიკული სტადიის კლინიკურ კურსზე.

გამოკვლეულია 75 პაციენტი არაალკოჰოლური სტეატოჰეპატიტით, თანმხლები I ხარისხის სიმსუქნით და თირკმლების ქრონიკული I-II სტადიის დაავადებით. მკურნალობის ეფექტურობის განსაზღვრისათვის პაციენტები ასაკის, სქესის, სიმსუქნის ხარისხის, არაალკოჰოლური სტეროჰეპატიტის ციტოლიზური სინდრომის აქტივობის და თირკმლების ქრონიკული დაავადების სტადიის მიხედვით რანდომიზებული იყო სამ ჯგუფად.

S-ადენოზილმეთიონინის დადგენილი ნეიროპროტექტორული თვისებები, პოტენცირებული მელდონიუმით, სავარაუდოდ, დაკავშირებულია ამ პრეპარატებით ენდოთელური დისფუნქციის მოხსნის, მიკროცირკულაციის გაუმჯობესების და თირკმლის ფიბროზის თავიდან აცილების შესაძლებლობასთან.

S-ადენოზილმეთიონინი (აგეპტა), დოზით 600 მგ სუბლინგვურად, პაციენტებში არაალკოჰოლური სტეატოჰეპატიტით სიმსუქნის და თირკმლის ქრონიკული დაავადების I-II სტადიის ფონზე, ღვიძლისა და თირკმლების ფიბროზის კონტროლის გზით დაზიანებულ ჰეპატოციტებზე ავლენს ძლიერ მემბრან-მასტაბილიზებელ მოქმედებას, სტაბილურად აქრობს დაავადების კლინიკური გამოვლინებებს, ამცირებს ციტოლიზის, ქოლესტაზის, მეზენქიმურ-ანთებითი სინდრომის ინტენსივობას, აინჰიბირებს ღვიძლის უკმარისობის და თირკმლის დისფუნქციის პროგრესირებას.

S-ადენოზილმეთიონინით (აგეპტა) და მელდონიუმით (ვაზონატი, 500 მგ/დღეში) კომპლექსური თერაპია აუმჯობესებს არაალკოჰოლური სტეატოჰეპატიტის და თირკმლების ქრონიკული დაავადების სინდრომების კორექციას, ვინაიდან ვაზონატი დაკვირვების მწვავე და გრძელვადიან პერიოდებში ახდენს S-ადენოზილმეთიონინის მოქმედების პოტენცირებას.

THE IMPACT OF 12-MONTH GROWTH HORMONE REPLACEMENT THERAPY ON LIPID METABOLISM AND ADIPOSE TISSUE DISTRIBUTION IN GEORGIAN PATIENTS WITH ADULT GROWTH HORMONE DEFICIENCY

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Adult Growth hormone deficiency (AGHD) is a rare disorder, which is characterized by the inadequate growth hormone (GH) secretion from the anterior pituitary gland. AGHD has been estimated to affect 1 in 100,000 people annually. About 15-20% of cases represent the transition of childhood GH deficiency into adulthood. The disorder affects males and females equally [1].

The primary causes of AGHD are different hypothalamic-pituitary lesions, including trauma, surgical injury, subarachnoid hemorrhage and etc. GHD often coincides with the discovery of pituitary tumors, usually between the fourth and fifth decades of life [9]. AGHD causes several symptoms: reduced lean body mass, increased visceral fat, premature atherosclerosis, abnormal carbohydrate and lipoprotein metabolism, impaired cardiac function, reduced exercise capacity and decreased bone mineral density [5]. Recent cross-sectional surveys from various countries have confirmed much higher prevalence of cardiovascular and metabolic disorders in patients with GHD, in comparison with the general population [10].

Table 1. General characteristics of the study population

		GH replacement group n=10	Placebo group n=10
Sex	Females	8	3
	Males	2	7
BMI (kg/m^2)		28.9 ± 2.8	27.6 ± 3.9
Duration of Hypopituitarism		2 yrs±3months	2yrs±5 months

Trials on recombinant human GH have begun since 1980' and since that period large amount of data has been accumulated. Recent double-blind, randomized, placebo-controlled trials have shown a remarkable decrease in low-density lipoprotein cholesterol (LDL) and total cholesterol levels, following the GH replacement treatment in GHD adults, compared to the baseline values. In addition, GH treatment has shown beneficial impact on body fat distribution [2,6,7]. Furthermore, patients reported a significant improvement of their quality of life [3,8].

Several studies show not remarkable, but partial improvement of lipid profile after GH treatment. One of the authors reported a significant reduction of total cholesterol levels after 6 months of GH treatment, however plasma triglycerides elevated [4].

The impact of GH replacement therapy on lipid profile and body fat distribution was never studied in Georgian people. As GHD is one of the reasons of dyslipidemia and increased visceral fat mass, we decided to evaluate the effect of GH replacement therapy on plasma lipid metabolism and fat distribution in our population.

Material and methods. Double-blind, placebo controlled study was carried at the National Institute of Endocrinology (Tbilisi, Georgia). The study protocol was approved by local ethics committee.

Inclusion criteria for the study were: diagnoses of acquired growth hormone deficiency, age ≥18 years, compensation on replacement hormone doses (vasopressin, thyroid, adrenal) for at least 6 months prior to the screening.

Patients were excluded from the study if: there was a contraindications to GH treatment; participation in other clinical trial within 6 months of screening; active malignant diseases (except the surgically removed basal cell carcinoma); a new diagnosis of pituitary adenoma within the 15 months of screening; presence of untreated adrenal insufficiency; active acromegaly in the past 4 years or active Cushing's syndrome in the past 1,5 year; diagnosis of type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus (HBA1c ≥8%).

Based on inclusion and exclusion criteria twenty patients (11 females and 9 males) were enrolled in a randomized, double blind, placebo-controlled study (Table 1).

All patients were randomly distributed into two groups. Patients in the first group were treated with GH and patients in the second group were given placebo.

A Human growth hormone, comprised of the authentic human GH sequence was injected intramuscularly. The starting dose was 0,33 IU/kg and later was down titrated by ≈ 25-50%, according to individual characteristics.

All patients in both groups were recommended to follow healthy diet. Dietary recommendations were changed every 2 months. Other medications that could affect lipid metabolism and body distribution were forbidden during the whole study period.

GH deficiency was defined biochemically, based on the results of the blood GH, IGF and IGF binding protein 3 tests. All of them were essayed immunoenzymatically. GH deficiency was defined on the basis of stimulated GH response to insulin-induced hypoglycemia (blood glucose, ~2.2mmol/L) less than 10mU/l. According to test results, most patients had severe GH deficiency (below 4 mU/l).

In order to determine impact of the GH treatment on the lipid spectrum and adipose tissue distribution, the assessments were collected on baseline and after 6 and 12 months of the study.

Serum cholesterol and triglyceride levels were assayed enzymatically. High density lipoprotein (HDL) cholesterol was assayed after precipitation of other lipoproteins with dextran sulfate and magnesium. LDL cholesterol was calculated from Fried Wald's formula.

Fat mass distribution was analyzed by dual-energy x-ray absorptiometry (DXA) in the following areas: Legs, Trunk, Android, Gynoid and total body. Adipose tissue was calculated in the percentages.

Data were analyzed by SPSS 18 (SPSS Inc., Chicago, IL, USA).All data are presented as the mean +- SD or median (range). ANOVA test was used to see the differences in group means in normally distributed data, in case of non-normally distributed data, the Mann-Whitney U test andWilcoxon's test were used for unpaired and paired comparisons, respectively.

Results and their discussion. A total of 20 patients were enrolled in the study. At baseline, all patients in both groups had dyslipidemia. After 12 months of treatment mean values of low density lipoprotein cholesterol (LDL-CH), total cholesterol (CH) and triglycerides (TG) were increased in GH treated patients, compared to the control group (median increase in LDL-CH, CH and TG were 0.1mmol/l, 0.1mmol/l and 0.3mmol/l, respectively). In contrast, the favorable effect was seen in high density lipoprotein cholesterol (HDL-CH) levels with the median increase in 0.2mmol/l). The most significant increase was shown by TG (Fig. 1).

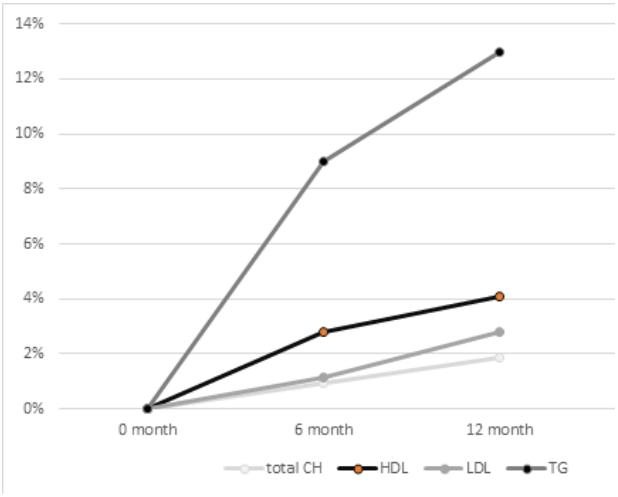

Fig. 1. Percentage change in median lipid profile (TG, Total CH, HDL, LDL) in the treatment group

The total CH /HDL and LDL/HDL cholesterol ratios were not decreased either. However, there was a decrease of total CH, LDL-CH and TG levels in control group. None of the patients received statin therapy or other additional medications that could have effect on lipid metabolism, thus we presume, it could be result of the healthy diet and physical activity, which was better followed in the control group (Table 2).

The percentage of body fat distribution was also elevated in all examined areas in the treatment group (DXA: Legs +10.22%, Trunk: +7.43%, Android: +5.59%, Gynoid: +10.59%, Total body :+7.6%) after 6 and 12 month of GH replacement therapy.

In the control group the values of fat distribution in different areas, obtained after 6 and 12 months of the study, were almost similar to the baseline values (Table 3).

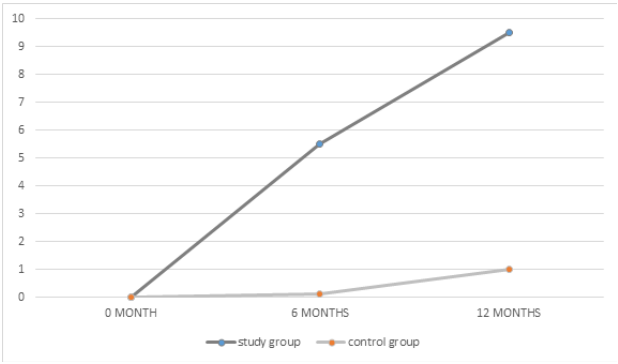

Fig. 2. Trend of total fat (Region %Fat) in GH treatemnt and control groups (% change vs previous)

When the results were adjusted by the gender or by presence or absence of additional pituitary hormone deficiencies, the results remained the same.

It is evident, that our study has not shown any improvements in lipid profile and body fat distribution in GH treated patients. Dyslipidemia was worsened after 12 months of GH replacement therapy, while patients in the placebo group had showed much better results of the whole lipid profile. Moreover, we cannot consider the elevation of HDL-CH in the GH group as the partial improvement, because the same trend was seen in the patients from the control group. Furthermore, there was an increase in adipose tissue distribution percentages in GH treated patients, compared to the control group patients. Thus, according to our results, the role of GH in the improvement of lipid spectrum in aGHD patients can be considered as ineffective.

The results of our study were not in line with Beshyah-Henderson's study results, which showed complete improvement of lipid profile in aGHD patients, after 18 months of GH therapy [2]. Murray's and coworkers'

Table 2. GH effect on lipid profile in treatment and placebo groups (the mean ± SD), mmol/l

Lipid Profile	Treatment group			Control group		
Total cholesterol	5.44±1.1	5.49±1.1	5.54±0.9	4.96±1.2	4.9±1.27	4.8 ±0.97
HDL-CH	0.8 ±0.7	0.95±0.23	1±0.8	1.2±0.98	1.25±0.7	1.35 ±1.1
LDL-CH	3.55 ±1.3	3.59±1.6	3.65±1.5	3.1±1.12	3±1.2	2.9 ±1.3
Triglycerides	2.2 ±0.56	2.4±1.1	2.5±0.4	1.5±0.9	1.5±0.8	1.4 ±0.7

Table 3. Percentages of Adipose tissue distribution in different areas on baseline level and after 6 and 12 months of the study in GH treatment and control groups

Areas	Treatment group			Control group		
Legs	28.12%±5.41	30.4%±3.45	38.34%± .56	29.22%±4.66	30.27%±4.23	30.12%±7.77
Trunk	38.24%±7.88	43.33%±4.44	45.67%± 5.98	40.4%±5.55	40.6%±4.99	39.9%±4.5
Android	42.21%±8.72	43.3%±5.56	48.8 %± 5.99	45.23%±6.78	46%±6.89	45.77%±7.1
Gynoid	35.11%±4.45	40.8%±5.9	45.7%± 4.78	39.2%±5.51	40.44%±5.14	40.2%±5.07
Total	32.3%±6.65	35.5%±5.45	39.9%±7.34	34.77%±5.56	34.9%±6.11	35.2% ±6.76

Statistically 68% of repeat scans fall within 1SD (±0.8%)

study has also shown a remarkabledecrease in LDL and totalcholesterol levels in the GHD adults, following GH replacement treatment,compared to the baseline level and the same profile of placebo group [7]. The reason of remarkably different results may be various including environment, nutritional habits, lifestyle and etc. Moreover, there are some other important factors that might influence the results, such as different GH doses or injection frequency, preexisting lipid profile, coexisting illnesses and etc.

Though our study has not shown expected improvement in lipid profile and body fat distribution it still has practical values. Present study is a good example that people in different countries differ between each other and performance of national studies are important to determine the effect of treatment for individual population.

Our study had several limitations, such as small study population and the short study duration. In hope to receive favorable effect on study parameters we decided to prolong the trial for the next 12 months**.**

Conclusion. Twelve-month GH replacement therapy in Georgian adults with GHD did not show beneficial effect on lipid profile and body fat distribution. As 12-month study period might not be enough to determine the full impact of GH on lipid profile and body fat distribution we decided to prolong the observation for the next 12 months.

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SUMMARY

THE IMPACT OF 12-MONTH GROWTH HORMONE REPLACEMENT THERAPY ON LIPID METABOLISM AND ADIPOSE TISSUE DISTRIBUTION IN GEORGIAN PATIENTS WITH ADULT GROWTH HORMONE DEFICIENCY

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Growth hormone deficiency (GHD) is one of the reasons of significant metabolic morbidities inchildren and adults. The aim of our study was to evaluate the impact of growth hormone (GH) replacement therapy on lipid profile and adipose tissue distribution in adults with GHD.

Twenty hypopituitary adults, aged 40.75±2.2 years (mean ± SE, range 20.5-60), with adult onset GHD (aGHD) were enrolled in a randomized, double blind, placebo-controlled study. 10 patients received recombinant growth hormone injection once weekly for 12 months, and the rest 10 patients (as control group) received placebo. The patients were selected from the basis of National Institute of Endocrinology.

After 12 months of treatment mean values of low density lipoprotein cholesterol (LDL-CH), total cholesterol (CH) and triglycerides (TG) were increased in GH treated patients, compared to the control group (median increase in LDL-CH, CH and TG were 0.1 mmol/l, 0.1 mmol/l and 0.3mmol/l, respectively). In contrast, the favorable effect was seen in high density lipoprotein cholesterol (HDL-CH) levels with the median increase of 0.2 mmol/l). Furthermore, there was an increase in adipose tissue distribution percentages, in GH treated patients (DXA: Legs +10.22%, Trunk: +7.43%, Android: +5.59%, Gynoid: +10.59%, Total body: +7.6%), compared to the control group, in which adipose tissue distribution was slightly improved or remained unchanged.

Since the results of 12-month growth hormone treatment therapy did not show any improvements in lipid profile and adipose tissue distribution, the decision was made to prolong the study for the next 12 months.

Keywords: growth hormone deficiency, pituitary gland, lipid profile, adipose tissue distribution, growth hormone replacement therapy.

РЕЗЮМЕ

ВЛИЯНИЕ ЗАМЕСТИТЕЛЬНОЙ ТЕРАПИИ ГОРМОНОМ РОСТА НА ЖИРОВОЙ ОБМЕН И РАСПРЕДЕЛЕНИЕ ЖИРОВОЙ ТКАНИ У ВЗРОСЛЫХ ПАЦИЕНТОВ С ДЕФИЦИТОМ ГОРМОНА РОСТА, РЕЗУЛЬТАТЫ 12-МЕСЯЧНОГО ИССЛЕДОВАНИЯ

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Дефицит гормона роста является причиной метаболического расстройства как у детей, так и взрослых.

Целью данного исследования явилась оценка эффективности заместительной терапии гормоном роста для улучшения метаболизма липидов и распределения жировой ткани у взрослых с приобретенным дефицитом гормона роста.

В исследовании приняли участие 20 пациентов Национального института эндокринологии с дефицитом гормона роста, из них 11 женщин и 9 мужчин (средний возраст 40,75±2,2 лет). Рандомизированное исследование проведено посредством двойного слепого метода. 10 пациентам проведена заместительная терапия гормоном роста, остальные составили группу контроля без терапии.

Спустя 12 месяцев пациентам основной и контрольной групп проведено биохимическое исследование крови. Результаты процентного распределения жировой ткани и липидного профиля у пациентов основной группы были следующими: липопротеин низкой плотности и общий индекс холестерина составили, в среднем, 0,1 ммоль/л, скорость триглицеридов увеличилась в сравнении с первоначальными данными, в среднем, по группе на 0,3 ммоль/л. Удовлетворительный результат выявлен со стороны липопротеина высокой плотности в увеличении показателей, в среднем, на 0,2 ммоль/л.

Отрицательные результаты выявлены в процентном распределении жировой ткани пациентов основной группы, которое определялось методом двойной энергетической абсорбциометрии: нижние конечности +10,22%, туловище: +7,43%, абдоминальная часть + 5,59%, гиноидная часть + 10,59%, по всему телу +7,6%. Аналогичные показатели у пациентов контрольной группы были слегка улучшены или не были изменены.

На основании результатов проведенного исследования следует заключить, что заместительная терапия гормоном роста не оказала положительного эффекта на процентное распределение жировой ткани и липидного профиля. Полученные данные являются результатами первого этапа исследования, которое длилось 12 месяцев.

რეზიუმე

ზრდის ჰორმონის ჩანაცვლებითი თერაპიის გავლენა ცხიმოვან ცვლასა და ცხიმოვანი ქსოვილის გადანაწილებაზე მოზრდილ პაციენტებში ზრდის ჰორმონის დეფიციტით, 12-თვიანი კვლევის შედეგები

ნ. ბოსტოღანაშვილი, თ. ზერეკიძე, შ. ჯანჯღავა, მ. ლომიძე

ივ. ჯავახიშვილის სახელობის თბილისის სახელმწიფო უნივერსიტეტი, კლინიკური ენდოკრინოლოგიის კათედრა; ენდოკრინოლოგიის ეროვნული ინსტიტუტი, თბილისი, საქართველო

ზრდის ჰორმონის (ზჰ) უკმარისობა წარმოადგენს მეტაბოლური დარღვევების მიზეზს როგორც ბავშვებში, ასევე მოზრდილებში. კვლევის მიზანი იყო ზრდის ჰორმონის ჩანაცვლებითი თერაპიის (ზჰთ) გავლენის დადგენა ლიპიდური ცვლის და ცხიმოვანი ქსოვილის გადანაწილების მაჩვენებლებზე მოზრდილებში ზრდის ჰორმონის შეძენილი უკმარისობით.

კვლევაში მონაწილეობდა ზრდის ჰორმონის უკმარისობის მქონე 20 პაციენტი (11 ქალი, 9 მამაკაცი), საშუალო ასაკი - 40.75±2.2 წ. პაციენტები შერჩეული იყო ენდოკრინოლოგიის ეროვნული ინსტიტუტის ბაზიდან. რანდომული კვლევა ჩატარდა ორმაგი ბრმა მეთოდით. 10 პაციენტი, რომელიც იღებდა ჩანაცვლებით ზრდის ჰორმონს, განაწილდა სამკურნალო ჯგუფში, ხოლო დანარჩენი 10 პაციენტი, რომელიც მედიკამენტს არ იღებდა, საკონტროლო ჯგუფში.

ზჰთ-ის დაწყებიდან 12 თვის შემდეგ ლიპიდური პროფილის ბიოქიმიური და ცხიმოვანი ქსოვილის პროცენტული გადანაწილება შეფასება ინსტრუმენტული გზით როგორც საკვლევ, ასევე საკონტროლო ჯგუფებში. საკვლევი ჯგუფის პაციენტებში დაბალი სიმკვრივის ლიპოპროტეინებისა და საერთო ქოლესტერინის მაჩვენებელმა საშუალოდ 0,1 მმოლ/ლ-ით, ხოლო ტრიგლიცერიდების მაჩვენებელმა, საშუალოდ, 0,3 მმოლ/ლ-ით მოიმატა საწყისს მაჩვენებლებთან შედარებით. დამაკმაყოფილებელი შედეგი აჩვენა მაღალი სიმკვრივის ლიპოპროტეინებმა, საშუალოდ, 0,2 მმოლ/ლ-ით მატებით საწყისს მაჩვენებელთან შედარებით.

უარყოფითი შედეგები გამოვლინდა ცხიმოვანი ქსოვილის პროცენტულ გადანაწილებაში, რო-

მელიც განისაზღვრა ორმაგი ენერგეტიკული აბსორბციომეტრით (ქვედა კიდური +10.22%, ტორსი +7.43%, ვისცერარულ-აბდომინური ნაწილი +5.59%, გინოიდური ნაწილი +10.59%, მთელი სხეული +7.6%). საკონტროლო ჯგუფში იმავე გამოკვლევების მაჩვენებლები იყო მცირედ გამოუმჯობესებული ან არ იყო შეცვლილი. ლიპიდური ცვლისა და ცხიმოვანი ქსოვილის პროცენტული გადანაწილების მაჩვენებლების გაუმჯობესების მხრივ, ზჰჭთ არ აღმოჩნდა ეფექტური. აღნიშნული მონაცემები წარმოადგენს 12-თვიანი პერიოდის შემაჯამებელ შედეგებს.

ПАТОЛОГИЯ КОЖИ ПРИ САХАРНОМ ДИАБЕТЕ: КЛИНИКО-ПАТОГЕНЕТИЧЕСКИЕ КОРРЕЛЯЦИИ (ОБЗОР)

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Согласно данным Всемирной Организации Здравоохранения (ВОЗ) за 2014 г., количество больных сахарным диабетом (СД) среди взрослого населения планеты составило около 422 миллионнов [5]. Среди осложнений СД клиническую и социальную значимость имеет диабетическая ангиопатия, полинейропатия, ретинопатия, нефропатия, синдром диабетической стопы. [5,16]. Также немаловажную роль играет и диабетическая дермопатия, на которую клиницистам стоит обращать внимание. По сведениям разных авторов, дерматологические проблемы наблюдаются у 40-70% пациентов с СД [8,14]. Причем риск развития патологии кожи при СД обратно коррелирует с эффективностью коррекции метаболических нарушений, варьируя в пределах 30-60% при адекватном гликемическом контроле, до 94% при его неэффективности [9].

При обсуждении клинических аспектов патологии кожи при СД стоит отметить некоторый дуализм: с одной стороны, дерматологические изменения могут быть первой клинической манифестацией СД [14], с другой – кожа, как наиболее крупный орган, является плацдармом реализации ключевых патогенетических механизмов развития диабета [15].

Как известно, СД может вести к развитию диабет-специфических поражений кожи (диабетическая дермопатия, диабетическая склеродерма, диабетические буллы, диабетические раны) [8]. С другой стороны, наличие СД предопределяет более высокую частоту развития других дерматологических поражений (инфекции кожи и придатков, воспалительные дерматозы, доброкачественные и злокачественные новообразования и пр.) [12,14]. В основе дерматологических проблем при СД лежат ключевые системные нарушения, включая микроангиопатию, полинейропатию, метаболические нарушения (гипергликемия, конечные продукты гликозилирования, дислипидемия), нарушение иммунологической реактивности [3,9,15]. Одним из наиболее ранних и частых неспецифических проявлений вовлечения кожи в патологический процесс при СД является развитие ксероза и кожного зуда, появление которых считается следствием микроангиопатии, ведущей к нарушению трофики и гидратации кожи, дисфункции тучных клеток, а также полинейропатии [1,8,12,24]. Последняя ассоциирована не только с нарушением сенсорной функции кожи и регуляцией сосудистого тонуса, но также с изменением баланса нейромедиторов и нейротрофических факторов, модулирующих микроциркуляцию, пролиферацию и дифференцировку клеток эпидермиса и дермы [14,15,18]. Не менее типичным вариантом поражения кожи при СД являются кожные инфекции (бактериальные или грибковые), которые выявляются, по данным разных авторов, у 30-42% пациентов, и являются отражением нарушения барьерных свойств кожи и иммунологической реактивности при СД [8,21]. Хотя в современной литературе представлено достаточное количество работ, посвященных изучению дерматологических проблем при СД, стоит отметить, что они в большей степени сфокусированы на описании эпидемиологии и клинической картины поражения кожи при СД [9,14,19]. Но при этом существует ряд пробелов в интерпретации патогенетических механизмов, определяющих развитие патологии кожи при СД.

Целью данного обзора является анализ механизмов развития различных вариантов патологии кожи при сахарном диабете.

Профилактика развития данных изменений базируется на знаниях ключевых патофизиологических механизмов, которые приведены ниже.

Эффекты гипергликемии и конечных продуктов гликозилирования на кожу

В основе развития большинства вариантов пора-

жения кожи при СД лежит гипергликемия и эффекты конечных продуктов гликозилирования (AGEs). Гипергликемия ингибирует пролиферацию и миграцию кератиноцитов, синтез белков, вызывает апоптоз эндотелиальных клеток, стимулирует синтез оксида азота в фагоцитах, ведет к нарушению хемотаксиса и фагоцитарной активности нейтрофилов [4,21]. Результатом этих изменений является снижение количества клеток базального слоя, сглаживание эпидермо-дермальной границы, ограничение экспрессии соответствующих кератинов и уменьшение общей концентрации ДНК в эпидермисе [21,27]. Однако при этом в коже пациентов с СД могут наблюдаться и противоположные изменения – усиление пролиферации кератоцитов и развитие акантоза, что связывают с эффектами гиперинсулинемии и инсулинорезистентности (ИР) [11,16]. Кроме того, в эпидермисе кожи пациентов с СД определяется нарушение процесса кератинизации, сопровождающееся увеличением количества и площади корнеоцитов – терминально дифференцированных кератиноцитов [12]. Следствием этого является развитие гиперкератоза, регистрируемого на ранних этапах диабетической дермопатии, при черном акантозе и пр. [14,19]. В роговом слое эпидермиса диабетической кожи отмечено также изменение липидного состава: снижение уровня триглицеридов и повышение уровня церамидов, холестерола и жирных кислот, по сравнению с контролем [21].

Гипергликемия ведет также к развитию существенных морфологических и биохимических изменений в дерме, которые во многом связаны с дисбалансом процессов синтеза и деградации внеклеточного матрикса, с последующим нарушением гистоархитектоники [27]. Еще 40 лет назад Moczar et al. [18] продемонстрировали нарушение ультраструктуры фибробластов, выделенных из биоптатов диабетической кожи. AGE напрямую меняют свойства коллагена, снижая его растворимость и упругость, повышая ригидность и устойчивость к энзиматической деградации при ремоделировании [28]. Последнее может объяснять роль AGEs в развитии фиброза при диабетической дермопатии и склеродермии. Не менее важным механизмом склеротических изменений в диабетической коже является изменение дифференцировки адипоцитов подкожной жировой клетчатки в миофибробласты, с последующей продукцией и накоплением коллагена в глубоких слоях кожи, что ведет к увеличению ее толщины и ригидности, например, при диабетической склеродерме [17]. У ряда пациентов с СД данные изменения ведут к нарушению подвижности суставов кистей и стоп. С другой стороны, диабет сопровождается фрагментацией и исчезновением эластических волокон в субэпителиальной зоне дермы, изменением толщины, количества и архитектоники коллагеновых волокон, что вызвано увеличением количества матриксных металлопротеиназ (MMP), обеспечивающих деградацию компонентов межклеточного вещества дермы [10,28]. Последний факт (в частности, повышение уровней MMP2 и MMP9 в коже при СД) играет критическую роль в снижении объема гиалуроновой кислоты и ремоделировании микроциркуляторного русла, особенно в тонкой коже области лица, волосистой части головы и предплечий [17,27]. Эти изменения во многом аналогичны таковым при старении, в связи с чем СД считают одним из ключевых промотеров старения кожи [10].

Еще одним механизмом промоции старения кожи при СД2 является развитие провоспалительных событий [3]. Конечные продукты гликозилирования, образующихся в результате гликирования белков, липидов и нуклеиновых кислот [10] являются мощными стимуляторами образования активных радикалов кислорода (АРК), при этом они нарушают работу антиоксидантных систем, угнетая элиминацию АРК [10,21]. Это в конечном итоге, ведет к нарушению функционирования внутриклеточных и внеклеточных белков, индуцирующих активацию воспалительных цитокинов через путь, запускаемый ядерным фактором κβ (NF-κβ) [21]. Рецепторы к AGEs (RAGE) относятся к мультилигандным рецепторам семейства иммуноглобулинов, кодируемых геном, расположенным на 6 хромосоме вблизи генов главного комплекса гистосовместимости I и II класса [6], т.е. паттернраспознающие рецепторы, связывающие помимо AGEs, ряд других молекул, включая S-100/кальгрнулин, амфотерин (high motility group protein B1 – HMGP-B1), β-амилоидные пептиды. В коже данный вид рецепторов экспрессируется разными клетками, включая: кератиноциты, дендритные клетки, эндотелиоциты, фибробласты, макрофаги [2,6,14]. Это определяет провоспалительную активацию как иммунных клеток (макрофагов, лимфоцитов), так и резидентов кожи – кератиноцитов и фибробластов, в которых усиливается экспрессия провоспалительных факторов и хемокинов, стимулирующих рекрутирование лейкоцитов [8,24]. Связывание RAGE с лигандом включает несколько сигнальных каскадов, в частности митоген-активируемые протеинкиназы (MAPKs), киназы, регулируемые внеклеточными сигналами (ERK) 1 и 2, фосфатидил-инозитол 3 киназу, p21Ras, стресс-активируемую киназу/c-Jun-N-терминальную киназу и Janus-киназы, вовлеченные в регуляцию клеточного роста и гибели [10]. Кроме того, стимуляция RAGE в клетках ведет к активации транскрипционного фактора NF-κB с последующей транскрипцией ряда провоспалительных генов [10,28]. Следствием этого является увеличение в дерме количества клеток, инициирующих воспаление – макрофагов с превалированием M1-фенотипа [3,29].

Изменения в коже, связанные с инсулинорезистентностью

Несмотря на то, что гипергликемия и AGE являются общим патогенетическим механизмом СД 1 и 2 типов, выявлена определенная специфика дерматологических нарушений при разных видах СД. Так, специфичными для СД1 типа считаются липоидный некроз, витилиго и диабетические буллы [18]. Хотя данные варианты поражения кожи описаны и при СД2 типа [1,9]. Для последнего более характерными являются акрохордоны (фиброэпителиальные поли-

пы), черный акантоз (acantosis nigricans), эруптивные ксантомы, диабетическая склеродерма, андрогенная алопеция, акне, псориаз и др. [12,16]. Данная ассоциация обусловлена наличием системных изменений вследствие метаболического синдрома (дислипидемии, ИР) у пациентов с СД2. Основная часть пациентов с ожирением и СД2 страдают вторичной ИР, которая характеризуется сочетанными вариантами изменения функционирования инсулиновых рецепторов и пострецепторной передачей сигнала. Считается, что ИР является результатом накопления и дисфункции висцеральной жировой ткани [6]. Гипертрофия адипоцитов сопровождается изменением спектра секретируемых адипокинов, накоплением М1 макрофагов и лимфоцитов [4]. Следствием этих нарушений является системное повышение уровней фактора хемотаксиса моноцитов (MCP-1), фактора некроза опухолей (TNF-α), интерлейкинов (IL-6, IL-8 и IL-18), лептина, резистина и ингибитора активатора плазминогена (PAI)-1 [16]. При этом клетки кожи находятся в условиях двойного дисбаланса: дефицита инсулина и избытка провоспалительных цитокинов [28]. Инсулин играет важную роль в поддержании гомеостаза и функционировании кожи. В норме инсулин регулирует равновесие между процессами пролиферации и дифференцировки кератиноцитов [11]. Рецепторы к инсулину относятся к семейству рецепторных тирозинкиназ. К этому семейству относятся также рецепторы к многочисленным факторам роста, включая инсулиноподобый фактор роста (IGF), эпидермальный фактор роста (EGF), фактор роста фибробластов (FGF), фактор роста тромбоцитарного происхождения (PDGF), а также рецепторы колониестимулирующих факторов и некоторых цитокинов [25]. Показано, что гиперинсулинемия повышает продукцию IGF-1 и 2 в печени, что ведет к повышению системного уровня этих факторов роста [16]. Кроме того, доказана возможность перекрестной активации инсулином рецепторов к IGF-1, которые экспрессируются кератиноцитами и фибробластами, что ведет к повышению пролиферации этих клеток [25]. Активность IGF-1 регулируется уровнем IGF-связывающих белков (IGFBPs), которые повышают период полужизни IGF-1 и регулируют пул метаболически «свободного» IGF-1. У пациентов с ожирением и гиперинсулинемией уровни IGFBP-1и IGFBP-2 снижаются, что способствует увеличению плазменной концентрации свободного IGF-1. Повышение биоактивного IGF-1 стимулирует рост и дифференцировку клеток [14]. Этим объясняются гиперкератоз, папилломатоз при черном акантозе, а также формирование доброкачественных новообразований кожи – акрохордонов [11]. Зачастую усиление пролиферативных процессов в коже при этом сопровождается нарушением пигментного обмена, как правило, с гиперпигментацией [7,30]. Данный феномен связывают с эффектом активации Е3 рецепторов к простагландину Е2 [30]. Продукция последнего повышается вследствие усиления экспрессии в кератиноцитах и клетках дермы NF-kB и ЦОГ-2 (циклоогсигеназа) [15]. Активация Е3-рецепторов меланоцитов сопряжена с усилением их пролиферации, повышением локального образования МСГ из предшественника – проопиомеланокортина, что в конечном итоге ведет к накоплению меланина [7,22,30].

Не менее значимым механизмом связи между ИР и патологией кожи при СД2 являются эффекты инсулина на продукцию половых гормонов. Инсулин и IGF-1 оказывает мощное стимулирующее влияние на активность 17-гидроксилазы в яичниках, что определяет избыточную продукцию андрогенов, особенно 17-гидроксипрогестерона [11]. Помимо этого, повышение уровня инсулина способствует снижению продукции в печени SHBG (глобулина, связывающего половые гормоны), что определяет более выраженные эффекты свободного тестостерона на клетки мишени [25]. В коже мишенями андрогенов является пило-себацеозная единица. Увеличение уровня и интенсивности трансдукции сигналов андрогенов ведет к росту пролиферации себоцитов, повышению липогенеза и их секреторной активности, пролиферации клеток в области воронки корня волоса, гиперплазии сальных желез, промотируя развитие акне [11]. Аналогичный эффект на сальные железы оказывает и IGF-1 [25]. IGF-1 является мощным промотером роста в пубертатном периоде и играет центральную роль в развитии акне и индукции гиперандрогении [19] и по факту, является фактором, обеспечивающим сигнальную взаимосвязь между инсулинорезистентностью и развитием акне. Кроме того, в исследованиях in vitro показано, что инсулин и IGF-1 могут также стимулировать рост волосяных фолликулов, что, по всей вероятности, ведет к развитию гирсутизма [21]. Однако возможно и альтернативное влияние избыточного уровня инсулина на рост волос. Так, показано, что гиперинсулинемия ведет к повышению активности 5-альфа-редуктазы в клетках волосяного сосочка, что ведет к увеличению конверсии тестостерона в дигидротестостерон, следствием чего является развитие андрогенной алопеции [8].

Механизмы нарушения периферической толерантности к антигенам при СД

Спектр дерматологических проблем у пациентов с СД имеет определенный парадокс – с одной стороны пациенты с СД более восприимчивы к развитию оппортунистической инфекции, а с другой – у них повышается вероятность развития реакций гиперчувствительности, разных вариантов воспалительных дерматозов и аутоиммунной патологии [11,16]. Это связывают с нарушением функции одного из ключевых модераторов поддержания иммунологического гомеостаза кожи – дендритных клеток (ДК). На сегодня среди ДК кожи принято выделять типичные (стабильные) ДК, присутствующие в коже в норме, и плазмоцитоидные ДК (пДК), которые появляются в коже только при воспалении [2]. По локализации типичные ДК делят на эпидермальные клетки Лангерганса и дермальные ДК (дДК). После получения сигнала о повреждении ДК активируются, захватывают антиген, а его процесс сопровождается миграцией клеток через систему лимфатических сосудов кожи в

регионарные лимфатические узлы [2]. При этом активация разных ДК имеет различные последствия. Предполагается, что основным эффектом активации клеток Лангерганса является развитие толерантности к антигенам посредством стимуляции Treg (Т-клетки-супрессоры) [20]. Тогда как созревание дермальных ДК может вести к активации разных вариантов иммунного ответа через активацию Th1, Th2 или Th17 [2]. Предполагается, что разные подтипы дДК способны активировать разные виды иммунного ответа. Важнейшим фактором активации и детерминации фенотипа ДК является микроокружение, в котором находятся эти антиген-презентирующие клетки [20]. Последний факт приобретает особое значение в условиях СД, обеспечивающего комбинацию в коже комплекса патогенетических факторов, включая: гипергликемию, эндотелиальную дисфункцию, оксидативный стресс, цитокиновый дисбаланс, дисфункцию тучных клеток [10,24].

Изучение статуса ДК при СД показало весьма противоречивые данные. С одной стороны, обнаружено, что в периферической крови пациентов с СД снижается количество как миелоидных, так и плазмоцитоидных ДК [23]. Однако экспериментальные исследования выявили параллелизм процессов дегенерации периферических нервов и развития полинейропатии, накопления зрелых ДК в роговице глаза [13]. Аналогичные результаты получены другими авторами, доказавшими ассоциацию между диабетической нейропатией и дисфункцией ДК в периферических тканях и органах при СД, отражающих специфику нейро-иммунных взаимоотношений при СД в разных тканях. Аналогично этому, в коже пациентов с синдромом диабетической стопы выявлено повышение количества ДК, в первую очередь – клеток Лангерганса. При этом авторы показали непосредственную связь между количеством клеток Лангерганса и вероятностью развития диабетических ран [25].

К факторам, стимулирующим активацию ДК, помимо классического стимулятора – бактериального липополисахарида, относятся активные радикалы кислорода, образование которых, как уже было указано, повышено в условиях гипергликемии. Показано, что АРК стимулируют миелоидные ДК, стимулируют их активацию и созревание, что может способствовать промоции воспалительных событий. Кроме того, инсулин и IGF-1 также являются стимуляторами созревания ДК, активируя экспрессию в них scavenger receptors (SR-A) и захват окисленных липопротеинов низкой плотности [20]. Это предопределяет усиленную активацию дендритных клеток, в том числе в коже, в условиях СД2. Активация ДК может стимулировать рекрутирование моноцитов и накопление макрофагов [2,26], что связывают с развитием диабетических осложнений. Проведенные ранее исследования показали, что аналогичная закономерность характерна и для кожи - повышение количества макрофагов сопряжено с развитием диабетических ран и нарушением их заживления [4,29]. Данный феномен определяется нарушением метаболических процессов в клетках: дислипидемия ассоциирована с накоплением липидов в макрофагах, что ведет к особым вариантам воспаления, например, при эруптивной ксантоме и кольцевидной гранулеме, ассоциированными с накоплением в гистиоцитах липидов, задержкой механизмов разрешения воспаления и хронизацией воспаления [20]. Кроме того, отмечено нарушение метаболизма L-аргинина с усиленной активацией iNOS с развитием провоспалительных событий, оксидативного и нитроксильного стресса, нарушением механизмов разрешения воспаления, прогрессирующей альтерацией и фиброзом [3,17,29]. Увеличение количества и дисфункция ДК и макрофагов в диабетической коже может объяснить более высокую вероятность развития воспалительных дерматозов, например – псориаза, хотя по сей день трактовка ассоциации псориаза и СД базируется преимущественно на констатации роли ИР. Во-первых, кожные проявления ИР во многом аналогичны нарушениям в эпидермисе, наблюдаемым при псориазе (гиперпролиферация при нарушенной дифференцировке кератиноцитов). Во-вторых, выявленная тесная ассоциация развития псориаза и метаболического синдрома с ИР может объясняться уже обсуждаемым фактором хронического воспаления, развивающегося в результате дисфункции висцеральной жировой ткани [14]. Так, у пациентов с псориазом показано снижение уровня противовоспалительного адипонектина при повышении таких провоспалительных агентов, как оментин, резистин, васфатин, интерлейкин-6, а также TNF-α [11]. Последний считается одним из наиболее значимых цитокинов, вовлеченных в развитие псориаза [15]. С другой стороны, не менее известными является роль TNF-α в нарушении чувствительности к инсулину через угнетение тирозинкиназной активности инсулиновых рецепторов [11,25].

Таким образом, СД2 характеризуется высокой частотой и вариабельностью поражения кожи. Ключевыми механизмами развития патологии кожи при СД2 являются гипергликемия, микроангиопатия, инсулинорезистентность, изменение баланса факторов роста и половых гормонов, а также дисфункция антиген-презентирующих клеток и макрофагов кожи. Комплекс этих факторов определяет нарушение барьерной функции кожи, дисбаланс процессов пролиферации, дифференцировки и гибели клеток, изменение программы старения кожи, нарушение периферических механизмов толерантности к антигенам, что сопровождается повышением риска развития инфекций, воспалительных дерматозов и неоплазий.

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SUMMARY

SKIN PATHOLOGY IN DIABETES MELLITUS: CLINICAL AND PATHOPHYSIOLOGICAL CORRELATIONS (REVIEW)

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Skin pathology is registered in vast majority of patients with diabetes mellitus (DM). Despite the abundance of publications on dermatological problems in DM, there is still a number of gaps to be discussed in terms of pathophysiological mechanisms. The goal of this review was to assess the mechanisms of development of different skin pathologies under DM. One of the key pathogenic mechanisms of skin lesions in diabetes is hyperglycemia and the effects of the advanced glycation end products, inducing oxidative stress, endothelial dysfunction and inflammation; that in its turn can accelerate the mechanisms of skin aging, the development of diabetic dermopathy and scleredema diabeticorum. Imbalance of growth factors, cytokines and hormones under insulin resistance, is associated with increased proliferation of keratinocytes, fibroblasts and sebocytes, mast cell dysfunction and melanogenesis disorders in acanthosis nigricans, acrochordons, acne and inflammatory dermatitis in diabetic patients. In addition, authors discuss the role of dendritic cells and macrophages dysfunction in impairment of peripheral tolerance and diabetic wounds pathogenesis in patients with DM.

Keywords: diabetes mellitus, hyperglycemia, advanced glycation end products, insulin resistance, skin.

РЕЗЮМЕ

ПАТОЛОГИЯ КОЖИ ПРИ САХАРНОМ ДИАБЕТЕ: КЛИНИКО-ПАТОГЕНЕТИЧЕСКИЕ КОРРЕЛЯЦИИ (ОБЗОР)

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Патология кожи регистрируется у большинства пациентов, страдающих сахарным диабетом (СД). Несмотря на множество публикаций, посвященных дерматологическим проблемам при СД, существует ряд пробелов в интерпретации патогенетических механизмов, определяющих развитие патологии кожи при СД.

Целью данного обзора явился анализ механизмов развития различных вариантов патологии кожи при сахарном диабете.

Одним из ключевых патогенетических механизмы поражения кожи при СД являются гипергликемия и эффекты конечных продуктов гликозилирования, ведущие к развитию оксидативного стресса, эндотелиальной дисфункции и воспалению; что вызывает ускорение механизмов старения кожи, развитие диабетической дермопатии и склеродермии. Изменение баланса факторов роста, цитокинов и гормонов на фоне инсулинорезистентности связано с усилением пролиферации кератиноцитов, фибробластов и себоцитов, дисфункцией тучных клеток и нарушением меланогенеза при черном акантозе, акрохордонах, акне и дерматитах у диабетических пациентов.

В статье обсуждается также роль дисфункции дендритных клеток и макрофагов в нарушении толерантности к антигенам и развитии диабетических ран при сахарном диабете.

რეზიუმე

კანის პათოლოგია შაქრიანი დიაბეტის დროს: კლინიკურ-პათოგენეზური კორელაციები (მიმოხილვა)

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კანის პათოლოგია რეგისტრირდება შაქრიანი დიაბეტით დაავადებულ პაციენტთა უმეტესობაში. შაქრიანი დიაბეტის დროს დერმატოლოგიური პრობლემებისადმი მიძღვნილი პუბლიკაციების სიმრავლის მიუხედავად, არსებობს გარკვეული ხარვეზები შაქრიანი დიაბეტის დროს განვითარებული დერმატოლოგიური დარღვევების პათოგენეზის ახსნაში. წარმოდგენილი მიმოხილვის მიზანს შეადგენდა კანის პათოლოგიის სხვადასხვა ვარიანტის განვითარების მექანიზმების ანალიზი შაქრიანი დიაბეტის დროს. ერთ-ერთ საკვანძო პათოგენეზურ მექანიზმს წარმოადგენს ჰიპერგლიკემია და გლიკოზირების საბოლოო პროდუქტების ეფექტები, რაც იწვევს ოქსიდაციური სტრესის განვითარებას, ენდოთელურ დისფუნქციას და ანთებას. აღნიშნული აჩქარებს კანის დაბერების პროცესებს, დიაბეტური დერმოპათიის და სკლეროდერმიის განვითარებას. ზრდის ფაქტორების, ციტოკინების და ჰორმონების ბალანსის შეცვლა დიაბეტიან პაციენტებში ინსულინრეზისტენტობის ფონზე შეუღლებულია კერატინოციტების, ფიბრობლასტებისა და სებოციტების პროლიფერაციის გაძლიერებასთან, პოხიერი უჯრედების დისფუნქციასთან და მელანოგენეზის დარღვევასთან შავი აკანტოზის, აკროქონდრონების, აკნესა და დერმატიტების დროს. სტატიაში, ასევე, განხილულია დენდრიტული უჯრედების და მაკროფაგების დისფუნქციის როლი ანტიგენების მიმართ ტოლერანტობის დარღვევაში და დიაბეტური ჭრილობების განვითარებაში შაქრიანი დიაბეტის დროს.

СЕКРЕЦИЯ МЕЛАТОНИНА У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА, СТРАДАЮЩИХ ОЖИРЕНИЕМ

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Ожирение широко распространенное заболевание метаболизма, которое по данным ВОЗ считается глобальной хронической проблемой. Ожирением страдает не только взрослое население, но также дети и подростки [2,17]. Многочисленные эпидемиологические исследования показали, что заболевание имеет тенденцию роста. Предположительно, к 2030 г. 60% мировой популяции или 3,3 млрд. людей будут страдать избыточным весом или ожирением. За последнее десятилетие в большинстве европейских стран наблюдается тенденция увеличения количества больных данным заболеванием на 10-40%, причем у мужчин на 10-25%, а у женщин на 10-30% [7,18]. По данным американских экспертов Kushner R.F., Bessesen D.H. [14] ожирение провоцирует развитие: сахарного диабета (57%), артериальной гипертензии и ишемии сердца (17%), остеоартроза и остеопороза (14%), холелитиаза (у 30%), онкологических заболеваний груди, матки и толстого кишечника (11%) [14].

Особенно опасным является абдоминальное ожирение у женщин репродуктивного возраста. Многочисленными экспериментами установлена роль ожирения в генезе репродуктивной дисфункции [1]. Выявлено, что увеличение массы жировой ткани на 20% вызывает нарушение менархе (45%), а также первичное бесплодие (33,6%). С ожирением связаны также: гиперэстрогения, гиперплазия матки и патология яичников, у 30% отмечается вероятность формирования синдромов гиперандрогении и поликистоза яичников [6,13].

Эндокринно-метаболические аспекты развития ожирения в репродуктивном возрасте все еще вызывают усиленный интерес исследователей. В литературных источниках последних лет широко рассматривается роль нарушений метаболизма углеводов и липидов в патогенезе ожирения [17]. Исходя из этого, особый интерес вызывает изучение мелатонина,как эндогенного нейроэндокринного регулятора протекающих в организме процессов. В настоящее время установлена роль мелатонина в функциональной регуляции эндокринной и иммунной систем [3]. С возрастом, уровень мелатонина понижается, что негативно отражается на функционироваании многих органов и систем. Выявлены изменения секреции мелатонина у пациентов при депрессии, нейродегенеративных заболеваниях, язвенных болезнях, ревматоидном артрите, циррозе печени и при онкологических заболеваниях [8,15]. Существуют данные об изменении секреции мелатонина у больных метаболическим синдромом, ожирением печени, сахарным диабетом второго типа и артериальной гипертензией [4,11]. Менее изучены особенности секреции мелатонина у женщин, страдающих ожирением, не установлены референсные нормативы мелатонина.

Целью исследования явилось изучение особенностей секреции мелатонина у женщин репродуктивного возраста, страдающих ожирением с учетом степени и длительности заболевания.

Материал и методы. Исследования проводились на базе ООО „Национальный институт эндокринологии". Отобраны больные амбулаторной популяции, которым, согласно критериям ВОЗ диагностировано ожирение. Проведено одномоментное обследование 80 пациентов с избыточным весом и ожирением, которые составили основную группу. Контрольную группу составили 40 условно здоровых, нормальной конституции женщин, индекс массы тела которых (ИМТ) <25. Основными критериями включения в основную группу являлись: репродуктивный возраст (16-35 лет), индекс массы тела больше 25 и согласие пациента об участии в обследовании. Не обследовались пациенты с острыми соматическими патологиями, с ишемической болезнью сердца, с хроническими патологиями печени и почек и больные сахарным диабетом.

В процессе обследования использовался вопросник, содержащий демографические и антропометрические данные, социальные и бытовые факторы, соматические патологии (ожирение, артериальная гипертензия, сахарный диабет, сердечно-сосудистые заболевания, дислипидемия, калькулезный холецистит), степень наследственной отягощенности, субъективные жалобы, информацию о сопутствующих хронических заболеваниях. Пациентам основной группы провели ультрасонографию печени и яичников, тест толерантности к глюкозе, определили количество инсулина натощак и после нагрузки глюкозой, а также определили спектр липидов крови. Для интерпретации полученных данных использованы нормы, представленные в „Reference Ranges for adults and children,, W. Heil,V. Ehrhardt, 2008 (Roche), соответствующие возрасту и полу.

Определение секреции метаболита мелатонина – 6 -гидроксимелатонин-сульфат (6-COMT) проводилось в утренней моче тест-системой IBL: Melatonin sulfate Urine Elisa иммуноферментным методом [16]. Мелатонин определен у 56 пациентов основной группы и у 16 контрольной.

Статистический анализ полученных данных обработан пакетом программы Microsoft Excell 2010 и SPSS/v15. Определялись медиана, мода, максималь-

ные и минимальные количественные показатели мелатонина. Корреляция изменчивости оценивалась с помощью р и критерия Пирсона. Достоверным критическим значением р было <0,05.

Результаты и их обсуждение. Средний возраст обследуемых составлял 29.7±5.0 лет. Антропометрические данные основной группы представлены следующим образом: вес -94.2±14.9 кг, рост - 164.4±12.2 см, ИМТ -34.4±5.2 кг/м^2, объем талии-99.2±12.6 см. В контрольной группе вес-56.0±5.2 кг, рост-166.2±4.6 см, ИМТ - 20.0±1.8кг/м^2, объем талии-60.1±10.4 см.

В основной группе длительность течения заболевания составляла 7.49±7.04. Длительность заболевания 36 (45%) пациентов не превышала 5 лет, 26 (32.5%) пациентов болели 5-10 лет, а 18 (22.5%) более 10 лет. В основной группе нарушение менархэ наблюдалось у 16.25%, в контрольной группе - у 10.0% (c^2-0.420, P-0.517).

Со стороны наследственной патологии, в обоих группах отмечался высокий уровень тиреопатии (33.8% и 42.5%, соответственно), диабета (41.3% и 40%), соответственно, инфаркта миокарда (28.8% и 27.5%) и онкологических заболевании (26.3% и 30.0%). Наследственная предрасположенность к ожирению отмечалось у 50% основной группы и у 20.0% контрольной (P-0.003). В основной группе, со стороны сопутствующих соматических заболеваний, преобладала опорно-двигательная патология (P-0.009), распространение аллергии (P-0.442) и гастроэнтерологических заболеваний (P-0.028). распространение аллергии (P-0.442) и гастроэнтерологических заболеваний (P-0.028).

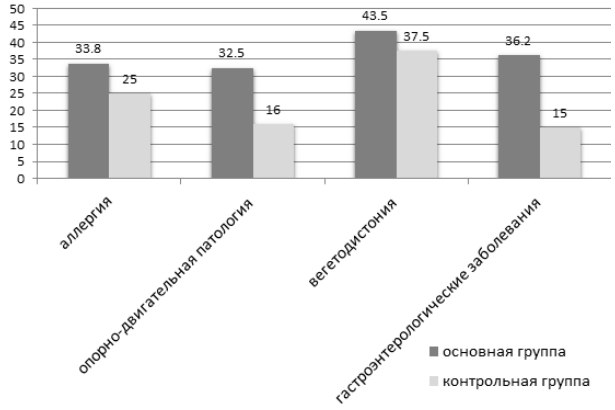

Диаграмма. Сопутствующая соматическая патология в обследуемом контингенте (n=120)

Увеличение артериального давления зафиксировано в 4 (5%) случаях. Легкая степень ожирения печени отмечалась у 61.3% (n=49), средняя степень – у 13.8% (n=11), а тяжелая степень – у 8.8% (n=7). У 3.8% (n=5) пациентов с ожирением отмечен холелитиаз, варикоз нижних конечностей – у 20% (n=24). Ультрасонографическое обследование выявило поликистоз яичников у 10 (12.5%) пациентов, увеличение размера яичников – у 13 (16.3%) больных. Отмеченные патологии в контрольной группе не наблюдались.

По данным теста определения толерантности к глюкозе у 6 (7.5%) пациентов отмечались показатели, превыщающие норму, а после нагрузки - у 4 (5.0%) больных. Исследования показали, что уровень инсулина натощак повышен у 24 (30%), а после нагрузки – у 50 (62.5%) пациентов. Инсулинорезистентность в основной группе выявлена у 49 (61.3%) пациентов, в контрольной группе – только в одном (2.5%) случае (c^2-35.490, P-0.0001).

В процессе исследования детально был изучен липидный профиль с учетом длительности и степени ожирения. Полученные средние данные соответствовали возрастным нормам. Привлекло внимание незначительное понижение количества липопротеидов высокой плотности (49.3±9.5). Вместе с тем у 37.5% (30 пациентов) обследуемых отмечалось повышение уровня общего холестерина (220.56±11.4). У 48 (60%) пациентов был повышен уровень липопротеинов низкой плотности (127.8±16.5). У 18 (22.5%) пациентов отмечалось повышение количества триглицеридов (191.1±39.6). Статистический анализ показал, что длительность заболевания (больше 10 лет), достоверно коррелирует с дислипидемией (P=0.027). Определение уровня мелатонина проводили в утренней моче, так как по литературным данным, выработка основного метаболита мелатонина -6-сульфатоксимелатонина полностью отражает его синтез ночью. Количественные показатели определились у 56 (70%) пациентов основной группы и у 17 (42.5%) – контрольной.

Результаты исследования показали, что средний уровень мелатонина у больных ожирением составляет 129.4±124.9 - это на 17% превышает уровень такового у условно здоровых женщин репродуктивного возраста; медиана на 22% , а мода на 34% превышали данные контрольной группы. В обеих группах отмечался довольно широкий диапазон между максимальными и минимальными данными. Необходимо отметить неоднородный характер изменений мелатонина в обеих группах. В ряде случаев выявлен низкий уровень мелатонина, в основной группе – у 26.8% (n=21), а в контрольной – у 29.4% (n=12).

На основании полученных данных, в основной группе с секрецией мелатонина достоверно коррелировала наследственная отягощенность инфарктом миокарда (P=0.030), неррациональное питание, в частности -избыток углеводов (P=0.051), возраст пациента (P=0.022), увеличение размера яичников (P=0.050). В контрольной группе – наследственная отягощенность инфарктом миокарда (P=0.029) и избыточный прием углеводов (P=0.012).

Итак, в процессе обследования изучены особенности клиники больных ожирением репродуктивного возраста. В обследуемом контингенте, с точки зрения наследственной отягощенности соматическими заболеваниями, велика доля тиреопатии, диабета, инфаркта миокарда и онкологической патологии. Статистически достоверна наследственная отягощенность ожирением (P-0.003). Со стороны сопутствующих

Таблица. Показатели секреции мелатонина в обследуемом контингенте (n=120)

Мелатонин (мг/мл) / Группа	M	STDEV	MEDIANE	MODE	MAX	MIN
Основная (n=56)	129.4	124.9	106.8	125.7	490.1	11.3
Контрольная (n=17)	107.5	103.9	83.2	83.2	354.9	5.1

соматических заболеваний, у больных ожирением, превалировали гастроэнтерологические заболевания (P-0.028). Среди клинических симптомов ожирения достоверны: гипертрихоз (P-0.042), отеки в области конечностей (P-0.003) и запоры (P-0.024). Со стороны нарушения углеводного и липидного обмена привлекли внимание инсулинорезистентность, которая выявлена у 61.3% (n=49) основной группы и дислипидемия у 60% (n=48) больных ожирением.

Современные исследования молекулярных механизмов ожирения позволяют объяснить основы патофизиологических связей данного состояния с ассоциированными заболеваниями. Наши данные показали, что нарушение липидного обмена представляет собой одно из центральных звеньев в патогенезе ожирения [12].

Результаты проведенных исследований касательно секреции мелатонина несколько отличаются от литературных данных. Необходимо отметить, что механизмы гиперпродукции мелатонина до конца не установлены. В новейшей литературе представлено несколько гипотез об увеличении уровня мелатонина. Увеличение секреции мелатонина при абдоминальном ожирении может быть связано с гиперлептинемией, которая регулирует чувство насыщения на уровне вентро- и дорсомедиального ядер гипоталамуса [5,10]. Стимуляция паравентрикулярного ядра вызывает активацию симпатической системы и катехоламинов, усиливает секрецию пролактина и мелатонина. По данным других авторов [8,9], ночная гиперактивация симпатической системы и метаболические нарушения у больных ожирением представляют собой дополнительный фактор увеличения секреции мелатонина. Существует мнение об активизации компенсаторных механизмов при ожирении. В частности, оксидационный стресс, развивающийся при нарушениях метаболизма, обусловливает усиление выработки мелатонина как сильного антиоксиданта. Соответственно этой точки зрения, увеличение экскреции мелатонина можно рассматривать как один из маркеров нарушений метаболизма при ожирении, для установления специфичности которого желательно продолжить широкомасштабные, углубленные исследования.

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SUMMARY

METABOLIC SECRETION IN REPRODUCTIVE AGE WOMEN WITH OBESITY

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For the last decade melatonin has attracted attention as a neuroregulator in pathogenesis of obesity and metabolic syndrome. The aim of our study is to evaluate the characteristics of metabolic secretion in obese women of reproductive age.

The study was conducted on the total number of 120 women. Eighty women with obesity formed the case group, and forty healthy women – the control group. Carbohydrate metabolism, lipid profile and serum levels of melatonin were evaluated in all study subjects. According to the results, 61.3% of the total study population had insulin resistance and 60% had dyslipidemia. Melatonin hypersecretion, with the mean level of melatonin 129.4±124.9, was observed in the case group. The mean level of melatonin in the control group was 107.5±10.9, which was 17% less than in the case group. Melatonin secretion was in significant correlation with patients' age (P=0.022), family history of myocardial infarction (P=0.030), excess carbohydrate intake (P=0.051) and enlarged ovaries (P=0.050). Our results confirm the relationship between obesity, metabolic abnormalities (insulin resistance, dyslipidemia) and melatonin hypersecretion in women of reproductive age.

Keywords: melatonin, obesity, reproductive age women, dyslipidemia, insulin resistance.

РЕЗЮМЕ

СЕКРЕЦИЯ МЕЛАТОНИНА У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА, СТРАДАЮЩИХ ОЖИРЕНИЕМ

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Целью исследования явилось изучение особенностей секреции мелатонина у женщин репродуктивного возраста, страдающих ожирением. В исследовании приняли участие 120 женщин репродуктивного возраста, из них 80 пациентов с избыточным весом и ожирением составили основную группу, 40 условно здоровых - контрольную группу. Изучали углеводный обмен, липидный спектр и количественные показатели мелатонина. В основной группе инсулинорезистентность выявлена в 61.3% (n=49), дислипидемия в 60% (n=48). В этом же группе отмечалось повышение секреций мелатонина. Результаты исследования показали, что средний уровень мелатонина у больных ожирением составил 129.4±124.9, что на 17% выше в сравнении с контрольной группой. На основании полученных данных, в основной группе с повышенной секрецией мелатонина достоверно коррелировала наследственная отягощенность инфарктом миокарда (P=0.030), нерациональное питание, в частности - избыток углеводов (P=0.051), возраст пациента (P=0.022), увеличение размера яичников (P=0.050). Результаты исследования выявили связь между увеличеннной секрецией мелатонина на фоне ожирения и нарушениями метаболизма (инсулинорезистентность, дислипидемия) у женщин репродуктивного возраста.

რეზიუმე

მელატონინის სეკრეცია სიმსუქნის მქონე რეპროდუქციული ასაკის ქალებში

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კვლევის მიზანს შეადგენდა მელატონინის სეკრეციის თავისებურებების შესწავლა სიმსუქნის მქონე რეპროდუქციული ასაკის ქალებში.

კვლევაში ჩართული იყო 120 რეპროდუქციული ასაკის ქალი, მათგან სიმსუქნით დაავადებული 80 ქალი გაერთიანდა ძირითად ჯგუფში, ხოლო 40 ჯანმრთელი – საკონტროლო ჯგუფში. შესწავლილი იქნა ნახშირწლოვანი ცვლა, ლიპიდური სპექტრი და მელატონინის რაოდენობრივი მაჩვენებლები. კვლევის შედეგების თანახმად სიმსუქნით დაავადებულ 49 (61,3%) პაციენტს აღენიშნებოდა ინსულინრეზისტენტობა, ხოლო 48 (60%) პაციენტთან გამოვლინდა დისლიპიდემია. ძირითად ჯგუფში დაფიქსირდა მელატონინის სეკრეციის გაძლიერება. საშუალო მაჩვენებელი 129,4±124,9, რაც 17%-ით აღემატებოდა საკონტროლო ჯგუფის მონაცემებს (107.5±10.9). მელატონინის სეკრეციის ცვლილებებთან სარწმუნო კორელაციაში იყო პაციენტის ასაკი (P=0.022), მიოკარდის ინფარქტით მემკვიდრული დატვირთვა (P=0.030), ნახშირწყლების ჭარბი მიღება (P=0.051) და საკვერცხეების ზომის მატება (P=0.050). კვლევის შედეგები ადასტურებს კავშირს რეპროდუქციული ასაკის ქალებში სიმსუქნეს, მეტაბოლურ დარღვევებსა (ინსულინრეზისტენტობა, დისლიპიდემია) და მელატონინის სეკრეციის გაძლიერებას შორის.

MODERN APPROACHES TO FRACTIONAL EXHALED NITRIC OXIDE AS A USEFUL BIOMARKER FOR ALLERGIC ASTHMA PHENOTYPING AND MANAGEMENT

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Asthma is a serious global health problem affecting all age groups, with increasing prevalence in many countries [8].Unfortunately, there remains a substantial fraction of patients with poorly controlled asthma and this disease causes approximately 346,000 deaths worldwide every year [14], with widely varying case fatality rates that may reflect differences in management.

Airway inflammation is considered to be a central pathological characteristic of asthma. The degree of airway inflammation is positively correlated with disease severity and its reducing is cornerstone of asthma management. The increased knowledge of the deep interplay between the pathophysiological pathways of chronic airway inflammation and remodeling in asthma has led to consider asthma as heterogeneous disease, requiring information on biomarkers for diagnosis and management [30].

An evidence-based guidelines support the use of fractional exhaled nitric oxide (FeNO), as a non-invasive biomarker to detect eosinophilic airway inflammation, determining the likelihood of corticosteroid responsiveness, monitoring of airway inflammation to determine the potential need for corticosteroid, and unmasking of nonadherence to corticosteroid therapy [20].

Asthma phenotypes and FeNO

Now it is generally accepted that "Asthma" isn't a single disease, but an umbrella diagnosiswhich comprises heterogeneous condition, with different recognizable clusters, often called as "asthma phenotypes" [8,31].

Phenotyping of asthma has become a mandatory part of the diagnostic workup of all patients especially, who do not respond satisfactorily to standard therapy with inhaled corticosteroids (ICS).

The background pathology of asthma is often but not always due to eosinophilic airway inflammation. The two are not synonymous. Also it should be noted, that asthma is a clinical diagnosis and there is no single diagnostic test for the disease [2].

Current Global Initiative for Asthma (GINA) guidelines recommend making the diagnosis and management of asthma based on identifying both a characteristic pattern of respiratory symptoms and variable expiratory airflow limitation .

Nevertheless, normal lung function tests do not exclude a diagnosis of asthma, especially for intermittent or mild cases [20]and they provide no information about underlying airway inflammation, the central pathophysiologic feature of asthma. This has a number of practical consequences including both over and under diagnosis of asthma [19].

The potential use of exhaled nitric oxide in monitoring asthma is being investigated because of its association with eosinophilic airway inflammation. Elevated levels of FeNO are reported as a biomarker for detection an allergic (Th2-associated) asthma phenotype. In conjunction with symptom scores and lung function tests, FeNO measurement could provide a more useful and effective approach for asthma.

Biology of FeNO.

Nitric oxide (NO) for a long time was considered to be only an air pollutant gaseous molecule. However, this view has been greatly modified since the 1987 discovery that the free radical NO is the previously uncharacterized endothelial-derived relaxing factor, with important role in most human organ systems.

Soon (1990s) the physiologist Lars Gustafsson reasoned that if NO is formed in the lungs, it should be possible to detect this diffusible gas molecule in exhaled breath. This molecule can be detected in exhaled gas as the fraction of exhaled NO. Follow-Up studies demonstrated that levels are high in asthma and decrease after steroid. This was the start of a new era in respiratory research, that of the broad interest in markers that can be measured noninvasively in exhaled air [1].

Within the respiratory system, NO regulates vascular and bronchial tone, facilitates the coordinated beating of ciliated epithelial cells, and acts as an important neurotransmitter for non-adrenergic, non-cholinergic neurons that run in the bronchial wall [4].

FeNO levels directly depend on the enzyme nitric oxide synthases (NOS) to generate NO.

Three different NOS isoenzymes have been described in mammals.

Constitutive NOS (cNOS) isoenzymes, include: neuronal NOS (NOS1) and endothelial NOS (NOS3) and inducible NOS (NOS2). These enzymes all catalyze the adduction of the guanidino nitrogen of the amino acid arginine to molecular oxygen, yielding NO and water. Both cNOS are activated by calcium ions to produce small amountsof NO, which is presumed to play a local regulatory role, such as neurotransmission (nNOS) and regulation of local blood flow (eNOS) [25]. In contrast, inducible NOS (iNOS) is not constitutively expressed, but is induced by inflammatory stimuli and produces NO, independent of calcium ion influx. While not constitutively active in most settings, iNOS is constitutively expressed in the airway epithelium of normal and asthmatic subjects [9]. iNOS also has the capacity to generate large quantities of NO when transcriptionally upregulated by inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha, interleukin 1 (IL-1)-beta, interferon (IFN)-gamma, IL-4, and IL-13. In vitro evidence suggests that this upregulation can be abolished by glucocorticoids in vitro and in vivo [1].

One important aspect of allergic inflammation in asthma exactly is the migration of Th2 cells and eosinophils into the airway, in most cases initiated by immunoglobulin IgE sensitization to aeroallergens. The inflammation is driven by the activation of mast cells, and particularly of antigen-specific T-helper cells (Th) type 2 that produce the typical Th2 cytokines IL-4, -5 and -13. IL-4 is crucial in the primary sensitization process, whereas IL-13 seems to be more important in eliciting airway changes during secondary allergen exposure [1]. IL-5 seems to be the main cytokine involved in the differentiation and activation of the eosinophilic granulocyte [12].

FeNO has long been regarded as a surrogate marker of eosinophilic airway inflammation.

However, recent clinical information suggests that FeNO is a marker of Th2-mediated inflammation, which often includes airway eosinophilia, rather than eosinophilic inflammation per se. For example, FeNO levels correlate better with bronchial eosinophils than with sputum eosinophils [13]. The disconnect between FeNO and eosinophilic inflammation has been highlighted by studies with monoclonal antibodies (mAb) against IL-5 and IL-13, which show that treatment with mepolizumab, an anti-IL-5 mAb, significantly reduces blood and sputum eosinophils without affecting FeNO levels [30], while treatment with lebrikizumab, an anti-IL-13 mAb, significantly reduces FeNO levels without reducing blood eosinophils [6].

Thus, current knowledge indicates that the increase in FeNO in allergic asthma phenotype depends primarily on the activity of IL-4/IL-13 in the bronchial wall, inducing iNOS expression in the bronchial epithelium [1].

MEASUREMENT OF FeNO.

Exhaled NO can be measured with several techniques. chemiluminescence method is highly sensitive and it became the gold standard for clinical measurement of FeNO. There are available online and offline methods to collect exhaled air and measure FeNO.

The portable devices based on electrochemical sensors use is increasing, as evidenced in published clinical studies on exhaled NO and have also been approved by US Food and Drug Administration (FDA) [29].

FeNO is measured in parts per billion (ppb), a constant exhalation rate of 0.050 L/second(for online measurements) or 0.35 L/second (for offline measurements), maintained within ± 10% for 6 s, and with an oral pressure of 5–20 cm H2O to ensure soft palate closure and further minimize nasal NO leakage [3].

Confounding factors

FeNO values can be influenced by several constitutive and exogenous factors: including genetics, age, sex, atopy, weight and height, current smoking, and diet, with clinically significant or only small effects.

FeNO levels increase with age, most likely due to increases in airway mucosal surface area [13]. The affect of atopy on NO levels is controversial [23].

It is well acknowledged that smoking reduces FeNO both in healthy and asthmatic subjects [18]. Current cigarette smoking is associated with a 40–60% and previous smoking of around 10% decrease in FeNO levels [1]. However, FeNO is still raised in smokers with asthma, compared to smokers without asthma, and it has been shown that FeNO can differentiate asthma from non-asthma with asthma-like symptoms equally well in smokers as in never smokers [15]. No clear guidelines exist for the use of exhaled NO in smoking asthmatics, indicating a need for more knowledge in this field.

FeNO increases following consumption of nitrate rich food. This effect may last up to 15 h after intake [1]. So it is preferable to ask patients to refrain from a meal consisting primarily of green-leaved vegetables on the day of assessment.

Spirometric maneuvers may transiently reduce FeNO and ATS/ERS guidelines recommend performing FeNO measurements before. According to the guidelines we have to ask patients to refrain from physical exercise 1 h before measurement [3].

Rhinovirus infections Increase of 50-150%. It is recommended Repeat measurement after at least 14 days [13].

Cut Points for FeNO.

In 2011, the American Thoracic Society (ATS) guidelines suggested that the use of clinically meaningful cut-points rather than reference values have to be used in FeNO levels interpretation.It has also been concluded to categorize FeNO measurements as low, intermediate, and high, with differing cut points for children younger than 12 years of age and adults. Specifically, the guidelines stated FeNO values <25 ppb (20 ppb in children <12 years) a low likelihood of eosinophilic inflammation and corticosteroid response, while FeNO values >50 ppb (35 ppb in children <12 years) indicate otherwise. The most crucial consideration is whether the patient has current respiratory symptoms or an existing diagnosis of airway disease. As well as cautious interpretation of intermediate FeNO levels (25 ppb to 50 ppb in adults, 20 ppb to 35 ppb in children) depends on whether the symptomatic patient presents for an initial diagnosis or is being treated and monitored over time. The guidelineadvisedthat a rising FE_{NO} with a greater than 20 percent change and more than 25 ppb (20 ppb in children) from a previously stable level suggests increasing eosinophilic airway inflammation, but there are wide inter-individual differences. A decrease in FE_{NO} greater than 20 percent for values over 50 ppb or more than 10 ppb for values less than 50 ppb may be clinically important.

Some authors advocated and ATS/ERS guidelines 2011 recommended when monitoring individual patients with asthma and assessing their treatment requirements, achieving a “personal best” rather than “normal” values is more helpful.

However, several factors have been identified that affect FE_{NO} values and further studies are needed to get more reliable FeNO cut-off values for treatment decisions[11].

FeNO in clinical use

FeNO has been shown to be useful in clinical practice as a noninvasive biomarker of asthma, rather than just symptoms or airflow limitation. FeNO values of themselves do not justify a diagnosis or change in treatment. Rather, they need to be interpreted in relation to the clinical context[6]. FENO testing is recommended as an option to help diagnose asthma in adults and children in situations in which objective evidence is needed [17]. These recommendations are based on a number of research results: in a study comparing FeNO and sputum cell counts against serial peak flow recordings and spirometry in children and adults, the sensitivity of spirometry was lower (47%) than that of either FeNO (88%) or sputum eosinophils (86%). FeNO and sputum eosinophils additionally exhibited a specificity of 92% as compared with 73% for spirometry [27].

Assessment of airway inflammation in clinical practice would prove useful, as patients with asthma-like symptoms but with normal lung function are reported to benefit from steroid treatment [24]. In contrast, importantly, those with baseline FeNO levels in predefined normal ranges are less likely to respond to ICS [26].

So,It has been considered, that as an adjunct to traditional methods FeNO would help in asthma diagnosis, as a detector of allergic asthma phenotype and on the other hand in selection ICS-responsive inflammatory airway disease.

Because FeNO levels predict ICS responsiveness, and, more importantly, lack of ICS responsiveness, the ATS guidelines (2011) recommend using FeNO in monitoring airway inflammation in patients with established asthma. Though, it is accumulating conflicting evidences on whether FENO monitoring can improve management of asthma [5,13], butmost studies found a benefit to FeNOmeasurement [7,22].

One concern is that some of the negative results were due to specific design and methodological issues, sample size, clinical parameters, the application of different FeNO algorithms and devices, that may have led to incorrect conclusions [13,28].

It is clear, that prevention of exacerbations is an important goal in the management of asthma and prediction of imminent exacerbations before the onset of clinical symptoms and airway obstructions could be of considerable value.FeNO use has been associated with lower exacerbation rates in clinical studies. When asymptomatic children in clinical remission stopped taking steroids, a FeNO level of more than 49 ppb 2 to 4 weeks later was an effective predictor of asthma relapse [21].

Current therapies based on inhaled corticosteroids and long-acting β-agonists remain effective in a large proportion of patients with allergic asthma , but ~10% (considered to have “severe asthma”) do not respond to these treatments. In this regard analytical clustering methods have revealed phenotype with high Th2-mediated inflammation. There are emerging data on FeNO value to predict therapeutic response to treatments targeted towards Th2-associated cytokines, such are: anti-IgE, anti-IL4Ra, anti-IL-13 antibodies [6,10].

Nonadherence ICS is a major contributing factor to treatment failure in asthma management. FeNO may have a beneficial outcome for assessment of corticosteroid treatment compliance, as responds rapidly and dosedependently to ICS treatment [16].

Additional advantages for FENO include the noninvasive and easily executable nature of the test.

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SUMMARY

MODERN APPROACHES TO FRACTIONAL EXHALED NITRIC OXIDE AS A USEFUL BIOMARKER FOR ALLERGIC ASTHMA PHENOTYPING AND MANAGEMENT

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Asthma is a pathologically heterogeneous disease, consisting of several phenotypes. Different types of airway inflammation are the cornerstone feature of this condition. Fraction of nitric oxide in exhaled air (FENO) has been proposed as a noninvasive, specific biomarker for eosinophilic airway inflammation and has been shown to be elevated in patients with allergic asthma phenotype. More recent studies indicate that FeNO identifies T-helper cell type 2 (Th2)–mediated airway inflammation with a high predictive value for identifying inhaled corticosteroid (ICS) responsive airway inflammation. Taking into account the accumulated evidence,it is possible to consider, that FeNO testing has an important role in the assessment of patients with suspected asthma and in the management of established asthmadiagnosis. In conjunction with symptom scores and lung function tests, FeNO measurement could provide a more useful and effective approach for asthma in terms of: (1) detecting the presence of Th2–mediated airway inflammation, (2) determining the likelihood of ICS responsive (and lack of course), (3) monitoring of airway inflammation to determine risk for future impairment or loss of asthma control during reduction/cessation of ICS treatment, (4) unmasking (otherwise unsuspected) non-adherence to corticosteroid therapy and (5) in severe asthma cases tailoring treatment with biological drugs. However, more work is still needed to address outstanding questions about its exact role in guiding asthma management and better define the use of FENO in different clinical settings.

Keywords: asthma, exhaled nitric oxide, Th2–mediated inflammation, phenotype.

РЕЗЮМЕ

СОВРЕМЕННЫЕ ПОДХОДЫ К ОКИСИ АЗОТА В ВЫДЫХАЕМОМ ВОЗДУХЕ КАК ЗНАЧИМОМУ БИОМАРКЕРУ, СПОСОБСТВУЮЩЕМУ ИДЕНТИФИКАЦИИ И ОПРЕДЕЛЕНИЮ ТАКТИКИ ВЕДЕНИЯ АЛЛЕРГИЧЕСКОГО ФЕНОТИПА АСТМЫ

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Бронхиальная астма является патофизиологически гетерогенным заболеванием. Ее фенотипы характеризуются различными типами воспаления дыхательных путей. В качестве неинвазивного специфического биологического маркера эозинофильного воспаления предложено исследование содержания оксида азота в выдыхаемом воздухе (FeNO). Доказано его повышение у пациентов с аллергическим фенотипом бронхиальной астмы.

Более поздние исследования убедительно доказали важность определения FeNO с целью идентификации TH2-опосредованного воспаления дыхательных путей, что имеет высокую прогностическую ценность для уточнения эффективности и оптимизаций кортикостероидной терапии. Накопленный опыт

позволяет считать, что тестирование FeNO играет значимую роль как в оценке пациентов с подозрением на бронхиальную астму, так и в лечении пациентов с уже диагностированным заболеванием.

В сочетании с клиническими данными и стандартными тестами исследования легочной функции, мониторинг FeNO следует рассматривать как дополнительный метод, способствующий: (1)Диагностике Th2-опосредованного воспаления дыхательных путей; (2)Прогнозированию эффективности ингаляционных глюкокортикоидов; (3)Мониторингу воспалительного процесса в дыхательных путях для определения риска ухудшения течения болезни или потери контроля над астмой в случае снижения дозы или отмены терапии глюкокортикоидами; (4) Определению низкой комплаентности пациентов; (5)Выявлению фенотипически неблагоприятных форм бронхиальной астмы, требующих подключения биологической терапии.

На сегодняшний день некоторые аспекты клинической значимости FeNO и влияния на него различных факторов являются не полностью изученными, что диктует необходимость проведения дальнейших исследований.

რეზიუმე

ამოსუნთქული აზოტის ოქსიდის, როგორც მნიშვნელოვანი ბიომარკერის განსაზღვრის თანამედროვე მიდგომები ალერგიული ასთმის ფენოტიპირებასა და მართვაში

ნ. მგალობლიშვილი, მ. გოთუა

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი;
ალერგიისა და იმუნოლოგიის ცენტრი, თბილისი, საქართველო

ბრონქული ასთმა წარმოადგენს პათოგენეზურად ჰეტეროგენულ დაავადებას, რომლის ფენოტიპები ხასიათდება სასუნთქ გზებში ქრონიკულად მიმდინარე ანთებითი რეაქციების სხვადასხვა ტიპით. ამოსუნთქულ ჰაერში არსებული ფრაქცირებული აზოტის ოქსიდი (FeNO) განიხილება, როგორც სასუნთქი გზების ეოზინოფილური ანთების არაინვაზიური, სპეციფიკური ბიომარკერი. FeNO-ს მომატებული დონე ნაჩვენებია ბრონქული ასთმის ალერგიული ფენოტიპის დროს. კვლევები ადასტურებენ FeNO-ს როლს სასუნთქი გზების სპეციფიკურად T-ჰელპერული უჯრედების მე-2 ტიპით (Th2)-გაშუალებული ანთების შეფასებაში. მას გააჩნია კორტიკოსტეროიდული თერაპიის ეფექტურობის მაღალი პრედიქტორული ინდექსი. დაგროვილი მონაცემების საფუძველზე შესაძლებელია მივიჩნიოთ, რომ FeNO-ს განსაზღვრა მნიშვნელოვანია, როგორც საეჭვო, ასევე დადასტურებული ასთმის დიაგნოზის მქონე პაციენტთა დაავადების მართვაში. კლინიკურ და გარეგანი სუნთქვიის ფუნქციის მონაცემებთან კავშირში იგი განიხილება, როგორც დამატებითი კვლევა, რომელიც გვეხმარება: (1) Th2-გაშუალებული სასუნთქი გზების ანთების გასაზღვრაში; (2) საინჰალაციო კორტიკოსტეროიდით მკურნალობის მოსალოდნელი ეფექტურობის შეფასებაში; (3) ბაზისური თერაპიის ოპტიმიზაციის დროს ასთმის კონტროლის მონიტორინგში გამწვავებათა რისკების გათვალისწინებით; (4) პაციენტის მკურნალობის დაბალი კომპლაენსის გამოვლენაში; (5) მძიმე, სტეროიდრეფრაქტერული ასთმის შემთხვევაში ბიოლოგიური პრეპარატების გამოყენების სარგებლის განსაზღვრაში.

ამავე დროს, აღსანიშნავია, რომ FeNO-ს განსაზღვრის კლინიკური მნიშვნელობის სხვადასხვა საკითხი კვლავ განხილვისა და შემდგომი კვლევის საგანია.

METABOLIC PROFILE OF SERUM FATTY ACIDS IN PATIENTS WITH COMORBIDITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CHRONIC PANCREATITIS

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According to contemporary concepts as regards pathogenesis of inflammatory diseases, one of leading links in formation and progress of both COPD and chronic pancreatitis (CP) is disturbed balance of antioxidant defense system and lipids peroxidation [4,6,9]. Such misbalance leads to formation of reactive oxygen metabolites and launch of chain reaction cascade, causing antioxidant protection system overload and hyperactivity of destabilizing processes. The latter creates severe, sometimes irreversible structural functional disturbances in cell membrane [7,11,12].

Fatty acids (FAs) are among cell membrane basic structural components, important in functional activity of membrane proteins and receptors, so they are one of substantial factors defining biological membrane electrophysiological properties [1,5]. Stable fatty acid disturbances under chronic hypoxia, immune misbalance and prolonged effect of pathogen factor, which take place in chronic inflammatory process, may deeply affect cell function disturbance and aggravate inflammatory reactions even more [3,8,10]. But under comorbidity circumstances when more than one chronic inflammatory process take place, these changes may favor substantial deterioration of disease running – more frequent and prolonged exacerbations, accelerated progress and early formation of complications.

Objective - study of blood serum fatty acid metabolic profile in patients with comorbidity of COPD and chronic pancreatitis.

Materials and methods. 238 patients were examined, of them 131 with combined COPD and CP run (main group) and 107 with isolated COPD run (comparison group). Patients were attracted with I and II stages of bronchial obstruction – spirometric class GOLD1 and GOLD2. The main group patients were of age 28 to 65, 46,9±5,8 years on the average, whereas isolated COPD patients were in age range 30 to 68 years, 48,1±7,9 years on the average. COPD anamnesis duration was 13,1±4,2 years in the main group, CP average duration being 11,9±4,7 years. In comparison group COPD anamnesis was 12,8±4,9 years on the average Patients of both groups were commensurable as per their gender, age, degree of bronchial obstruction, duration of disease. To obtain normative results 20 actually healthy people were examined as well (control group).

In study of fatty acid spectrum biological materials were prepared and gas chromatography analysis of blood serum lipid fatty acid spectrum performed according to methodology by L.V.Sazonenko et al. [2]. In blood serum lipid fatty acid spectrum 9 most informative FAs were found: C14:0 myristic, C15:0 pentadecanoic, C16:0 palmitic, C17:0 margaric, C18:0 stearic, C18:1 oleic, C18:2 linoleic, C18:3 linolenic and C20:4 arachidonic.

Peaks of FAs under study were identified by comparison with retention time of standard FAs' peaks. Blood lipid FAs were quantified by area normalization of FA methyl derivative peaks and their percentage was determined.

Means of software "Microsoft Excel" and "STATISTICA 6.0" have performed statistical data. All values are expressed as mean (M) and standard deviation (σ). The difference was considered to be significant at $p<05$.

Results and their discussion. Our research showed that isolated COPD progress was accompanied by changes in contents of particular acids, and these changes were differently directed (Table 1).

Palmitic acid content was reduced by 42,5% as compared with control group, which may be caused by activation of lipid free radical oxidation process mostly at the account of cell membrane phospholipids layer. Simultaneously stearic acid level was reliably reduced by 49,7% and that of oleic acid by 27,7%. This together with palmitic acid content reduction confirms that phospholipid lecithin fraction takes part in pathological process.

At the same time substantial increase of arachidonic acid – 5 times versus control group - indicates activation of inflammatory processes in body and may be treated as indicator of endogenous intoxication existence. Under such circumstances this is a result of deregulation in synthesis of arachidonic acid metabolites (prostaglandins, prostacyclins, thromboxanes and leukotrienes), which are important mediators of inflammation and sources of endotoxinemia [3,8,10].

That is, COPD progress is accompanies by charges in FAs spectrum indicating that cell membranes are involved in pathological process. As a result of such changes lipid complex unsaturation grows (total SFAs content is reduced by 18,2%) which leads to subsequent activation of lipid peroxidation and chronic inflammatory process support.

At the same time total level of polyunsaturated (Σ PSFA) and unsaturated (Σ USFA) FAs is also different between groups: it significantly exceeds normal values (2,1 times and 1,3 times respectively) due to increased content of linoleic (1,5 times) and arachidonic (4,9 times) acid which may also favor eicosanoid synthesis disturbance and, thus, succession and force of both local and general inflammatory reaction [3,5,8].

In study of FAs level variations in connection with COPD severity degree certain correlations were found

Table 1. The content of fatty acids in patients with isolated COPD, (M±σ)

Fatty acids, %	COPD (n=107)	Control group (n=20)	Statistical significance*
$C_{14:0}$	8,9±0,7	-	
$C_{15:0}$	4,1±0,4	-	
$C_{16:0}$	24,1±1,1	41,9±0,9	t=4,356, p<0,001
$C_{17:0}$	1,9±0,2	-	
$C_{18:0}$	7,6±0,6	15,1±1,1	t=4,722, p<0,001
$C_{18:1}$	17,5±0,9	24,2±0,6	t=2,733, p=0,006
$C_{18:2}$	23,8±1,1	16,0±1,4	t=2,621, p<0,007
$C_{18:3}$	1,7±0,4	-	
$C_{20:4}$	13,8±0,7	2,8±0,3	t=5,994, p<0,001
Σ SFAs	46,6±1,4	57,0±1,3	t=4,118, p<0,001
Σ USFAs	56,8±1,2	43,0±1,3	t=4,228, p<0,001
Σ PSFAs	39,3±1,4	18,8±1,4	t=4,168, p<0,001

SFAs - saturated fatty acids, USFAs - unsaturated fatty acids, PSFAs - polyunsaturated fatty acids;
** - differences between groups*

Table 2. The content of fatty acids in patients with comorbidity of COPD and chronic pancreatitis, (M±σ)

Fatty acids, %	COPD and CP (n=131)	Control group (n=20)	Statistical significance*
$C_{14:0}$	6,2±0,5	-	
$C_{15:0}$	2,5±0,3	-	
$C_{16:0}$	24,9±1,2	41,9±0,9	t=4,351, p<0,001
$C_{17:0}$	1,3±0,3	-	
$C_{18:0}$	5,8±0,5	15,1±1,1	t=5,123, p<0,001
$C_{18:1}$	16,1±1,0	24,2±0,6	t=2,172, p=0,031
$C_{18:2}$	28,9±1,2	16,0±1,4	t=3,910, p=0,002
$C_{18:3}$	1,6±0,3	-	
$C_{20:4}$	13,6±0,9	2,8±0,3	t=5,368, p<0,001
Σ SFAs	40,7±1,3	57,0±1,3	t=4,121, p<0,001
Σ USFAs	60,2±1,2	43,0±1,3	t=4,198, p<0,001
Σ PSFAs	44,1±1,2	18,8±1,4	t=4,312, p<0,001

** - differences between groups*

with palmitic (r=-0,473, p<0,05), oleic (r=-0,523, p<0,05), stearic (r=-0,491, p<0,05), linoleic (r=0,685, p<0,01) and arachidonic (r=0,798, p<0,01) acids. Such changes are an appropriate consequence of lipid peroxidation process hyperactivation under progressing inflammatory changes in bronchial tree in the course of bronchial obstruction degree growing.

At the same time in patients of main group arachidonic acid content was 4,9 times above normal, that of linoleic acid 1,8 times on the ground of decrease in palmitic acid content to 1,5 times below normal, oleic acid 1,5 times and stearic acid 2,5 times (Table 2).

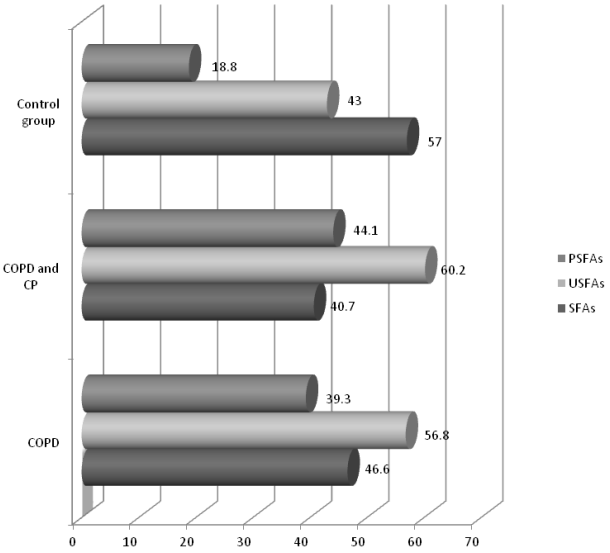
Simultaneous increase of arachidonic and linoleic acids ensures higher unsaturation of fatty acids and total PSFAs value of 44,1±1,8% (at normal 18,8±1,4%); it must be noted that just relation of Omega-3 and Omega-6 FAs classes in PSFAs is the decisive factor in pathology formation. Buoyant synthesis of linoleic acid which is a precursor of arachidonic acid and opponent of the latter in lipid membrane composition, initiates competitive control mechanism of inflammatory eicosanoid synthesis. Such imbalance in arachidonic and linoleic acids levels may disturb microviscosity in cell membrane lipid biolayer causing malfunction in microcirculation processes [1,5].

The result of such FAs fluctuations in patients of main group is substantially increased polyunsaturation of blood fatty acid spectrum on the grounds of reduced total concentration of SFAs that control antioxidant properties.

In comparison of values for isolated COPD patients and comorbid COPD and CP patients unidirectional deviations in concentrations of basic FAs were observed in both groups (Table 3).

Thus, although concentrations of basic FAs mostly did not have significant discrepancies, nevertheless, concentration changes of stearic and linoleic acids were significantly more expressed, which caused saturation level reduction and increased unsaturation of fatty acids.

Total content of saturated and unsaturated FAs in patients of main groups was significantly different from both control group values and comparison group values (Pic.).



Pic. The total content of saturated and unsaturated FAs, %

Table 3. The content of fatty acids in examined patients, (M±σ)

Fatty acids, %	COPD (n=107)	COPD and CP (n=131)	Statistical significance*
$C_{14:0}$	8,9±0,7	6,2±0,5	t=2,025, p=0,046
$C_{15:0}$	4,1±0,4	2,5±0,3	t=2,335, p=0,025
$C_{16:0}$	24,1±1,1	24,9±1,2	p>0,05
$C_{17:0}$	1,9±0,2	1,3±0,3	t=2,015, p=0,047
$C_{18:0}$	7,6±0,6	5,8±0,5	t=2,225, p=0,031
$C_{18:1}$	17,5±0,9	16,1±1,0	p>0,05
$C_{18:2}$	23,8±1,1	28,9±1,2	t=4,245, p<0,001
$C_{18:3}$	1,7±0,4	1,6±0,3	p>0,05
$C_{20:4}$	13,8±0,7	13,6±0,9	p>0,05
Σ SFAs	46,6±1,4	40,7±1,3	t=4,125, p<0,001
Σ USFAs	56,8±1,2	60,2±1,2	t=2,279, p=0,024
Σ PSFAs	39,3±1,4	44,1±1,2	t=2,404, p=0,018

** - differences between groups*

As in isolated COPD group, total content of unsaturated (1,4 times) and polyunsaturated (2,4 times) fatty acids took place due to increasing content of linoleic and arachidonic acids which also may cause malfunction of eicosanoid synthesis which may result in persistent character of inflammatory process as well as in its latent progress under clinical remission of the disease.

Conclusion. In the course of blood serum lipid fatty acid composition study in isolated COPD patients and patients with COPD combined with CP the content of particular FAs was found amended which indicated cell membrane disorder due to activation of lipid peroxidation on the ground of antioxidant protective system suppression.

In both groups arachidonic acid content substantially grew, indicating eicosanoid formation deregulation and activation of inflammatory processes in organism causing appearance of endogenous intoxication syndrome. Under comorbidity circumstances the presence of concomitant CP substantially strengthened the expression of such deviations due to increase of unsaturation level and the sum of PSFAs which is indicative of lipid peroxidation processes intensification, and this may be treated as one of additional factors of pathology progressing under this "nosological duo".

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SUMMARY

METABOLIC PROFILE OF SERUM FATTY ACIDS IN PATIENTS WITH COMORBIDITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CHRONIC PANCREATITIS

[1]Zhelezniakova N., [1]Pasiyeshvili L., [1]Bocharova T., [1]Pasiieshvili T., [2]Zhelezniakov O.

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Objective - study of blood serum fatty acid metabolic profile in patients with comorbidity of COPD and chronic pancreatitis.

238 patients were examined, of them 131 with combined COPD and chronic pancreatitis and 107 with isolated COPD run. In study of fatty acid spectrum biological materials were prepared and gas chromatography analysis of blood serum lipid fatty acid spectrum performed according to methodology by L.V.Sazonenko et al.

The study showed that COPD exacerbation was accompanied with by changes in contents of particular fatty acids both in patients with isolated COPD and in patients with comorbidity in comparison with almost healthy patients. In comparison of values for isolated COPD patients and comorbidity of COPD and chronic pancreatitis patients unidirectional deviations in concentrations of basic FAs were observed in both groups. Although concentrations of basic FAs mostly did not have probable discrepancies, nevertheless, concentration changes of stearic and linoleic acids were significantly more expressed, which caused saturation level reduction and increased unsaturation of fatty acids.

The presence of concomitant chronic pancreatitis in patients with COPD substantially strengthened the expression of FAs spectrum deviations due to increase of unsaturation level and the sum of PSFAs which is indicative of lipid peroxidation processes intensification, and this may be treated as one of additional factors of pathology progressing.

Keywords: fatty acids, chronic obstructive pulmonary disease, chronic pancreatitis.

РЕЗЮМЕ

МЕТАБОЛИЧЕСКИЙ ПРОФИЛЬ ЖИРНЫХ КИСЛОТ СЫВОРОТКИ КРОВИ У ПАЦИЕНТОВ С КОМОРБИДНОСТЬЮ ХРОНИЧЕСКОГО ОБСТРУКТИВНОГО ЗАБОЛЕВАНИЯ ЛЕГКИХ И ХРОНИЧЕСКОГО ПАНКРЕАТИТА

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Цель - изучить метаболический профиль жирных кислот сыворотки крови у пациентов с коморбидностью хронического обструктивного заболенивая легких и хронического панкреатита.

Обследовано 238 пациентов, из них 131 с коморбидностью хронического обструктивного заболенивая легких (ХОЗЛ) и хронического панкреатита и 107 с изолированным ХОЗЛ. При изучении спектра жирных кислот подготовку биологического материала и газохроматографический анализ спектра жирных кислот в сыворотке крови проводили по методу Л.В Сазоненко и соавт.

Исследование показало, что обострение ХОЗЛ сопровождалось изменениями содержания отдельных жирных кислот как в группе с изолированным ХОЗЛ, так и в группе с сопутствующей патологией по сравнению с почти здоровыми пациентами. При сопоставлении параметров пациентов с изолированным ХОЗЛ и больных с коморбидностью ХОЗЛ и хронического панкреатита были выявлены однонаправленные изменения в концентрациях основных жирных кислот в обеих группах. Несмотря на то, что в показателях уровня большинства жирных кислот не выявлено достоверных различий, тем не менее, изменения концентрации стеариновой и линолевой кислот были значительно более выраженными, что ведет к снижению уровня насыщенности и повышению ненасыщенности жирных кислот.

Наличие сопутствующего хронического панкреатита у пациентов с ХОЗЛ существенно усиливало девиации жирнокислотного спектра сыворотки крови за счет увеличения уровня ненасыщенности и суммы полиненасыщенных жирных кислот, что свидетельствует об интенсификации процессов перекисного окисления липидов и может рассматриваться как один из дополнительных факторов прогрессирования патологии.

რეზიუმე

სისხლის შრატში ცხიმოვანი მჟავების მეტაბოლური პროფილი პაციენტებში ერთდროულად მიმდინარე ფილტვების ქრონიკული ობსტრუქციული დაავადებით და ქრონიკული პანკრეატიტით

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ხარკოვის ეროვნული სამედიცინო უნივერსიტეტი; ჯანდაცვის კომუნალური დაწესებულება "ხარკოვის საქალაქო პარინატალური ცენტრი", უკრაინა

კვლევის მიზანს წარმოადგენდა სისხლის შრატში ცხიმოვანი მჟავების მეტაბოლური პროფილის განსაზღვრა პაციენტებში ერთდროულად მიმდინარე ფილტვების ქრონიკული ობსტრუქციული დაავადებით და ქრონიკული პანკრეატიტით.

გამოკვლეულია 238 ავადმყოფი, მათ შორის 131 ერთდროულად მიმდინარე ფილტვების ქრონიკული ობსტრუქციული დაავადებით (ფქოდ) და ქრონიკული პანკრეატიტით, ხოლო 107 – იზოლირებული ფქოდ-ით. ცხიმოვანი მჟავების სპექტრის შესწავლისას ბიოლოგიური მასალის მომზადება და ცხიმოვანი მჟავების სპექტრის გაზოქრომატოგრაფიული ანალიზი სისხლის შრატში ხორციელდებოდა ლ. საზონენკოს და თანაავტორების მეთოდის მეშვეობით. ჩატარებული კვლევის შედეგებმა ცხადჰყო, რომ ფქოდ-ის გამწვავებას თან ახლავს ცალკეული ცხიმოვანი მჟავების შემცველობის ცვლილებები როგორც ფქოდ-ის იზოლირებულ ჯგუფში, ასევე ჯგუფში თანდართული პათოლოგიით შედარებით ჯანმრთელ პაციენტებთან. იზოლირებული ფქოდ-ით და ერთდროულად ფქოდ-ით და ქრონიკული პანკრეატიტით ავადმყოფების პარამეტრების შეპირისპირებისას გამოვლინდა ერთმიმართული ცვლილებები ძიროთადი ცხიმოვანი მჟავების კონცენტრაციებში ორივე ჯგუფში. მიუხედავად, იმისა, რომ ცხიმოვანი მჟავების უმრავლესობის დონის მაჩვენებლებში სარწმუნო სხვაობა არ გამოვლინდა, სტეარინის და ლინოლეის მჟავების კონცენტრაციის ცვლილებები მკვეთრად იყო გამოხატული. ფქოდ-ით და თანდართული პანკრეატიტით პაციენტების სისხლის შრატში საგრძნობლად მომატებული იყო ცხიმოვანი მჟავების სპექტრის დევიაცია, ცხიმოვანი მჟავების გაუჯერებლობის და პოლიგაუჯერებლობის დონის მაჩვენებლების ზრდის ხარჯზე, რაც მიუთითებს ლიპიდების ზეჟანგოვანი ჟანგვის პროცესის ინტენსიფიკაციაზე და შეიძლება განხილული იყოს,როგორც პათოლოგიის პროგრესირების ერთ-ერთი დამატებითი ფაქტორი.

ТАКТИКА ЛЕЧЕНИЯ КОГНИТИВНОЙ ДИСФУНКЦИИ В ПОСЛЕОПЕРАЦИОННОМ ПЕРИОДЕ

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Послеоперационная когнитивная дисфункция развивается в раннем и сохраняется в позднем послеоперационном периоде, клинически проявляется в виде нарушений памяти, затруднения концентрации внимания и нарушений других высших функций коры головного мозга [1,2,6].

Клиническими исследованиями установлено, что при использовании общей анестезии, наблюдаются изменения перфузии головного мозга, внутричерепная гипертензия и другие нарушения, как следствие использования анестезиологических препаратов, являющихся причиной возникновенияе различных нарушений высшей мозговой функции. В раннем послеоперационном периоде когнитивная дисфункция определяется примерно в 30% случаях после хирургических вмешательств, которые выполнены с помощью общей анестезии, и продолжает наблюдаться в течение трех месяцев у 10% пациентов [5-7]. Выявлено, что послеоперационная когнитивная дисфункция имеет обратное развитие на ранних стадиях, поэтому необходимо корректировать нарушения с самого начала и предотвращать их [9,10].

В послеоперационном периоде возможно развитие различных нарушений центральной нервной системы в виде психопатологических и психотических реакций, делирия, судорожного синдрома, послеоперационной когнитивной дисфункции, нарушения цикла сна-бодрствования и координации, возникновения острого нарушения мозгового кровообращения, острой сенсоневральной тугоухости, спастической параплегии. Степень и выраженность патологических изменений со стороны центральной нервной системы зависит от вида анестезии, соматического состояния и неврологического статуса пациента в предоперационном периоде, от возраста. В подавляющем большинстве случаев на фоне общего угнетения функций центральной нервной системы наблюдается снижение памяти, внимания, реактивности, нарушения функции координации. Среди этих нарушений когнитивные изменения, возможно, выделить в ходе исследования ментального статуса, проявляющегося во внешности, поведении, ориентации, концентрации внимания, эмоциональном состоянии, мышлении, в познавательных процессах (память, способность логического суждения, речь, восприятие, праксис и исполнительные функции) [6].

При обсуждении данной темы следует учитывать основные теории влияния наркоза для разработки и совершенствования схем общей анестезии, определения доз и соотношений препаратов с целью достижения минимального токсического эффекта, учитывая клеточно-молекулярные механизмы [5-7]. С учетом вышеизложенного, авторами разработана биохимическая теория.

В патогенезе возникновения когнитивной дисфункции в послеоперационном периоде выделяются основные факторы общей анестезии: метаболические, гемореологические, гипоксические, токсичные. Изучение этиопатогенетических механизмов когнитивной дисфункции, возникающих как следствие общей анестезии, позволит в дальнейшем разработать адекватные методы профилактики данной патологии, которая является актуальной задачей современной анестезиологии и неврологии.

Целью исследования является разработка тактики адекватной нейропротекторной терапии пациентам с послеоперационными когнитивными дисфункциями на основании определения общего когнитивного дефицита.

Материал и методы. Исследование проведено в хирургических отделениях различного профиля на базе Харьковской городской клинической больницы скорой и неотложной медицинской помощи им. проф. А.И. Мещанинова. Обследовано 110 пациентов молодого и среднего возраста (38,5±5,6 г.) и 96 пациентов пожилого возраста (73,3±7,9 г.) с хирургической патологией, из них 88 мужчин и 118 женщин. Оперативное вмешательство проводили в условиях общей многокомпонентной анестезии с искусственной вентиляцией легких с использованием пропофола и фентанила, тиопентала-натрия и фентанила. Для достижения цели проведено исследование когнитивной сферы у пациентов различных возрастных групп: молодого, среднего и пожилого возраста, с острой хирургической патологией до операции и на 1, 7, 30 сутки после оперативного вмешательства. Полученные данные сравнивались с таковыми предоперационного периода.

Использованы стандартные клинические и лабораторные методы. Когнитивную сферу исследовали посредством шкалы MMSE, теста рисования часов, теста «10 слов», батареи тестов на лобную дисфункцию, метода Шульте. Пациенты были информированы о ходе заболевания, объеме оперативного вмешательства и возможных осложнений. Рассчитывали показатель общего когнитивного дефицита.

Результаты и их обсуждение. В дооперационном периоде в группе больных молодого и среднего воз-

Таблица. Оценка результатов состояния когнитивной функции на различных этапах исследования

	До операции	1 сутки	7 сутки	1 месяц
Шкала MMSE (28-30 баллов)	Молодой и средний возраст: 27,1±1,1	25,3±1,8	27,8±0,9	28,2±0,7
	Пожилой возраст: 24,3±1,7	18,9±2,1	20,8±1,9	21,8±1,4
Тест «10 слов» Лурия (9-10 слов)	Молодой и средний возраст: 8,1±0,4	6,8±0,5	8,7±0,2	9,1±0,6
	Пожилой возраст: 6,1±0,6	5,1±0,4	5,8±0,4	6,8±0,3
FAB (18 баллов)	Молодой и средний возраст: 17,3±0,6	17,1±0,7	17,6±0,8	17,1±0,3
	Пожилой возраст: 15,1±1,4	13,1±0,8	14,6±0,6	15,2±0,4
Метод Шульте (40-50 слов)	Молодой и средний возраст: 54,1±1,6	70,2±1,1	60,3±1,4	53,8±2,1
	Пожилой возраст: 59,1±1,4	97,8±1,7	79,1±1,8	64,8±1,6
Тест рисования часов (10 баллов)	Молодой и средний возраст: 9,8±0,2	9,4±0,5	9,5±0,4	9,6±0,3
	Пожилой возраст: 9,2±0,8	7,9±1,1	8,1±0,7	9,4±0,5

раста отмечались одинаковые значения. По данным шкалы MMSE показатель был ниже нормы на 9,0%, показатели теста рисования часов - в пределах нормы; по шкале FAB показатели были ниже на 5,5%, по методу А.Р. Лурия - ниже на 15,0%, показатели по методике Шульте находились в пределах нормы. В дооперационном периоде в группе больных пожилого возраста показатель шкалы MMSE был ниже нормы на 23,3%, теста рисования часов - ниже на 10,0%, по шкале FAB - ниже на 16,6%, по методу А.Р. Лурия данные пациентов были ниже на 40,0%, а по методике Шульте - на 16,6% ниже нормы (таблица).

Исследование когнитивной функции на 1, 7 и 30 сутки после операции позволило разработать и сформулировать схему с включением в комплекс лечебных программ цитиколина и цитофлавина (Патент на полезную модель №89336 2014) [9].

Анализ результатов полученных исследований на разных этапах выявил, что в каждой возрастной группе на седьмые сутки исследования у пациентов была восстановлена когнитивная функция до значений дооперационного периода. У части пациентов отмечались незначительные изменения показателей, а у другой - ухудшение состояния когнитивной функции в сравнении с дооперационным периодом. На основании полученных результатов исследования разработана и предложена к использованию формула подсчета общего когнитивного дефицита (ОКД), которая позволяет разработать соответствующую тактику ведения данных пациентов в послеоперационном периоде в каждом конкретном случае (Патент Украины на изобретение №113265 2016) [10].

Суть способа заключается в назначении схемы лечения на основе диагностики степени и структуры когнитивной дисфункции по анализу результатов на 7 сутки после операции. Определяются величины процентных отклонений каждого результата исследования от нормы и показатель общего когнитивного дефицита по сумме значений процентного отклонения от нормы результатов исследования когнитивных нарушений. В случаях, когда показатель общего когнитивного дефицита составляет 20% и больше назначаются цитиколины [10].

В ходе исследования 41% пациентов в группе больных молодого и среднего возраста на 7 сутки по данным шкалы MMSE показатель когнитивной функции находился ниже нормы на 10%; по тесту рисования часов - в пределах нормы, по шкале FAB - ниже на 11%, по методу А.Р. Лурия - ниже на 10%, а по методике Шульте - на 17% ниже нормы. Показатель ОКД составил = 10%+0%+11%+10%+17%/5=9,6%. Дальнейшее лечение когнитивной дисфункции не рекомендовано.

У 34% пациентов в группе молодого и среднего возраста на 7 сутки по данным шкалы MMSE показатель был ниже нормы на 20%, показатели теста рисования часов ниже нормы на 10%, по шкале FAB - дефицит составил 22% от нормы, по методу А.Р. Лурия - ниже на 40%, а по методике Шульте - на 29%

ниже нормы. ОКД 0%+10%+22%+40% +29%/5=24,2%. Назначено дальнейшее лечение с использованием цитоколина по схеме.

У 28% пациентов пожилого возраста на 7 сутки по данным шкалы MMSE показатель был ниже нормы на 40%, показатели теста рисования часов ниже нормы на 30%, по шкале FAB - дефицит 22% от нормы, по методу А.Р. Лурия - ниже на 60%, а показатель по методике Шульте - на 44% ниже нормы. ОКД=40%+30%+22%+60%+ 44%/5 = 39,2%. Назначено дальнейшее лечение с использованием цитоколина по схеме.

У 54% пациентов пожилого возраста на 7 сутки по данным шкалы MMSE показатель когнитивной функции был ниже нормы на 20%, показатель теста рисования часов - ниже нормы на 10%, шкалы FAB - на 22%. По методу А.Р. Лурия данные пациентов были ниже на 30% от нормы, а при исследовании по методике Шульте - на 29% ниже нормы. Таким образом, ОКД=20%+10%+22%+30%+29%/5 = 22,2%. Назначено дальнейшее лечение с использованием цитоколина по схеме.

Выводы. Полученные результаты исследования когнитивной функции на 1, 7 и 30 сутки после операции позволили разработать схему включения в комплекс лечебных программ цитиколина и цитофлавина. В каждой возрастной группе на седьмые сутки исследования выявлена различная динамика восстановления когнитивной функции в сравнении с дооперационным периодом. Это позволило предложить формулу подсчета общего когнитивного дефицита, с помощью которой возможно разработать соответствующую тактику ведения пациентов в послеоперационном периоде в каждом конкретном случае.

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SUMMARY

TACTICS OF CHOOSING COGNITIVE DYSFUNCTION THERAPY IN THE POSTOPERATIVE PERIOD

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The aim of the study is to formulate the tactics of assigning adequate neuroprotective therapy to patients with postoperative cognitive dysfunctions on the basis of subtracting the indicator of the total cognitive deficiency.

To achieve this goal, we conducted a study of cognitive function in patients of different age groups: young age, middle age, elderly age with acute surgical pathology before surgery and at 1, 7, 30 days after surgery compared with preoperative data. Methods of research. The study of the cognitive sphere: scale MMSE, test drawing hours, test "10 words", battery tests for frontal dysfunction, method Schulte. The indicator of the total cognitive deficiency was calculated.

The results of the study of cognitive function made it possible to formulate a scheme for the use of citicoline and cytoflavin in a complex of therapeutic programs. In each age group, on the seventh day of the study, there were patients with different dynamics of cognitive function recovery for the preoperative period. This allowed us to develop and propose a formula for calculating the total cognitive deficit, which makes it possible to formulate appropriate tactics for managing patients in the subsequent period in each specific case. We determine the values of the percentage deviations of each study result from the norm and the indicator of the total cognitive deficit by the sum of the values of the percentage deviation from the norm of the results of the study of cognitive impairment.

Keywords: cognitive function, neurology, anesthesiology.

РЕЗЮМЕ

ТАКТИКА ЛЕЧЕНИЯ КОГНИТИВНОЙ ДИСФУНКЦИИ В ПОСЛЕОПЕРАЦИОННОМ ПЕРИОДЕ

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Целью исследования явилась разработка тактики адекватной нейропротекторной терапии пациентам с послеоперационными когнитивными дисфункциями с учетом показателя общего когнитивного дефицита.

Проведено исследование когнитивной функции у пациентов разных возрастных групп: молодого, среднего и пожилого возраста с острой хирургической патологией до операции и на 1, 7, 30 сутки после оперативного вмешательства.

В ходе исследования использованы стандартные клинические и лабораторные методы. Для исследования когнитивной сферы применялись шкала MMSE, тест рисования часов, тест «10 слов», метод А.Р. Лурия, метод Шульте. Рассчитывали показатель общего когнитивного дефицита.

Анализ результатов исследования когнитивной функции на 1, 7 и 30 сутки после операции позволил разработать схему включения в комплекс лечебных программ цитиколина и цитофлавина. В каждой возрастной группе на седьмые сутки исследования были пациенты с разной динамикой восстановления когнитивной функции в сравнении с дооперационным периодом. Это позволило предложить формулу подсчета общего когнитивного дефицита, с помощью которой возможно разработать соответствующую тактику ведения пациентов в послеоперационном периоде в каждом конкретном случае.

რეზიუმე

კოგნიტიური დისფუნქციის მკურნალობის ტაქტიკა პოსტოპერაციულ პერიოდში

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კვლევის მიზანს წარმოადგენდა ადეკვატური ნეიროპროტექტორული თერაპიის ტაქტიკის შემუშავება პაციენტებში პოსტოპერაციული კოგნიტიური დისფუნქციით საერთო კოგნიტიური დეფიციტის მაჩვენებლის გათვალისწინებით.

ჩატარებულია მწვავე ქირურგიული პათოლოგიის მქონე სხვადასხვა ასაკობრივი ჯგუფის - ახალგაზრდა, საშუალო და ხანდაზმული - პაციენტების კოგნიტური ფუნქციის კვლევა ოპერაციამდე, ოპერაციის შემდგომ პირველ, მეშვიდე და ოცდამეათე დღეს. კვლევის დროს გამოყენებული იყო სტანდარტული კლინიკური და ლაბორატორიული მეთოდები, კოგნიტიური სფეროს კვლევისათვის - MMSE შკალა, საათების ხატვის ტესტი, ტესტი “10 სიტყვა”, ტესტების ნაკრები შუბლის დისფუნქციაზე, შულტეს მეთოდი. გამოითვლებოდა საერთო კოგნიტიური დისფუნქციის მაჩვენებელი. შედეგების ანალიზმა შესაძლებელი გახადა ციტოკოლინის და ციტოფლავინის ჩართვის სქემის შემუშავება სამკურნალო პროგრამების კომპლექსში. ყველა ასაკობრივ ჯგუფში კვლევის მეშვიდე დღეს აღინიშნა პაციენტები კოგნიტიური დისფუნქციის აღდგენის სხვადასხვა დინამიკით, წინასაოპერაციო პერიოდთან შედარებით. ამ გარემოებამ შესაძლებელი გახადა საერთო კოგნიტიური დეფიციტის გამოთვლის ფორმულის შეთავაზება, რომელიც იძლევა თითოეულ კონკრეტულ შემთხვევაში პაციენტის მართვის შესაბამისი ტაქტიკის შემუშავების საშუალებას პოსტოპერაციულ პერიოდში.

ОСОБЕННОСТИ ЭЛЕМЕНТНОГО СТАТУСА БОЛЬНЫХ ВИТИЛИГО

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Дисхромии составляют около 10% всей дерматологической патологии. Среди них наиболее распространенной, тяжелой в косметическом отношении, воздействующей на психику больного является витилиго. Это заболевание встречается у 3-4% лиц с кожной патологией, чаще у лиц с темной кожей. Вопрос о причинах и механизмах исчезновения меланоцитов в витилигинозных пятнах по сей день окончательно не разрешен. Широко обсуждаются следующие теории развития витилиго: аутоиммунная деструкция меланоцитов, внутренний дефект структуры и функции меланоцитов, дефект защиты от действия свободных

радикалов, укорочение жизнеспособности и дисрегуляции апоптоза меланоцитов, изменение мембранных липидов меланоцитов, деструкция меланоцитов нейрохимическими веществами, вирусная инфекция, конвергентная теория [8-10].

Витилиго это мультифакторное заболевание, причем в каждом конкретном случае могут быть включены разные механизмы его патогенеза и разные уровни нарушения образования меланина в коже. Неясность этиологии и патогенеза, упорное и хроническое течение, склонность к распространению кожного процесса обуславливают трудности лечения витилиго.

Кожа представляет собой один из наиболее метаболически активных органов. Выполняя ряд жизненно важных функций (барьерная, защитная, дыхательная, выделительная, обменная, иммунная) она нуждается в микроэлементах [4,6].

Как известно стабильность химического состава организма является одним из важнейших и обязательных условий его нормального функционирования. В настоящее время из 92 встречающихся в природе химических элементов 81 обнаружен в организме человека [1-3]. Химические реакции, протекающие в организме, схематически можно представить следующим образом: субстрат + фермент + микроэлемент из аминокислоты тирозина под действием фермента тирозиназы. Микроэлемент медь играет роль катализатора в этой фотохимической реакции. Определение содержания микроэлементов в коже больных витилиго методом нейтронно-активационного анализа выявило значительное уменьшение концентрации меди как в очаге витилиго так и в коже вокруг депигментиорванных пятен [5]. Изучение роли эссенциальных и токсичных элементов в патогенезе витилиго позволит расширить спектр методов лечения данной патологии.

Целью исследования явилось определение элементного статуса волос у больных различными клиническими формами витилиго.

Материал и методы. Под наблюдением находилось 25 больных (15 женщин и 10 мужчин) различными клиническим формами витилиго в возрасте от 18 до 65 лет, с давностью заболевания от 6 мес. до 20 лет. При подборе клинического материала руководствовались классификацией, предложенной в англоязычной литературе: сегментарное витилиго (n=12) (segmental vitiligo - SV) - область поражения находится в границах одного сегмента и имеет одностороннее расположение. Несегментарное витилиго (non segmental vitiligo -NSV) - область поражения выходит за

Таблица. Содержание химических элементов в волосах больных витилиго (M±m мкг/г)

Элементы	Сегментарное витилиго, n=12	Несегментарное витилиго, n=13		Условные нормы	
основные		Фокальное, n=6	Акрофациальное, n=7	минимум	максимум
Ca	450,32±23,45	460±25,1	570,56±25,6	300,00	700,00
Zn	170,23±7,6	110±5,2	**60,34±4,5**	120,00	200,00
K	150,14±5,6	120±6,7	110,56±6,5	70,00	170,00
I	2,5±0,5	2,0±0,3	2,5±0,3	0,40	4,00
Cu	7,6±1,3	8,0±1,5	**4,5±0,6**	9,00	30,00
Se	1,5±0,5	0,8±005	**0,1±0,02**	0,30	1,20
Fe	31,81±3,65	13,0±1,7	10,5±0,35	15,00,	35,00
Mn	1,7±0,7	1,6±0,5	**0,2±0,02**	0,50	2,00
Cr	2,6±0,9	2,0±0,8	3,5±0,45	0,50	5,00
токсичные					
Ba	4,4±0,4	-	-	0,00	5,00
Pb	-	5,58	**7,8±0,25**	0,00	5,00
As		-	-	0,00	2,00
Hg	-	-	-	0,00	2,00
Cd	-	0,8	**1,56±0,5**	0,00	1,00
Zr	-	-	-	0,00	2,00
Sn	-	-	-	0,00	3,00
Bi	-	-	-	0,00	2,00
W	-	-	-	0,00	2,00
	-	-	-		

выделены статистически значимые различия (p<0,01)

пределы одного сегмента и имеет симметричное двустороннее расположение. Эта группа включала 13 больных, из них фокальное витилиго - 6 (одно или несколько белых пятен в определённом участке тела). Вульгарное или генерализрванное витилиго включало больных акрофациальным витилиго с депигментированными очагами на лице и конечностях - 7. У 10 пациентов при клиническом обследовании обнаружены невусы Сеттона. Контрольную группу составили 15 практически здоровых лиц.

Для оценки микроэлементного статуса организма забирали прикорневую часть волос в зоне затылка и проводили анализ методом рентгеновской флюоресцентной спектроскопии - МВИ 081/12 -4502 -00 на рентгенофлюоресцентном спектрометре СЭП -01 «Элвакс» (Центр медицинской элементологии «Лаборатория биоэлемент») [7].

Статистическую обработку результатов исследований проводили общепринятыми статистическим методами. Достоверность различий данных оценивалась с использованием критериев Стьюдента.

Результаты и их обсуждение. Результаты проведенного исследования элементного состава волос больных витилиго представлены в таблице.

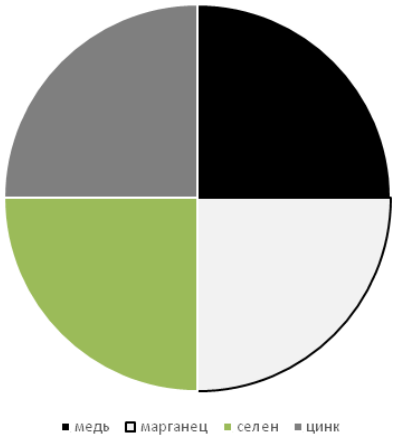

Рис. 1. Содержание химических элементов в волосах практически здоровых лиц

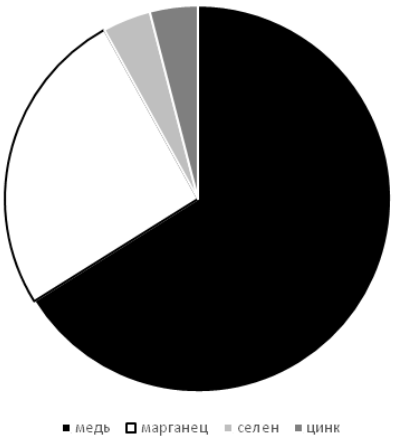

Рис. 2. Содержание химических элементов в волосах больных несегментарным витилиго

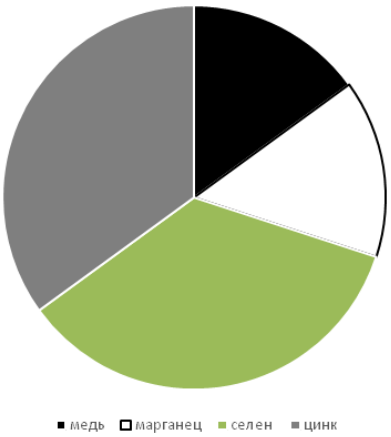

Рис. 3. Содержание химических элементов в волосах больных сегментарным витилиго

Из в таблицы явствует, что минеральный состав волос у больных различными клиническим формами витилиго характеризуется отклонением от условных норм. Так, у больных сегментарной формой витилиго концентрация основных элементов практически не отличается от нормы (цинк, марганец, цинк, селен). Незначительное нарушение баланса эссенциальных элементов отмечено в концентрации меди (7,6±1,3) при условной норме от 9,0 до 30,0. Токсичные и условно токсичные элементы в волосах у данной группы больных не определяются.

В группе больных несегментарным витилиго (фокальная, акрофациальная формы) установлено достоверное понижение уровня эссенциальных (основных) элементов - марганца , меди, цинка и селена. В группе больных фокальным витилиго концентрация этих элементов выражалась в следующих единицах, 110±5,2; 8,0±1,5; 0,8±0,05; 1,6±0,5, соотвественно.

В группе больных акрофациальным витилиго установлено достоверное понижение уровня цинка, меди, селена, марганца. Концентрация этих элементов выражалась в следующих единицах - 60,34±4,5; 4,5±0,6; 0,1±0,02; 0,2±0,02, соотвественно.

Медь и марганец действуют как антиоксиданты, поскольку являются компонентами многих клеточных ферментов, включая супероксиддисмутазу, обезвреживающую свободные радиалы. Имеются данные, что при длительном дефиците марганца могут наблюдаться пигментные изменения (витилиго), нарушение синтеза меланина.

Известно, что селен - необходимый элемент для организма. Он предохраняет клетки от повреждающего действия свободных радикалов и тяжелых металлов (кадмий, ртуть, мышьяк). Являясь значимым компонентом системы антиоксидантной защиты организма, он обладает противоопухолевым действием, поддерживает детоксикационную функцию печени, активен в присутствии витамина Е. Недостаток селе-

на приводит к нарушению стабильности мембран и процессов микросомального окисления во всех клетках организма, с последующим нарушением функций основных органов и систем. Цинк входит в состав более 70 ферментов, без которых невозможны основные биохимические процессы в организме. Цинк также является кофактором одной из изоформ супероксиддисмутазы. Для борьбы с окислительным стрессом необходимо, прежде всего, обеспечить собственную антиоксидатную систему необходимыми для ее нормального функционирования кофакторами (марганец, селен, цинк, медь).

Наличие токсичных и потенциально токсичных элементов наблюдали у больных акрофациальной формой витилиго в 4 случаях - в виде незначительного повышения уровня свинца и кадмия. Известно, что избыточное накопление свинца и кадмия обуславливает напряжение разных функциональных систем. В основе механизма проявлений интоксикации данными элеметами лежит непосредственное воздействие на ядерный хроматин, косвенное воздействие осуществляется путем замещения других элементов или изменения активности ряда ферментных систем.

Таким образом, полученные в результате проведенного исследования данные еще раз подтверждают значение роли определенных химических элементов в патогенезе хронических заболеваний. Все элементные дисбалансы объединяются рядом общих закономерностей развития и сопровождаются нарушением иммунного гомеостаза со снижением иммунной резистентности.

Правильный подход к пониманию механизмов возникновения витилиго позволит предложить новые эффективные схемы его лечения, а целенаправленное применение средств, содержащих макро- и микроэлементы, максимально обеспечит эффективность лечения определенных форм витилиго.

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SUMMARY

ELEMENTAL STATUS OF PATIENTS WITH VARIOUS FORMS OF VITILIGO

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Vitiligo is a multifactorial disease in which, in each specific case of its manifestation, different mechanisms of its pathogenesis and different levels of melanin formation in the skin can be involved. Skin is one of the most metabolically active organs. Carrying out a number of vital functions (barrier, protective, respiratory, excretory, metabolic, immune, etc.), it needs microelementss. Of the 92 naturally occurring chemical elements, 81 are found in the human body. Lack of the vital elements, leads to the emergence of diseases, which are based on deficiency, excess or imbalance of micro- and macroelements in the body. To assess the elemental status of patients with various forms of vitiligo, fluorescent x-ray spectroscopy was used. The method has good informativeness, since the hair most fully reflects the level of content of both toxic and vital elements.

According to the results obtained, in patients with segmental vitiligo, a slight decrease in the content of manganese and copper was detected in the hair. In the group of patients with non-segmental form of vitiligo, along with a significant decrease in the concentration of basic elements (on average from 20 to 50%) copper, manganese, selenium, zinc, there was an increase in the indices of such toxic elements as lead and cadmium.

The data of multi-element hair analysis, as are confirmed by well-known information about the role of certain chemical elements in the pathogenesis of vitiligo, also allow us to make new assumptions about the possible relationship between the violation of the microelement balance of the organism with the emergence and peculiarity of the flow of various forms of vitiligo. The correct approach to understanding the mechanisms of the emergence of vitiligo, will allow to offer new effective schemes for the treatment of vitiligo.

Keywords: segmental vitiligo, micro- and macroelements.

РЕЗЮМЕ

ОСОБЕННОСТИ ЭЛЕМЕНТНОГО СТАТУСА БОЛЬНЫХ ВИТИЛИГО

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Витилиго - мультифакторное заболевание, при котором в каждом конкретном случае его проявления, могут быть задействованы различные механизмы его патогенеза и разные уровни нарушения образования меланина в коже. Кожа является одним из наиболее метаболически активных органов. Выполняя ряд жизненно важных функций (барьерная, защитная, дыхательная, выделительная, обменная, иммунная) она нуждается в микроэлементах. Из 92 встречающихся в природе химических элементов, 81 обнаружен в организме человека. Недостаток жизненно важных элементов приводит к возникновению заболеваний, в основе которых лежит дефицит, избыток или дисбаланс микро - и макроэлементов в организме. Для оценки элементного статуса больных различными формами витилиго применен метод флюоресцентной рентгеновской спектроскопии волоса. Метод обладает высокой информативностью, так как в волосах наиболее полно отражается уровень содержания как токсичных, так и жизненно необходимых элементов.

Согласно полученным результатам у больных сегментарным витилиго выявлено незначительное понижение содержания в волосах марганца и меди. В группе больных несегментарной формой витилиго, наряду со значительным понижением концентрации основных элементов (медь, марганец, селен, цинк), отмечено повышение показателей таких токсичных элементов, как свинец и кадмий.

Полученные в результате проведенного исследования данные еще раз подтверждают значение роли определенных химических элементов в патогенезе хронических заболеваний. Все элементные дисбалансы объединяются рядом общих закономерностей развития. Все они сопровождаются нарушением иммунного гомеостаза со снижением иммунной резистентности.

რეზიუმე

ქიმიური ელემენტების სტატუსი ვიტილიგოთი დაავადებულ პაციენტებში

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი დერმატოვენეროლოგიის დეპარტამენტი; "საქარტველოს ვიტილიგოს ასოციაცია"; სამედიცინო ელემენტოლოგიის ცენტრი „ლაბორატორია ბიოელემენტი", თბილისი, საქარტველო

ვიტილიგო მულტიფაქტორული დაავადებაა, მისი ყოველი შემთხვევა დაკავშირებულია დაავადების პათოგენეზის ცალკეულ რგოლთან და კანში მელანინის წარმოქმნის დარღვევის სხვადასხვა დონესთან. კანი მეტაბოლურად აქტიური ორგანოა. მისი სიცოცხლისთვის მნიშვნელოვანი ფუნქციების შესრულებისათვის მრავალი მიკროელემენტი სჭირდება. ბუნებაში არსებული 92 ელემენტიდან 81 აღმოჩენილია ადამიანიას ორგანიზმში. სიცოცხლისთვის მნიშვნელოვანი ელემენტების უკმარისობა იწვევს დაავადებებს, რომლის მიზეზია მიკრო- და მაკროელემენტების დეფიციტი, სიჭარბე ან მათი დისბალანსია. ადამიანის ორგანიზმში მიკროელემენტთა შემცველობის შესაფასებლად, სხვა ბიოსუბსტრატებტან ერთად, მაღალი ინფორმტიულობით გამოირჩევა თმის ღერი, რადგან სწორედ თმაში წარმოებს მიკროელემენტების კონცენტრირება და იგი შედარებით სრულად ასახავს ტოქსიური და ესენციური ელემენტების შემცველობას.

მიღებული მონაცემების თანახმად ვიტილიგოს სეგმენტური ფორმის შემთხვევაში თმაში გამოვლინდა მანგანუმის და სპილენძის კონცენტრაციის უმნიშვმელო შემცირება. არასეგმენტური ვიტილიგოს შემთხვევაში ძირითადი ელემენტების (მანგანუმი, სპილენძი, თუთია, სელენი) კონცენტრაციის მნიშვნელოვან შემცირებასთან ერთად გამოვლინდა ზოგიერთი ტოქსიკური ელემენტების მაჩვენებლების მატება (ტყვია და კადმიუმი).

თმის მიკროელემენტების ანალიზის შედეგები ადასტურებენ კარგად ცნობილ მონაცემებს განსაზღვრული მიკროელემენტების მნიშვნელობაზე ვიტილიგოს პათოგენეზში და ასევე მიკროელემენტების ბალანსის დარღვევის სავარაუდო კავშირზე დაავადების სხვადასხვა ფორმის მიმდინარეობის თავისებურებებთან.

CHARACTERISTICS OF ARTICULAR SYNDROME IN SYSTEMIC VASCULITIS

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The prevalence of systemic vasculitis (SV) is steadily rising in the world, accounting 2-3 cases per 10 thousand population [8,14]. Currently, the study of SV refers to the most dynamically developing areas of rheumatology, while emphasizing both the clinical and pathogenetic commonality of these diseases, and certain differences of separate nosological forms [1,2,10]. Differential diagnosis is rather complicated, because the clinical symptoms of SV are characterized by the presence of "crossed syndromes" [3].

The articular syndrome is one of the main signs of Takayasu's arteritis (TAA) [5], microscopic polyangiitis (MPA) [20], Wegener's granulomatosis with polyangiitis (GPA) [16,17], cryoglobulinemic vasculitis (CGV) [12,19]. Joint damage in the form of arthritis or arthralgia is observed in 65-70% of the patient number with eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome (EPA) [9], in 40-50% of CGV [18], in 45-65% of Henoch-Shonlein purpura (HSP) [4,6,15], the knee and ankle joints are involved in the pathological process most often [7]. In MPA, the number of patients with musculoskeletal changes increases within the first 5 years after debut of the disease, when, among other things, the decrease in periarticular bone mineral density begins to develop [11].

It should be noted that in the contemporary literature, only the frequency of arthropathy in patients with SV is noted. The purpose and objectives of this study are the research of separate joint lesion in TAA, MPA, GPA, EPA, HSP, CGV and polyarteriitis nodosa (PAN), their X-ray sonographic characteristics, the relationship between severity of articular syndrome and extraarticular manifestations of diseases, and the aspects of the arthritis pathogenesis in such category of patients.

Material and methods. Under supervision were 525 patients with SV, the characteristics of which are presented in Table. 1. The ratio of the patients' number with HSP, MPA, CGV, PAN, TAA, GPA and EPA was 7: 4: 3: 1: 1: 1: 1. According to the generally recognized Chapel Hill nomenclature (USA, 2012), TAA refers to SV of large-vessels, PAN-medium. Small vessel vasculitis includes GPA, EPA and HSP, which is characterized by IgA-dominant immune deposits in the small blood vessels, and CGV, in which cryoglobulin immune deposits are responsible for small blood vessel vasculitis What is more, MPA, GPA and EPA are associated with antineutrophil cytoplasmic antibodies, HSP and CGV are immune complex SV [13]. Women tend to prevail in TAA, men – in PAN, at a ratio of 3: 1 and 2: 1 respectively, younger age patients were with HSP, and older - with CGV. It should be emphasized that the clinical characteristics of patients are presented at the time of their examination. So, at the previous stages, all examined with MPA, HSP and CGV had skin changes, 93% with HSP - joint syndrome. In cases of PAN, MPA and CGV, peripheral nervous system lesions (mono- and polyneuropathy, radiculopathy, and motron metatarsalgia) were exceeded, and the central nervous system lesions (discirculatory encephalopathy, cerebral circulation violation, corticoneural and pseudobulbar syndromes) prevailed in patients with TAA and GPA. 55% of TAA patients had aortic heart disease, 17% had myocardial infarction, 21% - a cerebral stroke. 36% patients with PAN were carriers of viral hepatitis B antigen (HBV), and 29% patients with CGV - hepatitis C (HCV). Cryoglobulins were detected in 97% of the patients with CGV at the time of the examination, increased level of immunoglobulin (Ig) A - in 72% of the patients with HSP, antineutrophil cytoplasmic antibodies - in 75% with GPA, in 71% with MPA and 57% with EPA (the ratioes of antibodies to myeloperoxidase and proteinase-3 were 1: 6, 2: 1 and 8: 1 correspondingly). The level of eosinophils in blood of the patients with EPA was 15.1±2.12% of the number of white blood cells or 2.1±0.82 10^9/l.

X-ray examination of peripheral joints, sacroiliac joints, spine and lungs was performed on the "Multix-Compact-Siemens" apparatus (Germany), ultrasound examination of joints and internal organs - on "Envisor-Philips" (Netherlands), electrocardiographic - on «MIDAC-EK1T» (Ukraine) and «Bioset-8000» (Germany), echocardiographic - on «HD-11-XE-Philips» (Netherlands), spirographic - on «Master -Scope-Jaeger »(Germany), study of the alveolar-capillary membrane – on «Master-Screen-Body-Jaeger »(Germany). "BS-200" and "Olympus-AU640" analyzers (Japan), "PR2100-Sanofi diagnostic Pasteur" reader (France), immunoblot "Euroline-Euroimmun" (Germany), computer tensiometers «ADSA-Toronto» (Germany-Kana-da) and «PAT2-Sinterface» (Germany) were used to evaluate the laboratory indices.

The number of painful joints (NPJ), the Lunsbury indices (iL), iDAS and iDAS28 were estimated, the integrated severity of arthropathy index (iSA) were calculated by the formula:

$iSA = \sqrt{iL} \bullet DAS.$

The statistical processing of the obtained research results was carried out using a computer variational, nonparametric, correlation, one (ANOVA) and multivariate (ANOVA / MANOVA) dispersion analysis (programmes "Microsoft Excel and Statistica-Stat-Soft», USA). Mean values (M), their standard errors (m), standard deviations

Table 1. Characteristics of the examined patients with SV

Indices	Group of patients with SV (n=525)						
	TAA	PAN	MPA	GPA	EPA	HSP	CGV
Number of patients in groups	29	39	116	28	27	193	93
Men/women %	24/76	62/38	41/59	57/43	44/56	51/49	41/59
Age (M±m), years	44,2±2,48	44,2±1,88	44,8±1,23	46,0±2,41	40,4±2,59	26,2±0,72	52,3±1,28
Duration of the disease (M±m, years)	10,4±1,98	8,5±1,30	6,4±0,70	4,3±0,83	10,7±2,05	9,0±0,60	4,6±0,62
II-III stage of activity, %	86	79	85	93	85	72	92
Acute course, %	–	15	28	56	–	19	43
Signs of lesion, %							
skin	17	31	82	21	52	64	85
skeletal muscle	48	54	38	36	37	15	26
heart	76	80	51	50	48	31	61
liver	28	56	56	46	33	22	62
spleen	4	13	8	7	19	7	25
nervous system	21	90	48	46	37	18	40
kidney	62	62	67	64	56	67	68
Kidney failure, %	35	26	35	29	26	18	32
Glomerular filtration rate, ml/min	107,1 ±4,78	104,4 ±4,18	101,2 ±2,51	108,2 ±3,99	110,5 ±4,34	110,3 ±1,92	103,3 ±2,68

(SD), correlation coefficients, dispersion criteria, Student, Wilcoxon-Rao, McNamara-Fischer and reliability of statistical indicators were estimated.

Results and their discussions. Such joint lesions as arthritis or arthralgia, are noted in 32% of patients with GPA, in 41% patients with TAA, 47% - with HSP, 52% - with PAN, 63% - with MPA and EPA, 67% - CGV, and monoaligoarthritis - in 33; 50; 54; 25; 58; 18 and 50% of observations respectively. According to the one-factor dispersion analysis, the development of articular syndrome in MPA is influenced by changes in skeletal muscles and lungs, in GPA – by the duration of the disease, changes in the skin, heart and liver, in HSP – by the age of the patients, degree of the pathological process activity, skin lesions and kidneys, in EPA - only by skin syndrome, in CGV – by myositis/myalgia, pneumopathy and nephropathy. The occurrence of arthropathy depends on the severity of extra-articular manifestations of PAN, MPA, GPA, HSP, CGV.

Taking into account the frequencies of arthropathy formation in MPA and CGV, we conducted an additional analysis. It turned out that the articular syndrome in patients with MPA is reliably affected by the indicators of the ratio between systolic pressure in the pulmonary artery to the peripheral arterial pressure and diffusion capacity of the lungs, and in cases of CGV - parameters of pulmonary vascular resistance and end diastolic volume of the right ventricle.

As demonstrated by the performed ANOVA, the character of articular syndrome in TAA depends on the parameters of fibrinogen in blood, in PAN - on the concentration of circulating immune complexes and antibodies to native deoxyribonucleic acid (aDNA), in MPA - on the level of antibodies to proteinase-3, in GPA - on the content of the latter and the values of fibronectin in blood, in EPA - on C-reactive protein indications in blood and the presence of antibodies to myeloperoxidase, in HSP - on parameters of IgA, indices of platelet and red blood cells aggregation, thromboxane A2, prostacyclin and prostaglandin E2, in CGV - on tumor necrosis factor-γ, endothelin-1 and prostaglandin F_{2a}. It is necessary to emphasize that in PAN there is a significant influence HBV-carrier on the development of joint lesions. In such patients, the joint syndrome is detected in all cases, whereas it is only in 48% of cases without HBV (the differences are high-significant).

The frequency of the separate joint involvement in the pathological process and the presence of X-ray sonography signs of arthropathy are represented in generalized form in table. 2,3 at that features of the articular syndrome in patients with different variants of SV have been revealed. For EPA, there were typical lesions of vertex and sternoclavicular joints, for AAT - proximal interphalangeal joints of hand, humeral and knee articulations, for PAN - ulnar and metatarsophalangeal, for MPA - wrist and ankle, for CGV - sacroiliac and vertebra. In turn, the changes in the sternoclavicular junctions refer to the "joints-exclusion" in AAT, GPA and CGV, ankle, sacroiliac and vertebrae – in GPA, elbow – in TAA, shoulder –in EPA and CGV.

There are typical changes in meniscus horns and the presence of intra-articular bodies of Pellagri-Shtaydi and Hoff for TAA, and Baker cysts - for PAN. Tendovaginitis

Table 2. Typical and atypical signs of arthropathy in patients with SV

	TAA	PAN	MPA	GPA	EPA	HSP	CGV
1					⊕		⊗
2	⊗			⊗	⊕		⊗
3	⊕						
4							
5			⊕			⊕	
6	⊗	⊕				⊕	
7	⊕				⊗		⊗
8							
9		⊕					
10			⊕	⊗			
11	⊕						
12							
13				⊗			⊕
14	⊗			⊗			⊕

Joints: 1 - maxillary; 2 - sternoclavicular; 3 - proximal interphalangeal of hands; 4 - metacarpophalangeal; 5 - wrist; 6 - ulnar; 7 - humeral; 8 - proximal interphalangeal of foot; 9 - metatarsophalangeal; 10 - ankle; 11 - knee; 12 - hip; 13 - sacroiliac; 14 - vertebrae. Å - typical signs; Ä - absence of signs

Table 3 Typical and atypical symptoms of musculoskeletal system lesions in patients with SV

	TAA	PAN	MPA	GPA	EPA	HSP	CGV
I	⊗	⊕	⊗				⊕
II	⊗		⊗	⊗			
III							
IV		⊕		⊗	⊕		
V		⊕			⊕		⊗
VI	⊗			⊗	⊗		⊗
VII			⊗	⊗			
VIII			⊗	⊗			⊗
IX			⊗	⊗			
X	⊕	⊕		⊗			
XI	⊗			⊗			
XII	⊕			⊗			
XIII				⊗			
XIV	⊕						

Symptoms: I - tendovaginitis; II - enthesopathy; III - epiphyseal osteoporosis; IV - subchondral sclerosis; V - osteocystis; VI - osteousuras; VII - ligamentosis; VIII - aseptic necrosis; IX - arthrocalcinates; X - changes in the meniscus; XI - Baker's cysts; XII - bodies of Pellagri-Shtaydi; XIII - chondromic bodies; XIV - the bodies of Hoff; Å - a typical symptom; Ä - absence of a symptom

can be considered typical for PAN and CGV, subchondral sclerosis and osteocystosis - for patients with GPA and EPA. It is noted the absence of cases of tendovaginitis and entesopathy in TAA and MPA, and on the whole a scanty variety of "x-ray sonographic landscape of articular syndrome" in cases of GPA.

According to the multifactorial analysis of Wilcoxon-Rao, the character of the arthropathy course in patients with MPA depends on the lung and heart lesions, in the case of HSP - on the involvement of lung and liver, in CGV - on renal pathology and integral gravity of extraarticular signs of the disease. As ANOVA / MANOVA testifies, the integral X-ray and sonographic signs of joint changes in patients with PAN depend on the disease ac-

Table 4. Indices of joint syndrome in patients with SV (M±m)

SV	Index				
	NPJ, abs	IL, balls	iDAS, r.u.	iDAS 28, r.u.	iWA, r.u.
TAA	10,6±3,10	78,7±14,38	2,4±0,50	3,4±0,51	22,7±6,10
PAN	11,9±2,68	60,6±9,30	2,2±0,32	2,9±0,32	19,3±4,25
MPA	8,5±1,38	58,7±4,85	1,7±0,19	2,7±0,20	15,0±2,29
GPA	14,4±4,79	48,0±17,07	2,3±0,62	3,3±0,67	18,8±8,33
EPA	13,1±2,91	60,8±12,12	2,0±0,27	2,9±0,29	16,7±4,11
HSP	7,7±0,87	60,8±4,54	1,5±0,18	2,5±0,19	13,9±2,10
CGV	7,3±1,32	53,8±4,37	1,2±0,09	2,2±0,10	9,5±1,26

tivity degree and the severity of extraarticular manifestations, with MPA - on the nature of nephropathy, and with HSP - pneumopathy.

As performed by ANOVA, the age of patients with TAA, PAN, MPA and EPA affects the frequency of the maxillary articulation lesions. The changes in proximal interphalangeal joints of brushes closely related with the age of the patients with TAA, knee joints - with PAN, sternoclavicular, wrist and proximal interphalangeal feet - with MPA, wrist and shoulder - with HSP. The presence of cardiopathy (disturbance of myocardial excitability, electrical conduction of the heart, changes in the myocardium, endocardium and cardiac valves, diastolic and systolic dysfunction of the left ventricle) have a dispersive effect on the lesions of proximal interphalangeal joints of the fingers, wrist and ankle in patients with TAA, but only on the wrist - with CGV. Metatarsophalangeal articulation lesion in TAA depend on the nature of nephropathy (urinary or nephrotic syndrome, the condition of kidney function), in the case of PAN - wrist, CGV - proximal interphalangeal foot and hip.

The origin of tendovaginitis in PAN and EPA is closely related to hepatic pathology, entesopathy in MPA and HSP - to renal disease. The appearance of intraarticular bodies (chondromic, Pellagri-Shtaydi, Hoff) occurs in parallel with an increase of the disease duration in TAA patients, and they are determined by the severity of the skin-muscular syndrome in PAN patients. Bone-destructive signs of the musculoskeletal system disorders depend on extraarticular manifestations of SV. It should be noted that Baker's cysts in MPA and lesions of the maxillary joints in HSP are observed exclusively in men, whereas the incidence of lesions of proximal interphalangeal joints of brushes and metacarpophalangeal joints in patients with HSP significantly prevails in the female group, respectively in 3,7 and 3.2 times.

As can be seen from Table. 4, the greatest number of painful joints (NPJ) is peculiar to patients with GPA, and the greater integral severity of the joint syndrome is typical for patients with TAA. According to the dispersion analysis, parameters of NPJ in PAN are closely related to the severity of skin lesions, in MPA - to acute course of the disease, in HSP - to changes in the nervous system and in CGV - to severity of hepatic pathology.

The degree of severity of articular syndrome assessed by iSA, in PAN and HSP depends on the functional state of the kidneys, in MPA and HSP - on the integral severity of the extraarticular signs of the disease. In addition, iSA is affected by the overall disease activity in the group of patients with HSP. Whereas the severity of arthropathy grows with an increase in the duration of MPA course, then in patients with HSP its decreases (Fig. 1). In turn, in both groups of SV patients, iSA grows, according to the increase in the integrated severity of extrarenal manifestations of diseases (Fig. 2).

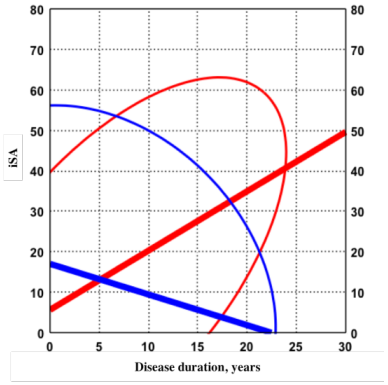

Fig. 1. The relationship between iSA indicators with MPA duration (red curves) and HSP (blue)

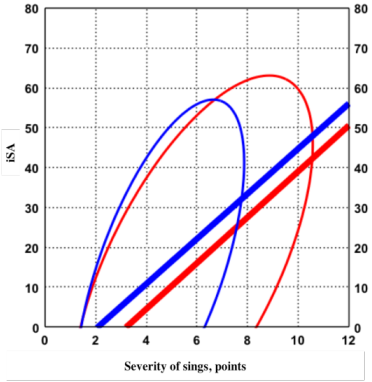

Fig. 2. The relationship between iSA indicators and the severity of MPA symptoms (red curves) and HSP (blue)

The prevalence of articular syndrome in patients with TAA is significantly influenced by the indices of circu-

lating immune complexes in blood and antibodies to cardiolipin, with MPA – by levels of rheumatoid factor (RF), fibrinogen, aDNA, endothelin-1, homocysteine and module of viscoelasticity of blood serum, with GPA – by concentration of RF, antibodies to myeloperoxidase, IgG, cyclic guanosine monophosphate and surface viscosity of blood, with HSP - aDNA, anti-cardiolipin and tumor necrosis factor-α, with CGV - RF and IgM. The severity of the joint syndrome course in cases of AAT, PAN and MPA is associated with the seropositivity of the diseases by RF, GPA - with the presence of antibodies to proteinase-3, EPA - with the content of fibronectin, HSP - with levels of IgA, b2-microglobulin and RF, CGV - with bulk viscosity, surface elasticity, relaxation with thromboxane A2. According to the correlation analysis, iSA index directly relates to RF parameters in blood in patients with MPA, and vice versa - with its viscoelasticity, and in patients with HSP - to IgA concentration, with CGV - to the level of thromboxanemia.

Taking into account the statistical processing of the obtained results of studies, relevant conclusions having a certain practical importance have been made: 1) prognostic factors with respect to the frequency of development and course of joint pathology in patients with PAN are HBV-carrier, and in MPA, HSP and CGV - severity of extraarticular signs of diseases; 2) RF parameters in blood in TAA, PAN, MPA, HSP and CGV > 20 IU / ml (> M±SD patients with SV) are considered risk factors for the severe course of arthropathy.

Conclusion. Such joint damage as arthritis or arthralgia is revealed in 32% of patients with GPA, 41% - with AAT, 47% - with HSP, 52% - PAN, 63% - MPA and EPA, 67% - CGV, which has gender differences, depends on the duration of the disease, the degree of activity of the pathological process, the severity of extra-articular signs, lung function and the state of hemodynamics in the lesser circulation, the frequency of lesions of individual bone articulations, tendovaginitis, enthesopathy and X-ray sonography signs of the joint syndrome. There has been its own dimorphism in different nosologies, in patients with PAN it is associated with the carriage of HBV, and in the pathogenetic constructs of arthropathy in SV there are disorders of the immunity system (immuno-inflammatory proteins, cytokines, various antibodies), rheological properties of blood and endothelial functions of blood vessels. And the high RF parameters in blood are risk factors for the severe course of joint damage in cases of TAA, PAN, MPA, HSP and CGV.

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SUMMARY

CHARACTERISTICS OF ARTICULAR SYNDROME IN SYSTEMIC VASCULITIS

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The purpose of the study – investigation the separate joint lesion in systemic vasculitis, their X-ray sonographic characteristics, the correlation of the articular syndrome severity with extra-articular manifestations of the diseases, as well as aspects of the arthritis pathogenesis in this category of patients.

The study included 525 patients in the ratio of the examined with Henoch-Schonlen purpura, microscopic polyangiitis, cryoglobulinemic vasculitis, polyarteritis nodosa, Takayasu's arteritis, Wegener's granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis Churg-Strauss as a 7:4:3:1:1:1:1. Joint's damage in the form of arthritis or arthralgia observed in 32-67% different groups of patients, that depending on the disease duration, the degree of the pathological process's activity, extraarticular signs severity, lung parenchyma involving and hemodynamic status in the pulmonary circulation. The frequency of the certain bone lesions, existence of tenosynovitis and enthesopathies, X-ray sonographic signs of articular syndrome in different kind of vasculitis has its own gender dimorphism. The immune system malfunction, the rheological properties of blood and endothelial function of vessels collaborate in pathogenetic constructions of arthropathy. What is more, the high value of rheumatoid factor in blood associates with severe course of joint damage. Joint syndrome at different variants of systemic vasculitis is progressing in 1/3-2/3 of cases, this syndrome has definite features of clinical course and pathogenesis.

Keywords: vasculitis systemic, joints, clinic, pathogenesis.

РЕЗЮМЕ

ХАРАКТЕРИСТИКА СУСТАВНОГО СИНДРОМА ПРИ СИСТЕМНЫХ ВАСКУЛИТАХ

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Целью исследования явилось изучение поражения отдельных суставов при системных васкулитах, их рентгеносонографических особенностей, взаимосвязи тяжести артикулярного синдрома с внесуставными проявлениями заболеваний, а также аспектов патогенеза артритов у данной категории больных. Под наблюдением находилось 525 больных. Соотношение числа обследованных с васкулитом Шенлайна-Геноха, микроскопическим полиангиитом, криоглобулинемическим васкулитом, узелковым полиартериитом, аортоартериитом Такаясу, гранулематозом с полиангиитом Вегенера и эозинофильным гранулематозным полиангиитом Черджа-Стросса составило 7:4:3:1:1:1:1. Поражение суставов в виде артрита или артралгий наблюдалось у 32-67% больных в разных группах. Тип поражения суставов при выше перечисленных заболеваниях зависел от длительности заболеваний, степени активности патологического процесса, тяжести экстраартикулярных признаков, вовлечения в процесс легочной паренхимы и состояния гемодинамики в малом круге кровообращения. Частота поражений отдельных костных сочленений, наличие тендовагинитов, энтезопатий и рентгеносонографических признаков суставного синдрома при разных васкулитах имеет свой гендерный диморфизм. В патогенетической этиологии артропатии участвуют нарушения иммунной системы, реологических свойств крови и эндотелиальной функции сосудов. Высокие уровни ревматоидного фактора в крови ассоциированы с риском развития тяжелого течения суставного синдрома.

Суставной синдром при разных вариантах системных васкулитов развивается в 1/3-2/3 случаев, имеет свои особенности патогенеза и клинического течения.

რეზიუმე

სახსროვანი სინდრომის დახასიათება სისტემური ვასკულიტების დროს

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კვლევის მიზანს შეადგენდა სისტემური ვასკულიტების დროს ცალკეული სახსრის დაზიანების, მათი რენტგენოსონოგრაფიული თავისებურებების, არტიკულურ სინდრომსა და დაავადებების არასახსროვან გამოვლინებებს შორის ურთიერთკავშირის, ასევე, ამ კატეგორიის პაციენტებში ართრიტის პათოგენეზის ასპექტების შესწავლა. დაკვირვების ქვეშ იმყოფებოდა 525 პაციენტი.

გამოკვლეულ პაციენტთა თანაფარდობა შენ-

ლაინ-ჰენოხის ვასკულიტით, მიკროსკოპიული პოლიანგიიტით, კრიოგლობულინემიური ვასკულიტით, კვანძოვანი პოლიარტეტიიტით, ტაკაიასუს აორტოარტერიიტით, გრანულომატოზით ვეგენერის პოლიანგიიტით და ჩერჯ-სტროსის გრანულომატოზური პოლიანგიიტით შეადგენდა 7:4:3:1:1:1:1–ს. სახსრების დაზიანება ართრიტის, ან ართრალგიის სახით პაციენტთა სხვადასხვა ჯგუფში აღინიშნა შემთხვევათა 32-67%-ში. სახსრების დაზიანების ტიპი ზემოჩამოთვლილი დაავადებების დროს დამოკიდებული იყო დაავადების ხანგრძლივობაზე, პათოლოგიური პროცესის აქტივობის ხარისხზე, სახსარგარე ნიშნების სიმძიმეზე, პროცესში ფილტვის პარენქიმის ჩართულობასა და ჰემოდინამიკის მდგომარეობაზე სისხლის მიმოქცევის მცირე წრეში. ცალკეულ ძვალთშესახსრების დაზიანები სიხშირეს, ტენდოვაგინიტების, ენტეზოპათიების და სახსროვანი სინდრომის ნიშნების არსებობას სხვადასხვა ტიპის ვასკულიტის დროს ახასიათებს გენდერული დიმორფიზმი. ართროპათიის პათოგენეზურ ეტიოლოგიაში მონაწილეობს დარღვევები იმუნურ სისტემაში, სისხლის რეოლოგიურ თვისებებსა და სისხლძარღვების ენდოთელურ ფუნქციაში. სისხლში რევმატოიდული ფაქტორის მაღალი მაჩვენებლები ასოცირებულია სახსროვანი სინდრომის მძიმე მიმდინარეობის განვითარების რისკთან.

სახსროვანი სინდრომი სისტემური ვასკულიტის სხვადასხვა ვარიანტის დროს ვითარდება შემთხვევათა 1/3-2/3-ში, აქვს პათოგენეზის და კლინიკური მიმდინარეობის თავისებურებანი.

ASSESSMENT OF NEURODEVELOPMENTAL OUTCOMES IN INFANTS 6-12 MONTHS OF AGE ACCORDING TO IMPACT OF PERINATAL RISK FACTORS

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Infants exposed to some perinatal risk factors are at increased risk of neurodevelopmental problems throughout early childhood. Multiple risk factors are associated with increased risks of perinatal morbidity and mortality, however long term neurodevelopmental outcome of survivors is poorly described. According to literature data infants were significantly more likely to have neurodevelopmental impairment compared to healthy control infants, when assessed at 6-12 months and 2-3 years of age [1,12].

Studies have suggested that some early-childhood neurosensory and developmental outcomes for some groups of infants, who were born with some neonatal pathologies, such as extremely prematurity [4], neonatal infections and early-onset sepsis [3], hypoxic-ischemic encephalopathy, CNS malformation, intracranial hemorrhage [17] and others, thereafter were become critically ill during the neonatal period and were treated, but stayed at risk for adverse neurodevelopmental outcomes, have improved over the last decade. Even so it is not clear whether this trend applies to population of infants, who born healthy, but had been impacted by pathologies of pregnancy/delivery or other perinatal risks.

Authors have usually presented a single-center analysis, which have shown influence of separate factors identified as important risk factors. Major neurologic abnormalities, cognitive delays and impairs psychomotor development during the first year of life are presented in all cases of studied population [17]. There are identified significant correlations between these single risk factors, related to neonatal pathologies, and neurodevelopmental adversities. However, there are no large, recent analyses to examine whether neurodevelopmental outcomes improved, worsened, or remained the same for those vulnerable infants born healthy, but impacted by combination of factors and pathological conditions related to their development before birth.

Literature was reviewed the associations between some maternal pathological conditions exposure during pregnancy and labor with child neurodevelopment, which were stronger at neonatal period than at older ages. At the same time, information about the persistence of this association at later ages is limited.

The purpose of this research was: a. assessment of risk predictors for adverse neurodevelopmental outcome at age of 6 month and 12 month in divided groups of infants, partition of which had implemented by birth as healthy or with neonatal pathologies and b. to report developmental follow-up data from a case-control prospective study of infants exposed to separate and combination impact of risk factors.

Material and methods. Between January 2015 and December 2016, we prospectively enrolled 1018 live-born infants, information about which we had received from the medical reports of the participating clinics in Tbilisi (capital of Republic of Georgia) and Mtskheta, Dusheti (districts of Georgia), and included them in the study.

At the first stage of research it was conducted descriptive population-based prospective pilot study, as a result of which:

a. were defined three study groups: I (Low Risk) Group with healthy born 715 newborns; II (Risk) Group with healthy 215 newborns born from pathological pregnancy and/or delivery and III (High Risk) Group with 88 newborns born with different disorders manifested at neonatal period;

b. was revealed risk factors, which were common (distinguished by high prevalence rates) and highly associated (characterized by high reliability risk ratio measures) with epidemiological distribution of the pathological conditions (such as "maternal age <17Y>35Y", "pathologies of pregnancy", "pathologies of delivery", "gestation age of newborns <37 week"), and outcomes of newborns, as described in previous publication.

Within second phase of research, including postnatal follow-up, the children from whole population were assessed at 6 and 12 months of age by a family doctors who was not involved in the care of these children during the neonatal period. During these visits the examinations were performed in following areas of function: Gross motor, Fine motor, Language, Personal-social (consisted of a developmental, neurological and behavioral assessments; medical history; and parent interviews) by using the Denver Developmental screening Test (Denver II). For the developmental category of infants there were established two means of variability: "normal development" and "abnormal development".

Epidemiological measurements, such as point prevalence (PP) and odds ratio (OR) of impact of risk factors, were investigated to quantify how strongly the presence or absence of risk factors were associated with the two ways (normal or abnormal development) of infant's development in a given population.

Point prevalence measured like the proportion (expressed as a percentage) of newborns, who was influenced by determined risk factors at a particular date of medical examinations by the formula: Point Prevalence = Number of existing cases of infants within an exposed group (affected by a particular single risk factor) ÷ Number of infants in whole study group on this date x 100%.

The odds ratio (OR), its standard error and 95% confidence interval are calculated according to Altman, 1991. Test of significance: the P-value is calculated according to Sheskin, 2004 (p. 542).

The association between the candidate risk factors and delayed motor or mental development, described as normal or abnormal development, was analyzed by Chi-square test of independence. Statistical analysis of these data was performed using the SPSS version 12.0.1 (SPSS Inc., Chicago, IL). A P value of less than 0.05 was considered significant.

Results and their discussion. *1.1 Statistical measurements of neurodevelopmental outcomes*

There was a great difference of the developmental outcomes evaluated neurologically and by Denver II test at age of 6 month and 12 month and the appropriate values of their prevalence between the risk groups.

At the first stage of evaluation (conducted at age of 6 month) abnormal development was identified totally in 92 cases (PP-9.0% from whole population). These cases were distributed in groups: in groups with infants estimated at the time of birth as healthy developmental impairments were identified in 8 cases in I study group (PP – 1.1% from 715 infants) and 27 cases in II Group (PP – 12.6% from 215 infants). On the other hand, in most vulnerable III Group (where were placed newborns because of born with some neonatal pathologies) critically large amount of infants had been assessed as abnormal (PP – 64.8% or 57 cases from 88 infants).

At the second stage of research (at age of 12 month) the number of infants with some neurological developmental abnormalities was decreased to 36 cases (PP- 3.5%) in whole population: to 2 cases in I Group (PP – 0.3%), to 13 cases in II Group (PP – 6.1%) and to 21 cases in III Group (PP – 23.9%) particularly (Table 1).

In I Low Risk Group only "maternal age" (giving birth at age 17 years/less and 35 years/over) and "birth before 37 weeks of gestation" were defined as risk factors (totally 34 cases), the impact of risk factors, such as pathologies of pregnancy and/or delivery, were not observed there. Infants included in II Risk Group and III high Risk Group (totally 290 cases) were under the influence by at least one of the four researched risks, such as «pathologies of pregnancy», «pathologies of delivery», «maternal age (<17Y, >35Y)»(exceptionally in III Group the impact of any factor was not observed for the 13 infants, but there were revealed some neonatal pathologies).

Table 1. Distribution of the neurological outcomes among groups

Risk Groups	Total number (% from whole population)	Assessment Age	Number of infants with Abnormal Development	Point Prevalence (PP-%) inside groups
I - Low Risk Group	715 (70.2%)	6 month	**8**	**1.1%**
		12 month	**2**	**0.3%**
II - Risk Group	215 (21.1%)	6 month	**27**	**12.6%**
		12 month	**13**	**6.1%**
III – High Risk Group	88 (8.7%)	6 month	**57**	**64.8%**
		12 month	**21**	**23.9%**

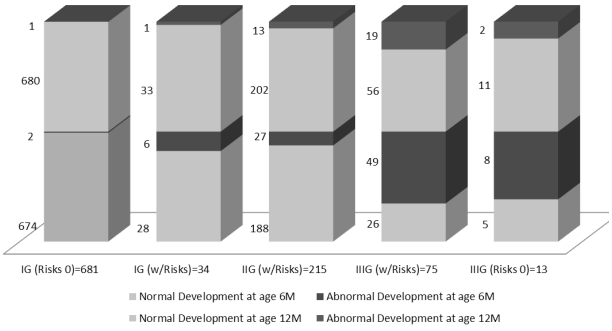

Fig. 1. Distribution of outcomes in groups in relation to risk factor's influence

In that part of the population, who hadn't affected by any researched risks (681 cases from I Group and 13 cases from III Group), evaluation at the age of 6 month revealed infants with abnormal development: 2 cases in I Group and 8 cases in III Group (totally 10 cases), evaluation at the age of 12 month – 1 cases in I Group and 2 cases in III Group (totally 3 cases), respectively. While in the other part of population influenced by some risk factors (324 cases from all groups) number of infants with abnormal development was totally 82 at the age of 6 month (6 from I Group, 27 from IIG and 49 from III G) and 33 at age of 12 month (1 from I Group, 13 from IIG and 19 from III G).

Accordingly, the prevalence of neurodevelopmental adversities at the end of one year study period, measured within the population of healthy born children, was 0.1% if it was not revealed the influence of studied risk factors and increased to 1.5% as a result of impact of risk factors. On the other hand, prevalence of observed abnormal development, measured within infant's population, who was diagnosed as having neonatal pathology, was 2.3% if risk factors were not exposed, and increased to 21.6% under influence of risk factors.

Statistical analysis showed that an abnormal developmental outcomes were more frequent when researched risk factors were exposed (OR-23.18, CI 95% - 11.83 to 45.41 - at age of 6 month; OR – 26.12, CI 95% - 7.95 to 85.85 – at age of 12 month) as well, as correlation of these risk factors with neurodevelopmental adverse outcomes was significant ($p<0.001$).

1.2 Correlations between separate risk factors and outcomes

To evaluate the importance of each risk factor selected 1018 children, according to presence or absence of this factor, were divided all time into two sub-groups: first group with exposed risk factor and second control group – without risk factor exposition. The chi-square test of independence had been used for calculation of association between two categorical variables – "risk factor exposition" and positive/negative outcomes (expressed through terms – "normal development" or "abnormal development").

Maternal age and neurodevelopmental outcomes

In the group of infants with maternal age of 17-34YY there were less cases of neurodevelopmental abnormalities (PP-3.2% or 27 cases), than in the group with maternal age <17Y>35Y (PP-37.7% or 66 cases). Statistical analysis by chi-square test of independence revealed a significant correlation between maternal age and neurodevelopmental outcomes at age of 6 month as well, as at age of 12 month ($p<0.001$).

Pathologies of pregnancy and neurodevelopmental outcomes

Anemia, preeclampsia/hypertension, nephropathy/urinary tract infections, gestational diabetes, habitual aborter with current pregnancy, poor fetal growth, excessive fetal growth, placenta previa without hemorrhage, hemorragia from placenta previa were regarded as pathologies of pregnancy in this study. In sub-group of infants with maternal pathologies of pregnancy (118 cases from II Group and 46 cases from III Group) there were more cases of neurodevelopmental disorders (PP - 29.9%) than in group of infants who hadn't been influenced by these maternal pathologies (PP – 5.0%). There was founded that occurrence of the adverse neurodevelopment in presence of maternal pathologies of pregnancy was significantly higher than in absence of its particular exposure at age of 6 month (OR-8.04 CI 95% - 5.11 to 12.65 $p<0.01$) as well as at age of 12 month (OR – 10.55 CI 95% - 5.22 to 21.32 $p<0.01$).

Table 2. Evaluation of risk factors for neurodevelopmental outcomes by chi-square test of independence

Risk Factors	OR		CI 95%		P
	6M	12M	6M	12M	
Maternal Age <17Y >35Y vs =17-34YY	19.03	12.61	11.5875 to 31.2412	6.0740 to 26.1627	0.001
Pathological/ Normal Pregnancy	8.04	10.55	5.1050 to 12.6505	5.2241 to 21.3164	0.01
Pathological/ Normal Delivery	5.76	3.73	3.60 to 9.22	1.82 to 7.67	0.05
Gestation Age <37 weeks vs >37 weeks	37.76	58.83	21.46 to 66.45	27.05 to 127.95	0.000

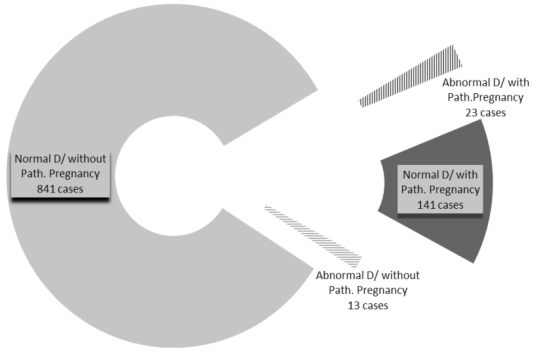

Fig. 2. Developmental outcomes at age of 12 month in relation to influence of pathological pregnancy

Pathologies of delivery and neurodevelopmental outcomes

In this study group there were revealed premature rupture of membranes, unengaged head at term and prolonged delivery as pathologies of delivery. From a total population pathological deliveries were found in II group (in 97 cases) and in III group (in 1 cases with single exposure and in 30 cases combined with other risk factors). Prevalence of abnormal development of infants within this subgroup was distributed: PP-28.1% at age of 6 month and 9.4% at age of 12 month. However, exclusively higher rate of prevalence has been observed in children with a combined effect of risk factors. Performing chi-square test, the correlation of risks of pathological deliveries with neurodevelopmental outcomes was measured as significant at age of 6 month (OR-5.76 CI 95% - 3.60 to 9.22 $p<0.05$) as well as at age of 12 month (OR – 3.73 CI 95% - 1.82 to 7.67 $P<0.05$).

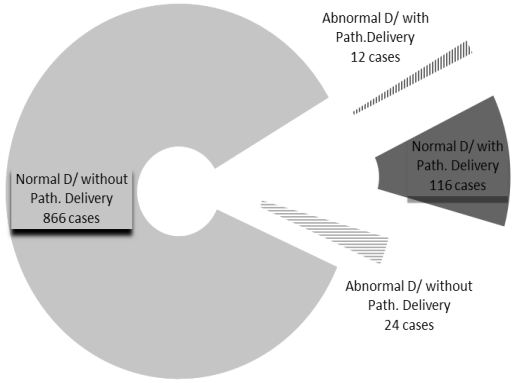

Fig. 3. Developmental outcomes at age of 12 month in relation to influence of pathological delivery

Gestation age and neurodevelopmental outcomes

74 (7.3%) of the infants in whole population were born preterm, 48 of them (64.9%) had abnormal 6-month neurodevelopmental scores and then 23 of them (31.1%) again had 12-month developmental scores discrepancies. Compared with appropriate for gestational age infants, small for gestational age infants showed a significantly high risk of farther neurodevelopmental outcomes (OR – 37.76 CI 95% - 21.46 to 66.45 $P<0.001$) at age of 6 month and this association had been maintained at age of 12 month (OR – 58.83 CI 95% - 27.05 to 127.95 $P<0.001$).

The terms “adverse neurodevelopmental outcomes” and “abnormal development” are relatively new terms and includes a group of disorders with affected normal development of children caused by alterations in early brain growth, including intrauterin formation process [15]. Most neurodevelopmental impairments at an early age are associated with a life-long endurance and have a severe impact on normal brain functioning in adulthood [15]. The various adverse neurodevelopmental outcomes show similar features, including brain dysfunctioning (such as difficulties in sensor and motor systems, problems with speech and language) and a number of cognitive impairments (e.g. in learning and organizational skills) [1,11].

Our study has evaluated the prevalence of “abnormal neurodevelopmental outcomes” during first year of children’s life, equal to 9.0% at age of 6 month and 3.5% at age of 12 month in whole population. Literature exist a substantial difference in the prevalence of psycho-motor development for age with the WHO standard, showing a lower prevalence beginning at age 6 months. Most of them identify 7-11% of children aged 6-23 months as having developmental delays for age, whereas the standard identifies <3% [16]. For children aged 18-23 months, the differences in psycho-motor development for age essentially decrease as well as become clear the clinical features of neurodevelopment and improve the methods of clinical assessment.

Second important result of our research is the measurement of how it has been changed the values of prevalence during the first year of development within three risk groups of children. As expected, the smallest indicators were revealed and the prevalence rate was reduced significantly from 6 month to 12 month in I (Low Risk) Group – from 1.1% to 0.3% (-73%), however, in healthy born children from II (Risk) Group it was observed the least significant improvement – from 12.6% to 6.1% (-48%), that suggests about the difficulties in clinical evaluation of minor delays of children neurodevelopment at an early age and about need to distinguish the risk group of healthy born children with some criteria, described by the authors [4,7,13], which will be screen more detailed and frequently.

The majority of modern researches have studied prevalence of neurodevelopmental outcomes among children with neonatal pathologies, such as prematurity, low birth weight, cerebral palsy, epilepsy, neonatal sepsis, meningitis, intracranial hemorrhage etc. In our study we have not divided III (High Risk) Group by pathologies, we have studied summarized value of prevalence for this group to compare with the values of the first two groups and as a result we have identified that the prevalence rate was significantly high, but also declined considerably: from 64.8% to 23.9% (-63%).

Numerous association studies have been performed to test for association between risk factors and adverse neurodevelopmental outcomes. Multiple risk factors, including maternal prenatal risk factors and perinatal/neonatal pathologies, act during early development of a fetus and may contribute to the genesis of adverse neurodevelopmental outcomes. Most risk factors are difficult to be assigned and quantified.

In several studies are described that maternal prenatal features, such as adverse maternal age [9], and risk factors affected child development during prenatal, perinatal and postnatal periods have been correlated with several typically unobserved or inadequately measured characteristics that are relevant for fetal/child health and are identifying as a minor delay in normal development of the psycho-motor sphere [1]. If ignored, these may lead to increase the existence and severity of finally formed developmental disabilities in future.

We found correlations between infant's neurodevelopmental adversities, usually appeared during the first year of life and four separate risk factors, such as maternal age (<17Y>35Y), maternal pathological pregnancy, maternal pathological delivery and prematurity.

The significant influence of a very low and higher maternal age on abnormal neurodevelopmental outcomes is reported by Ogawa K. et al. Authors noted, that advanced maternal age (≥ 35) is related to greater risk for adverse birth outcomes and farther development of children compared to younger women, especially for maternal complications, including cesarean section, preeclampsia, severe preeclampsia and placenta previa, which are strongly associated with children health status. The effect of maternal age on risk of infant's development was confirmed in our research too, where the association between them was defined as very significant ($p<0.001$) [9].

Pathological pregnancy [6,9] and delivery [2,7,10] are also already known as a significant risk factor from other studies. Some autors indicate, that the absolute risks of perinatal mortality, fetal neurologic morbidity, birth trauma, 5-minute Apgar score <7 and neonatal asphyxia was about two- to five-fold higher in the pathological delivery group than in the planned vaginal delivery group (Berhan Y). Using age-appropriate intelligence scales, the authors found statistically significant difference in the intelligent quotients of children born with pathological pregnancy, such as with perinatal infections asymptomatic at birth and children without them [3]. According to Morrison J. (2017) children with these infections by age 2 were found to have scores that were 7 points lower compared to the controls ($p<0.05$) [8]. Similarly, infants from our study population had lower neurodevelopmental scores compared to children with normal development dependent of maternal health status, such as normal progress of pregnancy and delivery. We had not identified specific pathologies, but we had found that the presence of any pathology is associated with the adverse neurodevelopment of infant and more significant correlation is defined in cases of pregnancy pathologies (OR-10.55 $p<0.01$) than in cases of pathological delivery (OR-3.73 $p<0.05$).

Gestational age is most researched and probable risk factor for neurodevelopmental disorders in infants today. The proportion of infants at risk of developmental delay is high, even for those born at 32-34 week's gestation [11], which raises the question of including these children in follow-up. In french population based cohort of preterm neonates, Pierrat V. et al. [11] showed that there was a statistically important decrease in the rate of cerebral palsy but the risk of developmental delay was high, even in children born moderately preterm. Other authors also confirm that small for gestational age infants are subject to an increased risk for adverse short- and long-term outcome compared with appropriate for gestational age infants and these long-term outcomes were affected by increased risk for neurodevelopmental impairment (24.7% vs 5.6%; OR, 5.5) and growth delay (21.2% vs 7.4%; OR, 3.4) [15]. As a result of a short-term, namely one-year observation, we revealed that gestation age is strongly associated (OR-58.83 $p<0.001$) with lower scores on neurodevelopmental outcomes compared to other risk factors.

Conclusion. Coexistence of revealed risk factors increased probability of adverse neurological outcomes in infants at age of 6 month as well as at age of 12 month. There was a statistically important association between infant's 1-year neurological outcomes and perinatal risk factors, such as maternal age (<17Y>35Y), pathologies of pregnancy and delivery as well as gestation age (<37 weeks).

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SUMMARY

ASSESSMENT OF NEURODEVELOPMENTAL OUTCOMES IN INFANTS 6-12 MONTHS OF AGE ACCORDING TO IMPACT OF PERINATAL RISK FACTORS

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The purpose of this research was to investigate the developmental follow-up of infants (at age of 6 month and 12 month), exposed to separate and combination impact of perinatal risk factors, compared with not exposed cases, within the prospective cohort study.

Between January 2015 and January 2017, in this research we prospectively enrolled 1018 live-born infants from the medical reports of the participating clinics in Tbilisi (capital of Republic of Georgia) and Mtskheta, Dusheti (districts of Georgia).

Within postnatal follow-up, the children from whole population were assessed at 6 and 12 months of age by family doctors using the Denver Developmental Screening Test (Denver II). The association between the risk factors and neurodevelopmental outcomes was analyzed by Chi-square test of independence. Statistical analysis of these data was performed using the SPSS version 12. (SPSS Inc., Chicago, IL). A P value of less than 0.05 was considered as significant.

Prevalence of abnormal development in whole population was revealed 9.0% or 92 cases at age of 6 month and 36 cases or 3.5% at age of 12 month. Point prevalence of farther neurodevelopmental adversities for healthy born children not influenced by studied risk factors was 0.1% and for infants with impact of the risk factors - 1.5%; on the other hand, prevalence of observed abnormal development in infant's population who had neonatal pathologies was 2.3% if risk factors were not exposed and 21.6% under influence of risk factors.

Statistical analysis showed that an abnormal developmental outcomes were more frequent when researched risk factors were exposed (OR-23.18, CI 95% - 11.83 to 45.41 - at age of 6 month; OR – 26.12, CI 95% - 7.95 to 85.85 – at age of 12 month) as well, as correlation of these risk factors with neurodevelopmental adverse outcomes was significant ($p<0.001$). Significant correlations were identified for separate risk factors, such as maternal age (<17Y>35Y), pathologies of pregnancy and delivery as well as gestation age (<37 weeks).

Coexistence of revealed risk factors increased probability of adverse neurological outcomes in infants at age of 6 month as well as at age of 12 month. There was a statistically important association between infant's 1-year neurological outcomes and these perinatal risk factors.

Keywords: infants, neurodevelopmental problems, perinatal risk factors.

РЕЗЮМЕ

ОЦЕНКА РЕЗУЛЬТАТОВ РАЗВИТИЯ НЕРВНОЙ СИСТЕМЫ У МЛАДЕНЦЕВ В ВОЗРАСТЕ 6-12 МЕСЯЦЕВ В ЗАВИСИМОСТИ ОТ ВОЗДЕЙСТВИЯ ПЕРИНАТАЛЬНЫХ ФАКТОРОВ РИСКА

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Целью исследования явился анализ неврологических последствий раздельного или комбинированного воздействия факторов перинатального риска у младенцев в сравнении с теми случаями, где не наблюдалось такого воздействия.

В период с 2015-2017 гг. проведено проспективное когортное исследование младенцев в возрасте 6 и 12 месяцев. В исследование было включено 1018 младенцев, неврологическое обследование которых проводилось в районных медицинских центрах городов Тбилиси, Мцхета и Душети семейными врачами с использованием Денверского скринин-теста оценки развития (Денвер II).

Взаимосвязь влияния факторов риска и результатов неврологического развития исследуемых младенцев проанализирована методом исчисления Odds Ratio и критерия Chi-square test. Статистический анализ полученных данных выполнен с использованием программы SPSS v.12. Результаты считались достоверными при значении p<0,05.

Суммарный показатель распространенности выявленных у младенцев задержек развития составил 92 (9,0%) в возрасте 6 месяцев и 36 (3,5%) - в возрасте 12 месяцев. Показатель распространенности более поздних неврологических осложнений у здоровых детей, не подверженных влиянию вышеуказанных факторов риска, составил 0,1%, тогда как этот показатель у здоровых младенцев, подвергшихся воздействию факторов риска, составил 1,5%. Распространенность задержек в неврологическом развитии младенцев, перенесших различные неонатальные патологии, но не подверженных влиянию перинатальных факторов риска, составила 2,3%, этот же показатель, при воздействии факторов риска составил 21,6%. Статистический анализ показал, что задержка в развитии у младенцев наблюдалась чаще под воздействием перинатальных факторов риска (OR-23.18, CI 95% 11.83 - 45.41 - в возрасте 6 месяцев, OR - 26.12, CI 95% 7.95 - 85.85 - в возрасте 12 месяцев); корреляционная связь между указанными факторами риска и неблагоприятными исходами развития нервной системы оценена как положительная (p<0,001). Положительные корреляции выявлены и в случае влияния отдельных факторов риска, таких как материнский возраст (<17>35), патология беременности и родов, гестационный возраст при рождении (<37 недель).

Наличие перинатальных факторов риска увеличивает вероятность развития неблагоприятных неврологических исходов у младенцев в возрасте 6 и 12 месяцев.

რეზიუმე

6 და 12 თვის ჩვილების ნეიროგანვითარების შეფასება მათზე პერინატალური რისკ-ფაქტორების ზეგავლენის პირობებში

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კვლევის მიზანს წარმოადგენდა 6 და 12 თვის ასაკის ჩვილების ნეიროგანვითარების შეფასება და განვითარების დარღვევების ანალიზი მათზე პერინატალური რისკ ფაქტორების ზეგავლენის ჭრილში.

პროსპექტური კოჰორტული კვლევა ჩატარდა 2015-2017 წწ. ქ. თბილისის, მცხეთისა და დუშეთის რაიონებში. კვლევაში ჩართული იყო 1018 ჩვილი, რომელთა ნევროლოგიური შეფასება განხორციელდა დენვერის სკრინინგ-ტესტის გამოყენებით (დენვერ II).

პერინატალურ რისკ-ფაქტორებსა და ჩვილებში გამოვლენილ ნევროლოგიური განვითარების დარღვევებს შორის ურთიერთკავშირების გამოსავლენად გამოყენებული იყო Odds Ratio მეთოდი, მონაცემების შეფასება განხორციელდა Chi-square test-ის საშუალებით. მოღებული მონაცემების დამუშავება განხორციელდა SPSS პროგრამით, v. 12. სარწმუნოდ ითვლებოდა P-მაჩვენებელი 0.05-ზე ნაკლები.

კვლევაში ჩართულ ჩვილებში ნერვული სისტემის განვითარების ჯამური მაჩვენებელი 6 თვის ასაკისთვის შეადგენდა 92 (9%), ხოლო 12 თვის ასაკისთვის – 36 (3.5%). იმ ჩვილებში, რომლებიც ახალშობილობის პერიოდში შეფასდნენ ჯანმრთელებად და რისკ-ფაქტორების ზეგავლენის ქვეშ არ იმყოფებოდნენ, განვითარების შეფერხება გამოვლინდა მხოლოდ 0.1%-ში რისკ-ფაქტორების ზემოქმედების შემთხვევაში მაჩვენებელმა შეადგინა 1.5%. ნეონატალურ პერიოდში ავადობის ისტორიის მქონე ჩვილებში ნევროლოგიური განვითარების შეფერხებამ რისკ-ფაქტორების ზეგავლენის გარეშე შეადგინა 2.3%, რისკ-ფაქტორების ზეგავლენის შემთხვევაში კი – 21.6%.

სტატისტიკურმა ანალიზმა გამოავლინა, რომ ჩვილებში ნერვული სისტემის განვითარების შეფერხების სიხშირის მაჩვენებელი მატულობს პერინატალური რისკ-ფაქტორების ზეგავლენით (OR -23.18, CI-95% 11.83 - 45.41 – 6 თვის ასაკში, OR - 26.12, CI-95% 7.95 - 85.85 - 12 თვის ასაკში). კორელაციური დამოკიდებულება ცვლადებს შორის შეფასდა, როგორც სარწმუნო (P<0,001). დადებითი კორელაციური კავშირები დაფიქსირდა ისეთი ცალკეულ რისკ ფაქტორების ზეგავლენის შემთხვევაში, როგორიცაა დედის ასაკი (<17>35 წწ.), ორსულობისა და მშობიარობის პათოლოგიები, დღენაკლულობა (გესტაციური ასაკი <37 კვირა).

კვლევის შედეგებზე დაყრდნობით ავტორებს გამოტანილი აქვთ დასკვნა, რომ პერინატალური რისკ-ფაქტორების ზემოქმედებით იზრდება ჩვილებში ნევროლოგიური დარღვევების გამოვლენის ალბათობა.

СТРУКТУРА И ФАКТОРЫ РИСКА ВРОЖДЕННЫХ ПОРОКОВ РАЗВИТИЯ

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Врожденные пороки развития (ВПР) относятся к числу наиболее часто встречаемых патологий у новорожденных и детей первого года жизни. В структуре перинатальной и младенческой смертности в развитых странах Европы и Северной Америки врожденные пороки развития занимают первое место [1]. При этом имеются резервы для снижения летальности новорожденных с данной патологией путем внедрения организационных мероприятий. Известно, что 40-50% детей с аномалиями развития может быть сохранена жизнь при своевременной диагностике и хирургической коррекции врожденного дефекта у плода и новорожденного ребенка в первые часы жизни [2].

По данным ВОЗ, в мире ежегодно рождается 4-6% детей с ВПР, летальность при этом составляет 30-40%. Среди новорожденных частота ВПР, выявляемых в течение первого года жизни, достигает 5%. Врожденные пороки развития лидируют и в структуре причин перинатальной смертности. Влияние врожденных аномалий на общую структуру младенческой смертности возрастает. Исследования, проведенные в разных странах, показали, что 25-30% всех перинатальных потерь обусловлены анатомическими дефектами органов. Среди мертворожденных ВПР выявляются в 15-20% случаев [1,2].

По данным Министерства Здравоохранения Республики Казахстан (РК), в городе Алматы в последнее время отмечается рост числа детей с врожденными пороками развития. Считается, что 10% врожденных пороков развития обусловлены действием вредных факторов окружающей среды, 10% - хромосомными изменениями, а 80% обычно носят смешанный характер [3].

Согласно государственной программе развития здравоохранения Республики Казахстан «Денсаулық на 2016-2019 гг.», система пренатальной дородовой диагностики является приоритетным направлением развития здравоохранения.

По данным Национального генетического регистра (НГР) РК, в стране ежегодно рождается около 4500 детей с ВПР и каждый пятый новорожденный умирает от этой патологии. В связи со сложившейся ситуацией с 2007 г. в Республике Казахстан внедрена программа генетического скрининга беременных и новорожденных, реализация которой позволит создать в стране надежную систему раннего выявления и предупреждения рождения детей с генетическими нарушениями, что обеспечит значимый социально-экономический эффект и является подтверждением заботы государства о генофонде будущих поколений [17].

С 2007 по 2014 г. скрининг прошли 1 350 083 беременных; предупреждено рождение 9308 детей с летальными ВПР и 1160 с хромосомной патологией [17].

Охват населения пренатальным скринингом в различных регионах республики различается: по официальным данным, на 2014 г. самый высокий отмечался в г. Астане (82%), г. Алматы (74%), Западно-Казахстанской (92%), Павлодарской (99%), Карагандинской (94%) и Актюбинской (92%) областях, самый низкий (практически отсутствует пренатальный скрининг) - в Южно-Казахстанской (36%), Костанайской (34%), Мангистауской (37%), Атырауской (37%) областях; в Алматинской области выявлен невысокий показатель (58%). В 2014 г. было прервано 1460 беременностей с ВПР, не совместимыми с жизнью; в 2013 г. таких случаев было 1369. В случае, когда принимается решение о донашивании беременности, сразу же ставится вопрос о последующем оперативном вмешательстве у новорожденного. По данным НГР РК, внедрение пренатального скрининга снизило частоту ВПР у новорожденных с 13,9 в 2006 г. (до начала скрининга) до 10,6 на 1000 новорожденных в 2014 г., частоту ВПР «строгого учета» с 7,1 до 3,6 на 1000 новорожденных соответственно [17].

По мнению ряда авторов, учитывая высокий процент неблагоприятных исходов, длительность и сложность лечения и оказания медико-педагогической коррекции дефектов и социальной помощи детям-инвалидам, страдающим врожденными и наследственными заболеваниями, основные усилия должны быть направлены на предупреждение рождения детей с ВПР [1,5,6,8,12,13,16].

Согласно результатам исследования, основанного на многолетних данных контроля за случаями ВПР в Венгрии, внедрение профилактических программ позволяет предотвратить до 50% пороков развития [13, 15].

Согласно классификации, принятой ВОЗ (1983), можно выделить три уровня профилактики: первичная, вторичная и третичная. В настоящее время наибольшее внимание исследователей и организаторов здравоохранения привлекают методы вторичной профилактики, направленные на выявление ВПР у плода на ранних сроках беременности путем пренатальной диагностики, прежде всего, ультразвукового исследования, с последующей элиминацией патологического плода.

Осуществление указанных мероприятий до наступления жизнеспособности плода позволяет добиться значительного снижения показателей младенческой смертности по причине ВПР [7].

Признавая необходимость методов вторичной профилактики, очевидна практически повсеместная недооценка первичных мероприятий, направленных на предотвращение самого факта возникновения ВПР у плода и, таким образом, позволяющих снизить частоту случаев ВПР и избежать при этом роста частоты психологически крайне тяжелых процедур прерывания беременности.

Актуальность первичной профилактики не вызывает сомнений и в связи с наблюдаемой неблагоприятной динамикой заболеваемости ВПР, несмотря на непрерывное улучшение качества пренатальной диагностики, что объясняется значительным распространением факторов риска [1, 4, 11].

Целью данного исследования явилось определение структуры и факторов риска врожденных пороков развития плода, разработка путей совершенствования профилактических мероприятий.

Для достижения поставленной цели определены следующие задачи:

1. Оценить структуру врожденных пороков развития плода в г. Алматы.

2. Определить факторы риска возникновения ВПР плода.

3. Разработать предложения по совершенствованию профилактических мероприятий по предупреждению ВПР.

Материал и методы. Проведен анализ отчетных данных клиник Алмалинского района г. Алматы за 2016 г. и материалов анкетирования 174 беременных, у которых были диагностированы ВПР плода в возрасте 16-46 лет.

При сборе материалов и формировании групп респондентов соблюдены принципы сплошной выборки, ее качественной и количественной репрезентативности.

Определен объем выборки, исходя из положения, что объектом исследования являются беременные женщины.

Для обработки банка данных применялись методы современной медицинской и математической статистики (группировка данных по возрасту, построение таблиц и графиков, расчет абсолютных и относительных величин, структурных процентов, среднего арифметического значения и его стандартной ошибки).

$$\sigma = \sqrt{\frac{\sum (x - \bar{X})^2}{n}},$$

где: σ-стандартная ошибка, ∑(x - $\bar{X}$)2 - сумма разности квадратов между каждым показателем и средней арифметической величиной; n - объем выборки.

$$T_{1,2} = \bar{X} \pm \frac{s_0}{\sqrt{n}} \cdot c_\gamma$$

где: T1,2 – нижняя и верхняя граница доверительного интервала

$\bar{X}$ – выборочное среднее арифметическое

s_0 – среднее квадратичное отклонение по выборке (несмещенное)

n – размер выборки

γ – доверительная вероятность

Статистическая обработка данных проводилась с использованием пакета прикладных программ SPSS версия 19.0 на персональном компьютере Asus Intel Core i5 2,8 ГГц.

Результаты и их обсуждение. Врожденные пороки и аномалии занимают лидирующие позиции в структуре детской смертности и инвалидности. С целью снижения риска появления детей с подобными нарушениями необходимо тщательно изучить причины врожденных пороков. Причины врожденных пороков разделены на 2 большие группы: эндогенные и экзогенные.

Эндогенные причины врожденной патологии, вызывающие появление врожденных пороков и аномалий - мутации генетического материала, перезревание половых клеток, гормональные нарушения, возраст родителей. Экзогенные причины врожденных пороков – физические факторы, микроорганизмы, вредные привычки.

Влияние состояния здоровья и возраста родителей на будущее потомство известно с давних времен. Увеличение частоты рождения малышей с врожденными пороками и аномалиями развития у взрослых родителей обусловлено комплексом эндогенных и экзогенных причин, вызывающих старение половых клеток.

С целью изучения влияния факторов на вероятность формирования врожденного порока развития плода проанализированы истории 4578 беременных женщин, находящихся на учете в женских консультациях Алмалинского района г. Алматы за 2016 г., из них детально изучены данные 174 (3,8%) женщин, у которых обнаружены ВПР плода.

Структура ВПР плода по анатомической локализации у женщин была неоднородной. Наиболее распространенными локализациями ВПР являлись множественные пороки развития - 38 (21,8%) случаях, пороки развития сердца и крупных сосудов - 33 (19,0%) случая, пороки развития центральной нервной системы - 29 (16,7%) и пороки мочеполовой системы – 18 (10,4%) случаев (таблица 1).

В отчетах ВОЗ за 2015 г. указывается на тенденцию к повышению распространенности редких генетических врожденных пороков и увеличение риска неонатальной и детской смертности, умственной отсталости и тяжелых врожденных пороков у детей.

В этой связи нами изучена структура заболеваний 26 (14,9%) женщин, у которых были диагностированы генетические нарушения (таблица 2).

Из таблицы 2 явствует, что по нозологическим формам в данной категории беременных наблюда-

Таблица 1. Структура ВПР плода по анатомическим локализациям

Наименование локализация ВПР плода	Абсолютное число	% всего, M±m
Множественные ВПР	38	21,8±3,13
Сердце и крупные кровеносные сосуды	33	19,0±2,97
Центральная нервная система	29	16,7±2,83
Мочевыделительная и половая системы	18	10,4±2,3
Пищеварительная система	8	4,6±1,59
Челюстно-лицевая система	7	4,0±1,49
Диафрагмальная грыжа	7	4,0±1,49
Костно-мышечная система	5	2,9±1,27
Дыхательная система	3	1,7±0,98
Генетические нарушения	26	14,9±2,7
Всего	**174**	**100**

Таблица 2. Распределение хромосомных нарушений у плода

Распределение хромосомных нарушений	Абсолютное число	% всего, M±m
синдром Дауна	15	57,8±9,69
синдром Эдварса	3	11,5±6,26
синдром Тернера, синдром Кляйнфельтера, трисомия Х-хромосомы	3	11,5±6,26
прочие	5	19,2±7,72
Всего	**26**	**100**

ются следующие виды генетических нарушений: диагноз синдрома Дауна установлен в 15 случаях, что составляет 57,8% в структуре женщин с верифицированными хромосомными болезнями плода; значительно реже отмечается синдром Эдварса – в 3 (11,5%) случаях, также в 3 (11,5%) случаях верифицированы аномалии числа половых хромосом, среди них синдром Тернера, синдром Кляйнфельтера, трисомия Х-хромосомы.

Прочие хромосомные нарушения, включающие аномалии структуры хромосом, генные дефекты, отмечались в 5 случаях, что составило 19,2% в структуре исследуемой категории женщин.

Исследуемую группу с учетом причин возникновения ВПР плода можно распределить на две подгруппы: наследственные (генные мутации) и приобретенные, в ходе внутриутробного развития, что соответствует мировым данным и является мультифакторным. При этом, удельный вес генетических (наследственных) нарушений - 14,9%, приобретенные, в ходе внутриутробного развития – 85,1%. В структуре приобретенных ВПР лидирующее положение отводится порокам развития: множественные пороки развития (21,8%), пороки развития сердца и крупных сосудов (19,0%), пороки развития центральной нервной системы (16,7%).

Для выявления основных факторов риска, способствующих развитию ВПР плода исследовались следующие данные: кровное родство между родителями, количество и частота беременностей, наличие и частота абортов, пороков развития в анамнезе, наличие соматических и инфекционных заболеваний в период беременности и вредные привычки. Для решения поставленной задачи проведен социологический опрос женщин, у которых диагностированы ВПР плода.

На первом этапе социологического исследования дана социально-демографическая характеристика опрошенных респондентов. За исследуемый период в анкетировании приняли участие 174 женщин в возрасте от 16 до 46 лет.

Как следует из таблицы 3, наибольшую долю в структуре участников анкетирования составили респонденты в возрасте от 30 до 46 лет (69,0%), что вполне укладывается в сроки репродуктивного возраста.

Кровное родство между родителями не обнаружено.

С целью определения влияний количества и частоты беременностей на ВПР социологическому анализу подверглись данные анамнеза беременностей и их колиечства - от 1 до 9 и более, ее частоте - от 1 раза в год до 1 раза в 4 года и количестве абортов.

Таблица 3. Распределение респондентов по возрасту

Возраст	Абсолютное число	% всего, M±m
младше 18	8	4,6±1,59
18-19	16	9,2±2,19
20-24	12	6,9±1,92
25-29	18	10,3±2,3
30-34	35	20,1±3,04
35-39	48	27,6±3,39
40 и старше	37	21,3±3,1
Всего	**174**	**100**

Таблица 4. Количество беременностей в анамнезе

Количество беременностей (раз)	Абсолютное число женщин	% всего, M±m	ДИ 95%
1-2	10	5,7±1,76	2,18÷9,22
3-4	23	13,2±2,57	8,06÷18,34
5-6	78	44,8±3,77	37,26÷52,34
7-8	55	31,6±3,52	24,56÷38,64
9 и более	8	4,7±1,59	1,42÷7,78
Всего	**174**	**100**	**100**

Таблица 5. Распределение респондентов по частоте беременности

Частота беременности	Абсолютное число	% всего, M±m	ДИ 95%
Отсутствие беременности	7	4,1±1,49	1,02÷6,98
в 1 год 1 раз	43	24,7±3,27	18,16÷31,24
в 2 года 1 раз	71	40,8±3,73	33,34÷48,26
в 3 года 1 раз	35	20,1±3,04	14,02÷26,18
в 4 года 1 раз и более	18	10,3±2,3	5,7÷14,9
Всего	**174**	**100**	**100**

Таблица 6. Частота абортов в анамнезе

Частота абортов (раз)	Абсолютное число	% всего, M±m	ДИ 95%
1-2 раз	21	12,1±2,47	7,16÷17,04
3-4 раз	66	37,9±3,68	30,54÷45,26
5-6 раз	45	25,9±3,32	19,26÷32,54
7 и более	23	13,2±2,57	8,06÷18,34
Отсутствуют	19	10,9±2,36	6,18÷15,62
Всего	**174**	**100**	**100**

Как следует из таблицы 4, среди исследуемой группы наибольший удельный вес (76,4 %) составили женщины, которые в анамнезе имели 5-6 и 7-8 беременностей 44,8% и 31,6%, соответственно.

При изучении структуры частоты беременностей в год выявлено, что у большинства женщин – 71 (40,8%) и 43 (24,7%) в анамнезе наблюдается беременность в 2 года 1 раз и в 1 год 1 раз, соответственно, т.е. у тех лиц, которые не придерживались рекомендованных перерывов между беременностями (таблица 5).

Как видно из таблицы 6, наблюдается приверженность женщин к прерыванию беременности путем проведения аборта (89,1%), при этом наибольший удельный вес составляет 3-4 раза и 5-6 раз.

Данные о количестве и частоте беременностей и

абортов в анамнезе свидетельствуют об отсутствии приверженности женщин принципам планирования семьи, проявляющееся в интервалах между беременностями менее чем 2 года (65,5%) и высокой приверженностью прерывания беременности через проведение аборта (89,1%). Большее количество (76,4%) женщин с ВПР плода имеют в анамнезе от 5 до 8 беременностей.

Выкидыши на ранних стадиях, рождение недоношенного плода, развитие ВПР и синдром внезапной смерти новорожденных - все эти случаи связаны с неспособностью плода получать главное для своего развития — достаточное количество кислорода.

Для того, чтобы определить фактор действия алкоголя и курения респондентам задавался вопрос о вредных привычках - употреблении алкоголя и/или курении во время беременности».

Респонденты, отметившие факт курения во время беременности составили 19±2,97%; алкоголя - 14,4±2,66% 8,0±2,06% злоупотребляли и алкоголем и курением (рис.).

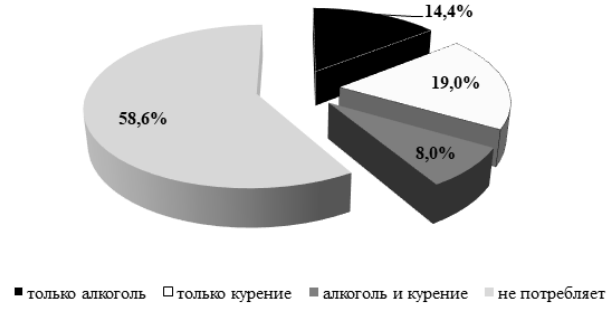

Рис. Распределение вредных привычек респондентов

Приверженность к вредным привычкам (41,4%), особенно женщинами репродуктивного возраста указывает на низкий уровень санитарной грамотности, несоблюдение законодательных норм и рекомендации, ограничивающих злоупотребление табачными изделиями и алкоголем.

Рассмотрено также влияние на возникновение ВПР плода различных соматических патологий: онкологических, хронических воспалительных заболеваний и заболеваний щитовидной железы, ожирения, аутоиммунных заболеваний и врожденных пороков сердца у женщин с ВПР плода.

Выявлено, что среди 174 женщин 70 (40,2%) имели соматические заболевания. Хронические воспалительные заболевания - 12,6±2,52%, заболевания щитовидной железы - 10,3±2,3%, аутоиммунные заболевания - 6,9±1,92%, онкологические заболевания и врожденные пороки сердца - 2,9±1,27% (таблица 7).

Известно, что большинство вирусов свободно проходят через плаценту, внедряются в эмбриональные клетки, размножаются в них, приводят к гибели плода либо к возникновению ВПР. Показатели различных инфекционных заболеваний среди респондентов приведены в таблице 8.

Выявлено, что больше половины женщин - 51,7% перенесли инфекционные заболевания в период беременности, из них ОРВИ - 20,1±3,04%, ЦМВ – 9,8±2,25%, герпетическая инфекция – 4,0±1,49%, венерические инфекции – 1,7±0,98% и другие инфекционные заболевания - 16,1±2,79%.

Наличие более чем у 50% респондентов инфекционных, у 40% хронических неинфекционных заболеваний свидетельствует о низком индексе здоровья женщин репродуктивного возраста, что определяется как отрицательный фактор, формируя дефекты развития плода.

Выводы:

В структуре врожденных пороков развития пло-

Таблица 7. Структура соматических заболеваний

Соматические заболевания	**Абсолютное число**	**% всего, M±m**
Онкологические заболевания	5	2,9±1,27
Хронические воспалительные заболевания	22	12,6±2,52
Заболевания щитовидной железы	18	10,3±2,3
Ожирение	8	4,6±1,59
Аутоиммунные заболевания	12	6,9±1,92
Врожденные пороки сердца у женщин	5	2,9±1,27
Без заболевания	104	59,8±3,72
Всего	**174**	**100**

Таблица 8. Структура инфекционных заболеваний, перенесенных во время беременности

Вид инфекции (выявленные во время беременности)	**Абсолютное число**	**% всего, M±m**
ЦМВ	17	9,8±2,25
Герпес	7	4,0±1,49
ОРВИ	35	20,1±3,04
Венерические инфекции	3	1,7±0,98
Другие	28	16,1±2,79
Отсутствуют	84	48,3±3,79
Всего	**174**	**100**

да в г. Алматы выявлены наследственные (генные мутации) и приобретенные пороки развития. Удельный вес генетических (наследственных) нарушений составил 14,9%; приобретенных в процессе внутриутробного развития – 85,1%. Среди генетических нарушений диагноз синдрома Дауна установлен в 57,8%, синдром Эдварса –11,5%, аномалии числа половых хромосом - 11,5%, прочие хромосомные нарушения - 19,2% случаев. Приобретенные ВПР имеют мультифакторный характер, лидирующее положение занимают множественные пороки развития (21,8%), пороки развития сердца и крупных сосудов (19,0%), пороки развития центральной нервной системы (16,7%).

Возраст от 30 до 46 лет (69,0%) составляет основную концентрацию женщин с ВПР плода. В ходе исследования выявлено, что 41,4% женщин подвержены нарушениям поведенческих факторов (потребление алкоголя и табачных изделий). Несоблюдение планирования семьи, интервалов между беременностями более чем 2,5 года (65,5%), прерывание беременности через аборты (89,1%) доминируют по сей день. Часто встречаются также хронические соматические (40,2%) и инфекционные заболевания (51,7%), низкий индекс здоровья беременных женщин.

- Во избежание развития ВПР необходимо повышать санитарную грамотность по соблюдению правил здорового образа жизни, так как частая или несвоевременная беременность, частые аборты подвергают женщин повышенному риску возникновения проблем со здоровьем, что способствует развитию врожденных пороков развития.

- Необходимо активизировать меры эффективной профилактики и ужесточения ответственности злоупотребления вредными привычками среди женщин репродуктивного возраста.

- Популяризация здорового образа жизни обеспечит повышение индекса здоровья женщин репродуктивного возраста.

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SUMMARY

STRUCTURE AND RISK FACTORS FOR CONGENITAL MALFORMATIONS

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Congenital malformations and anomalies occupy leading positions in the structure of infant mortality and disability. In order to reduce the risk of children with these disorders, it is necessary to carefully study the causes of congenital malformations. In this connection, the structures and risk factors of congenital malformations of the fetus were studied and recommendations for the improvement of preventive measures were developed.

When studying the structure of congenital malformations of the fetus in Almaty, hereditary and acquired causes of congenital malformation are identified. In the course of the study, the main risk factors for fetal development of the fetus were studied, where the main predictors were identified. The main age of women, 30-46 years old, whose pregnancy is susceptible to fetal malformation, has been determined. On the basis of the data obtained, recommendations are given on improving the sanitary literacy among women, creating a healthy lifestyle and ensuring prevention.

Keywords: congenital malformations, pregnancy, prenatal diagnosis, sanitary literacy, gene mutations, risk factors.

РЕЗЮМЕ

СТРУКТУРА И ФАКТОРЫ РИСКА ВРОЖДЕННЫХ ПОРОКОВ РАЗВИТИЯ

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Врожденные пороки и аномалии занимают лидирующие позиции в структуре детской смертности и инвалидности. Для устранения риск-факторов появления детей с подобными нарушениями необходимо тщательно проанализировать причины врожденных пороков и разработать рекомендации по совершенствованию профилактических мероприятий.

Результаты анализа структуры и риск-факторов врожденных пороков развития плода позволили определить наследственные и приобретенные причины их развития. В процессе исследования установлены основные факторы риска развития врожденных пороков развития плода и их предикторы. Определен возраст женщин (30-46 лет), беременность которых чаще подвержена развитию пороков у плода. На основании полученных данных разработаны рекомендации по повышению санитарной грамотности среди женщин, формированию сохранения здорового образа жизни и обеспечению профилактики.

რეზიუმე

თანდაყოლილი მანკების განვითარების სტრუქტურა და რისკ-ფაქტორები

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ბავშვთა ინვალიდობისა და სიკვდილიანობის სტრუქტურაში მნიშვნელოვანი ადგილი უჭირავს თანდაყოლილ მანკებს და ანომალიებს.

კვლევის მიზანს წარმოადგენდა ნაყოფის განვითარების თანდაყოლილი მანკების სტრუქტურის და რისკ-ფაქტორების ანალიზი და მათი პროფილაქტიკის ღონისძიებების გამომუშავება. შესწავლილი და გაანალიზებულია 16-46 წ. 174 ორსულის მდგომარეობა, რომელთაც გამოუვლინდა ნაყოფის თანდაყოლილი მანკი. მასალის დამუშავებისას გამოყენებული იყო თანამედროვე სამედიცინო და მათემატიკური სტატისტიკის მეთოდები.

კვლევის მსვლელობაში დადგენილია მანკის განვითარების ძირითადი რისკ-ფაქტორები და მათი პრედიქტორები. განისაზღვრა ქალების ასაკი (30-46 წ.), რომელშიც უფრო ხშირად ვითარდება ნაყოფის ანომალია და მანკი. ჩატარებული კვლევის შედეგებზე დაყრდნობით შემუშავებულია რეკომენდაციები ქალების სანიტარული ცოდნის ამაღლების, ჯანმრთელი ცხოვრების წესის ფორმირებისა და პროფილაქტიკური ღონისძიებების განხორციელების შესახებ.

ПРЕДОСТАВЛЕНИЕ ПРАВА НА ЗДРАВООХРАНЕНИЕ ДЕТЯМ – ВНУТРЕННЕ ПЕРЕМЕЩЕННЫМ ЛИЦАМ (ОТДЕЛЬНЫЕ АСПЕКТЫ)

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Нарушение территориальной целостности Украины, оккупация Крыма и «гибридная война» на территории Донецкой и Луганской областей, заставили многие семьи с детьми покинуть места своего проживания. Данные Министерства социальной политики по состоянию на май 2017 характеризуют количество вынужденных переселенцев как 1 млн. 584 тыс. человек (почти 1 млн. 300 тыс. семей). Больше всего внутренне перемещенных лиц (ВПЛ) находится в Донецкой области - 528 тыс., в Луганской - 289,7 тыс., в Харьковской - 196,7 тыс., в г. Киеве – 167 тыс. Среди общего количества ВПЛ 806,6 тыс. пенсионеров, 57,6 тыс. человек с инвалидностью, 241 тыс. детей. [2] По демографическому разрезу, в Украине дети составляют пятую часть населения. Таким образом, по оценкам экспертов, среди общего числа перемещенных лиц должно быть минимум 20-25% детей, что составляет около 500 000. [16] Согласно данным ООН, которые превышают официальную статистику, количество вынужденных переселенцев составляет около 2 300 000: столько человек вынужденно покинули места своего проживания в зоне конфликта и уехали в другие регионы Украины и зарубежные государства. [19]

В сравнении с ситуацией в других государствах, по данным мониторингового центра по вопросам недобровольных перемещений, численность ВПЛ в мире вдвое превышает численность беженцев и составляет 33 300 000 лиц. Острой является проблема в Сирии, Колумбии, Судане, Нигерии, Ираке. По состоянию на декабрь 2015 г. количество ВПЛ в Сирии достигало 6 600 000, в Колумбии – 6 270 436, Ираке – 3 290 310, Судане – 3 182 286, Йемене – 2 509 068, Нигерии – 2 095 812 ВПЛ [20].

От конфликта на Донбассе, по подсчетам УГКП ООН, пострадало 5 млн. украинских граждан. По данным ЮНИСЕФ 1,7 млн. пострадавших – дети (или 34% от всего количества). [5] Однако официальная статистика в полном объеме ситуацию не отражает, поскольку не все ВПЛ поставлены на официальный учет. В большинстве случаев переселенцами являются целые семьи и матери с детьми. При этом возникает проблема осуществления и защиты отдельных прав детей - внутренне перемещенных лиц (далее - дети-ВПЛ).

В научной литературе имеется ряд исследований по проблеме осуществления отдельных прав ВПЛ - собственности, трудовых и социальных прав. Однако научных работ, посвященных проблемам осуществления и защиты права детей из числа ВПЛ на охрану здоровья немногочисленно, что и обусловливает актуальность данного исследования.

Материал и методы. Данное исследование базируется на междисциплинарном подходе к анализу проблемы обеспечения права детей-ВПЛ на охрану здоровья с применением диалектического, сравнительно-правового и системного методов.

Обеспечение прав детей-ВПЛ осложняется тем, что дети, больше чем взрослые, подвергаются психологическим травмам в ситуации вынужденного переселения, что приводит к различным эмоциональным расстройствам (ухудшение коммуникативного общения с окружающими, появление раздражительности, агрессивности, тревожности, утрата доверия к другим) и негативно сказывается на их адаптации в новых условиях проживания.

Для понятия смысла «права на охрану здоровья» необходимо проанализировать международно-правовые акты, содержащие дефиниции этого права. В частности, ч. 1 ст. 25 Всеобщей декларации прав человека [8] гарантирует право на такой жизненный уровень, включая пищу, одежду, жилище, медицинский уход и необходимое социальное обслуживание, которые необходимы для поддержания здоровья. Право на охрану здоровья гарантируют также ст. 11 Европейской социальной хартии [7], ст. 5 Международной конвенции о ликвидации всех форм расовой дискриминации [11], ч. 1 ст. 24 Конвенции о правах ребенка [10], ч.1 ст. 12 Международного пакта об экономических, социальных и культурных правах [12], п. 1.6. ч. 1 Декла-

рации о политике в сфере соблюдения прав пациента в Европе. Таким образом, большинство международных актов либо прямо закрепляют термин «право на здоровье», либо используют подобные понятия. Проанализированная научная литература подтверждает разный подход к пониманию понятия права на охрану здоровья. Так, по мнению С. Гладуне [3], Р. Стефанчук, А. Зелинского [21] «одним из естественных прав человека является право на здоровье», другие авторы [1,6] придерживаются позиции, что «человек имеет естественное право на охрану здоровья или право человека на охрану здоровья как общесоциальное явление» [17]. В отдельных научных источниках встречаем также и случаи использования авторами обоих терминов [22].

Конституция Украины (ст. 49) гарантирует каждому, в том числе детям-ВПЛ, право на охрану здоровья, медицинскую помощь и страхование. Возможность осуществления этого права обеспечивается государственным финансированием медицинских, санитарных, оздоровительных и профилактических программ, а также созданием условий доступа граждан к медицинскому обслуживанию. Кроме того, гарантируется, что медицинская помощь в государственных и коммунальных учреждениях здравоохранения оказывается бесплатно.

ВПЛ гарантируется не только оказание необходимой медицинской помощи, но и обеспечение лекарственными средствами (ст. 9 Закона Украины «Об обеспечении прав и свобод внутренне перемещенных лиц»).

Что касается полномочий органов государственной власти и местного самоуправления в сфере обеспечения права на охрану здоровья ВПЛ, то анализ статьи 11 Закона Украины «Об обеспечении прав и свобод внутренне перемещенных лиц», позволяет установить, что ВПЛ гарантируется право на охрану здоровья:

1) на уровне Министерства здравоохранения, которое наделено обязанностью обеспечивать организацию оказания медицинской помощи и медицинского обслуживания, а также осуществлять комплексные мероприятия по санитарно-эпидемиологической безопасности населения и карантинных мероприятий по месту фактического проживания ВПЛ;

2) на уровне местных государственных администраций, которые должны обеспечивать организацию работы медицинских учреждений по оказанию необходимой помощи населению с учетом пребывания на соответствующей территории ВПЛ;

3) на уровне органов местного самоуправления, обязанных обеспечивать предоставление медицинской помощи в коммунальных учреждениях здравоохранения с учетом сведений о ВПЛ, проживающих в соответствующем населенном пункте.

Кроме того, статьей 11 Закона Украины «Об обеспечении прав и свобод внутренне перемещенных лиц» на местные государственные администрации возложена обязанность предоставлять ВПЛ, в случае необходимости, медико-психологическую помощь.

Статья 38 Закона Украины «Основы законодательства Украины о здравоохранении» [14] отмечает, что каждый пациент, достигший 14 лет и обратившийся за оказанием ему медицинской помощи, имеет право на свободный выбор врача, если последний может предложить свои услуги, и выбор методов лечения в соответствии с его рекомендациями. Каждый пациент имеет право, если это оправдано его состоянием, быть принятым в любом учреждении здравоохранения по своему выбору, если это учреждение имеет возможность обеспечить надлежащее лечение. Спорным считаем вопрос возраста. Ввиду особой сложности медицинских услуг, необходимо запретить совершать манипуляции в отношении несовершеннолетних без письменного согласия законных представителей (родителей или лиц, их заменяющих). Таким образом, необходимо повысить возраст, при котором ребенок может принимать те или иные решения в сфере медицины с 14 до 16 лет и внести соответствующие изменения в ч. 2 и ч. 3 ст. 284 ГК Украины и ст. 43 Основ законодательства об охране здоровья относительно пациента, не достигшего возраста 16 лет, а также пациента, признанного в установленном законом порядке недееспособным, то есть медицинское вмешательство должно осуществляться с согласия их законных представителей.

В соответствии с Законом Украины «О свободе передвижения и свободном выборе места проживания в Украине» [15], регистрация места жительства или места пребывания лица или ее отсутствие не могут являться основанием для ограничения реализации прав и свобод, предусмотренных Конституцией Украины. Таким образом, даже если лицо не было учтено как ВПЛ, то в соответствии с Законом Украины «О свободе передвижения и свободном выборе места проживания в Украине», регистрация места жительства или места пребывания лица или ее отсутствие не могут быть основанием для ограничения реализации прав и свобод, предусмотренных Конституцией Украины.

Согласно информации Министерства охраны здоровья Украины, за медицинской помощью из числа временно перемещенных лиц (по состоянию на 01.01.2016) обратилось 338 826 человек. Проведено 298 558 медицинских инструментальных исследований и осмотров ВПЛ. У женщин указанной категории родилось 5534 младенцев. В бюджетном запросе на 2016 г. в составе медицинской субвенции МОЗ Украины были предусмотрены расходы резервного фонда медицинской субвенции (4 367 905,0 тыс. грн.) и расходы для Донецкой и Луганской областей, на которых органы государственной власти временно не осуществляют свои полномочия (856 462, 4 тыс. грн.) [18].

В одной только Харьковской области с мая 2014 по март 2017 г., из числа ВПЛ за медицинской помо-

щью обратилось 133 743 лица, из них 43 036 детей. Из общего числа обратившихся, стационарную медицинскую помощь вторичного и третичного уровней получили 37 035 лиц, из них 13 258 дети. Амбулаторную медицинскую помощь получили 96 708, из них 29 778 детей. Кроме этого, в учреждениях здравоохранения Харьковской области за указанный период произошло 1518 родов. В Киевской области из числа ВПЛ за медицинской помощью обратились: 23687 взрослых и 10672 детей, из них госпитализированы: взрослых 4971 и 1587 детей. Учтено 8325 взрослых и 4945 детей, родились 675 детей [9].

Вынужденно перемещенным лицам с различной патологией предоставляется специализированная и квалифицированная медицинская помощь. Из числа вынужденно перемещенных лиц: 465 были больны сахарным диабетом, которых обеспечили инсулином; 562 больных туберкулезом - препаратами для противотуберкулезной терапии; 266 ВИЧ/СПИД инфицированных - специфическим лечением. Зафиксировано 6346 обращений с онкологической патологией; 18 больным хронической болезнью почек предоставлена высокоспециализированная медицинская помощь с применением методов заместительной почечной терапии, в частности: гемодиализ («искусственная почка»), перитонеальный диализ, а также иммуносупрессивная терапия (для больных, перенесших трансплантацию почки и других органов). Социальное обслуживание граждан, которым государством законодательно гарантировано право на социальную защиту и поддержку, осуществляется через разветвленную сеть социальных учреждений – территориальные центры социального обслуживания (оказание социальных услуг), которые обеспечивают граждан социальными услугами непосредственно по месту их проживания. Такие социальные услуги организованы в каждой административно-территориальной единице региона.

За медицинской помощью из числа временно перемещенных лиц обратился 144561 ребенок (за неделю - 590), из них на медицинский учет поставлено 78 695 детей. Психологами Госслужбы по чрезвычайным ситуациям вместе с представителями других органов государственной власти, общественных (волонтерских) организаций психологическая помощь предоставлена 178. 829 ВПЛ (за неделю - 260), в том числе 49347 детям (за неделю - 36) [13]. В процентном выражении численность детей ВПЛ составила 17,2%, т.е. дети чаще нуждались в медицинской помощи, чем взрослые. Кроме того, дети войны (дети-свидетели боевых действий) нуждаются в восстановлении и психоэмоционального состояния здоровья.

Право на охрану здоровья связано с возможностью детей отдыхать и восстанавливать свое здоровье. По официальным сообщениям, ввиду оккупации Украина потеряла 120 оздоровительных лагерей в Крыму и 70 – в Луганской и Донецкой областях. Это – четверть всех учреждений, которые имела Украина. [5] В то же время из-за отсутствия жилья, довольно часто встречаются случаи размещения для временного проживания семей ВПЛ в санаториях, пансионатах, лагерях отдыха.

Решить проблему оздоровления детей-ВПЛ пытаются в каждой области Украины. Например, на территории Черкасской области находится 1692 ребенка из семей ВПЛ. В течение 2015-2017 гг. оздоровлено 1434 ребенка. Однако за счет областного бюджета оздоровлен только 31 ребенок. В Сумской области услуги по оздоровлению предоставлены 389 детям, к индивидуальной консультативно-просветительской работе по оптимизации родительско-детских отношений, профилактике проявлений агрессивного поведения у детей, формированию навыков поведения в психотравмирующей ситуации привлечено 307 человек, осуществлено изучение и оценка потребностей 34 семей, социальным патронажем охвачено 8 семей. [9]

Вопрос обеспечения ВПЛ лекарственными средствами решен частично. Так, к примеру, в лечебно-профилактических учреждениях Черниговской области ведется учет больных, нуждающихся в обеспечении лекарственными средствами в рамках государственных программ и комплексных мероприятий, финансируемых из государственного бюджета. По состоянию на 1 апреля 2017, в области на учете находится 48 таких больных, которые ранее обеспечивались медикаментами за счет средств Государственного бюджета Украины. Управление охраны здоровья ежемесячно информирует МОЗ Украины о необходимости перераспределения средств для этой категории больных. На территории Хмельницкой области проживает 6716 внутренне перемещенных лиц, из них, по оперативным данным ЛПУ, 163 ВПЛ, нуждающихся в обеспечении лекарственными средствами и изделиями медицинского назначения в рамках государственных программ и централизованных мероприятий, финансируемых из государственного бюджета. Указанная категория населения обеспечивается в пределах бюджетного финансирования. [9]

К сожалению, официальная точная статистика по общему количеству погибших и раненых детей отсутствует. Согласно оперативной информации Донецкой и Луганской областных государственных администраций, со времени проведения антитеррористической операции только в 2014 г. погибло 60 детей [23].

Неоднократно в СМИ встречаются сообщения о несовершеннолетних, которые принимают непосредственное участие в боевых действиях, что подтверждает появление в Украине такой категории детей, как дети-комбатанты. Боевики используют детей для получения информации для разведки и даже участия в боевых действиях. К сожалению, отсутствует точная информация по количеству и возрасту детей, вовлеченных в боевые действия на Востоке Украины. По приблизительным оценкам в любой момент времени

в мире не меньше, чем 300 000 детей участвуют в конфликтах в качестве солдат. [24]

Запрет привлечения детей к военным конфликтам гарантируется на уровне международного права Факультативным протоколом об участии детей в вооруженных конфликтах (ратифицирован Украиной 23 июня 2004 г.) Конвенции ООН о правах ребенка (ратифицирована 27 февраля 1991), Римским уставом Международного уголовного суда (подписан от имени Украины 20.01.2000 г.), Конвенцией Международной организации труда №182 о запрещении и немедленных мерах по искоренению наихудших форм детского труда (ратифицирована Украиной 5 октября 2000), 17 резолюциями Совета безопасности ООН (принимались с 1999 г.; последняя - S/RES/2143 (2014) – выдана 7 марта 2014), касающихся защиты и реабилитации детей, которых затрагивает военный конфликт, а также принятыми в 2007 г. и подписанными Украиной Парижскими обязательствами по защите детей от незаконного привлечения или использования вооруженными силами или вооруженными группами и Парижскими принципами и руководящими указаниями в отношении детей, связанных с вооруженными силами или вооруженными группировками.

Кроме того, запрет участия детей в боевых действиях и вооруженных конфликтах предусмотрен национальным законодательством Украины. В частности, согласно ст. 30 Закона Украины «Об охране детства», запрещается участие детей в военных действиях, вооруженных конфликтах, в том числе вербовка и обучение детей с целью использования их в вооруженных конфликтах других государств или насильственных действиях, направленных на свержение государственной власти или нарушение территориальной целостности, а также использование детей в военных действиях и вооруженных конфликтах, привлечение их к не предусмотренных законами Украины военизированным или вооруженным формированиям.

В то же время, по нашему мнению, не следует привязывать получение статуса ребенка, пострадавшего в результате военных действий и вооруженных конфликтов, к месту регистрации ребенка как внутренне перемещенного лица, ведь не каждый такой ребенок будет ВПЛ, так же, как и не каждый ребенок из числа ВПЛ является пострадавшим от боевых действий. Именно поэтому, необходимо ч. 6 ст. 301 Закона Украины «Об охране детства» изложить в новой редакции, дополнив после слов «предоставляется органом опеки и попечительства по месту регистрации» словами «или фактического пребывания ребенка».

Выводы. Проведенный анализ позволяет констатировать, что дети-ВПЛ чаще нуждаются в медицинской помощи, чем другие внутренне перемещенные лица, и при осуществлении права на охрану здоровья они сталкиваются с такими проблемами, которые требуют максимально быстрого решения:

1) обеспечение доступа к качественной бесплатной медицинской помощи, независимо от места постановки на учет ребенка-ВПЛ;

2) недостаточное обеспечение детей-ВПЛ оздоровлением за счет бюджетного финансирования, в том числе в летний каникулярный период;

3) потеря почти четверти оздоровительных учреждений в результате оккупации Крыма и военного конфликта на отдельных территориях Луганской и Донецкой областей;

4) недостаточное финансирование для обеспечения потребностей лекарственными средствами детей-ВПЛ;

5) отсутствие обязательного проведения первичного медицинского осмотра детей-ВПЛ;

6) недостаточное финансирование и некачественная государственная помощь по восстановлению психоэмоционального состояния здоровья детей-ВПЛ.

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SUMMARY

IMPLEMENTATION OF THE RIGHT FOR HEALTH CARE FOR CHILDREN – INTERNALLY DISPLACED PERSONS (CERTAIN ASPECTS)

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The aim of the article is to do a research on selected issues related to realizing the right for health care for the children – internally dislocated persons. In order to achieve the given aim statistical data of the quantity of involuntarily dislocated persons including children and also the quantity of children registered with the health-care authority as well as the quantity of their requests for medical care have been analized. It has been determined that in case of involuntary dislocation children are more often exposed to trauma than adults which leads to different emotional disorders. The concepts of «the right for health care» in international legal acts, national legislation of Ukraine and scientific works have been analized. There have been defined three levels of the provision of the right for health care of internally dislocated persons.

It has been substantiated that the fact that a child has not been registered with the health-care authority as IRP can't be a ground for limitations in realization of his right on health care. During the research process it has been defined that children IRP need medical care more often than other internally dislocated persons and in realization of the right for health care they come across a number of problems that need urgent solution, including access to free of charge professional medical care, regardless of the fact of medical registration of a child IRP, insufficient funding for provision of the needs of children IRP with medications, absence of obligatory primary medical examination of children IRP, etc.

Keywords: internally dislocated persons, children, right for the health protection, medical care.

РЕЗЮМЕ

ПРЕДОСТАВЛЕНИЕ ПРАВА НА ЗДРАВООХРАНЕНИЕ ДЕТЯМ – ВНУТРЕННЕ ПЕРЕМЕЩЕННЫМ ЛИЦАМ (ОТДЕЛЬНЫЕ АСПЕКТЫ)

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Целью исследования явился анализ отдельных проблем реализации права на охрану здоровья детьми - внутренне перемещенными лицами.

Для достижения указанной цели проанализированы статистические данные вынужденно перемещенных лиц (ВПЛ), в том числе детей, а также детей, поставленных на медицинский учет и количество их обращений за медицинской помощью. Установлено, что в ситуации вынужденного переселения дети чаще взрослых подвергаются психологическим травмам, которые приводят к различным эмоциональным расстройствам.

Проанализировано понимание понятия «права на охрану здоровья» в международно-правовых актах, национальном законодательстве Украины и научных трудах. Выделены три уровня обеспечения права на здоровье внутренне перемещенных лиц. Обосновано, что если дети не поставлены на учет как ВПЛ, это не может быть основанием для ограничения реализации их права на охрану здоровья. В процессе исследования установлено, что дети-ВПЛ чаще нуждаются в медицинской помощи, чем другие внутренне перемещенные лица, и при осуществлении права на охрану здоровья они сталкиваются с рядом проблем, требующих максимально быстрого решения, в том числе обеспечение доступа к качественной бесплатной медицинской помощи, независимо от постановки на учет детей-ВПЛ, недостаточное финансирование для обеспечения потребностей детей-ВПЛ лекарственными средствами, отсутствие их обязательного первичного медицинского осмотра.

რეზიუმე

ქვეყნის შიგნით გადაადგილებულ პირთა რიცხვიდან ბავშვების მიერ ჯანმრთელობის დაცვის უფლების განხორციელება (ცალკეული ასპექტები)

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კვლევის მიზანს წარმოადგენს ქვეყნის შიგნით გადაადგილებულ პირთა რიცხვიდან ბავშვების მიერ ჯანმრთელობის დაცვის უფლების განხორციელების ცალკეული პრობლემების გამოკვლევა. აღნიშნული მიზნის მისაღწევად გაანალიზებული იყო იძულებით გადაადგილებულ პირთა, მათ შორის ბავშვების სტატისტიკური მონაცემები,ასევე სამედიცინო აღრიცხვაზე აყვანილ ბავშვთა რაოდენობა და სამედიცინო დახმარების მისაღებად მათი მიმართვების რაოდენობა. დადგენილია, რომ იძულებით გადაადგილების სიტუაციაში ბავშვები უფროსებთან შედარებით უფრო ხშირად განიცდიან ფსიქოლოგიურ ტრავმას, რაც სხვადასხვა ემოციური აშლილობის განვითარებას განაპირობებს. გაანალიზებულია "ჯანმრთელობის დაცვის უფლების" ცნების საერთაშორისო სამართლებრივ აქტებში უკრაინის ეროვნულ კანონმდებლობასა და სამეცნიერო ნაშრომებში წარმოდგენილი ცნებები. გამოყოფილია ქვეყნის შიგნით გადაადგილებულ პირთა ჯანმრთელობის დაცვის უფლების უზრუნველყოფის სამი დონე.

დასაბუთებულია, რომ მაშინაც კი, როდესაც ბავშვი არ არის აყვანილი აღრიცხვაზე როგორც ქვეყნის შიგნით გადაადგილებული პირი, აღნიშნული არ შეიძლება წარმოადგენდეს მისთვის ჯანმრთელობის დაცვის უფლების რეალიზაციის შეზღუდვის საფუძველს. ანალიზის ჩატარების შედეგად დადგენილია, რომ ქვეყნის შიგნით გადაადგილებულ ბავშვებს უფრო ხშირად ესაჭიროებათ სამედიცინო დახმარება, ვიდრე ქვეყნის შიგნით გადაადგილებულ სხვა პირებს. ამასთან, ჯანმრთელობის დაცვის უფლების განხორციელების პროცესში ბავშვები მთელ რიგ ისეთ პრობლემებს განიცდიან, რომელიც მაქსიმალურად სწრაფ გადაწყვეტას მოითხოვს. მათ შორის აღსანიშნავია ხარისხიანი უფასო სამედიცინო დახმარების ხელმისაწვდომობის უზრუნველყოფა ბავშვის როგორც ქვეყნის შიგნით გადაადგილებული პირის აღრიცხვაზე აყვანის მიუხედავად, ქვეყნის შიგნით გადაადგილებული ბავშვებისთვის სამკურნალო საშუალებების მოთხოვნილების უზრუნველყოფის არასაკმარისი დაფინანსება, ქვეყნის შიგნით გადაადგილებული ბავშვებისთვის სავალდებულო პირველადი სამედიცინო გასინჯვის არარსებობა და სხვა.

QUANTITATIVE ASSESSMENT OF THE RESULTS OF VIMENTIN IMMUNOHISTOCHEMICAL EXAMINATION IN FIBROBLASTS AND ENDOTHELIOCYTES OF THE PLACENTAL VILLI IN THE ASPECT OF PRETERM MATURATION OF THE CHORIONIC TREE AND IRON DEFICIENCY ANEMIA OF GRAVIDAS

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Preterm maturation of chorionic villi is considered to be placental pathology occurring during the fetal period of human development [4,5]. The essence of preterm maturation of chorionic villi is that pathological factors cause accelerated maturation of the chorionic villi. It can be determined by histological structure of the chorionic villi [1,5], as well as by immunohistochemical changes in accumulation of specific placental proteins in trophoblast – hormones (placental lactogen and chorionic gonadotropin [2]) and the enzyme placental alkaline phosphatase [3]. The aspects syndicated are studied under conditions of iron deficiency anemia of pregnancy. Nowadays there is the lack of findings concerning disorders of stroma chorionic villi maturation which in the fetal period include the cells of stroma (fibroblasts, Hofbauer cells), connective tissue fibers, extracellular matrix and fetal vessels [4-6]. Specific names of chorionic villi are recommended to be used in the fetal period of development –intermediate immature villi, intermediate mature villi, terminal villi, stem villi [5]. The stroma components of the indicated chorionic villi can be examined by means of different immunohistochemical methods. One of the perspective methods to assess maturation of the chorionic villi can be immunohistochemical examination of vimentin [5,9-11]. By means of immunohistochemical method vimentin in the chorionic villi can be determined in those cells of the stroma as fibroblasts, macrophages, pericytes, endotheliocytes [5,9,10]. The interest to vimentin is associated with the fact that in the course of cellular differentiation vimentin content can change. The fact whether or no iron deficiency anemia influences on vimentin accumulation in the stroma cells of chorionic villi both under conditions of normal and disturbed maturation of chorionic villi remains unknown.

Objective - the purpose of the study was to determine quantitative parameters of vimentin in fibroblasts and endotheliocytes of chorionic villi during immunohistochemical examination of the placenta with preterm maturation of the chorionic tree in case of iron deficiency anemia of gravidas in two different terms of gestation – 29-32 and 33-36 weeks of gestation.

Material and methods. 182 placentas were examined. Design of the study supposes two main groups to investigate different terms of gestation (29-32 and 33-36 weeks of pregnancy) and three groups of comparison separately for every term of gestation.

The main groups of the study were the groups including placentas with preterm maturation of the chorionic tree taken from women with iron deficiency anemia of pregnancy.

The use of comparison groups was essential to understand the effect of preterm maturation or iron deficiency anemia separately on vimentin accumulation. In addition, physiological pregnancy and preterm labor with a normal rate of chorionic villi development were investigated. It was necessary to find the tendencies of the examined pathology concerning the common course of pregnancy.

Thus, the following groups of the study were formed:

The main group №1- the examination of combined IDAG and preterm maturation of the chorionic tree in 29-32 weeks of gestation.

The comparison group №1A – the examination of preterm maturation of the chorionic tree without anemia in labour in 29-32 weeks of gestation.

The comparison group №1B – the examination of IDAG in 29-32 weeks of gestation when the structure of the chorionic tree corresponds to the term of gestation.

The comparison group №1C – the examination without any anemia in 29-32 weeks of gestation when the structure of the chorionic tree corresponds to the term of gestation.

The main group №2 – the examination of combined IDAG and preterm maturation of the chorionic tree in 33-36 weeks of gestation.

The comparison group №2A – the examination of preterm maturation of the chorionic tree without any anemia in labour in 33-36 weeks of gestation.

The comparison group №2B – the examination of IDAG in 33-36 weeks of gestation when the structure of the chorionic tree corresponds to the term of gestation.

The comparison group №2C – the examination without any anemia in 33-36 weeks of gestation when the structure of the chorionic tree corresponds to the term of gestation.

The number of observations for every group of the investigation is presented in the Table.

The placental tissue was fixed in phosphate buffered neutral 10% formalin solution with further bypassing the material and preparing paraffin blocks. By means of a sliding microtome the cuts were made 5 micrometers thick keeping to appropriate requirements. According to DAKO recommendations by means of immunohistochemical method further detection of vimentin (using antibodies Clone V9) expression in trophoblast structures was determined (polymeric system of detection with the stain diaminobenzidine).

Table. Optic density of immunohistochemical staining on vimentin in fibroblasts and endothelium of chorionic villi in case of preterm maturation of the chorionic tree and iron-deficiency anemia of pregnancy (M±m)

Groups of the study	**Number of examined placentas**	**Optic density of staining (units of optic density) in fibroblasts**	**Optic density of staining (units of optic density) in endothelium**
Physiological pregnancy	21	0,244±0,0016	0,448±0,0029
29-32 weeks of gestation			
The main group №1- the examination of combined IDAG and preterm maturation of the chorionic tree	18	0,118±0,0010 p 1A<0,001 p 1Б=0,002 p 1B<0,001	0,301±0,0026 p 1A<0,001 p 1B<0,001
The comparison group №1A – the examination of preterm maturation of the chorionic tree without anemia	19	0,176±0,0014	0,348±0,0028
The comparison group №1B – the examination of IDAG when the structure of the chorionic tree corresponds to the term of gestation	20	0,126±0,0012	0,308±0,0025
The comparison group №1B without IDAG when the structure of the chorionic tree corresponds to the term of gestation	21	0,208±0,0013	0,365±0,0027
33-36 weeks of gestation			
The main group №2 – the examination of combined IDAG and preterm maturation of the chorionic tree	20	0,146±0,0010 p 2A<0,001 p 2Б<0,001 p 2B<0,001	0,352±0,0029 p 2A<0,001 p 2B<0,001
The comparison group №2A – the examination of preterm maturation of the chorionic tree without any anemia	22	0,202±0,0015	0,385±0,0028
The comparison group №2B – the examination of IDAG when the structure of the chorionic tree corresponds to the term of gestation	20	0,164±0,0011	0,349±0,0026
The comparison group №2B – without IDAG when the structure of the chorionic tree corresponds to the term of gestation	21	0,221±0,0012	0,390±0,0028

note: p1A – probability of difference of average values of the main group №1 with the group of comparison №1A;
p1B – *probability of difference of average values of the main group №1 with the group of comparison №1B;*
p2A – *probability of difference of average values of the main group №2 with the group of comparison №2A;*
p2B – *probability of difference of average values of the main group№2 with the group of comparison №2B;*
If probability is not indicated in the Table it was more than 0,05

Optic density of specific staining was measured in relative units of optic density by means of computer microdensitometry method (from 0 – absence of staining, absolute transparency; to 1 – maximal staining, absolute non-transparency) by means of computer program ImageJ (version 1.48v, free license, T. Ferreira, National Institute of Health, USA, 2015) [7]. Optic density of staining was applied as a measure of immunohistochemical concentration [2,3].

Arithmetic mean and its error were calculated. The groups were compared by means of bilateral unpaired Stu-

dent criterion in the medium of computer program PAST 3.15 (free license) [6]. Preliminary testing for the norm was made in samples by means of Shapiro-Wilki method. Statistically significant were differences with $p \leq 0,05$.

Results and their discussion. Positive immunohistochemical staining for vimentin in the stroma of intermediate mature and terminal villi was found in fibroblasts and endotheliocytes, and in intermediate immature villi of Hofbauer cells. Since the subject of our study was premature maturation of the chorionic tree, detection of the quantitative characteristics of Hofbauer cells was not of statistical use due to a small number of immature villi in the majority of the groups examined. It should be noted that immunohistochemical staining on vimentin was weak in Hofbauer cells, optic density ranged within the limits of 0,064-0,088 in the units of optic density. The cytoplasm of fibroblasts was stained more intensively, but endotheliocytes were stained the most intensively (Fig.). Although very big difference of optic density values can be found even within the borders of one blood vessel, which, to our opinion, reflects considerably various degree of endotheliocyte maturation. As to the distribution of staining on vimentin it always was of fine granular character.

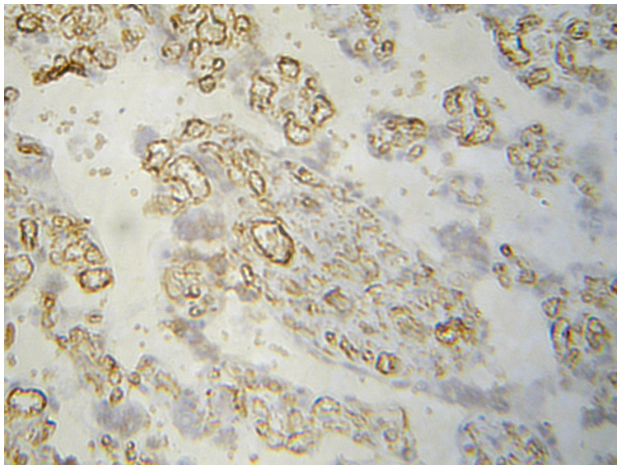

Fig. Placenta of a woman in 31 weeks of gestation with preterm maturation of the chorionic tree and iron-deficiency anemia of pregnancy. Immunohistochemical method on vimentin (antibodies Clone V9) with diaminobenzidine. Staining of nuclei with Mayer's hematoxylin. Ob. 20^x, Oc. 10^x

The data concerning average values of optic density of staining are presented in Table. The data obtained are indicative of the fact that optic density of staining on vimentin both in fibroblasts and endotheliocytes is the highest in case of physiological pregnancy. Even in case of preterm maturation of the chorionic tree without IDAG the values of optic density of staining do not achieve the rates characteristic for physiological pregnancy.

In similar by their pathology groups of the study optic density of staining on vimentin was always higher in the term of gestation 33-36 weeks as compared to the term of gestation 29-32 weeks. It was very important information as together with other data it proved our hypothesis concerning the fact that concentration of vimentin in fibroblasts and endotheliocytes can reflect the degree of maturation of these cells and correspondingly –the degree of maturation of the placental chorionic villi stroma.

As to the fibroblasts their characteristic feature was that during both terms of gestation involved in the study in combination with IDAG and preterm maturation the lowest average values of optic density of staining on vimentin were found, even lower than in those studies when the structure of the chorionic tree corresponds to the term of gestation.

As to the endotheliocytes in both terms of gestation in association with IDAG and preterm maturation the lowest average values were found, although, in an average they did not differ ($p>0,05$) from the studies with IDAG when the structure of the chorionic tree corresponds to the term of gestation.

Conclusions.

1. Vimentin concentration (optic density of immunohistochemical staining) in the cytoplasm of fibroblasts and endotheliocytes of the intermediate and terminal placenta villi can be a criterion of maturation of the placental chorionic tree.

2. Iron deficiency anemia paradoxically causes immaturity of fibroblasts and endotheliocytes of the intermediate and terminal placental villi even in placentas with determined preterm maturation of the chorionic tree by means of histological method.

Prospects of further studies are: to determine the mechanisms of reduced vimentin accumulation in fibroblasts and endotheliocytes of the placental chorionic villi in case of disorders of their maturation.

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SUMMARY

QUANTITATIVE ASSESSMENT OF THE RESULTS OF VIMENTIN IMMUNOHISTOCHEMICAL EXAMINATION IN FIBROBLASTS AND ENDOTHELIOCYTES OF THE PLACENTAL VILLI IN THE ASPECT OF PRETERM MATURATION OF THE CHORIONIC TREE AND IRON DEFICIENCY ANEMIA OF GRAVIDAS

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The objective of our study was to investigate quantitative parameters of vimentin in fibroblasts and endotheliocytes of the chorionic villi by means of immunohistochemical examination of placenta with preterm maturation of the chorionic tree with iron-deficiency anemia of pregnancy in two different terms of gestation – 29-32 weeks and 33-36 weeks.

182 placentas were examined. The study design included two main groups of investigation of the above terms of gestation and three groups of comparison. Quantitative parameters of vimentin in the cytoplasm of fibroblasts and endotheliocytes of the placenta intermediate and terminal villi were considered on the basis of staining optic density measured by means of computer microdensitometry method.

Immunohistochemical staining on vimentin was determined in the cytoplasm of fibroblasts and endotheliocytes of the placenta intermediate and terminal villi in all the groups of the study. The main results are presented in the conclusions.

Optic density of immunohistochemical staining on vimentin in the cytoplasm of fibroblasts and endotheliocytes of the placenta intermediate and terminal villi was found to be a criterion to determine maturation of the placenta chorionic tree. Iron-deficiency anemia paradoxically causes immaturity of fibroblasts and endotheliocytes of the placenta intermediate and terminal villi even in those placentas where preterm maturation of the chorionic tree is determined.

Keywords: preterm maturation of the chorionic tree, iron-deficiency anemia, vimentin.

РЕЗЮМЕ

КОЛИЧЕСТВЕННАЯ ОЦЕНКА РЕЗУЛЬТАТОВ ИММУНОГИСТОХИМИЧЕСКОГО ИССЛЕДОВАНИЯ ВИМЕНТИНА В ФИБРОБЛАСТАХ И ЭНДОТЕЛИОЦИТАХ ВОРСИНОК ПЛАЦЕНТЫ В АСПЕКТЕ ПРЕЖДЕВРЕМЕННОГО СОЗРЕВАНИЯ ХОРИАЛЬНОГО ДЕРЕВА И ЖЕЛЕЗОДЕФИЦИТНОЙ АНЕМИИ У БЕРЕМЕННЫХ

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Целью исследования явилось определить количественные параметры виментина в фибробластах и эндотелиоцитах хориальных ворсинок при иммуногистохимическом исследовании плаценты с преждевременным созреванием хориального дерева при железодефицитной анемии беременных в два разных периода гестации - 29-32 и 33-36 недель.

Исследовано 182 плаценты. Дизайн исследования предусматривал выделение двух основных групп исследования вышеуказанных сроков гестации и по три группы сравнения. О количественных параметрах виментина в цитоплазме фибробластов и эндотелиоцитов промежуточных и терминальных ворсинок плаценты судили на основе величины оптической плотности окраски, которую измеряли методом компьютерной микроденситометрии.

Иммуногистохимическое окрашивание на виментин определялось в цитоплазме фибробластов и эндотелиоцитов промежуточных и терминальных ворсинок плаценты во всех группах исследования. Основные результаты отражены в выводах.

Установлено, что оптическая плотность иммуногистохимического окрашивания на виментин в цитоплазме фибробластов и эндотелиоцитов промежуточных и терминальных ворсинок плаценты может служить критерием зрелости хориального дерева плаценты. Железодефицитная анемия парадоксально вызывает незрелость фибробластов и эндотелиоцитов промежуточных и терминальных ворсинок даже в плацентах, в которых гистологическим методом установлено преждевременное созревание хориального дерева.

რეზიუმე

პლაცენტის ვილების ფიბრობლასტებში და ენდოთელიოციტებში ვიმენტინის იმუნოჰისტოქიმიური გამოკვლევის შედეგების რაოდენობრივი შეფასება ქორიონული ხის ნაადრევი სიმწიფის და ორსულთა რკინადეფიციტური ანემიის პირობებში

ა. გარვასიუკი, ი. დავიდენკო

უკრაინის უმაღლესი სახელმწიფო საგანმანათლებლო დაწესებულება "ბუკოვინის სახელმწიფო სამედიცინო უნივერსიტეტი", ჩერნოვცი, უკრაინა

კვლევის მიზანს წარმოადგენდა ქორიონული ვილების ფიბრობლასტებში და ენდოთელიოციტებში ვიმენტინის რაოდენობრივი პარამეტრების განსაზღვრა იმუნოჰისტოქიმიური კვლევის მეშვეობით პლაცენტაში ქორიონული ხის ნაადრევი სიმწიფის და რკინადეფიციტური ანემიის პირობებში, გესტაციის ორ სხვადასხვა პერიოდში – 29-32 და 33-36 კვირა.

გამოკვლეულია 182 პლაცენტა. კვლევის დიზაინით გათვალისწინებული იყო გესტაციის სხვადასხვა პერიოდის მიხედვით (29-32 და 33-36 კვირა) ორი ძირითადი და სამ-სამი შედარების ჯგუფის გამოყოფა.

ვიმენტინის რაოდენობრივი პარამეტრების განსაზღვრა ფიბრობლასტების და ენდოთელიოციტების ციტოპლაზმაში პლაცენტის შუალედურ და ტერმინალურ ვილებში ხდებოდა შეფერადების ოპტიკური სიმჭიდროვის საფუძველზე კომპიუტერული მიკროდენსიტომეტრიული მეთოდის გამოყენებით.

დადგენილია, რომ შუალედური და ტერმინალური ვილების ფიბრობლასტების და ენდოთელიოციტების ციტოპლაზმაში იმუნოჰისტოქიმიური შეფერადების ოპტიკური სიმჭიდროვე შეიძლება გამოყენებული იყოს პლაცენტის ქორიონული ხის სიმწიფის კრიტერიუმად.

რკინადეფიციტური ანემია პარადოქსულად იწვევს შუალედური და ტერმინალური ვილების ფიბრობლასტების და ენდოთელიოციტების უმწიფრობას იმ პლაცენტებშიც კი, რომლებშიც ჰისტოლოგიური მეთოდით დადგენილია ქორიონული ხის ნაადრევი სიმწიფე.

INFLUENCE OF METABOLIC SYNDROME ON CONDITION OF MICROCIRCULATORY BED OF ORAL CAVITY

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Metabolic syndrome (MS) can be characterized as the clustering of combination of impaired glucose regulation, metabolic disorders accompanied by abdominal obesity, hyperglycemia, high blood pressure and dyslipidemia [3,9]. MS has a close connection with the development of cardiovascular diseases and type 2 diabetes mellitus [5,14] in connection with which he attracts the attention of doctors of many specialties, including dentists from one point of view and pathogenetic mechanism of MS could be connected with blood supplying disturbance generally, and with condition of microcirculatory bed (MCB) from other point of view [2].

Simultaneously we need declare that pathogenetic links of MS could be recognized as a risk factor for the development of periodontitis [1,13] due to reports about potentially significant association between MS and periodontitis, and patients with MS have a higher risk for periodontal disorder [4,12]. It is generally accepted for today that the origin of pro-inflammatory state derived from excessive calorie intake and over nutrition and other chronic inflammatory diseases could be realized in oxidative stress which has been proposed as a potential common link to explain relationship among each component of MS and periodontitis [9] and it looks logical that microcirculatory bed could be one of most important side in development of oral tissue injuring.

In this case, the morphogenesis of changes in the tissues of the oral cavity in the metabolic syndrome remains an unenlightened question with isolated and often contradictory works devoted it. Detection of changes in microcirculatory bed of oral cavity in metabolic syndrome could be important for completion of named gap for developing of adequate therapeutical measure for prevention of pathological periodontal disorder that was the purpose of our study.

Material and methods. We performed experimental investigation for study of the morpho-functional state of tissues of the oral mucosa in metabolic syndrome that allows to eliminate the influence of somatic pathology and social factors, allows to detect involvement of MCB in development of tissual disorder in oral cavity in MS.

This report presents the results of the study of 12 experimental animals (white male rats 1.5-2 months of age) which were under simulation of the metabolic syndrome for 70 days using a diet in which the oral pork fat was daily administered orally (40% of the rat weight), and 10% fructose adlibitum solution was used also instead of drinking water. Prior to the experiment, the body weight (*g*) and the abdominal circumference (at the mid-torso level, *cm*) were measured in rats. Intact animals formed a comparison group.

The specimens of soft tissues of the oral cavity were stained with hematoxylin and eosin (H&E), according to van Gieson, according to Rego, according to Mallory, PAS-reaction was performed after the routine proceeding. The microscopic study was performed on a microscope "Olympus BX-41" with subsequent processing by the program "Olympus DP-soft version 3.2". Morphometric studies were performed in the gingival zone which was chosen for morphological interpretation. Statistical analysis of the study results was performed on a personal computer using Microsoft Excel and Statistica-10 database software. The criteria of non-parametric statistics were used in order to assess the significance of differences in sample populations. Statistical comparison was performed using Mann-Whitney test for statistical analysis. Spearman's rank correlation coefficient (r) was counted for measure of the strength of relationship between paired data**.** The accepted level of significance was $p<0.05$.

The procedure was done strictly in compliance with the Helsinki Declaration, European Convention for the protection of vertebrate animals (18.03.1986), European Economic Society Council Directive on the Protection of Vertebrate Animals (24.11.1986) after approval from the Regional Ethical Review Board at State Institution «The Institute of Stomatology and Maxillo-facial Surgery NAMS of Ukraine», protocol № 83 (16.03.2016).

Results and their discussion. The body weight and the abdominal circumference measuring shows increasing of the circumference of the middle part of the body for 28% (in the comparison group for 16% ($p<0.001$) as a result of MS simulation with fat high and fructose in drinking water diet. Pale and moderate edematous condition of the oral mucosa has been revealed during its visual examination in group with MS modeling. The number of carious teeth was 2.7 ± 0.2 in the study group (1.8 ± 0.2 in intact animals, $p = 0.01$).

Histological investigation of obtained microspecimens shows that MS modeling process is implemented by complex of pathological changes in oral mucosa (Fig. 1). Squamous epithelium is characterized by uneven thickness (Fig. 1a) with the presence of intraepithelial lymphocytes, eosinophils, signs of proliferation in the basal cellular layer, moderate development of papillomatous changes. There are areas of focal pronounced thinning of the epithelium (up to 2-3 cells in thickness).

There are multiple keratohyalin grains in the cytoplasm of epithelial cells of the granular layer. Appearance of lights vacuoles has been revealed in the cytoplasm of the epitheliocytes in all layers with dimensions that are often comparable to the size of the nuclei. There are sings of

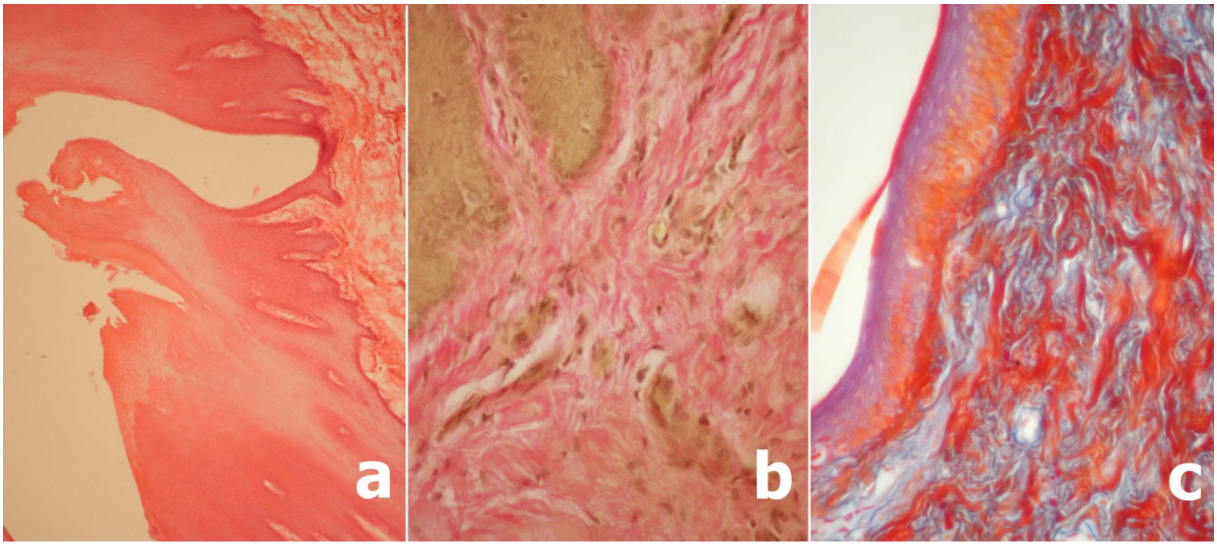

Fig. 1. Uneven thickness of squamous epithelium with the presence of degenerative changes and appearance of inflammatory cells under the basal membrane mainly, H&E stain, magnification x100 (a); uneven congestion of microcirculatory bed vessels with empty and filled lumens, formation of perivascular inflammatory infiltrates, swelling of connective tissue fibers, appearance collagen connective tissue fibers, staining according to van Gieson, magnification x400 (b); sclerotic changes in lamina propria of mucosa, thickening of vascular walls in MCB of lamina propria, staining according to Mallory, magnification x400, (c)

Table. Specific volume of structural components (%)

Parameter \ Group	Intact animals	Animals with MS modeling
Specific density of MCB vessels (%)	27.40±8.31	13.16±1.94*
Specific density of rough connective tissue (%)	21.47±6.38	39.87±5.39*

** p<0.05 significant difference between groups with MS modeling and intact animals*

epithelial proliferation penetrating into the underlying tissue in the form of bulbous outgrowths, less often tapes or strands similar. The PAS reaction is slightly positive in the epithelium with the presence of zones of weak staining localized mainly in the basal areas but with clear detection of basal membrane. Simultaneously there are areas with infiltration by inflammatory cells both in the lamina propria and epithelium of the oral cavity that could be recognized as development of periodontitis.

Morphofunctional state of the microcirculatory bed has been changed in the study group in comparison with the control group with pronounced disorder observed in the vessels of the periodontium (Fig. 1). The vasculature is characterized by uneven blood filling with background of desolate vessels that have fallen lumens and presence of sharply expanded blood-filled capillaries. There is a presence of small blood clots in the lumen of the vessels, which are more often localized in postcapillaries and venules. Endotheliocytes are flattened more often, with signs of desquamation. The processes of vascular new formation are not expressed. Presence of different stages sclerotic processes has been noted in the vascular walls and perivascular space. The highest concentration of blood vessels has been detected in layers of loose fibrous connective tissue of the gum. It is found that most of the blood vessels are located in the gingival zone and less concentrated is in the apical region. Vascular density of the microcirculatory bed is decreased more than twice from 27.4±8.3% to 13.16±1.9% (Table.) according to morphometric studies in comparison with the control group ($p<0.05$).

Both massive and focal injuries have been revealed in lamina propria of the mucosa with muscular lamina involvement in slides stained with iron hematoxylin according to Rego (Fig. 2): the intensely stained black or dark gray fibers are alternated with areas of light gray color (Fig. 2). Moreover, such foci have been determined in different tissue structures and were very common both in epithelium and in lamina propria (Fig. 2a). Staining with iron hematoxylin according to Rego is an indicator of the mosaic of metabolic changes as consequence of the hypoxia development; and that is important, areas of such changes are coincided with the presence of inflammatory infiltrates (Fig. 2b,c) of the mucosal plate and the zone of the most pronounced changes in the epithelium. So, it could be suggested that changes in the microcirculatory bed are realized in the development of inflammatory changes in the lamina propria of the mucosa and than in sclerotic disorders which have been revealed well in slides stained according to Van Gieson and to Mallory (Fig. 1b,c). Specific density of rough connective tissue is increased about twice from 21.47±6.38% to 39.87±5.39% (Table) in lamina propria according to morphometric studies in comparison with the control group ($p<0.05$). Spearman's rank correlation coefficient (r) between specific densities of MCB vessels and rough connective tissue (%) is 0.87.

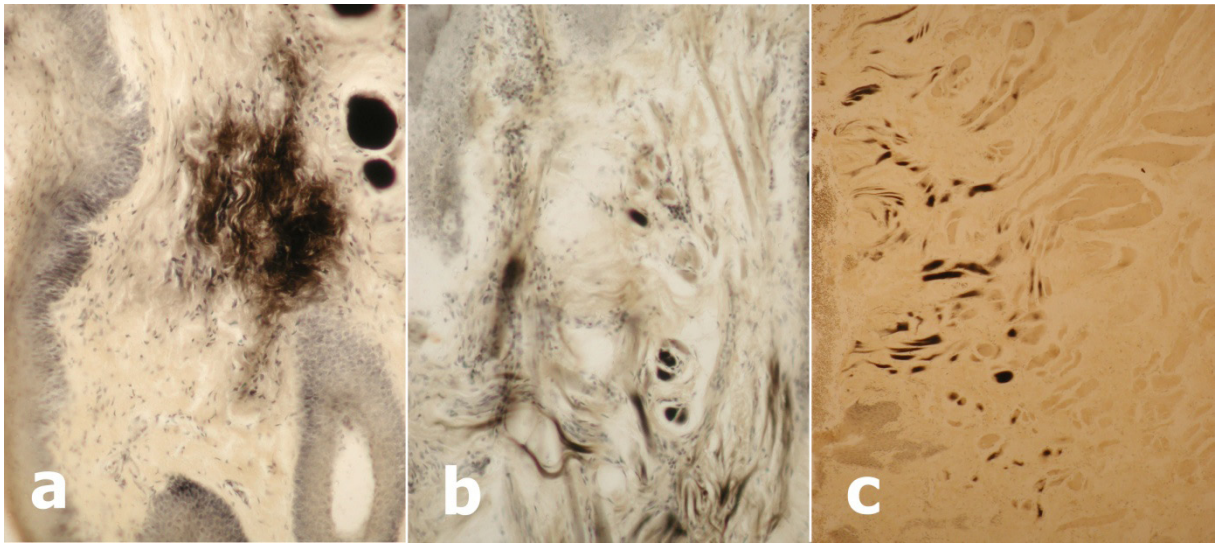

Fig. 2. Focal injuries in lamina propria with involvement of connective tissue fibers, uneven stained epithelial cells, staining according to Rego, magnification x200 (a); indicator of the mosaic of metabolic changes as consequence of the hypoxia development in muscular connective tissue fibers and formation of inflammatory infiltrates, staining according to Rego, magnification x100 (b); area of massive inflammatory infiltrate (left) and injured myocytes beside, staining according to Rego, magnification x100 (c)

Superficial papillary layer of the lamina propria consists of loose connective tissue which is represented mainly elastic fibers. Reticular layer is located deeper and is represented by rough connective tissue fibers. There are inflammatory cellular elements between connective tissue fibers (fibroblasts, histiocytes, lymphocytes, mast cells, macrophages and other) with diffuse and focal location. Signs of accumulation of inflammatory exudate have been demonstrated as defibration both in superficial and reticular layers.

So as result of our work we can affirm one more additionally to other authors [2] that the MS per se is associated with both dysfunction of the large and small microcirculation. We have shown that vascular dysfunction in the MS affects small vessels and may link development of hypoxia with activation of connective tissue that leads to sclerotic changes in oral mucosa. Sclerotic process is final stage of oral mucosa transformation as hypoxic injuring of tissue is realized in inflammation with appearance signs of periodontitis as changes in epithelium and lamina propria.

Mounting evidence suggests that the MS adds to the burden of vascular damage and microvascular dysfunction may promote the progression of macrovascular disease through direct and indirect mechanisms [8].

Our results are combined with studies in literature indicating that periodontal pathology could be developed in MS. There are data that increase in the duration of MS and the presence of complications in other organs caused by the disease result in a more sever form of periodontal pathology [17]. Pathogenesis of periodontal inflammation might involve inhibition of cell death, through the apoptotic factors, due to the DNA damage by the product of catalysis [10, 11] with highest levels activity found at sites of chronic inflammation.

We suggest and support [8] that a synthesis of current and emerging therapeutic interventions might provide the basis for an improved strategy aimed at preventing microangiopathy related morbidity with vasculoprotective properties that is logical and attractive, but requires further investigation in oral cavity relation. Future interventional studies are required to determine whether individually or simultaneously improving the components of the MS will lead to enhancement of microcirculatory function. The investigation of a possible relationship between the inflammatory pathology of periodontal tissues and microvascular complications of other organs showed that microvascular complications were diagnosed more frequently in the presence of a more severe inflammatory pathology of periodontal tissues [17]. Changes in cellular component with reducing cells of inflammatory origin could prove positive process in oral mucosa that is summarize as combination of connective tissue with fibroblasts, fibrocytes, histiocytes which have an important role in reparation with many studies in literature have examined the effect of different method of therapy on fibroblast cell growth and reducing of inflammation [6,7,18]. Inflammatory process in the oral cavity could be characterized by morphological picture with inflammatory, degenerative, dyscirculatory changes which are accompanied by disturbance of nitric oxide synthase with significant changes of it activity [15] and changes in antioxidant balance [16] that also could be used in creation of preventive measures.

Conclusions. It is established that metabolic syndrome is realized in significant changes in the microcirculatory bed of the periodontal, which can underlie the pathogenesis of inflammatory changes. Microcirculation disorders are characterized by significant changes in microangioarchitecture with uneven congestion, reduced specific volume of MCB vessels, thickening of vascular walls. Specific density of MCB vessels is changed from 27.40±8.31 % to 13.16±1.94 % statistically. Growth of connective tissue is developed as result of hypoxia with presence of collagen fibers in all layers of oral mucosa lamina propria. Specific density of rough connective tissue is increased from 21.47±6.38 % to 39.87±5.39 %.

Conflict of Interest Statement. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUMMARY

INFLUENCE OF METABOLIC SYNDROME ON CONDITION OF MICROCIRCULATORY BED OF ORAL CAVITY

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Metabolic syndrome (MS) can be characterized as the clustering of combination of impaired glucose regulation, metabolic disorders accompanied by abdominal obesity, hyperglycemia, high blood pressure and dyslipidemia. Detection of changes in microcirculatory bed (MCB) of oral cavity in metabolic syndrome could be important for completion of gap for developing of adequate therapeutical measure for prevention of pathological periodontal disorder that was the purpose of our study.

We performed experimental investigation with modulation of MS (on white male rats 1.5-2 months of age) during 70 days using a diet in which the oral pork fat was daily administered orally (40% of the rat weight), and 10% fructose ad libitum solution was used also instead of drinking water. Obtained specimens of soft tissues of the oral cavity were stained with histological and histochemical methods. The microscopic study with statistical analysis was performed.

As result of our work it is established that metabolic syndrome is realized in significant changes in the microcirculatory bed of the periodontal, which can underlie the pathogenesis of inflammatory changes. Microcirculation disorders are characterized by significant changes in microangioarchitecture with uneven congestion, reduced specific volume of MCB vessels, thickening of vascular walls. Specific density of MCB vessels is changed from 27.40±8.31 % to 13.16±1.94 % statistically. Growth of connective tissue is developed as result of hypoxia with presence of collagen fibers in all layers of oral mucosa lamina propria. Specific density of rough connective tissue is increased from 21.47±6.38 % to 39.87±5.39 %.

Keywords: metabolic syndrome, microcirculatory bed, oral cavity, histology, experiment.

РЕЗЮМЕ

ВЛИЯНИЕ МЕТАБОЛИЧЕСКОГО СИНДРОМА НА СОСТОЯНИЕ МИКРОЦИРКУЛЯТОРНОГО РУСЛА ПОЛОСТИ РТА

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Метаболический синдром (МС) можно охарактеризовать как кластеризацию комбинации нарушенной регуляции глюкозы, метаболических нарушений, сопровождающихся абдоминальным ожирением, гипергликемией, высоким кровяным давлением и дислипидемией. Выявление изменений в микроциркуляторном русле (МЦР) полости рта при МС позволит ликвидировать пробел в знаниях о патологии пародонта, что может быть использовано для разработки адекватных терапевтических мероприятий для профилактики патологии пародонта, что и явилось целью данного исследования.

МС моделировали на белых крысах-самцах в возрасте 1,5-2 месяцев в течение 70 дней с использованием диеты, согласно которой крысам перорально вводили свинной жир ежедневно (40% от веса крысы), вместо питьевой воды использовали 10% раствор фруктозы. Полученные образцы мягких тканей ротовой полости окрашивались гистологическими и гистохимическими методами. Проведено микроскопическое исследование со статистическим анализом.

Установлено, что МС реализуется значительными изменениями в микроциркуляторном слое пародонта, что, по всей вероятности, лежит в основе патогенеза воспалительных изменений. Нарушения микроциркуляции характеризуются значительными измене-

ниями в микроангиоархитектонике с неравномерным кровенаполнением, уменьшением удельного объема сосудов МЦР и утолщением сосудистых стенок. Удельная плотность сосудов МЦР изменяется с 27,40±8,31% до 13,16±1,94%. В результате гипоксии активизируется рост соединительной ткани с преобладанием коллагеновых волокон во всех слоях слизистой оболочки полости рта. Удельная плотность грубой соединительной ткани увеличивается с 21,47±6,38% до 39,87±5,39%.

რეზიუმე

მეტაბოლური სინდრომის გავლენა პირის ღრუს მიკროცირკულაციური კალაპოტის მდგომარეობაზე

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მეტაბოლური სინდრომი (მს) ხასითდება როგორც გლუკოზის რეგულაციისა და აბდომინური სიმსუქნით თანხვედრილი მეტაბოლური დარღვევების, ჰიპერგლიკემიის, მაღალი არტერიული წნევის და დისლიპიდემიის კომბინაციების კლასტერიზაცია. მეტაბოლური სინდრომის დროს პირის ღრუს მიკროცირკულაციურ კალაპოტში განვითარებული ცვლილებების გამოვლენა შესაძლებელს გახდის აღმოიფხვრას ხარვეზები წარმოდგენებში პაროდონტის პათოლოგიის შესახებ, რაც შეიძლება გამოყენებულ იქნას ადეკვატური თერაპიული ღონისძიებების შესამუშავებლად პაროდონტის პათოლოგიის პროფილაქტიკისათვის. სწორეთ ეს წარმოადგენდა კვლევის მიზანს.

ავტორებმა მოახდინეს მეტაბოლური სინდრომის მოდელირება 1.5-2 თვის ასაკის მამრ თეთრ ვირთაგვებზე დიეტის გამოყენებით 70 დღის განმავლობაში: ყოველდღიურად, პერორალურად მიეწოდებოდათ ღორის ქონი (სხეულის მასის 40%); ხოლო სასმელი წყლის ნაცვლად - ფრუქტოზას 10%-იანი ხსნარი. პირის ღრუს რბილი ქსოვილების ნიმუშების შეღებვა ხდებოდა ჰისტოლოგიური და ჰისტოქიმიური მეთოდების გამოყენებით. ჩატარდა მიკროსკოპული კვლევა და სტატისტიკური ანალიზი.

დადგენილია, რომ მეტაბოლური სინდრომი რეალიზდება მნიშვნელოვანი ცვლილებებით პაროდონტის მიკროცირკულაციურ კალაპოტში, რაც შეიძლება გახდეს ანთებითი პროცესების განვითარების მიზეზი. მიკროცირკულაციის დარღვევები ხასიათდება სისხლის მიმოქცევის მნიშვნელოვანი ცვლილებებით, არათანაბარი სისხლსავსეობით, მიკროცირკულაციური სისხლძარღვების ხვედრითი მოცულობის შემცირებით, სისხლძარღვთა კედლის გასქელებით. მიკროცირკულაციური სისხლძარღვების ხვედრითი მოცულობა შეიცვალა 27,40±8,31%-დან 13,16±1,94%-მდე. ჰიპოქსიის შედეგად პირის ღრუს ლორწოვანი გარსის ყველა შრეში გააქტიურდა შემაერთებელი ქსოვილის ზრდა კოლაგენური ბოჭკოების სიჭარბით. უხეში შემაერთებელი ქსოვილის ხვედრითი მოცულობა გაიზარდა 21,47±6,38%-დან 39,87±5,39%-მდე.

EXPRESSION OF CYCLIN E IN BASAL-LIKE BREAST CARCINOMA

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Invasive ductal carcinoma is the most prevalent type amongst other histological types of breast carcinoma, which, according to various literature sources, accounts for 40-75% of total breast cancer cases [1,3]. In addition, it has been shown that treatment and prognosis of the disease depends on its clinical, histological and biological characteristics: gene expression analysis has revealed several different subtypes of invasive ductal carcinoma [10]. These subtypes incorporate estrogen receptor (ER) negative group, ER – positive group, including luminar subtypes A and B, HER2 – positive group and so-called normal breast like tumor subtypes. The mentioned subtype significantly differs from one another both by prognosis as well as by therapeutic target spectrum [5,11].

In this aspect, the group of hormone receptor (ER/PR) and HER2 negative tumors evoke special interest; they are also called triple-negative tumors and account for 2-18% of breast cancer [14]. The above mentioned ER/

PR/HER2 – negative tumors include so-called basal-like tumors, which express basal type cytokeratins (verified by gene expression analysis) [12].

This group, however, incorporates both basal-like type and also the tumors, which do not express basal cytokeratins [11,12]. Additionally, the interest of researchers towards basal-like tumors is further increased by absence of optimal options of targeted therapy for this subgroup, which is mostly accounted by sparse knowledge about carcinogenesis (stages and/or main players) of these tumors.

It is known that the cell cycle is regulated by consecutive formation and degradation of different cyclins. Cyclins in human body activate several cyclin-dependent kinases, which play important role in key phases of cell cycle. Findings demonstrating the expression of incompatible cyclins lead to suggestion that some of these cyclins may be involved in oncogenesis, acting as protooncogens.

The study of Cyclin E (its immunohistochemical expression and prognostic value) in basal-like carcinomas is very interesting, as in general, importance of its shift in carcinogenesis is well known [7], specifically, the increasing expression of Cyclin E correlates with the stage and degree of malignancy of tumors.

To evaluate Cyclin E activity level in basal-type breast carcinoma, also the molecular features of this tumor and its probable prognostic value. In case of breast carcinoma, low molecular Cyclin E isoforms are estimated as important pathogenetic and prognostic factor from early stages in "early stage node" negative tumor, as markers of prognostic value (patients).

It has been shown that the basal-like breast cancer variant is characterized in general by typical immune-profile: namely, by expression of cytokeratin CK5/6, CR14, CK/17, Vimentin and Her-1 [2,3]. But more intense degree of necrosis and uniformly higher expression of CD117 and Caspase-3 in this particular histological type of tumor set the new agenda for study goals, making more detailed morphologic analysis and inclusion of additional immunomarkers with their interpretation more significant. In this aspect, we considered the study of Cyclin E immune-profile to be of higher actuality in basal-like breast cancer tissue.

Material and methods. The study used the field post-operative and/or biopsy materials (paraffin blocks) from 362 patients, who underwent surgery for breast cancer between 2008-2009 years in National Cancer Center of Tbilisi and their medical records.

3μm tissue samples were taken from paraffin blocks for immunohistochemical studies. Immunohistochemical study was performed by cytokeratin 5 (clone XM26; dilution 1:100; Novocastra Laboratories), cytokeratin 17 (clone E2; dilution 1:40; Novocastra Laboratories) and Cyclin E (clone 13A; dilution 1:100; Novocastra Laboratories). Antigen reduction was performed in 0.01M citrate buffer with pH 6.0 + TWEEN, 100^0 C (pressure cooker). Antigen-antibody complex was detected by use of Novolink Polimer Delection System (Novocastra Laboratories). From the samples studied, immunohistochemistry in 53 cases revealed the so-called triple negative (ER/PR/HER2 negative) phenotype. From the studied samples, stage I was observed in 11 cases; stage IIA – in 24 cases, IIB – in 0 cases, IIIA -in 6 cases, IIIB and IIIC were 0, and stage IV was observed in 3 cases respectively. The usage of material underwent special procedures of granting access from ethical committee of National Cancer Center, with provisions of anonymity for personal data.

Statistical analysis of data was done by SPSS-14 softwere program.

Results and their discussion. As demonstrate in our material, most of the triple-negative breast cancer samples show low differentiation grade: Grade 1 frequency accounted for 1.8% (1/53), Grade 2 was seen in 28.3% of cases (15/53) and Grade 3 was seen in 69.8% cases (37/53) respectively. Further study on cytokeratins expression showed that CK5 was expressed in 66% of cases (35/53), while CK17 was found in 49% (26/53). 24.5% of cases was positive for CK5/CK17 both (19/53). 9.4% of cases appeared to be CK2/CK17 negative (5/53). Distribution of abovementioned markers according to malignancy grade of breast cancer is shown in Diagramma 1.

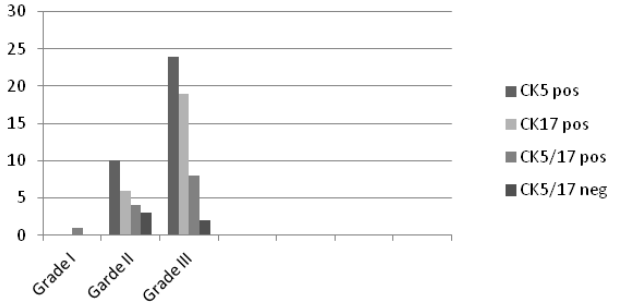


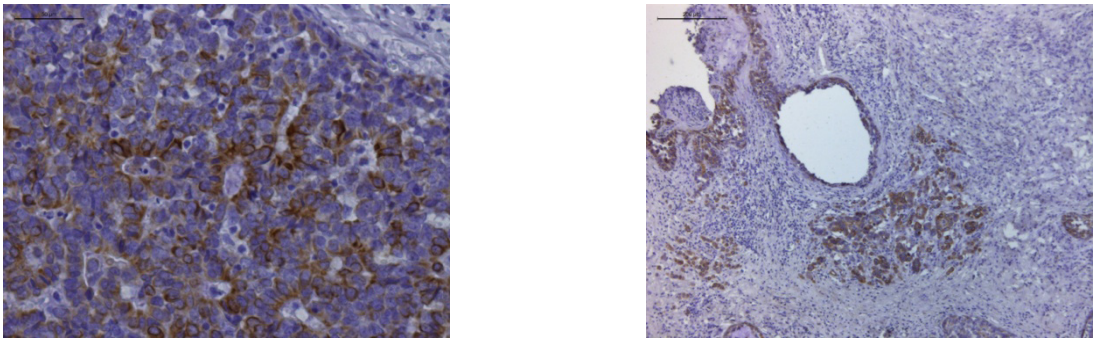
Diagramma 1. Correlation of basal-like cytokeratin negative breast cancer expression with different grades of malignancy in triple

Basal-like tumor with stably high expression of cytokeratins was found in 48 cases of triple-negative cancer cases overall, out of 53 (Fig. 1).

After obtaining of this finding, we continued the study of that 48 cancer cases in the aspect of Cyclin E expression, which could be positive for at least one basal-like cytokeratin (90.5%).

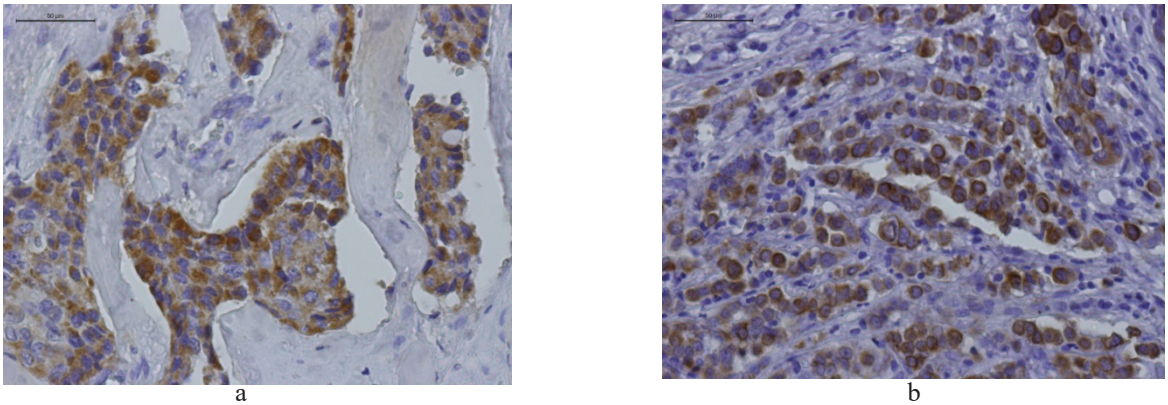
The study results showed that Cyclin E was positive in 58.3% (28/48) of 48 cases which were positive for basal layer cell markers. Correlation of these markers with the stages of basal-like breast cancer is shown in table 2 (r=0.029).

According to our data, it's evident that expression of Cyclin E is related with more advanced clinical stage (Fig. 2, Cyclin E and CK5/17).

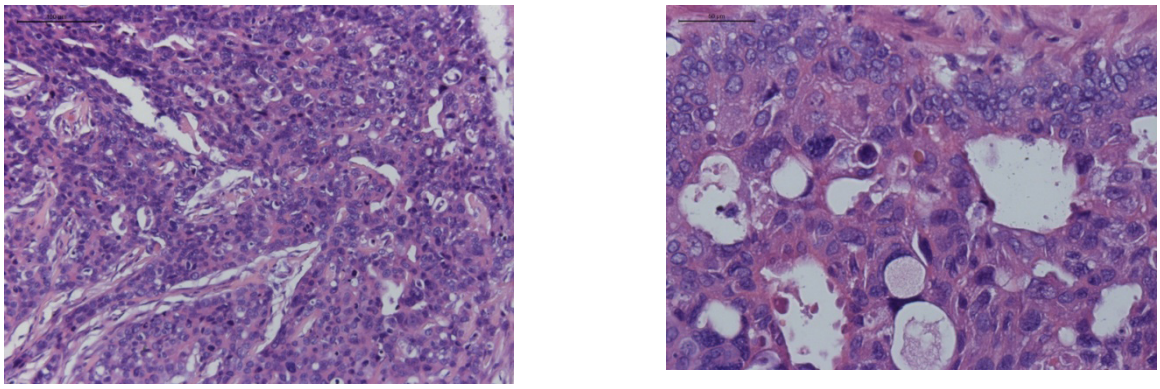


a b

Fig.1. Cytoplasmic expression of CK5/17 in basal-like cancer cell: a -moderate expression; b -week expression. x200. Immunoperoxidase reaction



a b



c d

Fig. 2. Basal-like tumor immunostaining: a. Cyclin E, x200;b. CK5/17 x200. Immunoperoxidase reaction. c, d – invasive ductal carcinoma with basal like phenotype. H&E staining, x400

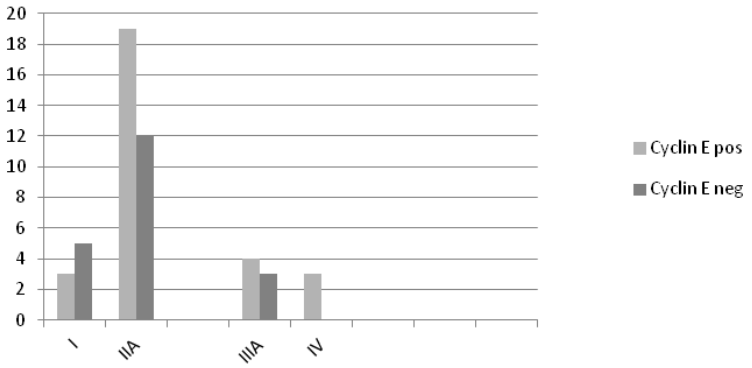


Diagramma 2. Cyclin E expression in different stages of basal-like breast cancer

The results of the study demonstrated that triple-negative cancer cases mostly involved tumors with poor differentiation (70.5%, Grade 3) [4,8]. Our data verifies that their triple negative immune profile shows expression of basal-like cytokeratin CK5/17 (91.1%) [6]. In general, by our data, expression of one or two cytokeratin is related with higher grade of malignancy. We assume that intensive expression of transcription factors and rapid interchanging of G – S phases of cell cycle are presumably leading to gene amplification, and Cyclin E plays one of the leading roles in this sequence of events in dysregulation point of view. In addition, the expression of Cyclin E is seen specifically in basal-like tumors (54.8%), or they are negative for it (45.4%).

Importantly, expression of Cyclin E in basal-like types of breast cancer is in direct correlation with III-IV clinical stage and respectively, with poor prognosis [13].

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SUMMARY

EXPRESSION OF CYCLIN E IN BASAL-LIKE BREAST CARCINOMA

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Results of study under 362 patients biopsy materials in Tbilisi National Cancer Center were shown that basal-like type breast carcinoma is characterizes by different reaction on Cyclin E, CK5/17 and ER/PR immunoreactivities. Basal-like tumor immunoreactivity on Cyclin E differs based they clinical stage and seen maximum correlation with III-IV stage and poor prognosis.

Keywords: Basal-like breast carcinoma, Cyclin E, CK5/17 immunoreactivities.

РЕЗЮМЕ

ЭКСПРЕССИЯ CYCLIN E В КЛЕТКАХ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ БАЗАЛЬНО-КЛЕТОЧНОГО ТИПА

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Изучена экспрессия Cyclin E в операционно< материале от 362 пациентов с диагнозом рака молочной железы базально-клеточного типа.Показано, что в карциномах указанного гистологического типа отмечается гетерогенность по экспрессии Cyclin E, CK5/17 и ER/PR. Иммуноэкспрессия Cyclin E возрастает в прямой корреляции с тяжестью клинического течения болезни, особенно III-IV стадии, и неблагоприятным прогнозом.

რესიუმე

Cyclin E ექსპრესია ძუძუს ბაზალურ-უჯრედოვან კარცინომის ქსოვილებში

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თბილისის ეროვნული ონკოლოგიური ცენტრის ბაზაზე შესწავლილია 362 პაციენტის ძუ-

ძუს კიბოს ბიოპტატები ბაზალურ-უჯრედოვანი ტიპის კარცინომის ჰისტოლოგიურ ვარიანტში.

გამოკვლეულია Cyclin E, CK5/17 и ER/PR რეცეპტორთა იმუნოექსპრესია.

დადგენილია, რომ აღნიშნულ ფაქტორებს აქვთ დიფერენცირებული იმუნოექსპრესია, მაგრამ Cyclin E რეაქცია პირდაპირ აღმავალ კორელაციაში იმყოფება დაავადების კლინიკური სიმძიმის სტადიასა (III-IV) და არაკეთილსაიმედო პროგნოზთან.

VON WILLEBRAND FACTOR IMMUNOHISTOCHEMICAL STAINING QUANTITATIVE OPTICAL DENSITY PARAMETERS IN THE ENDOTHELIUM AND FIBRINOID OF THE PLACENTA DURING SECUNDINES INFLAMMATION AND CONCOMITANT IRON DEFICIENCY ANEMIA IN GRAVIDAS

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Von Willebrand factor is often used as an activation marker or marker of endothelial dysfunction [8,4]. In the recent years, other functions of von Willebrand factor have been identified, which suggests that this protein is involved in several other vascular processes [6]: angiogenesis and vascularization, proliferation of leiomyocytes. Shortly after von Willebrand factor was identified as a plasma protein, its ability to be adsorbed by collagen was reported as well. There are new suggestions about von Willebrand as a pro-inflammatory agent. An increased concentration of this protein was detected in plasma, particularly, in bacterial and viral infections and autoimmune diseases. It is suggested that the inflammation can be a general stimulus for the release of endothelial cells - the ULVWF (with ultra-high von Willebrand factor), which can lead to a deficiency of ADAMTS13-metaloproteinase, which, in turn, is able to break up and formulate its multimers of normal and low molecular weight. As a result, ULVWF multimers can be stored in endothelial cells of blood vessels and blood plasma for a long time to cause adhesion and aggregation of platelets, which can lead to thrombosis. This confirms the connection between the inflammation and thrombosis. [2].

The quantitative characteristics concerning the optical density of von Willebrand factor immunohistochemical staining in the placenta are to be found only in several studies [3-5, 9], but the aspect of inflammation and iron deficiency anemia in pregnant women has not been addressed in these studies.

The aim of the study was to establish optical density quantitative parameters of von Willebrand factor immunohistochemical staining in the endothelium and fibrinoid of placenta during acute and chronic inflammation of the secundines combined with iron deficiency anemia in pregnant women.

Materials and methods. The total number of 198 placentas was examined, including those studied during physiological pregnancy on the background of iron deficiency anemia in gravidas without the secundines inflammation (for comparison purposes).

The numbers observed in specific research groups are presented in Tables 1 and 2.

The material was kept in a buffered neutral 10% formalin solution for 20-22 hours, followed by dehydrating in the ascending battery of alcohols and placing in paraffin at 56*C. The immunohistochemical techniques were performed on sections made from the paraffin blocks (after deparaffinization) using the von Willebland visualization of primary antibodies by a polymeric system (DAKO) with a diaminobenzidine dye. Digital copies of the image were obtained using the microscope Delta Optical Evolution 100 (Planar Lenses) and the digital camera Olympus SP-550UZ. The method of computer microdensitometry was implemented in the medium of computer program ImageJ (1.48, W. Rasband, National Institutes of Health, USA) [10]. The optical density of the histochemical staining was measured in relative units (in the range from 0 to 1, based on the logarithmic transformations of the brightness index in gradations from 0 to 255).

The arithmetic mean and its error (for optical density) were calculated using the computer program PAST 3.16 (free license, O. Hammer, 2017) [7]. Differences in the average tendencies were determined with the help of a two-sided odd *t*-test with a preliminary check on the normality of distribution in statistical samples. Statistically significant differences were considered at $p \leq 0.05$.

Results and their discussion. The inflammation was diagnosed based on the histological sections having been stained with hematoxylin and eosin. Polymorphonuclear leukocytes with the admixture of individual lymphocytes prevailed in acute forms of inflammation in the nidus of infection. In chronic forms of inflammation lymphocytes were predominantly determined in the focus of research.

In both forms of inflammation, altered changes in local cells and interstitial edema were observed.

During the course of conducting immunohistochemical studies it was found that the specific von Willebrand factor immunohistochemical staining was noticed in several structures of the placenta: in endothelial cells of blood vessels, in the fibrinoid at different localizations, and sometimes on the surface of the trophoblasts of the placental chorionic villi. Our article presents the results of quantitative parameters of the optical density of the immunohistochemical staining for the von Willebrand factor of the endothelial cell cytoplasm and the fibrinoid of the chorionic and basal plates in accordance with the localization of the inflammatory process.

During the physiological pregnancy the intensity of the staining for the von Willebrand factor was more pronounced in the endothelium of the blood vessels (Fig. 1, 2), in comparison to the fibrinoid (Fig. 3, 4), with the degree of perforation varied considerably among the endothelial cells of the blood vessel. Although, it was characterized by the same feature. Small groups of various shaped circular cells were found in the histological sections of placenta preparations with the signs of chronic inflammation. These cells were also intensively stained for the von Willebrand factor. This phenomenon can probably be interpreted as the process of neoplasm of blood vessels, i.e. these facts reflect the processes of angiogenesis.

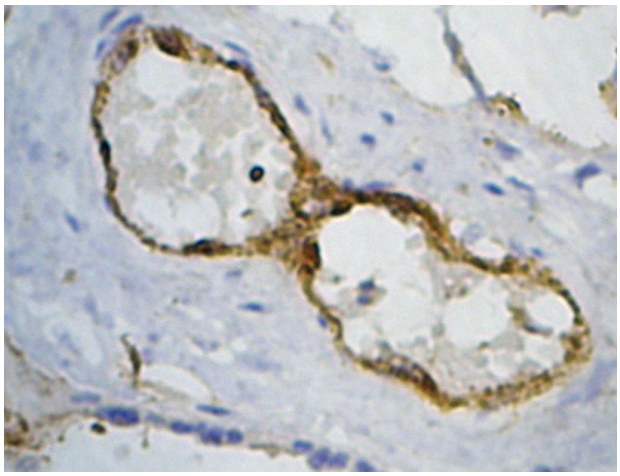

Fig.1. Von Willebrand factor in the endothelium of the blood vessel of the chorionic plate of the placenta. Observation of the physiological pregnancy. Immunohistochemical technique using primary antibodies against von Willebrand factor. Ob.40^{x}.Oc.10^{x}

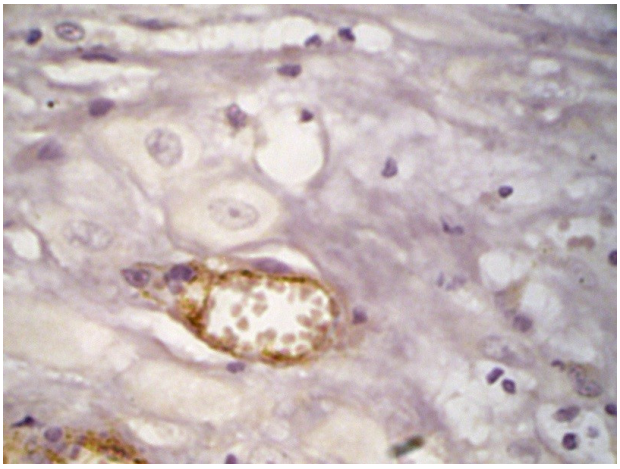

Fig.2. Von Willebrand factor in the endothelium of the blood vessel of the basal plate of the placenta. Observation of the physiological pregnancy. Immunohistochemical technique using primary antibodies against von Willebrand factor. Ob.40^{x}.Oc.10^{x}

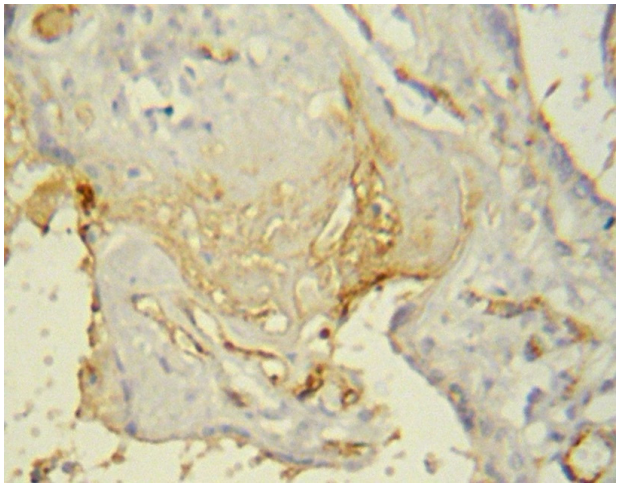

Fig.3. Von Willebrand factor in the fibrinoid of the chorionic plate of the placenta. Observation of the physiological pregnancy. Immunohistochemical technique using primary antibodies against von Willebrand factor. Ob.40^{x}.Oc.10^{x}

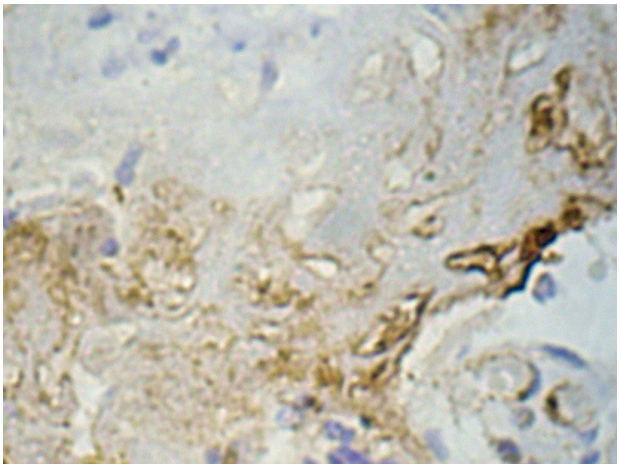

Fig.4. Von Willebrand factor in the fibrinoid of the basal plate of the placenta. Observation of the physiological pregnancy. Immunohistochemical technique using primary antibodies against von Willebrand factor. Ob.40^{x}.Oc.10^{x}

Table 1. Optical density of the immunohistochemical staining in the fibrinoid and endotheliocytes of the blood vessels of the placenta (immunohistochemical technique using primary antibodies against von Willebrand factor) during physiological pregnancy and iron deficiency anemia in pregnant women (M±m)

Structures	**Research groups**	
	Observation of physiological pregnancy (n=20)	Observation of non-inflammatory iron deficiency anemia in pregnant women (n=21)
Endotheliocytes of the chorionic plate	0,228±0,0025	0,322±0,0021 (P<0,001)
Fibrinoid of the chorionic plate	0,124±0,0021	0,149±0,0020 (P<0,001)
Endotheliocytes of the basal plate	0,374±0,0022	0,385±0,0028 (P=0,003)
Fibrinoid of the basal plate	0,142±0,0019	0,168±0,0022 (P<0,001)

Table 2. Optical density of the immunohistochemical staining in the endotheliocytes of the blood vessels of the placenta (immunohistochemical technique using primary antibodies against von Willebrand factor) in combination with different forms of the secundines inflammation and iron deficiency anemia in pregnant women (M±m)

Research groups	**Observation of the secundines inflammation in pregnancy without anemia**	**Observation of the secundines inflammation in iron deficiency anemia of pregnant women**
Acute chorioamnionitis (endothelium of the chorionic plate was studied)	0,323±0,0024 (n=23)	0,386±0,0025 (n=21) P<0,001
Chronic chorioamnionitis (endothelium of the chorionic plate was studied)	0,328±0,0025 (n=20)	0,385±0,0027 (n=21) P<0,001
Acute basal deciduitis (endothelium of the basal plate was studied)	0,396±0,0027 (n=16)	0,408±0,0029 (n=15) P=0,005
Chronic basal deciduitis (endothelium of the basal plate was studied)	0,398±0,0029 (n=21)	0,416±0,0032 (n=20) P=0,005

Table 3.Optical density of the immunohistochemical staining in the fibrinoid of the placenta (immunohistochemical technique using primary antibodies against von Willebrand factor) in combination with different forms of the secundines inflammation and iron deficiency anemia in pregnant women (M±m)

Research groups	**Observation of the secundines inflammation in pregnancy without anemia**	**Observation of the secundines inflammation in iron deficiency anemia of pregnant women**
Acute chorioamnionitis (fibrinoid of the chorionic plate was studied)	0,126±0,0029 (n=23)	0,152±0,0028 (n=21) P<0,001
Chronic chorioamnionitis (fibrinoid of the chorionic plate was studied)	0,158±0,0030 (n=20)	0,171±0,0036 (n=21) P=0,009
Acute basal deciduitis (fibrinoid of the basal plate was studied)	0,146±0,0024 (n=16)	0,170±0,0029 P=0,001 (n=15)
Chronic basal deciduitis (fibrinoid of the basal plate was studied)	0,170±0,0033 (n=21)	0,181±0,0034 (n=20) P=0,026

As to the fibrinoid, of both chorionic and basal plates, it should be mentioned that the von Willebrand factor in it was visualized in the form of thread-like chaotic oriented structures.

For the purpose of comparison, the optical density quantitative analysis of the von Willebrand factor immunohistochemical staining was conducted in the endothelium and fibrinoid of the placenta during physiological pregnancy and iron deficiency anemia in gravidas. Average data on the processes, which concern the observations of physiological pregnancy and iron deficiency anemia are given in Table 1.

It is obvious from the previously mentioned data that the intensity of the optical density of staining in the endothelial cells and fibrinoid in physiological pregnancy in different placental structures significantly differs. The von Willebrand factor is higher in endothelial cells than in fibrinoid, which confirms the findings of a visual assessment of the intensity of histological sections perforation, and the staining is most pronounced in the basal plate of the placenta.

Furthermore, iron deficiency anemia in gravidas (IDAG) causes an increase in the optical density of staining in all the studies, with the maximum indices in the basal plate of the placenta, both in the endothelial cells and in the fibrinoid.

These indicators are important in terms of estimating the optical density of the immunohistochemical staining as the key indicator of von Willebrand factor level.

According to the data given in Table 2, it was found that in all the forms of inflammation of the secundines and the structures under study, the optical density of the von Willebrand immunohistochemical staining in the endothelium of the blood vessels significantly increases in comparison with the physiological pregnancy. However, in relation to non-inflammatory IDAG, there are no statistically significant mean differences in the average trends between observations. The inflammation on the background of iron deficiency anemia in gravidas contributes to a rapid increase in the indices, with the highest data in the endothelial cells of the basal plate in chronic basal deciduitis.

At the same time, it was marked that, as an average tendency, anemia is accompanied by statistically higher significant indicators in acute and chronic forms of chorioamnionitis than in basal deciduitis.

According to the data in Table 3, only in chronic forms of chorioamnionitis and basal deciduitis, the optical density of staining in the fibrinoid of the chorionic and basal plate of the placenta, is higher than in physiological pregnancy. And in comparison with IDAG in absence of the inflammation, the intensity of staining increases only in the fibrinoid of the chorionic plate in chronic chorioamnionitis, while in acute forms, the indices are significantly lower than in the comparison group. It was found, at the same time, that the quantitative parameters of the von Willebrand factor staining optical density in all the inflammatory forms combined with IDAG, significantly increase in the corresponding structures of the placenta, in comparison with physiological pregnancy and inflammation of the placenta, with the maximum numbers reported during acute chorioamnionitis and basal deciduitis. It should be emphasized that only chronic inflammatory processes in combination with IDAG cause a change in the indices compared with IDAG without an inflammation.

Conclusions. 1. The intensity of the von Willebrand factor staining optical density in the endothelium of the blood vessels is more pronounced in comparison with the fibrinoid. This pattern is observed both in cases of physiological pregnancy and the secundines inflammation.

2. The von Willebrand factor immunohistochemical staining optical density is significantly increased in the endothelium of blood vessels in all forms of the secundines inflammation, in comparison with physiological pregnancy. At the same time, iron deficiency anemia of pregnant women is accompanied with maximum levels of optical density in the endothelium, whereas in chronic forms of inflammation, the average indices are higher than those for acute forms of inflammation.

3. In the fibrinoid of the chorionic or basal plate, the staining optical density of von Willebrand factor does not change in acute forms of the secundines inflammation, but increases with chronic forms. In this case, iron deficiency anemia in pregnant women is accompanied by maximum levels of the staining optical density in the fibrinoid, and in chronic forms of inflammation, the average indices are higher than those with the acute forms of inflammation.

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SUMMARY

VON WILLEBRAND FACTOR IMMUNOHISTOCHEMICAL STAINING QUANTITATIVE OPTICAL DENSITY PARAMETERS IN THE ENDOTHELIUM AND FIBRINOID OF THE PLACENTA DURING SECUNDINES INFLAMMATION AND CONCOMITANT IRON DEFICIENCY ANEMIA IN GRAVIDAS

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The aim of the research was to set the optical density quantitative parameters of the von Willebrand factor immunohistochemical staining (vWF) in the endothelium and fibrinoid of the placenta during the secundines inflammation concomitant with iron deficiency anemia in gravidas.

The total number of 198 placentas was studied. The immunohistochemical technique was performed using the visualization of the primary antibodies to vWF with a diaminobenzidine dye polymer system. The optical density of the histochemical staining was measured by means of computer microdensitometry after the digital copies of the images had been obtained.

All the cases of the secundines inflammation and the structures under study were found to have a significant increase in the optical density of the vWF immunohistochemical staining in the endothelium of the blood vessels as compared to the physiological pregnancy. Iron deficiency anemia in gravidas (IDAG) contributes to an increase in the indices of the inflammation, the highest data pertaining to the endothelial cells of the placental basal plate in chronic basal deciduitis.

The optical density of the staining in the fibrinoid of the chorionic and basal plates during chronic forms of chorioamnionitis and basal deciduitis is higher than the optical density inherent in physiological pregnancy. The intensity of staining increases in presence of all the forms of inflammation on the background of IDAG in comparison with physiological pregnancy with placenta inflammation. Compared with IDAG in absence of the inflammatory processes, only chronic inflammatory processes reveal a change in indices.

Consequently, the optical density of the staining significantly increases in the endothelium of blood vessels in all forms of the secundines inflammation, in comparison with the physiological pregnancy, whereas in fibrinoid the same process is reported only in chronic course. In this case, IDAG is accompanied by maximum levels of optical density in the endothelium and fibrinoid, whereas in chronic, the average indices are higher than those in acute forms.

Keywords: von Willebrand factor, inflammation of the placenta, iron-deficiency anemia in gravidas.

РЕЗЮМЕ

КОЛИЧЕСТВЕННЫЕ ПАРАМЕТРЫ ОПТИЧЕСКОЙ ПЛОТНОСТИ ИММУНОГИСТОХИМИЧЕСКОЙ ОКРАСКИ НА ФАКТОР von WILLEBRAND В ЭНДОТЕЛИИ И ФИБРИНОИДЕ ПЛАЦЕНТЫ ПРИ СОЧЕТАННЫХ ВОСПАЛЕНИИ ПОСЛЕДА И ЖЕЛЕЗОДЕФИЦИТНОЙ АНЕМИИ У БЕРЕМЕННЫХ

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Целью исследования явилось установление количественных параметров оптической плотности иммуногистохимического окрашивания на фактор фон Виллебранда в эндотелии и фибриноиде плаценты при сочетанном воспалении последа и железодефицитной анемии беременных.

Изучено 198 плацент. Иммуногистохимическую оценку проводили с использованием первичных антител на фактор фон Виллебранда (vWF) с визуализацией полимерной системой красителя диаминобензидина. Оптическая плотность гистохимического окрашивания измерялась с помощью компьютерной микросенситометрии после получения цифровых копий изображения.

Обнаружено, что в сравнении с физиологической беременностью при наличии воспаления последа и исследуемых структур значительно увеличена оптическая плотность иммуногистохимического окрашивания на vWF в эндотелии кровеносных сосудов. Железодефицитная анемия беременных (IDAG) способствует повышению показателей воспаления.

Оптическая плотность окрашивания в фибриноиде хорионической и базальной пластинки выше,

чем оптическая плотность при физиологической беременности только при наличии хронических форм хориоамнионита и воспаления базальной мембраны. По сравнению с физиологической беременностью и воспалением плаценты, повышенная интенсивность окрашивания отмечается при всех формах воспаления, сочетанного с IDAG. Сравнительный анализ показал, что изменение показателей отмечается только при хронических воспалительных процессах и отсутствует при наличии IDAG без воспаления.

Следовательно, по сравнению с физиологической беременностью, при всех формах воспаления последа оптическая плотность окрашивания в эндотелии кровеносных сосудов значительно возрастает, тогда как в фибриноидах такой же процесс прослеживается только при хроническом течении. В этом случае IDAG сопровождается максимальными уровнями оптической плотности в эндотелии и фибриноиде, тогда как при хроническом воспалении средние показатели выше, чем при острой форме.

რეზიუმე

იმუნოჰისტოქიმიური შეფერადების ოპტიკური სიმკვრივის რაოდენობრივი პარამეტრები ენდოთელიუმისა და პლაცენტის ფიბრინოიდის Willebrand-ის ფაქტორზე

ვ. ილიკა, ნ. დავიდენკო

უმაღლესი სახელმწიფო საგანმანთლებლო დაწესებულება
“ბუკოვინის სახელმწიფო სამედიცინო უნივერსიტეტი”, ჩერნოვცი, უკრაინა

კვლევის მიზანს შეადგენდა იმუნოჰისტოქიმიური შეფერადების ოპტიკური სიმკვრივის რაოდენობრივი პარამეტრების დადგენა Willebrand-ის ფაქტორზე პლაცენტის გარკვეული სტრუქტურების ანთებისა და ორსულების რკინადეფიციტური ანემიის (IDAG) თანხვედრის დროს.

გამოკვლეულია 198 პლაცენტა. იმუნოჰისტოქიმიური მეთოდიკა სრულდებოდა პარაფინურ ანათლებზე Willebrand-ის ფაქტორის მიმართ პირველადი ანტისხეულების გამოყენებით და მათი ვიზუალიზაციით დიამინობენზიდინიანი პოლიმერული სისტემით. კომპიუტერული მიკროდენსიტომეტრიის მეთოდით გამოსახულების ციფრული ასლების მიღების შემდგომ იზომებოდა ჰისტოქიმიური შეფერადების ოპტიკური სიმკვრივე.

დადგენილია, რომ შესწავლილ სტრუქტურებში ანთების ყველა ფორმის დროს,ფიზიოლოგიურ ორსულობასთან შედარებით, საშუალოდ, იმუნოჰისტოქიმიური შეფერადების ოპტიკური სიმკვრივე Willebrand-ის ფაქტორზე მნიშვნელოვნად მატულობს. IDAG ანთების დროს ხელს უწყობს ამ მაჩვენებლის ზრდას, ამასთან, ყველაზე მაღალი მაჩვენებლები დაფიქსირდა პლაცენტის ბაზალური ფირფიტის ენდოთელიოციტებზე ქრონიკული ბაზალური დეციდუიტის დროს.

ქორიონული და ბაზალური ფირფიტის ფიბრინოიდში ქორიონამნიონიტის ქრონიკული ფორმების და ბაზალური დეციდუიტის დროს შეფერადების სიმკვრივე მეტია, ვიდრე ფიზიოლოგიური ორსულობისას. IDAG და ანთების ყველა ფორმის დროს, ფიზიოლოგიურ ორსულობასა და პლაცენტის ანთებასთან შედარებით, შეფერადების სიმკვრივე იზრდება.

ამრიგად, სისხლძარღვების ენდოთელიუმში ანთების ყველა ფორმის დროს, ფიზიოლოგიურ ორსულობასთან შედარებით, შეფერადების ოპტიკური სიმკვრივე მატულობს, ფიბრინოიდში კი – მხოლოდ ქრონიკული მიმდინარეობის პირობებში. ამასთან, IDAG-ს თან ახლავს ოპტიკური სიმკვრივის მაქსიმალური მაჩვენებლები ენდოთელიუმსა და ფიბრინოიდში, ხოლო ქრონიკული ანთების დროს საშუალო მაჩვენებლები მწვავე ფორმების მაჩვენებლებზე მაღალია.

DYNAMICS OF CHANGES IN INDICES OF ENDOGENOUS INTOXICATION IN PATIENTS WITH ACUTE SMALL INTESTINAL OBSTRUCTION IN CASE OF REAMBERIN USE IN THE COMPREHENSIVE TREATMENT

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Despite the improvement of surgical treatment methods and intensive care, acute small intestinal obstruction (ASIO) remains one of the important problems of the urgent surgery and refers to the most severe disorders of abdominal cavity organs functions [1, 2].

The development of enteral insufficiency is the most important in the formation of critical state in case of ASIO. It is accompanied by intense increase in endotoxicosis caused by a complex of metabolic disorders [3]. Metabolic disorders in ASIO cause free radical processes activation promoting peroxy radicals formation. Accumulation of products of lipids free radical oxidation leads to the dissociation of oxidative phosphorylation and inhibits electron transfer in the respiratory chain of mitochondria. As a result, energy-dependent functions are suppressed and multiple organ failure develops. In case of intoxication and hypoxia, mitochondria respiratory chain loses the ability to take electrons from other substrates except for amber acid, which is one of the intermediate compounds of Krebs cycle and the substrate of the second complex of the mitochondria respiratory chain. Thereby, many energy-dependent processes in cells occur during amber acid oxidation [4]. Additional exogenous intake of amber acid significantly enriches energy failure in the body [5].

There is no evidence in the available literature that enteral insufficiency is associated with mitochondria dysfunction. However, some authors consider that the very origin of enteral insufficiency is associated with dysfunction of mitochondria of small intestinal muscular layer [6]. This causes the improvement of existing and the search for new adequate and pathogenetically grounded methods of comprehensive surgical treatment of patients with ASIO with the use of the newest high-potency medication.

The objective of the research was to study the change of endogenous intoxication stages depending on the time of ASIO development and their correction with Reamberin solution.

Material and methods. The clinical stage of the research was based on the results of a comprehensive examination of 202 patients with ASIO who underwent inpatient treatment at the surgical department of the Ivano-Frankivsk Central City Clinical Hospital, Ukraine. The control group included 30 apparently healthy individuals. The patients included 98 (48.5%) men and 104 (51.5%) women. The largest number of patients included the patients of ripe age (45.0) according to the age ratio. Young and middle age patients constituted 41.0%, the patients of elderly and senile age amounted 14%. Admission of all patients to the clinic was urgent in the period from 12 to 72 hours from the onset of the disease. Particularly, 19.8% of the patients were admitted during the period up to 12 hours, 19.3% of the patients were admitted during the period up to hours, 43.1% of the patients – up to 48 hours, 7.4% of the patients – up to 72 hours. The most common cause of ASIO development was the presence of adhesive process in the abdominal cavity (55.4%) as a result of prior surgical interventions on the abdominal organs.

Surgical intervention was aimed at the elimination of the obstruction and the endogenous intoxication control. ASIO elimination without bowel resection was performed in 155 (76.7%) patients. 47 (23.3%) patients underwent ASIO elimination with subsequent bowel resection. On admission to the hospital, all patients were performed standard laboratory and instrumental examinations.

Statistical processing of the research results was conducted using software and mathematical complex for computers and BM PC Exel-7.0 based on Microsoft Windows 1985-2005 as well as programs for statistical processing Analys + Soft, 2007. The law of sample distribution for normality was verified by Shapiro-Wilk test (Herasymov, 2007). In order to test the hypothesis of mean values equality, Student-Fischer test was used for normally distributed samples and Wilcoxon-Mann-Whitney test was applied for the samples with the distribution different from the normal one (Yu.E. Lekh, 2006). The content of medium mass molecules (MMM) in blood plasma was determined according to G.I. Gabrielian method, malonaldehyde (MA) was defined by testing with thiobarbituric acid (E.I.Korobeynikova, 1989). Diene conjugates (DC) content was determined by UV absorption of heptane and isopropanol extracts (V.V. Havrylov, 1986).

The patients were divided into two groups, namely the main group and the control one. Reamberin solution ("Polisan") was administered to 62 patients on the background of standard infusion-transfusion therapy in order to correct metabolic disorders and to neutralize toxic substance. The solution was administered in a dose of 400-800 ml 2 times a day intravenously by drop infusion at a rate of 90 drops per minute depending on the severity of the disease before the surgery and during the first 5 days of the postoperative period. Reamberin has antihypoxant and antioxidant value causing a positive effect on aerobic

Table. Dynamics of lipid peroxidation (LP) and medium mass molecules (MMM) indices in the patients with ASIO in the postoperative period

Terms after the surgery	Groups of patients	DC content (RU)	MA content (micromole/l)	MMM content (RU)
Normal rate		0.38±0.04	3.69±0.27	0.24±0.01
Before the surgery		0.62±0.03	5.49±0.29	0.44±0.02
1st day	Control	0.69±0.05	5.73±0.40	0.59±0.04**
	Main	0.64±0.04	5.79±0.46	0.59±0.02
5th day	Control	1.09±0.10***	6.36±0.47	0.54±0.03
	Main	0.78±0.02º	5.01±0.22ººº	0.46±0.02º
14th day	Control	0.82±0.08*	6.69±0.46*	0.53±0.05
	Main	0.62±0.05º	5.30±0.20º	0.41±0.03º

*note: * - probability of the difference between the index and the preoperative value, * - P<0.05; ** - P<0.01; *** - P<0.001; º - probability of the difference between the control and the main groups, º - P<0.05; ººº - P<0.001*

processes in a cell, reducing the production of free radicals and restoring the cellular energy potential [10]. The drug is authorized for use by Central Formulary Committee of the Ministry of Health of Ukraine. The content of medium mass molecules (MMM), malonaldehyde (MA) and diene conjugates (DC) in blood serum was determined at the patients' admission to the hospital and during 14 days of the postoperative period in order to determine the stage of endogenous intoxication (EI).

Results and their discussion. Investigation of the content of primary (DC) and secondary (MA) products of lipid peroxidation in blood serum in both groups indicated a significant intensification of lipid peroxidation processes. The toxicity of blood serum correlates with the level of lipid peroxidation products. One of their manifestations is the initiation of free radical oxidation in the target organs, especially in the liver, which is situated on the way of blood outflow from the intestine [7].

The level of lipid peroxidation (LP) indicators, namely DC, MA and MMM in blood serum of the patients with ASIO in both study groups was significantly increased before the surgery in comparison with the normal values (Table 1). Thus, DC, MA and MMM indices constituted 0.62±0.03 relative units (RU), 5.59±0.29 micromole/l, and 0.44±0.02 RU, respectively. The normal values were 0.38±0.04 RU, 3.69±0.27 micromole/l, and 0.24±0.01 RU. LP imbalance was observed in both groups on the first day of the postoperative period. Further increase in DC and MA concentration in blood serum was noted in both groups up to the 5th day of the postoperative period with gradual decrease on the 14th day, being higher than the initial level by 1.25 times in the main group, and by 1.5 times in the control group.

An increase in MMM level in the patients with ASIO was also observed up to the 5th day of the postoperative period (P<0.05) without returning to normal on the 14th day of the postoperative period.

DC, MA, and MMM content is always in blood serum in certain concentrations as a result of LP physiological processes and catabolism of endogenous and exogenous proteins in the body. An increase in these compounds content indicates a certain level of endogenous intoxication (EI) which depends on the effectiveness of protective detoxification mechanisms [8]. EI syndrome development in patients with ASIO depends on hepatic function which is responsible for toxins binding, inactivation and elimination. An increase in LP processes intensity has a disastrous influence on the microsomal system of hepatocytes detoxification and damages the membranes of the agranular endoplasmic reticulum resulting in the violation of spatial ratios of enzyme systems localized there. Putrefactive microflora intensively develops in patients with ASIO as a result of disturbance of digestion and absorption in the intestine. This microflora contributes to the enhanced MMM formation. MMM penetrate through the portal system to the liver as a result of protective dysfunction of the small intestinal mucous membrane and cause damage to hepatocytes by inhibiting DNA synthesis in them affecting mitochondria functional state. Having prooxidant effect, MMM activate LP processes [9].

According to our research, the decrease in EI indices level in patients with ASIO did not occur immediately after the small intestinal patency restoration and depended on the degree of hepatic parenchyma damage. For that reason the indices did not return to normal ones even on the 14th day of the postoperative period. Reamberin has the ability to improve the processes of internal respiration and immediately reduce the activity of LP processes in blood serum. The prescription of antihypoxant therapy, namely Reamberin, to the patients with ASIO in addition to commonly accepted treatment contributed to LP indices normalization. The decrease in MMM in blood serum was also observed in the main group due to detoxicative effect of Reamberin solution on hepatic function. According to the analysis of the short-term results of combined surgical treatment of patients with ASIO, the frequency of postoperative complications in the main subgroup of patients decreased by 1.2 times, in particular purulent-septic

complications decreased by 2.3 times in comparison with the control group as a result of Reamberin use. Postoperative mortality constituted 17.21% in the control group and 8.92% in the main group. The patients' stay in the hospital decreased from 19.2 bed-days in the control group to 17 bed-days in the main group, respectively.

According to the analysis of the immediate results of combined surgical treatment of patients with ASIO, the additional use of antihypoxant and antioxidant therapy reduces such indicators as the number of postoperative complications from 33.0% to 6.6%, the number of forced relaparotomies from 8.0% to 0.9%, indicators of postoperative mortality from 8% to 1.8%. The average bed day constituted 16.52 ± 2.14 days in Group I and 12.31 ± 1.15 days in Group II.

Conclusions.

1. The content of toxic high-level substances was found to increase significantly during the short period of time in the patients with ASIO with the increase of enteral insufficiency.
2. An increase in energy defficiency in tissue cells occurs in conditions of hypoxia due to the activation of free radical oxidation processes causing an inhibition of the antioxidant support network.
3. The use of Reamberin containing amber acid in the comprehensive treatment of patients with ASIO provided an opportunity to reduce the patients' hospital stay by 2.6 bed-days and mortality from 17.21 to 8.92%.
4. Reamberine has a pronounced antihypoxant and antioxidant value causing a positive effect on aerobic processes with the activation of energy potential in cells, contributing to the restoration of the motor-evacuation function of the intestine in case of ASIO in patients, providing an opportunity to apply the drug in a comprehensive surgical treatment.

Prospects for further research. The conception to determine the factors of formation, progression and mutual burdening of ASIO course is to be defined on the basis of the obtained data. Prognostic criteria will be formulated and protocols for emergency surgery will be developed taking into account the indicators of endogenous intoxication.

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SUMMARY

DYNAMICS OF CHANGES IN INDICES OF ENDOGENOUS INTOXICATION IN PATIENTS WITH ACUTE SMALL INTESTINAL OBSTRUCTION IN CASE OF REAMBERIN USE IN THE COMPREHENSIVE TREATMENT

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The objective of this research was to study changes in parameters, characterizing endogenous intoxication in patients with acute small bowel obstruction with Reamberin included into therapy scheme.

Full physical examination and surgical treatment of 202 patients with acute small bowel obstruction were conducted. The control group included 30 healthy individuals. Dynamics of such clinical biochemical parameters as medium mass molecules (MMM), malondialdehyde (MDA), diene conjugates (DC) in blood serum were analyzed in preoperative period and on the 1st, 5th and 14th day of postoperative period.

Significant free radical production occurred both in preoperative period and after surgical intervention. This was the reason to include antioxidant therapy using Reamberin (STPF «POLYSAN») in addition to basic treatment. The drug is approved for use by Central Formulary Committee of the Ministry of Health of Ukraine. All patients were divided into 2 groups depending on the treatment scheme. Group I consisted of 100 patients with acute small bowel obstruction who underwent the comprehensive treatment according to recommendations of the Ministry of Health of Ukraine № 297 dated 02.04.2010 (Standards of medical care for patients with urgent surgical diseases of the abdominal cavity). 102 patients of group II received the comprehensive treatment of antihy-

poxant and antioxidant therapy with Reamberin added to basic scheme. The main active ingredient of Reamberin is succinic acid. The drug was administered intravenously by drop infusion in a dose of 400 ml a day during 7-day period. Administration rate did not exceed 90 drops per minute. The medicine administration was started during complex preoperative preparation and then was done immediately after the completion of surgical treatment under resuscitation conditions.

It was shown that the use of Reamberin promotes effective correction of free radical imbalance, reduction of endogenous intoxication and postoperative complications.

Keywords: small intestine; endogenous intoxication; Reamberin.

РЕЗЮМЕ

ДИНАМИКА ИЗМЕНЕНИЙ ПОКАЗАТЕЛЕЙ ЭНДОГЕННОЙ ИНОКСИКАЦИИ У БОЛЬНЫХ С ОСТРОЙ ТОНКОКИШЕЧНОЙ НЕПРОХОДИМОСТЬЮ ПРИ ИСПОЛЬЗОВАНИИ В КОМПЛЕКСНОМ ЛЕЧЕНИИ РАСТВОРА РЕАМБЕРИНА

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Целью исследования явилось определение изменений показателей эндогенной интоксикации (ЭИ) у больных с острой тонкокишечной непроходимостью при включении в схему терапии препарата Реамберин.

Проведено комплексное обследование и хирургическое лечение 202 больных с острой тонкокишечной непроходимостью. Группой контроля были 30 практически здоровых субьекта. Изучены клинико-биохимические показатели в динамике: в дооперационном периоде, а также на 1-е, 5-е, и 14 сутки послеоперационного периода. Исследовано содержание молекул средней массы, малонового альдегида и диеновых коньюгатов в сыворотке крови.

Установлено, что как в дооперационном периоде, так и после хирургического лечения и возобновления проходимости тонкой кишки происходят значительные нарушения процессов свободно-радикального окисления, что стало основанием назначения антигипоксантно-антиоксидантной терапии препаратом Реамберин (ООО «НТФФ «ПОЛИСАН», г. Санкт-Петербург, Россия). Препарат разрешен ЦФК МОЗ Украины. В зависимости от схемы лечения больные были разделены на 2 группы. Первую группу составили 100 больных с острой тонкокишечной непроходимостью, комплексное лечение которых проводилось по общепринятой схеме, согласно рекомендациям МОЗ Украины от 02.04.2010 г. №297 (Стандарты оказания медицинской помощи больным с неотложными хирургическими заболеваниями органов брюшной полости). Вторую группу составили 102 пациента, в схему лечения которых был добавлен Реамберин. Препарат вводили внутривенно капельно 400-800 мл в сутки, скорость введения – 90 кап/мин, курс -7 суток. Введение препарата осуществляли при комплексной предоперационной подготовке и сразу после завершения оперативного лечения в условиях реанимационного отделения.

Установлено, что использование раствора реамберина способствует эффективной коррекции дисбаланса в системе свободно-радикального окисления, снижению эндогенной интоксикации и уменьшению послеоперационных осложнений.

რეზიუმე

ენდოგენური ინტოქსიკაციის მაჩვენებლების დინამიკა მწვავე წვრილნაწლავური გაუვალობის მქონე ავადმყოფების კომპლექსურ მკურნალობაში რეამბერინის ხსნარის გამოყენების პირობებში

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კვლევის მიზანს შეადგენდა ენდოგენური ინტოქსიკაციის მაჩვენებლების ცვლილებების შესწავლა მწვავე წვრილნაწლავური გაუვალობის დროს მკურნალობის სქემაში პრეპარატ რეამბერინის ჩართვის პირობებში.

ჩატარებულია მწვავე წვრილნაწლავური გაუვალობის მქონე 202 ავადმყოფის კომპლექსური გამოკვლევა და ქირურგიული მკურნალობა. საკონტროლო ჯგუფი შეადგინა 30 პრაქტიკულად ჯანმრთელმა პირმა. კლინიკურ-ბიოქიმიური მაჩვენებლები შესწავლილია დინამიკაში: ოპერაციამდელ პერიოდში, ოპერციის შემდგომ პირველ, მეხუთე და მეთოთხმეტე დღეს. შესწავლილია საშუალო მასის მოლეკულების, მალონური ალდეჰიდის და დიენური კონიუგატების შემცველობა სისხლის შრატში.

დადგენილია, რომ როგორც ოპერაციამდელ პერიოდში, ასევე წვრილი ნაწლავის გამავლობის ქირურგიული მკურნალობით აღდგენის

შემდეგ ვითარდება თავისუფალ-რადიკალური ჯანგვის პროცესების მნივნელოვანი დარღვევები, რაც საფუძვლად დაედო ანტიჰიპოქსიურ-ანტიოქსიდანტური მკურნალობის დანიშვნას პრეპარატით რეამბერინი. პრეპარატი ნებადართულია უკრაინის ჯანდაცვის სამინისტროს მიერ. მკურნალობის სქემის მიხედვით, პაციენტები დაიყო ორ ჯგუფად. I ჯგუფი შეადგინა 100 პაციენტმა მწვავე წვრილნაწლავური გაუვალობით, რომელთა კომპლექსური მკურნალობა ტარდებოდა დადგენილი სქემით, ანუ უკრაინის ჯანდაცვის სამინისტროს რეკომენდაციების შესაბამისად (02.04.2010, № 297); II ჯგუფი შეადგინა 102 პაციენტმა, რომელთა მკურნალობის სქემაში დამატებული იყო რეამბერინი. პრეპარატი შეყავდათ ინტრავენურად, წვეთოვანად, 400-800 მლ დღე-ღამეში, შეყვანის სიჩქარე – 90 წვეთი/წთ, კურსი – 7 დღე-ღამე. პრეპარატის შეყვანა იწყებოდა კომპლექსური წინასაოპერაციო მომზადების დროს და ოპერაციის დასრულებისთანავე, რეანიმაციის განყოფილების პირობებში.

დადგენილია, რომ რეამბერინის ხსნარის გამოყენება ხელს უწყობს დისბალანსის ეფექტურ კორექციას თავისუფალ-რადიკალური ჯანგვის სისტემაში, ენდოგენური ინტოქსიკაციის და ოპერაციის შემდგომი გართულებების შემცირებას.

COMPLEMENTARY AND ALTERNATIVE MEDICINE AND MEDICAL EDUCATION IN GEORGIA: STATE OF THE ART AND FURTHER PERSPECTIVES

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Complementary and Alternative Medicine (CAM) relates to a wide range of treatments for medical conditions that people use instead of or in addition to ordinary medicine. As CAM becomes increasingly popular among patients across the world, the appropriate education of future providers in this field has gained attention among medical educators and related expert circles to ensure safe practice of quality CAM [8,12,17].

In order to inform our study of CAM teaching in Georgia, we surveyed the literature regarding the prevalence of CAM teaching in medical school curricula internationally. The prevalence of CAM teaching varies in European Union, USA and other high-income countries, but in general most medical schools welcome further development of CAM in their curricula [6]. While only few universities provide specialized degrees dedicated specifically to CAM knowledge and skills, CAM curricula are implemented in over half of all medical schools in the United States through at least one course or clerkship. The majority of the CAM teaching courses (70.9%) were didactic electives. Only six schools required a CAM course or clerkship [8]. Other sources previously reported prevalence of CAM course teaching to be up to 98% among American medical schools [5]. European countries such as Germany, Austria, the Netherlands or Switzerland less commonly have comprehensive CAM curricula, but often teach specific CAM modalities, primarily homeopathy [6]. In summary, CAM teaching is becoming increasingly common in many high-income countries around the world [14].

In contrast, CAM was continuously being neglected by medical schools in low and mid-income countries despite evidence of its significant influence for example within African countries, notably the South African Republic [5].

Using CAM is quite common among medical students, and they generally hold positive attitudes towards CAM [1-4,9,10]. The majority of medical students favored the creation of CAM as a major subject. Professionalism improvement was also suggested to be one of the outcomes of CAM teaching to medical students.

In Georgia CAM has maintained stable demand, which is supposed to rise in the future [11]. On the other hand it is not clear what is the CAM education status of conventional medicine physicians and if or how such knowledge is delivered to medical students and physicians.

The aim of this mixed-methods study was to inform the process of implementing quality CAM curricula in Georgia and strategies for the inclusion of effective CAM curricula into medical education in Georgia.

This study's specific objectives were to: a) Analyze the current status of CAM education in the curricula of accredited medical school programmes and Continuous Professional Development courses in Georgia through qualitative interviews with expert responsible university staff. b) Assess attitudes of CAM through qualitative interviews with academicians, medical specialists and CAM practitioners towards the prospects of CAM integration into medical education curricula. c) Analyze learners' needs and attitudes regarding the development and implementation of CAM curricula through a survey administered to medical students.

Material and methods. We identified sixteen (16) medical schools and faculties accredited in Georgia using the World Directory of Medical Schools website. Each medical school's websites were thoroughly reviewed, primary to analyze the existing programme curricula leading to the degree of medical doctor (MD).

We conducted a total of 11 semi-structured interviews. We interviewed 5 medical education experts in the country, 3 of them heads of medical faculties. Additionally two representatives of Continuous Professional Development and Continuous Medical Education (CME) programme and credit providing organization were interviewed, one of them the organization's president. Additionally, we selected 4 CAM practitioners' professional organization representatives (representing Homeopathy, Traditional Georgian Medicine, Acupuncture and Anthroposophical Medicine) for semi-structured interviews using a purposive sampling approach.

Two different definitions were suggested to define CAM and Traditional Medicine, respectively [4,5]. The following topics were primarily discussed: Opportunities and need of CAM educational component introduction into MD and CME educational curricula; problems which stakeholders are facing in regards to this topic; possible strategies addressing the existing situation.

Expert interviews. We conducted all the interviews in the Georgian or Russian language at places convenient for the interviewees in a calm, comfortable atmosphere. The interview protocol was designed and pilot-tested on 3 volunteering medical education PhD students. The conversation was conducted in a "semi-flexible" way, and the respondents had freedom to express their ideas and talk about their CAM experience.

Each participant was introduced to the study and signed an informed consent form after reading an information paper and getting further verbal information about our study. Line by line, focused and theoretical coding approaches were used to build theories and conclusions [18].

Learner survey. Medical students' needs and attitudes were assessed using the Georgian Medical Students' Association member list. A specially designed questionnaire was distributed to systematically selected 100 local medical students.

Results and their discussion. The programme search did not identify any CAM dedicated courses in MD curricula. Some (probably little) content is delivered through history of medicine classes in one of the universities (with such keywords as "homeopathy"; "folk medicine" and others identifiable in the syllabi). Some amount of CAM knowledge is delivered through rehabilitation and/or wellness medicine, body manipulations teaching, etc.

Qualitative interviews. This is how a medical education expert commented the situation: *"The knowledge on CAM among physicians or students is unfortunately often based on certain [financial] interests, or on personal experience, but unfortunately it is not available in the form of structured modules in medical education"*.

The attitude of medical education experts was partly positive related to some CAM modalities, while skeptical to others. The frequency (and high rate) of success stories they have heard and the demand from patients make the experts reconsider their skeptical attitude towards CAM. the same can be attributed to physicians, who reported that many patients are referred to CAM specialists by conventional health specialists and vice versa.

A general consensus observed among the participating stakeholders was that future doctors should have at least some basic knowledge on CAM. A CAM expert practicing acupuncture (with a previous long career as a physician) stated: *"The question if CAM should be introduced into medical curricula is not a question to discuss. It needs to be implemented definitely."* A PCD expert stated that: *"it is elementary that some basic knowledge on some historical modalities such as homeopathy or Tibetan medicine is a must for a modern doctor, despite the limited evidence."* An interviewed dean said: *"We raise future doctors. Doctors have contact with patients, while the patients have various experiences with treatment approaches and products available in our country. These products are easily available. When a patient tells that he is using these methods, doctors must have some knowledge regarding these methods. Such questions, what is the effect of CAM on our patients' health; if it can be utilized together with the conventional medicine and others topics are very important.* Another dean stated: *"If such a practice represents risks for patients, we are obliged to address it in some form in our curricula"*.

Regarding the importance to introduce CAM as a CME course for physicians, a long time practitioner of homeopathy and head of professional union expressed the idea that many physicians prescribe homeopathic and other CAM preparations, not knowing what they are prescribing. *"If you ask them what you think about homeopathy, they will say it is a wrong direction. But in fact many of them prescribe the remedies themselves, and they should at least know what they are prescribing. They really don't know. This is risky"*. An idea suggesting necessary integration of knowledge was supported. For example, one of interviewed CAM experts said: "*Physicians should not be limited by frames. They should know their options. If a drug didn't help or a homeopathic remedy didn't help, maybe there is something else which can benefit the patient. A strong team uniting the sides and sharing the experience should be established. This way physicians will be aware that in such cases where they can't help a patient they should know what other options exists for a patient who needs relief."*

When asked if a course can be provided to medical schools to teach medical students, one of the CAM society leaders stated: *"Though there is no course ready at the moment, we can develop one according to the medical school requirements, using various available educational resources… Of course, it is possible to form such a programme."* An academic dean stated: *"A separate course can be created, not only covering the pharmacology aspects, but also discussing various approaches*

(maybe inviting various specialists to give lectures). I see this course like this, this should be taught in a complex way, with two or three days dedicated to each course". But some of the practitioners said that it is not enough to teach only theory, and students need to have some practical classes, in fact introducing certain CAM modalities as a separate subject. Others said that quite a lot could be taught regarding certain CAM system in as little time as a couple of days. The rest is a matter of self-education for those who get interested.

There was a conflicting position regarding the question of why such courses are not yet implemented? CAM practitioners suggested that academic staff in universities have a generally negative attitude. For example, a physician and professor of internal medicine we interviewed mentioned that medical curricula tend to be built according to the qualification requirements for MDs, which doesn't consider CAM skills or knowledge.

It was also recognized that medical curricula are often overloaded, and time restrictions are crucial in this case. A medical educator says: "*I myself am teaching pharmacology, and in our textbook there is a chapter which is dedicated to CAM approaches. Unfortunately we don't teach this chapter, due to the limits of time. I think it is necessary…"* Others prioritized such complicating reasons as no clarity on who should be teaching (as CAM is largely unregulated, while practitioners are not professionally certified) and what should be taught (with an idea that it should depend on prevalence of use, while such data is not available). *"In the existing reality, where CAM is not regulated, whom can we trust to teach future and practicing physicians?"* It was agreed that teaching must be objective, guaranteeing that physicians don't obtain more problems than benefit out of the content. Ideas on how much content should be taught ranged. The medical education experts were conservative and suggested that an elective subject is a good option. *"Unfortunately today we don't teach CAM in our university. But I personally as a dean have a great wish to introduce it in some form, at least as an elective subject, I think this knowledge is necessary. For the beginning it can be elective and in future might be transferred to general courses".* An MD programme dean suggested that it would be good to introduce the subject to medical residents. A CAM practitioner suggested that a foreign model can be introduced – blending face-to-face sessions with online work and independent work. A medical education expert: "*It should be delivered in an interactive format, in a form of discussion. Probably a problem based learning is preferred rather than didactic."* Sides agreed that a lot of work needs to be done, and currently there is no initiative or project working on this. One of the practitioners said: *"I think this should be led by youth. It needs a young health professional full of energy, knowledge and objectives good to patients".* A medical school dean noted: *"Today we can safely introduce CAM content for MD students through studies of public health (covering such topics as epidemiology, patient safety, medical ethics, expenses and others) while deeper integration of CAM into MD and CME curricula should be a step by step process based on an international collaboration."*

*Learner survey results***.** About half of the surveyed students were familiar with CAM (mostly stating they were "somewhat familiar), predominantly through literature. Most of them would like to receive further knowledge on CAM. The absolute majority (95%) would like the universities to develop a CAM course (if even only a few days long). About half said they would enroll in such a course if it was obligatory, another half would join in any case. Many of those who were familiar with CAM didn't exclude practice in one of the disciplines. It appears that a majority of students had used CAM previously, primarily herbs, homeopathy, dietary supplements, vitamins/minerals and manual therapy/massage.

Our findings, though limited by small sample size, support the findings abroad ([1-4,9,10]) that medical students' attitude is generally positive rather than negative, and they would generally welcome introduction of a CAM course. On the other hand, unlike in studies from abroad, medical students in Georgia have very limited academic knowledge on CAM. The high interest could be explained by high rate of personal experience of CAM treatments by students.

The fact that most medical schools have a packed curriculum, leaving very little or no time for CAM component (often as an elective subject) was earlier mentioned by Berman in 2001 [5]. The author also expressed the idea that unless qualification requirements are changed, will to change curricula will not be strong enough. The idea of using PBL classes to give students necessary knowledge was mentioned.

Qualification requirements for future doctors are in a developmental stage in this country. This doesn't allow the priorities to be defined firmly, resulting in great variations among the medical school programmes. In spite of time deficits as described by academic deans, doubts remain whether it is indeed impossible to introduce a short course on CAM.

In consideration of the possible adverse effects of CAM therapies, doctors should be aware of the high prevalence of CAM use among patients with diseases and be prepared to discuss that use with those patients. There is a wide variety of approaches to content and amount of studies on CAM to MD students. Curriculum planners should consider the importance of evaluating the impact of CAM inclusion in medial curriculums to better inform medical education planning, policy and implementation [5,13].

Many institutions globally, provide CME credits for CAM teaching [15] Innovative approaches, particularly the role of dual trained clinicians in CAM and conventional medicine, should be further explored within medical educational settings [13].

Conclusion. Based in this study's findings, as a first step of CAM integration into the medical curricula in Georgia, we recommend to develop and offer an an elec-

tive subject and/or public health based content teaching for MD students and CME courses for physicians. Interdisciplinary and international collaborations may help achieve best outcome, and safe practice of CAM in Georgia, forming a base for physician – CAM practitioner collaborations for quality care for patients in Georgia.

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SUMMARY

COMPLEMENTARY AND ALTERNATIVE MEDICINE AND MEDICAL EDUCATION IN GEORGIA: STATE OF THE ART AND FURTHER PERSPECTIVES

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Aim - complementary and alternative medicine (CAM) is popular in Georgia, but providers' training not well understood or regulated. The aim of this mixed-methods study was to inform the process of implementing quality CAM curricula in Georgia and strategies for the inclusion of effective CAM curricula into medical education in Georgia.

We analyzed existing medical curricula. We conducted a contextual analysis based of qualitative data collected from relevant medical education experts, qualified physicians, CAM practitioners and other stakeholders; and administered a quantitative MD students' survey to MD students.

CAM components are currently not represented in medical curricula in Georgia. Physicians largely lack adequate knowledge of CAM and its practice. All stakeholders supported that it would be beneficial to develop CAM educatory courses, both to future practitioners (medical students, initially as an elective subject) and practicing physicians (through CME).

We recommend development/integration of an elective subject and/or a curricular component as a first step of CAM integration into the medical curricula in Georgia for MD students and CME courses for physicians. Interdisciplinary and international collaborations may help achieve best outcome, and safe practice of CAM in Georgia, forming a base for physician – CAM practitioner collaborations for quality care for patients in Georgia.

Keywords: complementary alternative medicine medical education.

РЕЗЮМЕ

НЕТРАДИЦИОННАЯ И АЛЬТЕРНАТИВНАЯ МЕДИЦИНА И МЕДИЦИНСКОЕ ОБРАЗОВАНИЕ В ГРУЗИИ: РЕАЛЬНОСТЬ И ПЕРСПЕКТИВЫ

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Целью исследования явился анализ перспектив внедрения компонента нетрадиционной и альтернативной медицины в медицинские куррикулумы и курсы непрерывной профессиональной подготовки, действующие в Грузии.

Изучены и проанализированы существующие медицинские куррикулумы. Проведен контекстуальный анализ на основе количественных и качественных данных, полученных в результате сотрудничества с экспертами медицинского образования, врачами, специалистами нетрадиционной и альтернативной медицины (НАМ), студентами и другими заинтересованными лицами.

Изучаемый компонент отсутствует в куррикуллумах действующих программ. Врачи не владеют достаточными знаниями об альтернативных методах лечения. Необходимо внедрить курсы непрерывной профессиональной подготовки как для будущих, так и для практикующих врачей.

В результате проведенного исследования авторы рекомендуют внедрение факультативного предмета и/или компонента НАМ в медицинские куррикулумы для студентов медиков и соответсвующие курсы непрерывной профессиональной подготовки для врачей. Это улучшит безопасность пациентов и создаст основу для практического и научного сотрудничества врачей и специалистов альтернативной медицины.

რეზიუმე

კომპლემენტარული და ალტერნატიული მედიცინა და სამედიცინო განათლება საქართველოში: არსებული მდგომარეობა და მომავლის პერსპექტივები

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კვლევის მიზანს წარმოადგენდა კომპლემენტარული და ალტერნატიული მედიცინის საგანმანათლებლო კომპონენტის სამედიცინო განათლების დიპლომამდელ და დიპლომშემდგომ კურიკულუმებში ჩართვის საჭიროების ანალიზი.

ჩატარდა არსებული სამედიცინო კურიკულუმების შესწავლა/ანალიზი. შეგროვდა რაოდენობრივი და თვისობრივი მონაცემები სამედიცინო განათლების ექსპერტების, ექიმების, კომპლემენტარული და ალტერნატიული მედიცინის (კამ) პრაქტიკოსების, სტუდენტების და სხვა დაინტერესებული პირების ჩართულობით. შედგა კონტექსტუალური ანალიზი.

არსებულ სამედიცინო კურიკულუმებში კამ კომპონენტი არ აღმოჩნდა ჩართული. ექიმებს არ აქვთ სათანადო ცოდნა ამ სამკურნალო მეთოდების შესახებ. დადგენილია, რომ აუცილებელია ასეთი საგანმანათლებო კურსების შემუშავება და მიწოდება, როგორც მომავალი (პირველ ეტაპზე მხოლოდ არჩევითი საგნის ფორმით), ასევე მოქმედი ექიმებისთვის უწყვეთი პროფესიული განვითარების კურსების ფარგლებში.

ამ ეტაპისთვის მედიკოს სტუდენტებისთვის რეკომენდებულია კამ საგანმანათლებლო კომპონენტის არჩევითი საგნის ფორმატში შემუშავება/დანერგვა ან სხვა საგნების ფარგლებში მიწოდება. ექიმებისთვის კი - უწყვეთი პროფესიული განვითარების ფორმატში კურსების მიწოდება, პაციენტთა უსაფრთხოების, კამ პრაქტიკოსებს და ექიმებს შორის მეცნიერებაში და პრაქტიკაში თანამშრომლობის უზრუნველყოფის მიზნით.

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A COMPUTER MODELING STUDY OF BINDING PROPERTIES OF CHIRAL NUCLEOPEPTIDE FOR BIOMEDICAL APPLICATIONS

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Over the past five decades the attention of medicinal chemists has been concentrated on protein-ligand binding. However, in the recent years researchers started to search for small molecules, peptides or proteins that can bind to defined sites in RNA molecules in order to block or otherwise modulate their function. Unfortunately, computational methods for RNA-ligand docking are not as well studied as analogous methods for protein-ligand docking [2,5,16].

The use of molecules specifically aimed at controlling the cellular activities relevant in biomedicine, by means of the molecular recognition of nucleic acids, presents a subject of crucial scientific interest in the emerging fields of biochemistry and pharmaceutical chemistry. Due to the biological importance of poly rA as a target for regulation of gene expression, achievable by self-structure inducing drugs in poly rA-based mRNA tails, the significance of such molecular tools for developing innovative biomedical strategies, mainly in the field of anticancer therapy, is clear [8].

Nucleopeptides are nucleobase-decorated peptide structures that often show interesting properties of molecular binding, thus resulting good candidates for the development of innovative drugs suitable for anticancer and antiviral therapies [9,10].

The ability of a peptide-based molecular device to bind nucleic acids can be reinforced by cationic residues suitably introduced into the oligoamide backbone [7,11,12], and in this regard several recent literature sources report on succesful nucleopeptides containing basic amino acids that conferred the overall positively-charged nature of the construct, confirming ability to interact with the anionic nucleic acids [13,14].

Despite the interesting literature data on cationic nucleopeptides as nucleic acid-binders for biomedical applications, there is no information on any computer-based studies aimed at investigating how the above interaction could take place. Hence, our efforts by computer modeling approaches were directed to study the interactions occurring between a hexathymine nucleopeptide (cited as T6) and a 18 bases-long fragment of poly rA RNA (A18), used as a model system.

Material and methods. *The structure of the hexathymine nucleopeptide*

Nucleopeptides, however, can be also artificially synthesizes in laboratory with several chemical modifications and our interest in them is justified by their interesting properties, such as binding of several biomolecules (e.g. proteins or nucleic acids) of biomedical significance [15]. At present, the efforts of drug discovery and development are focused on identifying and optimizing drug candidates that act through inhibition of specific enzyme targets.

In this study special attention has been paid to the binding between the hexathymine nucleopeptide T6 and poly rA RNA (A18) and to T6/A18 molecular complexes formation analysis, because the T6 molecules are main candidates for drugs for antiviral and anticancer therapies and represent the main aim of the present research (Fig. 1).

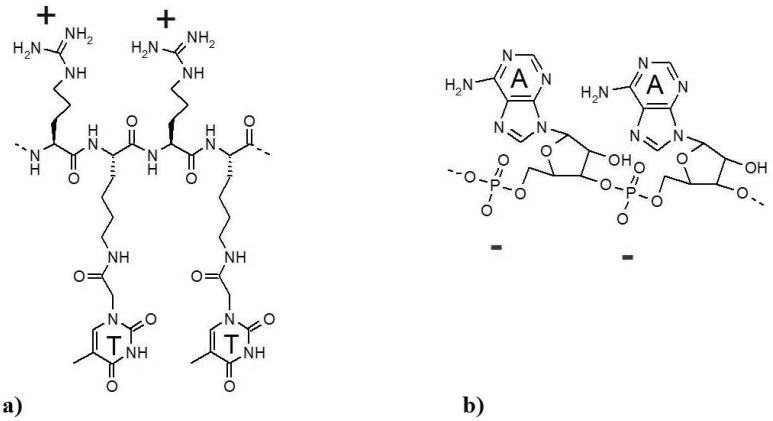
Binding experiments, performed by CD spectroscopy, showed that this peptide-like analog of DNA, resulted well soluble in water and did not present any tendency to self-aggregate, was able to interact with complementary DNA and RNA molecule inducing significant conformational structure variations of the nucleic acid, as observed in the case of the experiment with RNA [14].

After purification nucleopeptide was assayed in binding experiments with poly rA RNA. Such experiments were performed by Circular Dichroism (CD) under controlled pH and temperature conditions using concentrations of ligand corresponding to those reported in literature on analogous cases. The dramatic change in CD signal that followed the mixing of the two solutions containing the thymine nucleopeptide and poly rA clearly suggests the formation of nucleopeptide/RNA complex with a nucleobase T:A=2:1 ratio [15].

The method of computer modeling

In the beginning, we studied how one thymine T1 binded one adenine A1 and a large molecule of poly rA RNA (A18). Molecular mechanics Amber force field model has been applied for computer modeling using Hyperchem software [4]. For our model, we have selected partial charges calculated with Open Babel for mmff94 force field which had been reported to be well-suited for intermolecular interactions as used in Amber and Charmm [6,17]. Simulation temperature was 278K, simulation time - 50-100 ps.

On the basis of the obtained T1/A18 binding configurations we constructed T2, T3, T4, T5 and T6 molecules with configurations optimal for docking onto the receptor (A18). Our program Molecular Designer allowed us to select binding sites: e.g. we were able to select groups of atoms of the receptor to participate in the docking. Using Hyperchem software we ran geometry optimization for the modeled configuration of the drug to find its local conformational state (the steepest descent method has been applied) and only then, the molecular docking modeling procedure was performed for the optimized molecule of the drug. The start positions of a ligand and the receptor have been selected taking into account possible binding sites, and the starting distance between them was set to 3-4 Å.



a) b)

Fig. 1. Structural representation of the repeating units forming the cationic nucleopeptide T6 (a) and the anionic RNA A18 (b)

Results and their discussion. Computer modeling for conformational states calculated by Model Builder of Hyperchem allows us to confirm experimental results for the ability of a chiral nucleopeptide to bind a target such as poly rA RNA and to calculate the binding energy of the complex system (-72.18 kcal/mol). Calculated diagrams also show that there are several sites on the molecule capable of undergoing electrostatic or hydrogen bonding interactions. To obtain more accurate picture we should assign atomic partial charges to the molecules and perform conformational analysis according to the scheme described in the previous section.

Binding site identification is the first step in the structure-based design and usually relies on identification of concave surfaces on the receptor appropriate for ligand binding [1,3].

At the first stage of our research we consider the simplest case: one thymine T1 and one adenine A1. Conformational states of T1 and A1 have been calculated using Avogadro free software (Random Rotor Search method was selected for conformational analysis). From calculated conformational states for A1 we selected a position similar to A1 position in a single stranded RNA molecule.

For T1 we selected a position, which would enable the complementary-nucleobase interaction and the electrostatic interaction between the negative phosphate group of RNA and the positively charged residues of the nucleopeptide.

It has been found that the results of computer modeling depend on a force field. According to the data published in the literature Amber and Charmm force fields exhibit relevant results for tasks similar to ours [6].

It has been shown that the assignment of appropriate atomic partial charges was essential for obtaining meaningful results from any electrostatics calculation. We have selected mmff94 force field partial charges, which provide good results for intermolecular interactions using the common two-body additive Coulomb interactions [6,17].

Molecular mechanics Amber force field model has been applied for computer modeling using Hyperchem software. The results of geometry optimization demonstrate that molecules of T1 and A1 establish stable complexes due to the complementary-nucleobase interaction and the electrostatic interaction between the negative phosphate groups of RNA and the positively charged residues present in the cationic nucleopeptide structure. Both methods detect the above-mentioned interactions between the molecules. From the results of computer modeling presented in Fig. 2 it is apparent that there are two hydrogen bonds between nucleobases of the molecules and there are a few hydrogen bonds between the phosphate group of A1 and the positively charged residue of T1 (hydrogen bonds responsible for these interactions are shown by dashed lines). Nucleobases of the molecules are almost coplanar which is in agreement with the data reported in the scientific literature.

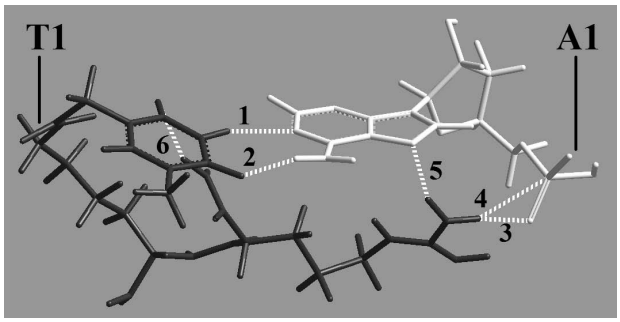


Fig. 2. T1 and A1 molecules after geometry optimization using Amber force field and mmff94 partial charges (simulation temperature is 278K, simulation time is 100 ps)

The computer modeling study performed by semi-empirical quantum mechanical methods AM1 and PM3 also detects hydrogen bonds between the nucleobases of the molecules and calculates similar positions for the molecules.

Hydrogen bonds between atoms of poly RNA and thymine molecules can be subdivided into five classes:

1. Intermolecular hydrogen bonds between nucleobases (bonds 1, 2);
2. Intermolecular hydrogen bonds between the phosphate group of poly RNA and the positively charged residue of a thymine molecule (bonds 3, 4).
3. Other intermolecular hydrogen bonds (bond 5);
4. Intramolecular hydrogen bonds of the thymine molecule (bond 6);
5. Intramolecular hydrogen bonds of the poly RNA molecule.

At the next stage of computer modeling we studied the interactions between T1 and a large molecule of poly rA RNA (A18). Stable configurations of molecular complexes calculated for the case of one thymine and poly rA RNA containing 18 adenines are shown in the Figs. 3 a) and b). Hydrogen bonds are shown by dashed lines. We can see that the molecules are bound mainly by the first and the second class bonds. Second class bonds are more flexible than first class bonds. This is why there are different configurations of the T1/A18 complexes.

Then we repeated the computer modeling procedure for the molecular complexes T2/A18, T3/A18, T4/A18, T5/A18 and T6/A18. Conformational states for the thymine nucleopeptide molecule containing a different number of thymines were obtained after geometry optimization of molecules constructed on the basis of conformational states calculated before for molecules with a lower number of thymines.

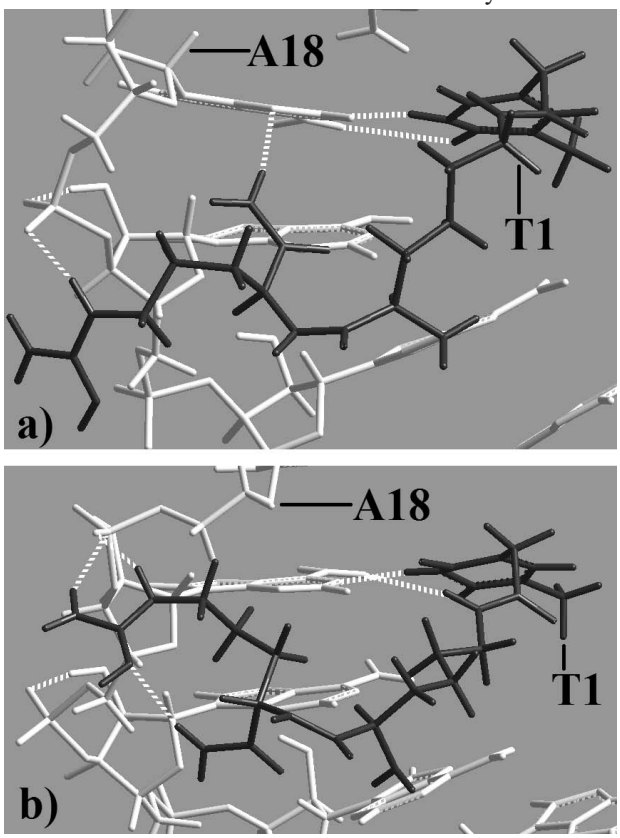
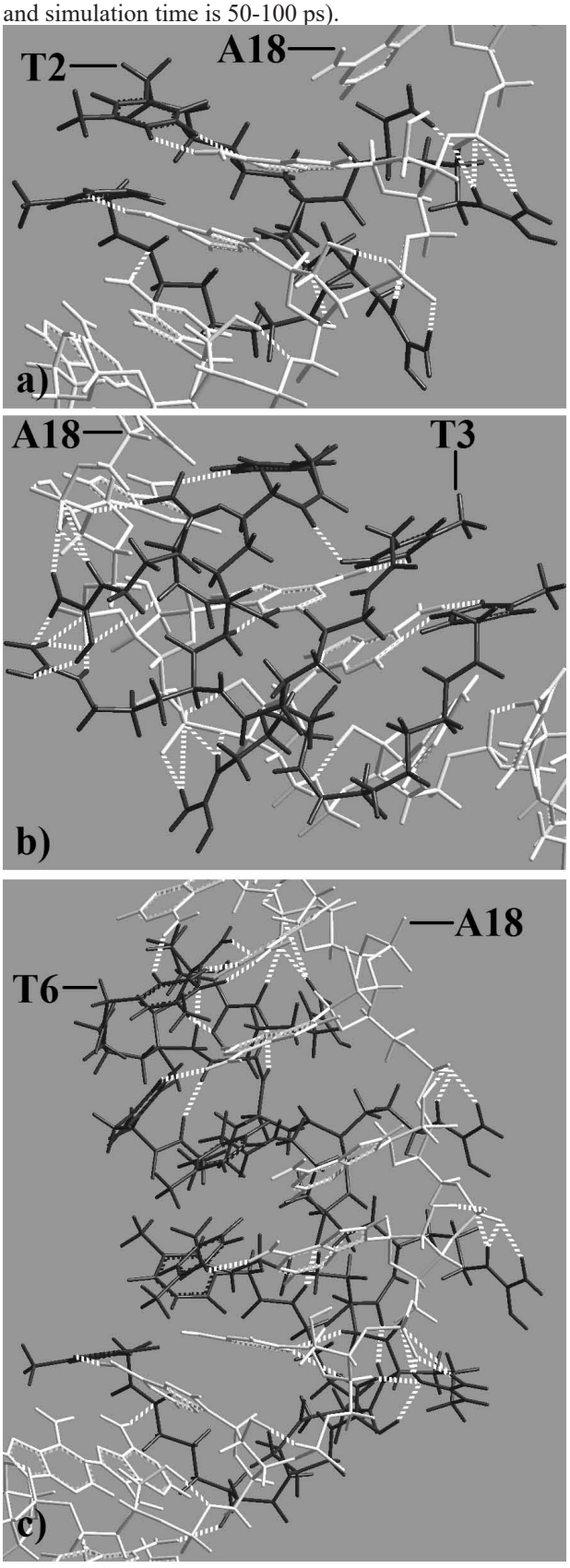


Fig. 3. Different bindings between the T1 and A18 molecules (hydrogen bonds are shown by dashed lines)

Next, we performed molecular docking procedures for T2/A18, T3/A18, T4/A18, T5/A18 and T6/A18 using both actual types of binding: first - shown in Fig. 3 a); and the second - in Fig. 3 b). Configurations of the thymine molecule generated by our computer program for different arrangements of docking sites on the A18 molecule were optimized later using the standard methods of geometry optimization provided by Hyperchem. The configurations with minimal potential energy were selected for molecular dynamics simulation.

Stable configurations of T2/A18, T3/A18 and T6/A18 complexes calculated for the second type binding are shown in Fig. 4 a), b), c) (simulation temperature is 278K, and simulation time is 50-100 ps).



Fig, 4. Stable configurations of T2/A18, T3/A18 and T6/A18 complexes (simulation temperature is 278K, simulation time is 50-100 ps)

Computer modeling of the T1/A18, T2/A18, T3/A18, T4/A18, T5/A18 and T6/A18 molecular complexes shows that molecules of thymine and poly RNA form stable complexes, where the average number of second class bonds is approximately two times greater than the average number of first class bonds.

The result of modeling demonstrates that almost all thymine nucleobases and phosphate groups participated in the binding. The number of H-H bonds between T6 and A18 molecules is about 20-25. The potential energy calculated for the binding is between -235 kcal/mol and -180 kcal/mol.

Proceeding from all these findings, we can confirm that the hexathymine nucleopeptide investigated in this work is an innovative molecular tool able to interact with RNA, and thus its application as RNA-binder could be beneficial in the biomedical research. Moreover, the results of the present study can be extended also to other cationic nucleobase-carrying peptides for which nucleic acid-binding ability is already known or, more interestingly, our computer-assisted approach could serve to predict which novel nucleopeptide modification could lead up to novel efficient nucleic acid-binding candidates for anticancer or antiviral strategies.

The computer modeling allows us to confirm experimental results for the ability of a chiral nucleopeptide to bind a target such as poly rA. The structures calculated by Hyperchem software show the formation of a nucleopeptide/RNA complex based on both H-bonds due to the complementary-nucleobase interaction and the electrostatic interaction between the negative phosphate groups of RNA and the positively-charged residues present in the cationic nucleopeptide structure. Calculated diagrams also show that there are several sites on the molecule capable of undergoing electrostatic or hydrogen bonding interactions.

The computer analysis of interactions between thymine nucleopeptide and poly RNA makes it possible to predict the optimal configuration of a thymine molecule during binding with poly RNA: slightly twisted and stretched thymine molecule lies on the molecule of poly RNA.

Remarkably, a significant role is played not only by the recognition of complementary nucleobases but is also a consequence of the electrostatic interaction occurring between anionic phosphodiester moieties and the cationic residues present in the nucleopeptide structures.

We can hypothesize that the object of our research, a thymine-containing nucleopeptide, binds the complementary polyadenylic RNA strand involving only some of the nucleobases (thymines) in the H-bond interaction with the adenine bases, while the remaining thymines are virtually free to form different interactions (e.g. aromatic interactions). By Circular Dichroism (CD) spectroscopic studies, performed in the Naples University on solutions of the nucleopeptide-RNA complexes at different concentrations under controlled pH and temperature conditions, we have obtained a more detailed quantitative information on the nature of the complexes.

In more detail, the results of these studies seem to indicate that the nucleopeptide binds poly rA with a stoichiometry involving a T/A ratio higher than 1. These results, together with the already mentioned data of molecular modeling, suggest that the nucleopeptide forms with the poly rA supramolecular complexes are held not only by the complementary nucleobase (A/T) recognition, but also by other weak interactions (e.g. hydrophobic or aromatic interactions furnished by unpaired nucleobases), which reinforce their structure. Thermal denaturation experiments conducted by UV spectroscopy did not reveal any sigmoidal melting curve (as expected in case of standard complexes of nucleic acids) in case of the nucleopeptide-RNA complexes. This can be ascribed to the different nature of the interactions occurring between the two ligands or to the higher stability of these hybrid complexes with respect to the natural (nucleic acid/nucleic acid) complexes.

Our research demonstrates how the complex use of computer modeling and bioengineering may help us to make the process of development of drugs for anticancer therapy more effective and faster.

Computer modeling makes it possible to estimate the contribution of different intermolecular hydrogen bonds into the binding between a nucleopeptide and RNA and may be used for optimization of the synthesis of anticancer and antiviral drugs.

In conclusion, based on the above-mentioned results we can state that the nucleopeptide object of the present research project is able to interact with poly rA, a RNA of strategic importance in a view of the innovative biomedical approaches, the properties of which are of obvious interest for further scientific investigation to be conducted soon by the researchers involved in the present project.

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SUMMARY

A COMPUTER MODELING STUDY OF BINDING PROPERTIES OF CHIRAL NUCLEOPEPTIDE FOR BIOMEDICAL APPLICATIONS

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Nucleopeptides often show interesting properties of molecular binding that render them good candidates for development of innovative drugs for anticancer and antiviral therapies. In this work we present results of computer modeling of interactions between the molecules of hexathymine nucleopeptide (T6) and poly rA RNA (A18). The results of geometry optimization calculated using Hyperchem software and our own computer program for molecular docking show that molecules establish stable complexes due to the complementary-nucleobase interaction and the electrostatic interaction between the negative phosphate group of poly rA and the positively-charged residues present in the cationic nucleopeptide structure. Computer modeling makes it possible to find the optimal binding configuration of the molecules of a nucleopeptide and poly rA RNA and to estimate the binding energy between the molecules.

Keywords: nucleopeptide, poly rA RNA, cancer, virus, geometry optimization, Amber.

РЕЗЮМЕ

КОМПЬЮТЕРНОЕ МОДЕЛИРОВАНИЕ СВЯЗЫВАЮЩИХ СВОЙСТВ ХИРАЛЬНОГО НУКЛЕОПЕПТИДА В БИОМЕДИЦИНСКИХ ЦЕЛЯХ

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Известно, что нуклеопептиды проявляют интересные свойства межмолекулярных взаимодействий, тем самым являясь хорошим материалом для разработки инновационных антираковых и антивирусных препаратов. В статье представлены результаты компьютерного моделирования взаимодействий между молекулами гексатиминового нуклеопептида (T6) и поли rA РНК (A18). Результаты геометрической оптимизации, рассчитанные с использованием программы Hyperchem и предложенной авторами программы для моделирования молекулярных структур, показали, что молекулы T6 и A18 стремятся образовать стабильные комплексы вследствие взаимодополняющего действия между нуклеобазами молекул и электростатического взаимодействия между отрицательно заряженной фосфатной группой РНК

и положительно заряженными фрагментами, присутствующими в катионовой структуре нуклеопептида. Компьютерное моделирование позволяет определить оптимальную конфигурацию молекул нуклеопептида и поли rA РНК и рассчитать энергию связи между ними.

რეზიუმე

ქირალური ნუკლეოპეპტიდის შემაკავშირებელი თვისებების კომპიუტერული მოდელირება ბიოსამედიცინო მიზნებისათვის

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ცნობილია, რომ ქირალურ ნუკლეოპეპტიდებს გააჩნია მოლეკულური ამოცნობის ისეთი თვისებები, რომლებიც იძლევა კიბოს საწინააღმდეგო და ანტივირუსული ინოვაციური წამლების დამზადების საშუალებას. ნაშრომში წარმოდგენილია ჰექსათიმინ ნუკლეოპეპტიდის (T6) და poly rA RNA (A18) მოლეკულების შეკავშირების კომპიუტერული მოდელირების შედეგები. Hyperchem პროგრამის და ავტორების მიერ შემოთავაზებული კომპიუტერული პროგრამის გამოყენებით შესრულებული მოლეკულური მოდელირების შედეგებმა გამოავლინა, რომ აზოტოვან ფუძეებს შორის ურთიერთქმედებით გამოწვეული ბმები და ელექტროსტატიკური ურთიერთქმედება რნმ-ის უარყოფითი ფოსფატის ჯგუფს და დადებითადდამუხტულ ნარჩენების შემცველ ნუკლეოპეპტიდურ სტრუქტურას შორის ქმნიან T6 და A18 მოლეკულების სტაბილურ კომპლექსებს. კომპიუტერული მოდელირება საშუალებას იძლევა განისაზღვროს ნუკლეოპეპტიდის და poly rA RNA-ის მოლეკულების ოპტიმალური კონფიგურაცია და შეფასდეს მათი შეკავშირების ენერგია.

ASSESSMENT OF THE LEVEL OF KNOWLEDGE OF MEDICAL PERSONNEL IN DIARRHEA AND HEMOLYTIC-UREMIC SYNDROME

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Diarrheal disease is the second leading cause of death in children under five years old. Globally, there are nearly 1.7 billion cases of childhood diarrheal disease every year. Diarrhea is a leading cause of malnutrition in children under five years old [3]. Pneumonia and diarrhea remain major killers of young children. Together, these diseases account for 29% of all deaths of children less than 5 years of age and result in the loss of 2 million young lives each year [14]. Children who are malnourished or have impaired immunity as well as people living with HIV are most at risk of life-threatening diarrhea. Diarrheal diseases are both preventable and treatable and most cases of death are associated with incorrect and late treatment [1,2,5,6,9,13]. Bloody diarhoea and dangerous clinical conditions Hemolytic Uremic syndrome (HUS) might be complications of diarhoeal diseases. Bloody diarrhea or HUS can develop, if person is infected shiga-toxin producing E. coli. Hemolytic Uremic syndrome (HUS) characterizes with triad of symptoms: Hemolytic anemia, acute thrombocytopenia and acute kidney failure. HUS is diarrheal, which develops after diarrhea and non diarrheal. Non diarrheal HUS develops without diarrhea and might be caused by different pathogens, bacteria or virus. An estimated 6% of STEC O157:H7 diarrhea is complicated with HUS and in 5% it could has lethal outcome. Other non O157:H7 might cause HUS, mainly for Europe [4,7]. HUS is especially dangearous among children [12]. Around 2,195 child dies with complications of diarrheal diseases every day, this number is larger than death caused with AIDS, TB and Malaria together, everyday [8].

The national communicable disease surveillance system of Georgia monitors diarrheal diseases. Nation-

al regulation mandates notification of diarrhea cases within 24 hours after registration. More than 3 epidemiologically-linked cases trigger an investigation. More than 34000 cases of diarrheal diseases were registered in 2016 including cases from 14 food borne outbreaks [10]. Bloody diarrhea and HUS outbreaks and sporadic cases have been registered in last decade in Georgia. In 2009 our team of investigators investigated an outbreak of HUS and Bloody diarrhea cases in Georgia and first time in our region we detected O104:H4 E. coli. HUS and bloody diarrhea are not the reportable conditions in Georgia [10]. As the conditions are non-reportable and neglected, a big number of medical personnel experiences lack of information of bloody diarrhea and HUS.

In this paper we reported the results of our survey conducted among medical personnel to determine their knowledge about diarrheal diseases and HUS.

Material and methods. To assess knowledge of medical personnel about bloody diarrhea and hemolytic uremic syndrome we conducted cross-sectional survey among medical personnel at different clinics in Tbilisi (capital of Georgia) and in three biggest regional cities (Zugdidi, Batumi and Kutaisi) of Georgia. A total of 12 clinics were selected from them 6 were in Tbilisi and 2 at each regional cities. We selected clinics providing diverse medical services including services for gastrointestinal diseases, infectious diseases and kidney diseases. Our selection included most clinics with capacity of care for patients with infectious diseases and kidney failure in Georgia. We designed and validated self administered questionnaire to assess the knowledge of bloody diarrhea and hemolytic uremic syndrome among medical professionals. We used convenience sampling methodology to sample participants from the clinics medical personnel. Sample size was calculated using true population sample size calculation formula in R for windows. The number of medical personnel in Georgia provided in the newest national statistical yearbook was considered as population for survey. The rate of correct knowledge was considered to be 50 % (P=0.5), the 95 % (CI 95%) confidence interval and 5% (delta=0.05) the margin of error was regarded as acceptable. After calculations we got the true sample size to be equal 379 participants.

We estimated the number of medical personnel in the clinics, selected and interviewed 5-10% of personnel. Survey questioners were self-administered and anonymous with no personal information. We collected filled questioners and entered into the electronic database. After collecting and entering all questionnaires into database data was entered into statistical package R for windows v3.3.2. Data was cleaned from missing and incorrect values and coded for data analysis. We did descriptive analysis of demographic and sociologic data of respondents. 8 questions were used to define knowledge of diarrhea diseases etiology, treatment, prophylactics and complications of diarrheal diseases. We had 5 questions to assess knowledge on HUS and its complication. We calculated total knowledge scores for diarrheal diseases and HUS separately. All correct answers were given one score and zero for incorrect answers. The total scores were divided in three levels of knowledge: low, middle, and high. 5 independent variables, including respondents': age, gender, geographic location of the clinics of respondents, medical specialty and duration of medical experience were tested using chi-square test for association to total scores. We applied multiple logistic regression model to identify possible factors (age, gender, geographic location, medical specialty and duration of medical experience) associated with respondents knowledge related to the diarrheal diseases, HUS and its complications. The results were presented as an odds ratio (OR) value with a 95% confidence interval (95%CI) and P<0.05. For data analysis we applied R statistical language using package R for windows v3.3.2 [11].

Ethical Considerations

This study is the one of the research study of the PHD program in preventive medicine, The name of PHD program "Epidemiological characteristics of bloody diarrhea and Hemolytic Uremic Syndrome and its prevention in Georgia". The institutional Review Board of Human Studies at the Tbilisi State Medical University provided ethical approval for the PHD program and for this study.

Results and thier discussion. *Univariate analysis.* We were able to interview 366 medical personnel using structured questionnaire. Among them 73% (267) were females and 27% (99) males. Mean age of participants was 40.8, IQR (27-52). A total of 64% (235) participants were recruited from clinics located in Tbilisi. From survey participants 83% (305) were physicians and 17% (61) were assistances of physicians. Survey participants had diverse medical specialty backgrounds: 39% (141) were pediatrics working in pediatric clinics, 31% (115) were infectious diseases specialists, 30% (110) were with various medical backgrounds from medical clinics, including urologists, emergency specialists and etc. 61% (223) of patients had more than 10 year experience of medical work (Table 1 and Fig.).

In descriptive analysis 48% (176) of participants had correctly answered on the question about death rate due to diarrheal diseases and its complication in the world. 95% (348) of participants identify the correct definition of diarrheal diseases. 74% (272) of participants provided correct answers to the question about the spread of diarrheal diseases in the world. Only 57% (208) of survey participants were able to identify etiology of diarrheal diseases. 65% (236) and 52% (189) of participants were able to correctly define minimal and maximal incubation periods and 95% (346) had correct information on treatment of diarrheal diseases. In the section of complications of diarrheal diseases only 61% (224) of participants

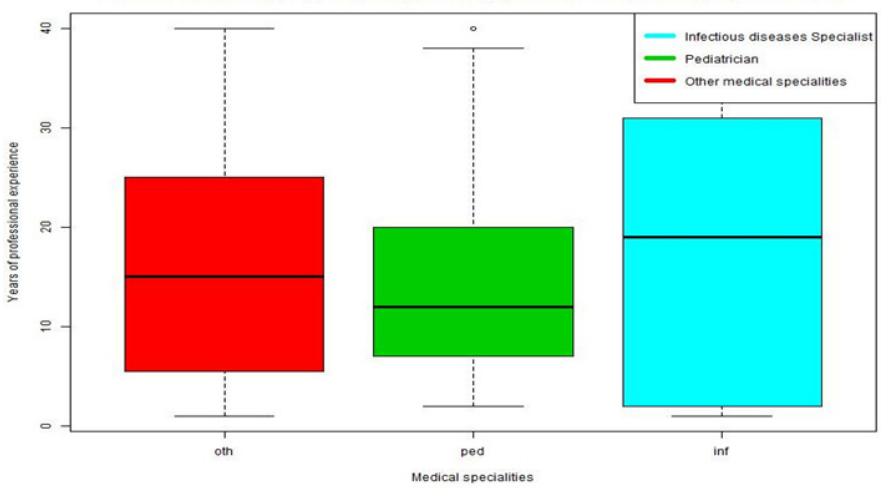

Fig. Distribution respondents medical specialties by years of medical experience

Table 1. Demographic characteristics of participants of knowledge survey about bloody diarrhea and hemolytic uremic syndrome among medical professionals in Georgia, 2016, N=366

Characteristics name/levels		All		Tbilisi		Regions	
		%	N	%	N	%	N
Category	levels	366	100	235	64	131	17
Age group	<30	109	30	87	37	22	17
	30+	257	70	148	63	109	83
Gender	Male	267	73	165	70	102	78
	Female	99	27	70	30	29	22
Speciality	Physician	305	83	196	83	109	83
	Physician assistant	61	17	39	17	22	17
Medical experience years	<10	143	39	120	51	23	18
	10+	223	61	115	49	108	82
Participant medical profession	Pediatrician	141	39	111	47	30	23
	Infectious Disease specialist	115	31	81	35	34	26
	Other (ER, Surgery, etc.)	110	30	43	18	67	51

were able to provide correct information about possible complications of diarrhea. 47% (168) of medical professionals were able to select correct definition of Hemolytic Uremic Syndrome (HUS) from multiple answers and 47% (170) correctly identifies etiological factors for HUS. 48% (171) identified correct treatment for HUS and 40% (143) correctly identifies basic principles of HUS prophylactics.

Multivariate analysis

Methods of bi and multivariate analysis were used to test association between knowledge of diarrheal diseases and predictor variables. Chi square test was used to test statistically significant association ($p<0.05$) between the levels of total diarrheal scores and predictor variables and multivariate logistic regression model was used to control confounders.

Geographic location of clinics ($X^2=0.87$, $p>0.05$) was not associated with total knowledge scores of diarrhea, other predictor factors including medical background ($X^2=34.0$, $p<0.001$), sex ($X^2=14.8$, $p<0.001$), age groups (age was divided in two categories <30 and 30+ years) ($X^2=7.6$, $p<0.05$) and working experience in years divided in two groups (<10 and 10+) ($X^2=12.2$, $p<0.05$) were significantly associated with total diarrheal knowledge scores.

Variables with significant association were included in the multivariate logistic model to calculate (OR, 95 % CI, p value). In multivariate logistic regression model we tested high total knowledge score of diarrhea as outcome variable. The model revealed that associated variables for this high knowledge score are: medical background in infectious diseases OR 0.35 (95% CI 0.19-0.67, $p<0.05$). Female sex OR 2.51 (95% CI 1.41-4.47, $p<0.05$) and having more than 10 years of medical experience OR 0.31(95% CI 0.13 - 0.75, $p<0.05$), Tables 2,3.

Table 2. Chi square test results between total knowledge diarrheal diseases score and predictor variables, diarrheal diseases and HUS knowledge survey, 2016

Category names	Levels	Total knowledge scores of diarrheal diseases				p
		Low	Middle	High	Total	
Gender	M	42	35	21	98	<0.001
	F	60	141	60	261	
Geographic location	Tbilisi	66	117	49	232	0.6
	Regions	36	59	32	127	
Age groups	<30	20	59	29	108	0.02
	30+	82	117	52	251	
Specialty	Pediatrician	24	86	31	141	<0.001
	Infect. Specialist	51	32	30	113	
	Other	27	58	20	105	
Working experience	<10	25	79	35	139	0.002
	10+	77	97	46	220	

Table 3. Multivariate logistic regression outcomes OR (95%CI, p value) among total knowledge diarrheal diseases score and predictor variables, diarrheal diseases and HUS knowledge survey, 2016

Category names	Odds Ratio	95% CI limits		p
References	OR	lower	upper	p<0.05 (sign.)
Gender ref. to female	2.51	1.41	4.47	0.001
Geographic location ref. regions	1.32	0.74	2.36	0.35
Age groups reference more than 30 years	0.93	0.37	2.34	0.87
Specialty type pediatrician ref. to Other (ER. Surgery etc.)	1.31	0.64	2.67	0.46
Specialty type Infectious Specialist ref. to Other (ER. Surgery etc.)	0.35	0.19	0.67	0.00
Working experience ref. to more than 10 year experience	0.31	0.13	0.75	0.01

Table 4. Chi square test results between total knowledge HUS score and predictor variables, diarrheal diseases and HUS knowledge survey, 2016

Category names	Levels	HUS knowledge total score			p
		Correct	Incorrect	Total	
Gender	M	57	38	95	<0.001
	F	200	53	253	
Geographic location	Tbilisi	174	54	228	0.15
	Regions	83	37	120	
Age groups	<30	87	17	104	<0.05
	30+	170	74	244	
Specialty	Pediatrician	112	21	133	<0.001
	Infect. Specialist	84	30	114	
	Other	61	40	101	
Working experience	<10	114	27	141	0.15
	10+	143	64	207	

Table 5. Multivariate logistic regression outcomes OR (95%CI, p value) among total knowledge HUS score and predictor variables, diarrheal diseases and HUS knowledge survey, 2016

Category names	Odds Ratio	95 % CI limits		p
References	OR	lower	upper	p<0.05 (sign.)
Gender ref. to female	2.08	1.19	3.65	0.01
Geographic location ref. regions	1.12	0.62	2.02	0.70
Age groups reference more than 30 years	0.44	0.18	1.08	0.07
Specialty type pediatrician ref. to Other (ER. Surgery etc.)	3.26	1.59	6.67	0.001
Specialty type Infectious Specialist ref. to Other (ER. Surgery etc.)	1.81	0.97	3.39	0.06
Working experience ref. to more than 10 year experience	0.87	0.39	1.96	0.74

Same statistical methods applied to test association between knowledge of Hemolytic Uremic Syndrome HUS and predictor variables. Geographic location of clinics (X2=2.08, p>0.05) was not significantly associated with highest total knowledge score of HUS, other predictor factors including medical background (X2=16.9, p<0.001), sex (X =12.9, p<0.001), age groups (age <30 and 30+ years) (X2=7.38, p<0.05) and working experience in years (<10 and 10+) (X =6.01, p<0.05) were significantly associated with variables of total knowledge score of HUS.

Variables with significant association were included in the multivariate logistic model to calculate (OR, 95% CI, p value). In multivariate logistic regression model we tested high knowledge of total diarrheal score as outcome variable. The model revealed that associated predictor variables for this high knowledge score are: medical background in pediatrics OR 3.26 (95% CI 1.59-6.67, p< 0.05), background in infectious diseases OR 1.81 (95% CI 0.97-3.39, p<0.05), and female sex OR 2.08 (95% CI 1.19-3.65, p<0.05), Tables 4, 5.

We conducted survey among medical professionals to test knowledge level of HUS and diarrheal diseases and to identify predictor variables for better knowledge. Female medical personnel more than 10 years of medical experience and medical background in infectious diseases have better knowledge on diarrheal disease and pediatricians have on HUS. The difference was not identified between geographic location and age. The level of knowledge of etiology, treatment and prevention of diarrheal diseases and HUS was comparatively low among other medical specialists who have no background in pediatrics and infectious diseases.

Timely and correct medical interventions are crucial to prevent complications of diarrheal diseases with HUS. We recommend trainings for medical specialists at the emergency departments and general practitioners to increase knowledge of diarrheal diseases and HUS to be able to identify those condition and to provide timely medical support for patients.

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SUMMARY

ASSESSMENT OF THE LEVEL OF KNOWLEDGE OF MEDICAL PERSONNEL IN DIARRHEA AND HEMOLYTIC-UREMIC SYNDROME

[1]Chokoshvili O., [2]Vepkhvadze N., [1]Tsertsvadze T., [3]Gabrichidze T., [2]Khorbaladze M.

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Survey have been conducted among medical professionals to test knowledge level of HUS and diarrheal diseases and to identify predictor variables for better knowledge.

Cross-sectional survey have been conducted among medical personnel at different clinics in Tbilisi and in regions of Georgia. Participants were selected from different clinics in Tbilisi and in three biggest regional cities (Zugdidi, Batumi and Kutaisi) of Georgia. A total of 12 clinics were selected from them 6 were in Tbilisi and 2 at each regional cities. Clinics were selected based on their ability to provide services for gastrointestinal diseases, infectious diseases and kidney diseases. Data were entered into electronic database and analyzed using R v3.3.2. Descriptive statistics and methods of multivariate analysis were used for data analysis.

366 medical personnel have been interviewed. 73% (267) were females and 27% (99) males. Mean age was 40.8, IQR (27-52). A total of 64% (235) participants were from clinics located in Tbilisi. In multivariate analysis background in infectious diseases, female sex and having more than 10 years of medical experience were significantly associated with the total knowledge score of diarrheal diseases ($p<0.05$). High total knowledge score of HUS was detected among pediatricians ($p<0.05$).

Trainings has been recommended for medical specialists to increase knowledge of diarrheal diseases and HUS to be able to identify those condition and to provide timely medical support for patients.

Keywords: diarrheal diseases, hemolytic uremic syndrome, knowledge level, medical professionals.

РЕЗЮМЕ

ОЦЕНКА УРОВНЯ ЗНАНИЙ МЕДИЦИНСКОГО ПЕРСОНАЛА ОТНОСИТЕЛЬНО ДИАРЕЙНЫХ ЗАБОЛЕВАНИЙ И ГЕМОЛИТИЧЕСКО-УРЕМИЧЕСКОГО СИНДРОМА

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Целью исследования явилась оценка уровня знаний о диарейных заболеваниях и гемолитическо-уремическом синдроме среди медицинского персонала для обеспечения своевременной медицинской помощи.

Применялся перекрестный дизайн исследования. Проведен опрос медицинского персонала двенадцати клиник г. Тбилиси и крупнейших региональных центров Грузии - гг. Батуми, Зугдиди и Кутаиси. Данные опроса внесены в электронную базу данных, проанализированы с помощью статистической программы R v3.3.2 и обработаны с применением методов описательной статистики и многофакторного анализа.

Опрошено 366 медицинских работников, из них 73% женщин и 27% - мужчин в возресте 27-52 года, средний возраст - 40,8 лет. 64% опрошенных являлись сотрудниками клиник и медицинских центров г. Тбилиси.

Многофакторный анализ выявил высокий уровень знаний о желудочно-кишечных заболеваниях среди женщин-инфекционистов со стажем работы в этой сфере более 10 лет ($p<0,05$). Уровень знаний о гемолитическо-уремическом синдроме (ГУС) высоким оказался среди педиатров ($p<0,05$).

По мнению авторов, необходимо проведение трейнингов для медицинских специалистов с целью повышения уровня знаний о ГУС и диарейных заболеваниях, что обеспечит своевременную идентификацию этих состояний и квалифицированную медицинскую помощь пациентам.

რეზიუმე

სამედიცინო პერსონალის ცოდნის დონის შეფასება დიარეებისა და ჰემოლიზურ-ურემიული სინდრომის შესახებ

[1]ო. ჩოკოშვილი, [2]ნ. ვეფხვაძე, [1]თ. ცერცვაძე, [3]თ. გაბრიჩიძე, [2]მ. ხორბალაძე

[1]ინფექციური პათოლოგიის, შიდსისა და კლინიკური იმუნოლოგიის სამეცნიერო-პრაქტიკული ცენტრი; [2]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი; [3]მ. იაშვილის სახ. ბავშვთა ცენტრალური საავადმყოფო, საქართველო

კვლევის მიზანს წარმოადგენდა სამედიცინო პერსონალის ცოდნის დონის შეფასება დიარეული დაავადებებისა და ჰემოლიზურ-ურემიული სინდრომის (ჰუს) შესახებ დროული სამედიცინო დახმარების უზრუნველყოფის თვალსაზრისით.

გამოყენებული იყო ჯვარედინ-სექციური კვლევის დიზაინი. კვლევაში მონაწილეები შერჩეული იყო თბილისის და საქართველოს სამი დიდი რეგიონული ცენტრის (ბათუმი, ზუგდიდი და ქუთაისი) კლინიკებიდან. შეირჩა 12 კლინიკა, მათგან 6 - თბილისში და ორ-ორი - თითოეულ დიდ ქალაქში. მონაცემების ანალიზი ჩატარდა სტატისტიკურ პროგრამაში R v3.3.2. მონაცემები დამუშავდა აღწერილობითი სტატისტიკის და მულტივარიაციული ანალიზის მეთოდებით.

კვლევაში მონაწილეობა მიიღო 366 სამედიცინო პერსონალმა, საშუალო ასაკი - 40.8 წ., მათგან 64% (235) შერჩეული იყო თბილისის კლინიკებში და სამედიცინო ცენტრებში. მულტივარიაციული ანალიზის მეშვეობით დადგენილია, რომ დიარეული დაავადებების შესახებ ცოდნის მაღალი დონე გამოვლინდა მედიცინის მუშაკ-ქალებში, რომელთა სამუშაო გამოცდილება აღემატება 10 წელს ინფექციურ დაავადებების სფეროში ($p<0,05$), ხოლო ჰუს-ის შესახებ ცოდნის დონის მაჩვენებელი მაღალი აღმოჩნდა პედიატრებში ($p<0,05$).

რეკომენდებულია სამედიცინო პერსონალისათვის ტრეინინგების ჩატარება დიარეული დაავადებების და ჰუს-ის შესახებ ცოდნის დონის ამაღლების მიზნით, რაც უზრუნველყოფს პაციენტებისათვის კვალიფიციური სამედიცინო დახმარების დროულ აღმოჩენას.

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